New Method Development to Streamline the Synthesis of *N*-Heterocycles

BY

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THESIS

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Contributions of Authors

Chapter I represents the introduction from my published review article (*Org. Biomol. Chem.* **2015**, *13*, 9720.) for which I was the first author under supervision of my advisor Tom Driver. Chapter II demonstrates a published manuscript (*Org. Lett.* **2013**, *15,* 824.) for which I was the second author and my contribution in this project is described in scheme 2.6, 2.7, 2.9, 2.10, and 2.11. The first author Chen Kong developed the project and she carried out the experiments in table 2.1 and scheme 2.4. Chapter III represents a published manuscript (*J. Org. Chem.* **2014**, *79*, 2781.) for which I was the first author and major contributor of this work. The second author Quyen Nguyen helped me finishing substrate table 3.5. Chapter IV describes a published manuscript (*J. Am. Chem. Soc.* **2016**, *138*, 13721.) for which I was the second author with equal contribution with the first author Chen Kong, who developed this project. My work is described in Scheme 4.7 – 4.10, Table 4.2, 4.3 and Figure 4.1 – 4.5. The contribution from the first author is described in Scheme 4.3, 4.5 and Table 4.1, 4.4, 4.5. The third author in this project Crystallan Jones observed the unusual reactivity of a substrate, which is described in Scheme 4.2. Chapter V represents a published manuscript (*J. Am. Chem. Soc.* **2015**, *137*, 6738) for which I was the first author with major contribution. The second author in this project was Fei Zhou, who helped me in finishing substrate table 5.3, 5.4 and running mechanistic experiments shown in Scheme 5.7 – 5.10. Chapter VI represents my unpublished work and will be published soon, for which I will be the first author with major contribution. Ogbeni Ekhomu, an undergraduate student at UIC, helped me preparing a few starting material in table 6.2.

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LIST OF ABBREVIATIONS

Ac	acetyl
Alk	alkyl
aq	aqueous
Ar	aryl
atm	atmosphere
azafluor	4,5-diazafluoren-9-one
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Bpin	pinacolborane borate
Bz	benzoyl
n-Bu	butyl
t-Bu	*tert*-butyl
Calcd	calculated
cat.	catalytic amount
Cbz	carboxybenyl
COD	1,5-cyclooctadiene
Cy	cyclohexyl
δ	chemical shifts in parts per million downfield from tetramethylsilane (NMR)
d	doublet
dba	dibenzylidene acetone
DABCO	1,4-diazabicyclo[2.2.2]octane
DCM	dichloromethane

LIST OF ABBREVIATIONS (continued)

DCE	1,2-dichloroethane
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
DEPT	distortionless enhancement by polarization transfer
DFT	Density Functional Theory
DMA	dimethylacetamide
DMB	2,4-dimethoxybenzyl
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMSO	dimethylsulfoxide
dppf	1,1'-bis(diphenylphosphino)ferrocene
EDG	electron-donating group
EI	electron impact ionization (in mass spectrometry)
Et	ethyl
equiv.	equivalent
EWG	electron withdrawing group
esp	α, α, α', α'-tetramethyl-1,3-benzenedipropionic acid
G	group, Gibbs free energy
g	gram
GC	gas chromatography
h, hrs	hour(s)
HR	high resolution (mass spectrometry)
Hz	Hertz

LIST OF ABBREVIATIONS (continued)

J	spin-spin coupling constant (NMR)
L	ligand
LDA	lithium diisopropyl amide
LHMDS	lithium bis(trimethylsilyl)amide
m	multiplet (NMR)
mp	melting point
[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
NMR	nuclear magnetic resonance
Ph	phenyl
Phen	phenanthroline

Piv	pivalyl, trimethylacetyl
PMB	*p*-methoxybenzyl
ppm	parts per million
Pr	propyl
i-Pr	isopropyl
n-Pr	propyl
Py	pyridine
q	quartet (NMR)
quint	quintet (NMR)
rt	room temperature
s	singlet (NMR)
sept	septet (NMR)
SFC	supercritical fluid chromoatography
t	triplet (NMR)
tf	trifluoromethanesulfonyl
TFA	trifluoro acetate
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
tmphen	3,4,7,8-tetramethyl-1,10-phenanthroline
Ts	*p*-toluenesulfonyl

SUMMARY

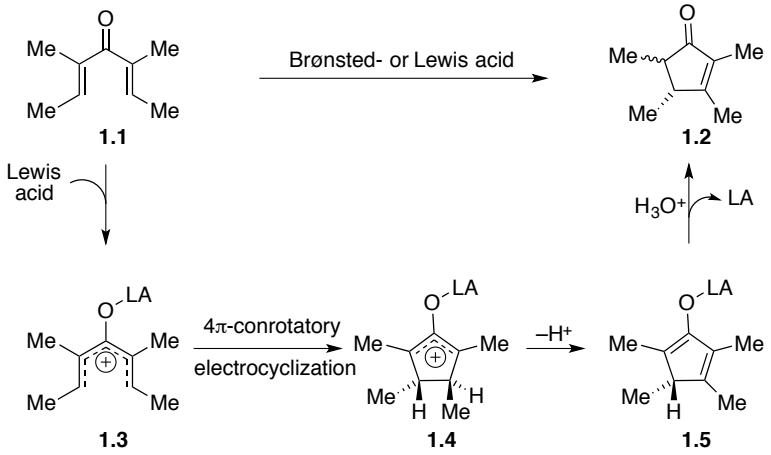
Nitrogen-heterocycles are an important class of molecules because of its widespread availability in pharmaceuticals, natural products and organic electronic materials. Significant research efforts were made to construct complex *N*-heterocycles starting from simple organic molecules. The research program in the Driver lab is focused on exploiting the reactivity of metal *N*-arylnitrene intermediates to create heterocycles. Our group has successfully used aryl azides as a nitrogen-atom source to create C–N bonds from sp^3-C–H bonds or sp^2-C–H bonds. The construction of C–N bonds through a domino electrocyclization–migration reactions was discussed in the first chapter. In the second chapter the reactivity of styryl azides was investigated to perform an electrocyclization, selective aminomethylene migration reaction. An efficient synthesis of styryl azides was described in the third chapter and use of these styryl azides were demonstrated by converting them into indole derivatives. In the fourth chapter, the reactivity of metal nitrene intermediates toward C–H bond aminations or electrocyclization reactions were examined in order to derive a general trend of reactivity of aryl azides. In the following chapters, we demonstrate that a similar reactivity pattern of aryl azides could also be accessed from nitroarenes. In chapter five we demonstrated that the reactivity of tetrasubstituted nitroarenes toward a cyclization-migration reaction could be unlocked by a palladium(II)-catalyst and $Mo(CO)_6$. In the final chapter we showed the potential of nitroarenes to undergo a reductive cyclization using $Pd(OAc)_2$ as catalyst and CO gas to afford indolines.

Chapter-I

Introduction: Construction of C–N bond Through Domino Electrocyclization–Migration Reaction

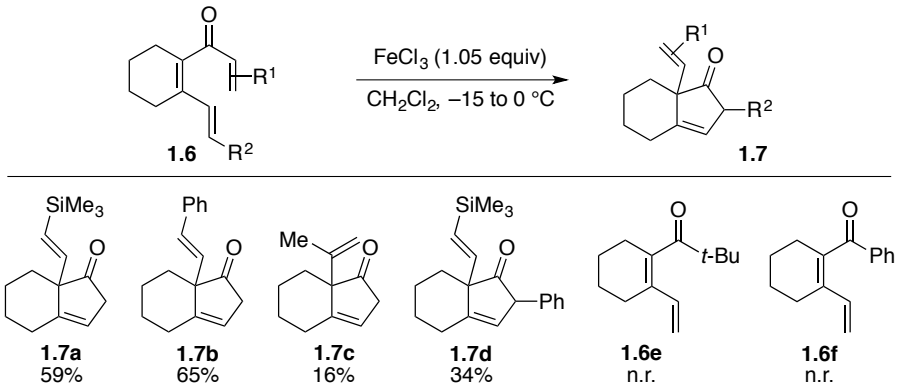
(The structure of this chapter followed the published review article: Assembly of functionalized carbocycles or *N*-heterocycles through a tandem electrocyclization-[1,2] migration reaction sequence. *Org. Biomol. Chem.* **2015**, *13*, 9720.)

The development of new methods to streamline the synthesis of *N*-heterocycles and carbocycles continues to motivate synthetic chemists because of their widespread occurence in natural products, pharmaceuticals and organic materials. Among them electrocyclization reactions have been developed to construct C–C bonds in carbocycles and C–N bonds in heterocycles. In particular, the Nazarov cyclization has received much attention to synthesize substituted cyclopentenones from simple divinyl ketones in a stereoselective fashion (Scheme 1.1).[1-9] The Nazarov cyclization reaction is often catalyzed by a Brønsted- or Lewis-acid; coordination of which generates the requisite oxyallyl cation **1.3**. This oxyallyl cation then undergoes a stereospecific 4π-electron-5-atom electrocyclization to form the C–C bond. Elimination of proton generates the cyclopentadiene **1.5**, which furnishes the cyclopentenone product **1.2** upon protonation.



Scheme 1.1. The Nazarov cyclization reaction

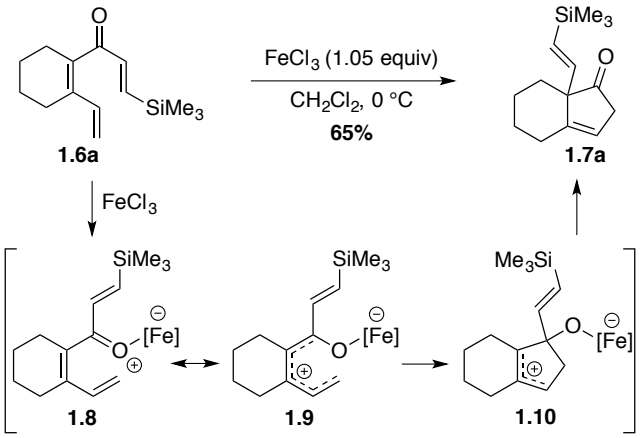
Nazarov cyclizations are often associated with 1,2 migration sequence and the first systematic study of a domino Nazarov cyclization-1,2 migration sequence was done by Denmark and co-workers.[10] They observed that exposure of vinyl dienyl ketone **1.6** to stoichiometric amounts of ferric chloride produces the unusual α-vinyl cyclopentenone **1.7** instead of the expected cyclopentenone, which was observed by Peel and Johnson with tin-substituted vinyl dienyl ketones (Scheme 1.2).[11] Denmark and Hite's transformation tolerates a range of dienyl- or vinyl substituents to produce α-vinyl cyclopentenones with a few exceptions: alkyl dienyl ketone **1.6e** or phenyl dienyl ketone **1.6f** were inert to reaction conditions.



Scheme 1.2. $FeCl_3$-promoted electrocyclization-1,2 migration to form α-vinyl cyclopentenones

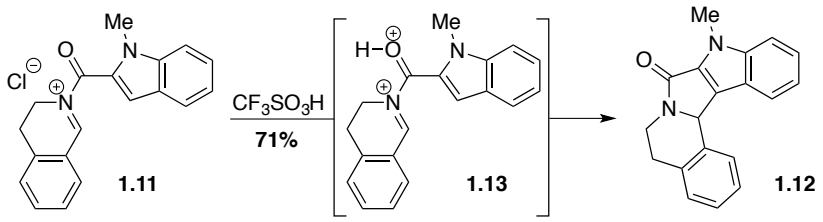
Based on reactivity trends and ^{13}C-labeling experiments, Denmark and Hite proposed that the formation of α-vinyl cyclopentenone occurs through an electrocyclization-1,2 migration pathway (Scheme 1.3). Coordination of the ketone to the Lewis acid $FeCl_3$ produces pentadienyl cation **1.9**, which triggers an

electrocyclization to form C–C bond in **1.10**. The authors proposed that the electrocyclic ring closure occurs via the linearly conjugated dienyl moiety instead of the cross-conjugated divinyl ketone. The resulting pentadienyl cation then undergoes a 1,2 vinyl migration to produce the product **1.7a** after dissociation of the Lewis acid.



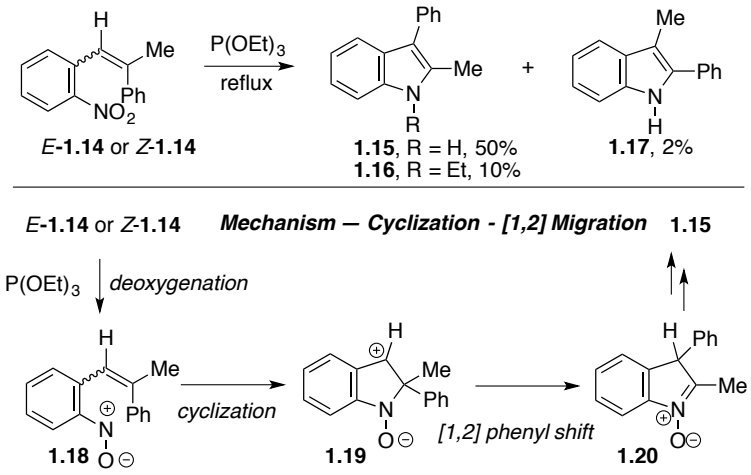
Scheme 1.3. Mechanism of $FeCl_3$-promoted electrocyclization-1,2 migration to form α-vinyl cyclopentenones

In contrast to the significant development of the Nazarov cyclization, replacing one of the carbon-atoms in the starting divenyl ketone with a nitrogen-atom has been less explored. Significant amount of challenges remained in generating and controlling an azapentadienyl cationic reactive intermediate. In effort to overcome these challenges, Klumpp and co-workers reported the first aza-Nazarov reaction in 2007.[12] They observed that exposure of *N*-acyliminium ions, such as **1.11** to super acidic F_3CSO_3H furnished pyrrolidinones **1.12** via azapentadienyl electrophile **1.13** (Scheme 1.4). Following their report, new methods have been developed to unlock the required electrophilic nitrogen from azide-,[13-16] imino-,[17-21] and azirine groups.[22,23]



Scheme 1.4. The aza-Nazarov reaction

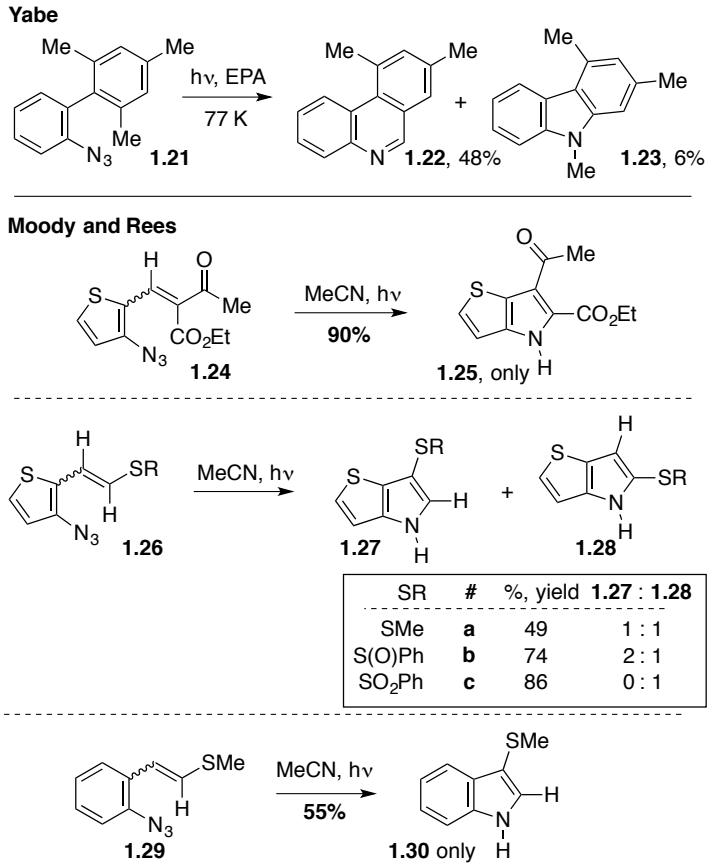
In comparison to Nazarov cyclization-1,2 migration processes, domino reactions in which the electrocyclization forms a C–N bond are surprisingly rare. In 1969, Sundberg and co-workers reported the conversion of β-phenyl-β-methyl-*ortho*-nitrostyrene to 2-methyl-3-phenyl indole using stoichiometric amount of triethyl phosphite (Scheme 1.5).[24,25] An excellent migratorial selectivity in favor of a 1,2-phenyl shift was observed to produce **1.15**. The authors observed that the indole formation was not dependent on the nitrostyrene isomer: both *E*- and *Z*-isomers were converted to product with nearly equal yield. Sundberg and Kotchmar proposed that indole formation occurred through a phosphite-mediated dexoygenation of the nitroarene to afford nitroso-intermediate **1.18** or nitrene,[26] which underwent a cyclization to afford **1.18**. Formation of this benzyl cation triggers a 1,2-phenyl shift to afford 3*H*-indole **1.20**. Reduction of *N*-oxide **1.20** by triethyl phosphite (additional reduction is not required from nitrene derived intermediate) followed by tautomerization generates 2-methyl-3-phenyl indole.



Scheme 1.5. Phosphite-mediated reductive cyclization-1,2 phenyl migration to form 2,3-disubstituted indole

In 1981, Moody, Rees and co-workers systematically studied electrocyclization-1,2 migration reactions that involve aryl azides (Scheme 1.6).[27-30] Their study originated from a finding by Yabe,[31] who reported that *ortho*-substituted biarylazides such as **1.21** underwent a low temperature photolysis to produce azine **1.22** as a major product and *N*-methylcarbazole **1.23** as a byproduct. They hypothesized that the byproduct appears from electrocyclization followed by methyl migration to *N*-atom. Moody, Rees and co-workers observed that these migration processes were a common phenomenon: irradiation of β,β-disubstituted 3-azido-2-alkenylthiophene azide **1.24** produced indole **1.25** where C–N bond formation was followed by selective 1,2-acyl group migration occurred. In addition to acyl migration, the authors also reported selective 1,2-sulfide and sulfoxide migration in preference to a hydrogen atom. They also observed that sulfide- and sulfoxide migration was competitive with C–H bond amination:[28] irradiation of thiophene azide **1.26** produced mixture of indoles **1.27** and **1.28**. In contrast,

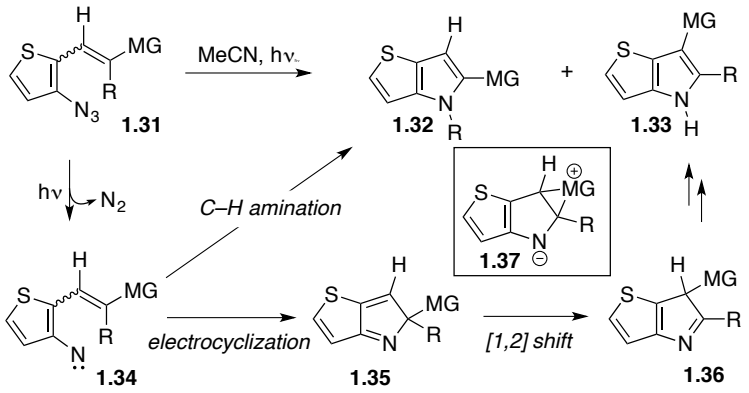
photolysis of β-sulfone substituted styryl azide **1.26c** afforded C–H bond amination product **1.28c** exclusively. When the thiophene azide moiety was replaced with a styryl azide (**1.29**), selective methyl sulfide migration was observed to afford indole **1.30**.[30]



Scheme 1.6. Irradiation of thiophene azides produce pyrrolothiophenes

The mechanism for the transformation of thiophene azides to pyrrolothiophenes was proposed by the authors to occur through an electrocyclization-1,2 migration pathway (Scheme 1.7). Irradiation of azide **1.31** produces nitrene **1.34**, which undergoes an electrocyclization reaction to produce thiophene-fused 2*H*-pyrrole **1.35**. A 1,5 migration from **1.35** produces thiophene-fused 3*H*-pyrrole **1.36**. The thieno[3,2-

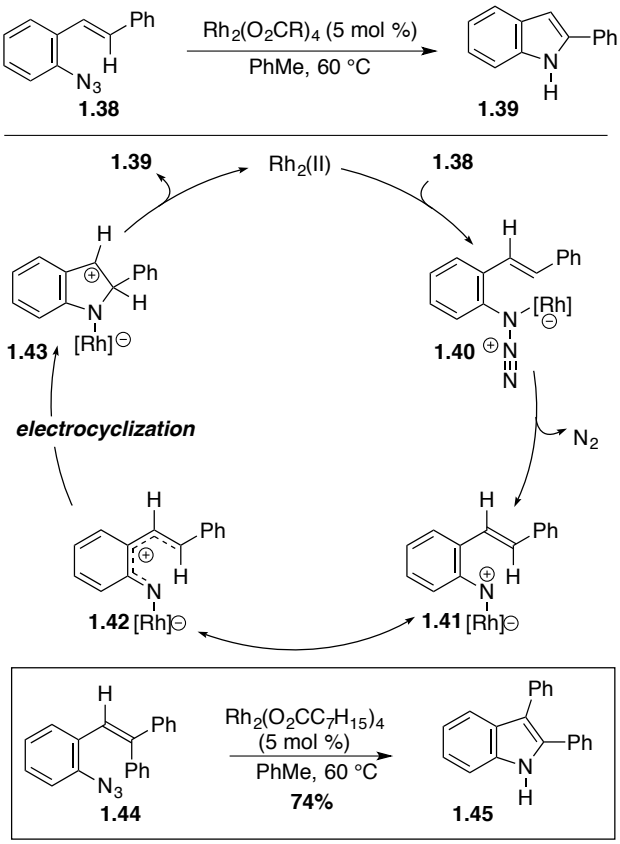
b]pyrrole product **1.33** is formed through either 1,3-hydrogen shift or two successive 1,5-hydrogen shifts. When R = H, nitrene **1.34** could undergo a C–H bond amination to afford thienopyrrole **1.32**. Based on established reactivity trends in 2*H*-indenes,[32-35] the authors proposed that the C–H bond amination products are formed through an electrocyclization–1,5-hydrogen migration pathway. The difference in migratory preferences of sulfide and sulfoxide versus the sulfone was attributed to the ability of lone pair of electrons on sulfur to form an episulfonium ion **1.37**, which results in the formation of the 1,2-migration product.



Scheme 1.7. Proposed mechanism for the formation of pyrrolothiophenes

In 2006, the Driver group reported that exposure of styryl azides to a Rh(II)-carboxylate complex afforded indoles (Scheme 1.8).[36,37] Their mechanistic experiments suggest that the amination occurs through a stepwise mechanism in which C–N bond formation occurs before C–H bond breaking.[38] Coordination of the Lewis acidic catalyst with azide occurs first followed by extrusion of N_2 to form rhodium nitrene **1.41**. They observed that electron-donating group accelerates the loss of N_2. In line with the observation, they proposed that delocalization of positive charge occurs into the adjacent

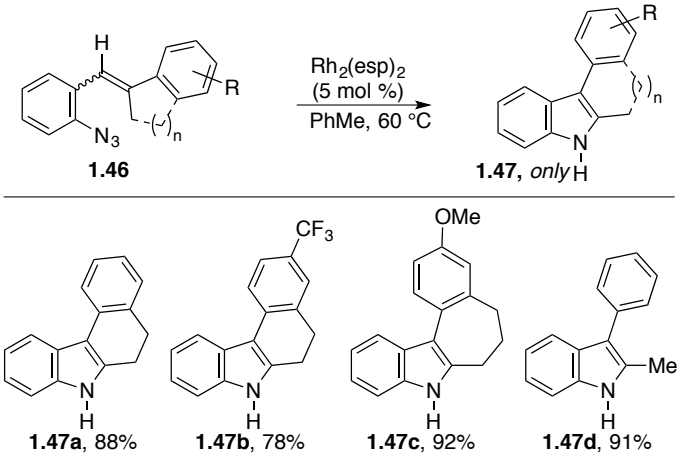
π-system to produce **1.42**. This electron movement promotes formation of C–N bond through 4π-electron-5-atom electrocyclization to produce benzyl cation **1.43**. A 1,5-hydride shift could afford indoles and regenerate the active catalyst. To support the step-wise mechanism, they exposed β,β-diphenylstyryl azide **1.44** to the reaction conditions: only 2,3-diphenylindole **1.45** was obtained in good yield.



Scheme 1.8. Rh_2(II)-Catalyzed *N*-heterocycle formation from aryl azides

The Driver group examined the migratory preference of β-substituents in styryl azides by exposing them towards Rh_2(II)-carboxylate catalysts. They synthesized β-methyl-β-aryl-substituted styryl azides to compare the migratory preferences of aryl- and

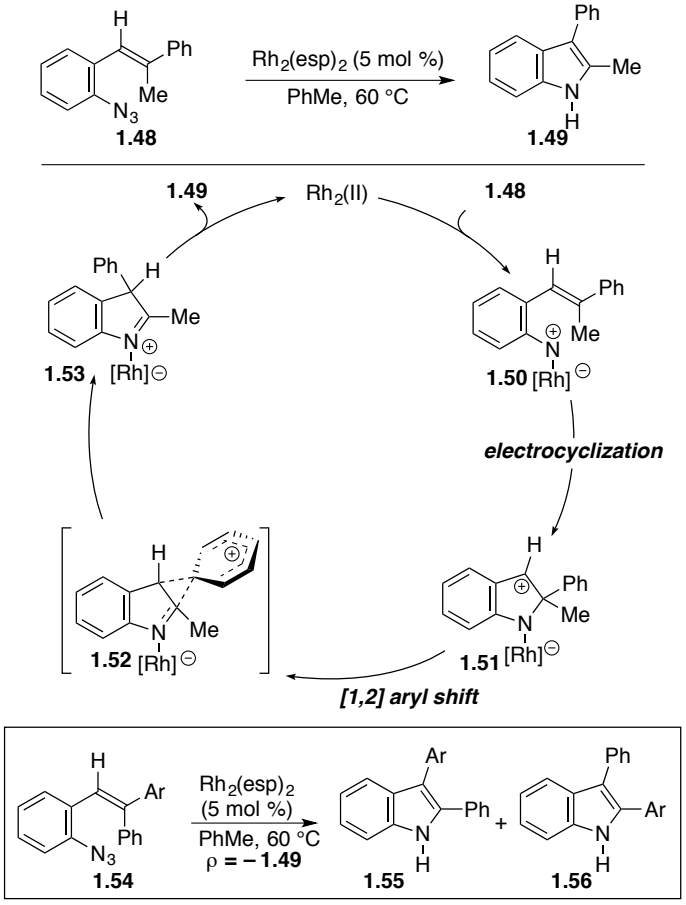
alkyl groups (Scheme 1.9).[39] They found that β,β-disubstituted styryl azides **1.46** produces indoles **1.47** when exposed to $Rh_2(esp)_2$ catalyst. A mixture of *E*- and *Z*-isomers of the starting styryl azides were converted to indoles, and in every case the aryl group migration was observed. The reaction tolerates different sizes of ring expansion without negatively affecting the yield of the transformations, and the conversion of acetophenone-derived substrate **1.46d** to 2-methyl-3-phenyl indole **1.47d** revealed that a tether was not required.



Scheme 1.9. Rh_2(II)-Catalyzed formation of 2-alkyl-3-aryl indoles from β,β-disubstituted styryl azides

The authors proposed a catalytic cycle to account for the selective aryl group migration (Scheme 1.10).[39] Coordination of the Lewis-acidic rhodium catalyst to the azide facilitates the extrusion of N_2 to form rhodium *N*-aryl nitrene **1.50**, which undergoes a 4π-electron-5-atom electrocyclization to produce **1.51**. They proposed that the selective 1,2-aryl migration occurs through the formation of cyclic phenonium ion

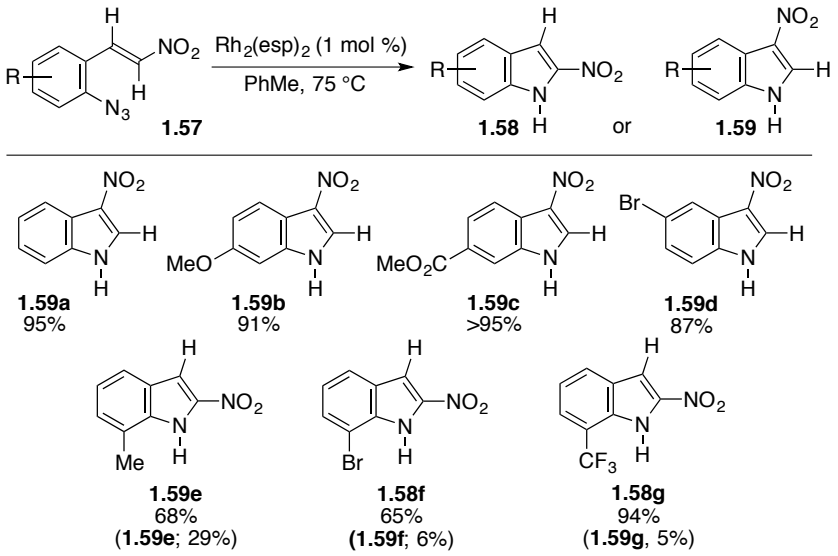
1.52 which results in the formation of 3*H*-indole **1.53**. Tautomerization of **1.53** produces indole **1.49**. In support of this mechanism, the authors examined the reactivity of β,β-diaryl substituted styryl azides toward $Rh_2(esp)_2$. The ratio of the resulted indoles was analyzed using the Hammett equation and the negative ρ-value of –1.49 (versus σ_{para}-values) supports the formation of the phenonium ion.



Scheme 1.10. $Rh_2(II)$-Catalyzed formation of 2-alkyl-3-aryl indoles from β,β-disubstituted styryl azides

In 2011, Driver and co-workers reported electrocyclization-1,2-nitro migration reaction from β-nitro-substituted styryl azides (Scheme 1.11).[40] While thermolysis of β-

nitro-substituted styryl azides afforded 2-nitroindoles **1.58**,[41] migration of $-NO_2$ group could be triggered in the presence of the $Rh_2(esp)_2$ to afford only 3-nitroindoles **1.59**. The transformation was insensitive to the electronic environment of the aryl azide moiety: both electron-donating and electron-withdrawing group underwent the reaction smoothly to afford indoles. In contrast, *ortho*-substituted styryl azides **1.57** formed 2-substituted nitroindoles **1.58** as the major product. The ratio of the 2-nitroindole increased as the *ortho*-substitutent became more electron withdrawing. The authors proposed that the additional *ortho*-substituent could lead to dissociation of the Rh_2(II)-carboxylate catalyst to result in metal free *N*-aryl nitrene formation, thermolysis of which produced 2-nitro indoles.



Scheme 1.11. Selective nitro group migration

Tantillo, Driver and co-workers performed DFT-calculations for the conversion of the β-nitro styrenes to indoles in order to investigate the role of the catalyst during

electrocyclization-migration reaction.[42] They calculated that in the presence of $Rh_2(esp)_2$ catalyst concerted nitro migration had an energy barrier of 12.1 kcal/mol compare to 26.0 kcal/mol for competing hydrogen migration (Figure 1a). This outcome is consistent with their finding that the nitro migration occurred in presence of the catalyst. Surprisingly, they observed that the calculated energy barrier for the 1,2-nitro shifts was also low in the absence of the catalyst (10.8 kcal/mol, Figure 1b). On the basis of these findings, they proposed that catalyst may or may not be present during migration process and the selectivity in the migration was independent on the catalyst identity. To strengthen their hypothesis they calculated the energy barrier of the 1,2-shift using several β-substituents, both in presence and absence of the catalyst. Their results suggest that the catalyst in not required for the migration process. Gribble and Pelkey reported that thermolysis of β-nitrosubsituted nitrostyrenes at 140 ºC produced 2-nitro indoles as the only product.[27] Tantilo and Driver attributed this result to the reversible nature of the nitro migration at higher temperature, leading to the formation of thermodynamic product (appears from hydrogen migration).

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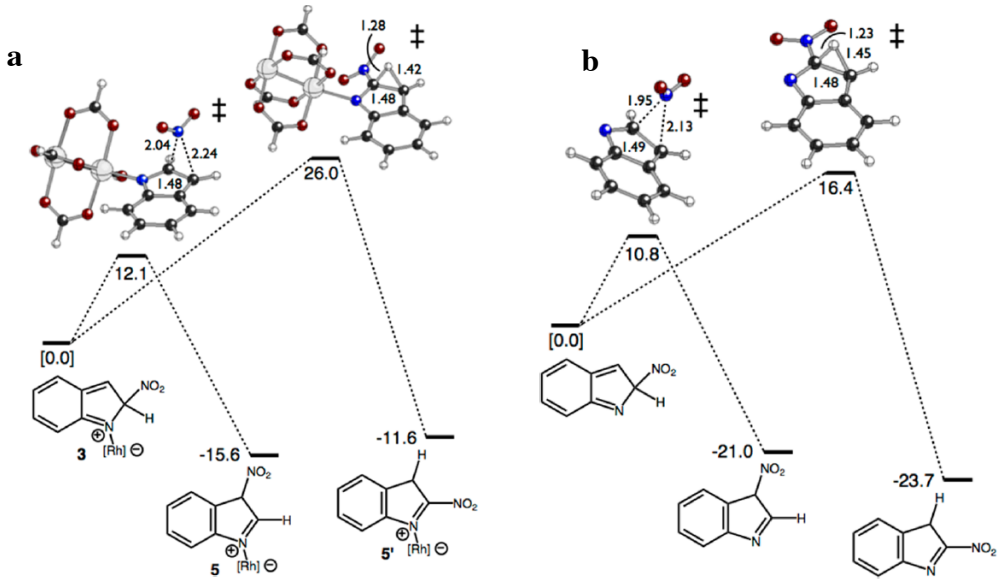
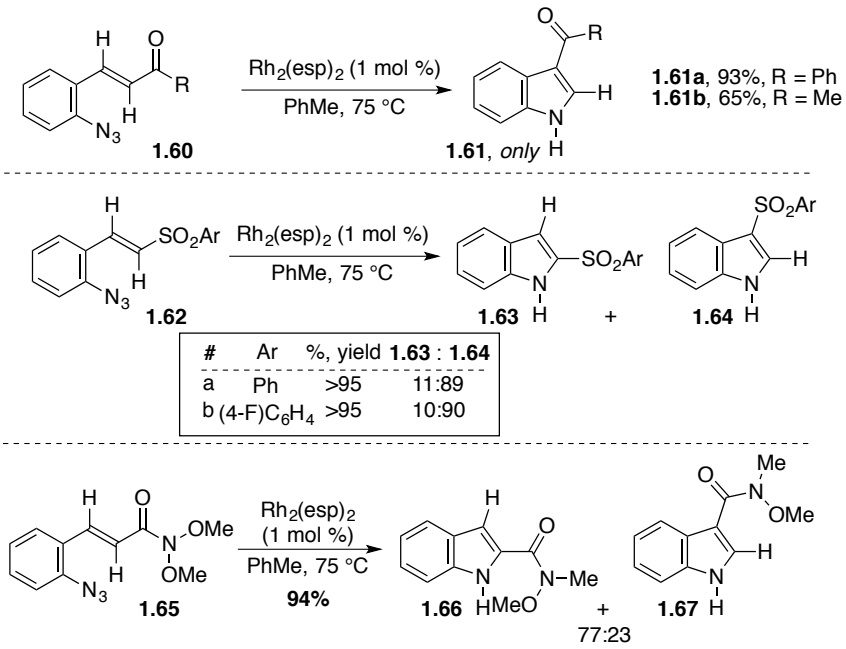


Figure 1. a) 1,5-Sigmatropic shifts for in presence of the catalyst. **b)** 1,5-Sigmatropic shifts for in absencee of thecatalyst. Free energies relative to that of **3** are shown in kcal/mol, calculated at the uM06/6-31+G(d,p)-SDD// uM06/LANL2DZ level of theory

In addition to nitro-group migration, the Driver group examined the reactivity of styryl azides bearing a series of electron-withdrawing β-substituents to test the migratory preferences.[40] Exposure of β-acyl substituted styryl azides **1.60** to $Rh_2(esp)_2$ triggered a selective 1,2-acyl migration to afford only 3-substituted indoles **1.61** (Scheme 1.12). The authors also observed that β-sulfone-substituted styryl azides **1.62** produced a mixture of 2- and 3-substituted products in which 3-substituted sulfone **1.64** predominates. The ratio of indoles was not dependent on the electronic nature of the migrating aryl sulfone: electron-neutral and -withdrawing aryl sulfone provided 90:10 ratio of 3- to 2-substituted indole. In contrast to ketone and sulfone migration, exposure of a β-amide-substituted styryl azide **1.65** to reaction conditions afforded a 77:23 mixture of 2- to 3-substituted

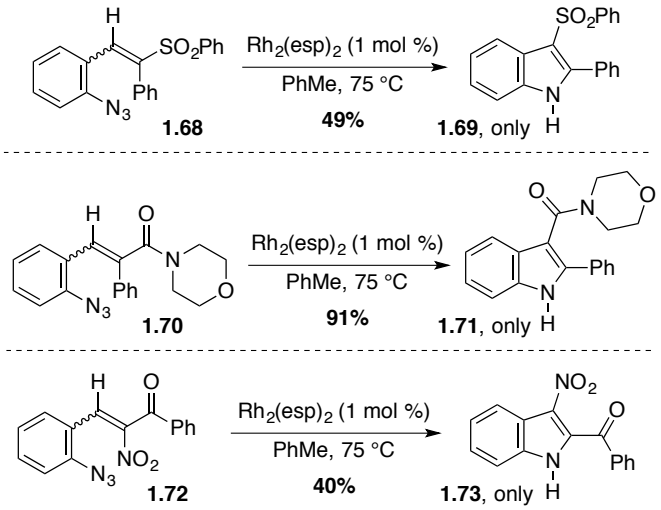
indoles. Esters did not participate in the migration process affording only the 2-carboxylate-substituted indole.



Scheme 1.12. Preference for electron-deficient groups to migrate over hydrogen

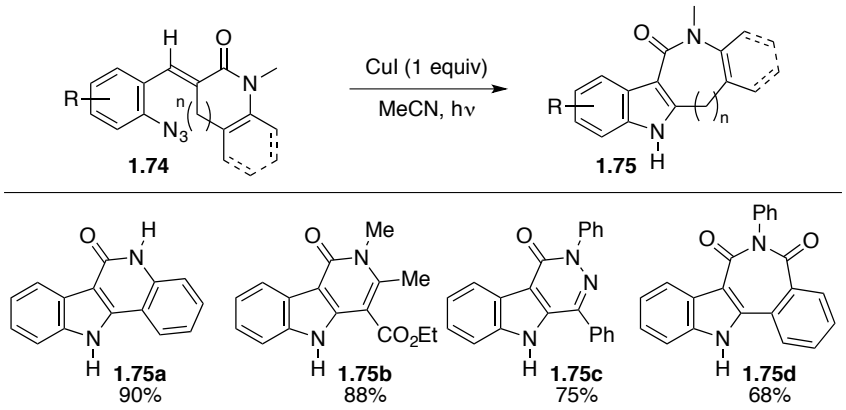
To create a migratory aptitude scale, the Driver group further examined the reactivity of several β,β-disubstituted styryl azides by synthesizing substrates that contained two β-substituents that were both established to migrate.[40] Upon exposure to Rh_2(esp), β-sulfonyl-β-phenyl substituted styryl azide produced only the 3-sulfonyl-2-phenyl indole **1.69** (Scheme 1.13). To compare the migratory aptitude between a phenyl- and amide groups, reactivity of **1.70** was examined: only amide group migrated to afford indole **1.71**. Submission of β-nitro-β-benzoyl substituted styryl azide resulted in selective nitro migration of give indole **1.73**. Combining the migration ability, the

authors proposed a migratory aptitude scale as follows: alkyl < aryl < amide < H < sulfonyl < ketone < nitro.



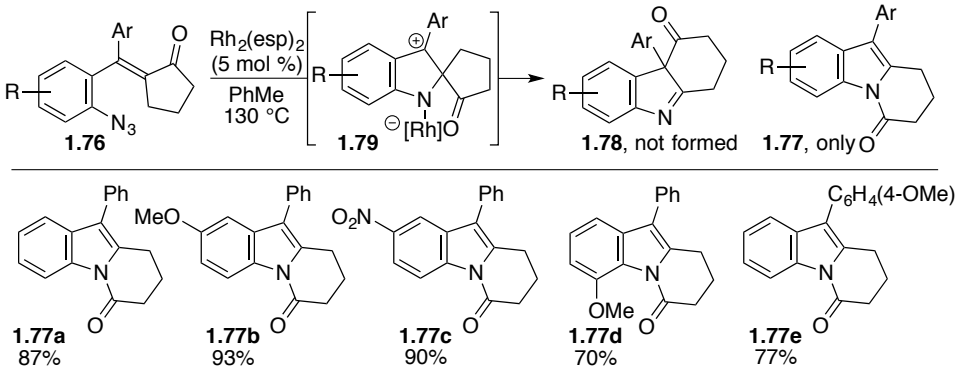
Scheme 1.13. Migratory preferences of β-substituent in β,β-disubstituted styryl azides

In 2010, Zhang and co-workers reported electrocyclization-1,2-amide migration reactions of β,β-disubstituted styryl azides using CuI (Scheme 1.14).[43] They observed that irradiation of styryl azide **1.74** in the presence of stoichiometric amount of CuI promoted the ring expansion through the exclusive migration of the amide to form 2,3-disubstituted indole **1.75**. The use of stoichiometric amount of CuI was necessary for good yields: reducing the amount of CuI reduced the yield of indole formation. Their transformation tolerated a broad range of functionality including esters and NH-amides without attenuation of the yield. A variety of ring expansions were triggered to produce 2,3-disubstituted indoles.



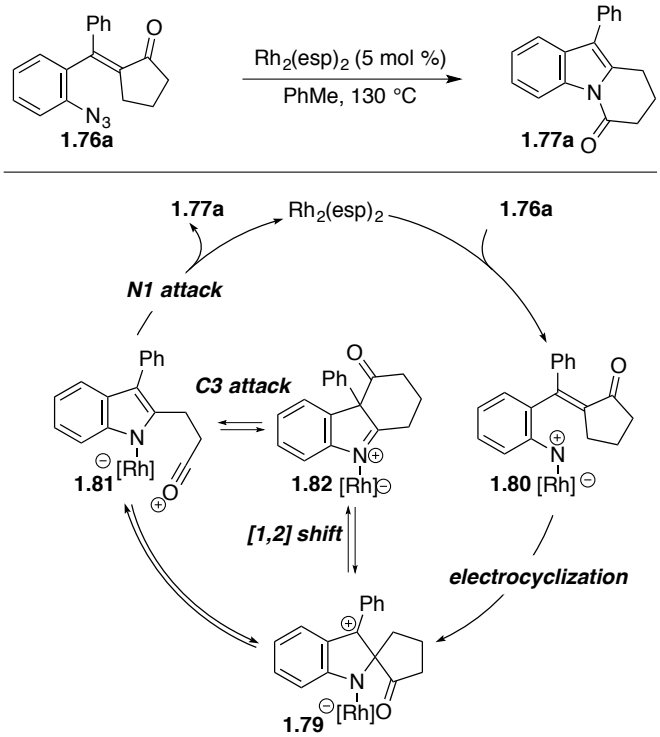
Scheme 1.14. Migratorial trends of trisubstituted styryl azides

The Driver group investigated the reactivity of trisubstituted styryl azides as potential substrates for a domino cyclization-1,2-migration reactions (Scheme 1.15).[44] They envisioned that exposure of styryl azide **1.76** to $Rh_2(esp)_2$ complex could provide benzyl cation **1.79**, which could trigger a 1,2-acyl migration to afford 3*H*-indole **1.78**. Exposure of styryl azides **1.76** to reaction conditions, however, produced 1,2,3-trisubstituted indoles **1.77** as the only product. Their transformation tolerates a range of substituents on both the aryl azide moiety and the α-substituent to furnish the products in good to excellent yields.



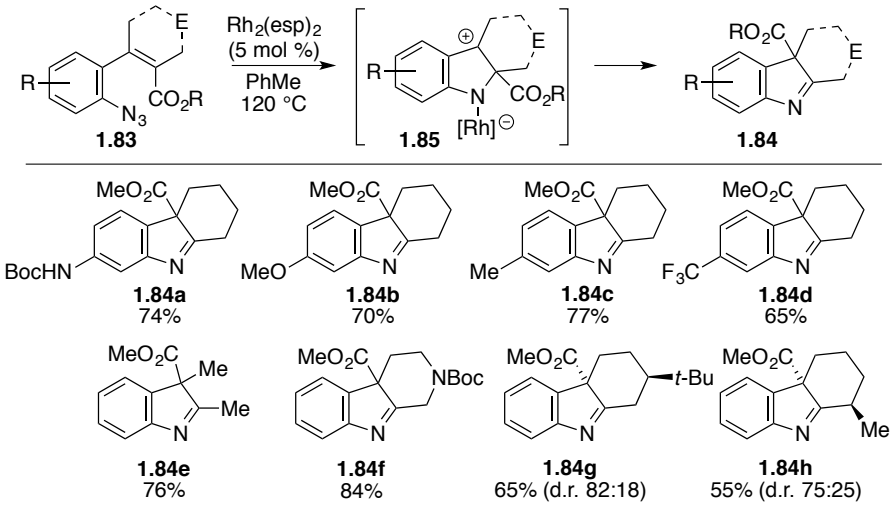
Scheme 1.15. Migratorial trends of trisubstituted styryl azides

The authors proposed a mechanistic cycle to account for the formation of 1,2,3-trisubstituted indoles from styryl azides (Scheme 1.16).[44] Coordination of rhodium catalyst with azide induces N_2 extrusion to form rhodium nitrene **1.80**. Delocalization of positive charge in **1.80** induces electrocyclization to form benzyl cation **1.79**, which fragments to form acylium ion **1.81**. A C3 nucleophilic attack to the acylium ion could be possible to generate 3*H*-indole **1.82**. Ban and co-workers reported that 3*H*-Indoles containing a 3-acyl group were unstable: isolation or purification of these *N*-heterocycles triggered fragmentation.[45,46] On the basis of their report, Driver proposed that C3 nucleophilic attack is reversible under reaction conditions. Nucleophilic attack from N1 position, however, appears to be irreversible to form the isolated indole product **1.77a** after dissociation of the Rh_2(II)-carboxylate catalyst.



Scheme 1.16. Proposed mechanistic cycle for the formation of 1,2,3-trisubstituted indoles from styryl azides

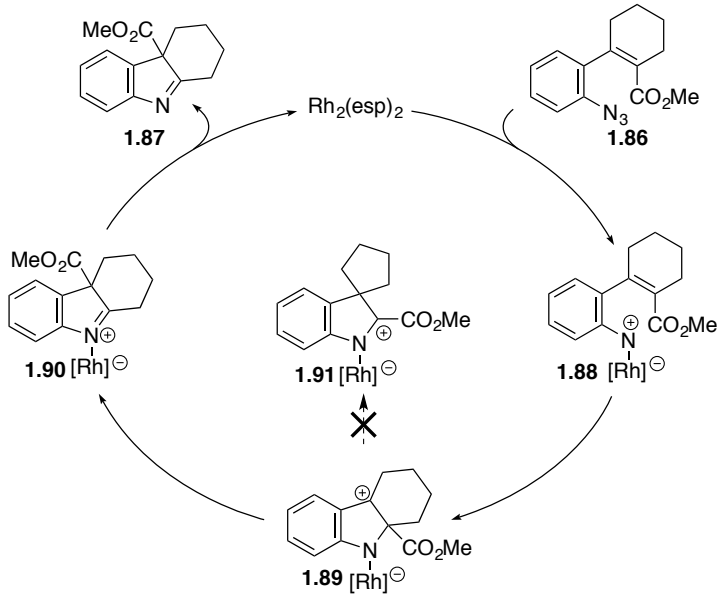
The formation 3*H*-indoles could be accessed from trisubstituted styryl azides by changing the identity of the β-substituent (Scheme 1.17). Kong and Driver reported that exposure of β-carboxylate substituted styryl azides **1.83** to $Rh_2(esp)_2$ afforded 3*H*-indoles **1.84**.[47] A wide range of substituents on the aryl azide were tolerated in their transformation enabling access to 3*H*-indoles (**1.84a** – **1.84d)** that cannot be formed as single isomers using Fischer- or interrupted Fischer-indole-type reactions. The cycloalkenyl *ortho*-substituent was not required for the transformation: trisubstituted styryl azide **1.83e** produced **1.83e** under reaction conditions. The reaction tolerates heteroatom substituent on the *ortho*-cycloalkenyl tether to give **1.84** in good yield. The authors also reported diastereoselective 3*H*-indole formation from allylic- and homoallylic substituted substrates; however, products were obtained in moderate yield and diastereoselectivity (**1.84g** and **1.84h**).



Scheme 1.17. Synthesis of 3*H*-indoles from trisubstituted styryl azides

The mechanism of the 3*H*-indole formation proposed by the Driver group is outlined in scheme 1.18.[47] Coordination of the $Rh_2(esp)_2$ catalyst with the styryl azide

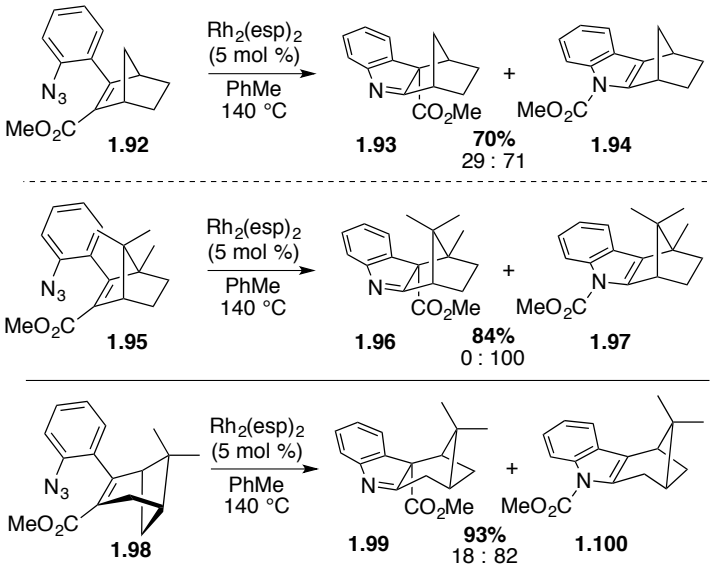
promotes extrusion of N_2 to form rhodium *N*-aryl nitrene **1.88**. Electrocyclization forms the C–N bond and generate benzyl cation **1.89**. From cation **1.89**, two 1,2 shifts are possible. An alkyl migration would go through an intermediate in which a positive charge is generated next to the carboxylate substituent **1.91**. In contrast, if the carboxylate group migrated, a more stable iminium ion **1.90** would be generated. Catalyst dissociation would then generate the product **1.87**.



Scheme 1.18. Potential catalytic cycle to produce 3*H*-indoles from trisubstituted styryl azides

The ester migration selectivity could be changed by increasing steric bulkiness around *ortho*-alkenyl substituent as reported by the Driver group (Scheme 1.19).[48] They observed that exposure of $Rh_2(esp)_2$ to *ortho*-[2.2.1] substituted **1.92** produced a mixture of products: carboxylate migration to the nitrogen-atom afforded **1.94** as the major product and carboxylate migration to the carbon-atom resulted in the formation of 3*H*-indole **1.93** as the minor product. Increasing the steric environment by adding methyl

substituents to the bridgehead prevented the formation of 3*H*-indole **1.96**; instead, indole **1.97** was obtained. When one of the allylic substituents was moved to the homoallylic position, 3*H*-indole **1.99** was formedas the minor product. The authors hypothesized that the 1,2-migration selectivity resulted from minimizing the destabilizing steric interactions between the bridgehead methyl groups and the carboxylate group.



Scheme 1.19. Effect of increasing the steric environment on the reaction outcome

Summary and Outlook

We have described domino electrocyclization-migration process to create *N*-heterocycles from the nitroarenes and styryl azides. While a series of methodical studies were performed by the Driver group to create indoles and 3*H*-indoles, there are still challenges remaining. In my opinion the major challenges include: 1) formation of six-membered ring through a 6π-electron-6-atom electrocyclization, 2) construction of C–N bonds in a stereoselective fashion and 3) exploitation of the reactivity of nitroarenes and anilines as

a nitrogen atom source toward cyclization-migration reaction. In the next few chapters, my attempts toward solving these problems will be discussed.

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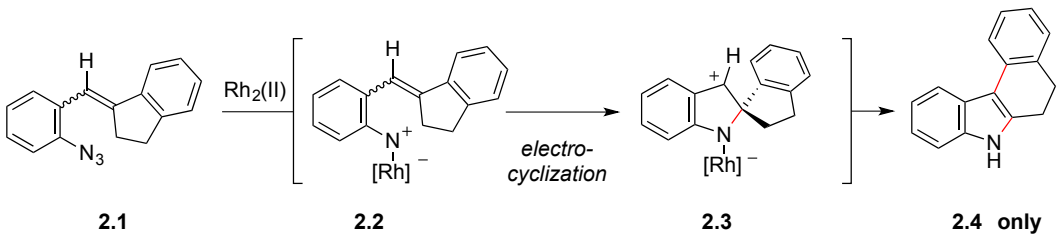
Chapter-II

Formation of 2,3-Fused Indole Heletrocycles by a Domino Electrocyclization, Selective 1,2-Aminomethylene Migration

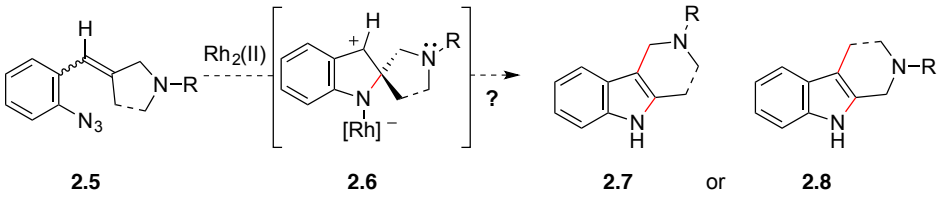
(The structure of this chapter followed the published article: Rh_2(II) catalyzed selective aminomethylene migration from styryl azides. Kong, C.; Jana, N.; Driver, T. G. *Org. Lett*. **2013**, *15*, 824.)

The central focus of research in Driver lab to exploit the reactivity of metal N-arylnitrene intermediate to undergo a variety of transformation.[1-6] In the past, we have shown that the styryl azide could be converted to indole by exposure of Rh_2(II)-catalyst.[1-6] Our mechanistic investigation suggested that the C–N bond forming event occurs by a 4π-electron-5-atom electrocyclization pathway.[5-7] We took advantage of this electrocyclization pathway to trigger a 1,2-migration reaction from β,β'-disubstituted styryl azides.[8] In addition, we distinguished the migratory preferences between two β-substituents if one of the substituent was replaced by an aryl group. For example, β,β'-disubstituted styryl azide **2.1** underwent a domino electrocyclization, 1,2-migration reaction when exposed to a Rh_2(II)-carboxylate complex to afford selective aryl group migration to product **2.4** as the only product (Scheme 1). Further, a series of intramolecular competition experiments established the migratory aptitude of other β-substituents to be: ester << alkyl << aryl < amide < H < sulfone < ketone << nitro.[9]



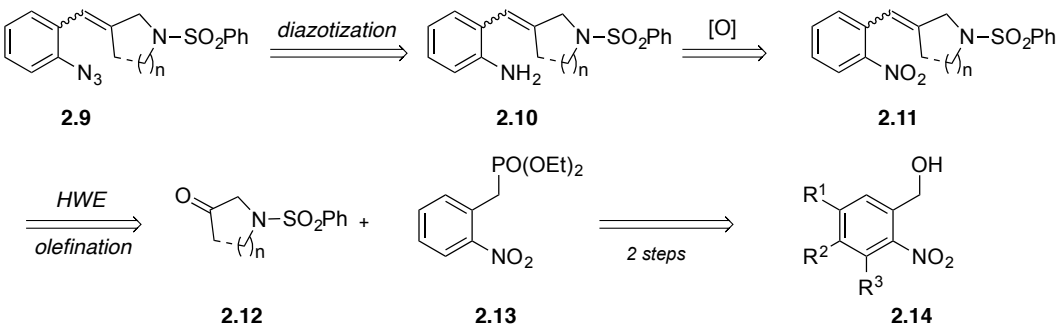
Scheme 2.1. Selective aryl group migration from β,β'-disubstituted styryl azide

The migratory preferences between the β-substituents explored earlier by us, however, differed significantly, and we were interested if the migration step could distinguish between two β-methylene units when one of the methylene groups is substituted with an amine (Scheme 2). The use of heteroatom to control the 1,2-migration pathway is very rare.[10-12] To test our hypothesis, we designed styryl azide **2.5** and we were curious if the β-aminomethylene substituent could differentiate in the 1,2 migration process when **2.5** is exposed to Rh_2(II)-catalyst to generate a single regioisomer of tetrahydrocarboline **2.7** or **2.8**. To differentiate the migratory preferences between a methylene and aminomethylene group, we describe in this project, a selective aminothylene group migration to afford useful indole heterocyles.



Scheme 2.2. Selective aminomethylene migration possible?

At the outset, we chose the model styryl azide **2.9** to study the electrocyclization, 1,2-migration reaction. From a retrosynthetic perspective, the styryl azide **2.9** could be constructed from nitrostyrene **2.11** by reduction of the nitrostyrene to aminostyrene **2.10** followed by diazotization. Horner–Wordsworth–Emmons olefination between ketone **2.12** and 2-nitrobenzyl phosphonate **2.13** could provide nitrostyrene **2.11**. The phosphonate ester could be obtained from commercially available alcohol **2.14** in two-steps—oxidation of alcohol to an aldehyde followed by Arbuzov reaction with $P(OEt)_3$.

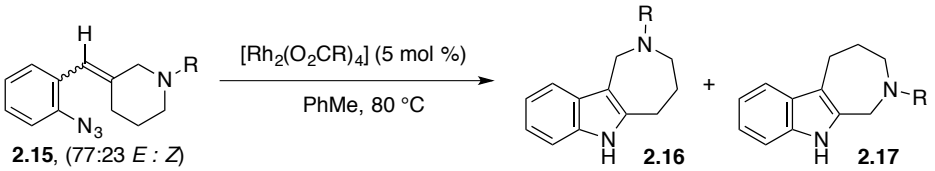


Scheme 2.3. Retrosynthetic plan to generate styryl azide.

2.1. Optimization of the reaction condition:

My colleague, Dr. Chen Kong, synthesized the styryl azide **2.15** to optimize the reaction conditions (Table 2.1). The protecting group, *N*-phenylsulfone, was chosen arbitrarily. While no reaction was observed in the absence of the catalyst, gratifyingly, exposure of the substrate to a Rh_2(II)-carboxylate complex did trigger *N*-heterocycle formation to produce aminomethylene migration product as well as methylene migration product (entries 1 – 4). The yield and selectivity of the reaction depends on the catalyst used and the best condition was obtained by employing either $Rh_2(O_2CC_7H_{15})_4$ or $Rh_2(esp)_2$ as a catalyst which provides only the amino methylene migration product in comparable yields (entries 5 and 6). The structure of the product was confirmed by X-ray crystallography. Interestingly, the yield and the selectivity of the reaction did not depend on the ratio of the starting *E:Z* mixture: both of the isomers were converted to indole. The effect of the *N*-protecting group on the reaction outcome was investigated next. While Boc- and benzoyl-protecting *N*-substituent in the starting styryl azide provided mixture of indole products, *N*-benzyl protected styryl azide resulted in the formation of selective aminomethylene migration product, albeit low in yield (entries 7 – 9).

Table 2.1. Survey of the reaction conditions.



2.15, (77:23 *E* : *Z*)

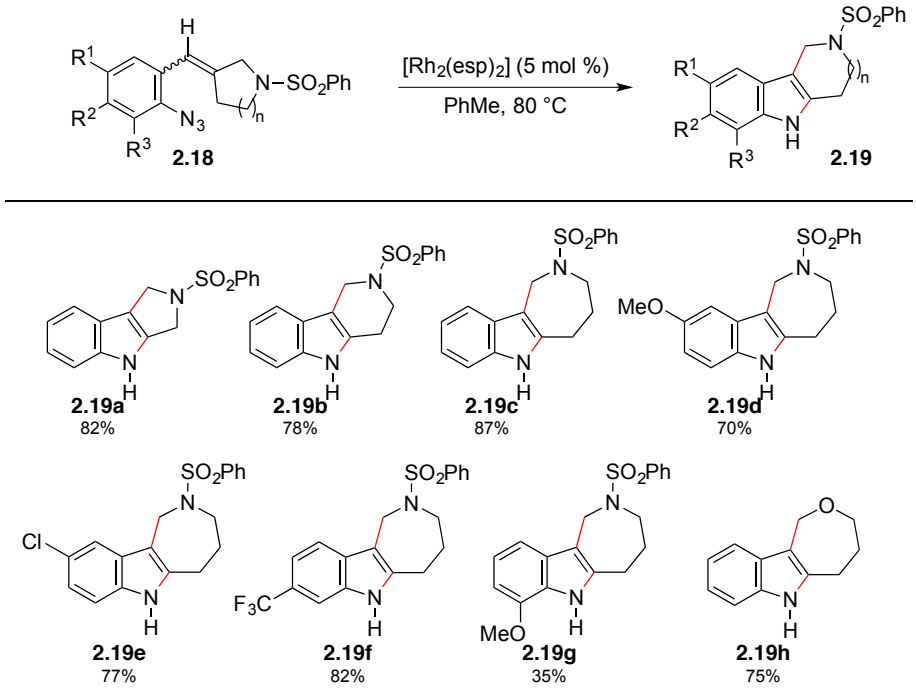
Entry	Catalyst	R	Yield [%][a]	**2.16** : **2.17**
1	...	SO_2Ph	n.r.	n.a.
2	$Rh_2(O_2CCH_3)_4$	SO_2Ph	n.r.	n.a.
3	$Rh_2(O_2CCF_3)_4$	SO_2Ph	36	88:20
4	$Rh_2(O_2CC_3F_7)_4$	SO_2Ph	32	86:14
5	$Rh_2(O_2CC_7H_{15})_4$	SO_2Ph	85	100:0
6	$Rh_2(esp)_2$	SO_2Ph	87	100:0
7	$Rh_2(esp)_2$	Boc	46	60:40
8	$Rh_2(esp)_2$	Bz	42	66:34
9	$Rh_2(esp)_2$	Bn	18	100:0

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

2.2. Survey of the substrate scope and limitations of the reaction.

Using the optimized reaction condition, Chen explored the scope and limitations of the reaction (Scheme 2.4). She found that four-, five- and six-membered cyclic β-substituent in the styryl azides underwent ring-expansion smoothly to give corresponding five-, six- or seven-membered heterocycles (**2.19a** – **2.19c**). The effect of changing the electronic nature of the aryl azides was investigated next. The reaction was insensitive to the electronics on the arene ring: electron-rich and -poor substrates were converted to product

with comparable yields (**2.19d – 2.19e**). Using our method we could prepare 5-substituted indole **2.19f** which cannot be prepared by Fischer-indole synthesis as a single regioisomer.[13-14] The *ortho*-methoxy substituent had an adverse effect on the reaction outcome: while the yield of the reaction dropped to 35%, *N*-heterocycle **2.19g** was formed as the only product. Finally, Chen showed that, selective ethereal methylene group migration could be triggered in **2.18h** to afford **2.19h** as the only product in 75% yield.

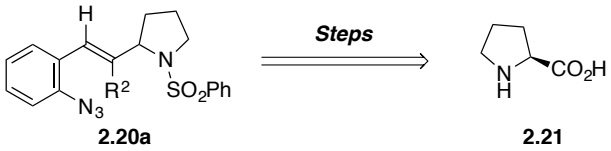


Scheme 2.4. Investigation of the substrate scope and limitations for the aminomethylene migration reaction

2.3. Design of the chiral L-proline derived styryl azide.

I joined the project in the beginning of my graduate study after Chen had optimized the reaction conditions. My task was to investigate the migration selectivity of styryl azide substrates in which the two β-substituents were not joined by a tether. Towards that end,

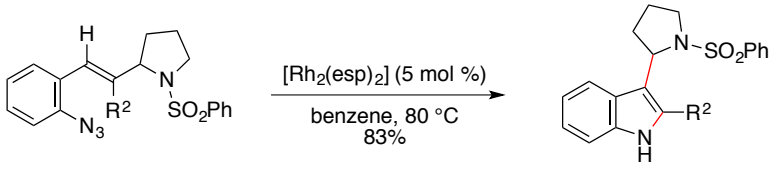
we designed azide precursor **2.20a** derived from naturally occurring L-proline **2.21**. We envisioned that the outcome of the subsequent cyclization, aminomethylene migration reaction would, not only provide a new batch of 2,3-disubstituted indoles, but also address few key mechanistic questions: The mechanistic investigation includes the nature of the reaction: (1) intramolecular or intermolecular migration and (2) if the migration occurs concerted or stepwise.



2.20a **2.21**

Scheme 2.5. Design of the new styryl azides derived form L-proline

In order to address these questions, I prepared chiral L-proline-derived styryl azide **2.20a**. We found that only the *E*-isomer of the substrate **2.20a** could be converted into 2,3-disubstituted indole **2.22a** smoothly, when exposed to the optimized reaction condition. In the reaction process, migration of only the pyrrolidine unit to the C-3 position was observed.

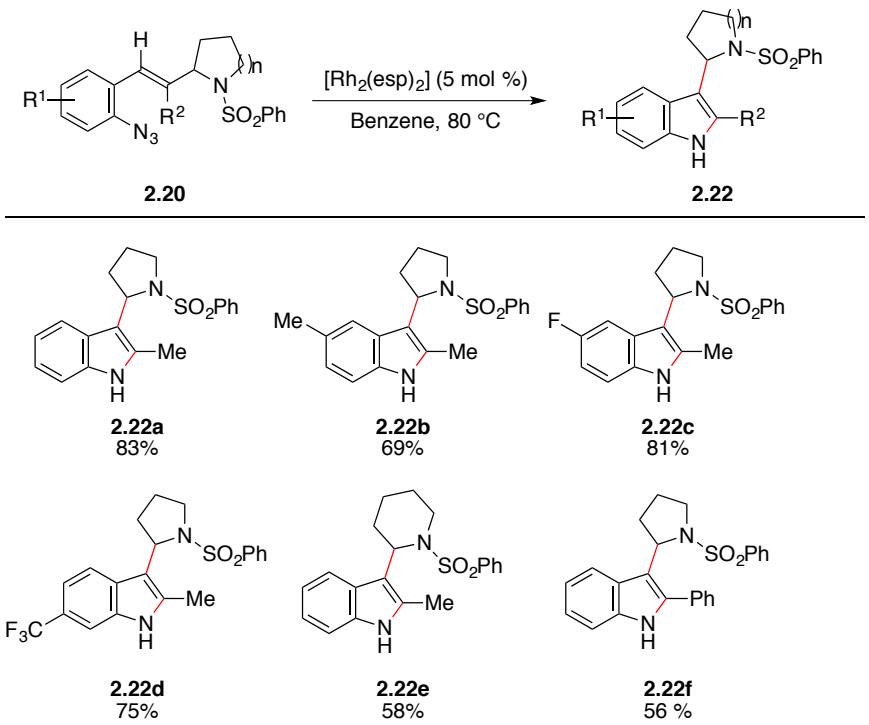


2.20a **2.22a**

Scheme 2.6. Investigation of the domino electrocyclization, 1,2-migration reaction from **2.20a**

2.4. Substrate scope and limitations for the proline-derived styryl azides

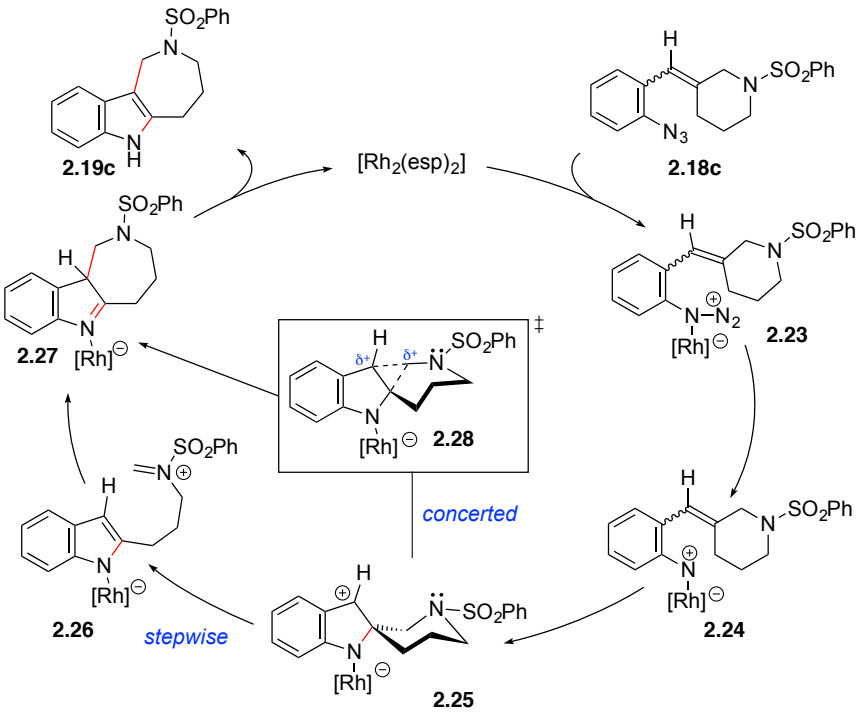
We found that only *E*-isomer of the proline-derived styryl azides were converted to indoles (Scheme 2.7). The lack of the reactivity in *Z*-isomer, we believe, originated from the destabilizing steric interaction between the Rh-nitrene intermediate and the pyrrolidine moiety. First, we have explored the electronic nature of the aryl azides by changing different *para*-substituent relative to azides: electron-neutral, -donating and -withdrawing group were tolerated without significant attenuation of yield (**2.22a** – **2.22c**). Gratifyingly, our method provided direct access to 5-substituted indole **2.22d**, which cannot be prepared by Fischer-indole synthesis as a single regioisomer.[13-14] The effect of ring-size was investigated next. The electrocyclization-migration reaction still occurred when the β-pyrrolidine was replaced with a pipiridinine, albeit with attenuated the yield (**2.22e**). Finally, we tested the migratory preference of the aminomethylene versus phenyl group. In contrast to our previous study, aminomethylene migrated preferentially over phenyl group (**2.22f**).



Scheme 2.7. Survey of the substrate scope for the proline derived styryl azides

2.5. Plausible mechanism for the formation of 2,3-disubstituted indole.

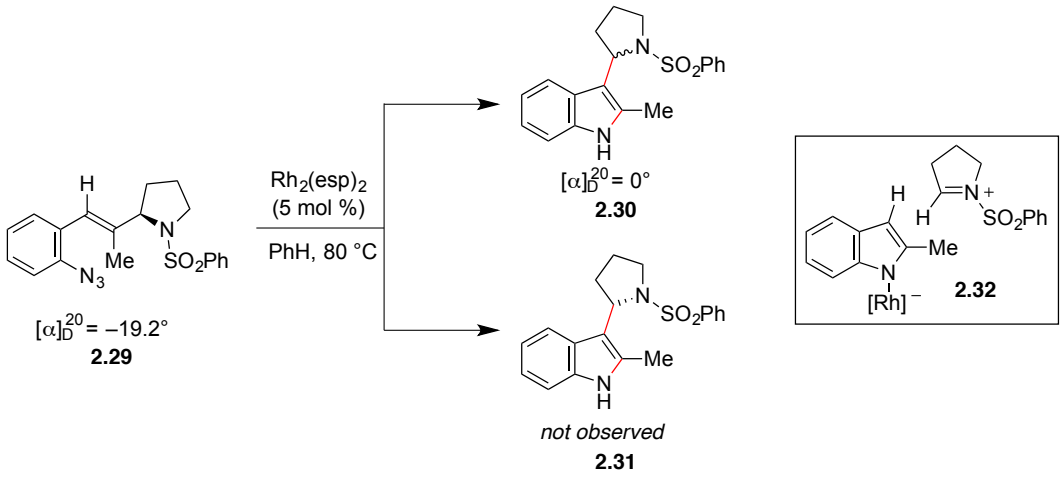
Based on reactivity trend, we have proposed a potential catalytic cycle for the cyclization-aminomethylene migration reaction (Scheme 2.8). Exposure of $Rh_2(esp)_2$ to the styryl azide **2.18c** produces a coordinated complex **2.23**,[15-16] which extrudes N_2 to generate Rh-nitrene **2.24**.[17-18] Consequently, a 4π-electron-5-atom electrocyclization produces benzyl cation **2.25**. The similar reactivity of both the *E* and *Z*-isomer in **2.18** suggests that N_2 extrusion precedes electrocyclization. Aminomethylene migration could occur stepwise via iminium ion **2.26**[19-23] or concerted through transition state **2.28**.[24-25] Dissociation of metal catalyst from **2.27** followed by tautomerization produces indole **2.19c** and regenerates the catalyst.



Scheme 2.8. Plausible mechanistic cycle for the formation of the 2,3-disubstituted indole

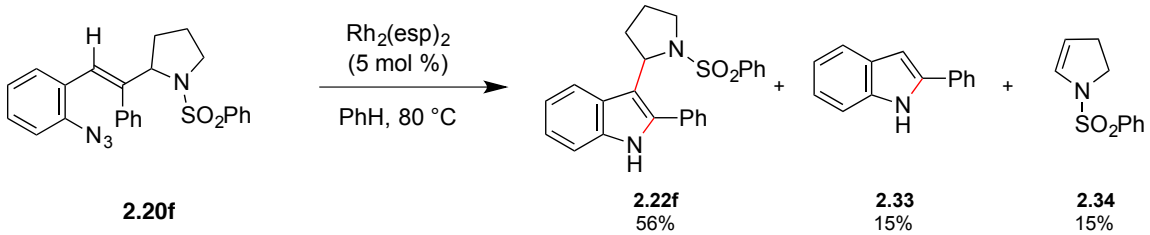
2.6. Probing the mechanism of aminomethylene migration

To differentiate between a stepwise and concerted migration process, we have examined the reactivity of chiral proline-derived styryl azide **2.29** toward the reaction conditions (Scheme 2.9). We envisioned that stepwise aminomethylene migration would lead to racemic indole product **2.30**, while the concerted migration would provide chiral indole **2.31**. When the chiral styryl azide **2.29** was exposed to the $Rh_2(esp)_2$ catalyst racemic indole **2.30** was produced. This outcome indicates that the aminomethylene migration event occurred through a stepwise fashion via the ion pair intermediate **2.32**. Hence, we ruled out the concerted pathway for the aminomethylene migration.



Scheme 2.9. Examination of nature of the aminomethylene migration

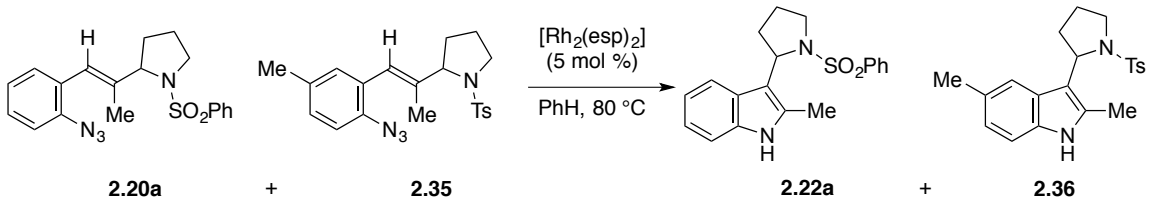
The formation of an ion pair intermediate was further supported by the reactivity of β-phenyl substituted styryl azide **2.20f** (Scheme 2.10). When it was treated using the optimal conditions, in addition to the major product **2.22f**, two minor products were observed: 2-phenyl indole **2.33** and 2,3-dihydropyrrole **2.34**. These elimination products, however, were limited to this β-phenyl substituted styryl azide **2.20f** substrate; β-methyl substituted styryl azide produced only 2,3-disubstituted indole.



Scheme 2.10. Evidence for the formation of an ion pair intermediate

In order to investigate if the ion pair intermediate **2.32** is able to escape from the solvent shell, I performed a crossover experiment (Scheme 2.11). Exposure of a 1:1

mixture of styryl azide **2.20a** and **2.35** to the optimal conditions provided only **2.22a** and **2.36**—no crossover product was observed under the reaction condition. This result indicates that the migration occurs before the ion pair can diffuse from the solvent shell.



Scheme 2.11. Crossover experiment

2.7 Conclusion.

In this project, we have shown selective aminomethylene migration can be triggered from β,β'-disubstituted styryl azides. The preference for aminomethylene migration is greater than methylene group and even aryl group. Combined with our previous studies, the migratory aptitude scale of β,β'-disubstituted styryl azides can be updated: ester << alkyl << aryl << aminomethylene < amide < H < sulfone < ketone << nitro. The mechanism study indicates the migration occurs by a stepwise pathway without the ion pair escaping from the solvent shell.

2.8 Experimental section.

(This part was taken from supporting information of my published paper: Kong, C.; Jana, N.; Driver, T. G. *Org. Lett.* **2013**, *15*, 824.)

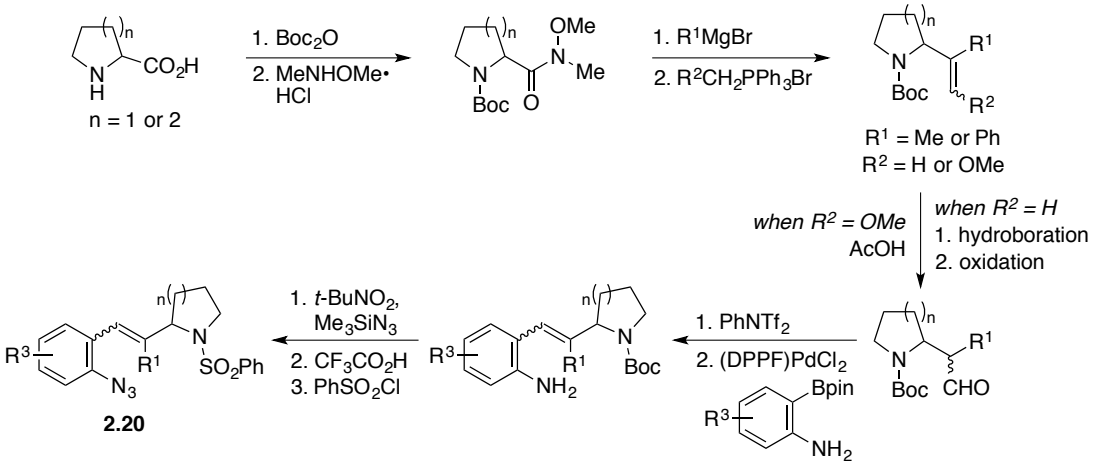
2.8.1 General. ^{1}H NMR and ^{13}C NMR spectra were recorded at ambient temperature using 500 MHz or 300 MHz spectrometers. The data are reported as follows: chemical

shift in ppm from internal tetramethylsilane on the δ scale, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz) and integration. High resolution mass spectra were obtained by peak matching. Melting points are reported uncorrected. Infrared spectroscopy was obtained using a diamond attenuated total reflectance (ATR) accessory. Analytical thin layer chromatography was performed on 0.25 mm extra hard silica gel plates with UV254 fluorescent indicator. Liquid chromatography was performed using forced flow (flash chromatography) of the indicated solvent system on 60Å (40 – 60 μm) mesh silica gel (SiO_2). Medium pressure liquid chromatography (MPLC) was performed to force flow the indicated solvent system down columns that had been packed with 60Å (40 – 60 μm) mesh silica gel (SiO_2). All reactions were carried out under an atmosphere of nitrogen in glassware, which had been oven-dried. Unless otherwise noted, all reagents were commercially obtained and, where appropriate, purified prior to use. Acetonitrile, Methanol, Toluene, THF, Et_2O, and CH_2Cl_2 were dried by filtration through alumina according to the procedure of Grubbs.[26] Metal salts were stored in a nitrogen atmosphere dry box.

2.8.2 Preparation of pyrrolidine substrates 14.

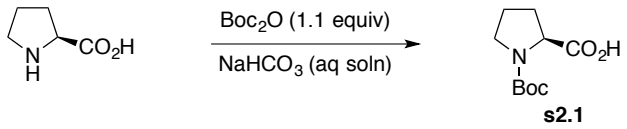
A. Synthetic route to substrates.

The pyrrolidine substrates **2.20** were synthesized following the route outlined in the scheme below.



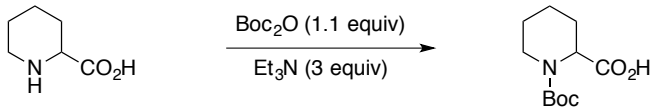
Scheme s4. Synthetic route to pyrrolidines **2.20**.

B. Boc-Protection of L-proline and pipecolinic Acid.



(*S*)-Pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester s2.1.[27] To a cooled solution (0 °C) of 15.07 g of L-proline (1 equiv, 130.9 mmol) in 200 mL of a saturated aqueous solution of $NaHCO_3$ (3 equiv, 393.0 mmol) was added dropwise a 30.8 mL of $(Boc)_2O$ (1.1 equiv, 144 mmol) in 150 mL of THF. The reaction was allowed to warm to room temperature. After 15h, the reaction mixture was concentrated *in vacuo*. The resulting residue was cooled to 0 °C and acidified with a 3N aqueous solution of HCl until a pH 2 was measured. The resulting solution was extracted with 3 × 500 mL of ethyl acetate. The combined organic phases were dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo* to afford the product, a white solid, as a 60:40 mixture of rotamers (27.9 g, 99%). mp 129 – 132 °C. $[\alpha]_D^{20}$: – 35.2 (*c* 0.5, MeOH). The spectral data for **s2.1** matched that reported by Huy and co-workers:[27] ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.35 (m, 0.60H), 4.25 (br s, 0.40H), 3.55 – 3.33 (m, 2H), 2.36 (br s, 0.58H), 2.04 (br s, 0.40H),

2.04 – 1.89 (m, 3H), 1.52 (s, 2H), 1.49 (s, 5H), 1.42 (s, 2H), -CO_2H proton not visible; Data for major rotamer: ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.8 (C), 154.1 (C), 80.4 (C), 59.0 (CH), 46.3 (CH_2), 30.7 (CH_2), 28.2 (CH_3), 23.6 (CH_2); diagnostic data for minor rotamer: ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.5 (C), 155.3 (C), 46.7 (CH_2), 29.4 (CH_2), 24.2 (CH_2); Data for mixture: ATR-FTIR (thin film): 2968, 2897, 1736, 1631, 1421, 1363, 1204, 1159, 1126 cm^{-1}.

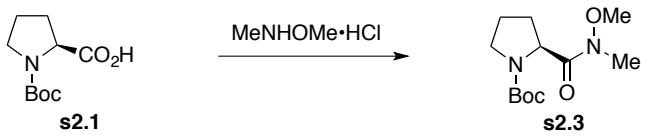


s2.2

Piperidine-1,2-dicarboxylic acid 1-*tert*-butyl ester s2.2.[28] To a cooled solution (0 °C) of 10.0 g of pipecolinic acid (77.4 mmol) in 11.8 mL of a triethylamine (3 equiv, 85.2 mmol) was added 20.27 g of $(Boc)_2O$ (92.9 mmol). The reaction was allowed to warm to room temperature. After 15h, the reaction mixture was concentrated *in vacuo*. The resulting residue was cooled to 0 °C and acidified with a 3N aqueous solution of HCl until a pH 2 was measured. The resulting solution was extracted with 3 × 250 mL of ethyl acetate. The combined organic phases were dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo* to afford the product, a white solid, as a 53:47 mixture of rotamer (17.4 g, 98%). mp 122 – 124 °C. The spectral data for **s2.2** matched that reported by Barbara and co-workers:[28] ^1H NMR (500 MHz, $CDCl_3$) δ 10.64 (s, 1H), 4.90 – 4.86 (br s, 0.53H), 4.75 – 4.67 (br s, 0.47H), 3.99 – 3.87 (m, 1H), 2.95 – 2.86 (m, 1H), 2.22 – 2.16 (m, 1H), 1.64 (br s, 4H), 1.42 (s, 3H), 1.40 (s, 6H), 1.30 – 1.25 (m, 1H); data for major rotamer: ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.6 (C), 156.2 (C), 80.3 (C), 53.6 (CH), 42.1 (CH_2), 28.3 (CH_3), 26.6 (CH_2), 24.8 (CH_2), 20.8 (CH_2); diagnostic data for minor rotamer:

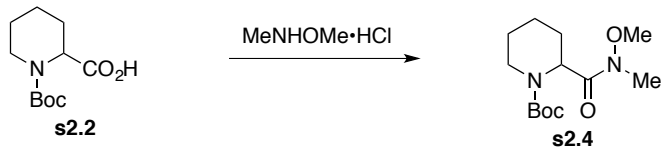
^{13}C NMR (125 MHz, $CDCl_3$) δ 155.6 (C), 54.7 (CH), 41.1 (CH_2); Data for mixture: ATR-FTIR (thin film): 2968, 2948, 1743, 1624, 1431, 1663, 1316, 1251, 1193, 1157 cm^{-1}.

C. Preparation of Weinreb amides.



(*S*)-2-(Methoxy-methyl-carbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester s2.3.[29] To a solution of *N*-Boc proline (10.0 g, 46.5 mmol, 1.0 equiv) in 200 mL of CH_2Cl_2 was added slowly 11.30 g of carbonyldiimidazole (69.7 mmol, 1.5 equiv). The resulting mixture was stirred at room temperature until CO_2 evolution ceased (ca. 15 min). Then 6.80 g of *N*,*O*-dimethylhydroxylamine hydrochloride (69.7 mmol, 1.5 equiv) was added, and the mixture was stirred at room temperature. After 15 h, the mixture was diluted with water, and the resulting mixture was extracted with 3 × 60 mL of CH_2Cl_2. The combined organic phases were dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. The resulting residue was purified by MPLC (10:90 – 50:50 EtOAc:hexane) to afford the product, a colorless liquid, as a 52:47 mixture of rotamers (10.8 g, 90%). $[\alpha]_D^{20}$: – 13.6 (c 0.5, CH_2Cl_2). The spectral data for **s2.3** matched that reported by Barluenga and co-workers:[29] ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.67 – 4.65 (m, 0.47H), 4.57 – 4.55 (m, 0.53H), 3.74 (s, 1.4H), 3.68 (s, 1.6H), 3.55 – 3.35 (m, 2H), 3.16 (s, 3H), 2.17 – 2.04 (m, 1H), 1.94 – 1.77 (m, 3H), 1.42 (s, 4H), 1.38 (s, 5H); Data for mixture: ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.9 (C), 173.3 (C), 154.5 (C), 153.9 (C), 79.5 (C), 79.4 (C), 61.3 (CH), 61.2 (CH), 56.8 (CH_3), 56.5 (CH_3), 45.9 (CH_2), 46.6 (CH_2), 32.4 (CH_3), 32.3 (CH_3), 30.5 (CH_2), 29.6 (CH_2), 28.5 (CH_3), 28.4 (CH_3), 24.1 (CH_2), 23.4

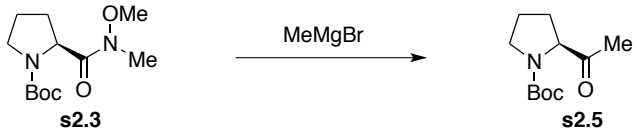
(CH_2). Data for mixture: ATR-FTIR (thin film): 2971, 2934, 2877, 1689, 1387, 1159, 1152 cm^{-1}.



s2.2 **s2.4**

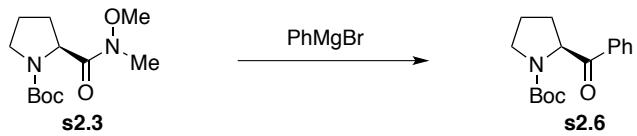
2-(Methoxy-methyl-carbamoyl)-piperidine-1-carboxylic acid *tert*-butyl ester s2.4. To a solution of **s2.2** (5.78 g, 25.2 mmol, 1.0 equiv) in 150 mL of CH_2Cl_2 was added slowly 5.31 g of carbonyldiimidazole (32.7 mmol, 1.5 equiv). The resulting mixture was stirred at room temperature until effervescence ceased (ca. 15 min). Then 2.95 g of *N*,*O*-dimethylhydroxylamine hydrochloride (30.2 mmol, 1.5 equiv) was added, and the mixture was stirred at room temperature. After 15 h, the mixture was diluted with water, and the resulting mixture was extracted with 3 × 60 mL of CH_2Cl_2. The combined organic phases were dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. The resulting residue was purified by MPLC (10:90 – 50:50 EtOAc:hexane) to afford the product, a white solid, as a 57:47 mixture of rotamers (5.90 g, 86%). mp 50 – 52 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.75 (br s, 0.57H), 4.61 (br s, 0.43H), 3.73 – 3.58 (m, 1H), 3.47 (s, 3H), 3.25 – 3.03 (m, 1H), 2.87 (s, 3H), 1.71 – 1.68 (m, 1H), 1.38 – 1.29 (m, 3H), 1.14 (br s, 11H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.1 (C), 155.8 (C), 79.1 (C), 60.9 (CH_3), 50.4 (CH), 42.1 (CH_2) , 31.7 (CH_3), 28.2 (CH_3), 26.2 (CH_2), 24.7 (CH_2), 19.4 (CH_2); diagnostic data for minor rotamer: ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.1 (C), 51.9 (CH), 41.1 (CH_2). Data for mixture: ATR-FTIR (thin film): 2975, 2938, 2863, 1665, 1367, 1251, 1160, 1047 cm^{-1}.

D. Preparation of ketones.



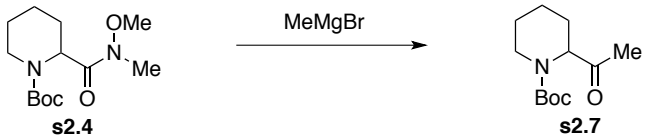
s2.3 **s2.5**

(*S*)-2-Acetyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester s2.5.[29] To a cooled solution of Weinreb amide **s2.3** (10.0 g, 38.7 mmol, 1 equiv) in 380 mL of diethyl ether at 0 °C, was added dropwise 18 mL of a 3 M solution of methylmagnesium bromide in ether (1.4 equiv). A white precipitate quickly appeared. The mixture was stirred at 0 °C. After 1 h, the reactives were quenched through the dropwise addition of a saturated aqueous solution of NH_4Cl. The resulting mixture was extracted with 3 × 60 mL of ether. The combined organic phases were dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. Purification by MPLC (5:100 – 20:100 EtOAc:hexane) afforded the product, a colorless liquid, as a 59:41 mixture of rotamers (7.43 g, 90%). $[\alpha]_D^{20}$: –46.0 (*c* 0.25, MeOH). The spectral data for **s2.5** matched that reported by Barluenga and co-workers:[29] ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.31 – 4.29 (m, 0.41H), 4.18 – 4.16 (m, 0.59H), 3.55 – 3.45 (m, 2H), 2.17 (m, 1H), 2.15 (s, 1H), 2.11 (s, 2H), 1.85 – 1.80 (m, 3H), 1.44 (s, 4H), 1.39 (s, 5H); data for major rotamar: ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.4 (C), 153.9 (C), 80.2 (C), 65.8 (CH), 46.7 (CH_2), 29.8 (CH_2), 28.3 (CH_3), 25.5 (CH_3), 23.8 (CH_2); diagnostic data for minor rotamer: 154.7 (C), 79.8 (C), 65.2 (CH), 26.5 (CH_3), 24.4 (CH_2). ATR-FTIR (thin film): 2975, 2873, 1686, 1387, 1363 cm^{-1}. HRMS (EI) *m/z* calculated for $C_{11}H_{19}O_3N$ $(M)^+$: 213.13650, found: 213.13620.



s2.3 **s2.6**

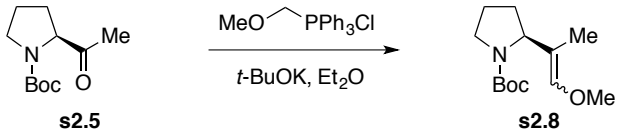
(*S*)-2-Benzoyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester s2.6.[30] To a cooled solution of Weinreb amide **s2.3** (1.0 g, 3.87 mmol, 1 equiv) in 38 mL of diethyl ether at 0 °C, was added dropwise 1.8 mL of a 3 M solution of methylmagnesium bromide in ether (1.4 equiv). A white precipitate quickly appeared. The mixture was stirred at 0 °C. After 1 h, the reactives were quenched through the dropwise addition of a saturated aqueous solution of NH_4Cl. The resulting mixture was extracted with 3 × 20 mL of ether. The combined organic phases were dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. Purification by MPLC (5:100 – 20:100 EtOAc:hexane) afforded the product, a white solid, as a 58:42 mixture of rotamers (0.98 g, 92%). mp 101 – 103 °C. $[\alpha]_D^{20}$: – 36.8 (*c* 0.25, CH_2Cl_2). The spectral data for **s2.6** matched that reported by Dieter and co-workers:[30] Data for mixture: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 – 7.94 (m, 2H), 7.59 – 7.53 (m, 1H), 7.53 – 7.43 (m, 2H), 5.44 – 5.32 (m, 0.42 H), 5.20 – 5.17 (m, 0.58 H), 3.69 – 3.42 (m, 2H), 2.32 – 2.27 (m, 1H), 1.94 – 1.83 (m, 3H), 1.46 (s, 3.5 H), 1.25 (s, 5.5 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.9 (C), 198.4 (C), 154.5 (C), 153.8 (C), 135.3 (C), 133.2 (CH), 128.7 (CH), 128.6 (CH), 128.5 (CH), 128.2 (CH), 79.8 (C), 61.4 (CH), 61.1 (CH), 46.8 (CH_2), 46.6 (CH_2), 30.9 (CH_2), 29.8 (CH_2), 28.5 (CH_3), 28.2 (CH_3), 24.2 (CH_2), 23.6 (CH_2), only visible peaks. ATR-FTIR (thin film): 2968, 2866, 1686, 1597, 1390, 1360 cm^{-1}. HRMS (EI) *m/z* calculated for $C_{16}H_{21}O_3N$ $(M)^+$: 275.15215, found: 275.15289.



s2.4 **s2.7**

2-Acyl-piperidine-1-carboxylic acid *tert*-butyl ester s2.7.[31] To a cooled solution of Weinreb amide **s2.4** (3.44 g, 12.6 mmol, 1 equiv) in 100 mL of diethyl ether at 0 °C, was added dropwise 12.6 mL of a 3M solution of methylmagnesium bromide in ether (1.4 equiv). A white precipitate quickly appeared. The mixture was stirred at 0 °C. After 1 h, the reactives were quenched through the dropwise addition of a saturated aqueous solution of NH_4Cl. The resulting mixture was extracted with 3 × 20 mL of ether. The combined organic phases were dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. Purification by MPLC (5:100 – 20:100 EtOAc:hexane) afforded the product, a colorless liquid, as a 43:57 mixture of rotamers (1.92 g, 67%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.69 (br s, 0.6H), 4.53 (br s, 0.4H), 4.03 (br s, 0.4H), 3.89 (br s, 0.5H), 2.84 (br s, 0.5H), 2.75 (br s, 0.5H), 2.17 (br s, 0.4H), 2.15 (br s, 0.5H),), 2.11 (s, 3H), 1.62-1.55 (m, 2H), 1.44 (s, 8H), 1.41 (s, 2H), 1.24-1.21 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.0 (C), 156.6 (C), 155.8 (C), 155.1 (C), 80.1 (C), 78.9 (C), 61.7 (CH) 60.6 (CH), 53.5 (CH_2), 42.7 (CH_2), 41.6 (CH_2), 40.9 (CH_2), 28.4 (CH_3), 26.7 (CH_3), 25.0 (CH_2), 23.7 (CH_2), 22.7 (CH_2), 21.7 (CH_2), 20.6 (CH_2), 18.7 (CH_2). ATR-FTIR (thin film): 2938, 2863, 1720, 1682, 1363, 1153 cm^{-1}. HRMS (ESI) *m/z* calculated for $C_{12}H_{21}NO_3Na$ $(M+Na)^+$: 250.1419, found: 250.1420.

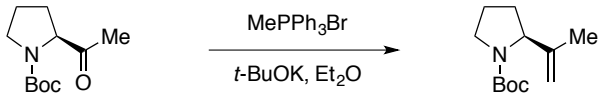
E. Wittig olefination



s2.5 **s2.8**

(*S*)-2-(2-Methoxy-1-methyl-vinyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester s2.8. To a cooled solution (0 °C) of methoxymethyl triphenylphosphonium chloride (24.35 g,

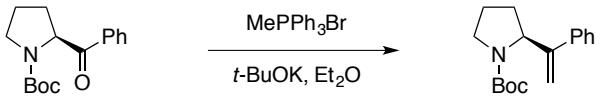
71.00 mmol, 2.5 equiv) in 115 mL of ether was added 8.92 g of potassium *tert*-butoxide (79.5 mmol, 2.8 equiv). After 30 min, a solution of 6.06 g of ketone **s67** (28.4 mmol, 1 equiv) in 115 mL of ether was added dropwise. After 2 h, the reactives in the mixture were quenched through the addition of ice-cold water. The resulting solution was extracted with 3 × 30 mL of ether and the combined organic phases were dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. Purification by MPLC (2:100 – 10:100 EtOAc:hexane) afforded the product, a colorless liquid, as a 67:33 mixture of rotamers (4.93 g, 72%). Spectral data for the mixture: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.78 (br s, 0.67H), 5.68 (br s, 0.33H), 4.65 (br s, 0.38H), 4.04 (m, 0.62H), 3.53 (s, 2H), 3.50 (s, 1H), 3.32 – 3.24 (m, 2H), 2.09 – 1.71 (m, 4H), 1.49 (s, 3H), 1.41 (s, 9H). Spectral data for the major rotamer: ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.7 (C), 142.9 (CH), 141.6 (C), 78.9 (C), 59.5 (CH_3), 55.0 (CH), 46.9 (CH_2), 31.9 (CH_2), 28.5 (CH_3), 24.3 (CH_2), 12.9 (CH_3); diagnostic data for the minor rotamer: ^{13}C NMR (125 MHz, $CDCl_3$) δ 60.0 (CH_3), 31.4 (CH_2), 9.5 (CH_3). Data for mixture: ATR-FTIR (thin film): 2971, 2931, 1686, 1383, 1363, 1159, 1129 cm^{-1}. HRMS (EI) *m/z* calculated for $C_{13}H_{23}NO_3$ $(M)^+$: 241.16780, found: 241.16861.



s2.5 **s2.9**

(S)-2-Isopropenyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester s2.9. To a cooled solution (0 °C) of methyltriphenylphosphonium bromide (6.28 g, 17.5 mmol, 2.5 equiv) in 28 mL of ether was added 2.21 g of potassium *tert*-butoxide (19.7 mmol, 2.8 equiv). After 30 min, a solution of 1.50 g of ketone **s2.5** (7.0 mmol, 1 equiv) in 28 mL of ether

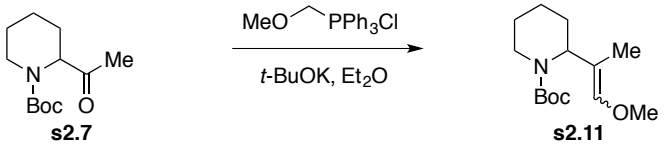
was added dropwise. After 2 h, the reactives in the mixture were quenched through the addition of ice-cold water. The resulting solution was extracted with 3 × 30 mL of ether and the combined organic phases were dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. Purification by MPLC (2:100 – 10:100 EtOAc:hexane) afforded the product, a colorless liquid, as a 54:46 mixture of rotamers (1.12 g, 76%). $[\alpha]_D^{20}$: – 14.0 (c 1.0, CH_2Cl_2). Spectral data for the mixture: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.75 – 4.66 (m, 2H), 4.20 (m, 0.46H), 4.10 (m, 0.54H), 3.42 – 3.36 (m, 2H), 1.95 (br s, 1H), 1.80 – 1.66 (m, 3H), 1.64 (s, 3H), 1.41 (s, 4H), 1.36 (s, 5H); spectral data for the major rotamer: ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.6 (C), 145.1 (C), 108.9 (CH_2), 79.0 (C), 62.2 (CH), 46.5 (CH_2), 31.3 (CH_2), 28.4 (CH_3), 22.9 (CH_2), 19.1 (CH_3); diagnostic data for the minor rotamer: ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.2 (C), 30.4 (CH_2), 23.5 (CH_2); data for mixture: ATR-FTIR (thin film): 2971, 2927, 2873, 1689, 1387, 1363, 1163, 1115, 1088 cm^{-1}.



s2.6 **s2.10**

(*S*)-2-(1-Phenyl-vinyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester s2.10.[32] To a cooled solution (0 °C) of methyltriphenylphosphonium bromide (2.95 g, 8.30 mmol, 2.5 equiv) in 28 mL of ether was added 1.04 g of potassium *tert*-butoxide (9.2 mmol, 2.8 equiv). After 30 min, a solution of 0.85 g of ketone **s2.6** (3.3 mmol, 1 equiv) in 28 mL of ether was added dropwise. After 2 h, the reactives in the mixture were quenched through the addition of ice-cold water. The resulting solution was extracted with 3 × 30 mL of ether and the combined organic phases were dried over Na_2SO_4, filtered and the filtrate

was concentrated *in vacuo*. Purification by MPLC (2:100 – 10:100 EtOAc:hexane) afforded the product, a colorless liquid, as a 66:34 mixture of rotamers (1.12 g, 76%). $[\alpha]_D^{20}$: 26.0 (*c* 1.0, CH_2Cl_2). The spectral data for **s2.10** matched that reported by Dieter and co-workers:[32] Spectral data for the mixture: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.29 (m, 5H), 5.24 (br s, 0.34 H), 5.20 (br s, 0.66 H), 4.98 (s, 1H), 4.91 (d, *J* = 6.5 Hz, 0.34 H), 4.75 (d, *J* = 8.0 Hz, 0.66 H), 3.56 – 3.45 (m, 2H), 1.77 – 2.00 (m, 3H), 1.62 (br s, 1H), 1.49 (s, 3H), 1.43 (s, 6H); spectral data for the major rotamer: ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.5 (C), 150.2 (C), 140.6 (C), 128.4 (CH), 127.5 (CH), 126.8 (CH), 110.8 (CH_2), 79.3 (C), 60.7 (CH), 46.5 (CH_2), 31.6 (CH_2), 28.5 (CH_3), 22.2 (CH_2); diagnostic data for the minor rotamer: ^{13}C NMR (125 MHz, $CDCl_3$) δ 30.7 (CH_2), 23.0 (CH_2); data for the mixture: ATR-FTIR (thin film): 2975, 2877, 1689, 1387, 1360, 1163, 1119, 1085 cm^{-1}.

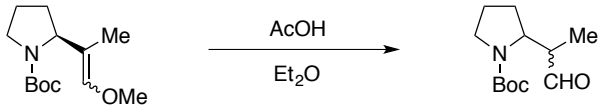


s2.7 **s2.11**

2-Isopropenyl-piperidine-1-carboxylic acid *tert*-butyl ester s2.11. To a cooled solution (0 °C) of methoxymethyl triphenylphosphonium chloride (6.30 g, 18.3 mmol, 2.5 equiv) in 60 mL of ether was added 2.30 g of potassium *tert*-butoxide (20.5 mmol, 2.8 equiv). After 30 min, a solution of 1.67 g of ketone **s2.7** (7.33 mmol, 1 equiv) in 40 mL of ether was added dropwise. After 2 h, the reactives in the mixture were quenched through the addition of ice-cold water. The resulting solution was extracted with 3 × 30 mL of ether and the combined organic phases were dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. Purification by MPLC (2:100 – 10:100 EtOAc:hexane)

afforded the product, a colorless liquid, as a 52:48 mixture of isomers (1.39 g, 74%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.70 (s, 0.5H), 5.66 (s, 0.5H), 4.71 (s, 0.5H), 4.57 (s, 0.5H), 3.86 (t, *J* = 12.3 Hz, 1H), 3.49 (s, 1.5H), 3.42 (s, 1.4H), 2.73 (td, *J* = 12.7, 3.7 Hz, 0.5H), 2.63 (td, *J* = 13.0, 2.7 Hz, 0.5H), 1.86 (dt, *J* = 12.0, 3.9 Hz, 0.5H), 1.80 (d, *J* = 12.7 Hz, 0.5H), 1.54 – 1.34 (m, 4H), 1.42 (s, 1.5H), 1.40 (s, 1.5H), 1.37 (s, 5H), 1.35 (s, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.5 (C), 155.2 (C), 143.9 (CH), 142.3 (CH), 113.5 (C), 111.4 (C), 79.0 (C), 78.7 (C), 59.5 (CH), 59.4 (CH), 52.6 (CH_3), 51.6 (CH_3), 40.7 (CH_2), 39.6(CH_2), 28.3 (CH_3), 26.2 (CH_2), 25.5 (CH_2), 24.7 (CH_2), 20.2 (CH_2), 19.5 (CH_2), 16.2 (CH_3), 11.2 (CH_3) only visible signals. ATR-FTIR (thin film): 2931, 2859, 1686, 1407, 1126 cm^{-1}. HRMS (EI) *m/z* calculated for $C_{14}H_{25}NO_3$ $(M)^+$: 255.18345, found: 255.18315.

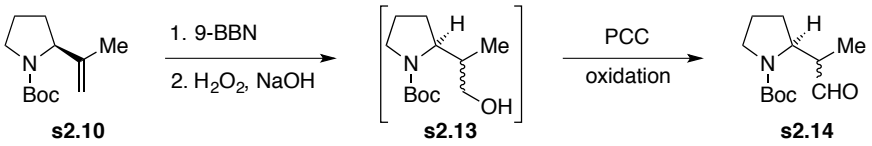
F. Preparation of the aldehydes.



s2.8 **s2.12**

2-(1-Methyl-2-oxo-ethyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester s2.12. To a solution of vinyl ether **s2.8** (5.00 g, 20.7 mmol) in 100 mL of diethyl ether was added 100 mL of a 6 M solution of acetic acid. After 24 h, the mixture extracted with 3 × 50 mL of ether. The combined organic phases were washed with 50 mL of a saturated aqueous solution of $NaHCO_3$ and 50 mL of brine. The resulting organic phase was dried over Na_2SO_4, filtered, and the filtrate was concentrated *in vacuo*. Purification of the resulting residue using MPLC (2:100 – 10:90 EtOAc:hexane) afforded the product, racemic, as a colorless oil (4.30 g, 92%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.38 (s, 1H), 6.46 (t, *J* = 7.0 Hz, 1H), 4.63 (br s, 1H), 3.15 (br s, 2H), 2.37 (q, *J* = 7.0 Hz, 2H), 1.72 (s, 3H), 1.68 (t, *J*

= 7.0 Hz, 2H), 1.42 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.2 (CH), 156.0 (C), 153.5 (CH), 139.8 (C), 79.3 (C), 40.1 (CH_2), 28.9 (CH_2), 28.4 (CH_3), 26.3 (CH_2), 20.8 (CH), 9.2 (CH_3) the extra C-signal is attributed to the enol tautomer of **s7**. ATR-FTIR (thin film): 3480 – 3250, 2795, 2934, 1682, 1519, 1394, 1367, 1248, 1159 cm^{-1}.

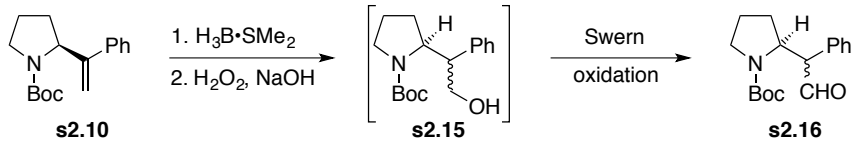


s2.10 **s2.13** **s2.14**

(*S*)-2-(1-Methyl-2-oxo-ethyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester s2.14. To a cooled solution (0 °C) of **s2.10** (1.40 g, 6.6 mmol) in 32 mL of THF was added 39.7 mL of a 0.5 M solution of 9-BBN in THF. After 3 h, 20 mL of H_2O_2 and 20 mL of an 3.0 M solution of NaOH in water were sequentially added. After 20 min, the resulting mixture was extracted with 3 × 20 mL of ethyl acetate. The combined organic phases were dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. Purified of the residue by MPLC (2:100 – 20:80 EtOAc:hexane) afforded the product, a colorless liquid, as a 66:34 diastereomeric mixture of alcohols (1.4 g, 93%). Alcohol **s2.13** was submitted to the subsequent oxidation step without further characterization.

To a cooled solution of alcohol **s2.13** (1.35 g, 5.9 mmol) in 30 mL of dichloromethane was added 1.0 g of silica gel. After 15 min, 2.54 g of pyridinium chlorochromate (11.8 mmol) was added portion wise and stirred the solution for 3h. The solution was then filtered through Celite™ , and the filtrate was concentrated *in vacuo* to afford a 66:34 mixture of diastereomers. The diastereomers could be separated by MPLC (2:100 – 10:100 EtOAc:hexane) to afford the product, a colorless liquid, as a 75:25 mixture of rotamers (1.09 g, 82%): $[\alpha]_D^{20}$: – 41.6 (*c* 0.25, CH_2Cl_2). Spectral data for the major

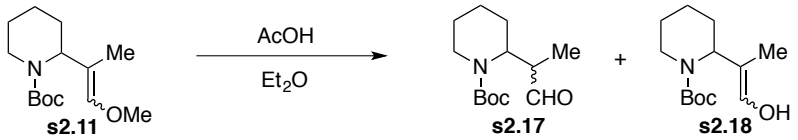
diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.71 (s, 0.74H), 9.61 (s, 0.26H), 4.14 – 4.10 (m, 1H), 3.58 – 3.28 (m, 1H), 3.23 – 3.18 (m, 1H), 2.76 – 2.61 (m, 1H), 2.13 – 1.64 (m, 4H), 1.42 (s, 9H), 1.01 (d, J = 7.5 Hz, 3H). Data for the major rotamer: ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.8 (C), 163.9 (C), 79.6 (C), 58.3 (CH), 49.4 (CH), 47.4 (CH_2), 29.1 (CH_2), 28.4 (CH_3), 24.2 (CH_2), 9.1 (CH_3); diagnostic data for the minor rotamer: 203.3 (C), 80.4 (C), 57.6 (CH), 46.8 (CH_2), 30.5 (CH_2), 23.5 (CH_2). ATR-FTIR (thin film): 2975, 2934, 2877, 1689, 1387, 1367, 1163, 1105 cm^{-1}. HRMS (EI) *m/z* calculated for $C_{12}H_{21}NO_3$ $(M)^+$: 227.15215, found: 227.15198.



s2.10 **s2.15** **s2.16**

(*S*)-2-(2-Oxo-1-phenyl-ethyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester s2.16. To a cooled solution (0 °C) of **s2.10** (0.80 g, 2.9 mmol in 32 mL of THF under Argon was added 5.8 mL of a 2 M solution of BH_3•DMS in THF. The progress of the reaction was monitored by TLC. When analysis revealed complete consumption of the starting material, 10 mL of H_2O_2 and 10 mL of 3.0 M solution of NaOH in water were consecutively added. After 20 min, the resulting mixture was extracted with 3 × 15 mL of ethyl acetate. The combined organic phases were dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. Purification by MPLC (2:100 – 20:80 EtOAc:hexane) afforded the product, a colorless liquid, as a diastereomeric mixture (0.65 g, 76%). Alcohol **s2.15** was submitted to the subsequent oxidation step without further characterization.

To a cold solution (–78 °C) of 0.24 mL of oxalyl chloride (2.83 mmol) in 15 mL of anhydrous CH_2Cl_2 was added 0.40 mL of DMSO (5.66 mmol). After 15 min, 0.55 g of alcohol **s2.15** (1.9 mmol) was added. After 50 min, 1.57 mL of Et_3N (11.3 mmol) was added drop wise to the reaction mixture. After addition, the reaction mixture was allowed to warm to room temperature. The reactives were quenched with water, and the resulting mixture was extracted with 3 × 20 mL of DCM. The combined organic phases were dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. Purification by MPLC (2:100 – 10:100 EtOAc:hexane) afforded the product, a colorless liquid, as a diastereomeric mixture (0.46 g, 86%). The major diastereomer was separated. $[\alpha]_D^{20}$: –50.4 (*c* 0.25, CH_2Cl_2). Spectral data for the major diastereomer (66:34 mixture of rotamers): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.81 (s, 1H), 7.39 – 7.32 (m, 3H), 7.25 – 7.18 (m, 2H), 4.54 – 4.47 (m, 1H), 3.74 – 3.69 (m, 1H), 3.40 – 3.19 (m, 2H), 1.86 (br s, 1H), 1.72 (br s, 1H), 1.61 – 1.58 (m, 2H), 1.52 (s, 3H), 1.47 (s, 6H); data for major rotamer: ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.7 (CH), 154.9 (C), 134.5 (C), 129.4 (CH), 129.1 (CH), 127.4 (CH), 79.7 (C), 63.5 (CH), 58.4 (CH), 46.6 (CH_2), 29.0 (CH_2), 28.5 (CH_3), 23.3 (CH_2); diagnostic data for minor rotamer: ^{13}C NMR (125 MHz, $CDCl_3$) δ 80.5 (C), 63.0 (CH), 22.4 (CH_2). ATR-FTIR (thin film): 2975, 2927, 1682, 1390, 1360, 1163, 1108 cm^{-1}.

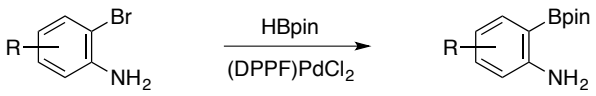


2-(1-Methyl-2-oxo-ethyl)-piperidine-1-carboxylic acid *tert*-butyl ester s2.17 and enol s2.18. To a solution of vinyl ether **s2.11** (1.37 g, 5.37 mmol) in 27 mL of diethyl ether

was added 27 mL of a 6 M solution of acetic acid. After 24 h, the mixture extracted with 3 × 50 mL of ether. The combined organic phases were washed with 50 mL of a saturated aqueous solution of $NaHCO_3$ and 50 mL of brine. The resulting organic phase was dried over Na_2SO_4, filtered, and the filtrate was concentrated *in vacuo*. Purification by MPLC (2:100 – 10:100 EtOAc:hexane) afforded the product, a colorless oil, as a mixture of the aldehyde and enol tautomer (0.967 g, 75%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.41 (s, 1H), 6.52 (td, J = 7.4, 1.1 Hz, 1H), 4.96 (s, 1H), 3.18 (d, J = 4.4 Hz, 2H), 2.41 (d, J = 7.0 Hz, 2H), 1.76 (s, 3H), 1.57 (s, 4H), 1.46 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.2 (CH), 156.0 (C), 154.2 (CH), 139.5 (C), 78.9 (C), 40.1 (CH_2), 29.7 (CH_2), 28.5 (CH_2), 28.3 (CH_3), 25.5 (CH_2), 20.7 (CH), 14.2 (CH), 9.1 (CH_3). ATR-FTIR (thin film): 3355, 2934, 1678, 1512, 1251, 1167 cm^{-1}. HRMS (ESI) *m/z* calculated for $C_{13}H_{23}NO_3Na$ $(M+Na)^+$: 264.1576, found: 264.1583.

G. Preparation of N-Boc protected styryl azide.

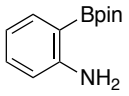
1. General procedure for the synthesis of the arylboronic acid pinacol esters.



To a mixture of 1.0 g of 2-bromo-aniline (5.8 mmol), 3.22 mL of Et_3N (23.2 mmol), 0.208 g of (dppf)$PdCl_2$ (0.25 mmol) in 20 mL of 1,4-dioxane, was added dropwise 2.53 mL of 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (17.4 mmol). The resultant mixture was refluxed at 120 °C. After 12h, the mixture was cooled to room temperature and diluted with 20 mL of NH_4Cl. The resulting aqueous phase was extracted with an additional 2 ×

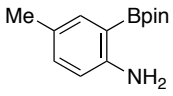
20 mL of CH_2Cl_2. The combined organic phases were washed with 1 × 30 mL of brine. The resulting organic phase was dried over Na_2SO_4, and was concentrated *in vacuo*. Purification via MPLC afforded the product.

2. Syntheses of arylboronic acid pinacol esters.



s2.19

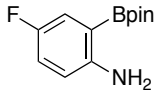
Aniline s2.19.[33] The general procedure was followed using 3.4 g of 2-bromo-aniline (20.0 mmol), 8.7 mL of 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (60.0 mmol), 0.82 g of (dppf)$PdCl_2$ (1.0 mmol), and 8.4 mL of Et_3N (80.0 mmol) in 100 mL of 1, 4-dioxane. Purification by MPLC (2:100 – 10:90 EtOAc: hexanes) afforded the product as a light yellow solid (3.02 g, 69%): mp 62 – 64 °C; The spectral data matched that reported by Driver and co-workers:[33] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (d, J = 7.5 Hz, 1H), 7.24 (t, J = 7.0 Hz, 1H), 6.70 (t, J = 7.0 Hz, 1H), 6.61 (d, J = 8.5 Hz, 1H), 4.76 (s, 2H), 1.36 (s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.7 (C), 136.8 (CH), 132.8 (CH), 116.9 (CH), 114.8 (CH), 83.5 (C), 25.0 (CH3); IR (thin film): 3486, 3380, 1624, 1605,1352, 1311, 1244, 1135, 1086, 847, 758, 654 cm^{-1}.



s2.20

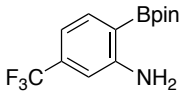
Aniline s2.20.[33] The general procedure was following using 0.66 mL of 2-bromo-4-methylaniline (5.37 mmol), 0.219 g of (dppf)$PdCl_2$ (0.270 mmol), 2.34 mL of 4,4,5,5-

tetramethyl-1,3,2-dioxaborolane (16.1 mmol) and 3.02 mL of Et_3N (21.5 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 (0.840 g, 36%), The spectral data matched that reported by Driver and co-workers:[33] ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.48 (s, 1H), 7.08 (d, *J* = 8.0 Hz, 1H), 6.57 (d, *J* = 8.0 Hz, 1H), 4.65 (s, 2H), 2.26 (s, 3H), 1.38 (s, 12H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 151.5 (C), 136.8 (CH), 133.7 (CH), 125.8 (C), 115.1 (CH), 83.5 (C), 67.1 (C), 25.0 (CH3), 20.3 (CH3); ATR-FTIR (thin film): 3500, 2980, 2244, 1618, 1576, 1496 cm^{-1}. HRMS (EI) *m/z* calculated for $C_{13}H_{20}BNO_2$ $(M)^+$: 233.1587, found: 233.1583.



s2.21

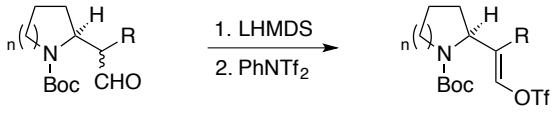
Aniline s2.21. The general procedure was following using 0.59 mL of 2-bromo-5-(trifluoromethyl)aniline (5.26 mmol), 0.214 g of $(dppf)PdCl_2$ (0.263 mmol), 2.28 mL of 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (15.7 mmol) and 3.0 mL of Et_3N (21.0 mmol) in 20 mL of 1,4-dioxane. Purification by MPLC (1:100 – 10:90 EtOAc: hexanes) afforded the product as a yellow solid (0.95 g, 76%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (dd, *J* = 9.0 Hz, 3.0 Hz, 1H), 6.92 (dt, *J* = 8.5 Hz, 3.0 Hz, 1H), 6.53 (dd, *J* = 9.0 Hz, 4.5 Hz, 1H), 4.59 (s, 2H), 1.34 (s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.2 (d, J_{CF} = 233.2 Hz, C), 149.8 (C), 121.6 (d, J_{CF} = 20.1 Hz, CH), 119.7 (d, J_{CF} = 23.7 Hz, CH), 116.0 (CH), 83.9 (C), 24.9 (CH_3), only visible peaks; ^{19}F NMR (282 MHz, $CDCl_3$) δ –129.5. ATR-FTIR (thin film): 3470, 3371, 2975, 2931, 1624, 1492, 1434, 1380, 1347, 1198, 1190, 1135, 1081, 963, 912 cm^{-1}.



s2.22

Aniline s2.22.[33] The general procedure was following using 0.59 mL of 2-bromo-5-(trifluoromethyl)aniline (4.16 mmol), 0.170 g of (dppf)$PdCl_2$ (0.200 mmol), 1.81 mL of 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (12.5 mmol) and 2.4 mL of Et_3N (16.6 mmol) in 20 mL of 1,4-dioxane. Purification by MPLC (1:100 – 10:90 EtOAc: hexanes) afforded the product as a yellow solid (0.86 g, 72%). The spectral data matched that reported by Driver and co-workers:[33] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, J = 7.5 Hz, 1H), 6.93 (d, J = 7.5 Hz, 1H), 6.83 (s, 1H), 5.03 (s, 2H), 1.38 (s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.9 (C), 137.6 (CH), 134.3 (q, J_{CF} = 32 Hz, C), 124.3 (q, J_{CF} = 272 Hz, CF_3), 112.6 (q, J_{CF} = 3.4 Hz, CH), 110.9 (q, J_{CF} = 4.5 Hz, CH), 84.0 (C), 29.9 (C), 24.8 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ –63.95. ATR-FTIR (thin film): 3499, 3397, 2980, 2958, 2929, 1622, 1508, 1437, 1333, 1245 cm^{-1}. HRMS (EI) *m/z* calculated for $C_{13}H_{17}BFNO_2$ $(M)^+$: 287.1304, found: 287.1310.

3. General procedure for preparation of the vinyl triflates.

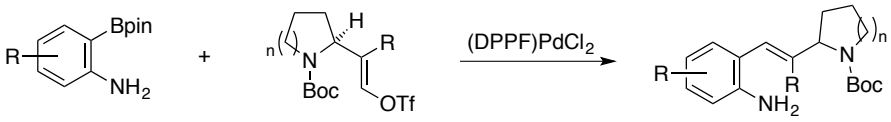


To a cooled solution (–78 °C) of LHMDS (5.15 g, 30.8 mmol, 2.0 equiv) in 75 mL of THF was added the aldehyde (15.4 mmol, 1 equiv). After addition, the resulting mixture was warmed to room temperature. After 1h, the reaction mixture was cooled to –78 °C, and a solution of $PhNTf_2$ (8.25 g, 23.1 mmol, 1.5 equiv) in 20 mL of THF was added.

The solution was stirred for overnight (for optical rotation experiment the reaction mixture was stirred for 3h). After 15 h (3 h for synthesis of optically active material), the reaction mixture was evaporated to dryness. The resulting residue was extracted with 3 × 30 mL of ethyl acetate. The combined organic phases were dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. The resulting residue was purified by MPLC to afford the triflate as colorless oil with 70 – 80% purity. The material was used in the subsequent Suzuki coupling reaction without addition purification or characterization.

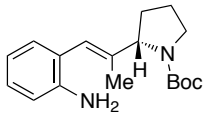
4. General procedure for the Suzuki cross coupling reaction.

Following the procedure of Driver and co-workers,[8] aniline was treated with vinyl triflate in the presence of (dppf)$PdCl_2$ to produce the desired styrene. Yields were not optimized.



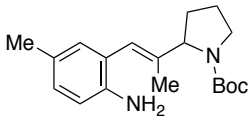
To a mixture of boronic ester (1.0 mmol), (dppf)$PdCl_2$ (0.1 mmol) in 10 mL of 1,4-dioxane was added 4 mL of a 3 M solution NaOH in water followed by crude triflate (1.1 mmol). The resultant mixture was refluxed at 120 °C. After 12 h, the mixture was cooled to room temperature and filtrated through a pad of celite. The filtrate was diluted with 20 mL of saturated NH_4Cl and extracted with an additional 2 × 20 mL of CH_2Cl_2. The combined organic phases were washed with 1 × 20 mL of brine. The resulting organic phase was dried over Na_2SO_4, and was concentrated *in vacuo*. Purification via MPLC afforded the product.

5. Syntheses of anilines using the Suzuki cross coupling reaction



s2.23

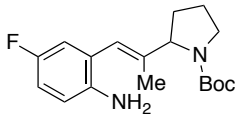
(*S*)-2-[2-(2-Amino-phenyl)-1-methyl-vinyl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester s2.23. The general procedure was followed by using 0.50 g of boronic ester **s2.19** (2.14 mmol), 0.85 g of crude vinyl triflate (1.1 mmol), 0.16 g of (dppf)$PdCl_2$ (0.24 mmol), 9 mL of 3 M NaOH in water in 25 mL of 1,4-dioxane. Purification by extraction followed by MPLC (5:100 – 20:100 EtOAc:haxane) afforded the product, a yellow liquid, as a 50:50 mixture of rotamers (0.52 g, 76%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.03 (br s, 1H), 6.97 (br s, 1H), 6.68 (br s, 2H), 6.10 (s, 1H), 4.31 (br s, 1H), 3.74 (br s, 2H), 3.45 (br s, 2H), 2.01 (br s, 1H), 1.93 – 1.80 (m, 3H), 1.65 (s, 1.5 H), 1.63 (s, 1.5 H), 1.46 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.7 (C), 154.4 (C), 144.7 (C), 144.1 (C), 141.7 (C), 139.8 (C), 131.0 (CH), 129.5 (CH), 127.6 (CH), 123.5 (C), 120.3 (CH), 119.4 (CH), 118.0 (CH), 117.4 (CH), 115.0 (CH), 114.6 (CH), 79.1 (C), 63.5 (CH), 63.3 (CH), 47.2 (CH_2), 47.0 (CH_2), 32.0 (CH_2), 30.6 (CH_2), 28.6 (CH_3), 23.8 (CH_2), 23.2 (CH_2), 14.8 (CH_3), only visible peaks. ATR-FTIR (thin film): 3463, 3358, 2971, 2931, 2873, 1682, 1617, 1488, 1455, 1397, 1367, 1302, 1255, 1159, 1119, 909, 728 cm^{-1}.



s2.24

2-[2-(2-Amino-5-methyl-phenyl)-1-methyl-vinyl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester s2.24. The general procedure was followed by using 0.57 g of boronic ester

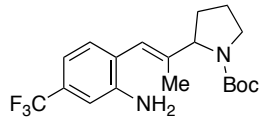
s2.20 (2.44 mmol), 0.96 g of crude vinyl triflate (2.69 mmol), 0.16 g of (dppf)$PdCl_2$ (0.24 mmol), 9 mL of a 3 M NaOH in water in 25 mL of 1,4-dioxane. Purification by extraction followed by MPLC (5:100 - 20:100 EtOAc:hexanes) afforded the product as yellow liquid with 75% purity (0.58 g, 75%). It was used in the next step without further purification.



s2.25

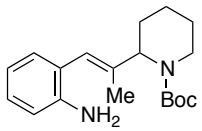
2-[2-(2-Amino-5-fluoro-phenyl)-1-methyl-vinyl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester s2.25. The general procedure was followed by using 0.26 g of boronic ester **s2.21** (0.95 mmol), 0.38 g of crude vinyl triflate (1.04 mmol), 0.06 g of (dppf)$PdCl_2$ (0.09 mmol), 4 mL of 3 M NaOH in water in 10 mL of 1,4-dioxane. Purification by extraction followed by MPLC (5:100 - 20:100 EtOAc:hexanes) afforded the product, a yellow solid, as a 66:33 mixture of rotamers (0.21 g, 72%). Spectral data for the major rotamer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.73 – 6.68 (m, 2H), 6.60 – 6.58 (m, 1H), 6.04 (s, 1H), 4.28 (br s, 1H), 3.67 – 3.54 (br m, 2H), 3.44 (br s, 2H), 2.10 (br s, 1H), 1.90 – 1.78 (m, 3H), 1.64 (s, 1H), 1.62 (s, 2H), 1.45 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.5 (d, J_{CF} = 237.2 Hz, C), 154.4 (C), 142.7 (C), 140.7 (C), 124.7 (C), 119.5 (CH), 118.6 (CH), 115.9 (d, J = 34.6 Hz, CH), 113.8 (d, J = 22.9 Hz, CH), 79.3 (C), 63.2 (CH), 47.2 (CH_2), 30.6 (CH_2), 28.5 (CH_3), 23.7 (CH_2), 14.7 (CH_3); diagnostic data for the minor rotamer: ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.2 (C), 47.0 (CH_2), 31.9 (CH_2), 23.1 (CH_2). Data for

mixture: ATR-FTIR (thin film): 3443, 3423, 3342, 2978, 2890, 1689, 1669, 1499, 1397, 136, 1251, 1163, 1119, 1095 cm^{-1}.



s2.26

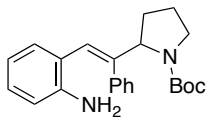
2-[2-(2-Amino-4-trifluoromethyl-phenyl)-1-methyl-vinyl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester s2.26. The general procedure was followed by using 0.24 g of boronic ester **2.22** (0.83 mmol), 0.24 g of crude vinyl triflate (0.91 mmol), 0.06 g of (dppf)$PdCl_2$ (0.08 mmol), 3.5 mL of 3 M NaOH in water in 10 mL of 1,4-dioxane. Purification by extraction followed by MPLC (5:100 - 20:100 EtOAc:haxane) afforded the product, a yellow solid, as a 66:34 mixture of rotamers (0.19 g, 62%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.03 – 6.99 (m, 1H), 6.94 – 6.85 (m, 2H), 6.06 (s, 1H), 4.29 – 4.28 (m, 1H), 4.15 (br s, 1H), 3.87 (br s, 1H), 3.55 – 3.44 (m, 2H), 2.11 (br s, 1H), 1.91 – 1.82 (m, 3H), 1.63 (s, 1H), 1.57 (s, 2H), 1.40 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.5 (C), 145.2 (C), 144.7 (C), 141.3 (C), 130.0 (CF_3), 129.6 (CH), 126.7 (C), 119.5 (CH), 113.6 (CH), 110.7 (CH), 79.3 (C), 63.3 (CH), 47.3 (CH_2), 30.6 (CH_2), 28.5 (CH_3), 23.8 (CH_2), 14.5 (CH_3); diagnostic data for minor rotamer: ^{13}C NMR (125 MHz, $CDCl_3$) δ 118.2 (CH_2), 114.2 (CH_2), 111.2 (CH), 31.9 (CH_2), 23.1 (CH_2), 14.1 (CH_3). ATR-FTIR (thin film): 3480, 3389, 2978, 2897, 1682, 1615, 1601, 1438, 1394, 1336, 1262, 1159, 1108, 1085 cm^{-1}.



s2.27

2-[2-(2-Amino-phenyl)-1-methyl-vinyl]-piperidine-1-carboxylic acid *tert*-butyl ester s2.27. The general procedure was followed by using 0.917 g of boronic ester **s2.19** (4.2 mmol), 1.42 g of crude vinyl triflate (3.8 mmol), 0.311 g of (dppf)$PdCl_2$ (0.38 mmol), 15 mL of a 3 M solution of NaOH in water in 40 mL of 1,4-dioxane. Purification by extraction followed by MPLC (2:100 - 20:100 EtOAc:haxane) afforded the product as yellow liquid (0.495 g, 41 %). Spectral data for the *Z*-isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.03 (t, *J* = 6.5 Hz, 2H), 6.68 (dd, *J* = 17.5, 7.9 Hz, 2H), 6.09 (s, 1H), 4.57 (s, 1H), 3.93 (s, 2H), 3.74 (dd, *J* = 13.4, 4.3 Hz, 1H), 3.13 (ddd, *J* = 13.8, 9.5, 4.7 Hz, 1H), 1.86 (s, 3H), 1.63-1.47 (m, 5H), 1.45 (s, 9H), 1.37 – 1.34 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.8 (C), 144.2 (C), 143.3 (C), 129.5 (CH), 127.6 (CH), 123.7 (C), 122.1 (CH), 117.8 (CH), 115.2 (CH), 79.5 (C), 53.9 (CH), 41.2 (CH_2), 28.7 (CH_2), 28.5 (CH_3), 23.8 (CH_2), 20.8 (CH_3), 19.9 (CH_2). Spectral data for the *E*-isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.05 (td, *J* = 7.6, 1.2 Hz, 1H), 6.99 (d, *J* = 7.4 Hz, 1H), 6.72 (td, *J* = 7.4, 0.6 Hz, 1H), 6.68 (d, *J* = 8.0 Hz, 1H), 6.09 (s, 1H), 4.76 (d, *J* = 3.8 Hz, 1H), 4.03 (d, *J* = 13.2 Hz, 1H), 3.65 (s, 2H), 2.90 (td, *J* = 12.6, 3.0 Hz, 1H), 2.09 (d, *J* = 13.1 Hz, 1H), 1.73 – 1.67 (m, 1H), 1.65 (s, 3H), 1.62 (dd, *J* = 7.9, 3.3 Hz, 2H), 1.53-1.50 (m, 2H), 1.48 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.5 (C), 144.1 (C), 138.1 (C), 129.9 (CH), 127.7 (CH), 123.8 (C), 121.4 (CH), 117.9 (CH), 115.0 (CH), 79.4 (C), 56.0 (CH), 40.6 (CH_2), 28.5 (CH_3), 26.7 (CH_2), 25.4 (CH_2), 19.7 (CH_2), 16.1 (CH_3). ATR-FTIR (thin film): 3456,

3348, 2938, 1675, 1407, 1153 cm^{-1}. HRMS (EI) *m/z* calculated for $C_{19}H_{28}N_2O_2$ $(M)^+$: 316.21508, found: 316.21450.

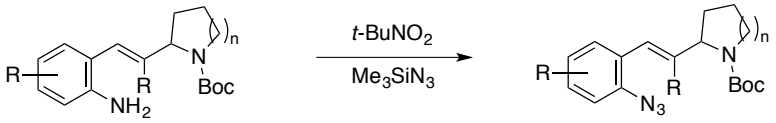


s2.28

2-[2-(2-Amino-phenyl)-1-phenyl-vinyl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester s2.28. The general procedure was followed by using 0.19 g of boronic ester **s2.19** (0.87 mmol), 0.38 g of crude vinyl triflate (0.95 mmol), 0.06 g of (dppf)$PdCl_2$ (0.09 mmol), 4 mL of 3 M NaOH in water in 10 mL of 1,4-dioxane. Purification by extraction followed by MPLC (5:100 – 20:100 EtOAc:hexanes) afforded the product with 70% purity as yellow viscous liquid. This was used in the next step without further purification or characterization

H. Preparation of styryl azides

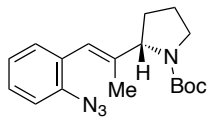
1. General procedure for the preparation of *N*-Boc-protected styryl azide.



To a cooled solution (0 °C) of aniline in MeCN (0.2 M) was added dropwise *t*-$BuNO_2$ (4.0 equiv) and Me_3SiN_3 (3.0 equiv). The resulting solution was warmed to room temperature. After 1h, analysis of the reaction progress using TLC indicated that the reaction was complete. The reaction mixture was concentrated *in vacuo*. Purification of

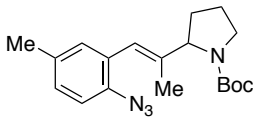
the residue by MPLC (0:100 – 5:95 EtOAc: hexanes) afforded *N*-Boc protected styryl azide.

2. Preparation of styryl azides.



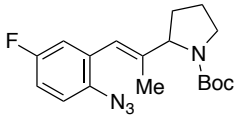
s2.29

(*S*)-2-[2-(2-Azido-phenyl)-1-methyl-vinyl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester s2.29. The general procedure was followed using 0.250 g of aniline **s2.23** (0.83 mmol), 0.39 mL of *t*-$BuNO_2$ (3.31 mmol) and 0.33 mL of Me_3SiN_3 (2.48 mmol) in 5 mL of MeCN. Purification by MPLC (0:100 – 10:90 EtOAc:hexanes) afforded the product, a yellow oil, as a 68:32 mixture of rotamers (0.247 g, 91%). $[\alpha]_D^{20}$: – 40.0 (*c* 0.125, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 – 7.18 (m, 2H), 7.13 – 7.09 (m, 2H), 6.22 (s, 1H), 4.37 (br s, 0.32 H), 4.27 (br s, 0.68 H), 3.46 – 3.55 (m, 2H), 2.10 (br s, 1H), 1.97 – 1.91 (m, 1H), 1.85 – 1.72 (m, 2H), 1.69 (s, 3H), 1.48 (s, 3H), 1.43 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.7 (C), 140.9 (C), 138.0 (C), 130.5 (CH), 129.9 (C), 127.7 (CH), 124.2 (CH), 119.0 (CH), 118.3 (CH), 79.2 (C), 63.8 (CH), 49.9 (CH_2), 31.9 (CH_2), 28.4 (CH_3), 23.2 (CH_2), 14.8 (CH_3); ATR-FTIR (thin film): 2977, 2120, 2086, 1693, 1484, 1386, 1291, 1164 cm^{-1}. HRMS (EI) *m/z* calculated for $C_{18}H_{24}N_4O_2$ $(M)^+$: 328.18992, found: 328.18896.



s2.30

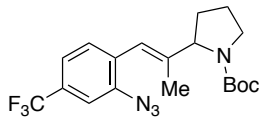
2-[2-(2-Azido-5-methyl-phenyl)-1-methyl-vinyl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester s2.30. The general procedure was followed using 0.230 g of aniline **s2.24** (0.73 mmol), 0.35 mL of *t*-$BuNO_2$ (2.92 mmol) and 0.29 mL of Me_3SiN_3 (2.19 mmol) in 4 mL of MeCN. Purification by MPLC (2:100 – 10:90 EtOAc:hexanes) afforded the product, a light yellow oil, as a 65:35 mixture of rotamers (0.219 g, 88%). Spectral data for the mixture: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.97 – 7.01 (m, 3H), 6.17 (s, 1H), 4.35 (br s, 0.35H), 4.25 (br s, 0.65H), 3.52 – 3.44 (m, 2H), 2.29 (s, 3H), 1.90 – 1.72 (m, 4H), 1.68 (s, 3H), 1.46 (s, 3H), 1.42 (s, 6H); Data for major rotamer: ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.6 (C), 140.6 (C), 135.2 (C), 133.8 (C), 131.1 (CH), 129.7 (C), 128.3 (CH), 119.0 (CH), 118.2 (CH), 79.1 (C), 63.8 (CH), 46.9 (CH_2), 31.8 (CH_2), 28.4 (CH_3), 23.1 (CH_2), 20.9 (CH_3), 14.9 (CH_3); diagnostic data for the minor rotamer: ^{13}C NMR (125 MHz, $CDCl_3$) δ 63.1 (CH), 30.9 (CH_2), 15.6 (CH_3); data for mixtures: ATR-FTIR (thin film): 2971, 2931, 2870, 2120, 2086, 1689, 1485, 1387, 1363, 1292 cm^{-1}. HRMS (EI) *m/z* calculated for $C_{19}H_{26}N_4O_2$ $(M)^+$: 342.20557, found: 342.20653.



s2.31

2-[2-(2-Azido-5-fluoro-phenyl)-1-methyl-vinyl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester s2.31. The general procedure was followed using 0.114 g of aniline **s2.25** (0.35 mmol), 0.17 mL of *t*-$BuNO_2$ (1.42 mmol) and 0.14 mL of Me_3SiN_3 (1.05 mmol) in 2 mL of MeCN. Purification by MPLC (0:100 – 10:90 EtOAc:hexanes) afforded the

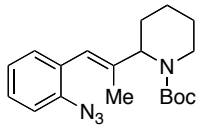
product, a light yellow oil, as a 65:35 mixture of rotamers (0.219 g, 88%). Spectral data for the mixture: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.03 (br s, 1H), 6.93 – 6.88 (m, 2H), 6.17 (s, 1H), 4.35 (br s, 0.35H), 4.25 (m, 0.65H), 3.53 – 3.44 (m, 2H), 2.11 – 2.08 (m, 1H), 1.93 – 1.88 (m, 1H), 1.84 – 1.74 (m, 2H), 1.70 (s, 3H), 1.47 (s, 3H), 1.41 (s, 6H); spectral data for major rotamer: ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.3 (d, J_{CF} = 242.2 Hz, C), 154.6 (CH), 142.2 (C), 133.8 (C), 131.6 (C), 119.5 (CH), 118.1 (CH), 117.0 (d, J_{CF} = 22.5 Hz, CH), 114.4 (d, J = 24.4 Hz, CH), 79.2 (C), 63.7 (CH), 46.9 (CH_2), 31.8 (CH_2), 28.4 (CH_3), 23.1 (CH_2), 14.9 (CH_3); diagnostic data for the minor rotamer: ^{13}C NMR (125 MHz, $CDCl_3$) δ 63.3 (CH), 23.4 (CH_2); ATR-FTIR (thin film): 2978, 2877, 2113, 1682, 1397, 1327, 1275, 1166 cm^{-1}. HRMS (EI) *m/z* calculated for $C_{18}H_{23}FN_4O_2$ $(M)^+$: 346.18050, found: 346.18117.



s2.32

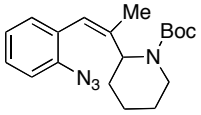
2-[2-(2-Azido-4-trifluoromethyl-phenyl)-1-methyl-vinyl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester s2.32. The general procedure was followed using 0.250 g of aniline **s2.26** (0.67 mmol), 0.24 mL of *t*-$BuNO_2$ (2.02 mmol) and 0.35 mL of Me_3SiN_3 (2.69 mmol) in 4 mL of MeCN. Purification by MPLC (0:100 – 10:90 EtOAc:hexanes) afforded the product, a yellow oil, as a 58:42 mixture of rotamers (0.248 g, 93%). Spectral data for the mixture: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.30 (m, 3H), 6.21 (s, 1H), 4.37 (br s, 0.42H), 4.27 (br s, 0.58H), 3.54 – 3.46 (m, 2H), 2.20 – 1.91 (m, 2H), 1.84 – 1.74 (m, 2H), 1.70 (s, 3H), 1.47 (s, 4H), 1.41 (s, 5H); data for major rotamer: ^{13}C NMR

(125 MHz, $CDCl_3$) δ 154.6 (C), 143.1 (C), 138.8 (C), 133.5 (C), 130.9 (CH), 130.0 (q, J_{CF} = 31.2 Hz, C), 123.7 (q, J_{CF} = 270.1 Hz, CF_3), 120.9 (CH), 117.9 (CH), 115.2 (C), 79.3 (C), 63.8 (CH), 46.9 (CH_2), 31.8 (CH_2), 28.4 (CH_3), 23.1 (CH_2), 15.0 (CH_3); diagnostic data for minor rotamer: ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.0 (C), 117.4 (CH), 63.2 (CH), 30.7 (CH_2), 15.6 (CH_3); data for the mixture: ATR-FTIR (thin film): 2977, 2111, 1686, 1399, 1329, 1169, 1129 cm^{-1}. HRMS (EI) *m/z* calculated for $C_{19}H_{23}F_3N_4O_2$ $(M)^+$: 396.17731, found: 396.17637.



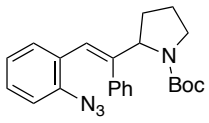
s2.33

(*E*)-1-Boc-2-(1-(2-azidophenyl)prop-1-en-2-yl)piperidine s2.33. The general procedure was followed using 0.230 g of aniline *E*-**s2.27** (0.73 mmol), 0.35 mL of *t*-$BuNO_2$ (2.9 mmol) and 0.30 mL of Me_3SiN_3 (2.2 mmol) in 10 mL of MeCN. Purification by MPLC (0:100 – 10:90 EtOAc:hexanes) afforded the product as a yellow oil (0.212 g, 85%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (t, *J* = 7.7 Hz, 1H), 7.19 (d, *J* = 7.5 Hz, 1H), 7.13 (d, *J* = 7.9 Hz, 1H), 7.09 (t, *J* = 7.5 Hz, 1H), 6.23 (s, 1H), 4.78 (s, 1H), 4.02 (d, *J* = 12.1 Hz, 1H), 2.86 (td, *J* = 12.9, 2.8 Hz, 1H), 2.11 (d, *J* = 13.6 Hz, 1H), 1.68 (s, 3H), 1.72 – 1.51 (m, 5H), 1.49 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.5 (C), 138.1 (C), 137.6 (C), 130.8 (CH), 130.1 (C), 127.8 (CH), 124.2 (CH), 121.2 (CH), 118.2 (CH), 79.4 (C), 56.0 (CH), 40.3 (CH_2), 28.5 (CH_3), 26.6 (CH_2), 25.5 (CH_2), 19.6 (CH_2), 16.1 (CH_3).



s2.34

(*Z*)-1-Boc-2-(1-(2-azidophenyl)prop-1-en-2-yl)piperidine s2.34. The general procedure was followed using 0.258 g of aniline *Z*-**s2.27** (0.82 mmol), 0.39 mL of *t*-$BuNO_2$ (3.3 mmol) and 0.34 mL of Me_3SiN_3 (2.4 mmol) in 10 mL of MeCN. Purification by MPLC (0:100 – 10:90 EtOAc:hexanes) afforded the product as a yellow oil (157 g, 56%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (t, *J* = 7.7 Hz, 1H), 7.19 (d, *J* = 7.4 Hz, 1H), 7.13 (d, *J* = 7.8 Hz, 1H), 7.09 (t, *J* = 7.5 Hz, 1H), 6.22 (s, 1H), 4.77 (s, 1H), 4.02 (d, *J* = 13.1 Hz, 1H), 2.86 (td, *J* = 12.9, 2.7 Hz, 1H), 2.10 (d, *J* = 13.8 Hz, 1H), 1.67 (s, 3H), 1.73 – 1.53 (m, 5H), 1.48 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.5 (C), 138.1 (C), 137.6 (C), 130.7 (CH), 130.1 (C), 127.8 (CH), 124.2 (CH), 121.3 (CH), 118.2 (CH), 79.4 (C), 56.0 (CH), 40.3 (CH_2), 28.5 (CH_3), 26.6 (CH_2), 25.5 (CH_2), 19.6 (CH_2), 16.1 (CH_3). ATR-FTIR (thin film): 2838, 2116, 2089, 1682, 1414, 1157 cm^{-1}. HRMS (EI) *m/z* calculated for $C_{19}H_{26}N_4O_2$ $(M)^+$: 342.20557, found: 342.20637.

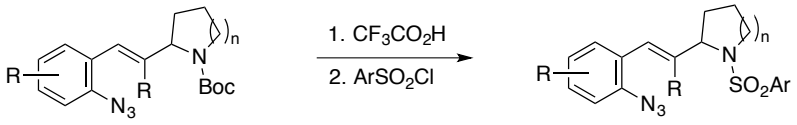


s2.35

2-[2-(2-Azido-phenyl)-1-phenyl-vinyl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester s2.35. The general procedure was followed using 0.06 g of aniline **s2.28** (0.16 mmol) in 2 mL of MeCN, 0.06 mL of *t*-$BuNO_2$ (0.49 mmol), 0.08 mL of Me_3SiN_3 (0.64 mmol). Purification by MPLC (0:100 – 10:90 EtOAc:hexanes) afforded the product, a yellow solid, as a 70:30 mixture of rotamers (0.06 g, 87%). mp 136 – 138 °C. Data for mixtures: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 – 7.23 (m, 3H), 7.16 – 7.05 (m, 4H), 6.71 – 6.65 (m,

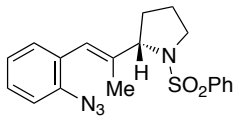
2H), 6.42 (s, 1H), 4.78 (br s, 0.30 H), 4.65 (br s, 0.70 H), 3.60 – 3.45 (m, 2H), 1.97 – 1.66 (m, 4H), 1.48 (s, 9H); data for major rotamer: ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.6 (C), 144.9 (C), 139.1 (C), 138.0 (C), 130.5 (CH), 129.2 (C), 129.1 (CH), 128.5 (CH), 127.6 (CH), 127.2 (CH), 124.0 (CH), 120.3 (CH), 118.0 (CH), 79.4 (C), 63.7 (CH), 46.9 (CH_2), 31.2 (CH_2), 28.6 (CH_2), 22.4 (CH_3); diagnostic data for minor rotamer: ^{13}C NMR (125 MHz, $CDCl_3$) δ 30.4 (CH_2). Data for mixtures: ATR-FTIR (thin film): 2971, 2920, 2123, 2093, 1682, 1475, 1394, 1166, 1115, 909 cm^{-1}. HRMS (EI) *m/z* calculated for $C_{23}H_{26}N_4O_2$ $(M)^+$: 390.20557, found: 390.20644.

4. General procedure for the preparation of *N*-sulfonyl protected styryl azide.



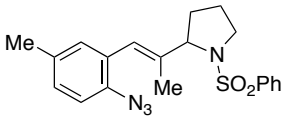
To a cooled solution (0 °C) of *N*-Boc protected styryl azide (1 equiv) in anhydrous CH_2Cl_2 was added dropwise trifluoroacetic acid (4 equiv). After 2 h, analysis of the reaction progress using TLC indicated that the deprotection was complete. The reaction mixture was concentrated *in vacuo*. The resulting residue was dissolved in anhydrous CH_2Cl_2 and cooled to 0 °C. To the resulting solution was added Et_3N (8 equiv). After 10 min, benzenesulfonyl chloride (2 equiv) was added and the solution was allowed to warm at room temperature. After 2 h, the solution was concentrated *in vacuo*, and the resulting residue was purified by MPLC (5:100 – 10:100 EtOAc:hexane) to afford the product.

5. Syntheses of *N*-sulfonyl styryl azides.



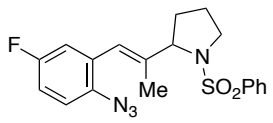
2.29

(*S*)-2-[2-(2-Azido-phenyl)-1-methyl-vinyl]-1-benzenesulfonyl-pyrrolidine 2.29. The general procedure was followed by using 0.119 g of azide **s2.29** (0.51 mmol), 0.16 mL of TFA in 2 mL of dichloromethane. Sulfonyl protection was accomplished using 0.57 mL of Et_3N (4.08 mmol) followed by the addition of 0.12 mL of benzenesulfonyl chloride (1.02 mmol). The reaction mixture was purified by MPLC (5:100 – 10:100 EtOAc:hexane) to afford the product as a yellow solid (0.112 g, 84% over 2 steps). $[\alpha]_D^{20}$: –19.6 (*c* 0.125, CH_2Cl_2); mp 103 – 105 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, *J* = 7.5 Hz, 2H), 7.57 (t, *J* = 7.5 Hz, 1H), 7.51 (t, *J* = 7.5 Hz, 2H), 7.27 – 7.21 (m, 2H), 7.13 – 7.07 (m, 2H), 6.45 (s, 1H), 4.15 (t, *J* = 6.5 Hz, 1H), 3.55 – 3.51 (m, 1H), 3.43 – 3.41 (m, 1H), 1.90 – 1.80 (m, 3H), 1.72 (s, 3H), 1.64 – 1.60 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.3 (C), 139.0 (C), 137.9 (C), 132.6 (CH), 130.7 (CH), 129.4 (C), 128.9 (CH), 127.9 (CH), 127.6 (CH), 124.3 (C), 121.7 (C), 118.2 (CH), 66.7 (CH), 49.6 (CH_2), 31.8 (CH_2), 24.1 (CH_2), 14.3 (CH_3). ATR-FTIR (thin film): 2972, 2878, 2113, 2094, 1482, 1443, 1346, 1291, 1160, 1092 cm^{-1}. HRMS (EI) *m/z* calculated for $C_{19}H_{20}O_2N_2S$ $(M–N_2)^+$: 340.12455, found: 340.12401.



2.20b

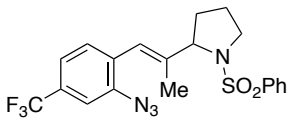
2-[2-(2-Azido-5-methyl-phenyl)-1-methyl-vinyl]-1-benzenesulfonyl-pyrrolidine 2.20b. The general procedure was followed by using 0.056 g of azide **s2.30** (0.16 mmol), 0.06 mL of TFA in 1 mL of dichloromethane. Sulfonyl protection was accomplished using 0.23 mL of Et_3N (1.63 mmol) followed by the addition of 0.04 mL of benzenesulfonyl chloride (0.32 mmol). The reaction mixture was purified by MPLC (5:100 – 10:100 EtOAc:hexane) to afford the product as a yellow solid (0.049 g, 79% over 2 steps). mp 107 – 109 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, *J* = 7.0 Hz, 2H), 7.58 (t, *J* = 7.5 Hz, 1H), 7.52 (d, *J* = 7.5 Hz, 2H), 7.07 – 7.01 (m, 3H), 6.40 (s, 1H), 4.14 (t, *J* = 6.0 Hz, 1H), 3.56 – 3.52 (m, 1H), 3.44 – 3.40 (m, 1H), 2.31 (s, 3H), 1.92 – 1.81 (m, 3H), 1.71 (s, 3H), 1.66 – 1.60 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.1 (C), 138.1 (C), 135.2 (C), 133.9 (C), 132.5 (CH), 131.3 (CH), 129.2 (C), 128.9 (CH), 128.6 (CH), 127.6 (CH), 121.8 (CH), 118.1 (CH), 66.7 (CH), 49.6 (CH_2), 31.8 (CH_2), 24.1 (CH_2), 20.9 (CH_3), 14.3 (CH_3). ATR-FTIR (thin film): 2978, 2931, 2120, 1448, 1333, 1295, 1159, 1092, 1007 cm^{-1}. HRMS (EI) *m/z* calculated for $C_{20}H_{22}O_2N_4S$ $(M)^+$: 382.14634, found: 382.14712.



14c

2-[2-(2-Azido-5-fluoro-phenyl)-1-methyl-vinyl]-1-benzenesulfonyl-pyrrolidine 2.20c. The general procedure was followed by using 0.100 g of azide **s2.31** (0.29 mmol), 0.09 mL of TFA (1.15 mmol) in 1 mL of dichloromethane. Sulfonyl protection was accomplished using 0.32 mL of Et_3N (2.32 mmol) followed by the addition of 0.07 mL of benzenesulfonyl chloride (0.58 mmol). The reaction mixture was purified by MPLC

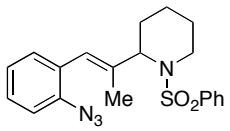
(5:100 – 10:100 EtOAc:hexane) to afford the product as a yellow solid (0.084 g, 76% over 2 steps). mp 90 – 92 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, J = 7.5 Hz, 2H), 7.58 (t, J = 7.5 Hz, 3H), 7.51 (t, J = 7.5 Hz, 1H), 7.07 – 7.04 (m, 1H), 6.97 – 6.92 (m, 2H), 6.41 (s, 1H), 4.13 (t, J = 7.5 Hz, 1H), 3.55 – 3.51 (m, 1H), 3.42 – 3.38 (m, 1H), 1.89 – 1.78 (m, 3H), 1.73 (s, 3H), 1.64 – 1.60 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.3 (d, J_{CF} = 242 Hz, C), 140.6 (C), 137.9 (C), 133.8 (C), 132.6 (CH), 131.1 (C), 129.0 (CH), 127.6 (CH), 120.8 (CH), 119.4 (CH), 117.3 (d, J_{CF} = 29.7 Hz, CH), 114.6 (d, J_{CF} = 23.4 Hz, CH), 66.5 (CH), 49.6 (CH_2), 31.8 (CH_2), 24.1 (CH_2), 14.5 (CH_3). ^{19}F NMR (282 MHz, $CDCl_3$) δ –118.6. ATR-FTIR (thin film): 3036, 2977, 2888, 2125, 2101, 1484, 1345, 1272 cm^{-1}. HRMS (EI) *m/z* calculated for $C_{19}H_{19}O_2N_4SF$ $(M)^+$: 386.12127, found: 386.12138.s



14d

2-[2-(2-Azido-4-trifluoromethyl-phenyl)-1-methyl-vinyl]-1-benzenesulfonyl-pyrrolidine 2.20d. The general procedure was followed by using 0.025 g of azide **s2.32** (0.064 mmol), 0.02 mL of TFA (0.26 mmol) in 1 mL of dichloromethane. Sulfonyl protection was accomplished using 0.09 mL of Et_3N (0.64 mmol) followed by the addition of 0.016 mL of benzenesulfonyl chloride (0.128 mmol). The reaction mixture was purified by MPLC (5:100 – 10:100 EtOAc:hexane) to afford the product as a yellow solid (0.021 g, 77% over 2 steps). mp 146 – 148 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (d, J = 7.5 Hz, 2H), 7.59 (t, J = 7.5 Hz, 1H), 7.52 (t, J =7.5 Hz, 2H), 7.34 (br s, 3H), 6.5

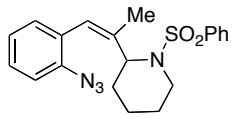
(s, 1H), 4.15 (t, J = 6.0 Hz, 1H), 3.57 – 3.53 (m, 1H), 3.42 – 3.37 (m, 1H), 1.92 – 1.78 (m, 3H), 1.74 (s, 3H), 1.65 – 1.60 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.5 (C), 138.8 (C), 137.8 (C), 133.1 (C), 132.7 (CH), 131.2 (CH), 130.1 (q, J_{CF} = 32.5 Hz, C), 129.0 (CH), 127.6 (CH), 123.7 (q, J_{CF} = 270 Hz, CF_3), 121.0 (CH), 120.6 (CH), 115.1 (CH), 66.5 (CH), 49.6 (CH_2), 31.8 (CH_2), 24.1 (CH_2), 14.6 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ –63.01. ATR-FTIR (thin film): 3063, 2982, 2859, 2109, 1418, 1329, 1275, 1010, 867 cm^{-1}. HRMS (EI) *m/z* calculated for $C_{20}H_{19}F_3N_4O_2S$ $(M–N_2)^+$: 408.11194, found: 408.11231.



E-**2.20e**

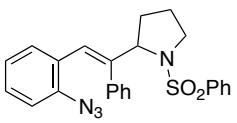
(*E*)-2-(1-(2-azidophenyl)prop-1-en-2-yl)-1-(phenylsulfonyl)piperidine *E*-2.20e. The general procedure was followed by using 0. 212 mg of azide **s2.33** (0.62 mmol), 5 mL of TFA in 20 mL of anhydrous dichloromethane. Sulphonyl protection was accomplished using 0.86 mL of Et_3N (6.2 mmol) followed by the addition of 0.24 mL of benzenesulfonyl chloride (1.86 mmol). The reaction mixture was purified by MPLC (3:100 – 5:100 EtOAc:hexane) afforded product as yellow solid (0.115 g, 49%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (d, J = 7.1 Hz, 2H), 7.56 (t, J = 7.3 Hz, 1H), 7.51 (t, J = 7.4 Hz, 2H), 7.27 (t, J = 7.7 Hz, 1H), 7.17 (d, J = 6.9 Hz, 1H), 7.13 (d, J = 8.0 Hz, 1H), 7.10 (t, J = 7.5 Hz, 1H), 6.35 (s, 1H), 4.58 (s, 1H), 3.73 (d, J = 14.0 Hz, 1H), 3.20 (td, J = 13.2, 2.4 Hz, 1H), 2.03 (d, J = 9.2 Hz, 1H), 1.82 – 1.75 (m, 1H), 1.71 (s, 3H), 1.60 – 1.48 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.3 (C), 138.1 (C), 136.7 (C), 132.2 (CH),

130.7 (CH), 129.7 (C), 129.0 (CH), 128.0 (CH), 127.2 (CH), 124.3 (CH), 122.9 (CH), 118.2 (CH), 58.6 (CH), 42.6 (CH_2), 26.6 (CH_2), 24.5 (CH_2), 19.6 (CH_2), 16.3 (CH_3).



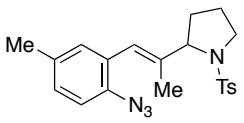
Z-**2.20e**

(*Z*)-2-(1-(2-azidophenyl)prop-1-en-2-yl)-1-(phenylsulfonyl)piperidine *Z*-2.20e. The general procedure was followed by using 0.150 g of azide **s2.34** (0.44 mmol), 5 mL of TFA in 20 mL of anhydrous dichloromethane. Sulphonyl protection was accomplished using 0.60 mL of Et_3N (4.4 mmol) followed by the addition of 0.17 mL of benzenesulfonyl chloride (1.32 mmol). The reaction mixture was purified by MPLC (3:100 – 5:100 EtOAc:hexane) to afford the product as a yellow solid (0.053 g, 32%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (d, *J* = 7.5 Hz, 2H), 7.56 (t, *J* = 7.3 Hz, 1H), 7.51 (t, *J* = 7.5 Hz, 2H), 7.27 (t, *J* = 7.7 Hz, 1H), 7.17 (d, *J* = 7.6 Hz, 1H), 7.13 (d, *J* = 7.9 Hz, 1H), 7.10 (t, *J* = 7.5 Hz, 1H), 6.35 (s, 1H), 4.58 (s, 1H), 3.73 (d, *J* = 14.0 Hz, 1H), 3.20 (td, *J* = 13.1, 2.3 Hz, 1H), 2.03 (d, *J* = 8.5 Hz, 1H), 1.71 (s, 3H), 1.60 – 1.48 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.3 (C), 138.1 (C), 136.7 (C), 132.2 (CH), 130.7 (CH), 129.7 (C), 129.0 (CH), 128.0 (CH), 127.2 (CH), 124.3 (CH), 122.9 (CH), 118.2 (CH), 58.6 (CH), 42.6 (CH_2), 26.6 (CH_2), 24.5 (CH_2), 19.6 (CH_2), 16.3 (CH_3). ATR-FTIR (thin film): 3060, 2940, 2120, 2086, 1445, 1285, 1150 cm^{-1}. HRMS (ESI) *m/z* calculated for $C_{20}H_{23}N_4O_2S$ $(M+H)^+$: 383.1542, found: 383.1546.



2.20f

2-[2-(2-Azido-phenyl)-1-phenyl-vinyl]-1-benzenesulfonyl-pyrrolidine 2.20f. The general procedure was followed by using 0.025 g of azide **s2.35** (0.064 mmol), 0.02 mL of TFA (0.26 mmol) in 1 mL of dichloromethane. Sulfonyl protection was accomplished using 0.09 mL of Et_3N (0.64 mmol) followed by the addition of 0.016 mL of benzenesulfonyl chloride (0.128 mmol). The reaction mixture was purified by MPLC (5:100 – 10:100 EtOAc:hexane) to afford the product as a yellow solid (0.023 g, 83% over 2 steps). ^{1}H NMR (500 MHz, $CDCl_3$ δ 7.25 – 7.23 (m, 3H), 7.16 – 7.05 (m, 4H), 6.71 – 6.65 (m, 2H), 6.42 (s, 1H), 4.78 (br s, 0.30 H), 4.65 (br s, 0.70 H), 3.60 – 3.45 (m, 2H), 1.97 – 1.66 (m, 4H), 1.48 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.6 (C), 138.5 (C), 138.3 (C), 138.0 (C), 132.6 (CH), 130.7 (CH), 129.4 (CH), 129.0 (CH), 128.7 (C), 128.6 (CH), 127.8 (CH), 127.5 (CH), 127.4 (CH), 124.0 (C), 122.8 (CH), 117.8 (CH), 66.1 (CH), 49.3 (CH_2), 31.5 (CH_2), 23.7 (CH_2); ATR-FTIR (thin film): 2927, 2857, 2120, 2089, 1482, 1441, 1343, 1289, 1157, 1095 cm^{-1}. HRMS (EI) *m/z* calculated for $C_{24}H_{22}N_4O_2S$ $(M)^+$: 430.14634, found: 430.14677.



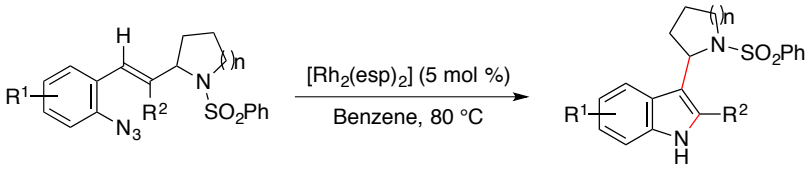
2.35

2-[2-(2-Azido-5-methyl-phenyl)-1-methyl-vinyl]-1-(toluene-4-sulfonyl)-pyrrolidine 14h. The general procedure was followed by using 0.145 g of azide **s2.30** (0.42 mmol), 0.16 mL of TFA (2.11 mmol) in 2 mL of dichloromethane. Sulfonyl protection was accomplished using 0.59 mL of Et_3N (4.20 mmol) followed by the addition of 0.16 g of tosyl chloride (0.84 mmol). The reaction mixture was purified by MPLC (5:100 – 10:100

EtOAc:hexane) to afford product as a yellow solid (0.126 g, 75%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.07 – 7.00 (m, 3H), 6.40 (s, 1H), 4.10 (t, *J* = 5.5 Hz, 1H), 3.51 – 3.54 (m, 1H), 3.38 – 3.40 (m, 1H), 2.42 (s, 3H), 2.31 (s, 3H), 1.92 – 1.80 (m, 3H), 1.73 (s, 3H), 1.65 – 1.60 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.3 (C), 139.3 (C), 135.2 (C), 135.0 (C), 132.9 (C), 131.3 (CH), 129.6 (CH), 129.3 (C), 128.6 (CH), 127.7 (C), 121.7 (CH), 118.1 (CH), 66.6 (CH), 49.6 (CH_2), 31.8 (CH_2), 24.1 (CH_2), 21.5 (CH_3), 20.9 (CH_3), 14.3 (CH_3). ATR-FTIR (thin film): 3375, 2920, 2849, 1686, 1539, 1329, 1157, 1088 cm^{-1}. HRMS (EI) *m/z* calculated for $C_{21}H_{24}N_4O_2S$ $(M)^+$: 396.16199, found: 396.16259.

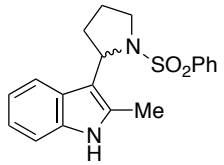
2.8.3 Rh_2(II)-catalyzed synthesis of 2,3-disubstituted indoles from styryl azides.

a. General procedure



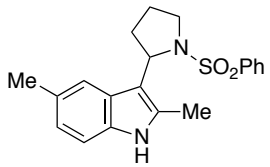
To a mixture of styryl azide and $Rh_2(esp)_2$ (5 mol%) was added benzene (0.1M). The resulting mixture was heated at 80 °C. After 16 h, the mixture was cooled to room temperature, diluted with CH_2Cl_2 and concentrated in vacuo. Purification of the residue by MPLC (3:97 – 20:80 EtOAc: hexanes) afforded the product.

b. Preparation of 2,3-disubstituted indoles



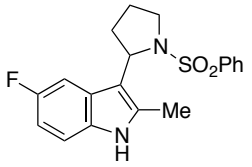
2.22a

3-(2-Benzenesulfonyl-pyrrolidin-1-yl)-2-methyl-1*H*-indole 2.22a. The optimal procedure was followed by using 0.028 g of styryl azide **2.20a** (0.076 mmol), 0.003 g of $Rh_2(esp)_2$ (0.004 mmol) in 1.5 mL of anhydrous benzene. The product was purified by MPLC (5:100 – 20:100 EtOAc:hexane) to afford the product as yellow solid (0.021 g, 83%). $[\alpha]_D^{20}$: 0 (*c* 0.125, CH_2Cl_2); ^{1}H NMR (500 MHz, acetone-d_6) δ 7.89 (s, 1H), 7.61 (d, *J* = 7.0 Hz, 2H), 7.45 (t, *J* = 7.0 Hz, 1H), 7.36 (dd, *J* = 7.5 Hz, 7.5 Hz, 3H), 7.20 (d, *J* = 8.0 Hz, 1H), 6.94 (t, *J* = 8.0 Hz, 1H), 6.84 (t, *J* = 8.0 Hz, 1H), 5.00 (t, *J* = 8.0 Hz, 1H), 3.76 – 3.72 (m, 1H), 3.68 – 3.63 (m, 1H), 2.45 (s, 3H), 2.15 – 2.11 (m, 2H), 1.95 – 2.04 (m, 1H), 1.66 – 1.63 (m, 1H); ^{13}C NMR (125 MHz, acetone-d_6) δ 139.2 (C), 135.8 (C), 132.5 (C), 131.9 (CH), 128.5 (CH), 127.0 (CH), 126.8 (C), 120.1 (CH), 118.4 (CH), 118.3 (CH), 111.3 (C), 110.4 (CH), 57.0 (CH), 49.4 (CH_2), 33.9 (CH_2), 25.0 (CH_2), 11.1 (CH_3). ATR-FTIR (thin film): 3338, 2967, 2925, 1698, 1462, 1331, 1250, 1155, 1087 cm^{-1}. HRMS (EI) *m/z* calculated for $C_{19}H_{20}N_2O_2S$ $(M)^+$: 340.12455, found: 340.12403.



2.22b

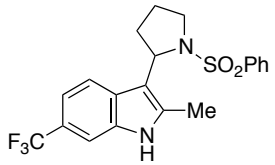
3-(1-Benzenesulfonyl-pyrrolidin-2-yl)-2,5-dimethyl-1*H*-indole 2.22b. The optimal procedure was followed by using 0.022 g of styryl azide **2.20b** (0.057 mmol), 0.0022 g of $Rh_2(esp)_2$ (0.003 mmol) in 2 mL of anhydrous benzene. The product was purified by MPLC (5:100 – 20:100 EtOAc:hexane) to afford the product as yellow solid (0.014 g, 69%). ^{1}H NMR (500 MHz, acetone-d_6) δ 9.71 (s, 1H), 7.57 (d, J = 7.5 Hz, 2H), 7.43 (t, J = 7.0 Hz, 1H), 7.33 (t, J = 7.5 Hz, 2H), 7.09 – 7.07 (m, 2H), 6.77 (d, J = 8.5 Hz, 1H), 4.98 (t, J = 7.5 Hz, 1H), 3.76 – 3.73 (m, 1H), 3.68 – 3.63 (m, 1H), 2.43 (s, 3H), 2.29 (s, 3H), 2.15 – 2.08 (m, 2H), 2.00 – 1.96 (m, 1H), 1.68 – 1.62 (m, 1H); ^{13}C NMR (125 MHz, acetone-d_6) δ 139.2 (C), 134.1 (C), 132.6 (C), 131.8 (CH), 128.3 (CH), 127.1 (C), 127.0 (C), 126.9 (CH), 121.6 (CH), 118.2 (CH), 110.6 (C), 110.0 (CH), 57.0 (CH), 49.3 (CH_2), 33.8 (CH_2), 25.0 (CH_2), 20.8 (CH_3), 11.1 (CH_3). ATR-FTIR (thin film): 3385, 2924, 2857, 1682, 1621, 1587, 1445, 1333, 1305, 1150, 1088; HRMS (EI) *m/z* calculated for $C_{20}H_{22}O_2N_2S$ $(M)^+$: 354.14020, found: 354.14082.



2.22c

3-(1-Benzenesulfonyl-pyrrolidin-2-yl)-5-fluoro-2-methyl-1*H*-indole 2.22c. The optimal procedure was followed by using 0.030 g of styryl azide **2.20c** (0.077 mmol), 0.003 g of $Rh_2(esp)_2$ (0.004 mmol) in 3mL of anhydrous benzene. The crude was purified by MPLC (5:100 – 20:100 EtOAc:hexane) to afford the product as a white solid (0.022 g, 81%). mp 134 – 136 °C. ^{1}H NMR (500 MHz, acetone-d_6) δ 9.96 (s, 1H), 7.59 (d, J = 7.0 Hz, 2H), 7.45 (t, J = 7.5 Hz, 1H), 7.35 (t, J = 7.5 Hz, 2H), 7.17 (dd, J = 8.5 Hz,

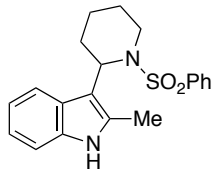
4.0 Hz, 1H), 7.01 (dd, J = 10.0 Hz, 2.0 Hz, 1H), 6.73 (t, J = 9.5 Hz, 1H), 4.96 (t, J = 7.5 Hz, 1H), 3.75 – 3.66 (m, 2H), 2.45 (s, 3H), 2.14 – 2.09 (m, 2H), 2.05 – 2.00 (m, 1H), 1.68 – 1.65 (m, 1H); ^{13}C NMR (125 MHz, acetone-d_6) δ 157.2 (d, J_{CF} = 228 Hz, C), 139.2 (C), 134.9 (C), 132.3 (C), 131.9 (CH), 128.4 (CH), 127.2 (C), 126.9 (CH), 111.5 (C), 111.0 (d, J_{CF} = 9.1 Hz, CH), 107.8 (d, J_{CF} = 25.7 Hz, CH), 103.3 (d, J_{CF} = 23.9 Hz, CH), 56.8 (CH), 49.4 (CH_2), 33.8 (CH_2), 25.0 (CH_2), 11.2 (CH_3). ^{19}F NMR (282 MHz, $CDCl_3$) δ –125.6. ATR-FTIR (thin film): 3369, 2978, 2877, 1580, 1482, 1448, 1326, 1153, 1088 cm^{-1}. HRMS (EI) m/z calculated for $C_{19}H_{19}FN_2O_2S$ $(M)^+$: 358.11513, found: 358.11438.



2.22d

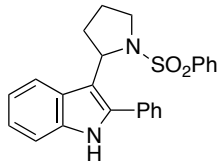
3-(1-Benzenesulfonyl-pyrrolidin-2-yl)-2-methyl-6-trifluoromethyl-1*H*-indole 2.22d. The optimal procedure was followed by using 0.030 g of styryl azide **2.20d** (0.069 mmol), 0.0026 g of $Rh_2(esp)_2$ (0.0034 mmol) in 1.5 mL of anhydrous benzene. The product was purified by MPLC (5:100 – 20:100 EtOAc:hexane) to afford the product as a white solid (0.021 g, 75%). mp 156 – 158 °C; ^{1}H NMR (500 MHz, acetone-d_6) 10.35 (br s, 1H), 7.59 – 7.53 (m, 4H), 7.43 (t, J = 7.5 Hz, 1H), 7.33 (t, J = 7.5 Hz, 2H), 7.12 (d, J = 8.5 Hz, 1H), 5.00 (t, J = 7.5 Hz, 1H), 3.79 – 3.75 (m, 1H), 3.73 – 3.68 (m, 1H), 2.50 (s, 3H), 2.28 – 2.14 (m, 2H), 2.04 – 2.00 (m, 1H), 1.72 – 1.68 (m, 1H); ^{13}C NMR (125 MHz, acetone-d_6) δ 139.1 (C), 136.4 (C), 134.6 (C), 131.9 (CH), 129.3 (C), 128.5 (CH), 126.9 (CH), 124.7 (q, J = 268 Hz, C), 121.5 (q, J = 31.1 Hz, C), 118.9 (CH), 115.0 (CH), 112.0 (C), 107.7 (q, J = 4.3 Hz, CH), 56.7 (CH), 49.4 (CH_2), 34.0 (CH_2), 25.0 (CH_2), 11.2 (CH_3); ^{19}F

NMR (282 MHz, $CDCl_3$) δ –55.88. ATR-FTIR (thin film): 3382, 2948, 2873, 1509, 1472, 1441, 1326, 1282, 1213, 1153, 1142, 1088, 1065, 1014, 918 cm^{-1}. HRMS (EI) *m/z* calculated for $C_{20}H_{19}F_3N_2O_2S$ $(M)^+$: 408.11194, found: 408.11224.



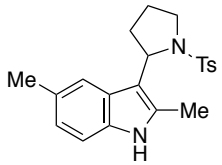
2.22e

2-Methyl-3-(1-(phenylsulfonyl)piperidin-2-yl)-1*H*-indole 2.22e. The general procedure was followed by using 0.0256 g of styryl azide ***E*-2.20e** (0.067 mmol), 0.0025 g of $Rh_2(esp)_2$ in 1.3 mL of anhydrous benzene. The product was purified by MPLC (5:100 – 20:100 EtOAc:hexane) to afford yellow solid product (0.014 g, 58%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.66 (s, 1H), 7.35 (d, *J*= 8.0 Hz, 1H), 7.30 (d, *J*= 8.3 Hz, 2H), 7.12 (t, *J*= 7.4 Hz, 1H), 7.04 (d, *J*= 8.1 Hz, 1H), 7.01 (t, *J*= 7.8 Hz, 2H), 6.95 (t, *J*= 7.6 Hz, 1H), 6.86 (t, *J*= 7.1 Hz, 1H), 4.56 (dd, *J*= 10.0, 3.9 Hz, 1H), 4.02 (td, *J*= 6.2, 4.4 Hz, 1H), 3.22 (ddd, *J*= 12.5, 9.3, 3.3 Hz, 1H), 2.40 (s, 3H), 2.33 – 2.25 (m, 1H), 1.84-1.81 (m, 2H), 1.72 (dd, *J*= 9.2, 5.0 Hz, 2H), 1.50 – 1.44 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.7 (C), 134.8 (C), 133.0 (C), 131.1 (CH), 127.6 (CH), 127.3 (C), 126.7 (CH), 120.7 (CH), 119.8 (CH), 119.1 (CH), 110.9 (C), 110.0 (CH), 55.1 (CH), 46.1 (CH_2), 31.7 (CH_2), 25.2 (CH_2), 23.2 (CH_2), 12.7 (CH_3). ATR-FTIR (thin film): 3382, 2924, 2857, 1445, 1298, 1150 cm^{-1}. HRMS (EI) *m/z* calculated for $C_{20}H_{22}N_2O_2S$ $(M)^+$: 354.14020, found: 354.13959.



2.22f

3-(1-Benzenesulfonyl-pyrrolidin-2-yl)-2-phenyl-1*H*-indole 2.22f. The optimal procedure was followed by using 0.0180 g of styryl azide **2.20f** (0.041 mmol), 0.0016 g of $Rh_2(esp)_2$ (0.002 mmol) in 1.5 mL of anhydrous benzene. The product was purified by MPLC (5:100 – 20:100 EtOAc:hexane) to afford the product as a white solid (0.0094 g, 56%). mp 158 – 160 °C; ^{1}H NMR (500 MHz, acetone-d_6) δ 10.28 (s, 1H) 7.65 (d, J = 7.0 Hz, 3H), 7.55 (t, J = 7.5 Hz, 2H), 7.51 – 7.43 (m, 2H), 7.38 – 7.33 (m, 3H), 7.26 (t, J = 8.0 Hz, 2H), 7.09 (t, J = 7.5 Hz, 1H), 6.97 (t, J = 7.5 Hz, 1H), 4.88 (t, J = 7.5 Hz, 1H), 3.76 – 3.71 (m, 2H), 2.31 – 2.25 (m, 2H), 1.53 – 1.50 (m, 2H); ^{13}C NMR (125 MHz, acetone-d_6) δ 137.8 (C), 136.8 (C), 135.9 (C), 133.3 (C), 132.0 (CH), 129.2 (CH), 128.6 (CH), 128.5 (CH), 127.8 (CH), 127.3 (CH), 126.6 (C), 121.5 (CH), 120.0 (CH), 118.9 (CH), 113.0 (C), 111.2 (CH), 57.2 (CH), 50.1 (CH_2), 34.8 (CH_2), 24.9 (CH_2); ATR-FTIR (thin film): 3358, 3053, 2971, 1699, 1452, 1340, 1248, 1163 cm^{-1}. HRMS (EI) m/z calculated for $C_{24}H_{22}N_2O_2S$ $(M)^+$: 402.14020, found: 402.14081.



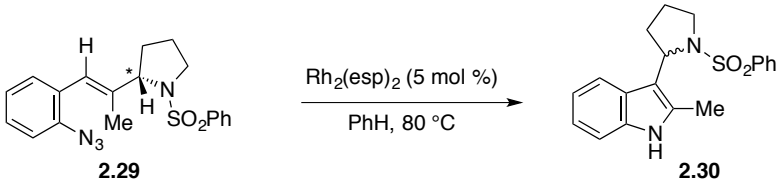
2.36

2,5-Dimethyl-3-[1-(toluene-4-sulfonyl)-pyrrolidin-2-yl]-1*H*-indole 2.36. The optimal procedure was followed by using 0.030 g of styryl azide **2.35** (0.076 mmol), 0.0028 g of

$Rh_2(esp)_2$ (0.0037 mmol) in 1.5 mL of anhydrous benzene. The product was purified by MPLC (5:100 – 20:100 EtOAc:hexane) to afford the product as a white solid (0.0023 g, 78%). ^{1}H NMR (500 MHz, acetone-d_6) δ 9.7 (s, 1H), 7.40 (d, J = 7.5 Hz, 2H), 7.09 – 7.03 (m, 4H), 6.77 – 6.76 (s, 1H), 4.95 (t, J = 7.5 Hz, 1H), 3.76 – 3.72 (m, 1H), 3.66 – 3.62 (m, 1H), 2.42 (s, 3H), 2.29 (s, 3H), 2.28 (s, 3H), 2.17 – 2.07 (m, 2H), 1.99 – 1.95 (m, 1H), 1.71 – 1.64 (m, 1H); ^{13}C NMR (125 MHz, acetone-d_6) δ 142.2 (C), 136.5 (C), 134.1 (C), 132.7 (C), 131.7 (C), 128.8 (CH), 128.3 (C), 126.8 (CH), 121.5 (CH), 118.3 (CH), 110.5 (C), 110.0 (CH), 56.9 (CH), 49.3 (CH_2), 33.8 (CH_2), 29.4 (CH_3), 25.0 (CH_2), 20.4 (CH_3), 11.1 (CH_3). ATR-FTIR (thin film): 3375, 2920, 2849, 1686.1593, 1329, 1157, 1088, 994, 804 cm^{-1}. HRMS (EI) m/z calculated for $C_{21}H_{24}N_2O_2S$ $(M)^+$: 368.15585, found: 368.15573.

2.8.4 Mechanistic experiments.

A. Examination of the stereochemistry of the [1,2] aminomethylene migration.

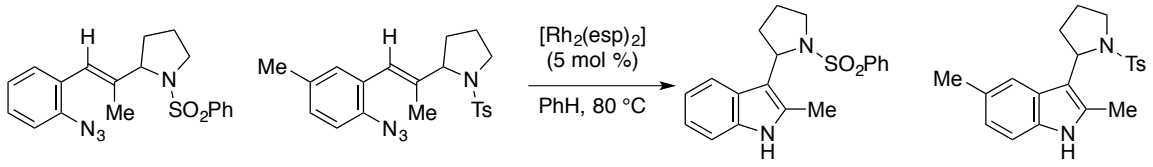


2.29 **2.30**

Under an N_2-atmosphere, a dry vial was charged with 0.028 g of optically active styryl azide **2.29** (0.076 mmol, $[\alpha]_D^{20}$ = –19.6° c 0.125, CH_2Cl_2) and 0.003 g of $Rh_2(esp)_2$ (0.004 mmol) and 1.5 mL of anhydrous benzene. The vial was sealed, and the resulting mixture was heated to 80 °C. After 16 h, the reaction mixture was cooled to room temperature and the volatiles were removed *in vacuo*. The resulting residue was purified by MPLC

(5:100 – 20:100 EtOAc:hexane) to afford **2.30** as yellow solid (0.021 g, 83%). The rotation of the product was measured to be $[\alpha]_D^{20} = 0.0°$ (*c* 0.125, CH_2Cl_2).

B. Double crossover experiment.



2.20a + **2.35** → **2.22a** + **2.36**

Under an N_2 atmosphere, a vial was charged with 0.016 g of **2.20a** (0.042 mmol) and 0.017 g of **2.35** (0042 mmol) and 0.0016 g of $Rh_2(esp)_2$ (0.002 mmol). To the resulting mixture was added 2 mL of anhydrous benzene. The mixture was heated at 80 °C. After 16 h, the reaction mixture was cooled to room temperature. The volatiles were removed *in vacuo* and the resulting residue was purified by MPLC (10:100 – 25:75 EtOAc:hexane) afforded only indoles **2.20a** and **2.35**. No cross over product was observed.

2.8.5. References.

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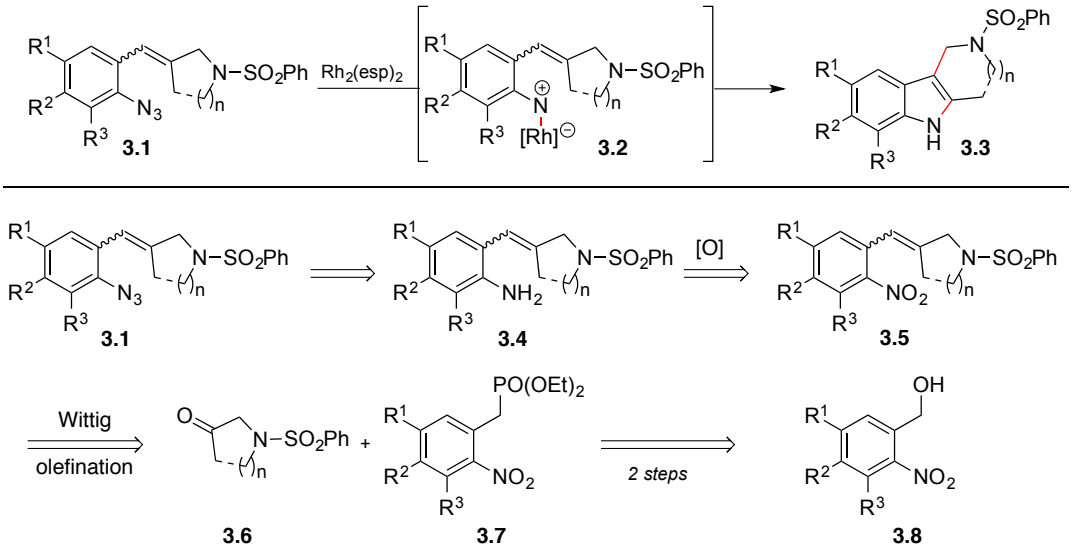
Chapter-III

Efficient Synthesis of 2,3-Disubstituted Indole Heterocycles by a Suzuki Cross-Coupling Reaction Followed by C–H Bond Amination

(The structure of this chapter followed the published review article: Development of a Suzuki cross-coupling reaction between 2-azidoarylboronic pinacolate esters and vinyl triflates to enable synthesis of [2,3] fused indole heterocycles. Jana, N.; Nguyen, Q.; Driver, T. G. *J. Org. Chem.* **2014**, *79*, 2781.)

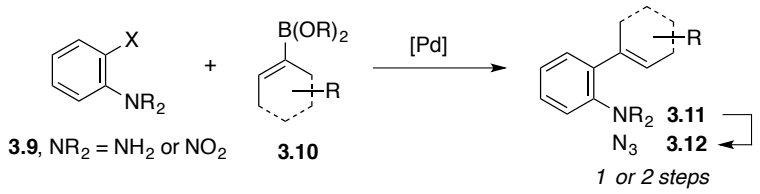
Indole derivatives are important class of molecules present in array of bioactive molecules to natural products.[1-5] The interesting biological activity of indoles led us to construct these heterocyclic scaffolds in a cost-effective way. Our group research is focused on accessing these heterocyclic indole by Rh(II)-catalyzed electrocyclization or C–H bond amination starting from styryl azides.[6-9] We have synthesized a wide range of indole heterocycles using our method, however the preparation of the starting styryl azide sometimes needs a number of steps.[10-12] As a result, the overall synthetic efficiency is reduced for our transformation.[13] For example, in a previous project,[14] we demonstrated that β,β'-disubstituted styryl azide could **3.1** undergo a electrocyclization followed by domino 1,2-migration to provide 2,3-disubstituted indole **3.3**. While the reactivity embedded in styryl azide **3.1** is interesting and appears to simplify access to this indole scaffold, our method is limited by the number of steps required to construct the starting azide (Scheme 3.1). The retrosynthetic scheme to access styryl azide is shown below. We have synthesized our starting styryl azide **3.1** from corresponding nitroarene **3.5** using a two-step procedure: oxidation of nitroarene **3.5** to aryl aniline **3.4** followed by diazotization of aniline to azide. The nitrostyrene **3.5** was obtained by a Wittig reaction between ketone **3.6** and benzyl phosphonate ester **3.7**, which was prepared in two-steps

from commercially available benzyl alcohol **3.8**: conversion of alcohol to a halide followed by the Arbuzov reaction to install phosphonate ester. The overall process involves five-steps to synthesize our starting styryl azides.



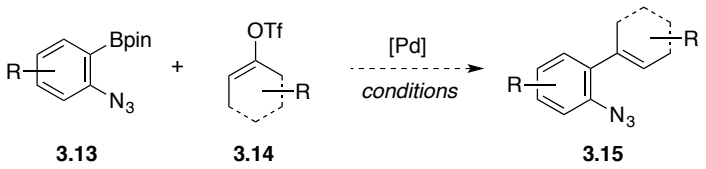
Scheme 3.1. Domino electrocyclization – migration reaction to access 2, 3-disubstituted indoles underscore the challenges in preparing the starting styryl azides

In attempt to reduce the number of steps to prepare our starting styryl azide, our group has used a Suzuki cross-coupling reaction between 2-nitro/amino-aryl halide **3.9** and vinylboronic acid **3.10** to install *ortho*-styryl moiety **3.11** (Scheme 3.2).[15] Conversion of nitro/amino group to azide group requires one- or two- more steps. This sequence of reaction more efficiently prepares the requisite styryl azides than the previous example and only requires two- to three-steps to generate the styryl azide.



Scheme 3.2. Previous strategies to prepare aryl azides

To further improve construction of the styryl azide, we envisioned a one-step Suzuki cross-coupling reaction between *ortho*-azido aryl boronates **3.13** with vinyl triflates **3.14** (Scheme 3.3). We chose *ortho*-azido aryl boronates because of its ease of access by diazotization of commercially available *ortho*- amino aryl boronates **3.9**.[16-17] On the other hand, vinyl triflate **3.10** could be prepared from corresponding ketone in one step.[18-21] Although azides are ubiquitous, there is still no report that uses cross-coupling reaction of *ortho*-azido aryl boronates.[22-23] To address the gap, we demonstrated a cross coupling reaction between *ortho*-azido aryl boronates and a vinyl triflate to enable a more moduler synthesis of styryl azides.



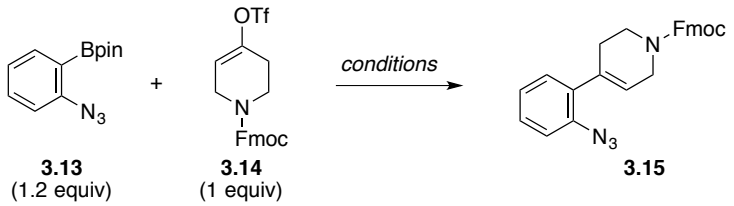
Scheme 3.3. New strategy to construct styryl azides

3.1. Optimization of reaction conditions:

At the outset of our study, we choose *ortho*-azido aryl boronates **3.16**, which could be prepared in gram scale from *ortho*-amino aryl boronates by diazotization (Table 3.1). The other cross-coupling reaction partner, vinyl triflate **3.17** was derived from Fmoc-

protected 4-piperidinone in order to find a functional group tolerant optimal condition. Our initial screen revealed that 10 mol % of $Pd(PPh_3)_4$, equivalent amount of Na_2CO_3 in 1,2-DME solvent at 100 °C provided the desired product **3.18** in 72% yield (entry 1, Table 1). Screening of different bases in presence of 10 mol % of $Pd(PPh_3)_4$ did not improve the yield significantly (entries 2-4). We were then curious if the ligand on palladium would have any effect on reaction outcome. Interestingly, Fu and coworkers' reaction condition, combination of 3 mol % of $Pd(OAc)_2$ and 10 mol % of PCy_3 provides improved yield (83%) at room temperature (entry 5).[24-25] A brief survey of other palladium catalyst revealed that $PdCl_2(PPh_3)_2$ could provide similar yield in comparison with Fu's reaction conditions (entry 6). Next, the identity of the base was examined, and switching from Na_2CO_3 to $NaHCO_3$ resulted increase in the yield (99%, entry 7). In contrast, a decrease in the reaction temperature from 80 °C to 70°C, however resulted in reduced yield (entry 8). To our delight, lowering catalyst loading at 80 °C from 10 mol % to 1 mol %, did not decrease the yield significantly (entries 9-11).

Table 3.1. Survey of reaction conditions for Suzuki Cross-Coupling Reaction between **3.13** and **3.14**



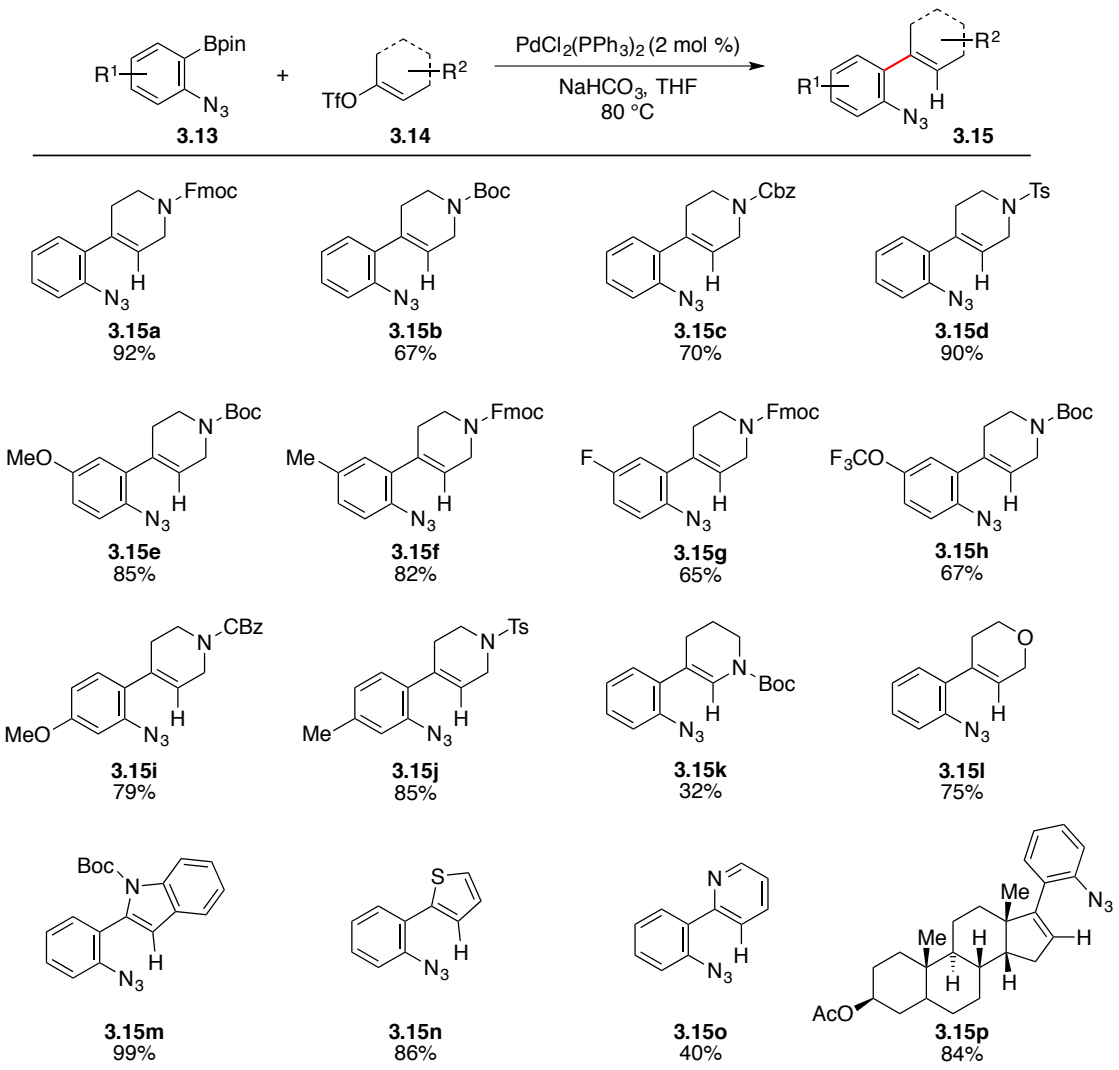
3.13 (1.2 equiv) **3.14** (1 equiv) **3.15**

entry	catalyst	mol %	Base	solvent	T (°C)	%, yield[a]
1	$Pd(PPh_3)_4$	10	Na_2CO_3	DME	100	72
2	$Pd(PPh_3)_4$	10	$NaHCO_3$	DME	100	74
3	$Pd(PPh_3)_4$	10	K_2CO_3	DME	100	60
4	$Pd(PPh_3)_4$	10	Et_3N	DME	100	37
5[b]	$Pd(OAc)_2 + PCy_3$	3	KF	THF	25	83
6	$PdCl_2(PPh_3)_2$	10	Na_2CO_3	THF	80	83
7	$PdCl_2(PPh_3)_2$	10	$NaHCO_3$	THF	80	99
8	$PdCl_2(PPh_3)_2$	10	$NaHCO_3$	THF	70	90
9	$PdCl_2(PPh_3)_2$	5	$NaHCO_3$	THF	80	96
10	$PdCl_2(PPh_3)_2$	2	$NaHCO_3$	THF	80	92
11	$PdCl_2(PPh_3)_2$	1	$NaHCO_3$	THF	80	94

[a] as determined using ^1H NMR spectroscopy using CH_2Br_2 as the internal standard. [b] 10 mol % PCy_3 has been used.

3.2. Scope and limitation of Suzuki cross-coupling reaction:

To demonstrate the scope and limitation of the Suzuki cross-coupling reaction, a variety of aryl azides and vinyl triflates were surveyed (Scheme 3.4). First, the identity of *N*-preotecting group on vinyl triflate was examined and a series of differentially *N*-protected vinyl triflates were converted to styryl azides with good to excellent yield (**3.15a – 3.15d**). Second, the substituent on the 2-azidoarylboron pinacolate ester was changed to see the reaction outcome. We observed that while ethereal- and methyl-substituent on arene moiety were tolerated, the yield was reduced in presence of fluorinated substituents (**3.15e – 3.15j**). Changing nitrogen-atom position in the vinyl triflate species had a deleterious effect in the cross coupling reaction: when the nitrogen-atom was was in conjugation with the olefin, the yield of the cross-coupling reaction was reduced to 32% (**3.15k**). When the heteroatom at 4-position relative to triflate was replaced by oxygen atom, the reaction proceeds smoothly (**3.15l**). Next, we surveyed the effect of placing heterocycles at *ortho*-position relative to azide: while indole- and thiophene-derived triflates undergo smooth reaction, pyridine-derived triflate resulted in low yield of the cross-coupling reaction processes (**3.15m – 3.15o**). Finally, we showed that our cross-coupling reaction contitions could work on complex substrates by converting 5,6-dehydroandrosterone-derived vinyl triflate to aryl azide **3.15p** in 84% yield.

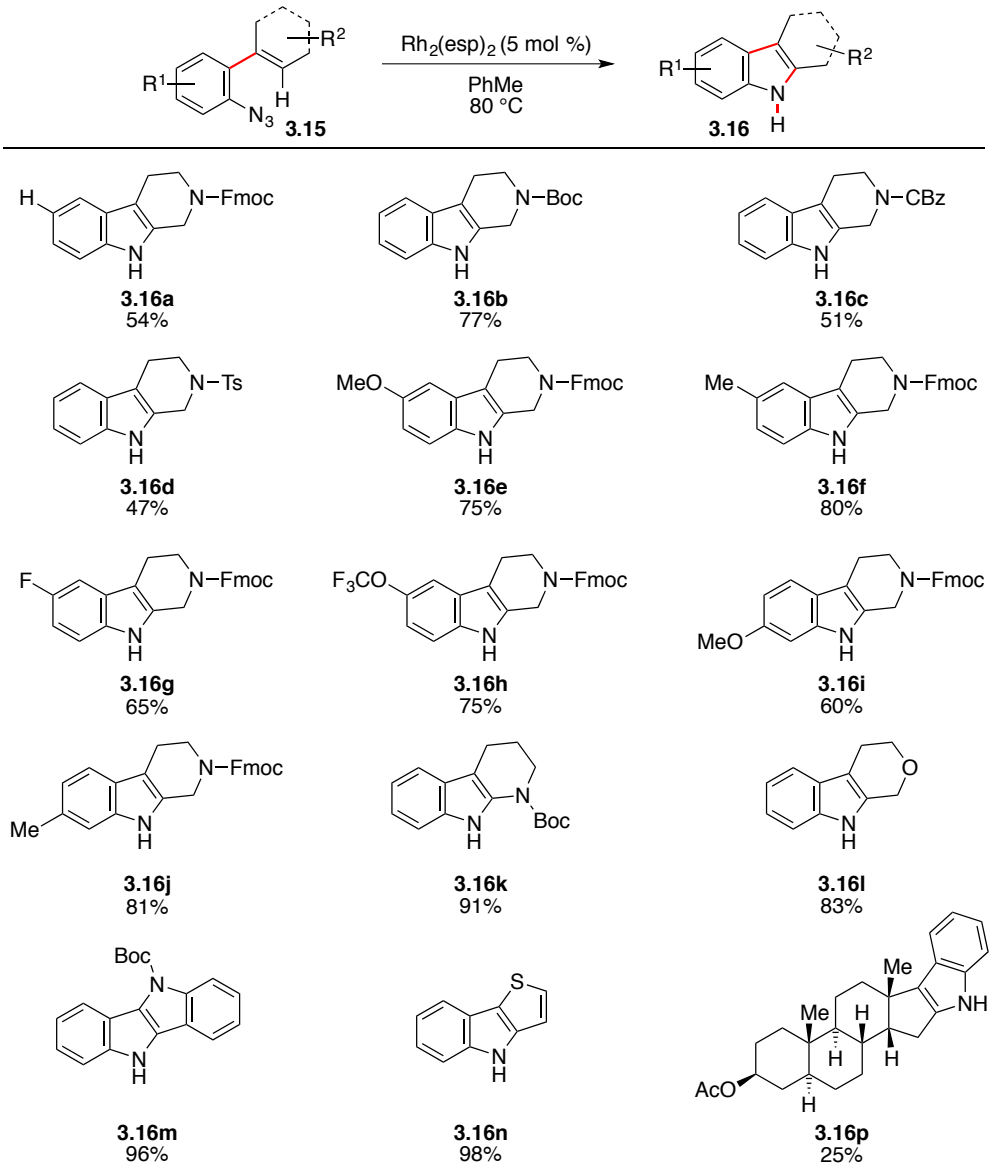


Scheme 3.4. Substrate scope for the Suzuki cross-coupling reaction

3.3. Conversion of *ortho*-substituted styryl azide to indole using $Rh_2(esp)_2$.

The synthetic utility of our cross-coupling reaction was illustrated by converting the product styryl azides into indoles using the Rh_2(II)-catalyzed methods developed in our laboratories (Scheme 6).[26-29] We chose Du Bois's $Rh_2(esp)_2$ as a catalyst to trigger this transformation because of its thermal stability.[30-31] First, the effect of *N*-substituent on the amination reaction was explored. Out of several *N*-protecting group that were screened, Boc-protected nitrogen substituent provided the best result (**3.16a – 3.16d**). Second, we

changed the electronic nature of the aryl azides and found that the reaction outcome did not depends on the electronic nature of the substituents—both electron releasing and donating substituents tolerates well to produce tetrahydrocarbolines (**3.16e – 3.16h**). Gratifyingly, we could trigger 5-substituted styryl azides to produce 6-substituted indoles which cannot be prepared by Fischer-indole synthesis as single regioisomers (**3.16i – 3.169j**).[32-33] In contrast to our Suzuki cross-coupling reaction, indole formation proceeded smoothly when the nitrogen-atom position was moved to conjugation with olefin (**3.16k**). Pyran-, indole- and thiophene derived styryl azides were converted to indoles with excellent yield (**3.16l – 3.16n**). Finally, we have shown that the complex styryl azide **3.15p** could be converted to indole **3.16p**, although in reduced yield.



Scheme 3.5. Substrate scope for the amination reaction

3.4. Conclusion

In conclusion, we developed a mild Suzuki cross-coupling reaction between 2-azidoarylboron pinacolate and vinyl triflate to generate styryl azide. We have achieved cross-coupling reaction of substrate containing azide functional group being present which is sparse. The strength of our cross-coupling reaction was demonstrated by

preparing several *ortho*-azido substituted styryl azides with few limitations—pipiridine-3-one and pyridine-2(1*H*)-one derived triflate resulted in poor yield. Finally, the styryl azides were successfully converted to complex indole heterocycles after exposure of $Rh_2(esp)_2$ catalyst.

3.5: Experimental section

(This part was taken from supporting information of my published paper: Jana, N.; Nguyen, Q.; Driver, T. G. *J. Org. Chem.* 2014, *79*, 2781.)

3.5.1: General.

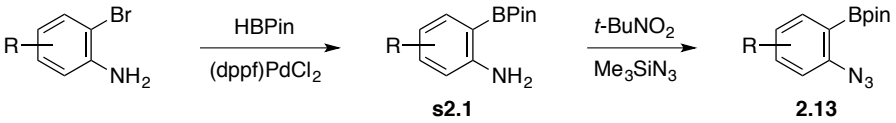
^{1}H NMR and ^{13}C NMR spectra were recorded at ambient temperature using 500 MHz or 300 MHz spectrometers. The data are reported as follows: chemical shift in ppm from internal tetramethylsilane on the δ scale, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet),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

appropriate, purified prior to use. Acetonitrile, Methanol, Toluene, THF, Et_2O, and CH_2Cl_2 were dried by filtration through alumina according to the procedure of Grubbs.[34] Metal salts were stored in a nitrogen atmosphere dry box.

3.5.2. Synthesis of 2-azidoarylboronic acid pinacolate esters.

A. Substrate synthesis overview.

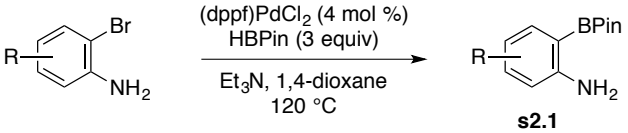
The 2-azidoarylboronic acid pinacolate ester reagents were constructed from substituted 2-bromoanilines following the process outlined in Scheme s1. Palladium-catalyzed borylation of substituted 2-bromoanilines was performed following the conditions reported earlier by us.[35] Azidation of **s3.1** using trimethylsilyl azide following the conditions reported by Zhang and Moses produced the requisite 2-azidoarylboronic pinacolate ester **3.15** for our method development.[17]



Scheme s3.1. Synthesis of 2-azidoarylboronic pinacolate ester reagents

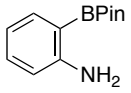
B. Synthesis of 2-aminoarylboronic acid pinacolate Esters.

1. General procedure.



To a mixture of 1.0 g of 2-bromoaniline (5.8 mmol), 3.22 mL of Et_3N (23.2 mmol), 0.208 g of (dppf)$PdCl_2$ (0.25 mmol) in 20 mL of 1,4-dioxane, was added dropwise 2.53 mL of 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (17.4 mmol). The resultant mixture was refluxed at 120 °C. After 12h, the mixture was cooled to room temperature and diluted with 20 mL of NH_4Cl. The resulting aqueous phase was extracted with an additional 2 × 20 mL of CH_2Cl_2. The combined organic phases were washed with 1 × 30 mL of brine. The resulting organic phase was dried over Na_2SO_4, filtered, and the filtrate was concentrated *in vacuo*. Purification via MPLC afforded the product.

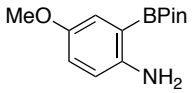
2. Characterization data for 2-aminoarylboronic acid pinacolate esters.



s3.1a

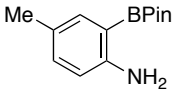
Aniline s3.1a.[35] The general procedure was followed using 3.40 g of 2-bromoaniline (20.0 mmol), 8.7 mL of 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (60.0 mmol), 0.816 g of (dppf)$PdCl_2$ (1.0 mmol), and 8.4 mL of Et_3N (80.0 mmol) in 100 mL of 1, 4-dioxane. Purification by MPLC (2:100 – 10:90 EtOAc: hexanes) afforded the product as a light yellow solid (3.02 g, 69%): mp 62 – 64 °C; the spectral data matched that reported by Driver and co-workers and this compound is also available commercially.[35] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (d, J = 7.5 Hz, 1H), 7.24 (t, J = 7.0 Hz, 1H), 6.70 (t, J = 7.0 Hz, 1H), 6.61 (d, J = 8.5 Hz, 1H), 4.76 (s, 2H), 1.36 (s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.7 (C), 136.8 (CH), 132.8 (CH), 116.9 (CH), 114.8 (CH), 83.5 (C), 25.0 (CH_3) only

visible peaks; IR (thin film): 3486, 3380, 1624, 1605,1352, 1311, 1244, 1135, 1086, 847, 758, 654 cm^{-1}.



s3.1b

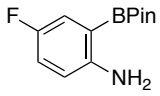
Aniline s3.1b.[15] The general procedure was followed using 0.850 g of 2-bromo-4-methoxyaniline (4.20 mmol), 1.83 mL of 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (12.6 mmol), 0.170 g of (dppf)$PdCl_2$ (0.210 mmol), and 2.34 mL of Et_3N (16.8 mmol) in 42 mL of 1,4-dioxane. Purification by MPLC (2:100 – 10:90 EtOAc: hexanes) afforded the product as a brown liquid (0.670 g, 64%); the spectral data matched that reported by Driver and co-workers:[15] ^1H NMR (500 MHz, $CDCl_3$) δ 7.15 (s, 1H), 6.85 (dd, J = 8.5, 3.0 Hz, 1H), 6.57 (d, J = 8.5 Hz, 1H), 4.47 (s, 2H), 3.76 (s, 3H), 1.34 (s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.4 (C), 148.0 (C), 120.6 (CH), 119.6 (CH), 116.5 (CH), 83.6 (C), 56.0 (CH_3), 25.0 (CH_3) only visible peaks; IR (thin film): 3456, 3366, 1494, 1421, 1359, 1304, 1226, 1037, 855, 829, 750 cm^{-1}.



s3.1c

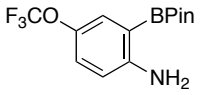
Aniline s3.1c.[36] The general procedure was followed using 0.930 g of 2-bromo-4-methylaniline (5.00 mmol), 2.20 mL of 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (15.0 mmol), 0.204 g of (dppf)$PdCl_2$ (0.25 mmol), and 2.78 mL of Et_3N (20.0 mmol) in 25 mL of 1,4-dioxane. Purification by MPLC (2:100 – 10:90 EtOAc: hexanes) afforded the

product as a light yellow solid (0.490 g, 42%): mp 60 °C; the spectral data matched that reported by Driver and co-workers:[36] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (s, 1H), 7.08 (d, J = 8.0 Hz, 1H), 6.57 (d, J = 8.0 Hz, 1H), 4.65 (s, 2H), 2.26 (s, 3H), 1.38 (s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.5 (C), 136.8 (CH), 133.7 (CH), 125.8 (C), 115.1 (CH), 83.5 (C), 67.1 (C), 25.0 (CH_3), 20.3 (CH_3); IR (thin film): 3500, 2980, 2244, 1618, 1576, 1496 cm^{-1}.



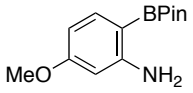
s3.1d

Aniline s3.1d.[14] The general procedure was followed using 0.950 g of 2-bromo-4-fluoroaniline (5.00 mmol), 2.2 mL of 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (15.0 mmol), 0.204 g of (dppf)$PdCl_2$ (0.25 mmol), and 2.78 mL of Et_3N (20.0 mmol) in 25 mL of 1,4-dioxane. Purification by MPLC (2:100 – 10:90 EtOAc: hexanes) afforded the product as a light yellow solid (0.900 g, 76%); the spectral data matched that reported by Driver and co-workers:[14] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (dd, J = 9.0 Hz, 3.0 Hz, 1H), 6.92 (dt, J = 8.5 Hz, 3.0 Hz, 1H), 6.53 (dd, J = 9.0 Hz, 4.5 Hz, 1H), 4.59 (s, 2H), 1.34 (s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.2 (d, J_{CF} = 233.2 Hz, C), 149.8 (C), 121.6 (d, J_{CF} = 20.1 Hz, CH), 119.7 (d, J_{CF} = 23.7 Hz, CH), 116.0 (CH), 83.9 (C), 24.9 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ –129.5; IR (thin film): 3470, 3371, 2975, 2931, 1624, 1492, 1434, 1380, 1347, 1198, 1190, 1135, 1081, 963, 912 cm^{-1}.



s3.1e

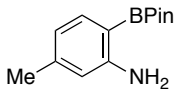
Aniline s3.1e. The general procedure was followed using 1.28 g of 2-bromo-4-trifluoromethoxyaniline (5.00 mmol), 2.20 mL of 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (15.0 mmol), 0.204 g of (dppf)$PdCl_2$ (0.25 mmol), and 2.78 mL of Et_3N (20.0 mmol) in 25 mL of 1,4-dioxane. Purification by MPLC (2:100 – 10:90 EtOAc: hexanes) afforded the product as a light yellow solid (0.970g, 59%): mp 63 – 67 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (s, 1H), 7.06 (d, J = 8.5 Hz, 1H), 6.54 (d, J = 9.0 Hz, 1H), 4.80 (s, 2H), 1.34 (s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.5 (C), 140.0 (C), 129.0 (CH), 126.0 (CH), 122.8 (q, J_{CF} = 253.5 Hz, C), 115.5 (CH), 84.0 (C), 24.9 (CH_3), only visible peaks; IR (thin film): 3477, 3374, 2992, 2980, 1627, 1492, 1436, 1532, 1211, 1163, 1094, 965, 852, 825 cm^{-1}.



s3.1f

Aniline s3.1f. The general procedure was followed using 1.01 g of 2-bromo-5-methoxyaniline (5.00 mmol), 2.20 mL of 4,4,5,5-tetramethyl-1,3,2-dioxaborolane 15.0 mmol), 0.204 g of (dppf)$PdCl_2$ (0.25 mmol), and 2.78 mL of Et_3N (20.0 mmol) in 25 mL of 1,4-dioxane. Purification by MPLC (2:100 – 10:90 EtOAc: hexanes) afforded the product as a light yellow oil (0.632 g, 46%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, J = 8.5 Hz, 1H), 6.27 (dd, J = 8.5 Hz, 2.0 Hz, 1H), 6.11 (d, J = 2.0 Hz, 1H), 4.82 (br s, 2H), 3.75 (s, 3H), 1.34 (s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.7 (C), 155.6 (C), 138.4

(CH), 103.8 (CH), 99.35 (CH), 83.3 (C), 54.9 (CH_3), 24.9 (CH), only visible peaks; IR (thin film): 2976, 2934, 2832, 2101, 1601, 1565, 1345, 1035, 836 cm^{-1}.

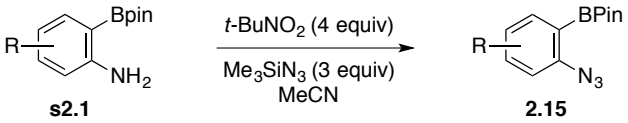


s3.1g

Aniline s3.1g.[37] The general procedure was followed using 0.930 g of 2-bromo-5-methylaniline (5.00 mmol), 2.20 mL of 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (15.0 mmol), 0.204 g of (dppf)$PdCl_2$ (0.25 mmol), and 2.78 mL of Et_3N (20.0 mmol) in 25 mL of 1,4-dioxane. Purification by MPLC (2:100 – 10:90 EtOAc: hexanes) afforded the product as a light yellow solid (0.791 g, 68%): mp 68 °C; the spectral data matched that reported by Marsden, Nelson and co-workers:[37] ^1H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, *J* = 7.5 Hz, 1H), 6.51 (d, *J* = 7.5 Hz, 1H), 6.4 (s, 1H), 4.64 (br s, 2H), 2.26 (s, 3H), 1.34 (s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.7 (C), 143.1 (C), 136.8 (CH), 118.2 (CH), 115.4 (CH), 83.4 (C), 24.9 (CH_3), 21.7 (CH_3), only visible peaks; IR (thin film): 3473, 3370, 2972, 1617, 1563, 1507, 1435, 1357, 1305, 1247, 1143, 1305, 1247, 1143, 1098, 1052, 857 cm^{-1}.

C. Synthesis of 2-azidoarylboronic acid pinacolate esters.

1. General procedure.

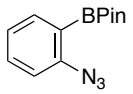


s2.1 **2.15**

To a cooled solution (0 °C) of aniline in MeCN (0.2 M) was added dropwise *t*-$BuNO_2$ (4.0 equiv) and Me_3SiN_3 (3.0 equiv). The resulting solution was warmed to room

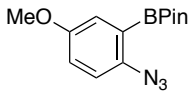
temperature. After 1.5 h, the reaction mixture was concentrated *in vacuo*. Purification of the residue by MPLC (0:100 – 5:95 EtOAc: hexanes) afforded the 2-azidoarylboronic acid pinacolate ester.

2. Characterization data for 2-azidoarylboronic acid pinacolate esters.



3.13a

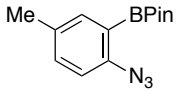
2-Azidophenylboronic acid pinacolate ester 3.13a.[38] The general procedure was followed by using 1.60 g of aniline **s2.1a** (7.30 mmol), 3.47 mL of *t*-$BuNO_2$ (29.2 mmol) and 2.90 mL of Me_3SiN_3 (21.9 mmol) in 36 mL of MeCN. Purification by MPLC (0:100 – 10:90 EtOAc:hexanes) afforded the product, a yellow oil (1.09 g, 61%); the spectral data matched that reported by Driver and co-workers:[38] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.5 Hz, 1H), 7.45 (t, *J* = 7.0 Hz, 1H), 7.15 – 7.10 (m, 2H), 1.36 (s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.8 (C), 137.0 (CH), 132.7 (CH), 124.2 (CH), 118.2 (CH), 84.0 (C), 24.8 (CH_3) only visible signals. ATR-FTIR (thin film): 2976, 2112, 2076, 1594, 1572, 1487, 1432, 1351, 1316, 1279, 1143, 1110, 1058, 1036, 836, 747 cm^{-1}.



3.13b

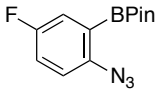
2-Azido-5-methoxyphenylboronic acid pinacolate ester 3.13b. The general procedure was followed by using 0.550 g of aniline **s3.1b** (2.0 mmol), 0.95 mL of *t*-$BuNO_2$ (8.0

mmol) and 0.80 mL of Me_3SiN_3 (6.0 mmol) in 10 mL of MeCN. Purification by MPLC (0:100 – 10:90 EtOAc:hexanes) afforded the product, a yellow solid (0.396 g, 72%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (d, *J* = 2.5 Hz, 1H), 7.07 (d, *J* = 9.0 Hz, 1H), 6.98 (dd, *J* = 8.5 Hz, 3.0 Hz, 1H), 3.81 (s, 3H), 1.36 (s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.3 (C), 137.3 (C), 120.9 (CH), 119.7 (CH), 118.6 (CH), 80.1 (C), 55.6 (CH_3), 24.8 (CH_3) only visible peaks. ATR-FTIR (thin film): 2976, 2934, 2118, 1484, 1409, 1341, 1231, 1143, 1052, 906, 724 cm^{-1}. HRMS (ESI) m/z calculated for $C_{13}H_{18}BN_3O_3Na$ $(M+Na)^+$: 298.1339, found: 298.1345.



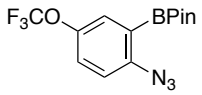
3.13c

2-Azido-5-methylphenylboronic acid pinacolate ester 3.13c. The general procedure was followed by using 0.518 g of aniline **s3.1c** (2.0 mmol), 0.95 mL of *t*-$BuNO_2$ (8.0 mmol) and 0.80 mL of Me_3SiN_3 (6.0 mmol) in 10 mL of MeCN. Purification by MPLC (0:100 – 10:90 EtOAc:hexanes) afforded the product, a orange oil (0.253 g, 49%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, *J* = 1.5 Hz, 1H), 7.26 (dd, *J* = 8.5 Hz, 1.5 Hz, 1H), 7.05 (d, *J* = 8.0 Hz, 1H), 2.31 (s, 3H), 1.36 (s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.1 (C), 137.4 (CH), 133.8 (C), 133.0 (CH), 118.2 (CH), 84.0 (C), 24.8 (CH_3), 20.7 (CH_3) only visible peaks. ATR-FTIR (thin film): 2979, 2924, 2118, 2092, 1579, 1487, 1400, 1345, 1312, 1269, 1146, 906, 730 cm^{-1}. HRMS (ESI) m/z calculated for $C_{13}H_{18}BN_3O_2Na$ $(M+Na)^+$: 282.1390, found: 282.1391.



3.13d

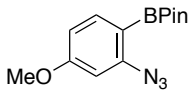
2-Azido-5-fluorophenylboronic acid pinacolate ester 3.13d. The general procedure was followed by using 0.526 g of aniline **s3.1d** (2.0 mmol), 0.95 mL of *t*-$BuNO_2$ (8.0 mmol) and 0.80 mL of Me_3SiN_3 (6.0 mmol) in 10 mL of MeCN. Purification by MPLC (0:100 – 10:90 EtOAc:hexanes) afforded the product, a red oil (0.373 g, 71%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (dd, J = 8.5 Hz, 3.0 Hz, 1H), 7.10 (ddd, J = 10.5 Hz, 7.5 Hz, 3.0 Hz, 1H), 7.05 (dd, J = 8.5 Hz, 4.0 Hz, 1H), 1.34 (s, 12 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.4 (d, J_{CF} = 242.9 Hz, C), 140.5 (C), 123.0 (d, J_{CF} = 20.5 Hz, CH), 119.9 (d, J_{CF} = 7.5 Hz, 1H), 119.1 (d, J_{CF} = 23.5 Hz, CH), 84.3 (C), 24.8 (CH_3), only visible peaks. HRMS (EI) *m/z* calcd for $C_{12}H_{15}BN_3O_2F$ $[M]^{+\cdot}$ 263.1241, found 263.1233. ATR-FTIR (thin film): 2989, 2121, 2092, 1485, 1416, 1319, 1200, 1143, 1126, 966, 916, 807, 763 cm^{-1}.



3.13e

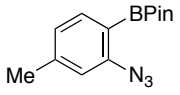
2-Azido-5-trifluoromethoxyphenylboronic acid pinacolate ester 3.13e. The general procedure was followed by using 0.658 g of aniline **s3.1e** (2.0 mmol), 0.95 mL of *t*-$BuNO_2$ (8.0 mmol) and 0.80 mL of Me_3SiN_3 (6.0 mmol) in 10 mL of MeCN. Purification by MPLC (0:100 – 10:90 EtOAc:hexanes) afforded the product, a brown oil 0.467 g, 71%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (s, 1H), 7.27 (d, J = 9.0 Hz, 1H), 7.13 (d, J = 9.0 Hz, 1H), 1.36 (s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.5 (C), 143.5 (C), 129.4

(CH), 124.9 (CH), 120.5 (q, J_{CF} = 255.2 Hz, C), 119.6 (CH), 84.4 (C), 24.7 (CH_3), only visible peaks. HRMS (EI) *m/z* calcd for $C_{13}H_{15}BN_3O_3F_3$ $[M]^{+\cdot}$ 329.1159, found 329.1158. ATR-FTIR (thin film): 2979, 2934, 2125, 2092, 1487, 1416, 1345, 1243, 1214, 1136, 1055, 956, 851 cm^{-1}.



3.13f

2-Azido-4-methoxyphenylboronic acid pinacolate ester 3.13f. The general procedure was followed by using 0.550 g of aniline **s3.1f** (2.0 mmol), 0.95 mL of *t*-$BuNO_2$ (8.0 mmol) and 0.80 mL of Me_3SiN_3 (6.0 mmol) in 10 mL of MeCN. Purification by MPLC (0:100 – 10:90 EtOAc:hexanes) afforded the product, a yellow oil (0.253 g, 46%): ^1H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.5 Hz, 1H), 6.67 (d, *J* = 2.0 Hz, 1H), 6.64 (m, 1H), 3.81 (s, 3H), 1.33 (s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.1 (C), 146.6 (C), 138.8 (CH), 110.0 (CH), 104.3 (CH), 83.7 (C), 55.3 (CH_3), 24.8 (CH_3), only visible peaks . ATR-FTIR (thin film): 2979, 2973, 2101, 1601, 1565, 136, 1228, 1151, 1111, 1035, 837, 649 cm^{-1}. HRMS (ESI) m/z calculated for $C_{13}H_{18}BN_3O_3Na$ $(M+Na)^+$: 298.1339, found: 298.1342.



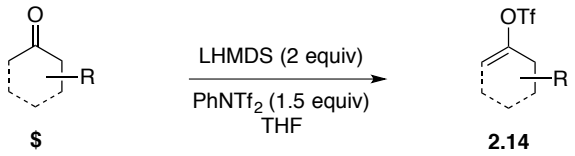
3.13g

2-Azido-4-methylphenylboronic acid pinacolate ester 3.13g. The general procedure was followed by using 0.518 g of aniline **s3.1g** (2.0 mmol), 0.95 mL of *t*-$BuNO_2$ (8.0

mmol) and 0.80 mL of Me_3SiN_3 (6.0 mmol) in 10 mL of MeCN. Purification by MPLC (0:100 – 10:90 EtOAc:hexanes) afforded the product, a orange oil (0.321 g, 62%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (d, *J* = 7.5 Hz, 1H), 6.94 (s, 1H), 6.93 (s, 1H), 2.63 (s, 3H), 1.35 (s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.8 (C), 142.9 (C), 137.1 (CH), 125.3 (CH), 118.8 (CH), 83.8 (C), 24.8 (CH_3), 21.6 (CH_3)). ATR-FTIR (thin film): 2979, 2931, 2102, 1615, 1556, 1341, 1257, 1153, 1120, 1055, 961, 863, 815 cm^{-1}. HRMS (ESI) m/z calculated for $C_{13}H_{18}BN_3O_2Na$ $(M+Na)^+$: 282.1390, found: 282.1394.

3.5.3: Preparation of vinyl triflates 3.14

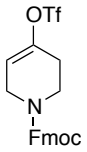
A. General procedure.



$ **2.14**

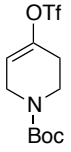
To a cooled solution (–78 °C) of 2.83 g of LHMDS (16.9 mmol, 1.1 equiv) in 75 mL of THF was added the ketone (15.4 mmol, 1 equiv). After addition, the resulting mixture was warmed to room temperature. After 1h, the reaction mixture was cooled to –78 °C, and a solution of 6.60 g of $PhNTf_2$ (18.5 mmol, 1.2 equiv) in 20 mL of THF was added. The solution was stirred for overnight. After 15 h, the reaction mixture was evaporated to dryness. The resulting residue was extracted with 3 × 30 mL of ethyl acetate. The combined organic phases were dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. The resulting residue was purified by MPLC to afford the triflate as colorless oil.

B. Characterization data for Vinyl Triflates 3.14.



3.14a

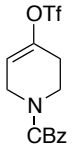
Triflate 3.14a. The general procedure was followed by using 4.95 g of Fmoc-protected 4-piperidinone (15.4 mmol,), 2.83 g LHMDS (16.9 mmol) in 75 mL of THF and 6.60 g of $PhNTf_2$ (18.5 mmol) in 20 mL of THF. Purification by MPLC (0:100 – 10:90 EtOAc:hexanes) afforded the product, a white solid (6.14 g, 88%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, J = 7.5 Hz, 2H), 7.55 (d, J = 7.5 Hz, 2H), 7.41 (t, J = 7.0 Hz, 2H), 7.32 (t, J = 7.5 Hz, 2H), 5.77 – 5.73 (br m, 1H), 4.50 (d, J = 5.5 Hz, 2H), 4.25 (t, J = 6.5 Hz, 1H), 4.12 – 4.00 (m, 2H), 3.68 – 3.56 (m, 2H), 2.44 – 2.34 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.0 (C), 147.1 (C), 143.8 (C), 141.4 (C), 127.9 (CH), 127.2 (CH), 124.9 (CH), 120.1 (CH), 118.5 (q, J_{CF} = 318.9 Hz, CF_3), 115.2 (CH), 67.4 (CH_2), 47.3 (CH), 41.7 (CH_2), 40.4 (CH_2), 27.8 (CH_2). ^{19}F NMR (282 MHz, $CDCl_3$) δ – 74.20. ATR-FTIR (thin film): 3067, 2943, 2355, 2332, 1692, 1417, 1199, 1136, 1121, 1047, 857 cm^{-1}



3.14b

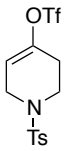
Triflate 3.14b.[39] The general procedure was followed by using 2.00 g of Boc-protected 4-piperidinone (10.03 mmol), 1.847 g LHMDS (11.0 mmol) in 50 mL of THF and 4.29 g of $PhNTf_2$ (12.0 mmol) in 15 mL of THF. Purification by MPLC (0:100 – 10:90

EtOAc:hexanes) afforded the product, a colorless oil (2.76 g, 83%); the spectral data of the product matched that reported by Fürstner and co-workers:[39] ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.75 (br s, 1H), 4.03 (m, 2H), 3.62 (t, J = 6.0 Hz, 2H), 2.42 (m, 2H), 1.46 (s, 9H); ATR-FTIR (thin film): 2982, 2927, 1669, 1491, 1419, 1271, 1246, 1203, 1137, 1065, 1010, 865 cm^{-1}.



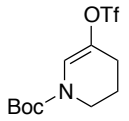
3.14c

Triflate 3.14c.[40] The general procedure was followed by using 0.250 g of Cbz-protected 4-piperidinone (1.07 mmol), 0.197 g LHMDS (1.18 mmol) in 5 mL of THF and 0.459 g of $PhNTf_2$ (1.28 mmol) in 3 mL of THF. Purification by MPLC (0:100 – 10:90 EtOAc:hexanes) afforded the product, a colorless oil (0.297 g, 76%); the spectral data of the product matched that reported by Patel and co-workers:[40] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (m, 5H), 5.78 (br m, 1H), 5.16 (s, 2H), 4.13 (br m, 2H), 3.72 (br m, 2H), 2.46 (br m, 2H); ATR-FTIR (thin film): 3076, 2849, 1698, 1666, 1416, 1236, 1137, 1062, 866, 752 cm^{-1}.



3.14d

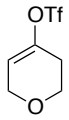
Triflate 3.14d.[41] The general procedure was followed by using 0.253 g of Ts-protected 4-piperidinone (1.0 mmol), 0.184 g LHMDS (1.1 mmol) in 5 mL of THF and 0.428 g of $PhNTf_2$ (1.2 mmol) in 3 mL of THF. Purification by MPLC (0:100 – 10:90 EtOAc:hexanes) afforded the product, a white solid (0.304 g, 79%); the spectral data of the product matched that reported by Dantale and Söderberg:[41] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, J = 8.5 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 5.72 (m, 1H), 3.78 (q, J = 3.0 Hz, 2H), 3.34 (t, J = 6.0 Hz, 2H), 2.47 (m, 2H), 2.43 (s, 3H); ATR-FTIR (thin film): 2963, 2924, 2862, 1698, 1598, 1417, 1340, 1201, 1160, 1068, 934, 862, 815 cm^{-1}.



3.14e

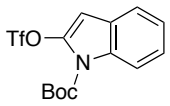
Triflate 3.14e.[42] To a stirred solution of 0.948 mL of diisopropylamine (7.03 mmol) in THF (15 mL) at 0 °C under an atmosphere of argon was added slowly 2.81 mL of n-butyl lithium (2.5 M in hexane, 7.03 mmol). The resulting solution was stirred at 0 °C for 10 min. The solution was then cooled to –78 °C followed by 1.00 g of *N*-Boc-3-piperidone (5.02 mmol) in THF (5 mL) was added dropwise to this solution, and it was stirred at –78 °C for 30 min. N-Phenyl-bis(trifluoromethanesulfonimide) 1.79 g (5.02 mmol) in THF (5 mL) was then added dropwise, and the solution allowed to warm slowly to rt overnight. The volatiles were removed under reduced pressure and purification by MPLC (0:100 – 10:90 EtOAc:hexanes) afforded the product, a brown oil (0.698 g, 44%); the spectral data of the product matched that reported by Wang and co-workers:[42] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (s, 0.30H), 7.06 (s, 0.49 H), 3.52 (br s, 2H), 2.43 (t, J = 6.5 Hz,

2H), 1.92 (quint, J = 6.0 Hz, 2H), 1.49 (s, 9H). ATR-FTIR (thin film): 2982, 2931, 2872, 1710, 1417, 1391, 1352, 1244, 1203, 1160, 910 cm^{-1}.



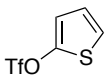
3.14f

Triflate 3.14f.[43] To a stirred solution of 0.760 mL of diisopropylamine (5.49 mmol) in THF (15 mL) at 0 °C under an atmosphere of argon was added slowly 2.19 mL of *n*-butyl lithium (2.5 M in hexane, 5.49 mmol). The resulting solution was stirred at 0 °C for 10 min. The solution was then cooled to –78 °C and tetrahydro-*4H*-pyran-4-one 0.500 g (4.99 mmol) in THF (5 mL) was added dropwise to this solution, and it was stirred at –78 °C for 30 min. N-Phenyl-bis(trifluoromethanesulfonimide) 1.96 g (5.49 mmol) in THF (5 mL) was then added dropwise, and the solution allowed to warm slowly to rt overnight. The volatiles were removed under reduced pressure and purification by MPLC (0:100 – 10:90 EtOAc:hexanes) afforded the product, a brown oil (0.787 g, 68%). The spectral data of the product matched that reported by Hall and co-workers:[43] ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.81 (m, 1H), 4.25 (q, J = 3.0 Hz, 2H), 3.88 (t, J = 5.5 Hz, 2H), 2.45 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.7 (C), 118.5 (q, J = 317.7 Hz, CF_3), 116.9 (CH), 64.2 (CH_2), 63.9 (CH_2), 28.4 (CH_2); ATR-FTIR (thin film): 2943, 2865, 2843, 1692, 1415, 1248, 1201, 1129, 1061, 1007, 868, 840 cm^{-1}.



3.14g

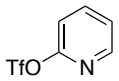
Triflate 3.14g.[44] To a stirred solution of 0.280 g of Boc protected 2-oxindole (1.20 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (0.345 g, 1.68 mmol) in dry dichloroethane (5 mL), Tf_2O (0.26 mL, 1.56 mmol) was added slowly under nitrogen atmosphere at 0 ºC. The reaction mixture was then slowly warmed to room temperature and stirred for 2h. After dilution with Et_2O, the organic layer was washed with NH_4OH and brine, dried over Na_2SO_4 and concentrated under reduced pressure Purification by MPLC (0:100 – 10:90 EtOAc:hexanes) afforded the product, a colorless oil (0.372 g, 85%); this product was reported by Shibata and co-workers:[44] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (d, J = 8.0 Hz, 1H), 7.55 (d, J = 8.0 Hz, 1H), 7.38 (t, J = 7.5 Hz, 1H), 7.28 (t, J = 7.0 Hz, 1H), 6.45 (s, 1H), 1.71 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.2 (C), 138.2 (C), 132.9 (C), 125.6 (CH), 125.1 (C), 123.7 (CH), 121.3 (CH), 118.9 (q, J_{CF} = 319.5 Hz), 115.6 (CH), 98.2 (CH), 86.3 (C), 28.1 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ –72.4; ATR-FTIR (thin film): 2979, 1745, 1594, 1433, 1318, 1212, 1156, 969 cm^{-1}.



3.14h

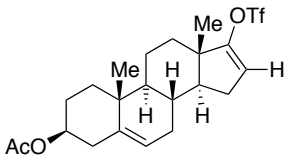
Triflate 3.14h.[45]. Under nitrogen atmosphere, 0.40 g of 2(*5H*)-thiophenone (4.0 mmol), 1.12 g of trifluoromethanesulfonic anhydride (4.00 mmol), 1.40 mL of triethylamine (10.0 mmol) and CH_2Cl_2 (5.8 mL) were placed in a 50 mL round bottom flask. The solution was then stirred at room temperature for 5 h. and concentrated under reduced

pressure. Purification by MPLC (0:100 – 10:90 EtOAc:hexanes) afforded the product, a colorless oil (0.371 g, 40%); the spectral data of the product matched that reported by Tsuchimoto and co-workers:[45] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.05 (dd, J = 6 Hz, 1Hz, 1H), 6.90 (m, 1H), 6.86 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.4 (C), 124.5 (CH), 121.2 (CH), 119.3 (q, J = 319.5 Hz, CF_3), 118.4 (CH); ATR-FTIR (thin film): 3112, 1591, 1542, 1426, 1247, 1206, 1127, 819 cm^{-1}.



3.14i

Triflate 3.14i.[46] To a solution of 1.00 g of 2-hydroxypyridine (10.5 mmol) in dry pyridine (40 mL), was added 2.12 mL of Tf_2O (12.6 mmol) dropwise at 0 °C. The resulting solution was then stirred at room temperature overnight, diluted with water, and extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by MPLC (0:100 – 10:90 EtOAc:hexanes) afforded the product, a colorless oil (1.80 g, 76%); the spectral data of the product matched that reported by Umemoto and Tomizawa:[46] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.40 (d, J = 5.0 Hz, 1H), 7.89 (t, J = 8.0 Hz, 1H), 7.38 (t, J = 7.0 Hz, 1H), 7.17 (d, J = 8.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.9 (C), 148.7 (CH), 141.0 (CH), 124.3 (CH), 118.6 (q, J_{CF} = 319 Hz, C), 115.2 (CH); ATR-FTIR (thin film): 3096, 3076, 1712, 1601, 1417, 1203, 1155, 1131, 880, 795 cm^{-1}.

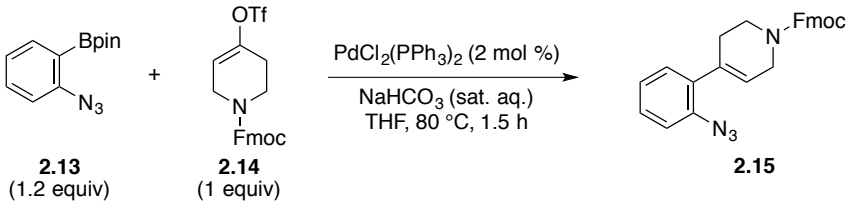


3.14j

Triflate 3.14j.[47].To a stirred solution of 0.500 g of dehydroisoandrosterone 3-acetate (1.51 mmol.) in CH_2Cl_2 (15 mL) was added 0.280 mL of Tf_2O (1.66 mmol) and the reaction was stirred at room temperature for five minutes. A solution of 0.21 mL of triethylamine (1.51 mmol) in 5 mL of CH_2Cl_2 was then added slowly. The resulting solution was stirred at room temperature for 3.5 hours. The reaction was quenched by addition of water and extracted with 2 × 10 mL of CH_2Cl_2 followed by 1 × 10 mL of brine. The resulting organic phase was dried over Na_2SO_4, and was concentrated *in vacuo*. Purification by MPLC (0:100 – 10:90 EtOAc:hexanes) afforded the product, a x oil (0.450 g, 64%); the spectral data of the product matched that reported by RajanBabu and co-workers:[47] ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.58 (s, 1H), 5.39 (s, 1H), 4.60 (m, 1H), 3.46 (br s, 1H), 2.33 – 2.21 (m, 3H), 2.03 (s, 3H), 1.98 (m, 2H), 1.86 (m, 2H), 1.77 (m, 2H), 1.65 (m, 2H), 1.49 (t, J = 8.0 Hz, 2H), 1.25 (t, J = 7.0 Hz, 2H), 1.14 (m, 1H), 1.05 (s, 3H), 0.99 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5 (C), 159.2 (C), 140.2 (C), 121.8 (CH), 118.6 (q, J_{CF} = 317.7 Hz, CF_3), 114.5 (CH), 73.7 (CH), 54.2 (CH), 50.4 (CH), 44.7 (C), 38.1 (CH_2), 36.9 (CH_2), 36.8 (C), 32.7 (CH_2), 30.5 (CH_2), 29.9 (CH_3), 28.6 (CH_2), 27.7 (CH_2), 21.4 (CH), 20.1 (CH_2), 19.2 (CH_3), 15.1 (CH_3). ^{19}F NMR (282 MHz, $CDCl_3$) δ – 74.02.

3.5.4. Synthesis of 2-alkenylaryl azides 11 by Suzuki cross-coupling reaction.

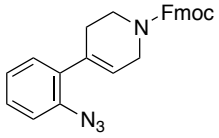
A. Optimal conditions.



2.13 (1.2 equiv) **2.14** (1 equiv) **2.15**

To a mixture of vinyl triflate (0.1 mmol), 2-azidoarylboronic acid pinacolate ester (0.12 mmol) and $PdCl_2(PPh_3)_2$ (2 mol %) in THF (0.1 M) was added saturated solution of $NaHCO_3$ (2 mL/mmol of boronic ester). The resulting solution was heated to reflux. After 1.5 h, the mixture was cooled to room temperature and diluted with 5 mL of cold water. The solution was extracted with 2 × 10 mL of ether followed by 1 × 10 mL of brine. The resulting organic phase was dried over Na_2SO_4, and was concentrated *in vacuo*. Purification by MPLC (3:97 – 20:80 EtOAc:hexane) afforded the product.

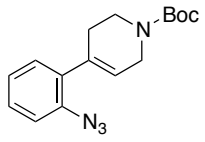
B. Characterization data for 2-Alkenylaryl azides.



3.15a

(9*H*-Fluoren-9-yl)methyl 4-(2-azidophenyl)-5,6-dihydropyridine-1(2*H*)-carboxylate 3.15a. The optimal procedure was followed by using 0.045 g of vinyl triflate **3.14a** (0.099 mmol), 0.029 g of 2-azidophenylboronic acid pinacolate ester **3.13a** (0.12 mmol), 0.0014 g of $PdCl_2(PPh_3)_2$ (2 mol %), 1.0 mL of THF and 0.24 mL of a saturated aqueous solution of $NaHCO_3$. Purification by MPLC (3:97 – 20:80 EtOAc:hexane) afforded the product as a colorless liquid (0.032 g, 92%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, J = 7.5 Hz, 2H), 7.62 (d, J = 7.0 Hz, 2H), 7.44 – 7.41 (m, 2H), 7.36 – 7.32 (m, 4H), 7.18 – 7.13 (m, 2H), 5.74 (br s, 1H), 4.49 (d, J = 6.5 Hz, 2H), 4.30 (t, J = 7.0 Hz, 1H), 4.15 (br s,

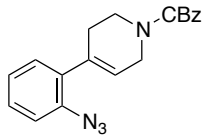
2H), 3.71 (br s, 2H), 2.51 (br s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.1 (C), 141.4 (C), 137.0 (C), 135.2 (C), 134.4 (C), 129.5 (CH), 128.6 (CH), 127.7 (CH), 127.1 (CH), 125.1 (CH), 123.3 (CH), 120.1 (CH), 118.6 (CH), 67.5 (CH_2), 47.4 (CH_2), 43.6 (CH), 40.6 (CH_2), 29.1 (CH_2) only peaks visible. Diagnostic data for minor rotamer: ^{13}C NMR (125 MHz, $CDCl_3$) δ 129.8 (CH), 124.9 (CH), 123.9 (CH). ATR-FTIR (thin film): 3064, 2950, 2125, 2089, 1696, 1678, 1423, 1286, 1228, 1191, 1110, 737 cm^{-1}. HRMS (ESI) m/z calculated for $C_{26}H_{23}N_4O_2$ $(M+H)^+$: 423.1820, found: 423.1821.



3.15b

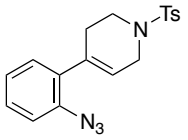
***tert*-Butyl 4-(2-azidophenyl)-5,6-dihydropyridine-1(2*H*)-carboxylate 3.15b.** The optimal procedure was followed by using 0.662 g of vinyl triflate **3.14b** (4.00 mmol), 1.18 g of 2-azidophenylboronic acid pinacolate ester **3.13a** (4.80 mmol), 0.028 g of $PdCl_2(PPh_3)_2$ (2 mol %), 40.0 mL of THF and 9.6 mL of a saturated aqueous solution of $NaHCO_3$. Purification by MPLC (3:97 – 20:80 EtOAc:hexane) afforded the product as a colorless liquid (0.805 g, 67%): ^{1}H NMR (500 MHz, $CDCl_3$) δ ; ^{13}C NMR (125 MHz, $CDCl_3$) δ only peaks visible. Diagnostic data for minor rotamer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (dt, J = 8 Hz, 1.5 Hz, 1H), 7.14 (t, J = 6.0 Hz, 2H), 7.09 (t, J = 7.5 Hz, 1H), 5.70 (br s, 1H), 4.04 (br s, 2H), 3.60 (br s, 2H), 2.46 (br s, 2H), 1.49 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.9 (C), 136.9 (C), 134.6 (C), 129.8 (CH), 128.5 (CH), 127.2 (C), 123.9 (C) 124.8 (CH), 118.6 (CH), 79.7 (C), 43.7 (CH_2), 39.9 (CH_2), 29.4 (CH_2), 28.5 (CH_3). ATR-FTIR (thin film): 2976, 2927, 2120, 2089, 1692, 1484, 1415, 1235, 1112,

750 cm^{-1}. HRMS (ESI) m/z calculated for $C_{16}H_{21}N_4O_2$ $(M+H)^+$: 301.1664, found: 301.1665.



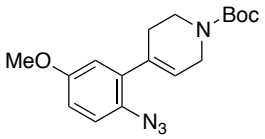
3.15c

Benzyl 4-(2-azidophenyl)-5,6-dihydropyridine-1(2*H*)-carboxylate 3.15c. The optimal procedure was followed by using 0.365 g of vinyl triflate **3.14c** (1.00 mmol), 0.294 g of 2-azidophenylboronic acid pinacolate ester **3.13a** (1.2 mmol), 0.014 g of $PdCl_2(PPh_3)_2$ (2 mol %), 1.0 mL of THF and 0.24 mL of a saturated aqueous solution of $NaHCO_3$. Purification by MPLC (3:97 – 20:80 EtOAc:hexane) afforded the product as a colorless liquid (0.234 g, 70%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.28 (m, 6H), 7.18 – 7.13 (m, 3H), 5.75 – 5.70 (m, 1H), 5.22 (s, 2H), 4.16 (d, *J* = 2.5 Hz, 2H), 3.73 (t, *J* = 5.5 Hz, 2H), 2.52 (br s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.9 (C), 137.0 (C), 135.5 (C), 134.7 (C), 129.5 (CH), 128.6 (CH), 128.2 (CH), 127.0 (CH), 124.9 (CH), 123.7 (C), 123.3 (CH), 121.3 (CH), 118.6 (CH), 67.5 (CH_2), 43.6 (CH_2), 40.6 (CH_2), 29.1 (CH_2). Diagnostic data for minor rotamer: ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.6 (C), 135.2 (C), 129.8 (CH), 128.7 (CH), 128.0 (CH). ATR-FTIR (thin film): 3080, 3028, 2839, 2121, 2092, 1672, 1487, 1428, 1377, 1290, 1234, 1195, 1143, 1110, 951, 747 cm^{-1}. HRMS (ESI) m/z calculated for $C_{19}H_{19}N_4O_2$ $(M+H)^+$: 335.1505, found: 335.1508.



3.15d

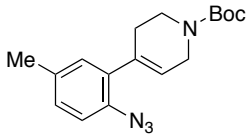
4-(2-Azidophenyl)-1-tosyl-1,2,3,6-tetrahydropyridine 3.15d. The optimal procedure was followed by using 0.0385 g of vinyl triflate **3.15d** (0.099 mmol), 0.029 g of 2-azidophenylboronic acid pinacolate ester **3.13a** (0.12 mmol), 0.0014 g of $PdCl_2(PPh_3)_2$ (2 mol %), 1.0 mL of THF and 0.24 mL of a saturated aqueous solution of $NaHCO_3$. Purification by MPLC (3:97 – 20:80 EtOAc:hexane) afforded the product as a yellow solid (0.0320 g, 90%): mp 106 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.30 – 7.27 (m, 1H), 7.1 (d, *J* = 8.0 Hz, 1H), 7.08 – 7.05 (m, 2H), 5.62 (br s, 1H), 3.75 (d, *J* = 3.0 Hz, 2H), 3.30 (t, *J* = 6.0 Hz, 2H), 2.54 (br s, 2H), 2.44 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.7 (C), 136.9 (C), 135.1 (C), 133.8 (C), 133.3 (C), 129.8 (CH), 128.8 (CH), 127.8 (CH), 124.9 (CH), 123.4 (C), 122.3 (CH), 118.5 (CH), 45.1 (CH_2), 43.0 (CH_2), 29.2 (CH_2), 21.6 (CH_3); ATR-FTIR (thin film): 2924, 2852, 2111, 2075, 1491, 1445, 1338, 1286, 1156, 1094, 919, 814, 730 cm^{-1}. HRMS (ESI) m/z calculated for $C_{18}H_{19}N_4O_2S$ $(M+H)^+$: 355.1226, found: 355.1229.



3.15e

(9*H*-Fluoren-9-yl)methyl 4-(2-azido-5-methoxyphenyl)-5,6-dihydropyridine-1(2*H*)-carboxylate 3.15e. The optimal procedure was followed by using 0.165 g of vinyl triflate **3.14b** (0.500 mmol), 0.166 g of 2-azido-5-methoxyphenylboronic acid pinacolate ester **3.13b** (0.600 mmol), 0.0070 g of $PdCl_2(PPh_3)_2$ (2 mol %), 5.0 mL of THF and 1.20 mL of a saturated aqueous solution of $NaHCO_3$. Purification by MPLC (3:97 – 20:80

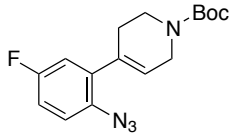
EtOAc:hexane) afforded the product as a yellow liquid (0.140 g, 85%): ^{1}H NMR (500 MHz, $CDCl_3$) δ ; ^{13}C NMR (125 MHz, $CDCl_3$) δ only peaks visible. Diagnostic data for minor rotamer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.00 (d, *J* = 8.5 Hz, 1H), 6.80 (dd, *J* = 8.5 Hz, 3.0 Hz, 1H), 6.67 (d, *J* = 3.0 Hz, 1H), 5.67 (br s, 1H), 4.01 (br s, 2H), 3.75 (s, 3H), 3.57 (t, *J* = 5.0 Hz, 2H), 2.42 (br s, 2H), 1.47 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.8 (C), 154.9 (C), 135.6 (C), 135.1 (C), 129.3 (C), 123.9 (CH), 119.6 (CH), 115.1 (CH), 113.8 (CH), 79.6 (C), 55.5 (CH_3), 43.7 (CH_2), 39.8 (CH_2), 29.2 (CH_2), 28.5 (CH_2). ATR-FTIR (thin film): 2977, 2924, 2827, 2112, 1595, 1484, 1415, 1364, 1284, 1238, 1163, 1109, 1033, 954 cm^{-1}. HRMS (ESI) m/z calculated for $C_{17}H_{23}N_4O_3$ $(M+H)^+$: 331.1770, found: 331.1771.



3.15f

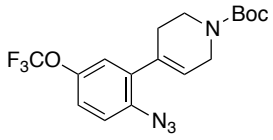
(9*H*-Fluoren-9-yl)methyl 4-(2-azido-5-methylphenyl)-5,6-dihydropyridine-1(2*H*)-carboxylate 3.15f. The optimal procedure was followed by using 0.165 g of vinyl triflate **3.14b** (0.500 mmol), 0.155 g of 2-azido-5-methylphenylboronic acid pinacolate ester **3.13c** (0.600 mmol), 0.0070 g of $PdCl_2(PPh_3)_2$ (2 mol %), 5.0 mL of THF and 1.20 mL of a saturated aqueous solution of $NaHCO_3$. Purification by MPLC (3:97 – 20:80 EtOAc:hexane) afforded the product as a yellow liquid (0.135 g, 82%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.07 (d, *J* = 8.0 Hz, 1H), 7.00 (d, 8.0 Hz, 1H), 6.96 (s, 1H), 5.66 (br m, 1H), 4.02 (d, *J* = 2.0 Hz, 2H), 3.59 (t, *J* = 5.0 Hz, 2H), 2.43 (br m, 2H), 2.29 (s, 3H), 1.48 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.9 (C), 135.3 (C), 134.6 (C), 134.4 (C), 134.4

(C), 130.4 (CH), 129.0 (CH), 123.9 (CH), 118.5 (CH), 79.6 (C), 43.7 (CH_2), 39.8 (CH_2), 29.4 (CH_2), 28.5 (CH_3), 20.7 (CH_3). only peaks visible. ATR-FTIR (thin film): 3080, 3054, 3025, 2918, 2114, 1698, 1603, 1494, 1458, 1170, 1112, 1080 cm^{-1}. HRMS (ESI) m/z calculated for $C_{17}H_{23}N_4O_2$ $(M+H)^+$: 315.1821, found: 315.1821.



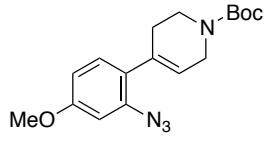
3.15g

(9*H*-Fluoren-9-yl)methyl 4-(2-azido-5-fluorophenyl)-5,6-dihydropyridine-1(2*H*)-carboxylate 3.15g. The optimal procedure was followed by using 0.165 g of vinyl triflate **3.14b** (0.500 mmol), 0.157 g of 2-azido-5-fluorophenylboronic acid pinacolate ester **3.13d** (0.600 mmol), 0.0070 g of $PdCl_2(PPh_3)_2$ (2 mol %), 5.0 mL of THF and 1.20 mL of a saturated aqueous solution of $NaHCO_3$. Purification by MPLC (3:97 – 20:80 EtOAc:hexane) afforded the product as a colorless liquid (0.103 g, 65%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.07 (dd, *J* = 6.0, 5.0 Hz, 1H), 6.99 (dt, *J* = 8.5, 2.5 Hz, 1H), 6.88 (dd, *J* = 9.0, 3.0 Hz, 1H), 5.74 (s, 1H), 4.04 (s, 2H), 3.60 (t, *J* = 5.0 Hz, 2H), 2.44 (s, 2H), 1.49 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.6 (d, J_{CF} = 243.7 Hz, C), 154.9 (C), 136.2 (d, *J* = 7.5 Hz, C), 132.8 (C), 125.2 (CH), 119.9 (d, *J* = 7.8 Hz, CH), 116.5 (d, *J* = 22.2 Hz, CH), 115.1 (d, *J* = 22 Hz, CH), 79.8 (C), 43.5 (CH_2), 39.6 (CH_2), 29.1 (CH_2), 28.5 (CH_3), only visible peaks; ^{19}F NMR (282 MHz, $CDCl_3$).– 118.26. HRMS (ESI) m/z calculated for $C_{16}H_{20}FN_4O_2$ $(M+H)^+$: 319.1571, found: 319.1570.



3.15h

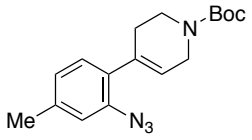
(9*H*-Fluoren-9-yl)methyl 4-(2-azido-5-trifluoromethoxyphenyl)-5,6-dihydropyridine-1(2*H*)-carboxylate 3.15h. The optimal procedure was followed by using 0.165 g of vinyl triflate **3.14b** (0.500 mmol), 0.197 g of 2-azido-5-trifluoromethoxyphenylboronic acid pinacolate ester **3.13e** (0.600 mmol), 0.0070 g of $PdCl_2(PPh_3)_2$ (2 mol %), 5.0 mL of THF and 1.20 mL of a saturated aqueous solution of $NaHCO_3$. Purification by MPLC (3:97 – 20:80 EtOAc:hexane) afforded the product as a brown liquid (0.129 g, 67%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 (dd, J = 8.5, 2.0 Hz, 1H), 7.12 (d, J = 9.0 Hz, 1H), 7.03 (d, J = 1.5 Hz, 1H), 5.74 (s, 1H), 4.05 (s, 2H), 3.60 (t, J = 5.0 Hz, 2H), 2.45 (s, 2H), 1.49 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.8 (C), 145.8 (C), 136.0 (C), 135.7 (C), 125.1 (C), , 122.5 (CH), 120.9 (CH), 120.4 (q, J_{CF} = 255.2 Hz, C), 119.7 (CH), , 79.8 (C), 43.8 (CH_2), 39.6 (CH_2), 29.1 (CH_2), 28.5 (CH_3), only visible peaks; ATR-FTIR (thin film): 3025, 2918, 2119, 1699, 1604, 1494, 1457, 1256, 1218, 1168, 1081, 1029 cm^{-1}. HRMS (ESI) m/z calculated for $C_{17}H_{20}F_3N_4O_3$ $(M+H)^+$: 385.1486, found: 385.1488.



3.15i

(9*H*-Fluoren-9-yl)methyl 4-(2-azido-4-methoxyphenyl)-5,6-dihydropyridine-1(2*H*)-carboxylate 3.15i. The optimal procedure was followed by using 0.165 g of vinyl triflate **3.14b** (0.500 mmol), 0.165 g of 2-azido-4-methoxyphenylboronic acid pinacolate ester

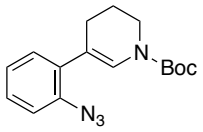
3.13f (0.600 mmol), 0.0070 g of $PdCl_2(PPh_3)_2$ (2 mol %), 5.0 mL of THF and 1.20 mL of a saturated aqueous solution of $NaHCO_3$. Purification by MPLC (3:97 – 20:80 EtOAc:hexane) afforded the product as a yellow liquid with 83% purity(0.158 g, 79%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.10 (d, *J* = 8.5 Hz, 1H), 6.69 (m, 1H), 6.68 (d, *J* = 2.5 Hz, 1H), 5.79 – 5.68 (br m, 1H), 4.06 (d, *J* = 2.0 Hz, 2H), 3.85 (s, 3H), 3.62 (t, *J* = 5.5 Hz, 2H), 2.45 (br s, 2H), 1.52 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.8 (C), 155.0 (C), 137.9 (C), 134.7 (C), 130.6 (CH), 127.4 (C), 123.5 (CH), 110.3 (CH), 104.6 (CH), 79.8 (C), 55.5 (CH_3), 43.8 (CH_2), 39.9 (CH_2), 29.6 (CH_2), 28.6 (CH_3). ATR-FTIR (thin film): 2969, 2927, 2846, 2122, 2090, 1690, 1575, 1485, 1415, 1364, 1289, 1235, 1162, 1112, 750 cm^{-1}. HRMS (ESI) m/z calculated for $C_{17}H_{23}N_4O_3$ $(M+H)^+$: 331.1770, found: 331.1771.



3.15j

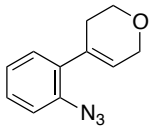
(9*H*-Fluoren-9-yl)methyl 4-(2-azido-4-methylphenyl)-5,6-dihydropyridine-1(2*H*)-carboxylate 3.15j. The optimal procedure was followed by using 0.165 g of vinyl triflate **3.14b** (0.500 mmol), 0.155 g of 2-azido-4-methylphenylboronic acid pinacolate ester **3.13g** (0.600 mmol), 0.0070 g of $PdCl_2(PPh_3)_2$ (2 mol %), 5.0 mL of THF and 1.20 mL of a saturated aqueous solution of $NaHCO_3$. Purification by MPLC (3:97 – 20:80 EtOAc:hexane) afforded the product as a colorless liquid (0.133 g, 85%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.03 (d, *J* = 8.0 Hz, 1H), 6.92 (s, 1H), 6.89 (d, *J* = 7.5 Hz, 1H), 5.66 (br s, 1H), 4.02 (br s, 2H), 3.59 (br s, 2H), 2.44 (br s, 2H), 2.34 (s, 3H), 1.49 (s, 9H); ^{13}C NMR

(125 MHz, $CDCl_3$) δ 154.9 (C), 138.6 (C), 136.6 (C), 135.0 (C), 131.7 (C), 129.6 (CH), 125.7 (CH), 123.5 (CH), 119.1 (CH), 79.6 (C), 53.5 (CH_2), 43.8 (CH_2), 39.8 (CH_2), 28.5 (CH_3), 21.1 (CH_3); ATR-FTIR (thin film): 2972, 2924, 2103, 1691, 1412, 1363, 1292, 1235, 1163, 1110, 1054, 973, 808 cm^{-1}. HRMS (ESI) m/z calculated for $C_{17}H_{23}N_4O_2$ $(M+H)^+$: 315.1821, found: 315.1821.



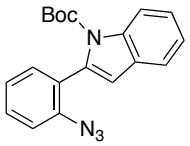
3.15k

***tert*-Butyl 2-(2-azidophenyl)-5,6-dihydropyridine-1(2*H*)-carboxylate 3.15k.** The optimal procedure was followed by using 0.0360 g of vinyl triflate **3.14e** (0.099 mmol), 0.029 g of 2-azidophenylboronic acid pinacolate ester **3.13a** (0.12 mmol), 0.0014 g of $PdCl_2(PPh_3)_2$ (2 mol %), 1.0 mL of THF and 0.24 mL of a saturated aqueous solution of $NaHCO_3$. Purification by MPLC (3:97 – 20:80 EtOAc:hexane) afforded the product as a colorless liquid (0.020 g, 33%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (t, *J* = 8.0 Hz, 1H), 7.21 – 7.19 (m, 1H), 7.15 – 7.11 (m, 2H), 7.08 – 7.06 (m, 0.38H), 6.93 (br s, 0.58H), 3.62 (br s, 2H), 2.40 (t, *J* = 6.0 Hz, 2H), 1.94 (br s, 2H), 1.49 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.3 (C), 133.8 (C) 130.1 (CH), 127.8 (CH), 124.8 (CH), 121.0 (C), 118.7 (CH), 117.8 (CH), 115.0 (C), 80.9 (C), 42.4 (CH_2), 28.4 (CH_3), 26.2 (CH_2), 21.7 (CH_2); ATR-FTIR (thin film): 2924, 2852, 2111, 2075, 1491, 1445, 1338, 1286, 1156, 1094, 919, 814, 730 cm^{-1}. HRMS (ESI) m/z calculated for $C_{16}H_{20}N_4O_2Na$ $(M+Na)^+$: 323.1481, found: 323.1484.



3.15l

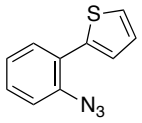
4-(2-Azidophenyl)-3,6-dihydro-2*H*-pyran 3.15l. The optimal procedure was followed by using 0.0230 g of vinyl triflate **3.14f** (0.099 mmol), 0.029 g of 2-azidophenylboronic acid pinacolate ester **3.13a** (0.12 mmol), 0.0014 g of $PdCl_2(PPh_3)_2$ (2 mol %), 1.0 mL of THF and 0.24 mL of a saturated aqueous solution of $NaHCO_3$. Purification by MPLC (3:97 – 20:80 EtOAc:hexane) afforded the product as a yellow solid (0.015 g, 75%): mp 37 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (t, *J* = 6.5 Hz, 1H), 7.18 – 7.11 (m, 3H), 5.79 (br s, 1H), 4.31 – 4.30 (m, 2H), 3.91 (t, *J* = 5.5 Hz, 2H), 2.48 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.0 (C), 134.3 (C), 134.0 (C), 129.7 (CH), 128.5 (CH), 126.0 (CH), 124.9 (CH), 118.6 (CH), 65.6 (CH_2), 64.4 (CH_2), 29.2 (CH_2); ATR-FTIR (thin film): 2957, 2927. 2846, 2817, 2121, 2082, 1575, 1487, 1439, 1380, 1290, 1130, 845, 750 cm^{-1}. HRMS (ESI) m/z calculated for $C_{11}H_{11}N_3O$ $(M)^+$: 201.0900, found: 201.0902.



3.15m

***tert*-Butyl 2-(2-azidophenyl)-1*H*-indole-1-carboxylate 3.15m.** The optimal procedure was followed by using 0.0360 g of vinyl triflate **3.14g** (0.099 mmol), 0.029 g of 2-azidophenylboronic acid pinacolate ester **3.13a** (0.12 mmol), 0.0014 g of $PdCl_2(PPh_3)_2$ (2 mol %), 1.0 mL of THF and 0.24 mL of a saturated aqueous solution of $NaHCO_3$. Purification by MPLC (3:97 – 20:80 EtOAc:hexane) afforded the product as a yellow

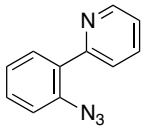
solid (0.030 g, 99%): mp 87 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25 (d, *J* = 8.5 Hz, 1H), 5.70 (d, *J* = 7.5 Hz, 1H), 7.42 (t. *J* = 7.5 Hz, 1H), 7.40 (d, *J* = 6.5 Hz, 1H), 7.35 (t, *J* = 8.5 Hz, 1H), 7.26 (t, *J* = 8.0 Hz, 1H), 7.23 – 7.20 (m, 2H), 6.53 (s, 1H), 1.35 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.9 (C), 138.9 (C), 136.9 (C), 136.0 (C), 130.8 (CH), 129.4 (CH), 128.9 (C), 127.3 (C), 124.5 (CH), 122.8 (CH), 120.6 (CH), 117.9 (CH), 117.8 (CH), 115.4 (CH), 110.5 (CH), 83.2 (C), 27.7 (CH_3); ATR-FTIR (thin film): 3070, 2979, 2937, 2115, 2089, 1734, 1455, 1328, 1302, 1224, 1153, 1130, 1020, 740 cm^{-1}. HRMS (ESI) m/z calculated for $C_{19}H_{19}N_4O_2$ $(M+H)^+$: 335.1505, found: 335.1508.



3.15n

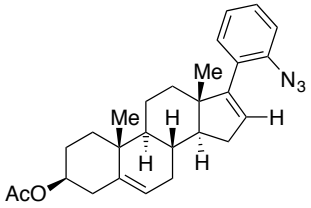
2-(2-Azidophenyl)thiophene 3.15n. The optimal procedure was followed by using 0.094 g of vinyl triflate **3.14h** (0.400 mmol), 0.119 g of 2-azidophenylboronic acid pinacolate ester **3.13a** (0.485 mmol), 0.0014 g of $PdCl_2(PPh_3)_2$ (2 mol %), 4.0 mL of THF and 0.8 mL of a saturated aqueous solution of $NaHCO_3$. Purification by MPLC (3:97 – 20:80 EtOAc:hexane) afforded the product as a colorless liquid (0.059 g, 86%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (d, *J* = 7.5 Hz, 1H), 7.46 (d, *J* = 3.5 Hz, 1H), 7.39 (d, *J* = 5.5 Hz, 1H), 7.35 (t, *J* = 7.5 Hz, 1H), 7.26 (d, *J* = 7.5 Hz, 1 H), 7.18 (t, *J* = 7.5 Hz, 1H), 7.12 (dd, *J* = 5.0, 3.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 119.1 (CH), 125.0 (CH), 126.2 (CH), 126.8 (CH), 127.2 (CH), 128.6 (CH), 130.1 (C), 136.4 (C), 139.1 (C) only visible signals; ATR-FTIR (thin film): 3106, 3070, 2128, 2089, 1572, 1489, 1295, 1267, 733 cm^{-}

[1]. HRMS (ESI) m/z calculated for $C_{10}H_7N_3S$ $(M)^+$: 201.0360, found: 201.0361.



3.15o

2-(2-Azidophenyl)pyridine 3.15o. The optimal procedure was followed by using 0.110 g of vinyl triflate **3.14i** (0.48 mmol), 0.143 g of 2-azidophenylboronic acid pinacolate ester **3.13a** (0.58 mmol), 0.0068 g of $PdCl_2(PPh_3)_2$ (2 mol %), 4.8 mL of THF and 0.96 mL of a saturated aqueous solution of $NaHCO_3$. Purification by MPLC (3:97 – 20:80 EtOAc:hexane) afforded the product as a yellow liquid (0.037 g, 40%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.71 (d, *J* = 4.5 Hz, 1H), 7.74 (t, *J* = 7.5 Hz, 1H), 7.69 – 7.66 (m, 2H), 7.43 (t, *J* = 7.0 Hz, 1H), 7.27 – 7.23 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.8 (C), 149.6 (CH), 137.3 (C), 135.9 (CH), 132.3 (C), 131.5 (CH), 129.9 (CH), 125.1 (CH), 124.9 (CH), 122.2 (CH), 118.9 (CH); ATR-FTIR (thin film): 3051, 2920, 2363, 1652, 1620, 1592, 1495, 1449, 1339, 1187, 1099, 980, 766 cm^{-1}.



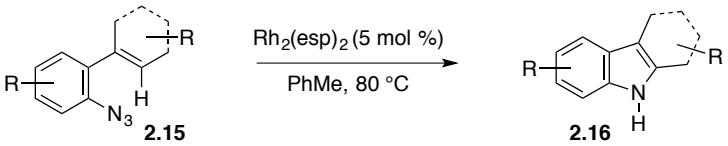
3.15p

3*S*,10*R*,13*S*)-17-(2-azidophenyl)-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15-dodecahydro-1*H*-cyclopenta-[*a*]phenanthren-3-yl acetate 3.15p. The optimal procedure was followed by using 0.0460 g of vinyl triflate **3.15j** (0.099 mmol), 0.029 g of

2-azidophenylboronic acid pinacolate ester **3.13a** (0.12 mmol), 0.0014 g of $PdCl_2(PPh_3)_2$ (2 mol %), 1.0 mL of THF and 0.24 mL of a saturated aqueous solution of $NaHCO_3$. Purification by MPLC (3:97 – 20:80 EtOAc:hexane) afforded the product as a yellow solid (0.036 g 84%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.27 (m, 1H), 7.17 – 7.12 (m, 2H), 7.09 – 7.06 (t, *J* = 7.0 Hz, 1H), 5.73 (br s, 1H), 5.41 (br s, 1H), 4.64 – 4.60 (m, 1H), 2.35 – 2.32 (m, 3H), 2.09 – 2.06 (m, 2H), 2.04 (s, 3H), 1.87 – 1.84 (m, 2H), 1.73 – 1.72 (m, 2H), 1.64 – 1.60 (m, 6H), 1.18 – 1.13 (m, 2H), 1.06 (s, 3H), 0.93 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5 (C), 151.1 (C), 140.0 (C), 138.0 (C), 130.5 (CH), 130.0 (C), 129.9 (CH) 128.1 (CH), 124.1 (CH), 122.5 (CH), 118.6 (CH), 73.9 (CH), 56.9 (CH), 50.4 (CH), 49.1 (C), 38.2 (CH_2), 36.9 (CH_2), 36.8 (C), 34.9 (CH_2), 32.2 (CH_2), 31.6 (CH_2), 30.7 (CH), 27.8 (CH_2), 21.5 (CH_3), 20.8 (CH_2), 19.3 (CH_3), 16.3 (CH_3); ATR-FTIR (thin film): 2934, 2853, 2121, 2082, 1728, 1484, 1374, 1240, 1029, 750 cm^{-1}. HRMS (ESI) m/z calculated for $C_{27}H_{33}N_3O_2$ $(M+Na)^+$: 454.2475, found: 454.2470.

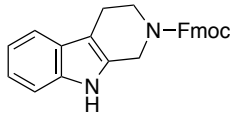
3.5.5. Rh_2(II)-catalyzed synthesis of [2,3]-fused indole heterocycles 2.16.

A. General Procedure.



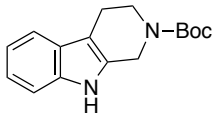
To a mixture of 2-alkenylaryl azide **3.15** and $Rh_2(esp)_2$ (5 mol %) was added toluene (0.1 M). The resulting mixture was heated at 80 °C. After 16 h, the mixture was cooled to room temperature, diluted with CH_2Cl_2 and concentrated *in vacuo*. Purification of the residue by MPLC (3:97 – 20:80 EtOAc: hexanes) afforded the product **3.16**.

B. Characterization data for [2,3]-fused indole heterocycles 2.16.



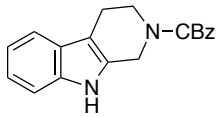
3.16a

(9*H*-Fluoren-9-yl)methyl 3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate 3.16a. The general procedure was followed by using 0.020 g of aryl azide **2.15a** (0.045 mmol), 0.0029 g of $Rh_2(esp)_2$ and 0.45 mL of toluene. Purification by MPLC (3:97 – 20:80 EtOAc: hexanes) afforded the product as a white solid (0.010 g, 54%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 – 7.71 (m, 3H), 7.61 – 7.58 (m, 2H), 7.49 (d, *J* = 7.5 Hz, 1H), 7.42 – 7.29 (m, 5H), 7.17 – 7.13 (m, 2H), 4.71 (s, 1H), 4.60 (s, 1H), 4.50 (m, 2H), 4.30 (m, 1H), 3.81 (m, 2H), 2.80 (t, *J* = 8Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.7 (C), 144.0 (C), 141.4 (C), 136.3 (C), 130.1 (C), 127.7 (CH), 127.1 (CH), 124.9 (C), 121.9 (C), 120.0 (CH), 119.7 (CH), 118.0 (CH), 111.9 (C), 110.9 (CH), 67.7 (CH_2), 47.4 (CH), 42.2 (CH_2), 42.0 (CH_2), 21.0 (CH_2), only visible peaks; ATR-FTIR (thin film): 3285, 3045, 2917, 3045, 2917, 2853, 1687, 1448, 1422, 1224, 1099, 906, 735 cm^{-1}. HRMS (ESI) m/z calculated for $C_{26}H_{23}N_2O_2$ $(M+H)^+$: 395.1766, found: 395.1760.



3.16b

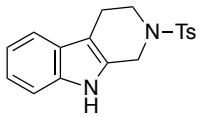
***tert*-Butyl 3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate 3.16b.**[48] The general procedure was followed by using 0.030 g of aryl azide **2.15b** (0.081 mmol), 0.0034 g of $Rh_2(esp)_2$ and 0.81 mL of toluene. Purification by MPLC (3:97 – 20:80 EtOAc: hexanes) afforded the product as a white solid (0.014 g, 51%). This product was previously reported by Kikuchi and co-workers.[48] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.44 (s, 0.48H), 7.91 (s, 0.32H), 7.48 (d, *J* = 7.5Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.15 (t, *J* = 7.5 Hz, 1H), 7.10 (t, *J* = 7.5 Hz, 1H), 4.67 (br s, 2H), 3.77 (br s, 2H), 2.80 (t, *J* = 5.5 Hz, 2H), 1.54 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.1 (C), 136.2 (C), 130.7 (C), 127.0 (C), 121.6 (CH), 119.4 (CH), 117.9 (CH), 110.9 (CH), 108.5 (C), 80.2 (C), 42.5 (CH_2), 41.8 (CH_2), 28.5 (CH_3), 21.5 (CH_2); ATR-FTIR (thin film): 3291, 3050, 2972, 2931, 1667, 1415, 1366, 1264, 1231, 1156, 1099, 731 cm^{-1}. HRMS (ESI) m/z calculated for $C_{16}H_{21}N_2O_2$ $(M+H)^+$: 273.1603, found: 273.1603.



3.16c

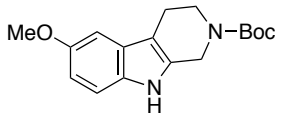
Benzyl 3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate 3.16c.[49] The general procedure was followed by using 0.030 g of aryl azide **3.15c** (0.081 mmol), 0.0034 g of $Rh_2(esp)_2$ and 0.81 mL of toluene. Purification by MPLC (3:97 – 20:80 EtOAc: hexanes) afforded the product as a white solid (0.014 g, 51%). This product was previously reported by Nolan and co-workers.[49] ^{1}H NMR (500 MHz, $CDCl_3$) *expect 16H, list 18H(18H expected)* δ 7.99 (s, 0.48H), 7.79 (s, 0.39H), 7.48 (br s, 1H), 7.39 – 7.30 (m, 6H), 7.16 (t, *J* = 7.5Hz, 1H), 7.11 (t, *J* = 7.5 Hz, 1H), 5.19 (m, 2H), 4.69 (m, 2H), 3.85 (m,

2H), 2.81 (br s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.8 (C), 136.2 (C), 130.2 (CH), 128.6 (CH), 128.1 (CH), 127.0 (CH), 121.8 (CH), 119.6 (CH), 118.9 (C), 117.9 (CH), 111.9 (C), 110.9 (CH), 108.5 (C), 67.5 (CH_2), 42.3 (CH_2), 42.1 (CH_2), 21.5 (CH_2); ATR-FTIR (thin film): 3405, 3054, 1689, 1447, 1426, 1264, 1224, 1098, 730 cm^{-1}. HRMS (ESI) m/z calculated for $C_{19}H_{19}N_2O_2$ $(M+H)^+$: 307.1448, found: 307.1448.



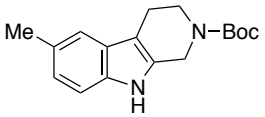
3.16d

2-Tosyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-*b*]indole 3.16d.[50] The general procedure was followed by using 0.030 g of aryl azide **3.15d** (0.081 mmol), 0.0032 g of $Rh_2(esp)_2$ and 0.84 mL of toluene. Purification by MPLC (3:97 – 20:80 EtOAc: hexanes) afforded the product as a white solid (0.013 g, 47%). The spectral data of this product matched that reported by Eilbracht and co-workers.[50] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.0 Hz, 3H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.29 (dd, *J* = 8.0 Hz, 3.5 Hz, 3H), 7.15 (t, *J* = 7.5 Hz, 1H), 7.08 (t, *J* = 7.5 Hz, 1H), 4.40 (s, 2H), 3.49 (t, *J* = 6.0 Hz, 2H), 2.84 (t, *J* = 5.5 Hz, 2H), 2.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.7 (C), 136.1 (C), 134.1 (C), 129.8 (CH), 128.5 (C), 127.6 (CH), 126.7 (C), 122.1 (CH), 119.8 (CH), 118.1 (CH), 110.9 (CH), 108.4 (CH), 44.2 (CH_2), 43.5 (CH_2), 21.5 (CH_3), 21.4 (CH_2); ATR-FTIR (thin film): 3385, 3045, 2911, 2856, 1589, 1452, 1342, 1165, 744 cm^{-1}. HRMS (ESI) m/z calculated for $C_{18}H_{19}N_2O_2S$ $(M+H)^+$: 327.1165, found: 327.1167.



3.16e

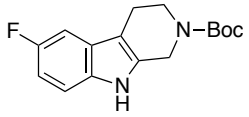
(9*H*-Fluoren-9-yl)methyl 3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate 3.16e.[51] The general procedure was followed by using 0.073 g of aryl azide **2.15e** (0.220 mmol), 0.0083 g of $Rh_2(esp)_2$ and 2.20 mL of toluene. Purification by MPLC (3:97 – 20:80 EtOAc: hexanes) afforded the product as a white solid (0.050 g, 75%). This product was previously reported by Rawal and co-workers.[51] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.52 (s, 0.56H), 7.92 (s, 0.35 H), 7.19 (d, *J* = 9.0 Hz, 1H), 6.94 (s, 1H), 6.81 (d. *J* = 8.5 Hz, 1H), 4.65 (br m, 2H), 3.86 (s, 3H), 3.77 (br s, 2H), 2.77 (t, *J* = 5.0 Hz, 2H), 1.55 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.4 (C), 154.0 (C), 131.6 (C), 131.3 (C), 127.4 (C), 111.6 (CH), 111.2 (CH), 108.1 (C), 100.4 (CH), 80.2 (C), 56.0 (CH_3), 42.7 (CH_2), 41.9 (CH_2), 20.6 (CH_3), 21.5 (CH_2); ATR-FTIR (thin film): 3288, 2979, 2931, 2898, 2846, 2362, 1670, 1594, 1416, 1367, 1214, 1169, 1133, 1094, 902, 727 cm^{-1}. HRMS (ESI) m/z calculated for $C_{17}H_{23}N_2O_3$ $(M+H)^+$: 303.1702, found: 303.1709.



3.16f

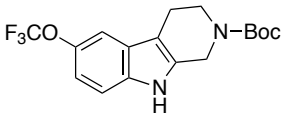
(9*H*-Fluoren-9-yl)methyl 3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate 3.16f. The general procedure was followed by using 0.064 g of aryl azide **3.15f** (0.200 mmol), 0.0077 g of $Rh_2(esp)_2$ and 2.0 mL of toluene. Purification by MPLC (3:97 – 20:80 EtOAc: hexanes) afforded the product as a white solid (0.046 g, 80%). ^{1}H NMR

(500 MHz, $CDCl_3$) δ 8.32 (s, 0.58H), 7.81 (s, 0.39H), 7.27 (s, 1H), 7.19 (d, *J* = 8.5 Hz, 1H), 6.98 (d, *J* = 8.0 Hz, 1H), 4.68 (s, 2H), 3.76 (br s, 2H), 2.78 (t, *J* = 5.0 Hz, 2H), 2.46 (s, 3H), 1.54 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.2 (C), 134.5 (C), 130.9 (C), 128.6 (C), 127.3 (C), 123.1 (CH), 117.7 (CH), 110.5 (CH), 107.9 (C), 80.1 (C), 42.7 (CH_2), 41.9 (CH_2), 28.6 (CH_3), 21.5 (CH_3), 21.2 (CH_2); ATR-FTIR (thin film): 3288, 3005, 2914, 1676, 1579, 1409, 1361, 1250, 1231, 1162, 1091, 913 cm^{-1}. HRMS (ESI) m/z calculated for $C_{17}H_{23}N_2O_2$ $(M+H)^+$: 287.1756, found: 287.1760.



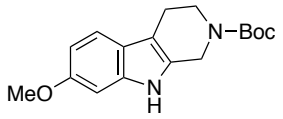
3.16g

(9*H*-Fluoren-9-yl)methyl 3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate 3.16g. The general procedure was followed by using 0.032 g of aryl azide **3.15g** (0.100 mmol), 0.0038 g of $Rh_2(esp)_2$ and 1.0 mL of toluene. Purification by MPLC (3:97 – 20:80 EtOAc: hexanes) afforded the product as a white solid (0.019 g, 65%: mp 174 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.71 (s, 0.63H), 7.95 (s, 0.32H), 7.26 (dd, *J* = 9.0 Hz, 4.0 Hz, 1H), 7.15 (d, *J* = 9.0 Hz, 1H), 6.92 (dt, *J* = 9.0 Hz, 2.0 Hz, 1H), 4.65 (m, 2H), 3.80 (s, 2H), 2.79 (t, *J* = 5.5 Hz, 2H), 1.58 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.9 (d, J_{CF} = 231 Hz, C), 155.5 (C), 132.7 (C), 127.4 (C), 111.4 (CH), 109.6 (d, J_{CF} = 22.9 Hz, CH), 108.6 (C), 102.9 (d, J_{CF} = 26.6 Hz, CH), 80.3 (C), 42.6 (CH_2), 41.9 (CH_2), 28.6 (CH_3), 21.4 (CH_2), only visible peaks; ^{19}F NMR (282 MHz, $CDCl_3$) δ – 125.26; ATR-FTIR (thin film): 2972, 2934, 2836, 2117, 1691, 1481, 1416, 1237, 1113, 958 cm^{-1}. HRMS (ESI) m/z calculated for $C_{16}H_{20}FN_2O_2$ $(M+H)^+$: 291.1508, found: 291.1509.



3.16h

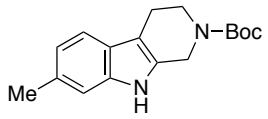
(9*H*-Fluoren-9-yl)methyl 3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate 3.16h. The general procedure was followed by using 0.039 g of aryl azide **3.15h** (0.101 mmol), 0.0038 g of $Rh_2(esp)_2$ and 1.00 mL of toluene. Purification by MPLC (3:97 – 20:80 EtOAc: hexanes) afforded the product as a white solid (0.027 g, 75%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.91 (s, 0.66H), 8.02 (s, 0.30H), 7.31 (s, 1H), 7.27 (d, J = 9.0 Hz, 1H), 7.01 (d. J = 9.0 Hz, 1H), 4.69 (br m, 2H), 3.77 (t, J = 5.5 Hz, 2H), 2.78 (t, J = 5.5 Hz, 2H), 1.55 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.6 (C), 143.1 (C), 134.5 (C), 132.9 (C), 127.3 (C), 120.9 (q, J_{CF} = 253.4 Hz, C), 115.4 (CH), 111.3 (CH), 110.5 (CH), 108.9 (C), 80.4 (C), 42.5 (CH_2), 41.9 (CH_2), 28.5 (CH_3), 21.3 (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$) δ – 58.5; ATR-FTIR (thin film): 3269, 2976, 2934, 2849, 1666, 1423, 1243, 1212, 1133, 1101, 896 cm^{-1}. HRMS (ESI) m/z calculated for $C_{17}H_{20}F_3N_2O_3$ $(M+H)^+$: 357.1424, found: 357.1426.



3.16i

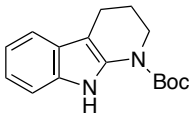
(9*H*-Fluoren-9-yl)methyl 3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate 3.16i. The general procedure was followed by using 0.440 g g of aryl azide **3.15i** (0.110 mmol, 83% pure), 0.0042 g of $Rh_2(esp)_2$ and 1.10 mL of toluene. Purification by MPLC (3:97 – 20:80 EtOAc: hexanes) afforded the product as a white solid ((0.020 g, 60%). ^{1}H

NMR (500 MHz, $CDCl_3$) δ δ 8.24 (s, 0.52 H), 7.75 (s, 0.37H), 7.35 (d, *J* = 8.5 Hz, 1H), 6.83 (s, 1H), 6.79 (d, *J* = 8.5 Hz, 1H), 4.62 (br s, 2H), 3.83 (s, 3H), 3.75 (s, 2H). 2.76 (br s, 2H), 1.52 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.2 (C), 155.2 (C), 137.0 (C), 129.3 (C), 121.5 (C), 118.5 (C). 118.4 (CH), 108.9 (CH), 95.0 (CH_2), 80.1 (C), 55.8 (CH_3), 42.6 (CH_2), 41.7 (CH_2), 28.5 (CH_3), 21.5 (CH_2); ATR-FTIR (thin film): 3297, 3008, 2979, 2908, 2830, 1665, 1631, 1478, 1421, 1365, 1249, 1231, 1155, 1112, 1032, 909, 815 cm^{-1}. HRMS (ESI) m/z calculated for $C_{17}H_{23}N_2O_3$ $(M+H)^+$: 303.1702, found: 303.1709.



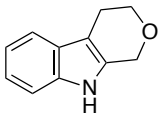
3.16j

(9*H*-Fluoren-9-yl)methyl 3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate 3.16j. The general procedure was followed by using 0.450 g g of aryl azide **2.15j** (0.142 mmol), 0.0054 g of $Rh_2(esp)_2$ and 1.40 mL of toluene. Purification by MPLC (3:97 – 20:80 EtOAc: hexanes) afforded the product as a white solid (0.033 g, 81%): mp 176 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.18 (s, 0.57H), 7.76 (s, 0.39H), 7.36 (d, *J* = 8.0 Hz, 1H), 7.09 (s, 1H), 6.94 (d, *J* = 8.0 Hz, 1H), 4.63 (br s, 2H), 3.76 (br s, 2H), 2.77 (t, *J* = 5.5 Hz, 2H), 2.45 (s, 3H), 1.53 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.3 (C), 136.7 (C), 131.3 (C), 130.0 (C), 124.9 (C), 121.1 (CH), 117.5 (CH), 110.9 (CH), 108.2 (C), 80.1 (C), 42.6 (CH_2), 41.8 (CH_2), 28.5 (CH_3), 21.8 (CH_3), 21.5 (CH_2); ATR-FTIR (thin film): 3308, 2979, 2917, 2853, 1672, 1414, 1365, 1306, 1230, 1160, 1099, 899, 799 cm^{-1}. HRMS (ESI) m/z calculated for $C_{17}H_{23}N_2O_2$ $(M+H)^+$: 287.1756, found: 287.1760.



3.16k

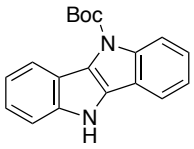
***tert*-Butyl 2,3,4,9-tetrahydro-1*H*-pyrido[2,3-*b*]indole-1-carboxylate 3.16k.** The general procedure was followed by using 0.030 g of aryl azide **3.15k** (0.081 mmol), 0.0038 g of $Rh_2(esp)_2$ and 1.0 mL of toluene. Purification by MPLC (3:97 – 20:80 EtOAc: hexanes) afforded the product as a yellow solid (0.021 g, 77%): mp 87 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.02 (s, 0.75H), 7.39 – 7.38 (m, 1H), 7.27 (m, 1H), 7.07 (m, 2H), 3.81 (t, *J* = 5.5 Hz, 2H), 2.74 (t, *J* = 6.0 Hz, 2H), 2.05 (m, 2H), 1.57 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.7 (C), 133.8 (C), 132.0 (C), 129.4 (C), 126.6 (C), 119.9 (CH), 119.4 (CH), 116.7 (CH), 110.5 (CH), 81.7 (C), 45.1 (CH_2), 28.4 (CH_3), 22.7 (CH_2), 19.2 (CH_2). ATR-FTIR (thin film): 3396, 2972, 2953, 2924, 2843, 1682, 1582, 1494, 1387, 1351, 1260, 1159, 1130, 740 cm^{-1}. HRMS (ESI) m/z calculated for $C_{16}H_{21}N_2O_2$ $(M+H)^+$: 273.1610, found: 273.1603.



3.16l

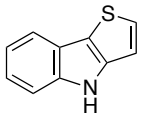
1,3,4,9-Tetrahydropyrano[3,4-b]indole 3.16l. The general procedure was followed by using 0.032 g of aryl azide **3.15l** (0.089 mmol), 0.006 g of $Rh_2(esp)_2$ and 1.0 mL of toluene. Purification by MPLC (3:97 – 20:80 EtOAc: hexanes) afforded the product as a brown solid (0.023 g, 83%): mp 111 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.52

(d, J = 7.5 Hz, 1H), 7.31 (d, J = 8.0 Hz, 1H), 7.18 (t, J = 7.5 Hz, 1H), 7.14 (t, J = 7.5 Hz, 1H), 4.80 (s, 2H), 4.05 (t, J = 5.5 Hz, 2H), 2.86 (t, J = 5.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.9 (C), 131.5 (C), 127.2 (C), 121.7 (CH), 119.6 (CH), 118.0 (CH), 110.9 (CH), 107.6 (CH), 65.8 (CH_2), 63.7 (CH_2), 22.2 (CH_2). ATR-FTIR (thin film): 3382, 2957, 2843, 2810, 1452, 1238, 1088, 747 cm^{-1}. HRMS (ESI) m/z calculated for $C_{11}H_{12}NO$ $(M)^+$: 174.0916, found: 174.0919.



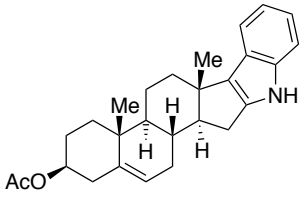
3.16m

***tert*-Butyl indolo[3,2-*b*]indole-5(10*H*)-carboxylate 3.16m.** The general procedure was followed by using 0.030 g of aryl azide **3.15m** (0.089 mmol), 0.0034 g of $Rh_2(esp)_2$ and 0.9 mL of toluene. Purification by MPLC (3:97 – 20:80 EtOAc: hexanes) afforded the product as a brown solid (0.030 g, 96%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.49 (m, 1H), 8.28 (br s, 1H), 8.18 (s, 1H), 7.64 (d, J = 7.5 Hz, 1H), 7.43 (d, J = 8.0 Hz, 1H), 7.36 (t, J = 7.5 Hz, 1H), 7.32 – 7.27 (m, 2H), 7.25 – 7.22 (m, 1H), 1.82 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.8 (C), 140.3 (C), 139.4 (C), 127.1 (C), 124.2 (CH), 124.0 (C), 122.9 (CH), 122.7 (CH), 121.5 (CH), 119.9 (CH), 118.7 (C), 117.4 (CH), 117.1 (C), 116.9 (CH), 111.8 (CH), 84.0 (C), 28.6 (CH_3). ATR-FTIR (thin film): 3425, 3402, 1725, 1449, 1364, 1348, 1302, 1243, 1141, 737 cm^{-1}. HRMS (ESI) m/z calculated for $C_{19}H_{19}N_2O_2$ $(M+H)^+$: 307.1440, found: 307.1447.



3.16n

4*H*-Thieno[3,2-*b*]indole 3.16n.[52] The general procedure was followed by using 0.025 g of aryl azide **3.15n** (0.012 mmol), 0.0047 g of $Rh_2(esp)_2$ and 1.4 mL of toluene. Purification by MPLC (3:97 – 20:80 EtOAc: hexanes) afforded the product as a white solid (0.021 g, 98%). The spectral data of the product matched that reported by Sapi and co-workers:[52] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.77 (d, *J* = 7.5 Hz, 1H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.38 (d, *J* = 5.0 Hz, 1H), 7.28 (t, *J* = 7.5 Hz, 1H), 7.21 (t, *J* = 7.5 Hz, 1H), 7.05 (d, *J* = 5.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.2 (C), 141.3 (C), 127.1 (CH), 122.9 (CH), 122.3 (C), 119.9 (CH), 118.9 (CH), 118.1 (C), 112.0 (CH), 111.7 (CH). ATR-FTIR (thin film): 3396, 3076, 3047, 1528, 1452, 1049, 1302, 1238, 1091, 743 cm^{-1}. HRMS (ESI) m/z calculated for $C_{10}H_8NS$ $(M+H)^+$: 174.0376, found: 174.0377.



3.16p

(4*S*,6a*R*,8a*S*)-6a,8a-Dimethyl-1,3,4,5,6,6a,6b,7,8,8a,13,14,14a,14b tetradecahydronaphtho[2',1':4,5]-indeno[2,1-*b*]indol-4-yl acetate 3.16p. The general procedure was followed by using 0.034 g of aryl azide **3.15p** (0.078 mmol), 0.0030 g of $Rh_2(esp)_2$ and 0.8 mL of toluene. Purification by MPLC (3:97 – 20:80 EtOAc: hexanes)

afforded the product as a brown solid (0.0080 g, 25%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.48 (m, 1H), 7.30 (dd, *J* = 6.5, 2.5 Hz, 1H), 7.08 – 7.05 (m, 2H), 5.44 (br s, 1H), 4.62 (m, 1H), 2.69 (dd, *J* = 14.5, 6.5 Hz, 1H), 2.54 – 2.49 (m, 1H), 2.40 – 2.36 (m, 3H), 2.11 (m, 2H), 2.05 (s, 3H), 1.91 – 1.88 (m, 3H), 1.78 – 1.72 (m, 3H), 1.62 – 1.58 (m, 2H), 1.20 – 1.17 (m, 2H), 1.12 (s, 3H), 1.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6 (C), 141.7 (C), 140.3 (C), 139.5 (C), 129.7 (C), 123.6 (C), 122.2 (CH), 120.3 (CH), 119.4 (C), 118.1 (CH), 111.5 (CH), 73.9 (CH), 61.4 (CH), 50.8 (CH), 41.9 (C), 38.2 (CH_2), 37.0 (C), 36.8 (CH_2), 36.1 (CH_2), 31.8 (CH_2), 30.5 (CH_3), 27.8 (CH_2), 27.3 (CH_2), 21.5 (C), 20.7 (CH_2), 19.3 (CH_3), 18.1 (CH_3). ATR-FTIR (thin film): 3370, 2946, 2898, 2846, 1708, 1452, 1364, 1250, 1036, 733 cm^{-1}. HRMS (ESI) m/z calculated for $C_{27}H_{34}NO_2$ $(M+H)^+$: 404.2587, found: 404.2590.

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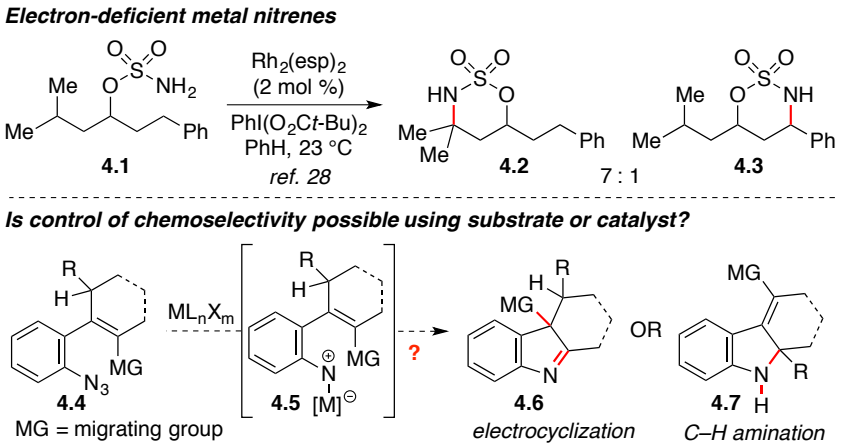
Chapter-IV

Controlling the Reactivity of Metal *N*-Aryl Nitrene to Achieve Chemoselective *N*-Heterocycles Formation by C–H Bond Amination or Electrocyclization

(The structure of this chapter followed the published article: Control of the Chemoselectivity of Metal *N*-Aryl Nitrene Reactivity: C–H Bond Amination versus Electrocyclization. Kong, C.[†]; Jana, N.[†]; Jones, C.; Driver, T. G. *J. Am. Chem. Soc.* **2016**, *138*, 13721. [†]equal contribution)

Controlling the reactivity in a metal-catalyzed transformation draws significant attention from synthetic organic chemists in orderto achieve chemoselective product formation. A voluminous amount of research has been reported to accomplish chemoselective product formation from same starting material and reagent by switching the catalyst identity; however, this control remains challenging in C–H bond amination reactions.[1-9] The reactivity pattern of metal-nitrene intermediates have been exploited to create C–N bonds from C–H bonds or π-systems.[1-5] Most of the time, however, these metal-nitrene intermediates must be substituted with a strong electron-withdrawing group in order to be reactive (Scheme 4.1).[10-27] For example, Du Bois and co-workers reported selective functionalization of a C–H bond from electron-withdrawing sulfamate ester to form six-membered heterocycles **4.2** and **4.3** in 7:1 ratio.[28] The detailed study by Du Bois and others[28-30] have established a selectivity trends, which allow the use of C–H bond amination reaction in the target-oriented syntheses.[31-34] In contrast, the reactivity pattern of metal–*N*-aryl nitrenes has not been explored in depth despite the widespread availability of the resulting *N*-heterocycles.[35-40] In addition to the C–H bond amination, *N*-aryl nitrenes also participate in elecytrocyclization reaction with an adjacent π-system to produce important *N*-heterocycles.[41] Controlling and understanding the reactivity of

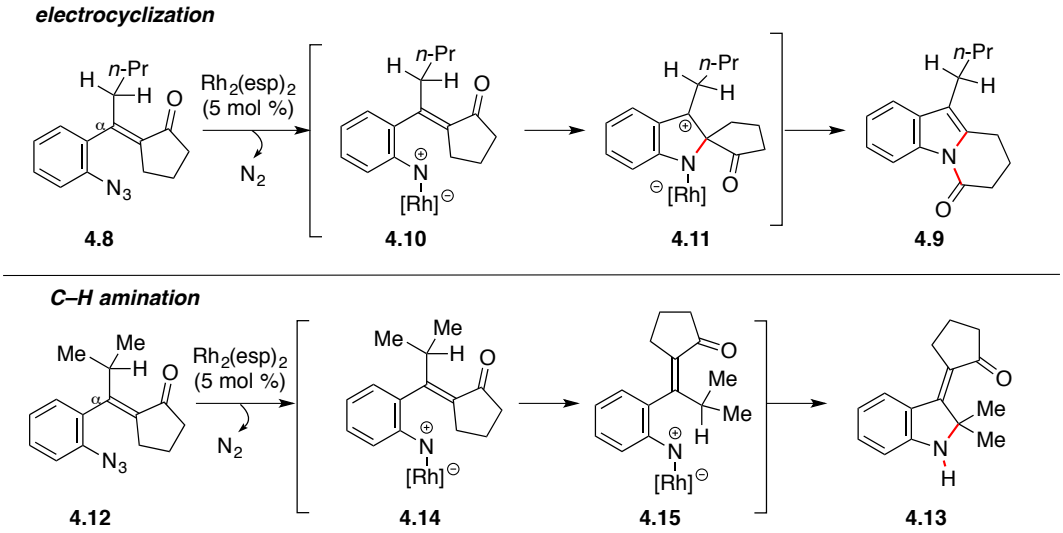
metal–*N*-aryl nitrenes toward electrocyclization and C–H bond amination reaction is crucial to perform target- and diversity-oriented syntheses. This understanding will appear from studying the reactivity of substrates having multiple reaction sites,[42] and applying the outcome into the origin of reactivity preferences to control the chemoselectivity.



Scheme 4.1. Substrate versus catalyst control of the chemoselectivity of the metal nitrene intermediate

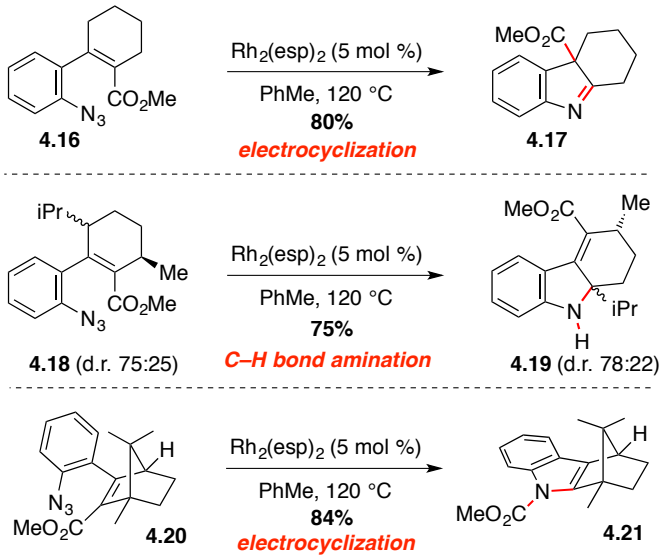
Our group has investigated the reactivity of *ortho*-substituted styryl azides and our studies revealed that certain substrates preferred to undergo a C–H bond amination instead of electrocyclization–migration reaction (Scheme 4.2).[43-56] For example, exposure of β-acyl substituted styryl azide **4.8** to a Rh_2(II)-catalyst underwent a electrocyclization–migration reaction to afford 1,2,3-trisubstituted indole **4.9**.[57] We observed that the identity of the α-substituent in these substrates had a significant impact on the reaction outcome. While substrate bearing α-aryl or α-*n*-alkyl substituent provided the 1,2,3-trisubstituted indole as the only product, introduction of α-isopropyl substituent changed the reaction

outcome: allylic C–H bond amination was observed as a major product to afford indole **4.13** from azide **4.12**.



Scheme 4.2. Chemoselective C–H bond amination instead of electrocyclization-migration reaction

In our effort toward forming 3*H*-indoles,[58-59] the presence of a tertiary allylic C–H bond, also changed the chemoselectivity of Rh_2(II)-catalyzed amination reaction (Scheme 4.3). For example, styryl azide **4.16** underwent an electrocyclization-migration reaction to produce **4.17**,[58] when exposed to $Rh_2(esp)_2$. In contrast, exposure of styryl azide **4.18** to reaction conditions preferred to form C–H bond amination product **4.19**. The preference for electrocyclization–migration reaction could be restored by conformationally locking allylic sp^3-C–H bond. For example, exposure of camphor-derived styryl azide **4.20** to the $Rh_2(esp)_2$ catalyst resulted in the formation of indole **4.21** by an electrocyclization followed by1,2-ester migration to nitrogen-atom.[59]



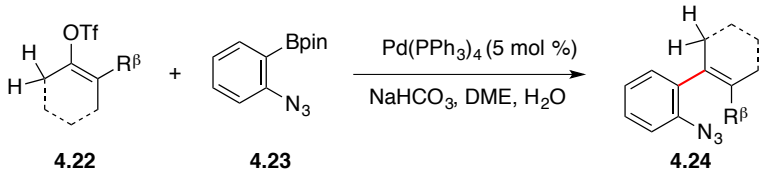
Scheme 4.3. Observation of an sp^3-C–H bond amination instead of electrocyclization-migration reaction

We were excited by these unexpected results of tertiary allylic C–H bond amination and wanted to investigate systematically, the role of the *ortho*-substituent had into the reaction outcome. To achieve this goal, we designed and synthesized substrates that had two potential reaction sites: an *ortho*-π system and an *ortho*-alkyl substituent relative to the azide. We envisioned that the steric- and electronic-environment of the reaction centers would effect in the reaction outcome to provide a general trend in reactivity, whether C–H bond amination or electrocyclization was favored. In addition to substrate control of reaction outcome, we also wanted to examine if catalysts could control the chemoselectivity.

4.1. Analysis of the reaction outcome by designing the substrate

4.1.1. Design of the substrate

To investigate the reactivity of the substrate where allylic C–H bond amination occurred in absence of tertiary allylic C–H bond, we prepared a series of styryl azides having α-*n*-alkyl substituent (Scheme 4.4). These substrates were prepared through a step-economical pathway, which involves a cross-coupling reaction between 2-azidoaryl-boronic pinacolate ester **4.23** and vinyl triflate **4.22** that was developed in Chapter III.[60]



4.22 **4.23** **4.24**

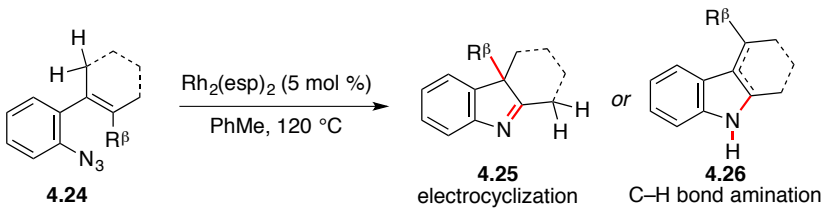
Scheme 4.4. Synthesis of α-*n*-alkyl substituted styryl azides

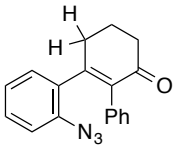
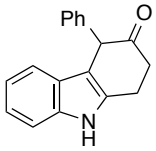
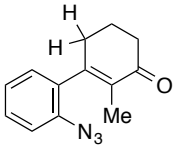
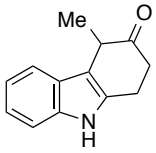
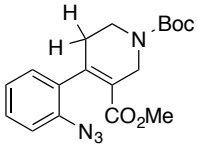
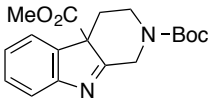
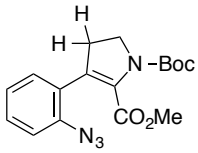
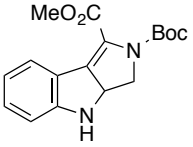
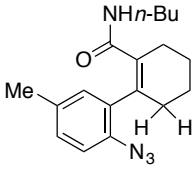
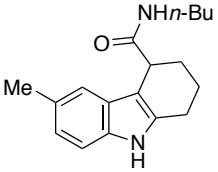
4.1.2. Reactivity trends of α-*n*-alkyl substituted styryl azides.

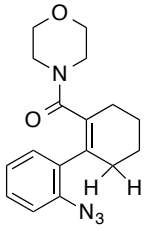
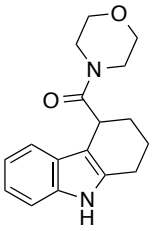
My colleague Dr. Chen Kong, synthesized a series of styryl azides and examined the reactivity of these azides toward $Rh_2(esp)_2$ (Table 4.1). While no reaction was observed in the absence of the catalyst, exposure of cyclic enone *ortho*-substitued styryl azides to the reaction conditions did trigger formation of indoles **4.26a** and **4.26b**, irrespective of the identity of the β-substituent (entries 1 and 2). An electrocyclization-migration reaction was observed from azide **4.24c** to afford **4.25c**;[58] in contrast, 3-oxoproline-derived styryl azide **4.24d** furnished secondary allylic C–H bond amination product **4.26d**, although the yield was reduced (entries 3 and 4). These results along with entries 1 and 2 indicates that the additional carbonyl- or *N*-Boc carbamate β-substituents favors allylic C–H bond amination by weakening of the allylic C–H bond.[61-64] While no reaction

occurred for β-primary amide substituted styryl azide **4.24e**, β-secondary amide substituted styryl azide **4.24f** produced only C–H bond amination product to afford indole **4.26f**, albeit in reduced yield. We explained this outcome as the amide should not have large effect on the allylic C–H bond strength, replacing carboxylate by amide, steric factor becomes prominent to favor a C–H bond amination.

Table 4.1. Allylic C–H bond amination versus electrocyclization



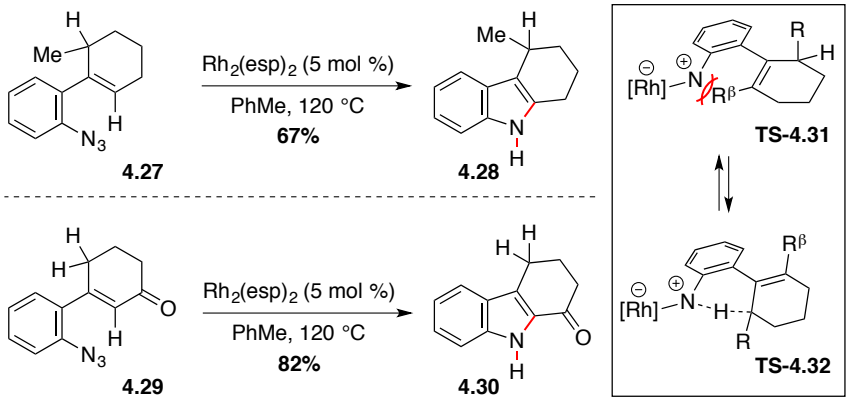
entry	#	styryl azide	*N*-heterocycle	yield, %[a]
1	a			84
2	b			85
3	c			84[b]
4	d			48
5	e			nr[c]

5	e			26

[a] Isolated after silica gel chromatography. [b] From ref 58. [c] Decomposition occurred when the reaction mixture was heated to 140 °C.

4.1.3. Effect of the changing steric environment on the reaction outcome

The effect of changing the steric nature at the reaction center was investigated next. For this study, my colleague Chen chose substrates where allylic C–H bond amination was observed (e.g. in **4.18** and **4.24a**) and replaced β-substituent by a hydrogen-atom to examine if reducing the steric pressure at β-position would promote the electrocyclization pathway (Scheme 4.5). To achieve the goal, she prepared styryl azide **4.27** where β-ester substituent was replaced by hydrogen, and **4.29** where β-phenyl substituent was replaced by hydrogen. To our surprise, exposure of styryl azides **4.27** and **4.29** to the reaction conditions resulted in the formation of corresponding indoles **4.28** and **4.30**. We postulated that the presence of bulky β-substituent raised the energy in the electrocyclization **TS-4.31** as electrocyclization requires planer transition state, and promotes allylic C–H bond amination through **TS-4.32**.[65-67] Replacing bulky substituents with hydrogen restored the electrocyclization pathway.



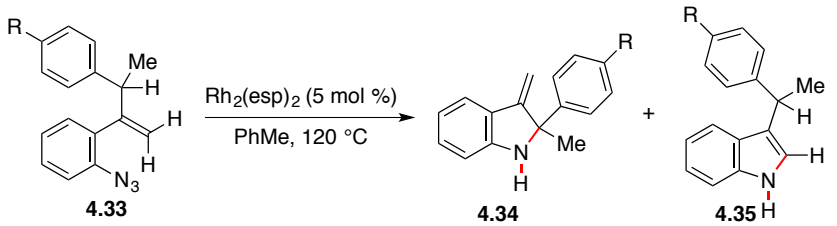
Scheme 4.5. Effect of changing steric environment on the reaction outcome

4.1.4. Investigation of reaction outcome by changing the electronic nature of the allylic C–H Bond reaction center

We envisioned that, further insight into the reaction mechanism could be gained by examining substrates in which two potential reaction sites had comparable reactivity. To make C–H bond amination competitive with electrocyclization, Chen Kong synthesized styryl azide **4.33** with sterically accessible *ortho*-alkenyl substituent, and replaced one of the tertiary allylic alkyl substituent with an aryl group (Table 4.2). The presence of aryl group in the substrates would allow us to examine the effect of changing electronic nature of the allylic C–H bond on the ratio of electrocyclization to amination. Chen and myself, examined the reactivity of styryl azide **4.33** toward $Rh_2(esp)_2$ complex to see if both heterocyclic products could be obtained. Gratifyingly, we found comparable ratio of both electrocyclization-migration product, indole **4.35** and C–H bond amination product, 2*H*-indole **4.34** with indole **4.35** as the major product. We observed that increasing the electron-deficiency in the *para*-substituent favored the electrocyclization-migration product. A linear correlation was obtained when the electrocyclization-migration/C–H bond amination product ratios were plotted against Hammett σ_{para} constants (Figure 4.1).[68]

The correlation graph consists of two intersecting line with positive slopes where the electron-donating substituents had much smaller ϱ-value of 0.33 compared with the electron-withdrawing substituents, which exhibited a large ϱ-value of 3.18. The intersecting lines indicates that a change in the mechanism happened or change in the rate-determining step occurred.

Table 4.2. The effect of changing the electronic nature of the allylic C–H bond reaction center on the reaction outcome



entry	#	R	σ_{para} [a]	σ_{mb} [b]	$\sigma_{JJ}^{\bullet}$ [b]	**4.34**:**4.35**	yield, %[c]
1	a	OMe	–0.27	–0.77	0.23	1:4	83
2	b	Me	–0.17	–0.29	0.15	1:5.1	94
3	c	H	0	0	0	1:5.8	82
4	d	F	0.06	–0.24	–0.02	1:10.7	66
5	e	Cl	0.23	0.11	0.22	1:13.0	56
6	f	OCF_3	0.35	...	...	1:83	84

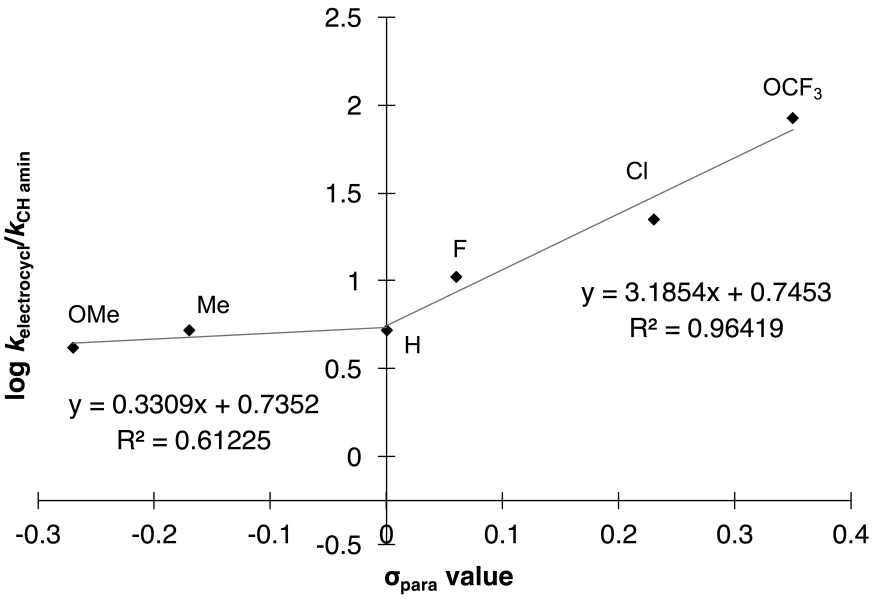


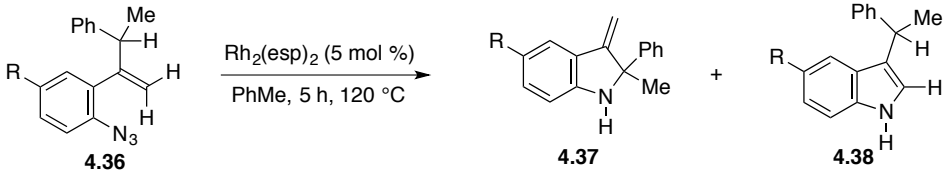
Figure 4.1. Investigation of the electronic nature at the allylic C–H bond reaction center: correlation of electrocyclization-migration to C–H bond amination product ratios with Hammett σ_{para} values

4.1.5. Investigation of reaction outcome by changing the electronic nature of the aryl azides

Using the same scaffold, the effect of changing electronic nature of the aryl azides into the heterocyclic product ratios was investigated next. For this study, I prepared a series of *para*-substituted styryl azide to examine the reactivity. When styryl azide **4.36** was exposed to the reaction conditions, I observed formation of both 2*H*-indole **4.37** and indole **4.38** (Table 4.3). A general trend in the reaction outcome was apparent: the presence of both electron-donating and -withdrawing substituents favored electrocyclization product. A V-shaped correlation was observed when the heterocyclic product ratios were plotted against Hammett σ_{para} constants (Figure 4.2).[68] The V-shaped curve indicates that either the mechanism or the identity of the rate-limiting step is

changing.[69-72] It could also indicate the presence of radical intermediate in one of the product-determining steps.[73-74]

Table 4.3. The effect of changing the electronic nature of aryl azides **4.36** on the reaction outcome



4.36 **4.37** **4.38**

entry	#	R	σ_{para} [a]	σ_{mb} [b]	$\sigma_{JJ}^{\bullet}$ [b]	**4.37**:**4.38**	yield, %[c]
1	a	OMe	–0.27	–0.77	0.23	1:12	78
2	b	Me	–0.17	–0.29	0.15	1:7.2	79
3	c	H	0	0	0	1.5.8	82
4	d	F	0.06	–0.24	–0.02	1:5	92
5	e	Cl	0.23	0.11	0.22	1:6.6	76
6	f	OCF_3	0.35	...	...	1:9.5	80

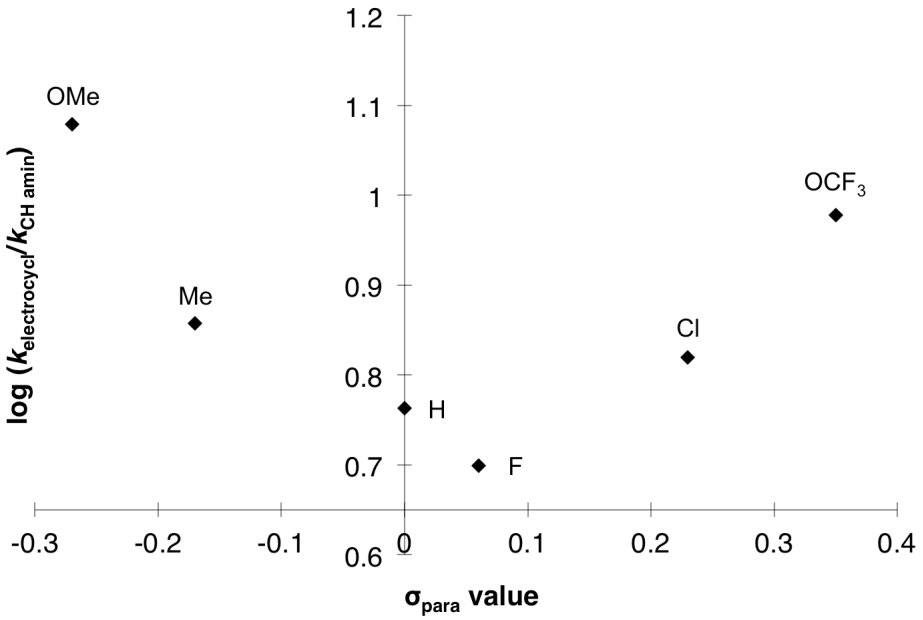
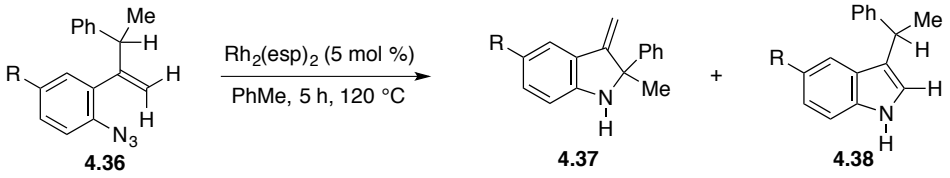
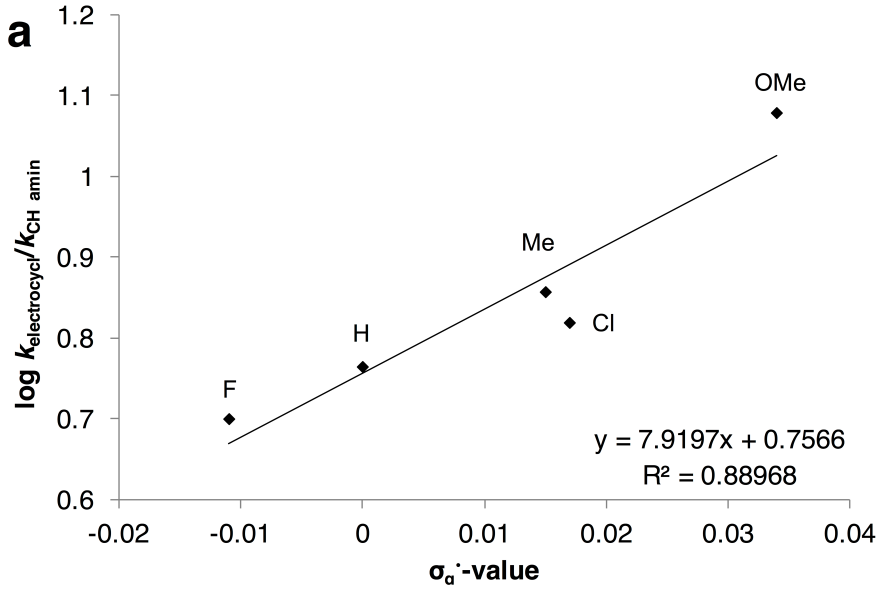


Figure 4.2. Investigation of the electronic nature at the aryl azide reaction center: correlation of the electrocyclization-migration to the C–H bond amination product ratios with Hammett σ_{para} values

To examine, if the radical intermediates were involved, we correlated our relative rate data with different radical $\sigma^{\bullet}$ substituent constants such as Arnold's $\sigma_{\alpha}^{\bullet}$-,[75-76] Creary's $\sigma_{C}^{\bullet}$-,[77-78] and Jackson's $\sigma_{J}^{\bullet}$-constants[79] (Figure 4.3). When we plotted the relative rates against these substituent constants, we did not observe any correlation using styryl azide **4.33**. In contrast, we observed a linear correlation using styryl azide **4.36**, when the product ratios were plotted against Arnold's $\sigma_{\alpha}^{\bullet}$-, Creary's $\sigma_{C}^{\bullet}$ -constants, which suggests the presence of a nitrogen-based radical in the product-determining step.





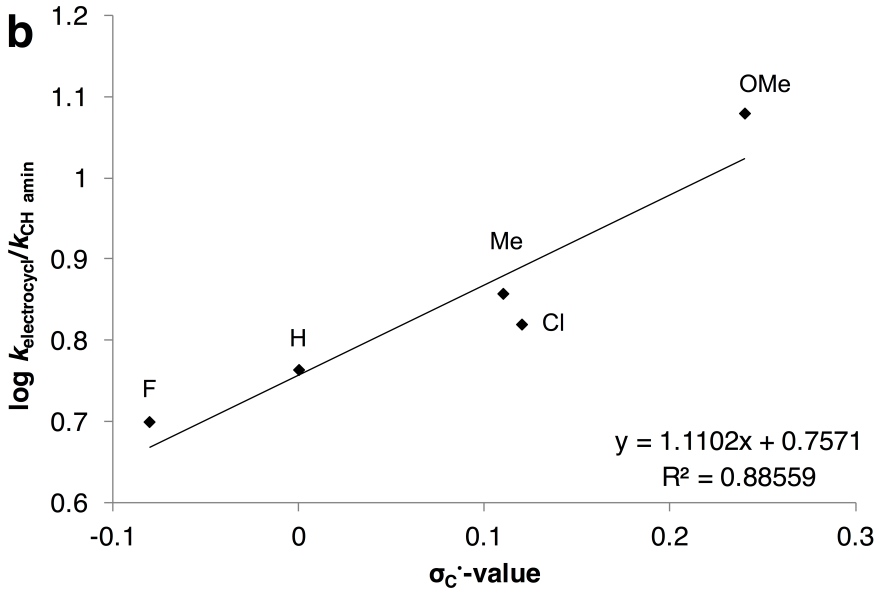
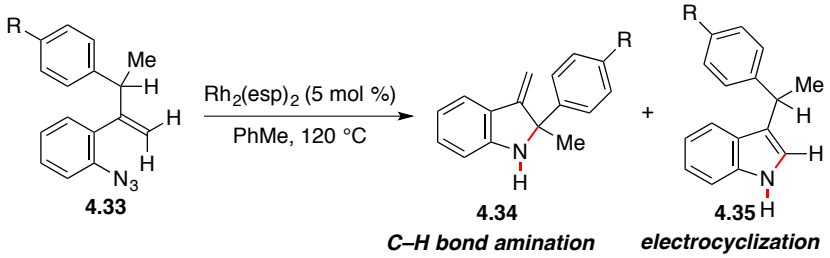
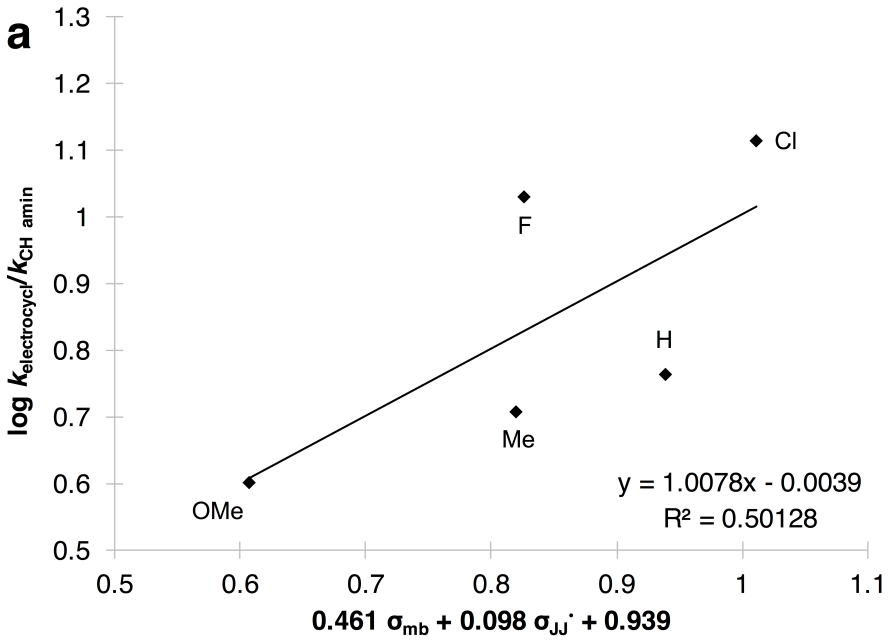


Figure 4.3. Correlation of heterocycle product ratios from styryl azide **36** with (a) Arnold's $\sigma_{\alpha}^{\bullet}$-constants and (b) Creary's $\sigma_{C}^{\bullet}$-constants

To further investigate the radical versus polar intermediacy in the product-determining step, we examined the correlation between the product ratios and Jiang and Ji's radical σ_{mb} and $\sigma^{\bullet}_{JJ}$ substituent constants,[80-82] which separate the polar (σ_{mb}) and spin ($\sigma^{\bullet}_{JJ}$) delocalization effects. To achieve the goal, a multiple variable linear regression method was used to plot the product ratio against σ_{mb} and $\sigma^{\bullet}_{JJ}$ substituent constants (log $k_{electrocycl}/k_{CHamin} = \varrho_{mb}\sigma_{mb} + \varrho_{JJ}{}^{\bullet}\sigma^{\bullet}_{JJ} + C$). When plotted, we did not observe linear correlation using styryl azide **4.33** (Figure 4.4a). We interpret this result to indicate that the electronic effects observed during the product-determining step are entirely polar in nature and that no radical character is built up on the benzyl position during this step. Gratifyingly, a linear correlation was obtained when the electronic nature of styryl azide **4.36** was explored and the equation we found to express the correlation was log $k_{rel} = -0.248\sigma_{mb} + 0.711\sigma^{\bullet}_{JJ} + 0.702$ (Figure 4.4b). The negative ϱ_{mb} value indicates an electrophilic metal *N*-aryl nitrene catalytic intermediate, and the positive $\varrho_{JJ}{}^{\bullet}$ value accounts for the spin density, which is localized on the nitrogen-atom.[80-82] The absolute magnitude of $|\varrho_{JJ}{}^{\bullet}/\varrho_{mb}| > 1$ suggests that the spin delocalization effect is more prominent than the polar substituent effect.[80-82] Combining both the results, our data suggest that rhodium *N*-aryl nitrene formed in early transition state in which slight C–H bond hemolysis has occurred.


R
Me
H
H
H
N3
4.33
Rh2(esp)2 (5 mol %)
PhMe, 120 °C
R
N
H
Me
4.34
C–H bond amination
+
R
Me
H
H
N
H
4.35
electrocyclization


a
log kelectrocycl/kCH amin
1.3
1.2
1.1
1
0.9
0.8
0.7
0.6
0.5
Cl
F
H
Me
OMe
y = 1.0078x - 0.0039
R² = 0.50128
0.5
0.6
0.7
0.8
0.9
1
1.1
0.461 σmb + 0.098 σJJ˙ + 0.939

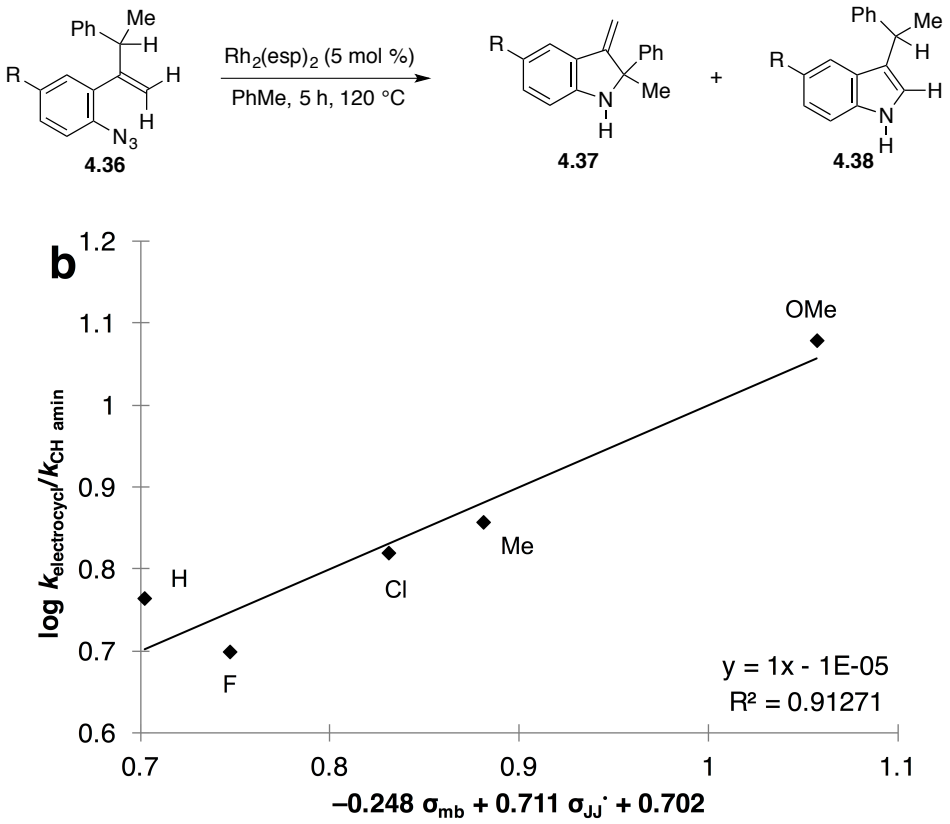
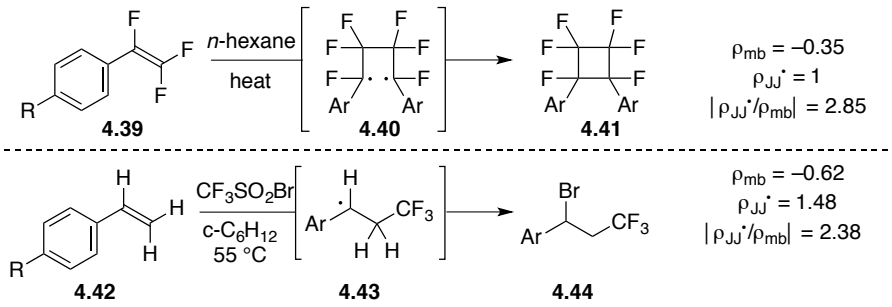


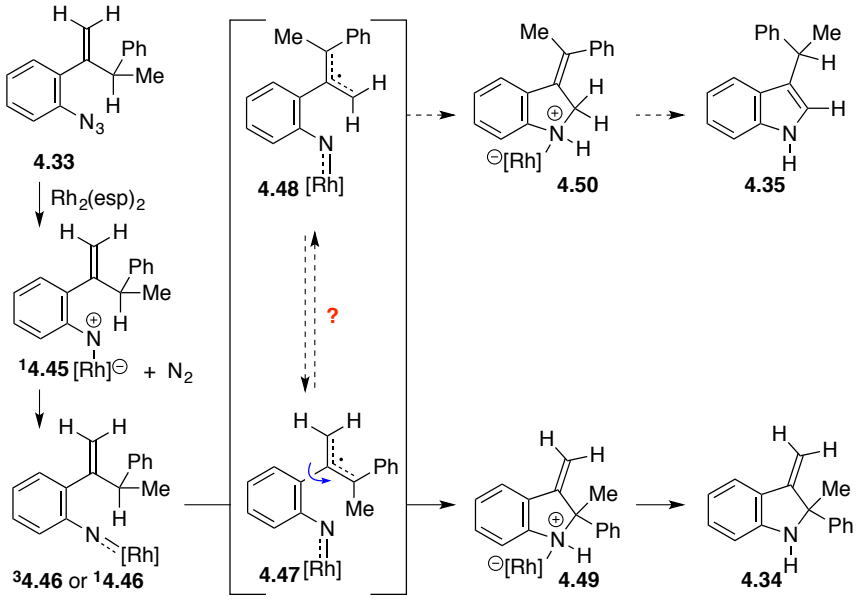
Figure 4.4. Correlation of the relative rate with Jiang and Ji's σ_{mb} and $\sigma_{JJ}^{\bullet}$ values: (a) substituent effect observed at the allylic C–H reaction site; (b) substituent effect observed on the aryl azide

In contrast to our conclusion from Jiang and Ji's plot that a nitrogen-centered radical was produced, the original report by Jiang and Ji's calculations were based on the formation of a benzyl carbon-centered radical.[80-82] In their report, the authors studied dimerization of styrenes **4.39** to produce cyclobutane **4.41**.[81] By changing electronic nature of the styrenes, relative rates of cyclobutane formation were calculated and plotted against multiple variables σ_{mb} and $\sigma_{JJ}^{\bullet}$. When plotted, a linear correlation was observed and expressed by the equation $\log k_{rel} = -0.35\sigma_{mb} + 1.0\sigma_{JJ}^{\bullet}$. The absolute magnitude of $|\varrho_{JJ}^{\bullet}/\varrho_{mb}| = 2.85$ suggests that the spin delocalization effect is more prominent than the

polar substituent effect and the authors proposed a radical intermediate **4.41** for their transformation. In a separate example, the reactivity of styrenes **4.42** toward monobromination was examined.[82] The calculated value of $|\varrho_{JJ}^{\bullet}/\varrho_{mb}|$ was found to be 2.38, suggesting a radical intermediate **4.43**, radical recombination of which formed **4.44**.

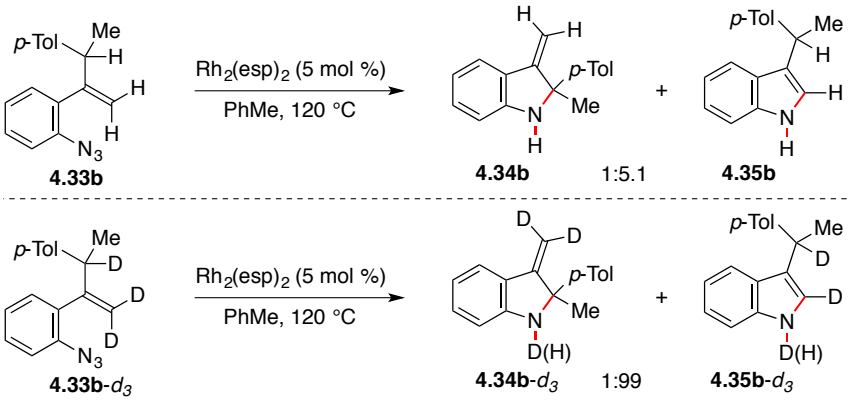


Based on the conclusion from Jiang and Ji's plot that a nitrogen-centered radical formed in our transformation, a H-atom abstraction-radical recombination pathway could also be possible for the formation of indole **4.35** (Scheme 4.6). Exposure of styryl azide **4.33** to $Rh_2(esp)_2$ produces rhodium nitrene species **4.45**. A DFT calculation study on our styryl azide substrates suggests that singlet rhodium nitrene **4.45** will be formed first which could relax into an energetically favored triplet species **4.46**.[83] While the calculations revealed that the triplet species was inert towards electrocyclization with the α-alkenyl substituent, it has the potential to undergo a H-atom bond abstraction from the weaker allylic C–H bond to generate allylic radical intermediate **4.47**. Radical recombination of **4.47** with the more substituted carbon-atom followed by dissociation of catalyst could provide 2*H*-indole **4.34**. As an alternative, C–C bond rotation in **4.47** could alleviate steric strain to generate **4.48**. Radical recombination of **4.48** with less substituted carbon-atom could furnish 2*H*-indole **4.50**, isomerization of which provides indole **4.35**.



Scheme 4.6. H-Atom abstraction-radical recombination as a potential common mechanism for 2*H*-indole and indole formation

To investigate if the formation of the 2*H*-indole and indole occurred through a common allyl radical intermediate, the reactivity of styryl azide **4.33b**-d_3 was examined (Scheme 4.7). We envisioned that the ratio of the product formation should not change for the D-labeled substrate since H-atom abstraction of the allylic C–H bond occurs for both and changing the bond strength should not affect the product ratio if the product-determining step occurs later. On the contrary, if indole **4.35** formed by electrocyclization pathway, then the formation of the 2*H*-indole will be significantly reduced as electrocyclization does not require breaking of stronger C–D bond. To test the assertion, we exposed styryl azide **4.33b**-d_3 to the reaction conditions, and observed exclusive formation of indole **4.35b**-d_3; trace amount of 2*H*-indole **4.34b**-d_3 was detected. The preference for the formation of indole **4.35b**-d_3 indicates that indole is formed by electrocyclization pathway, and not by the common allyl radical intermediate.



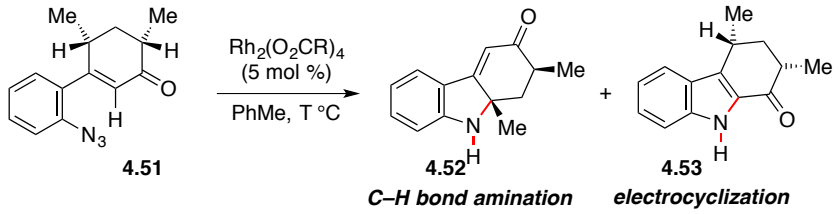
Scheme 4.7. Effect of changing isotopolog identity on the ratio of 2*H*-indole **4.34** and indole **4.35** using $Rh_2(esp)_2$

4.1.6. Investigation of the reaction outcome controlled by catalysts

As the change in the electronic nature of the aryl azide had a prominent effect on the reaction outcome, we hypothesized that the changing the identity of the ligand of the rhodium catalyst might also change the product ratio. To taste our hypothesis, we prepared styryl azide **4.51** containing *ortho*-cyclohexenone moiety, which contains a tertiary allylic C–H bond to make C–H bond amination more competitive with electrocyclization pathway (Table 4.4). When styryl azide **4.51** was exposed to $Rh_2(esp)_2$, both 2*H*-indole **4.52** and indole **4.53** were produced in 1:1.6 ratio (entry 1). The product ratio remained unchanged when the temperature was reduced from 120 to 110 °C. Without using catalyst, when the reaction mixture was heated at 120 °C, indole was observed in 15% yield; no 2*H*-indole was observed (entry 3). Changing the identity of the carboxylate ligand had a measurable effect on the reaction outcome. The $Rh_2(oct)_4$ catalyst provided comparable product ratio using $Rh_2(esp)_2$ with slightly attenuated in yield (entry 4). Changing the carboxylate ligand to more electron-donating caprolactamate resulted in the selective formation of indole **4.53** (entry 5).[84] In contrast to the small carboxylate and amide ligands, bulky chiral ligands on rhodium exhibited the

inverse selectivity toward the product formation to produce 2*H*-indole **4.52** as a major product. While the chiral Rh_2(*S*-DOSP)$_4$ favored slightly for the formation of 2*H*-indole **4.52**, increase in the ratio was observed (3.9:1) using Rh_2(*S*-PTAD)$_4$ (entries 6 – 7).[85-86] Further improvement for the formation of 2*H*-indole **4.52** could be achieved by reducing the reaction temperature from 110 to 90 °C: the 2*H*-indole formation was favored by the ratio of 4.8:1, however, yield was reduced at 90 °C.

Table 4.4. The effect on the reaction outcome by changing the identity of the Rh_2(II)-catalyst's ligands



entry	$Rh_2(O_2CR)_4$	T, °C	**4.52**:**4.53**	yield, %[a]
1	$Rh_2(esp)_2$	120	1:1.6	91
2	$Rh_2(esp)_2$	110	1:1.7	90
3	none	120	1:16	15
4	$Rh_2(oct)_4$	110	1:2.1	78
5	$Rh_2(cap)_4$	100	1:10	73
6	Rh_2(*S*-DOSP)$_4$	100	1.28:1	64[b]
7	Rh_2(*S*-PTAD)$_4$	110	3.9:1	84
8	Rh_2(*S*-PTAD)$_4$	100	4.4:1	85
9	Rh_2(*S*-PTAD)$_4$	90	4.8:1	61[c]

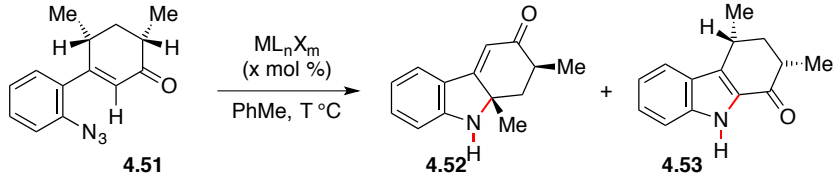
[a] As determined by ^{1}H NMR spectroscopy using CH_2Br_2 as the internal standard. [b] Only 84% conversion observed. [c] Only 72% conversion observed.

Next, we examined the effect of changing the identity of the metal on the reaction outcome. We envisioned that changing metal catalyst could exert a large impact in the C–N bond formation or C–H bond cleavage. In line with our hypothesis, changing the

identity of metal catalysts affected the reaction outcome: while $Rh_2(esp)_2$ produced mixture of products, exposure of styryl azide **4.51** to $[Ir(cod)(OMe)]_2$ resulted in the formation of only indole **4.53** in high yields (Table 4.5, entries 1 and 2). Selectivity toward the indole product could be also achieved by using 20 mol % of $FeBr_2$ or $FeBr_3$, however, low yield was observed using $FeBr_3$ as catalyst. In contrast to the indole formation, C–H bond amination product become the major product using cobalt or iron porphyrine complexes (entries 5 – 11).[87-88] A general trend for the preferential formation of the 2*H*-indole was observed: electron-donating porphyrine complexes gave higher selectivity for 2*H*-indole formation than electron-withdrawing porphyrine complex. As metal-porphyrine complexes are well known to catalyze *C*- and *N*-atom transfer by one-electron processes, we anticipated that these catalysts could produce higher activity if *H*-atom abstraction, radical-recombination was a plausible pathway.[89-90] In line with our hypothesis, as low as 2 mol % of CoTPP complex at 100 °C gave the C–H bond amination to electrocyclization product ratio 3.6:1. Changing the ligand from tetraphenylporphyrin (TPP) to octaethylporphyrin (OEP) improved the product ratio of **4.52**:**4.53** from 3.6:1 to 8:1, albeit in attenuated yield (entries 5 and 6). A similar preference for the formation of the 2*H*-indole was observed when metal catalyst identity was changed from cobalt to iron. Higher selectivity (17:1) toward formation of the 2*H*-indole was observed using Fe(TPP)Cl complex with 52 % overall yield (entry 7). In attempt to increase the yield of the amination reaction, the reaction temperature was increased from 100 to 125 °C; however, yield remained same with decrease in the ratio of the 2*H*-indole formation from 13:1 to 7.3:1. The effect of the electronic nature of the porphyrin ligands was investigated next: while electron-withdrawing iron

pentafluoroarylporphyrin gave poor selectivity for **4.52** (3.3:1), electron-donating iron tetramethoxyarylporphyrin resulted in improved selectivity for **4.53** to 17:1. The best selectivity for 2*H*-indole formation was achieved by using electron-donating iron octaethylporphyrin as a catalyst to give **4.52** in 60:1 ratio.

Table 4.5. Effect of changing the identity of the metal of the *N*-atom transfer catalyst on the reaction outcome

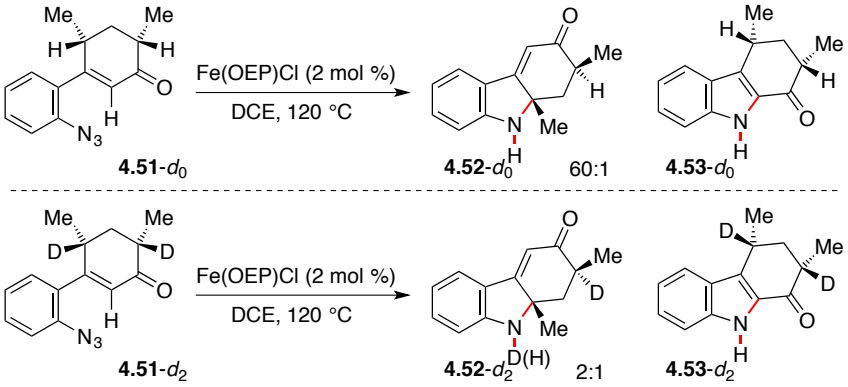


entry	ML_nX_m	mol %	T, °C	**4.52**:**4.53**	yield, %[a]
1	$Rh_2(esp)_2$	5	110	1:1.7	90
2	$[Ir(cod)(OMe)]_2$	5	110	0:100	88
3	$FeBr_2$	20	110	0:100	84
4	$FeBr_3$	20	110	0:100	41
5[b]	CoTPP	2	100	3.6:1	68
6[b]	CoOEP	2	100	8:1	18[c]
7[b]	Fe(TPP)Cl	2	100	13:1	52
8[b]	Fe(TPP)Cl	2	125	7.3:1	52
9[b]	Fe(TPFPP)Cl	2	110	3.3:1	72
10[b]	Fe(TOMePP)Cl	2	100	17:1	52
11[b]	Fe(OEP)Cl	2	100	60:1	77

[a] As determined by ^{1}H NMR spectroscopy using CH_2Br_2 as the internal standard. [b] Reaction performed in DCE with 100 wt % of 4 Å molecular sieves added. [c] Only 28% conversion observed.

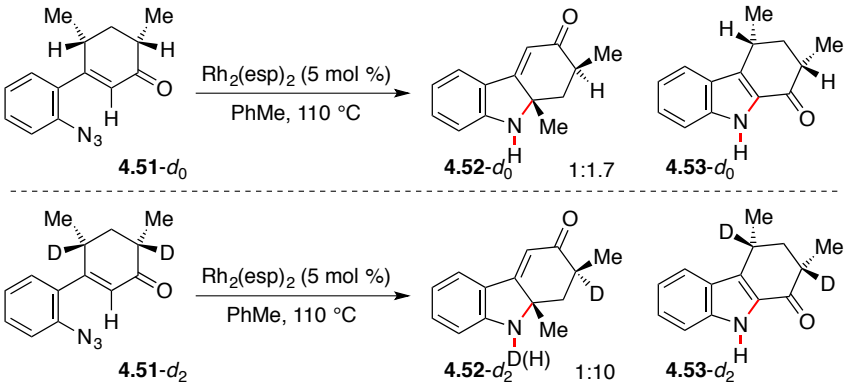
To determine if the indole and 2*H*-indole were forming by a common allyl radical intermediate, we examined the reactivity of styryl azide **4.51**-d_2 using iron octaethylporphyrin complex (Scheme 4.8). We anticipated that the product ratio from **4.51**-d_2 would be the same as with the **4.51**-d_0, if the resulted indole and 2*H*-indole was

formed by a common allyl radical intermediate. Exposure of **4.51**-d_2 to the optimal reaction conditions produced significant reduction in product ratio (2:1) for the 2*H*-indole formation. Similar to our previous investigation, we attributed the result to indicate that the indole is formed by electrocyclization pathway, whereas the 2*H*-indole is produced by the *H*-atom abstraction, radical-recombination pathway.



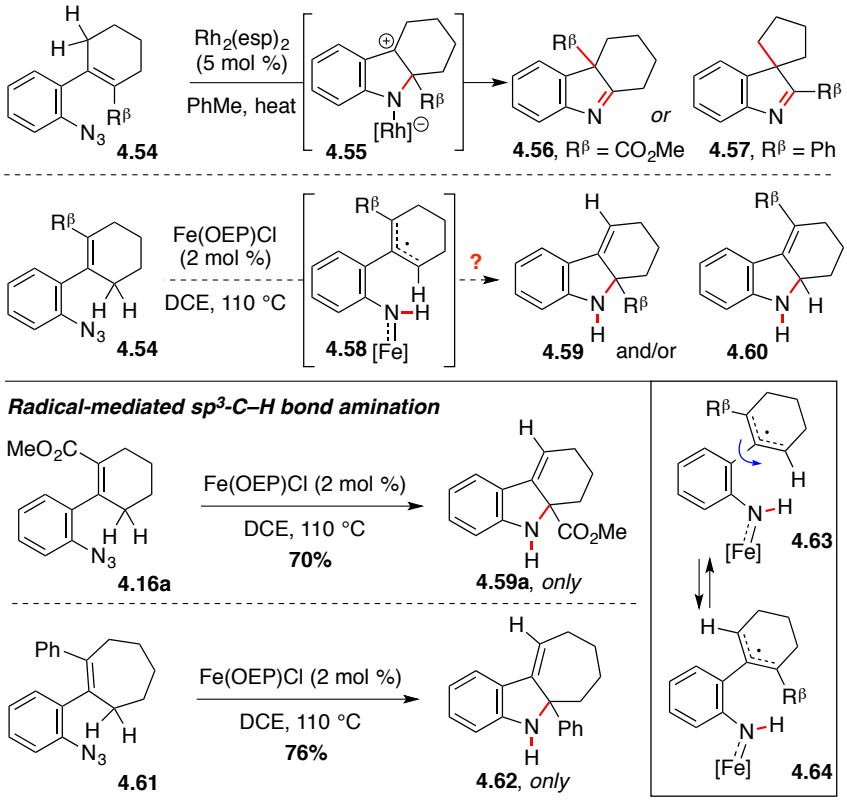
Scheme 4.8. Effect of changing isotopolog identity on the ratio of 2*H*-indole **4.52** and indole **4.53** using $Rh_2(esp)_2$ as the catalyst

To further strengthen our hypothesis that the two heterocycles formed by two separate pathways irrespective of the catalyst identity, the reactivity of the styryl azide **4.51**-d_2 towards $Rh_2(esp)_2$ catalyst was examined (Scheme 4.9). Exposure of **4.51**-d_0 to $Rh_2(esp)_2$ catalyst produced 1:1.7 ratio of 2*H*-indole **4.52**-d_0 to indole **4.53**-d_0. Similar to our previous result with Fe(OEP)Cl catalyst, indole **4.53**-d_2 was favored more heavily (1:10) from from **4.51**-d_2 using $Rh_2(esp)_2$. We interpret this data to support that two separate mechanisms leading to the two different products: electrocyclization-migration produces the indole, while allylic C–H bond amination affords the 2*H*-indole.



Scheme 4.9. Effect of changing isotopolog identity on the ratio of 2*H*-indole **4.52** and indole **4.53** using $Rh_2(esp)_2$ as the catalyst.

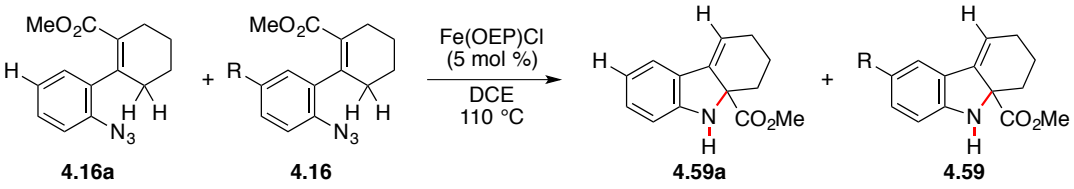
Finally, the reactivity of the β-substituted styryl azides was investigated using iron octaethylporphyrin complex. In our previous studies we observed that β-substituted styryl azide **4.54** underwent an electrocyclization–1,2-migration reaction to afford 3*H*-indoles such as **4.56** or **4.57**, depending on the nature of the β-substituents (Scheme 4.10). We anticipated that, using an iron octaethylporphyrin complex should change the reactivity of the intermediates by changing the process from two-electrons- to one-electron pathway. As a result, *H*-atom abstraction of the *N*-aryl nitrene would be facilitated to generate **4.58**, followed by radical-recombination could provide 2*H*-indoles such as **4.59** or **4.60**. To test our hypothesis, styryl azides **4.16a** and **4.61** were exposed to 2 mol % of Fe(OEP)Cl complex, and we observed formation of only 2*H*-indoles **4.59a** and **4.62**. We attributed the regioselectivity of C–N bond formation as a result of sufficiently long-lived allyl radical **4.63** formation, bond rotation of which generates **4.64** followed by recombination of nitrogen-centered radical with more substituted carbon-cantered radical to afford the 2*H*-indole. The use of radical trap such as TEMPO or 1,4-cyclohexadiene inhibited the 2*H*-indole formation, which further suggests that a one-electron process is occurring for the transformation.

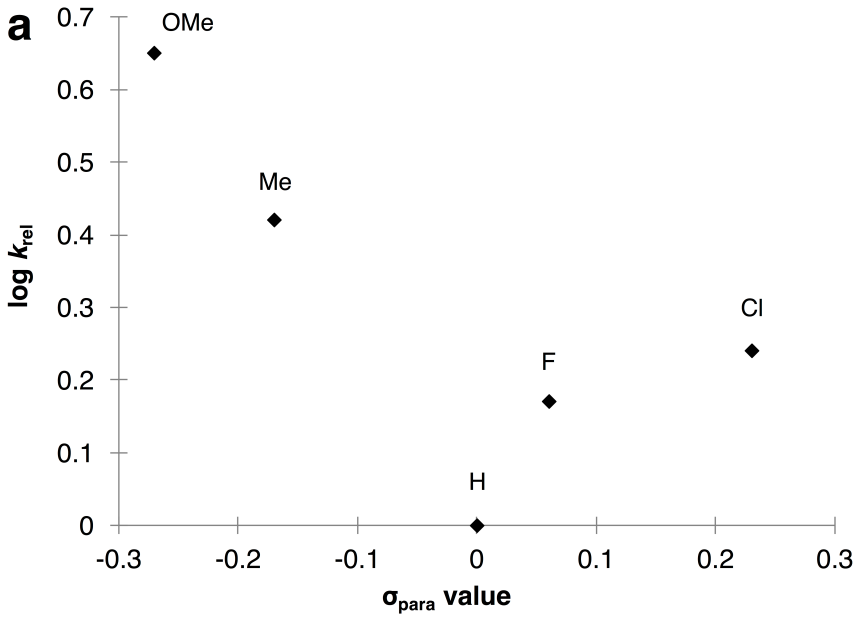


Scheme 4.10. Chemoselective 2*H*-indole formation by switching the identity of the catalyst

To further explore the reactivity of the catalytic intermediates generated from Fe(OEP)Cl, competition experiments were performed between styryl azide **4.16a** and a series of *para*-substituted styryl azides **4.16** (Figure 4.5). We observed that the presence of either electron-releasing or electron-withdrawing *para*-substituents accelerate the rate of the reaction. A V-shaped graph was observed when relative rates were plotted against Hammett σ_{para} values. As before, we interpreted the V-shaped curve to indicate the formation of radical intermediates (Figure 4.5a). To detect the amount of charge distribution on the *N*-atom, the relative rates were plotted against Jiang and Ji's radical σ_{mb} and $\sigma^{\bullet}_{JJ}$ substituent constants (Figure 4.5b). A linear correlation was observed expressed by the equation: $\log k_{rel} = -0.483\sigma_{mb} + 1.13\sigma^{\bullet}_{JJ} + 0.05$. The negative ϱ_{mb} value

indicates an electrophilic metal *N*-aryl nitrene catalytic intermediate, and the positive $\varrho_{JJ}^{\bullet}$ value suggests that the spin density is localized on the nitrogen-atom. The absolute magnitude of $|\varrho_{JJ}^{\bullet}/\varrho_{mb}| > 1$ suggests that the spin delocalization effect is more prominent than the polar substituent effect. Combining together, these correlations suggest that the radical intermediates are generated in the Fe-catalyzed 2*H*-indole formation.





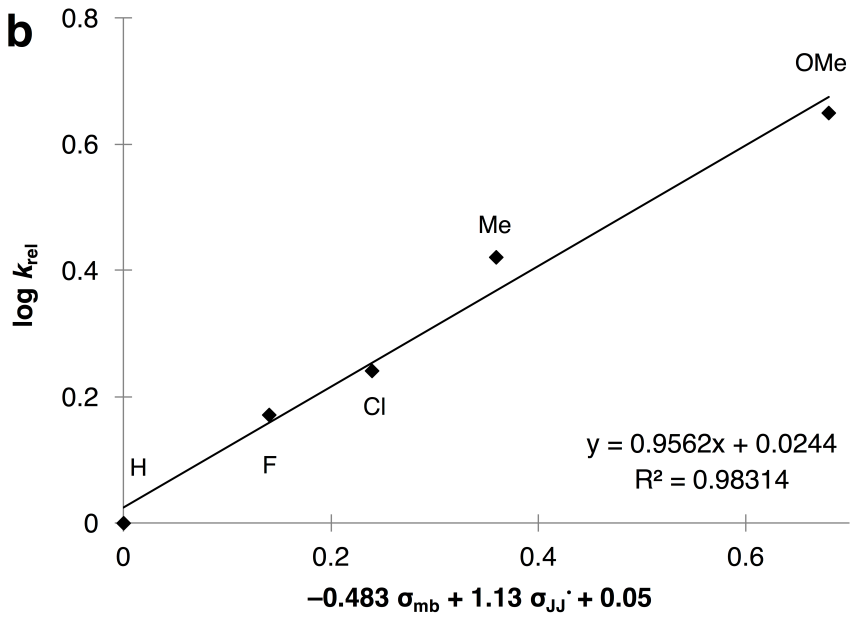


Figure 4.5. Correlation of relative rates between substituted styryl azides **4.16** and **4.16a** with (a) σ_{para}-constants and (b) Jiang and Ji's σ_{mb} and σ_{JJ}**.** values

4.1.7. Conclusion:

In this study, we have shown structure of the substrate and suitable choice of catalyst can control the reactivity embedded in metal *N*-aryl nitrenes. Electrocyclization pathway is favored for mono-β-substituted styryl azides and less sterically congested styryl azides; whereas, C–H bond amination is preferred for substrate where a weak allylic C–H bond is present. The tertiary allylic C–H bond amination preferred more than electrocyclization in substrates containing pre-activated β-amino or -carbonyl group, although the π-system was sterically accessible. In addition to substrate-controlled reaction outcome, we demonstrate that catalysts can control the reactivity of metal *N*-aryl nitrene. While the use of $[Ir(COD)OMe]_2$, $FeBr_2$ or $FeBr_3$ promote only electrocyclization, Fe(OEP)Cl triggers selective allylic sp^3-C–H bond amination in substrates where Rh_2(II) carboxylate provide the mixture of products. Our mechanism study suggests that this product mixture is formed in two-separate pathways:

electrocyclization promotes the indole formation, whereas *H*-atom abstraction and radical recombination produces the 2*H*-indole. These understanding from this study will provide us important outlook toward late stage C–H bond amination to synthesize complex molecules.

4.1.8. Experimental

(This part was taken from supporting information of my published paper: Kong, C.[†]; Jana, N.[†]; Jones, C.; Driver, T. G. *J. Am. Chem. Soc.* **2016**, *138*, 13721. [†]equal contribution)

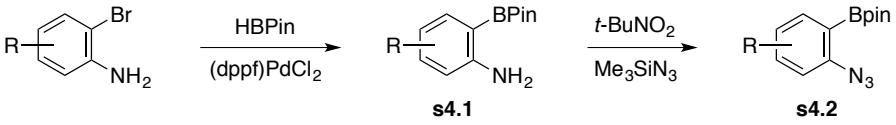
General. ^{1}H NMR and ^{13}C NMR spectra were recorded at ambient temperature using 500 MHz or 300 MHz spectrometers. The data are reported as follows: chemical shift in ppm from internal tetramethylsilane on the d scale, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz) and integration. High-resolution mass spectra were obtained by peak matching. Melting points are reported uncorrected. Analytical thin layer chromatography was performed on 0.25 mm silica gel plates with UV254 fluorescent indicator. Liquid chromatography was performed using forced flow (flash chromatography) of the indicated solvent system on 60Å (40 – 60 μm) mesh silica gel (SiO_2). Medium pressure liquid chromatography (MPLC) was performed using pumps to force flow the indicated solvent system down columns that had been packed with 60Å (40 – 60 μm) mesh silica gel (SiO_2). All reactions were carried out under an atmosphere of nitrogen in glassware that was oven-dried. Unless otherwise noted, all reagents were commercially obtained and, where appropriate, purified prior to use. Acetonitrile, methanol, toluene, THF, Et_2O, and

CH_2Cl_2 were dried by filtration through alumina according to the procedure of Grubbs.[91] Metal salts were stored in a nitrogen atmosphere dry box.

I. Synthesis of 2-azidoarylboronic acid pinacolate esters.

A. Substrate synthesis overview.

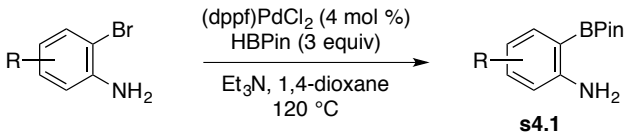
The 2-azidoarylboronic acid pinacolate ester reagents were constructed from substituted 2-bromoanilines following the process outlined in Scheme s1. Palladium-catalyzed borylation of substituted 2-bromoanilines was performed following the conditions reported earlier by us.[91] Azidation of **s1** using trimethylsilyl azide following the conditions reported by Zhang and Moses produced the requisite 2-azidoarylboronic pinacolate ester **s2** for our mechanism investigations.[92]



Scheme s4.1. Synthesis of 2-azidoarylboronic pinacolate ester reagents.

B. Synthesis of 2-aminoarylboronic acid pinacolate esters.

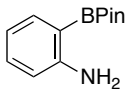
1. General procedure.



To a mixture of 1.0 g of 2-bromoaniline (5.8 mmol), 3.22 mL of Et_3N (23.2 mmol), 0.208 g of (dppf)$PdCl_2$ (0.25 mmol) in 20 mL of 1,4-dioxane, was added dropwise 2.53 mL of

4,4,5,5-tetramethyl-1,3,2-dioxaborolane (17.4 mmol). The resultant mixture was refluxed at 120 °C. After 12 h, the mixture was cooled to room temperature and diluted with 20 mL of NH_4Cl. The phases were separated and the resulting aqueous phase was extracted with an additional 2 × 20 mL of CH_2Cl_2. The combined organic phases were washed with 1 × 30 mL of brine. The resulting organic phase was dried over Na_2SO_4, filtered, and the filtrate was concentrated *in vacuo*. Purification via MPLC afforded the product.

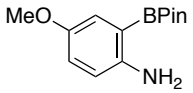
2. Characterization data for 2-aminoarylboronic acid pinacolate esters.



s4.1a

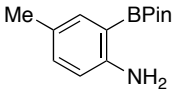
Aniline s4.1a.[91] The general procedure was followed using 3.40 g of 2-bromoaniline (20.0 mmol), 8.7 mL of 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (60.0 mmol), 0.816 g of (dppf)$PdCl_2$ (1.00 mmol), and 8.4 mL of Et_3N (80.0 mmol) in 100 mL of 1,4-dioxane. Purification by MPLC (2:100 – 10:90 EtOAc: hexanes) afforded the product as a light yellow solid (3.02 g, 69%): mp 62 – 64 °C; the spectral data matched that reported by Driver and co-workers and this compound is also available commercially.[91] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (d, *J* = 7.5 Hz, 1H), 7.24 (t, *J* = 7.0 Hz, 1H), 6.70 (t, *J* = 7.0 Hz, 1H), 6.61 (d, *J* = 8.5 Hz, 1H), 4.76 (s, 2H), 1.36 (s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.7 (C), 136.8 (CH), 132.8 (CH), 116.9 (CH), 114.8 (CH), 83.5 (C), 25.0 (CH_3) only

visible peaks; IR (thin film): 3486, 3380, 1624, 1605,1352, 1311, 1244, 1135, 1086, 847, 758, 654 cm^{-1}.



s4.1b

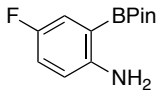
Aniline s4.1b.[93] The general procedure was followed using 0.850 g of 2-bromo-4-methoxyaniline (4.20 mmol), 1.83 mL of 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (12.6 mmol), 0.170 g of (dppf)$PdCl_2$ (0.210 mmol), and 2.34 mL of Et_3N (16.8 mmol) in 42 mL of 1,4-dioxane. Purification by MPLC (2:100 – 10:90 EtOAc: hexanes) afforded the product as a brown liquid (0.670 g, 64%); the spectral data matched that reported by Driver and co-workers:[93] ^1H NMR (500 MHz, $CDCl_3$) δ 7.15 (s, 1H), 6.85 (dd, J = 8.5, 3.0 Hz, 1H), 6.57 (d, J = 8.5 Hz, 1H), 4.47 (s, 2H), 3.76 (s, 3H), 1.34 (s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.4 (C), 148.0 (C), 120.6 (CH), 119.6 (CH), 116.5 (CH), 83.6 (C), 56.0 (CH_3), 25.0 (CH_3) only visible peaks; IR (thin film): 3456, 3366, 1494, 1421, 1359, 1304, 1226, 1037, 855, 829, 750 cm^{-1}.



s4.1c

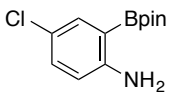
Aniline s4.1c.[93] The general procedure was followed using 0.930 g of 2-bromo-4-methylaniline (5.00 mmol), 2.20 mL of 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (15.0 mmol), 0.204 g of (dppf)$PdCl_2$ (0.250 mmol), and 2.78 mL of Et_3N (20.0 mmol) in 25 mL of 1,4-dioxane. Purification by MPLC (2:100 – 10:90 EtOAc: hexanes) afforded the

product as a light yellow solid (0.490 g, 42%): mp 60 °C; the spectral data matched that reported by Driver and co-workers:[93] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (s, 1H), 7.08 (d, J = 8.0 Hz, 1H), 6.57 (d, J = 8.0 Hz, 1H), 4.65 (s, 2H), 2.26 (s, 3H), 1.38 (s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.5 (C), 136.8 (CH), 133.7 (CH), 125.8 (C), 115.1 (CH), 83.5 (C), 67.1 (C), 25.0 (CH_3), 20.3 (CH_3); IR (thin film): 3500, 2980, 2244, 1618, 1576, 1496 cm^{-1}.



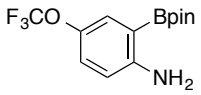
s4.1d

Aniline s4.1d. The general procedure was followed using 0.950 g of 2-bromo-4-fluoroaniline (5.00 mmol), 2.2 mL of 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (15.0 mmol), 0.204 g of (dppf)$PdCl_2$ (0.250 mmol), and 2.78 mL of Et_3N (20.0 mmol) in 25 mL of 1,4-dioxane. Purification by MPLC (2:100 – 10:90 EtOAc: hexanes) afforded the product as a light yellow solid (0.900 g, 76%); the spectral data matched that reported by Driver and co-workers: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (dd, J = 9.0 Hz, 3.0 Hz, 1H), 6.92 (dt, J = 8.5 Hz, 3.0 Hz, 1H), 6.53 (dd, J = 9.0 Hz, 4.5 Hz, 1H), 4.59 (s, 2H), 1.34 (s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.2 (d, J_{CF} = 233.2 Hz, C), 149.8 (C), 121.6 (d, J_{CF} = 20.1 Hz, CH), 119.7 (d, J_{CF} = 23.7 Hz, CH), 116.0 (CH), 83.9 (C), 24.9 (CH_3) only peaks visible; ^{19}F NMR (282 MHz, $CDCl_3$) δ –129.5; IR (thin film): 3470, 3371, 2975, 2931, 1624, 1492, 1434, 1380, 1347, 1198, 1190, 1135, 1081, 963, 912 cm^{-1}.



s4.1e

Aniline s4.1e. The general procedure was followed using 2.06 g of 2-bromo-4-chloroaniline (10.0 mmol), 4.33 mL of HBpin (30.0 mmol), 0.701 g of $(PPh_3)_2PdCl_2$ (1.00 mmol), and 5.60 mL of Et_3N (40.0 mmol) in 100 mL of 1,4-dioxane. Purification by MPLC (0:100 – 20:80 EtOAc: hexanes) afforded the product as a white solid (2.01 g, 79%). The product has previously been reported by Maleczka, Smith and co-workers:[94] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, J = 2.5 Hz, 1H), 7.13 (dd, J = 7.5 Hz, 2.5 Hz, 1H), 6.52 (d, J = 7.5 Hz, 1H), 4.65 (br s, 2H), 1.34 (s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.1 (C), 135.8 (CH), 132.5 (CH), 121.6 (C), 116.0 (CH), 83.9 (C), 24.9 (CH_3) only visible peaks. ATR-FTIR (thin film): 3485, 3388, 2978, 1619, 1482, 1416, 1351 cm^{-1}.



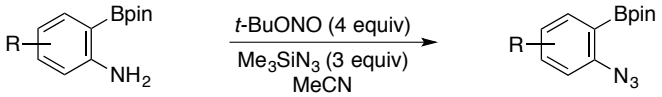
s4.1f

Aniline s4.1f. The general procedure for the Pd-catalyzed borylation reaction was followed using 1.28 g of 2-bromo-4-trifluoromethoxyaniline (5.00 mmol), 2.20 mL of 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (15.0 mmol), 0.204 g of $(dppf)PdCl_2$ (0.250 mmol), and 2.78 mL of Et_3N (20.0 mmol) in 25 mL of 1,4-dioxane. Purification by MPLC (0:100 – 20:80 EtOAc: hexanes) afforded the product as a light yellow solid (0.970 g, 59%): mp 63 – 67 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (s, 1H), 7.06 (d, J = 8.5 Hz, 1H), 6.54 (d, J = 9.0 Hz, 1H), 4.80 (s, 2H), 1.34 (s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.5 (C), 140.0 (C), 129.0 (CH), 126.0 (CH), 122.8 (q, J_{CF} = 253.5 Hz, C), 115.5 (CH), 84.0 (C), 24.9 (CH_3), only visible peaks; ^{19}F NMR (282 MHz, $CDCl_3$) δ –58.8; IR (thin film) 3477, 3374, 2992, 2980, 1627, 1492, 1436, 1532, 1211, 1163, 1094,

965, 852, 825 cm^{-1}.

C. Synthesis of 2-azidoarylboronic acid pinacolate esters.

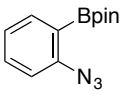
1. General procedure.



s4.1 **s4.2**

To a cooled solution (0 °C) of aniline in MeCN (0.2 M) was added dropwise *t*-BuONO (4.0 equiv) and Me_3SiN_3 (3.0 equiv). The resulting solution was warmed to room temperature. After 1.5 h, the reaction mixture was concentrated *in vacuo*. Purification of the residue by MPLC (0:100 – 5:95 EtOAc: hexanes) afforded the 2-azidoarylboronic acid pinacolate ester.

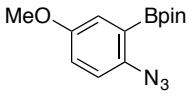
2. Characterization data for 2-azidoarylboronic acid pinacolate esters.



s4.2a

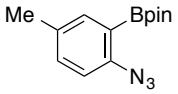
2-Azidophenylboronic acid pinacolate ester s4.2a. The general procedure was followed by using 1.60 g of aniline **s4.1a** (7.30 mmol), 3.47 mL of *t*-BuONO (29.2 mmol) and 2.90 mL of Me_3SiN_3 (21.9 mmol) in 36 mL of MeCN. Purification by MPLC (0:100

– 10:90 EtOAc:hexanes) afforded the product as a yellow oil (1.091 g, 61%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.5 Hz, 1H), 7.45 (t, *J* = 7.0 Hz, 1H), 7.15 – 7.10 (m, 2H), 1.36 (s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.8 (C), 137.0 (CH), 132.4 (CH), 124.2 (CH), 118.2 (CH), 84.0 (C), 24.8 (CH_3) only visible signals. ATR-FTIR (thin film): 2976, 2112, 2076, 1594, 1572, 1487, 1432, 1351, 1316, 1279, 1143, 1110, 1058, 1036, 836, 747 cm^{-1}.



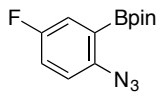
s4.2b

2-Azido-5-methoxyphenylboronic acid pinacolate ester s4.2b. The general procedure was followed by using 0.550 g of aniline **s4.1b** (2.0 mmol), 0.95 mL of *t*-$BuNO_2$ (8.0 mmol) and 0.80 mL of Me_3SiN_3 (6.0 mmol) in 10 mL of MeCN. Purification by MPLC (0:100 – 10:90 EtOAc:hexanes) afforded the product, a yellow solid (0.396 g, 72%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (d, *J* = 2.5 Hz, 1H), 7.07 (d, *J* = 9.0 Hz, 1H), 6.98 (dd, *J* = 8.5 Hz, 3.0 Hz, 1H), 3.81 (s, 3H), 1.36 (s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.3 (C), 137.3 (C), 120.9 (CH), 119.7 (CH), 118.6 (CH), 80.1 (C), 55.6 (CH_3), 24.8 (CH_3) only visible peaks. ATR-FTIR (thin film): 2976, 2934, 2118, 1484, 1409, 1341, 1231, 1143, 1052, 906, 724 cm^{-1}. HRMS (ESI) m/z calculated for $C_{13}H_{18}BN_3O_3Na$ $(M+Na)^+$: 298.1339, found: 298.1345.



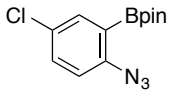
s4.2c

2-Azido-5-methylphenylboronic acid pinacolate ester s4.2c. The general procedure was followed by using 0.518 g of aniline **s4.1c** (2.00 mmol), 0.95 mL of *t*-BuONO (8.0 mmol) and 0.80 mL of Me_3SiN_3 (6.0 mmol) in 10 mL of MeCN. Purification by MPLC (0:100 – 10:90 EtOAc:hexanes) afforded the product as an orange oil (0.253 g, 49%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, *J* = 1.5 Hz, 1H), 7.26 (dd, *J* = 8.5 Hz, 1.5 Hz, 1H), 7.05 (d, *J* = 8.0 Hz, 1H), 2.31 (s, 3H), 1.36 (s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.1 (C), 137.4 (CH), 133.8 (C), 133.0 (CH), 118.2 (CH), 84.0 (C), 24.8 (CH_3), 20.7 (CH_3) only visible peaks. ATR-FTIR (thin film): 2979, 2924, 2118, 2092, 1579, 1487, 1400, 1345, 1312, 1269, 1146, 906, 730 cm^{-1}.



s4.2d

2-Azido-5-fluorophenylboronic acid pinacolate ester s4.2d. The general procedure was followed by using 0.526 g of aniline **s4.1d** (2.0 mmol), 0.95 mL of *t*-$BuNO_2$ (8.0 mmol) and 0.80 mL of Me_3SiN_3 (6.0 mmol) in 10 mL of MeCN. Purification by MPLC (0:100 – 10:90 EtOAc:hexanes) afforded the product, a red oil (0.373 g, 71%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (dd, *J* = 8.5 Hz, 3.0 Hz, 1H), 7.10 (ddd, *J* = 10.5 Hz, 7.5 Hz, 3.0 Hz, 1H), 7.05 (dd, *J* = 8.5 Hz, 4.0 Hz, 1H), 1.34 (s, 12 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.4 (d, J_{CF} = 242.9 Hz, C), 140.5 (C), 123.0 (d, J_{CF} = 20.5 Hz, CH), 119.9 (d, J_{CF} = 7.5 Hz, 1H), 119.1 (d, J_{CF} = 23.5 Hz, CH), 84.3 (C), 24.8 (CH_3), only visible peaks. HRMS (EI) *m/z* calcd for $C_{12}H_{15}BN_3O_2F$ $[M]^+$: 263.1241, found 263.1233. ATR-FTIR (thin film): 2989, 2121, 2092, 1485, 1416, 1319, 1200, 1143, 1126, 966, 916, 807, 763 cm^{-1}.



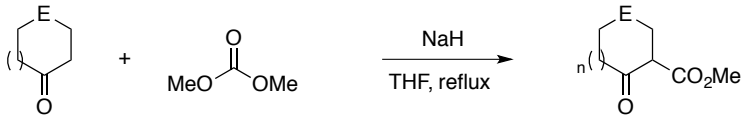
s4.2e

2-Azido-5-chlorophenylboronic acid pinacol ester s4.2e. The general procedure was followed by using 0.13 g of 2-amino-5-chlorophenylboronic acid pinacolate ester **s4.1e** (0.52 mmol), 0.27 mL of *t*-BuONO (2.1 mmol), 0.22 mL of Me_3SiN_3 (1.6 mmol) and 10 mL of MeCN. Purification by MPLC (1:99 – 5:95 EtOAc: hexanes) afforded the product, an orange oil (0.06 g, 42%); the spectral data matched that reported by Driver and co-workers: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.39 (d, J = 8.4 Hz, 1H), 7.06 (d, J = 8.5 Hz, 1H), 1.35 (s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.3 (C), 136.6 (CH), 132.1 (CH), 129.8 (C), 119.7 (CH), 84.4 (C), 24.8 (CH_3), only visible peaks. ATR-FTIR (thin film): 2980, 2119, 2085, 1480, 1402, 1334 cm^{-1}.

II. Preparation of vinyl triflates.

A. Preparation of β-ketoesters.

1. General procedures.



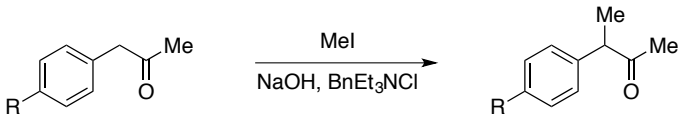
Method A: To sodium hydride (60% oil dispersion, 4 equiv) was added a solution of dimethyl carbonate (3 equiv) in dry THF (1 M). The mixture was stirred at reflux, and then a solution of ketone (1 equiv) in dry THF (2M) was added dropwise to the mixture using a syringe pump. After 2 – 12 hours, the reaction mixture was cooled using an ice

bath. After 20 min, the reaction mixture was diluted with ether. The mixture was hydrolyzed by the slow addition of a 1 M aqueous NH_4Cl solution, then poured into brine and extracted with diethyl ether (4 × 30 mL). The combined organic layers were dried over Na_2SO_4, filtered, and the filtrate was concentrated in *vacuo*. Purification of the residue by MPLC afforded the product.

Method B: To a solution of ketone (1 equiv) in dry THF (2M) was slowly added sodium hydride (60% oil dispersion, 2.5 equiv). After 30 min, a solution of dimethyl carbonate (2.5 equiv) in dry THF (1 M) was added dropwise and the solution was stirred at reflux. After 15 h, the reaction mixture was cooled using an ice bath. After 20 min, the reaction mixture was diluted with ether. The mixture was hydrolyzed by the slow addition of 1 M aqueous solution, then poured into brine and extracted with diethyl ether (4 × 30 mL). The combined organic layers were dried over Na_2SO_4, filtered, and the filtrate was concentrated in *vacuo*. Purification of the residue by MPLC afforded the product.

B. Preparation of 3-aryl-2-butanones.

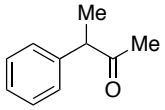
1. General procedure.



A mixture of benzyl methyl ketone (2.80 g, 20.9 mmol), 50% aqueous solution of NaOH (10.4 mL, 129 mmol), and benzyltrimethylammonium chloride (0.166 g, 0.73 mmol) was stirred vigorously using a mechanical stirrer. Methyl iodide (1.94 mL, 31.3 mmol) was

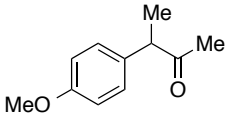
added slowly to this mixture, whose temperature of the solution was kept around room temperature using an ice bath. After 1 h, 20 mL of H_2O and 30 mL of ethyl acetate were added to the reaction mixture. The organic layer was separated, and was washed with H_2O until its pH became neutral. The resulting organic phase was washed with 10 mL of brine. The organic layer was separated and dried over Na_2SO_4, filtrated, and the filtrate was concentrated *in vacuo*. Purification via MPLC afforded the product.

2. Characterization Data for 3-Aryl-2-butanones.



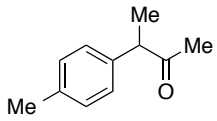
s4.3a

3-Phenyl-2-butanone s4.3a.[95] The general procedure was followed using 2.80 g of benzyl methyl ketone (20.9 mmol), 10.4 mL of a 50% aqueous soln. of NaOH, 0.166 g of benzyltrimethylammonium chloride (0.731 mmol) and 1.94 mL of MeI (31.3 mmol). Purification by MPLC (2:100 – 10:90 EtOAc: hexanes) afforded the product as a colorless liquid (1.96 g, 64%); the spectral data matched that reported by Maeda and co-workers:[95] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (t, J = 7.5 Hz, 2H), 7.25 (m, 1H), 7.20 (d, J = 8.0 Hz, 2H), 3.72 (q, J = 7.0 Hz, 1H), 2.02 (s, 3H), 1.37 (d, J = 7.0 Hz, 3H). ATR-FTIR (thin film): 3027, 2976, 2932, 1711, 1493, 1452, 1353, 1164, 1068 cm^{-1}.



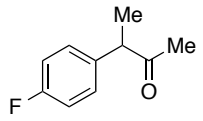
s4.3b

3-*para*-Methoxyphenyl-2-butanone s4.3b.[96] The general procedure was followed using 1.33 g of benzyl methyl ketone (8.09 mmol), 4.00 mL of a 50% aqueous soln. of NaOH, 0.0640 g of benzyltrimethylammonium chloride (0.283 mmol) and 0.750 mL of MeI (12.1 mmol). Purification by MPLC (2:100 – 10:90 EtOAc: hexanes) afforded the product as a white solid (0.576 g 50%); the spectral data matched that reported by Yamataka and co-workers:[96] ^{1}H NMR (500 MHz, $CDCl_3$,) δ 7.05 (d, J = 8.5 Hz, 2H), 6.79 (d, J = 8.5 Hz, 2H), 3.69 (s, 3H), 3.61 (q, J = 7.0 Hz, 1H), 1.95 (s, 3H), 1.27 (d, J = 7.0 Hz, 3H).



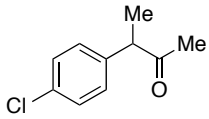
s4.3c

3-*para*-Methylphenyl-2-butanone s4.3c.[96] The general procedure was followed using 1.02 g of 4-methylbenzyl methyl ketone (6.88 mmol), 3.30 mL of a 50% aqueous soln. of NaOH, 0.054 g of benzyltrimethylammonium chloride (0.241 mmol) and 0.64 mL of MeI (10.3 mmol). Purification by MPLC (2:100 – 10:90 EtOAc: hexanes) afforded the product as a colorless oil (0.903 g, 81%); the spectral data matched that reported by Yamataka and co-workers:[96] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14 (d, J = 8.0 Hz, 2H), 7.11 (d, J = 8.0 Hz, 2H), 3.69 (q, J = 7.0 Hz, 1H), 2.32 (s, 3H), 2.03 (s, 3H), 1.36 (d, J = 7.0 Hz, 3H). ATR-FTIR (thin film) 2975, 2930, 1712, 1512, 1453, 1353, 1164, 1067 cm^{-1}.



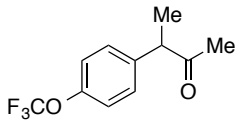
s4.3d

3-*p*-Fluorophenyl-2-butanone s4.3d.[97] The general procedure was followed using 0.500 g of 4-fluorobenzyl methyl ketone (3.28 mmol), 1.62 mL of a 50% aqueous soln. of NaOH, 0.026 g of benzyltrimethylammonium chloride and 0.31 mL of MeI (4.92 mmol). Purification by MPLC (2:100 – 10:90 EtOAc: hexanes) afforded the product as a colorless liquid (0.374 g, 68%); the spectral data matched that reported by Fu and co-workers:[97] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 (dd, J = 9.5 Hz, 5.5 Hz, 2H), 7.02 (t, J = 9.0 Hz, 2H), 3.73 (q, J = 7.0 Hz, 1H), 2.05 (s, 3H), 3.37 (d, J = 7.0 Hz, 3H). ATR-FTIR (thin film) 2978, 2933, 1712, 1600, 1507, 1354, 1221, 1158, 1067 cm^{-1}.



s4.3e

3-*para*-Chlorophenyl-2-butanone s4.3e.[96] The general procedure was followed using 1.08 g of 4-chlorobenzyl methyl ketone (6.40 mmol), 3.30 mL of a 50% aqueous soln. of NaOH, 0.051 g of benzyltrimethylammonium chloride and 0.60 mL of MeI (9.60 mmol). Purification by MPLC (2:100 – 10:90 EtOAc: hexanes) afforded the product as a colorless liquid (0.895 g, 77%); the spectral data matched that reported by Yamataka and co-workers:[96] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (d, J = 8.5 Hz, 2H), 7.11 (d, J = 8.5 Hz, 2H), 3.69 (q, J = 7.0 Hz, 1H), 2.00 (s, 3H), 1.32 (d, J = 7.0 Hz, 3H). ATR-FTIR (thin film): 2977, 2933, 1711, 1489, 1408, 1353, 1163, 1091, 1014 cm^{-1}.

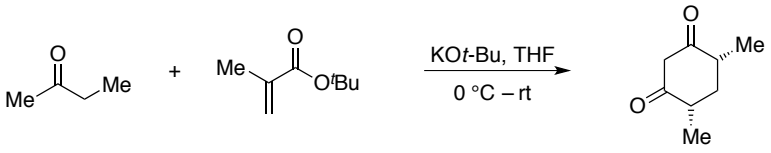


s4.3f

3-*para*-Trifluoromethoxyphenyl-2-butanone s4.3f. The general procedure was followed using 0.468 g of 4-trifluoromethoxybenzyl methyl ketone (2.14 mmol), 1.00 mL of a 50% aqueous soln. of NaOH, and 0.017 g of benzyltrimethylammonium chloride (0.075 mmol) and 0.20 mL of MeI (3.21 mmol). Purification by MPLC (2:100 – 10:90 EtOAc: hexanes) afforded the product as a colorless liquid (0.277 g, 56%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (m, 2H), 7.18 (m, 2H), 3.79 (m, 7.0 Hz, 1H), 2.07 (s, 3H), 1.38 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.2 (C), 148.3 (C), 139.2 (C), 129.2 (CH), 121.4 (CH), 120.4 (q, J_{CF} = 255.1 Hz, CF_3), 52.9 (CH), 28.5 (CH_3), 17.4 (CH_3). ATR-FTIR (thin film): 2980, 1715, 1508, 1356, 1255, 1209, 1158 cm^{-1}.

C. Preparation of cyclohexane-1,3-dione derivatives.

1. Preparation of 4,6-dimethylcyclohexane-1,3-dione.



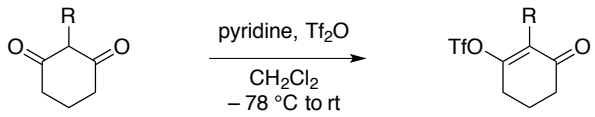
s4.4

4,6-Dimethylcyclohexane-1,3-dione s4.4.[98] To a solution of 0.66 mL of 2-butanone (7.38 mmol) in 60 mL of THF was added 7.38 mL of KO*t*-Bu in THF (7.38 mmol) at 0 °C. After 5 min, 1.00 mL of *tert*-butyl methacrylate (6.15 mmol) was added dropwise.

The reaction mixture was allowed to warm to room temperature. After 30 min, the reactives were quenched by the addition of 5 mL of a 1 M aqueous soln. of HCl. The resulting mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with 10 mL of a saturated aqueous solution of $NaHCO_3$ solution, followed by 10 mL of brine. The resulting organic phase was dried over Na_2SO_4, filtered, and the filtrate was concentrated *in vacuo*. Purification via MPLC (3:97 to 10:90 EtOAc:hexanes) afforded the major *cis*-isomer as a white solid (0.534 g, 62%). The spectral data matched that reported by Ishikawa, Satio and co-workers:[98] ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.45 and 3.34 (ABq, J = 16.0 Hz, 2H), 2.69 – 2.64 (m, 2H), 2.12 (dt, J = 13.5 Hz, 5.5 Hz, 1H), 1.12 (d, J = 6.5 Hz, 6H), only visible peaks; ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.6 (C), 58.2 (CH_2), 44.7 (CH), 35.8 (CH_2), 13.9 (CH_3). ATR-FTIR (thin film): 2966, 2932, 2874, 1684, 1707, 1567, 1456, 1319, 1266, 1215, 1162, 1110 cm^{-1}.

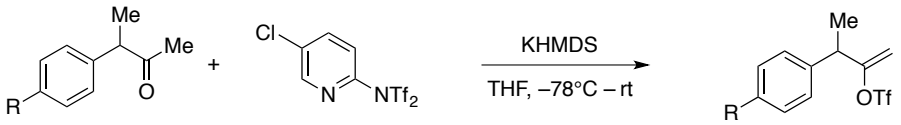
D. Synthesis of vinyl triflates:

1. General procedure:

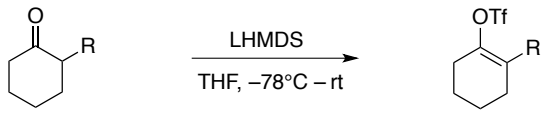


Method A: To a –78 °C solution of cyclohexane-1,3-dione (0.261 g, 2.33 mmol) and pyridine (0.38 mL, 4.66 mmol) in dichloromethane (10 mL) was slowly added trifluoromethanesulfonic anhydride (0.47 mL, 2.80 mmol). After 10 min, the reaction mixture warmed to room temperature. After 4 hours, the reactives were quenched through the addition of 5 mL of a 1 M aqueous soln. of HCl. The resulting mixture was

extracted with diethyl ether (3 × 10 mL). The combined organic layers were washed with 10 mL of a saturated aqueous solution of $NaHCO_3$ solution, followed by 10 mL of brine. The resulting organic phase was dried over Na_2SO_4, filtered, and the filtrate was concentrated *in vacuo*. Purification via MPLC (3:97 to 10:90 EtOAc:hexanes) afforded the product.

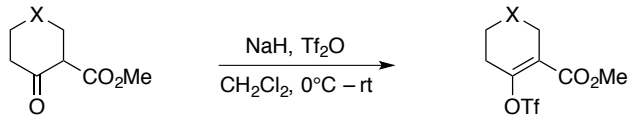


Method B: To a –78 °C solution of KHMDS (1.1 equiv) in THF (0.2 M) was slowly added a solution of 3-aryl-2-butanone (1.0 equiv) in THF. After 30 min, a solution of Comins' reagent (1.1 equiv) in THF was added dropwise. The resulting mixture was then gradually warmed to room temperature. After stirring for 15 h, the reactives were quenched by the addition of a saturated aqueous solution of NH_4Cl. The resulting mixture was extracted with EtOAc. The combined organic phases were washed by brine, and the resulting organic phases were dried over Na_2SO_4, filtered and the filtrate was concentrated in *vacuo*. Purification by MPLC (2:98 to 5:95 EtOAc:hexanes) afforded the product.



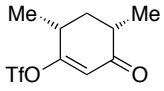
Method C: To a –78 °C solution of LHMDS (1.2 equiv) in THF (0.2 M) was slowly added a solution of 2-methylcyclohexanone (1.0 equiv) in THF. After stirring for 0.5 h, a solution of $PhNTf_2$ (1.2 equiv) in THF was added dropwise to the reaction. The resulting

mixture was then gradually warmed to room temperature. After stirring for 15 h, the reactives were quenched by the addition of a saturated aqueous solution of NH_4Cl. The mixture was then extracted with EtOAc. The combined organic phases were washed by brine, and the resulting organic phases were dried over Na_2SO_4, filtered and the filtrate was concentrated in *vacuo*. Purification by MPLC (2:98 to 5:95 EtOAc:hexanes) afforded the product.



Method D: To a 0 °C solution of β-ketoester (1.0 equiv) in CH_2Cl_2 (0.2 M) was slowly added NaH (60% dispersed in mineral oil, 1.2 equiv). After 30 min, trifluoromethanesulfonic anhydride (1.2 equiv) was added dropwise. The resulting mixture was then warmed to room temperature. After stirring for 15 h, the reactives were quenched by the addition of water. The mixture was then extracted with CH_2Cl_2. The combined organic phases were washed by brine, and the resulting organic phases were dried over Na_2SO_4, filtered and the filtrate was concentrated in *vacuo*. Purification by MPLC (2:98 to 5:95 EtOAc:hexanes) afforded the product.

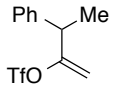
2. Characterization data for vinyl triflates.



s4.5a

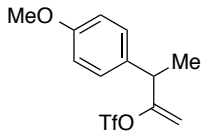
Vinyl triflate s4.5a. Method A was followed using 0.198 g of 4,6-dimethylcyclohexane-

1,3-dione **s4.4** (1.41 mmol), 0.23 mL of pyridine (2.82 mmol) and 0.29 mL of Tf_2O (1.69 mmol) in 14 mL of CH_2Cl_2. Purification by MPLC (2:98 to 10:90 EtOAc:hexanes) afforded the product as a colorless oil (0.367 g, 96%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.00 (s, 1H), 2.94 (m, 1H), 2.40 (m, 1H), 2.17 (dt, *J* = 13.5 Hz, 5.0 Hz, 1H), 1.47 (dt, *J* = 13.5 Hz, 11.0 Hz, 1H), 1.23 (d, *J* = 7.0 Hz, 3H), 1.10 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.3 (C), 169.4 (C), 118.4 (q, J_{CF} = 318.7 Hz, CF_3), 118.3 (CH), 41.1 (CH), 38.3 (CH), 34.3 (CH_2), 17.2 (CH_3), 14.0 (CH_3). ATR-FTIR (thin film): 2917, 2849, 1694, 1425, 1246, 1215, 1139 cm^{-1}.



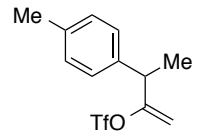
s4.5b

Vinyl triflate s4.5b. Method B was followed using 1.33 g of KHMDS (6.66 mmol), 0.898 g of ketone **s4.3a** (6.06 mmol) and 2.61 g of Comins' reagent (6.66 mmol) in 30 mL of THF. Purification by MPLC (2:98 to 10:90 EtOAc:hexanes) afforded the product as a yellow oil (0.958 g, 56%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.37 (m, 2H), 7.33 – 7.28 (m, 3H), 5.25 (d, *J* = 4.0 Hz, 1H), 5.05 (dd, *J* = 4.0 Hz, 1.5 Hz, 1H), 3.76 (q, *J* = 7.0 Hz, 1H), 1.52 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.8 (C), 140.3 (C), 128.8 (CH), 127.5 (CH), 118.6 (q, J_{CF} = 317 Hz, CF_3), 103.9 (CH_2), 44.2 (CH), 19.3 (CH_3), only visible peaks. ATR-FTIR (thin film): 2980, 1663, 1495, 1415, 1248, 1203, 1132, 1059 cm^{-1}.



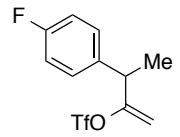
s4.5c

Vinyl triflate s4.5c. Method B was followed using 0.228 g of KHMDS (1.44 mmol), 0.234 g of ketone **s4.3b** (1.31 mmol) and 0.567 g of Comins' reagent (1.44 mmol) in 7 mL of THF. Purification by MPLC (2:98 to 10:90 EtOAc:hexanes) afforded the product as a colorless oil (0.244 g, 60%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 (d, J = 8.5 Hz, 2H), 6.91 (d, J = 8.5 Hz, 2H), 5.21 (d, J = 4.0 Hz, 1H), 5.01 (d, J = 4.0 Hz, 1H), 3.81 (s, 3H), 3.72 (q, J = 7.0 Hz, 1H), 1.49 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.3 (C), 159.0 (C), 132.3 (C), 128.5 (CH), 118.5 (q, J_{CF} = 317.6 Hz, CF_3), 114.2 (CH), 103.6 (CH_2), 55.1 (CH_3), 43.5 (CH), 19.3 (CH_3). ATR-FTIR (thin film): 2978, 2838, 1662, 1611, 1542, 1414, 1247, 1203, 1132, 1066 cm^{-1}.



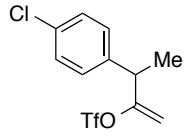
s4.5d

Vinyl triflate s4.5d. Method B was followed using 0.666 g of KHMDS (3.34 mmol), 0.492 g of ketone **s4.3c** (3.03 mmol) and 1.31 g of Comins' reagent (3.34 mmol) in 30 mL of THF. Purification by MPLC (2:98 to 10:90 EtOAc:hexanes) afforded the product as a colorless oil with 90% purity (0.676 g, 76%). The crude vinyl triflate was used in the subsequent cross-coupling reaction without additional purification.



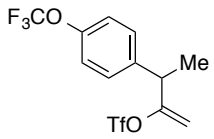
s4.5e

Vinyl triflate s4.5e. Method B was followed using 0.144 g of KHMDS (0.72 mmol), 0.100 g of ketone **s4.3d** (0.60 mmol) and 0.259 g of Comins' reagent (0.66 mmol) in 10 mL of THF. Purification by MPLC (2:98 to 10:90 EtOAc:hexanes) afforded the product as a colorless oil with 90% purity (0.100 g, 56%). The crude vinyl triflate was used in the subsequent cross-coupling reaction without additional purification.



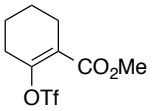
s4.5f

Vinyl triflate s4.5f. Method B was followed using 0.650 g of KHMDS (3.26 mmol), 0.541 g of ketone **s4.3e** (2.96 mmol) and 1.28 g of Comins' reagent (3.26 mmol) in 30 mL of THF. Purification by MPLC (2:98 to 10:90 EtOAc:hexanes) afforded the product as a colorless oil with 90% purity (0.652 g, 70%). The crude vinyl triflate was used in the subsequent cross-coupling reaction without additional purification.



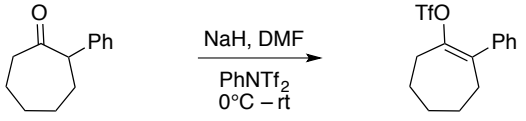
s4.5g

Vinyl triflate s4.5g. Method B was followed using 0.261 g of KHMDS (1.30 mmol), 0.253 g of ketone **s4.3f** (1.08 mmol) and 0.467 g of Comins' reagent (1.18 mmol) in 13 mL of THF. Purification by MPLC (2:98 to 10:90 EtOAc:hexanes) afforded the product as a colorless oil with 90% purity (0.240 g, 60%). The crude vinyl triflate was used in the subsequent cross-coupling reaction without additional purification.



s4.5h

Triflate s4.5h.[99] Method D was followed using 2.00 mL of methyl 2-oxocyclohexanecarboxylate (12.7 mmol), 0.608 g of NaH (15.2 mmol) and 2.56 mL of Tf_2O (15.2 mmol) in 60 mL of CH_2Cl_2. The crude product was afforded as brown oil (3.65 g, 100%). The spectral data matched that reported by Bols and co-workers:[99] ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.78 (s, 3H), 2.46 (dt, J = 5.6 Hz, 3.0 Hz, 2H), 2.38 (dt, J = 5.6 Hz, 3.0 Hz, 2H), 1.77 (dt, J = 5.8 Hz, 2.9 Hz, 2H), 1.65 (dt, J = 5.8 Hz, 2.9 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.1 (C), 151.8 (C), 122.8 (C), 118.3 (q, J_{CF} = 319.7 Hz, C), 52.1 (CH_3), 28.6 (CH_2), 26.1 (CH_2), 22.2 (CH_2), 21.0 (CH_2). The crude vinyl triflate was used in the subsequent cross-coupling reaction without additional purification.



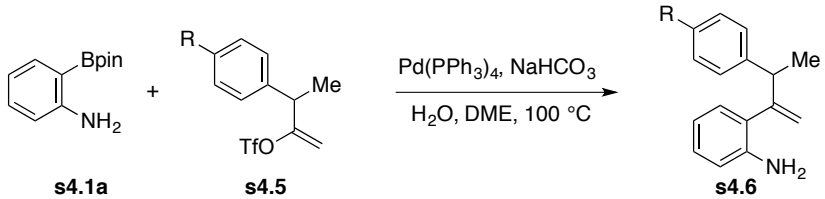
s4.5i

Vinyl triflate s4.5i. To a flame-dried round-bottom flask, 0.368 g of 2-

phenylcycloheptanone (1.95 mmol) was added to a suspension of 0.034 g of NaH (60% dispersed in mineral oil, 2.34 mmol) in 10 mL of DMF at 0 °C. The mixture was warmed to room temperature. After 30 minutes, 0.835 g of 1,1,1-trifluoro-*N*-phenyl-*N*-(trifluoromethylsulfonyl)-methanesulfonamide (2.34 mmol) was added. After an additional 12 hours, the reaction mixture was diluted with 20 mL of water and 50 mL of ethyl acetate. The phases were separated, and the organic phase was washed with 20 mL of brine and 20 mL of water. The resulting organic phase was dried over Na_2SO_4, filtered, and the filtrate was concentrated in *vacuo*. The crude mixture was purified by MPLC (3:97 – 20:80 EtOAc:hexanes) to afford the product as a transparent oil (0.375g, 60%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (t, J = 7.5 Hz, 2H), 7.30 (m, 1H), 7.25 (m, 2H), 2.70 (m, 2H), 2.56 (m, 2H), 1.84 – 1.77 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.5 (C), 139.1 (C), 131.1 (C), 128.2 (CH), 127.9 (CH), 127.6 (CH), 118.1 (q, J_{CF} = 317.5 Hz, CF_3), 34.0 (CH_2), 35.4 (CH_2), 30.9 (CH_2), 25.9 (CH_2), 24.5 (CH_2). ATR-FTIR (thin film): 2923, 2853, 1706, 1445, 1413, 1244, 1205, 1140, 990 cm^{-1}

III. Synthesis of 2-alkenylaryl amines by Suzuki cross-coupling reaction.

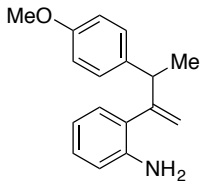
A. General procedure.



s4.1a **s4.5** **s4.6**

To a mixture of vinyl triflate **s4.5** (1 equiv), 2-aminoarylboronic acid pinacol ester **s4.1a** (1.1 equiv), and $Pd(PPh_3)_4$ (5 mol %) in dimethoxyethane (0.1 M) was added a saturated aqueous solution of $NaHCO_3$ (2 mL/mmol of boronic ester). The resulting mixture was heated to 100 °C. After 4 h, the mixture was cooled to room temperature and diluted with 5 mL of cold water. The solution was extracted with 2 × 10 mL of ether followed by 10 mL of brine. The resulting organic phase was dried over Na_2SO_4 and was concentrated *in vacuo*. Purification by MPLC (3:97 to 50:50 EtOAc:hexanes) afforded the product **s4.6**.

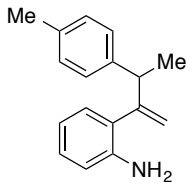
B. Synthesis of 2-alkenylaryl amines.



s4.6a

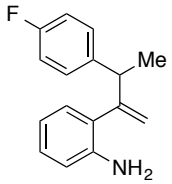
Styryl aniline s4.6a. The general procedure was followed by using 0.362 g of 2-aminoarylboronic acid pinacol ester **s4.1a** (1.65 mmol), 0.466 g of vinyl triflate **s11b** (1.50 mmol), 0.173 g of $Pd(PPh_3)_4$ (5 mol %), 3.0 mL of a saturated aq. soln. of $NaHCO_3$ and 15 mL of dimethoxyethane. Purification by MPLC (3:97 to 10:90 EtOAc:hexanes) afforded the product as yellow oil (0.270 g, 71%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 (d, *J* = 8.5 Hz, 2H), 7.06 (dt, *J* = 8.0 Hz, 1.5 Hz, 1H), 6.85 (m, 3H), 6.67 (m, 2H), 5.33 (s, 1H), 5.18 (s, 1H), 3.81 (q, *J* = 7.0 Hz, 1H), 3.80 (s, 3H), 3.67 (br s, 2H), 1.50 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.1 (C), 152.3 (C), 143.5 (C), 136.4 (C),

129.1 (CH), 128.8 (C), 128.7 (CH), 127.8 (CH), 117.8 (CH), 115.4 (CH), 114.2 (CH_2), 113.7 (CH), 55.2 (CH_3), 45.4 (CH), 20.3 (CH_3). ATR-FTIR (thin film): 3459, 3373, 2962, 2930, 2833, 1609, 1582, 1508, 1492, 1449, 1242, 1176, 1032 cm^{-1}.



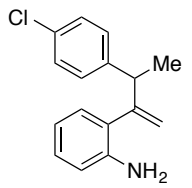
s4.6b

Styryl aniline s4.6b. The general procedure was followed by using 0.405 g of 2-aminoarylboronic acid pinacol ester **s4.1a** (1.85 mmol), 0.494 g of vinyl triflate **s11c** (1.68 mmol), 0.194 g of $Pd(PPh_3)_4$ (5 mol%), 3.6 mL of a saturated aq. soln. of $NaHCO_3$ and 20 mL of dimethoxyethane. Purification by MPLC (3:97 to 10:90 EtOAc:hexanes) afforded the product as yellow oil (0.320 g, 80%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 – 7.13 (m, 4H), 7.07 (dt, *J* = 8.0 Hz, 1.5 Hz, 1H), 6.86 (dd, *J* = 7.5 Hz, 1.0 Hz, 1H), 6.72 – 6.67 (m, 2H), 5.35 (s, 1H), 5.19 (s, 1H), 3.83 (q, 1H), 3.68 (s, 2H), 2.38 (s, 3H), 1.52 (d, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.1 (C), 143.4 (C), 141.3 (C), 135.8 (C), 129.1 (CH), 129.0 (CH), 128.2 (C), 127.8 (CH), 127.7 (CH), 117.9 (CH), 115.4 (CH), 114.4 (CH_2), 45.7 (CH), 21.1 (CH_3), 20.3 (CH_3). ATR-FTIR (thin film): 3460, 3373, 3019, 2966, 2926, 1610, 1511, 1492, 1449, 1295, 1259, 1065 cm^{-1}.



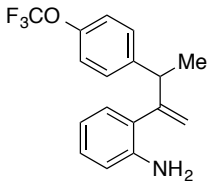
s4.6c

Styryl aniline s4.6c. The general procedure was followed by using 0.166 g of 2-aminoarylboronic acid pinacol ester **s4.1a** (0.76 mmol), 0.200 g of vinyl triflate **s11d** (0.69 mmol), 0.040 g of $Pd(PPh_3)_4$ (5 mol%), 1.5 mL of a saturated aq. soln. of $NaHCO_3$ and 10 mL of dimethoxyethane. Purification by MPLC (3:97 to 10:90 EtOAc:hexanes) afforded the product as yellow oil (0.122 g, 73%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 – 7.14 (m, 2H), 7.03 (dt, *J* = 8.0 Hz, 1.5 Hz, 1H), 6.97 – 6.93 (m, 2H), 6.76 (dd, *J* = 8.0 Hz, 1.5 Hz, 1H), 6.66 – 6.63 (m, 2H), 5.29 (s, 1H), 5.14 (s, 1H), 3.80 (q, *J* = 7.0 Hz, 1H), 3.62 (br s, 2H), 2.92 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.5 (d, J_{CF} = 242.3 Hz, C), 151.8 (C), 143.3 (C), 139.9 (C), 129.1 (d, J_{CF} = 7.37 Hz, CH), 129.0 (CH), 128.5 (C), 127.9 (CH), 117.9 (CH), 115.4 (CH), 115.0 (d, *J* = 20.1 Hz, CH), 114.5 (CH_2), 45.3 (CH), 20.2 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ –117.5. ATR-FTIR (thin film): 3469, 3380, 3023, 2966, 1612, 1506, 1493, 1450, 1218, 1157 cm^{-1}.



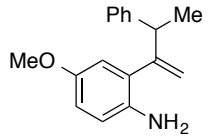
s4.6d

Styryl aniline s4.6d. The general procedure was followed by using 0.385 g of 2-aminoarylboronic acid pinacol ester **s4.1a** (1.76 mmol), 0.503 g of vinyl triflate **s11e** (1.60 mmol), 0.184 g of $Pd(PPh_3)_4$ (10 mol%), 3.2 mL of a saturated aq. soln. of $NaHCO_3$ and 15 mL of dimethoxyethane. Purification by MPLC (3:97 to 10:90 EtOAc:hexanes) afforded the product with 85% purity as yellow oil (0.333 g, 81%). The aniline **s15d** compound was carried on to the azidation step without further purification.



s4.6e

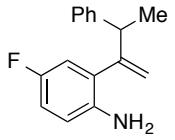
Styryl aniline s4.6e. The general procedure was followed by using 0.139 g of 2-aminoarylboronic acid pinacol ester **s4.1a** (0.63 mmol), 0.210g of vinyl triflate **s11f** (0.58 mmol), 0.033 g of $Pd(PPh_3)_4$ (5 mol%), 1.2 mL of a saturated aq. soln. of $NaHCO_3$ and 10 mL of dimethoxyethane. Purification by MPLC (3:97 to 10:90 EtOAc:hexanes) afforded the product as yellow oil (0.180 g, 75%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (d, *J* = 8.5 Hz, 2H), 7.10 (d, *J* = 8.5 Hz, 2H), 7.02 (t, *J* = 7.5 Hz, 1H), 6.73 (7.0 Hz, 1H), 6.36 (m, 2H), 5.28 (s, 1H), 5.14 (s, 1H), 3.83 (q, *J* = 7.0 Hz, 1H), 3.60 (s, 2H), 1.45 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.3 (C), 147.6 (C), 143.2 (C), 142.9 (C), 129.0 (CH), 128.9 (CH), 128.3 (C), 127.9 (CH), 120.1 (CH), 117.9 (CH), 115.4 (CH), 114.8 (CH_2), 45.3 (CH), 20.1 (CH_3), only peaks visible; ^{19}F NMR (282 MHz, $CDCl_3$) δ –58.3. ATR-FTIR (thin film): 3469, 3380, 2971, 1612, 1506, 1493, 1450, 1253, 1219, 1156, 1066, 1018 cm^{-1}.



s4.6f

Styryl aniline s4.6f. The general procedure was followed by using 0.146 g of 2-aminoarylboronic acid pinacol ester **s4.1b** (0.59 mmol), 0.149 g of vinyl triflate **s11a**

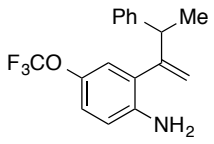
(0.53 mmol), 0.031 g of $Pd(PPh_3)_4$ (5 mol%), 1.2 mL of saturated aq. soln. of $NaHCO_3$ and 10 mL of dimethoxyethane. Purification by MPLC (3:97 to 10:90 EtOAc: hexane) afforded the product as yellow oil (0.091 g, 68%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.21 (m, 5H), 6.64 (dd, *J* = 8.5 Hz, 3.0 Hz, 1H), 6.59 (d, *J* = 8.5 Hz, 1H), 6.36 (d, *J* = 3.0 Hz, 1H), 5.33 (s, 1H), 5.15 (s, 1H), 3.84 (q, *J* = 7.0 Hz, 1H), 3.64 (s, 3H), 3.37 (s, 2H), 1.50 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.0 (C), 151.8 (C), 144.2 (C), 136.9 (C), 129.9 (C), 128.3 (CH), 128.0 (CH), 126.4 (CH), 116.6 (CH), 114.6 (CH), 114.6 (CH_2), 113.8 (CH), 55.6 (CH_3), 46.0 (CH), 20.1 (CH_3); ATR-FTIR (thin film): 3538, 3358, 3025, 2965, 2829, 1599, 1496, 1451, 1423, 1278, 1209, 1039 cm^{-1}.



s4.6g

Styryl aniline s4.6g. The general procedure was followed by using 0.179 g of 2-aminoarylboronic acid pinacol ester **s4.1d** (0.75 mmol), 0.192g of vinyl triflate **s11a** (0.68 mmol), 0.040 g of $Pd(PPh_3)_4$ (5 mol%), 1.3 mL of a saturated aq. soln. of $NaHCO_3$ and 10 mL of dimethoxyethane. Purification by MPLC (3:97 to 10:90 EtOAc:hexanes) afforded the product as yellow oil (0.135 g, 82%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.28 (m, 2H), 7.34 – 7.22 (m, 3H), 6.76 (dt, *J* = 8.0 Hz, 3.0 Hz, 1H), 6.56 (m, 2H), 5.36 (s, 1H), 5.17 (s, 1H), 3.80 (q, *J* = 7.0 Hz, 1H), 3.48 (s, 2H), 1.51 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ. 155.8 (d, J_{CF} = 233.2 Hz, C), 151.1 (C), 143.8 (C), 139.5 (C), 129.9 (d, J_{CF} = 7.5 Hz, C), 128.4 (CH), 127.8 (CH), 126.5 (CH), 116.2 (d, J_{CF} = 7.37 Hz, CH), 115.4 (d, J_{CF} = 22.7 Hz, CH), 115.1 (CH_2), 114.2 (d, J_{CF} = 22.0 Hz, CH), 45.9 (CH),

20.1 (CH_3); ATR-FTIR (thin film): 3439, 3373, 3026, 2968, 1601, 1584, 1494, 1264, 1180 cm^{-1}.



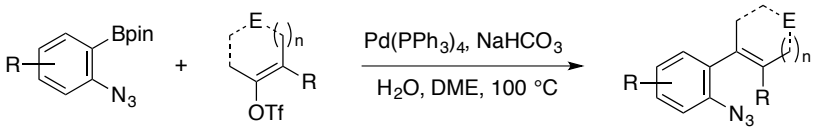
s4.6h

Styryl aniline s4.6h. The general procedure was followed by using 0.262 g of 2-aminoarylboronic acid pinacol ester **s4.1f** (0.86 mmol), 0.218 g of vinyl triflate **s11a** (0.79 mmol), 0.046 g of $Pd(PPh_3)_4$ (5 mol%), 1.6 mL of a saturated aq. soln. of $NaHCO_3$ and 10 mL of dimethoxyethane. Purification by MPLC (3:97 to 10:90 EtOAc:hexanes) afforded the product as yellow oil (0.180 g, 75%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.27 (m, 2H), 7.23 – 7.20 (m, 3H), 6.89 (dd, J = 8.5 Hz, 2.5 Hz, 1H), 6.65 (d, J = 2.5 Hz, 1H), 6.58 (d, J = 9.0 Hz, 1H), 5.40 (s, 1H), 5.18 (s, 1H), 3.79 (q, J = 7.0 Hz, 1H), 3.64 (s, 2H), 1.50 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.7 (C), 143.7 (C), 142.3 (C), 140.6 (C), 129.2 (C), 128.4 (CH), 127.7 (CH), 126.5 (CH), 122.2 (CH), 120.8 (CH), 120.7 (q, J_{CF} = 253.5 Hz, CF_3), 115.6 (CH), 115.1 (CH_2), 46.0 (CH), 19.9 (CH_3). ATR-FTIR (thin film): 3442, 3368, 3027, 2970, 1618, 1601, 1495, 1244, 1215 cm^{-1}.

IV. Synthesis of 2-alkenylaryl azides.

A. Preparation of 2-alkenylaryl azides by Suzuki cross-coupling reaction.

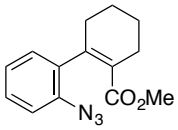
1. General procedure:



s4.2 **s4.5**

To a mixture of vinyl triflate **s4.5** (1 equiv), 2-azidoarylboronic acid pinacol ester **s4.2** (1.1 equiv), and $Pd(PPh_3)_4$ (10 mol %) in dimethoxyethane (0.1 M) was added a saturated aqueous solution of $NaHCO_3$ (2 mL/mmol of boronic ester). The resulting mixture was heated to 100 °C. After 1 h, the mixture was cooled to room temperature and diluted with 5 mL of cold water. The solution was extracted with 2 × 10 mL of ether followed by 10 mL of brine. The resulting organic phase was dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. Purification by MPLC (3:97 to 10:90 EtOAc:hexanes) afforded the product.

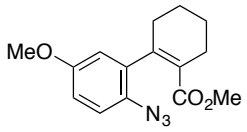
2. Preparation of 2-Alkenylaryl Azides



4.16a

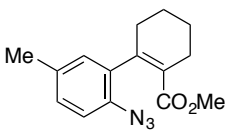
Styryl azide 4.16a.[100] The general procedure was followed by using 0.107 g of 2-azidophenyl boronate **s4.2a** (0.440 mmol), 0.114 g of vinyl triflate **s4.5h** (0.400 mmol), 0.0462 g of $Pd(PPh_3)_4$ (0.0400 mmol), 0.8 mL of a saturated aq. soln. of $NaHCO_3$ and 4 mL of dimethoxyethane. Purification by MPLC (3:97 to 10:90 EtOAc:hexanes) afforded the product as a yellow oil (0.070 g, 70%). The spectral data matched that reported by Driver and co-workers:[100] ^1H NMR (500 MHz, $CDCl_3$) δ 7.28 (t, J = 7.7 Hz, 1H), 7.13 (d, J = 8.0 Hz, 1H), 7.09 (t, J = 7.5 Hz, 1H), 6.99 (dd, J = 7.5 Hz, 1.2 Hz, 1H), 3.44 (s, 3H),

2.45 (s, 3H), 2.24 (dt, J = 24.5 Hz, 5.9 Hz, 1H), 1.74 (d, J = 3.7 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.4 (C), 145.3 (C), 136.3 (C), 135.8 (C), 128.5 (CH), 128.3 (C), 128.1 (CH), 124.7 (CH), 118.3 (CH), 51.2 (CH_3), 32.9 (CH_2), 26.1 (CH_2), 22.1 (CH_2), 22.0 (CH_2); ATR-FTIR (thin film): 2939, 2127, 1720, 1248 cm^{-1}. HRMS (EI) m/z calculated for $C_{14}H_{16}NO_2$ $[M + H - N_2]^+$: 230.1181, found: 230.1188.



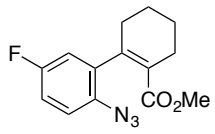
4.16b

Styryl azide 4.16b.[100] The general procedure was followed by using 0.086 g of 2-azidophenyl boronate **s4.2b** (0.315 mmol), 0.100 g of vinyl triflate **s4.5h** (0.347 mmol), 0.0462 g of $Pd(PPh_3)_4$ (0.0400 mmol), 0.6 mL of a saturated aq. soln. of $NaHCO_3$ and 4 mL of dimethoxyethane. Purification by MPLC (3:97 to 10:90 EtOAc:hexanes) afforded the product as a yellow solid (0.046 g, 54%). The spectral data matched that reported by Driver and co-workers:[100] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.02 (d, J = 7.5 Hz, 1H), 6.82 (dd, J = 9.0 Hz, 2.0 Hz, 1H), 6.54 (d, J = 2.5 Hz, 1H), 3.76 (s, 3H), 3.47 (s, 3H), 2.44 (m, 4H), 1.73 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.4 (C), 156.7 (C), 144.9 (C), 140.0 (C), 128.8 (C), 128.4 (C), 119.4 (CH), 113.9 (CH), 113.5 (CH), 55.6 (CH_3), 51.3 (CH_3), 32.8 (CH_2), 26.1 (CH_2), 22.2 (CH_2), 21.9 (CH_2); ATR-FTIR (thin film): 2939, 2114, 1714, 1488, 1284, 1242 cm^{-1}.



4.16c

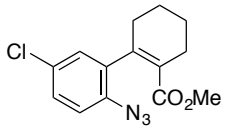
Styryl azide 4.16c.[100] The general procedure was followed by using 0.455 g of 2-azidoarylboronate **s4.2c** (1.76 mmol), 0.461 g of vinyl triflate **s4.5h** (1.60 mmol), 0.199 g of $Pd(PPh_3)_4$ (0.16 mmol), 3.2 mL of saturated aq. soln. of $NaHCO_3$ and 20 mL of dimethoxyethane. Purification by MPLC (3:97 to 10:90 EtOAc: hexane) afforded the product as yellow oil (0.260 g, 55%). The spectral data matched that reported by Driver and co-workers:[100] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.08 (d, J = 8.1 Hz, 1H), 7.01 (d, J = 8.1 Hz, 1H), 6.81 (s, 1H), 3.46 (s, 3H), 2.45 (s, 3H), 2.30 (s, 3H), 2.23 (m, 1H), 1.74 (d, J = 3.7 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.4 (C), 145.3 (C), 135.6 (C), 134.3 (C), 133.5 (C), 129.0 (CH), 128.8 (CH), 128.2 (C), 118.2 (CH), 51.2 (CH_3), 33.0 (CH_2), 26.1 (CH_2), 22.2 (CH_2), 22.0 (CH_2), 20.8 (CH_3). ATR-FTIR (thin film): 2937, 2858, 2110, 1707, 1229 cm^{-1}; HRMS (EI) m/z calculated for $C_{15}H_{18}NO_2$ $(M + H - N_2)^+$: 244.1338, found: 244.1332.



4.16d

Styryl azide 4.16d.[100] The general procedure was followed by using 0.246 g of 2-azidoarylboronate **s4.2d** (0.93 mmol), 0.245 g of vinyl triflate **s4.5h** (0.850 mmol), 0.106 g of $Pd(PPh_3)_4$ (0.090 mmol), 1.7 mL of saturated aq. soln. of $NaHCO_3$ and 10 mL of dimethoxyethane. Purification by MPLC (3:97 to 10:90 EtOAc: hexane) afforded the product as yellow oil (0.185 g, 77%). The spectral data matched that reported by Driver and co-workers:[100] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.06 (dd, J = 8.8 Hz, 4.7 Hz, 1H), 6.97

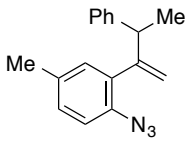
(td, J = 8.3 Hz, 2.9 Hz, 1H), 6.72 (dd, J = 8.7 Hz, 2.8 Hz, 1H), 3.48 (s, 3H), 2.44 (s, 2H), 2.37 (s, 1H), 2.24 (dt, J = 25.0 Hz, 6.3 Hz, 1H), 1.73 (d, J = 4.1 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.9 (C), 159.6 (d, J_{CF} = 245.7 Hz, C), 144.2 (C), 137.6 (d, J_{CF} = 8.8 Hz, C), 132.1 (C), 128.8 (C), 119.6 (d, J_{CF} = 9.2 Hz, CH), 115.4 (d, J_{CF} = 23.7 Hz, CH), 114.7 (d, J_{CF} = 23.9 Hz, CH), 51.3 (CH_3), 32.8 (CH_2), 26.0 (CH_2), 22.1 (CH_2), 21.9 (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$) δ –118.5. ATR-FTIR (thin film): 2937, 2113, 1720, 1485, 1236 cm^{-1}; HRMS (EI) m/z calculated for $C_{14}H_{15}NO_2F$ $(M + H - N_2)^+$: 248.1087, found: 248.1084.



4.16e

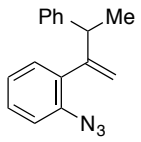
Styryl azide 4.16e.[100] The general procedure was followed by using 0.060 g of 2-azidoarylboronate **s4.2e** (0.22 mmol), 0.055 g of vinyl triflate **s4.5h** (0.20 mmol), 0.025 g of $Pd(PPh_3)_4$ (0.020 mmol), 0.4 mL of saturated aq. soln. of $NaHCO_3$ and 5 mL of dimethoxyethane. Purification by MPLC (3:97 to 10:90 EtOAc: hexane) afforded the product as yellow solid (0.040 g, 71%). The spectral data matched that reported by Driver and co-workers:[100] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (dd, J = 8.5 Hz, 2.4 Hz, 1H), 7.04 (d, J = 8.5 Hz, 1H), 6.98 (d, J = 2.3 Hz, 1H), 3.49 (s, 3H), 2.44 (s, 2H), 2.36 (s, 1H), 2.23 (dt, J = 25.4 Hz, 6.1 Hz, 1H), 1.73 (s, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.9 (C), 144.1 (C), 137.4 (C), 135.0 (C), 129.9 (C), 128.9 (C), 128.3 (CH), 128.0 (CH), 119.5 (CH), 51.4 (CH3), 32.9 (CH_2), 26.0 (CH_2), 22.1 (CH_2), 21.9 (CH_2). ATR-FTIR

(thin film): 2939, 2858, 2122, 2095, 1721, 1483, 1220 cm^{-1}; HRMS (EI) m/z calculated for $C_{14}H_{15}NO_2Cl$ $(M + H - N_2)^+$: 264.0791, found: 264.0792.



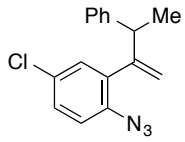
4.36b

Styryl azide 4.36b. The general procedure was followed by using 0.058 g of 2-azido-5-methylphenyl boronate **s4.2c** (0.22 mmol), 0.068 g of vinyl triflate **s4.5b** (0.20 mmol), 0.025 g of $Pd(PPh_3)_4$ (0.020 mmol), 0.4 mL of a saturated aq. soln. of $NaHCO_3$ and 8 mL of dimethoxyethane. Purification by MPLC (3:97 to 10:90 EtOAc:hexanes) afforded the product as a yellow oil (0.046 g, 72%): ^1H NMR (500 MHz, $CDCl_3$) δ 7.25 (m, 2H), 7.20 (m, 2H), 7.15 (t, *J* = 7.5 Hz, 1H), 7.02 (d, *J* = 8.0 Hz, 1H), 6.97 (d, *J* = 8.0 Hz, 1H), 6.73 (s, 1H), 5.13 (s, 1H), 5.02 (s, 1H), 3.95 (q, *J* = 7.0 Hz, 1H), 2.21 (s, 3H), 1.41 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.0 (C), 144.3 (C), 134.1 (C), 134.0 (C), 131.4 (CH), 128.9 (CH), 128.1 (CH), 127.9 (CH), 126.2 (CH), 118.1 (CH), 114.8 (CH_2), 45.1 (CH), 20.8 (CH_3), 20.4 (CH_3), only peaks visible; ATR-FTIR (thin film): 2969, 2922, 211, 2072, 1489, 1293 cm^{-1}. HRMS (EI) *m/z* calculated for $C_{17}H_{17}N_3$ $[M]^+$: 263.1422, found: 263.1421.



4.36c

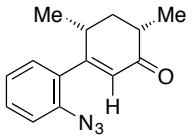
Styryl azide 4.36c. The general procedure was followed by using 0.381 g of 2-azidophenyl boronate **s4.2a** (1.55 mmol), 0.396 g of vinyl triflate **s4.5b** (1.40 mmol), 0.174 g of $Pd(PPh_3)_4$ (0.140 mmol), 3 mL of a saturated aq. soln. of $NaHCO_3$ and 15 mL of dimethoxyethane. Purification by MPLC (3:97 to 10:90 EtOAc:hexanes) afforded the product as a colorless oil (0.244 g, 69%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (m, 5H), 7.24 (tt, *J* = 6.9 Hz, 1.9 Hz, 1H), 7.17 (dd, *J* = 8.0 Hz, 0.6 Hz, 1H), 7.03 (m, 2H), 5.30 (s, 1H), 5.16 (s, 1H), 4.09 (q, *J* = 7.1 Hz, 1H), 1.54 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.9 (C), 144.4 (C), 137.1 (C), 135.4 (C), 131.0 (CH), 128.4 (CH), 128.3 (CH), 128.0 (CH), 126.3 (CH), 124.5 (CH), 118.3 (CH), 115.0 (CH_2), 45.3 (CH), 20.5 (CH_3); ATR-FTIR (thin film): 2968, 2120, 2092, 1484, 1282 cm^{-1}. HRMS (EI) *m/z* calculated for $C_{16}H_{15}N_3$ $[M]^+$: 249.1266, found: 249.1270.



4.36e

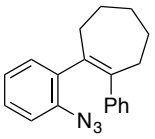
Styryl azide 4.36e. The general procedure was followed by using 0.160 g of 2-azido-5-chlorophenyl boronate **s4.2e** (0.570 mmol), 0.164 g of vinyl triflate **s4.5b** (0.520 mmol), 0.065 g of $Pd(PPh_3)_4$ (0.050 mmol), 1.0 mL of a saturated aq. soln. of $NaHCO_3$ and 10 mL of dimethoxyethane. Purification by MPLC (3:97 to 10:90 EtOAc:hexanes) afforded the product as a yellow oil (0.079 g, 47%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (m, 2H), 7.20 – 7.16 (m, 6H), 7.02 (d, *J* = 8.5 Hz, 1H), 6.91 (d, *J* = 2.5 Hz, 1H), 5.20 (s, 1H), 5.06 (s, 1H), 3.93 (q, *J* = 7.0 Hz, 1H), 1.42 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.7 (C), 143.8 (C), 136.9 (C), 135.7 (C), 131.3 (CH), 130.6 (CH), 129.9 (C), 129.7

(CH), 128.3 (CH), 126.4 (CH), 119.7 (CH), 115.7 (CH_2), 45.0 (CH), 20.3 (CH_3); ATR-FTIR (thin film): 2968, 2111, 2076, 1475, 1296 cm^{-1}. HRMS (EI) *m/z* calculated for $C_{16}H_{14}ClN_3$ $[M]^+$: 283.0876, found: 283.0870.



4.51

Styryl azide 4.51. The general procedure was followed by using 0.144 g of 2-azidophenyl boronate **s4.2a** (0.590 mmol), 0.145 g of vinyl triflate **s4.5a** (0.530 mmol), 0.067 g of $Pd(PPh_3)_4$ (0.050 mmol), 1.0 mL of a saturated aq. soln. of $NaHCO_3$ and 10 mL of dimethoxyethane. Purification by MPLC (3:97 to 10:90 EtOAc:hexanes) afforded the product, a yellow oil, as a 6:1 mixture of diastereomers (0.097 g, 75%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (t, *J* =7.6 Hz, 1H), 7.17 (d, *J* = 8.0 Hz, 1H), 7.14 (t, *J* = 7.6 Hz, 1H), 7.10 (dd, *J* = 7.6 Hz, 1.4 Hz, 1H), 5.92 (s, 1H), 3.28 (m, 1H), 2.55 (m, 1H), 2.15 (dt, *J* = 13.2 Hz, 4.6 Hz, 1H), 1.54 (td, *J* = 13.5 Hz, 11.2 Hz, 1H), 1.16 (d, *J* = 6.7 Hz, 3H), 0.86 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.8 (C), 164.1 (C), 136.5 (C), 131.8 (C), 129.5 (CH), 129.4 (CH), 128.9 (CH), 125.0 (CH), 118.2 (CH), 41.5 (CH), 40.7 (CH_2), 34.1 (CH), 19.9 (CH_3), 14.8 (CH_3). Characteristic data for minor diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.84 (s, 1H), 3.07 (m, 1H), 1.92 (d, *J* = 6.5 Hz, 3H), 1.03 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 129.8 (CH), 127.7 (CH), 118.6 (CH), 37.8 (CH_2), 15.3 (CH_3). ATR-FTIR (thin film): 2962, 2929, 2852, 2123, 1672, 1284 cm^{-1}. HRMS (ES) *m/z* calculated for $C_{14}H_{16}NO$ $[M + H - N_2]^+$: 214.1232, found: 214.1242.



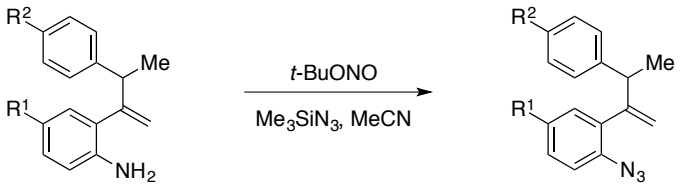
4.61

Styryl azide 4.61. The general procedure was followed by using 0.124 g of 2-azidophenyl boronate **s4.2a** (0.510 mmol), 0.148 g of vinyl triflate **s4.5i** (0.460 mmol), 0.053 g of $Pd(PPh_3)_4$ (0.046 mmol), 0.8 mL of a saturated aq. soln. of $NaHCO_3$ and 1.0 mL of dimethoxyethane. Purification by MPLC (3:97 to 10:90 EtOAc:hexanes) afforded the product as a yellow solid (0.096 g, 72%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13 – 7.07 (m, 3H), 7.04 – 7.01 (m, 2H), 6.98 (d, *J* = 8.0 Hz, 2H), 6.87 – 6.82 (m, 2H), 2.77 (m, 1H), 2.68 (m, 1H), 2.52 (m, 1H), 1.97 – 1.89 (m, 4H), 1.76 (m, 1H), 1.64 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.9 (C), 143.0 (C), 138.4 (C), 137.7 (C), 137.4 (C), 131.3 (CH), 128.1 (CH), 127.5 (CH), 127.3 (CH), 125.8 (CH), 124.4 (CH), 118.3 (CH), 36.5 (CH_2), 36.4 (CH_2), 32.7 (CH_2), 27.1 (CH_2), 26.4 (CH_2). ATR-FTIR (thin film): 3053, 2920, 2840, 2120, 2088, 1572, 1481, 1440, 1283, 1272, 1091 cm^{-1}; HRMS (ESI) m/z calculated for $C_{19}H_{20}N$ $[M + H - N_2]^+$: 262.1596, found: 262.1596.

B. Synthesis of styryl szides from aniline.

1. General procedure:

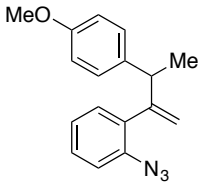
Following the procedure of Zhang and Moses,[101] the azides were prepared. Yields were not optimized.



s4.6

To a cooled solution of aniline **s4.6** in MeCN (0.1 M) was added dropwise *t*-BuONO (4 equiv) and Me_3SiN_3 (3 equiv). The resulting solution was warmed to room temperature. After 1h, visualization of the reaction progress using TLC indicated the consumption of the starting material. De–ionized water was added to the reaction mixture. The mixture then was extracted with 2 × 30 mL of CH_2Cl_2. The combined organic phases were washed with 20 mL of brine. The resulting organic phase was dried over Na_2SO_4, filtered, and the filtrate was concentrated *in vacuo*. Purification of the residue by MPLC (2:98 – 10:90 EtOAc: hexanes) afforded azide.

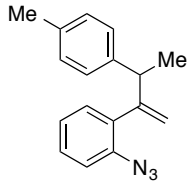
2. Preparation of Styryl Azides:



4.33a

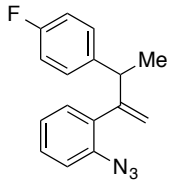
Styryl azide 4.33a. The general procedure was followed by using 0.270 g of aniline **s4.6a** (1.10 mmol), 0.52 mL of *t*-BuONO (4.0 mmol), 0.41 mL of Me_3SiN_3 (3.0 mmol) and 10 mL of MeCN. Purification by MPLC (2:98 – 10:90 EtOAc:hexanes) afforded the product as a yellow oil (0.224 g, 75%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (t, J = 7.6 Hz, 1H), 7.18 (d, J = 8.5 Hz, 2H), 7.14 (d, J = 8.0 Hz, 1H), 7.02 (t, J = 7.4 Hz, 1H), 6.98 (d, J

= 7.5 Hz, 1H), 6.85 (d, *J* = 8.6 Hz, 2H), 5.25 (s, 1H), 5.10 (s, 1H), 4.00 (q, *J* = 7.0 Hz, 1H), 3.80 (s, 3H), 1.48 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.0 (C), 152.2 (C), 137.0 (C), 136.4 (C), 135.4 (C), 130.9 (CH), 128.8 (CH), 128.3 (CH), 124.5 (CH), 118.3 (CH), 114.6 (CH_2), 113.6 (CH), 55.2 (CH_3), 44.5 (CH), 20.5 (CH_3); ATR-FTIR (thin film): 2965, 2833, 2119, 2090, 1509, 1286, 1244 cm^{-1}. HRMS (ES) *m/z* calculated for $C_{17}H_{18}NO$ $[M + H - N_2]^+$: 252.1388, found: 252.1394.



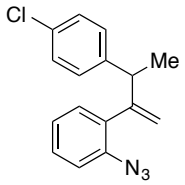
4.33b

Styryl azide 4.33b. The general procedure was followed by using 0.310 g of **s4.6b** (1.30 mmol), 0.66 mL of *t*-BuONO (5.2 mmol), 0.55 mL of Me_3SiN_3 (3.9 mmol) and 15 mL of MeCN. Purification by MPLC (2:98 – 10:90 EtOAc:hexanes) afforded the product as a colorless oil (0.320 g, 93%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (t, *J* =7.5 Hz, 1H), 7.16 (m, 5H), 7.03 (m, 2H), 5.29 (s, 1H), 5.14 (s, 1H), 4.04 (q, *J* = 7.0 Hz, 1H), 2.37 (s, 3H), 1.52 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.0 (C), 141.3 (C), 137.0 (C), 135.7 (C), 135.5 (C), 131.0 (CH), 129.0 (CH), 128.3 (CH), 127.8 (CH), 124.5 (CH), 118.3 (CH), 114.8 (CH_2), 44.9 (CH), 21.1 (CH_3), 20.6 (CH_3); ATR-FTIR (thin film): 2967, 2929, 2119, 2089, 1484, 1282 cm^{-1}. HRMS (EI) *m/z* calculated for $C_{17}H_{17}N_3$ $[M]^+$: 263.1422, found: 263.1429.



4.33d

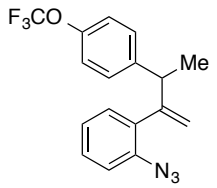
Styryl azide 4.33d. The general procedure was followed by using 0.194 g of aniline **s4.6c** (0.800 mmol), 0.38 mL of *t*-BuONO (3.2 mmol), 0.32 mL of Me_3SiN_3 (2.4 mmol) and 15 mL of MeCN. Purification by MPLC (2:98 – 10:90 EtOAc:hexanes) afforded the product as a colorless oil (0.150 g, 70%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (dd, J = 8.0 Hz, 1.5 Hz, 1H), 7.15 – 7.09 (m, 3H), 6.97 (dt, J = 7.5 Hz, 1.0 Hz, 1H), 6.93 – 6.88 (m, 3H), 5.17 (s, 1H), 5.05 (s, 1H), 3.95 (q, J = 7.0 Hz, 1H), 1.42 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.3 (d, J_{CF} = 229.7 Hz, C), 151.7 (C), 135.0 (C), 139.9 (C), 136.9 (C), 130.8 (CH), 129.2 (d, J_{CF} = 7.4 Hz, CH), 128.4 (CH), 124.4 (CH), 118.2 (CH), 114.9 (CH), 114.8 (d, J_{CF} = 5.5 Hz, CH), 44.3 (CH), 20.4 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ –117.8. ATR-FTIR (thin film): 2968, 2932, 2121, 2091, 1601, 1572, 1507, 1485, 1441, 1283, 1220, 1158 cm^{-1}. HRMS (ESI) *m/z* calculated for $C_{16}H_{15}FN$ [M – N_2 + H]$^+$: 240.1189, found: 240.1192.



4.33e

Styryl azide 4.33e. The general procedure was followed by using 0.310 g of **s4.6d** (1.20 mmol), 0.61 mL of *t*-BuONO (4.8 mmol), 0.50 mL of Me_3SiN_3 (3.6 mmol) and 10 mL of

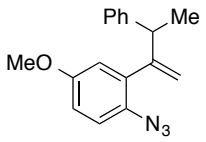
MeCN. Purification by MPLC (2:98 – 10:90 EtOAc:hexanes) afforded the product as a colorless oil (0.320 g, 94%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (m, 1H), 7.20 (m, 2H), 7.10 (m, 3H), 6.99 – 6.96 (m, 1H), 6.90 – 6.88 (m, 1H), 5.18 (s, 1H), 5.06 (s, 1H), 3.96 (q, *J* = 7.0 Hz, 1H), 1.41 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.4 (C), 142.9 (C), 136.9 (C), 134.9 (C), 131.8 (C), 130.8 (CH), 129.2 (CH), 128.4 (CH), 128.3 (CH), 124.5 (CH), 118.2 (CH), 115.1 (CH_2), 44.5 (CH), 20.3 (CH_3); ATR-FTIR (thin film): 2973, 2126, 2091, 1484, 1279 cm^{-1}. HRMS (EI) *m/z* calculated for $C_{16}H_{14}ClN_3$ $(M)^+$: 283.0876, found: 283.0878.



4.33f

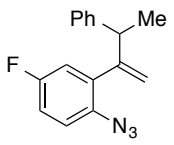
Styryl azide 4.33f. The general procedure was followed by using 0.100 g of aniline **s4.6e** (0.325 mmol), 0.15 mL of *t*-BuONO (1.30 mmol), 0.13 mL of Me_3SiN_3 (0.975 mmol) and 15 mL of MeCN. Purification by MPLC (2:98 – 10:90 EtOAc:hexanes) afforded the product, a colorless oil (0.086 g, 80%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 – 7.25 (m, 1H), 7.20 (d, *J* = 8.5 Hz, 2H), 7.11 – 7.07 (m, 3H), 6.98 (dt, *J* = 7.5 Hz, 1.0 Hz, 1H), 6.89 (dd, *J* = 8.0 Hz, 1.5 Hz, 1H), 5.17 (s, 1H), 5.06 (s, 1H), 3.98 (q, *J* = 7.0 Hz, 1H), 1.43 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.4 (C), 147.6 (C), 143.0 (C), 136.9 (C), 134.8 (C), 130.8 (CH), 129.1 (CH), 128.5 (CH), 124.5 (CH), 120.6 (CH), 118.2 (CH), 115.1 (CH), 44.5 (CH), 20.3 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ –58.33.

ATR-FTIR (thin film): 2969, 2122, 2093, 1633, 1506, 1485, 1252, 1219, 1157 cm^{-1}. HRMS (EI) *m/z* calculated for $C_{17}H_{15}F_3N_3O$ $(M+H)^+$: 306.1106, found: 306.1108.



4.36a

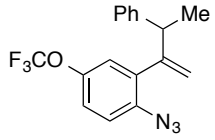
Styryl azide 4.36a. The general procedure was followed by using 0.085 g of **s4.6f** (0.34 mmol), 0.170 mL of *t*-BuONO (1.34 mmol), 0.14 mL of Me_3SiN_3 (1.0 mmol) and 10 mL of MeCN. Purification by MPLC (2:98 – 10:90 EtOAc:hexanes) afforded the product as a colorless oil (0.077 g, 83%): ^1H NMR (500 MHz, $CDCl_3$) δ 7.26 (m, 2H), 7.18 (m, 2H), 7.15 (t, *J* = 7.0 Hz, 1H), 7.00 (d, *J* = 8.5 Hz, 1H), 6.77 (dd, *J* = 8.5 Hz, 3.0 Hz, 1H), 6.42 (d, *J* = 3.0 Hz, 1H), 5.19 (s, 1H), 5.06 (s, 1H), 3.95 (q, *J* = 7.5 Hz, 1H), 3.66 (s, 3H), 1.43 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.3 (C), 151.6 (C), 144.2 (C), 136.3 (C), 129.4 (C), 128.2 (CH), 127.9 (CH), 126.2 (CH), 119.2 (CH), 116.2 (CH), 114.9 (CH_2), 113.8 (CH), 55.5 (CH_3), 45.2 (CH), 20.2 (CH_3); ATR-FTIR (thin film): 2966, 2834, 2115, 2074, 1488, 1286 cm^{-1}; HRMS (ES) *m/z* calculated for $C_{17}H_{18}NO$ $[M + H - N_2]^+$: 252.1388, found: 252.1393.



4.36d

Styryl azide 4.36d. The general procedure was followed by using 0.130 g of **s4.6g** (0.540 mmol), 0.28 mL of *t*-BuONO (2.15 mmol), 0.23 mL of Me_3SiN_3 (1.6 mmol) and

10 mL of MeCN. Purification by MPLC (2:98 – 10:90 EtOAc:hexanes) afforded the product as a colorless solid (0.098 g, 68%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (t, J = 7.5 Hz, 2H), 7.22 (t, J = 8.2 Hz, 3H), 7.05 (dd, J = 8.8 Hz, 4.7 Hz, 1H), 6.95 (td, J = 8.3 Hz, 2.9 Hz, 1H), 6.69 (dd, J = 9.0 Hz, 2.9 Hz, 1H), 5.28 (s, 1H), 5.13 (s, 1H), 4.01 (q, J = 7.3 Hz, 1H), 1.49 (d, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.2 (C, J_{CF} = 245.8 Hz), 150.8 (C), 143.9 (C), 137.0 (C), 132.9 (C), 128.3 (CH), 127.8 (CH), 126.4 (CH), 119.5 (CH, J_{CF} = 8.8 Hz), 117.7 (CH, J_{CF} = 22.1 Hz), 115.5 (CH_2), 115.0 (CH, J_{CF} = 22.1 Hz), 45.0 (CH), 20.4 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ –118.8. ATR-FTIR (thin film): 3027, 2969, 2118, 2078, 1484, 1270 cm^{-1}. HRMS (EI) *m/z* calculated for $C_{16}H_{14}N_3F$ $[M]^+$: 267.1172, found: 267.1185.

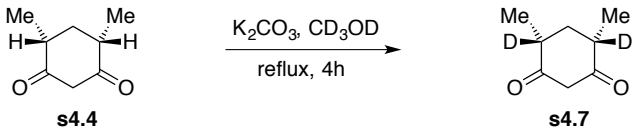


4.36f

Styryl azide 4.36f. The general procedure was followed by using 0.160 g of **s4.6g** (0.520 mmol), 0.27 mL of *t*-BuONO (2.1 mmol), 0.22 mL of Me_3SiN_3 (1.6 mmol) and 10 mL of MeCN. Purification by MPLC (2:98 – 10:90 EtOAc: hexanes) afforded the product as a colorless oil (0.170 g, 98%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (t, J = 7.6 Hz, 2H), 7.19 (d, J = 7.2 Hz, 3H), 7.10 (s, 2H), 6.79 (s, 1H), 5.30 (s, 1H), 5.12 (s, 1H), 3.97 (q, J = 7.0 Hz, 1H), 1.49 (d, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.4 (C), 145.4 (C), 143.7 (C), 136.7 (C), 135.8 (C), 128.3 (CH), 127.8 (CH), 126.4 (CH), 123.7 (CH), 120.9 (CH), 120.4 (CF_3, J_{CF} = 257.1 Hz), 119.3 (CH), 115.6 (CH_2), 45.1 (CH), 20.1 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ –58.7. ATR-FTIR (thin film): 2971, 2121, 2085, 1484, 1249,

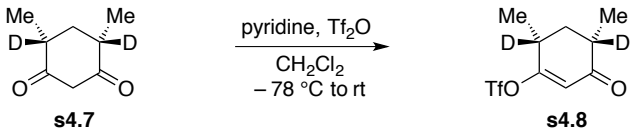
1216 cm^{-1}. HRMS (ES) *m/z* calculated for $C_{17}H_{15}NF_3O$ $[M + H - N_2]^+$: 306.1106, found: 306.1116.

V. Preparation of D-labeled substrates:

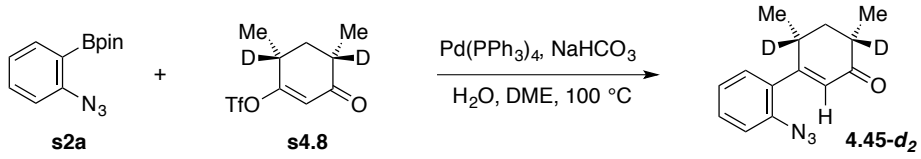


s4.4 **s4.7**

4,6-Dimethylcyclohexane-1,3-dione-4,6-*d*$_2$ s4.7. To a flame dried conical flask, 0.500 g of *cis*-4,6-dimethylcyclohexane-1,3-dione **s4.4** (3.56 mmol) in 10 mL methanol-d_4, was added 2.95 g of K_2CO_3 (21.4 mmol) and the mixture was refluxed at 90 °C. After 4 hours, the reaction mixture was then cooled to room temperature, and the reactives were quenched through the addition of 2.0 mL of acetic acid-d_4 (34.9 mmol). The mixture was then refluxed to reflux. After 2 hours, the solution was cooled to room temperature, and 10 mL of water was added to the reaction mixture. The resulting mixture was extracted with 2 × 20 mL of ethyl acetate, and the combined organic layers was extracted with 10 mL of brine. The resulting organic phase was dried over Na_2SO_4, filtered, and the filtrate was concentrated in *vacuo*. Purification by MPLC (2:98 to 50:50 EtOAc:hexanes) afforded the *cis*-isomer as a white solid (0.312 g, 61%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.46 and 3.38 (ABq, *J* = 16.0 Hz, 2H), 2.68 (m, 0.27 H), 2.12 (d, *J* = 13.5 Hz, 1H), 1.44 (m, 0.56 H), 1.14 (s, 6H), only peaks visible; ATR-FTIR (thin film): 2964, 2931, 2832, 2574, 1731, 1708, 1595, 1456, 1375, 1312, 1257, 1195 cm^{-1}.

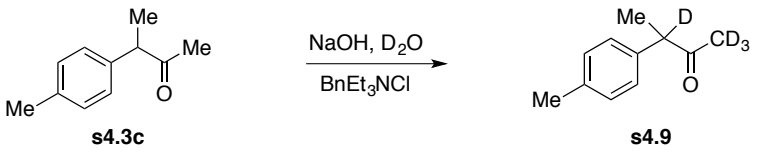


Vinyl triflate s4.8. To a –78 °C solution of 0.320 g of 4,6-dimethylcyclohexane-1,3-dione-4,6-d_2 **s4.7** (2.25 mmol) and 0.360 mL of pyridine (4.50 mmol) in dichloromethane (20 mL) at –78 °C was added 0.45 mL of trifluoromethanesulfonic anhydride (2.70 mmol) slowly. The reaction mixture was stirred for 10 min at –78 °C followed by warming it to room temperature. After 4 hours, the reaction mixture was then quenched with 3.0 mL of a 1M aq. solution of HCl. The resulting mixture was extracted with 3 × 10 mL of diethyl ether. The combined organic layer was washed with 10 mL of a saturated aq. solution of $NaHCO_3$ solution, followed by 10 mL of brine. The resulting organic phase was dried over Na_2SO_4, filtered, and the filtrate was concentrated *in vacuo* to produce the crude product as a brown oil (0.477 g, 77%). This crude product was used in the next step without further purification. ATR-FTIR (thin film): 2975, 2938, 1692, 1639, 1459, 1422, 1246, 1207, 1135, 1021 cm^{-1}.



Azide 4.45-d_2. To a mixture of 0.115 g of vinyl triflate **s4.8** (0.420 mmol), 0.113 g of 2-azidoarylboronic acid pinacol ester **s4.2a** (0.460 mmol), and 0.029 g of $PdCl_2(PPh_3)_2$ (10 mol %) in 4.6 mL of dimethoxyethane (0.1 M) was added a 0.90 mL saturated aq. solution of $NaHCO_3$ (2 mL/mmol of boronic ester). The resulting mixture was heated to 100 °C. After 1 h, the mixture was cooled to room temperature and diluted with 5 mL of

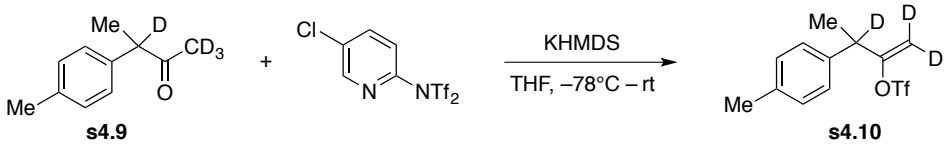
cold water. The solution was extracted with 2 × 10 mL of ether followed by 10 mL of brine. The resulting organic phase was dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. Purification by MPLC (3:97 to 10:90 EtOAc: hexanes) afforded the *cis*-isomer (0.058 g, 57%) as a yellow oil, 81% D was exchanged in the allylic position: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (t, *J* =7.0 Hz, 1H), 7.18 – 7.09 (m, 3H), 5.93 (s, 1H), 3.28 (m, 0.19 H), 2.55 (m, 0.21 H), 2.14 (d, *J* = 13.0 Hz, 1H), 1.52 (d, *J* = 12.5 Hz, 1H), 1.16 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.9 (C), 164.1 (C), 136.5 (C), 131.8 (C), 129.5 (CH), 129.4 (CH), 128.9 (CH), 125.0 (CH), 118.2 (CH), 41.4 (CD), 40.7 (CH_2), 34.1 (CD), 19.9 (CH_3), 14.8 (CH_3) only peaks visible (allylic methine CH signals present from the 19% unlabeled azide); ATR-FTIR (thin film): 2959, 2927, 2870, 2122, 1672, 1609, 1484, 1441, 1286, 1154 cm^{-1}. HRMS (ES) *m/z* calculated for $C_{14}H_{14}D_2NO$ $[M + H - N_2]^+$: 216.1357, found: 216.1362.



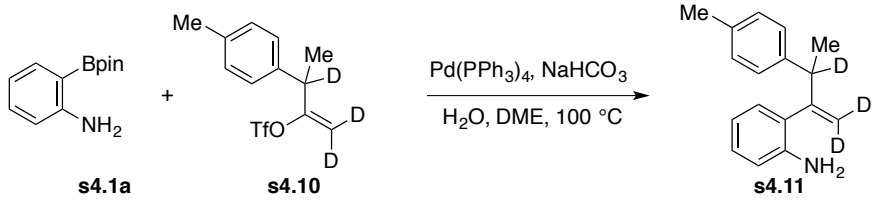
s4.3c **s4.9**

3-*para*-Methylphenyl-2-butanone-d_2 s4.9. A mixture of 0.200 g of 3-*para*-methylphenyl-2-butanone **s4.3c** (1.35 mmol), 16 mL of a 50% NaOH aqueous solution in D_2O (8.09 mmol), and 0.018 g benzyltrimethylammonium chloride (6 mol %) was stirred vigorously using a mechanical stirrer. The temperature of the solution was kept around room temperature by an ice bath. After stirring for 1 h, 20 mL of H_2O and 30 mL of ethyl acetate were added to the reaction mixture. The organic layer was separated, and was washed with H_2O until its pH became neutral. The resulting organic phase was extracted with 10 mL of brine. The organic layer was separated and dried over Na_2SO_4,

filtered, and the filtrate was concentrated *in vacuo* to produce a residue (0.196 g, 97%), which was submitted to the next step without additional purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14 (d, *J* = 8.0 Hz, 2H), 7.11 (d, *J* = 8.0 Hz, 2H), 2.33 (s, 3H), 1.36 (s, 3H); ATR-FTIR (thin film): 2975, 2930, 1708, 1513, 1451, 1372, 1266, 1243, 1126, 1007 cm^{-1}.



Vinyl triflate s4.10. To a –78 °C solution of 0.196 g of KHMDS (0.980 mmol) in 5.0 mL of THF (0.2 M) was slowly added a solution of 0.125 g of 3-*p*-methylphenyl-2-butanone-d_2 **s4.9** (0.800 mmol) in THF. After stirring for 0.5 h, a solution of 0.354 g of Comins' reagent (0.900 mmol) in THF was added dropwise to the reaction. The resulting mixture was then gradually warmed to room temperature. After stirring for overnight, the reaction was quenched by the addition of a saturated aq. solution of NH_4Cl. The mixture was then extracted with EtOAc. The combined organic phases were washed with brine. The resulting organic phase was dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. Purification by MPLC (2:98 to 5:95 EtOAc: hexane) afforded the product as a colorless oil (0.095 g, 39%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.12 (m, 4H), 2.34 (s, 3H), 1.46 (s, 3H); ATR-FTIR (thin film): 2980, 1622, 1514, 1415, 1248, 1140, 1024 cm^{-1}.



s4.1a s4.10 s4.11

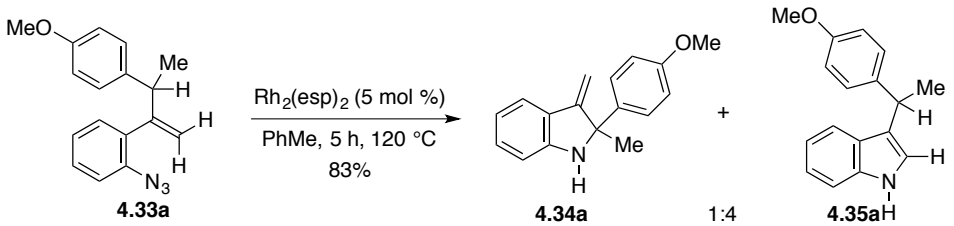
Aniline s4.11: To a mixture of 0.190 g of vinyl triflate **s4.10** (0.640 mmol), 0.128 g of 2-aminoarylboronic acid pinacol ester **s4.1a** (0.580 mmol), and 0.033 g of $Pd(PPh_3)_4$ (5 mol %) in 5.8 mL of dimethoxyethane (0.1 M) was added 1.2 mL of a saturated aq. solution of $NaHCO_3$ (2 mL/mmol of boronic ester). The resulting mixture was heated to 100 °C. After 4 h, the mixture was cooled to room temperature and diluted with 5 mL of cold water. The solution was extracted with 2 × 10 mL of diethyl ether followed by 10 mL of brine. The phases were separated, and the resulting organic phase was dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. Purification by MPLC (3:97 to 50:50 EtOAc:hexanes) afforded the product **s21** as a colorless oil (0.134 g, 96%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.09 (AB q, J = 8.0 Hz, 4H), 7.03 (dt, J = 8.0 Hz, 1.5 Hz, 1H), 6.82 (dd, J = 7.5 Hz, 1.0 Hz, 1H), 6.65 (m, 2H), 3.61 (s, 2H), 2.32 (s, 3H), 1.45 (d, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.8 (C), 143.3 (C), 141.2 (C), 135.7 (C), 129.0 (CH), 128.9 (CH), 128.8 (C), 127.8 (CH), 127.6 (CH), 117.8 (CH), 115.4 (CH), 45.2 (t, J_{CD} = 19.2 Hz, CD), 21.1 (CH_3), 20.2 (CH_3), only peaks visible; ATR-FTIR (thin film): 3459, 3372, 3018, 2965, 2927, 2869, 1611, 1512, 1490, 1447, 1295 cm^{-1}.

s4.11 4.33b-d_3

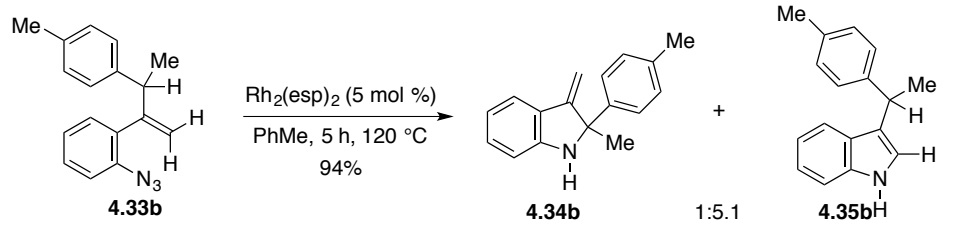
Azide 4.33b-d_3. To a cooled solution of 0.053 g of aniline **s4.11** (0.22 mmol) in 2.2 mL of MeCN was added dropwise 0.10 mL of *t*-BuONO (0.90 mmol) and 0.087 mL of Me_3SiN_3 (0.66 mmol). The resulting solution was warmed to room temperature. After 1h, visualization of the reaction progress using TLC indicated the consumption of the starting material. De–ionized water was added to the reaction mixture. The mixture then was extracted with 2 × 15 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 MPLC (2:98 – 10:90 EtOAc:hexanes) afforded azide as a colorless oil (0.053 g, 88%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (m, 1H), 7.11 – 7.04 (m, 5H), 6.97 (t, J = 7.5 Hz, 1H), 6.93 (m, 1H), 2.29 (s, 3H), 1.41 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.7 (C), 141.2 (C), 136.9 (C), 135.6 (C), 135.3 (C), 130.9 (CH), 128.9 (CH), 128.2 (CH), 127.7 (CH), 124.4 (CH), 118.2 (CH), 21.0 (CH_3), 20.4 (CH_3), only peaks visible; ATR-FTIR (thin film): 3019, 2966, 2927, 2870, 2122, 2088, 1585, 1572, 1512, 1481, 1439, 1287 cm^{-1}. HRMS (EI) *m/z* calculated for $C_{17}H_{15}D_3N$ $[M + H – N_2]^+$: 239.1628, found: 239.1625.

VI. Mechanistic study for Rh_2(II)-catalyzed electrocyclization and sp^3 C–H bond amination

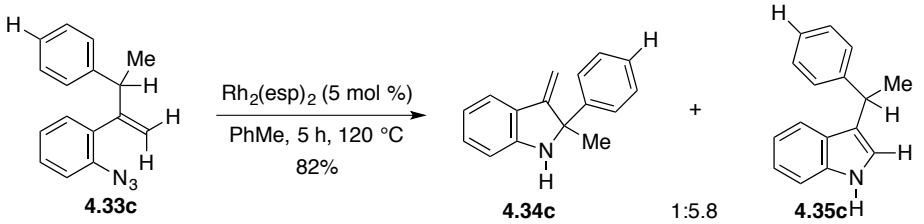
A. Hammett study: effect of changing the electronic nature of the allylic C–H bond on the reaction outcome



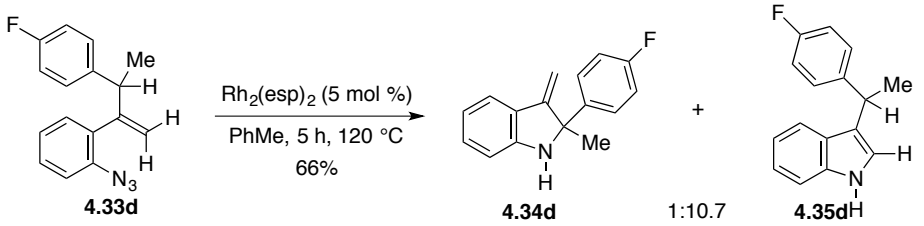
To a mixture of 0.0222 g of styryl azide **4.33a** (0.0790 mmol) and 0.0038 g of $Rh_2(esp)_2$ (0.0039 mmol) in a Schlenk tube was added 1.6 mL of toluene. The resulting mixture was heated to 120 °C. After 5 h, the mixture was cooled to room temperature, diluted with CH_2Cl_2 and concentrated *in vacuo* to afford a mixture of **4.34a** and **34.5a**. The resulting residue was dissolved in 0.5 mL of $CDCl_3$ and 7 μL of dibromomethane (0.1 mmol) was added. The area of the olefin C–H peak of **4.34a** was compared with benzylic C–H peak of **4.35a** to derive a ratio of **4.34a**:**4.35a** (1:4).



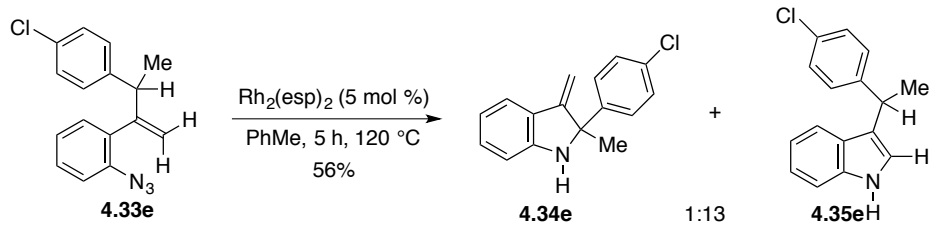
To a mixture of 0.0225 g of styryl azide **4.33b** (0.0850 mmol) and 0.0032 g of $Rh_2(esp)_2$ (0.0042 mmol) in a Schlenk tube was added 1.7 mL of toluene. The resulting mixture was heated to 120 °C. After 5 h, the mixture was cooled to room temperature, diluted with CH_2Cl_2 and concentrated *in vacuo* to afford a mixture of **4.34b** and **4.35b**. The resulting residue was dissolved in 0.5 mL of $CDCl_3$ and 7 μL of dibromomethane (0.1 mmol) was added. The area of the olefin C–H peak of **4.34b** was compared with benzylic C–H peak of **4.35b** to derive a ratio of **4.34b**: **4.35b** (1:5.1).



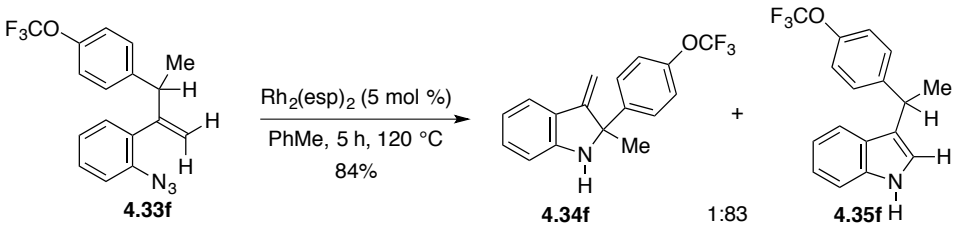
To a mixture of 0.013 g of styryl azide **4.33c** (0.052 mmol) and 0.0019 g of $Rh_2(esp)_2$ (0.0026 mmol) in a Schlenk tube was added 1.0 mL of toluene. The resulting mixture was heated to 120 °C. After 5 h, the mixture was cooled to room temperature, diluted with CH_2Cl_2 and concentrated *in vacuo* to afford a mixture of **4.34c** and **4.35c**. The resulting residue was dissolved in 0.5 mL of $CDCl_3$ and 7 μL of dibromomethane (0.1 mmol) was added. The area of the olefin C–H peak of **4.34c** was compared with benzylic C–H peak of **34.5c** to derive a ratio of **4.34c**:**4.35c** (1:5.8).



To a mixture of 0.0125 g of styryl azide **4.33d** (0.0460 mmol) and 0.0018 g of $Rh_2(esp)_2$ (0.0023 mmol) in a Schlenk tube was added 0.90 mL of toluene. The resulting mixture was heated to 120 °C. After 5 h, the mixture was cooled to room temperature, diluted with CH_2Cl_2 and concentrated *in vacuo* to afford a mixture of **4.34d** and **4.35d**. The resulting residue was dissolved in 0.5 mL of $CDCl_3$ and 7 μL of dibromomethane (0.1 mmol) was added. The area of the olefin C–H peak of **4.34d** was compared with benzylic C–H peak of **4.35d** to derive a ratio of **4.34d**:**4.35d** (1:10.7).

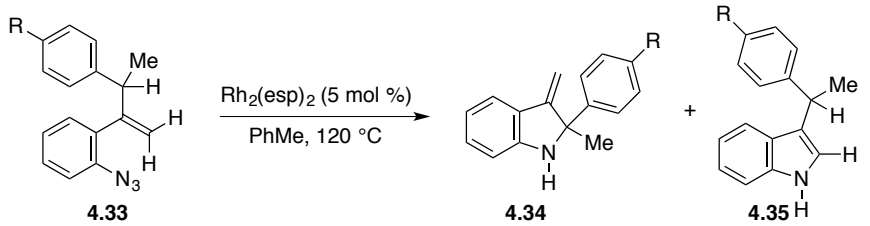


To a mixture of 0.0118 g of styryl azide **4.33e** (0.0420 mmol) and 0.0016 g of $Rh_2(esp)_2$ (0.0021 mmol) in a Schlenk tube was added 0.80 mL of toluene. The resulting mixture was heated to 120 °C. After 5 h, the mixture was cooled to room temperature, diluted with CH_2Cl_2 and concentrated *in vacuo* to afford a mixture of **4.34e** and **4.35e**. The resulting residue was dissolved in 0.5 mL of $CDCl_3$ and 7 μL of dibromomethane (0.1 mmol) was added. The area of the olefin C–H peak of **4.34e** was compared with benzylic C–H peak of **4.35e** to derive a ratio of **34.4e**:**4.35e** (1:13.0).



To a mixture of 0.0343 g of styryl azide **4.33f** (0.103 mmol) and 0.0039 g of $Rh_2(esp)_2$ (0.0051 mmol) in a Schlenk tube was added 2.0 mL of toluene. The resulting mixture was heated to 120 °C. After 5 h, the mixture was cooled to room temperature, diluted with CH_2Cl_2 and concentrated *in vacuo* to afford a mixture of **4.34f** and **4.35f**. The resulting residue was dissolved in 0.5 mL of $CDCl_3$ and 7 μL of dibromomethane (0.1 mmol) was added. The area of the olefin C–H peak of **4.34f** was compared with benzylic C–H peak of **4.35f** to derive a ratio of **4.34f**:**4.35f** (1:83).

Table s4.3. Effect of changing the electronic environment at the allylic C–H bond reaction center



4.33 4.34 4.35

entry	#	R	σ_{para} [a]	σ_{mb} [b]	$\sigma_{JJ}^{\bullet}$ [b]	$\sigma_{\alpha}^{\bullet}$ [c]	$\sigma_{C}^{\bullet}$ [d]	$\sigma_{J}^{\bullet}$ [e]	**4.34**:**4.35**	yield, %[c]
1	a	OMe	–0.27	–0.77	0.23	0.034	0.24	0.42	1:4	83
2	b	Me	–0.17	–0.29	0.15	0.015	0.11	0.39	1:5.1	94
3	c	H	0	0	0	0	0	0	1:5.8	82
4	d	F	0.06	–0.24	–0.02	–0.011	–0.08	0.12	1:10.7	66
5	e	Cl	0.23	0.11	0.22	0.017	0.12	0.18	1:13.0	56
6	f	OCF_3	0.35	…	…	…	…	…	1:83	84

[a] From ref.[102]. [b] From ref.[103]. [c] From ref.[104]. [d] From ref.[105]. [e] From ref.[106]. [f] As determined using ^{1}H NMR spectroscopy with CH_2Br_2 as an internal standard.

Figure s4.1. Effect of changing the electronic environment at the allylic C–H bond reaction center: correlation of heterocycle product ratios with Hammett σ_{para} values.

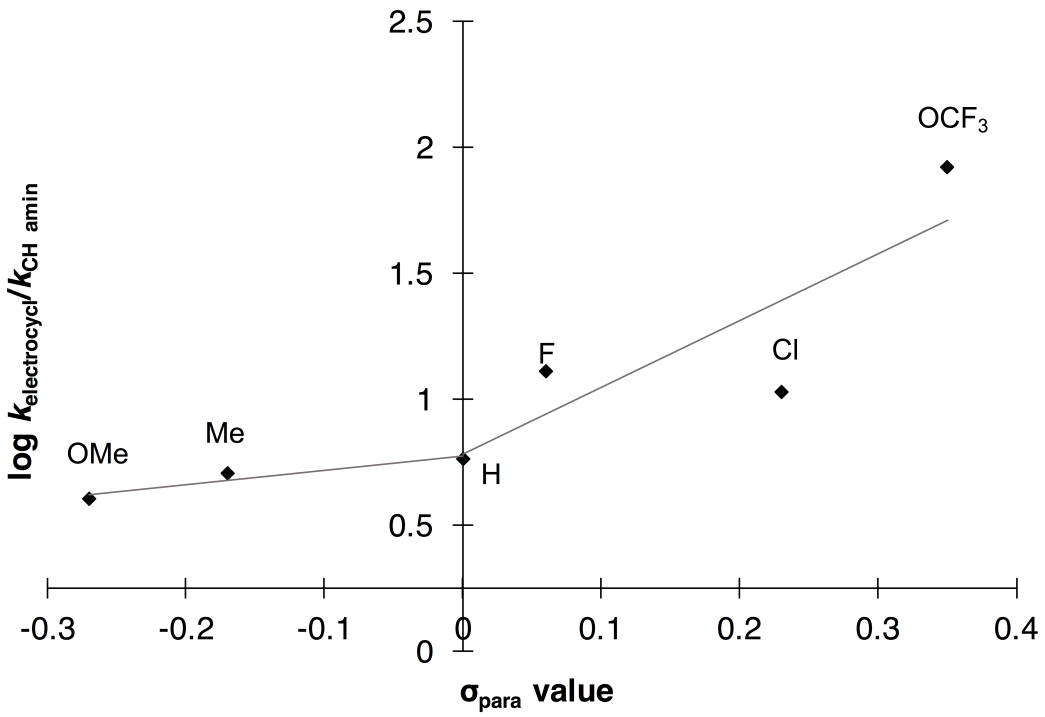


Figure s4.2. Correlation of heterocycle product ratios with Jiang and Ji σ_{mb} and $\sigma_{JJ}^{\bullet}$ values: substituent effect observed at the allylic C–H reaction site.

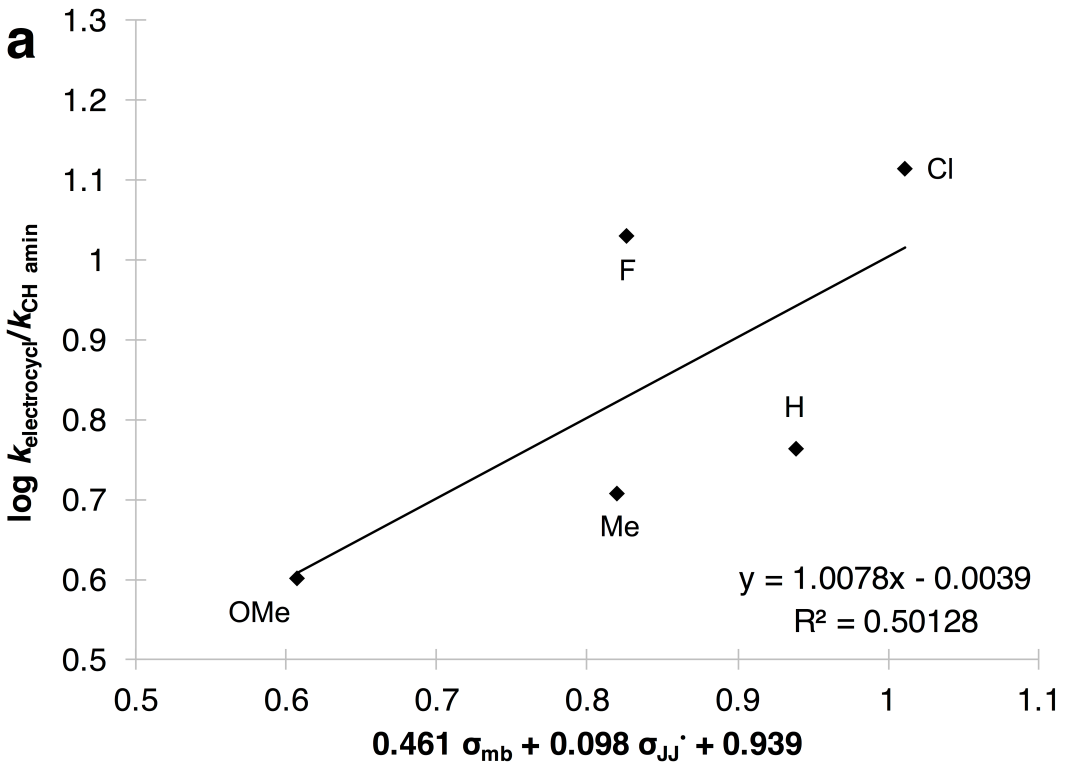


Figure s4.3. Correlation of heterocycle product ratios with Arnold's $\sigma_{\alpha}^{\bullet}$ values: substituent effect observed at the allylic C–H reaction site.

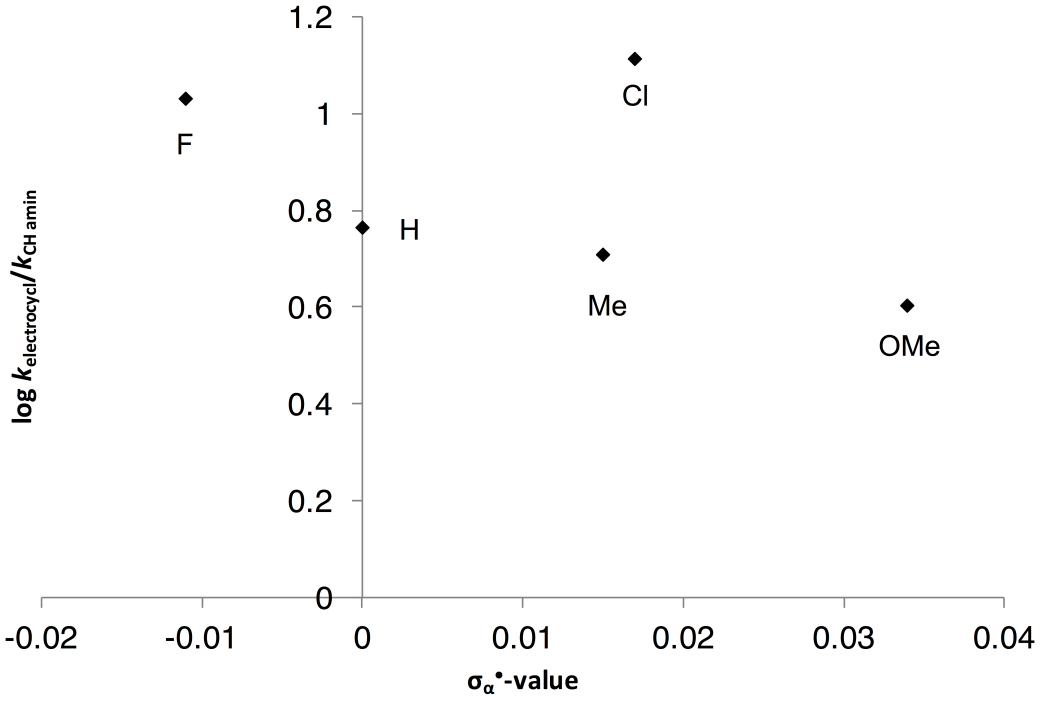


Figure s4.4. Correlation of heterocycle product ratios with Creary's $\sigma_C^{\bullet}$ values: substituent effect observed at the allylic C–H reaction site.

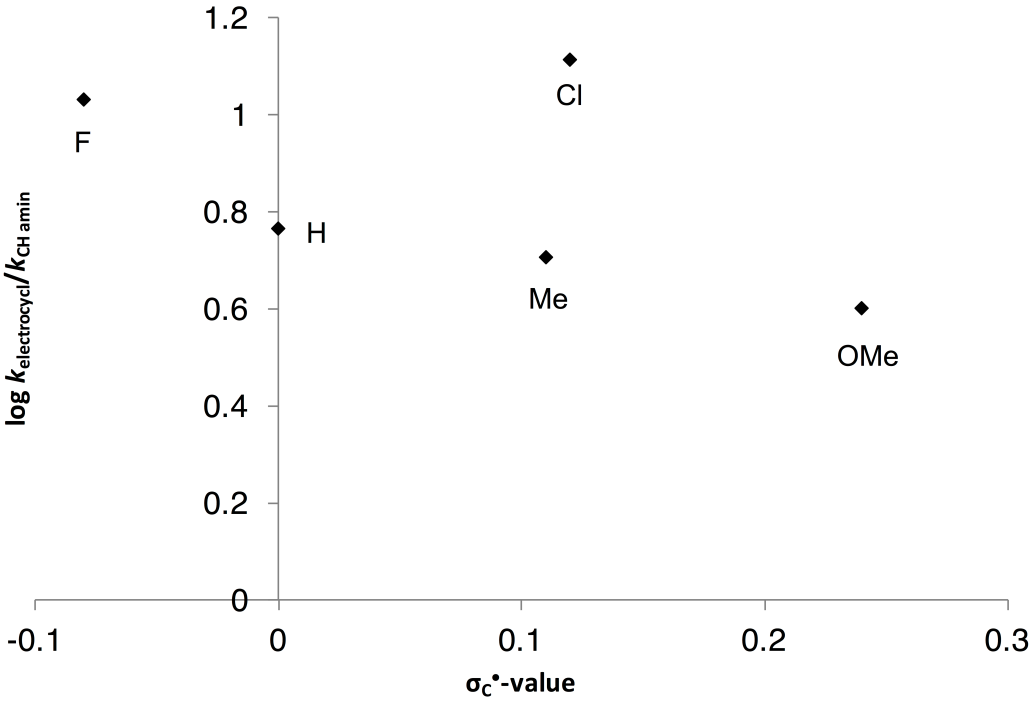
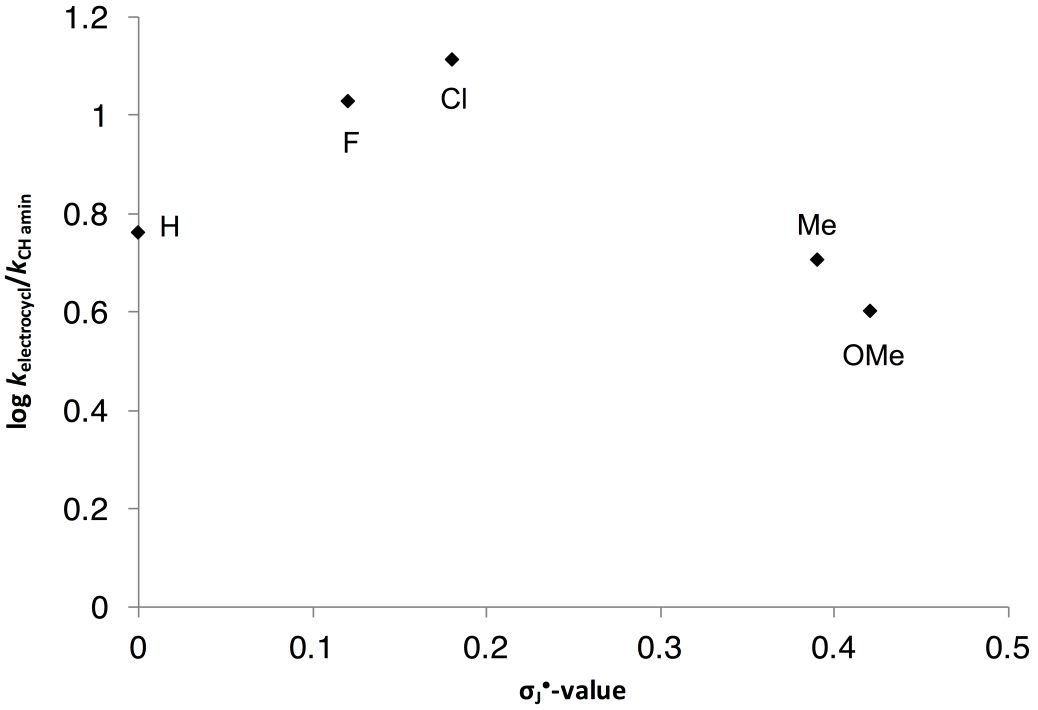
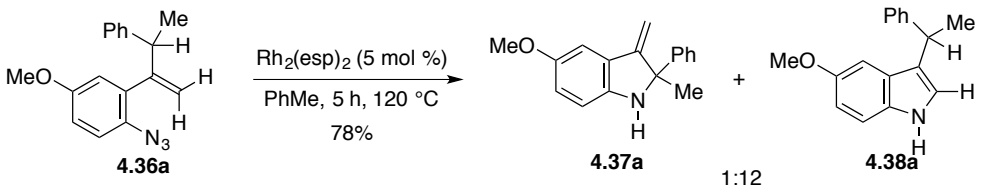


Figure s4.5. Correlation of heterocycle product ratios with Jackson's $\sigma_J^{\bullet}$ values: substituent effect observed at the allylic C–H reaction site.

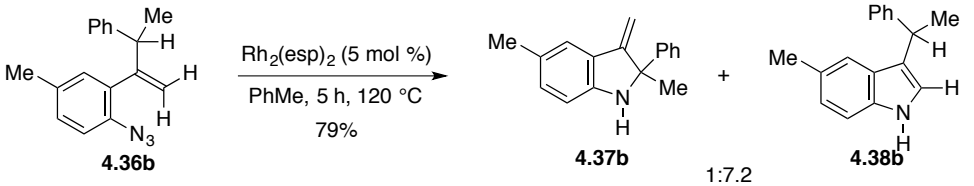


B. Hammett study: effect of changing the electronic nature of the rhodium aryl *N*-nitrene on the reaction outcome.

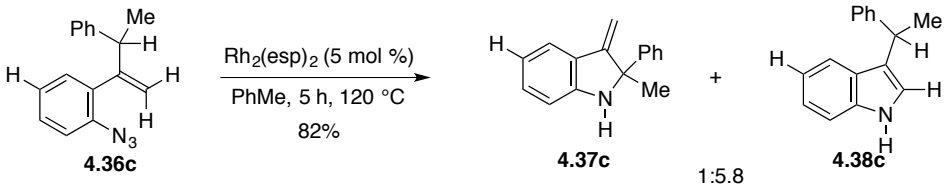


To a mixture of 0.0118 g of styryl azide **4.36a** (0.0420 mmol) and 0.0016 g of $Rh_2(esp)_2$ (0.0021 mmol) in a Schlenk tube was added 0.80 mL of toluene. The resulting mixture was heated to 120 °C. After 5 h, the mixture was cooled to room temperature, diluted with CH_2Cl_2 and concentrated *in vacuo* to afford a mixture of **4.37a** and **4.38a**. The

resulting residue was dissolved in 0.5 mL of $CDCl_3$ and 7 μL of dibromomethane (0.1 mmol) was added. The area of the olefin C–H peak of **4.37a** was compared with benzylic C–H peak of **4.38a** to derive a ratio of **34.7a**: **4.38a** (1:12).

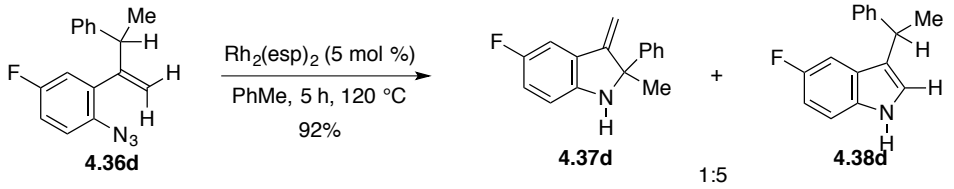


To a mixture of 0.0112 g of styryl azide **4.36b** (0.0420 mmol) and 0.0016 g of $Rh_2(esp)_2$ (0.0021 mmol) in a Schlenk tube was added 0.80 mL of toluene. The resulting mixture was heated to 120 °C. After 5 h, the mixture was cooled to room temperature, diluted with CH_2Cl_2 and concentrated *in vacuo* to afford a mixture of **4.37b** and **4.38b**. The resulting residue was dissolved in 0.5 mL of $CDCl_3$ and 7 μL of dibromomethane (0.1 mmol) was added. The area of the olefin C–H peak of **4.37b** was compared with benzylic C–H peak of **4.38b** to derive a ratio of **4.37b**: **4.38b** (1:7.2).

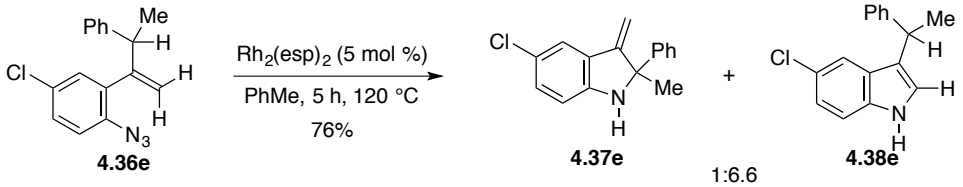


To a mixture of 0.0119 g of styryl azide **4.36c** (0.0480 mmol) and 0.0018 g of $Rh_2(esp)_2$ (0.0024 mmol) in a Schlenk tube was added 1.0 mL of toluene. The resulting mixture was heated to 120 °C. After 5 h, the mixture was cooled to room temperature, diluted with CH_2Cl_2 and concentrated *in vacuo* to afford a mixture of **4.37c** and **4.38c**. The

resulting residue was dissolved in 0.5 mL of $CDCl_3$ and 7 μL of dibromomethane (0.1 mmol) was added. The area of the olefin C–H peak of **4.37c** was compared with benzylic C–H peak of **4.38c** to derive a ratio of **4.37c**:**4.38c** (1:5.8).

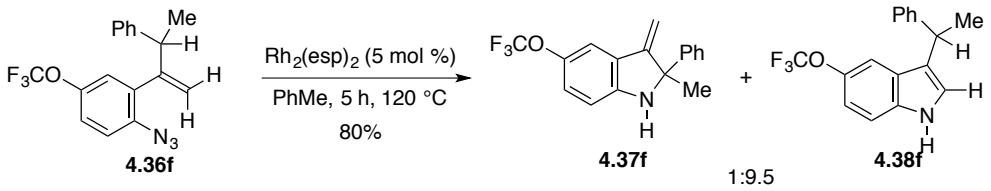


To a mixture of 0.0134 g of styryl azide **4.36a** (0.0500 mmol) and 0.0019 g of $Rh_2(esp)_2$ (0.0025 mmol) in a Schlenk tube was added 1.0 mL of toluene. The resulting mixture was heated to 120 °C. After 5 h, the mixture was cooled to room temperature, diluted with CH_2Cl_2 and concentrated *in vacuo* to afford a mixture of **4.37d** and **4.38d**. The resulting residue was dissolved in 0.5 mL of $CDCl_3$ and 7 μL of dibromomethane (0.1 mmol) was added. The area of the olefin C–H peak of **4.37d** was compared with benzylic C–H peak of **4.38d** to derive a ratio of **4.37d**: **4.38d** (1:5).



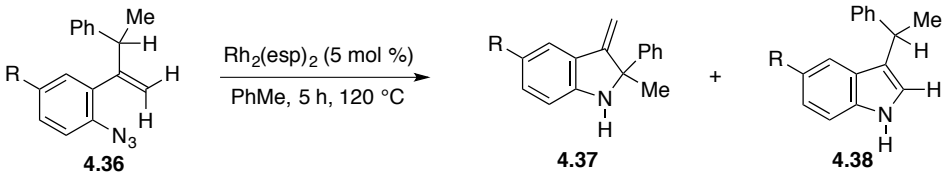
To a mixture of 0.0135 g of styryl azide **4.36e** (0.0480 mmol) and 0.0018 g of $Rh_2(esp)_2$ (0.0024 mmol) in a Schlenk tube was added 1.0 mL of toluene. The resulting mixture was heated to 120 °C. After 5 h, the mixture was cooled to room temperature, diluted with CH_2Cl_2 and concentrated *in vacuo* to afford a mixture of **4.37e** and **4.38e**. The resulting residue was dissolved in 0.5 mL of $CDCl_3$ and 7 μL of dibromomethane (0.1

mmol) was added. The area of the olefin C–H peak of **4.37e** was compared with benzylic C–H peak of **4.38e** to derive a ratio of **4.37e**:**4.38e** (1:6.6).



To a mixture of 0.0177 g of styryl azide **4.36f** (0.0530 mmol) and 0.0020 g of $Rh_2(esp)_2$ (0.0026 mmol) in a Schlenk tube was added 1.1 mL of toluene. The resulting mixture was heated to 120 °C. After 5 h, the mixture was cooled to room temperature, diluted with CH_2Cl_2 and concentrated *in vacuo* to afford a mixture of **4.37f** and **4.38f**. The resulting solid was dissolved in 0.5 mL of $CDCl_3$ and 7 μL of dibromomethane (0.1 mmol) was added. The area of the olefin C–H peak of **4.37f** was compared with benzylic C–H peak of **4.38f** to derive a ratio of **4.37f**: **4.38f** (1:9.5).

Table s4.4. Effect of changing the electronic nature of the rhodium *N*-aryl nitrene on the reaction outcome.



entry	#	R	σ_{para} [a]	σ_{mb} [b]	$\sigma_{JJ}^{\bullet}$ [b]	$\sigma_{\alpha}^{\bullet}$ [c]	$\sigma_{C}^{\bullet}$ [d]	$\sigma_{J}^{\bullet}$ [e]	**4.37**:**4.38**	yield, %[c]
1	a	OMe	–0.27	–0.77	0.23	0.034	0.24	0.42	1:12	78
2	b	Me	–0.17	–0.29	0.15	0.015	0.11	0.39	1:7.2	79

3	c	H	0	0	0	0	0	0	1.5.8	82
4	d	F	0.06	–0.24	–0.02	–0.011	–0.08	0.12	1:5	92
5	e	Cl	0.23	0.11	0.22	0.017	0.12	0.18	1:6.6	76
6	f	OCF_3	0.35	...	...	…	…	…	1:9.5	80

[a] From ref. [102]. [b] From ref. [103]. [c] From ref. [104]. [d] From ref. [105]. [e] From ref. [106]. [c] As determined using ^{1}H NMR spectroscopy with CH_2Br_2 as an internal standard.

Figure s4.6. Effect of changing the electronic environment of the rhodium *N*-aryl nitrene: correlation of heterocycle product ratios with Hammett σ_{para} values.

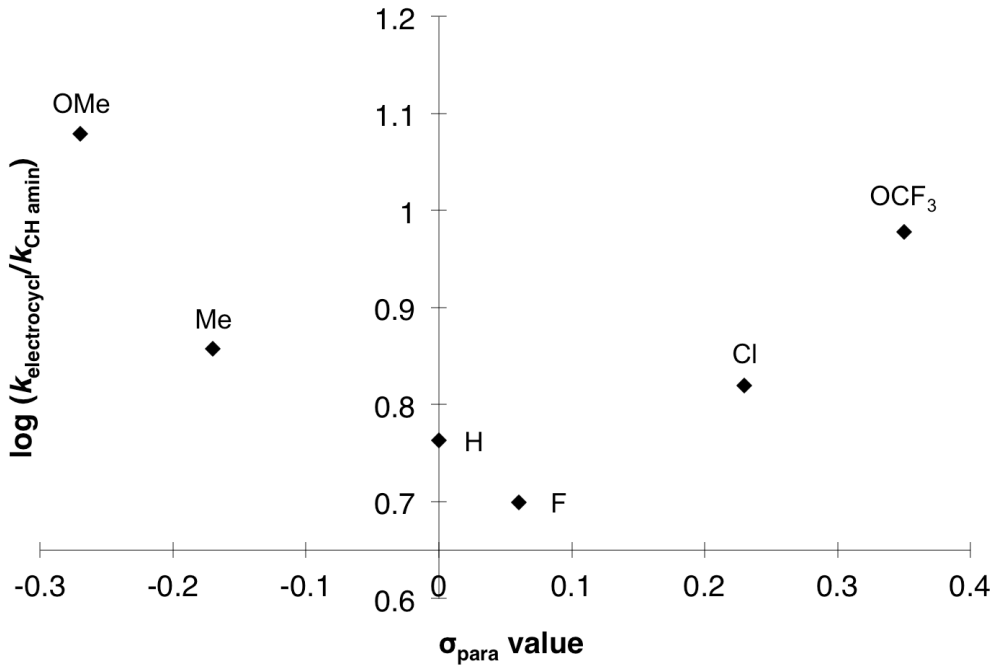


Figure s4.7. Correlation of heterocycle product ratios with Jiang and Ji σ_{mb} and $\sigma_{JJ}^{\bullet}$ values: substituent effect observed on the aryl azide.

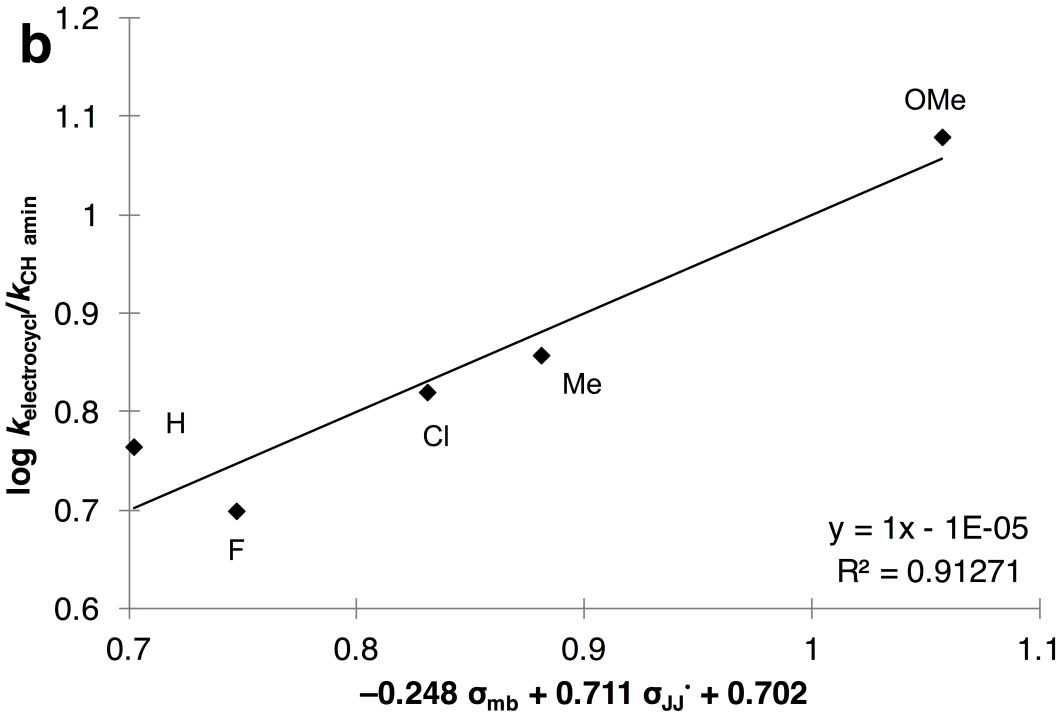


Figure s4.8. Correlation of heterocycle product ratios with Arnold's $\sigma_\alpha^{\bullet}$ values: substituent effect observed on the aryl azide.

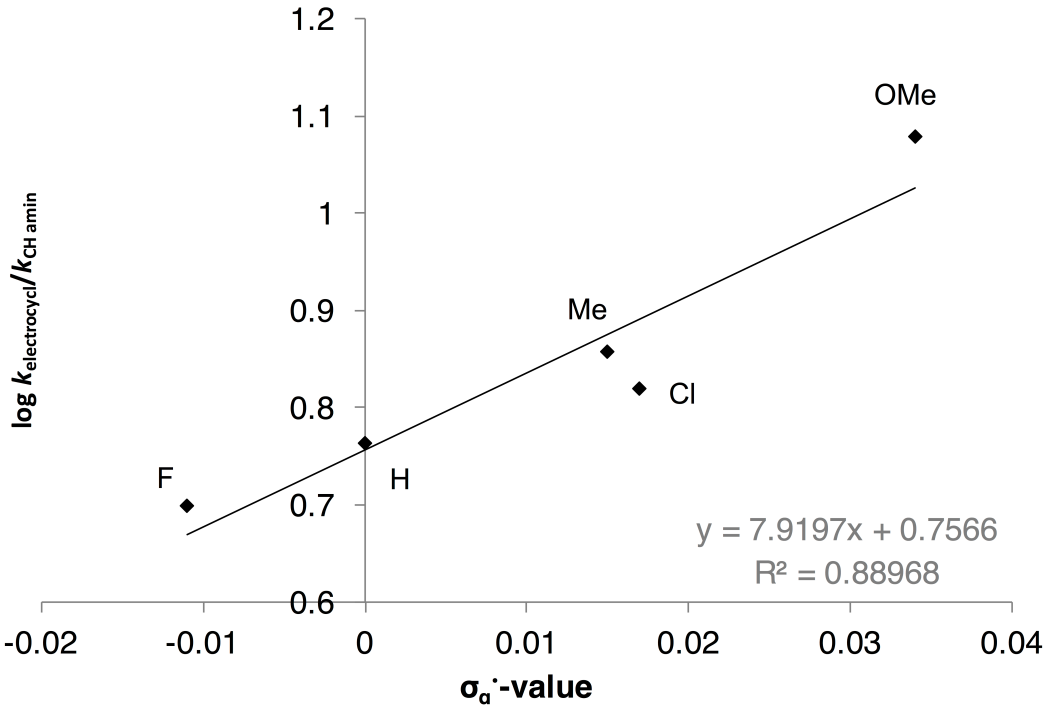


Figure s4.9. Correlation of heterocycle product ratios with Creary's $\sigma_C^{\bullet}$ values: substituent effect observed on the aryl azide.

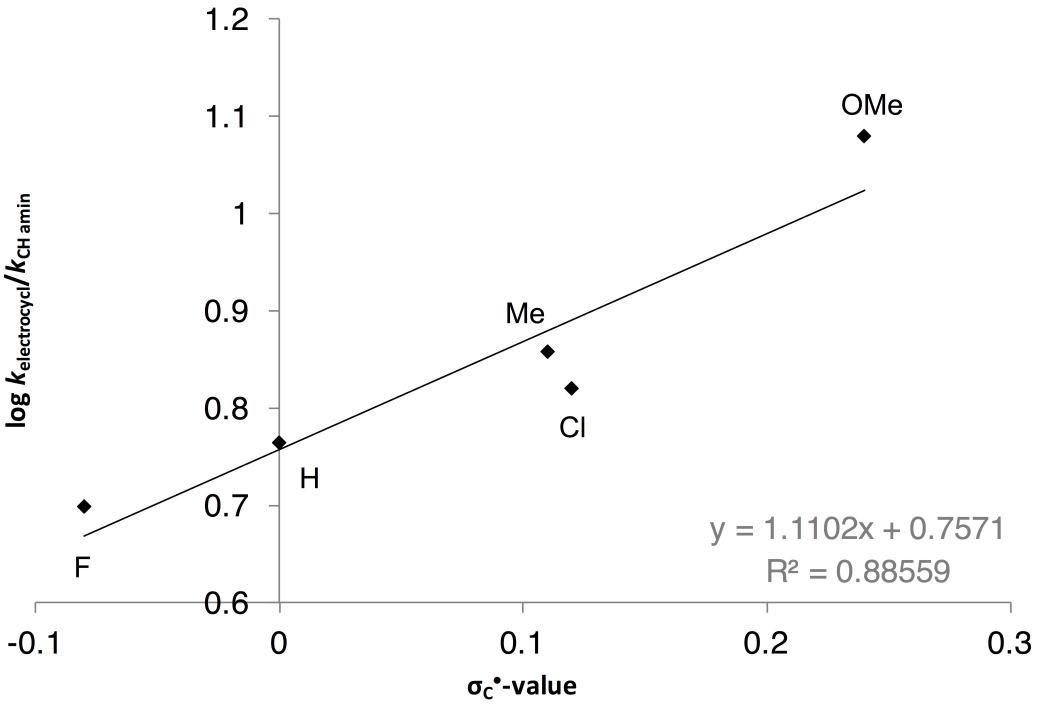
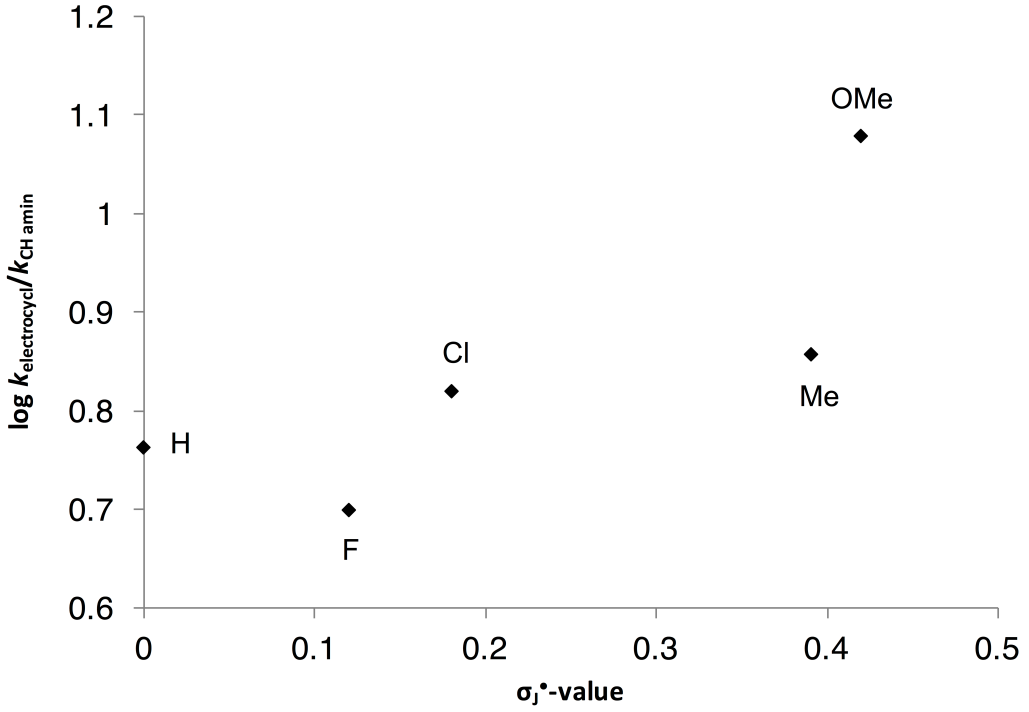
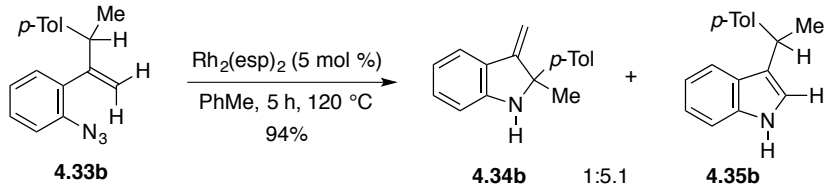


Figure s4.10. Correlation of heterocycle product ratios with Jackson's $\sigma_J^{\bullet}$ values: substituent effect observed on the aryl azide.

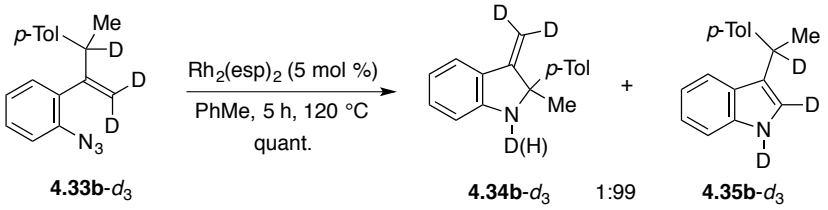


C. Relationship between isotopolog identity and ratio of 2*H*-indole 4.**33b and indole 4.34b using $Rh_2(esp)_2$ as the catalyst.**



To a mixture of 0.0225 g of styryl azide **4.33b** (0.0850 mmol) and 0.0032 g of $Rh_2(esp)_2$ (0.0042 mmol) in a Schlenk tube was added 1.7 mL of toluene. The resulting mixture was heated to 120 °C. After 5 h, the mixture was cooled to room temperature, diluted

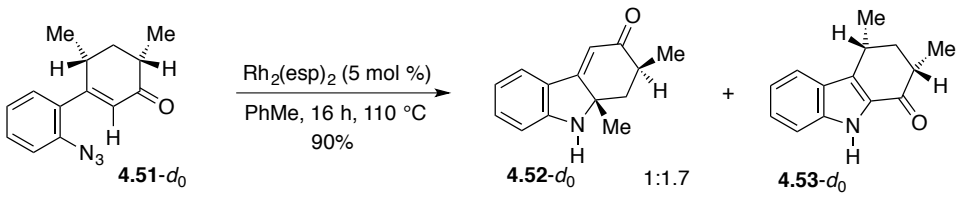
with CH_2Cl_2 and concentrated *in vacuo* to afford a mixture of **4.34b** and **4.35b**. The resulting residue was dissolved in 0.5 mL of $CDCl_3$ and 7 μL of dibromomethane (0.1 mmol) was added. The area of the olefin C–H peak of **4.34b** was compared with benzylic C–H peak of **4.35b** to derive a ratio of **4.34b**:**4.35b** (1:5.1).



4.33b-d_3 **4.34b**-d_3 1:99 **4.35b**-d_3

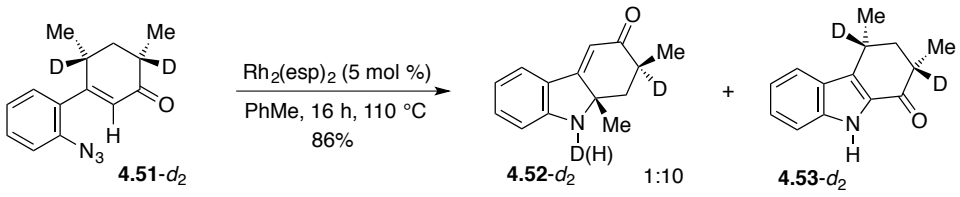
To a mixture of 0.0180 g of styryl azide **4.33b**-d_3 (0.0670 mmol) and 0.0025 g of $Rh_2(esp)_2$ (0.0033 mmol) in a Schlenk tube was added 1.3 mL of toluene. The resulting mixture was heated to 120 °C. After 5 h, the mixture was cooled to room temperature, diluted with CH_2Cl_2 and concentrated *in vacuo* to afford a mixture of **4.34b**-d_3 and **4.35b**-d_3. The resulting solid was dissolved in 0.5 mL of $CDCl_3$ and 7 μL of dibromomethane (0.1 mmol) was added. The area of the methyl CH_3 peak of **4.34b**-d_3 was compared with methyl CH_3 peak of **4.35b**-d_3 to derive a ratio of **4.34b**-d_3:**4.35b**-d_3 (1:99).

D. Relationship between isotopolog identity and ratio of 2*H*-indole 45-d_0 and indole 45-d_2 using $Rh_2(esp)_2$ as the catalyst.



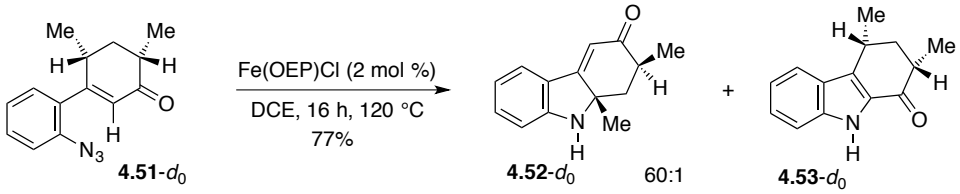
4.51-d_0 **4.52**-d_0 1:1.7 **4.53**-d_0

To a mixture of 0.0193 g of styryl azide **4.51**-d_0 (0.0800 mmol) and 0.0030 g of $Rh_2(esp)_2$ (0.0040 mmol) in a Schlenk tube was added 1.7 mL of toluene. The resulting mixture was heated to 110 °C. After 16 h, the mixture was cooled to room temperature, diluted with CH_2Cl_2 and concentrated *in vacuo* to afford a mixture of **4.52**-d_0 and **4.53**-d_0. The resulting residue was dissolved in 0.5 mL of $CDCl_3$ and 7 μL of dibromomethane (0.1 mmol) was added. The area of the $-CH_3$ peak of **4.526**-d_0 at 1.49 ppm was compared with $-CH_3$ peak of **4.53**-d_0 at 1.61 ppm to derive a ratio of **4.52**-d_0: **4.53**-d_0 (1:1.7). A 5:1 diastereomeric mixture was observed for compound **4.52**-d_0 and 6:1 diastereomeric mixture was observed for compound **4.53**-d_0.

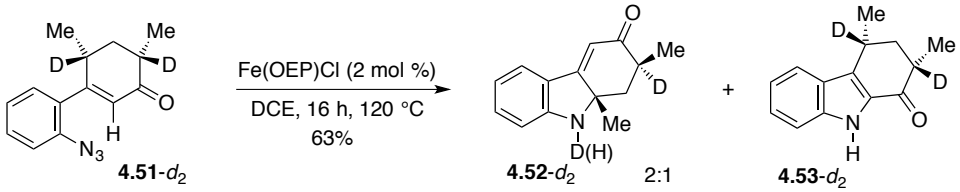


To a mixture of 0.0130 g of styryl azide **4.51**-d_2 (0.0530 mmol) and 0.0032 g of $Rh_2(esp)_2$ (0.0026 mmol) in a Schlenk tube was added 1.0 mL of toluene. The resulting mixture was heated to 110 °C. After 16 h, the mixture was cooled to room temperature, diluted with CH_2Cl_2 and concentrated *in vacuo* to afford a mixture of **4.52**-d_2 and **4.53**-d_2. The resulting solid was dissolved in 0.5 mL of $CDCl_3$ and 7 μL of dibromomethane (0.1 mmol) was added. The area of the $-CH_3$ peak of **4.52**-d_2 at 1.49 ppm was compared with $-CH_3$ peak of **4.53**-d_2 at 1.61 ppm to derive a ratio of **4.52**-d_2: **4.53**-d_2 (1:10). A 3:1 diastereomeric mixture was observed for compound **4.52**-d_2 and 10:1 diastereomeric mixture was observed for compound **4.53**-d_2.

E. Relationship between isotopolog identity and ratio of 2*H*-indole 45-d_0 and indole 45-d_2 using Fe(OEP)Cl as the catalyst.



To a mixture of 0.0115 g of styryl azide **4.51**-d_0 (0.0470 mmol) and 0.0006 g of Fe(OEP)Cl (0.0009 mmol) in a Schlenk tube was added 1.7 mL of toluene. The resulting mixture was heated to 120 °C. After 16 h, the mixture was cooled to room temperature, diluted with CH_2Cl_2 and concentrated *in vacuo* to afford a mixture of **4.52**-d_0 and **4.53**-d_0. The resulting residue was dissolved in 0.5 mL of $CDCl_3$ and 7 μL of dibromomethane (0.1 mmol) was added. The area of the $-CH_3$ peak of **4.52**-d_0 at 1.49 ppm was compared with $-CH_3$ peak of **4.53**-d_0 at 1.61 ppm to derive a ratio of **4.52**-d_0:**4.53**-d_0 (60:1). A 2.4:1 diastereomeric mixture was observed for compound **4.52**-d_0.

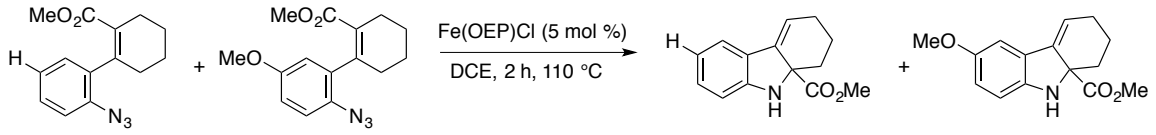


To a mixture of 0.0115 g of styryl azide **4.51**-d_2 (0.0470 mmol) and 0.0006 g of Fe(OEP)Cl (0.0009 mmol) in a Schlenk tube was added 0.8 mL of toluene. The resulting mixture was heated to 120 °C. After 16 h, the mixture was cooled to room temperature, diluted with CH_2Cl_2 and concentrated *in vacuo* to afford a mixture of **4.52**-d_2 and **4.53**-d_2. The resulting solid was dissolved in 0.5 mL of $CDCl_3$ and 7 μL of dibromomethane (0.1 mmol) was added. The area of the $-CH_3$ peak of **4.52**-d_2 at 1.49 ppm was compared with

–CH_3 peak of **4.53**-d_2 at 1.61 ppm to derive a ratio of **4.52**-d_2: **4.53**-d_2 (2:1). A 1:1 diastereomeric mixture was observed for compound **4.52**-d_2 and >20:1 diastereomeric mixture was observed for compound **4.53**-d_2.

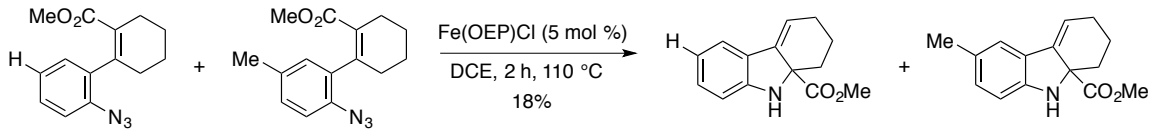
VII. Mechanistic study for Fe(OEP)Cl-catalyzed sp^3-C–H bond amination.

A. Hammett study: effect of changing the electronic nature of the iron *N*-aryl nitrene on the reaction outcome.



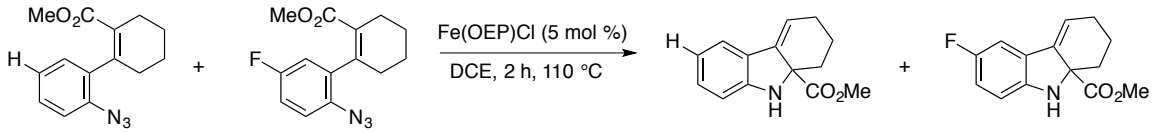
4.16a **4.16b** **4.59a** **4.59b**

To a mixture of 0.0100 g of styryl azide **4.16a** (0.038 mmol), 0.0145 g of styryl azide **4.16b**(0.050 mmol) and 0.0027 g of Fe(OEP)Cl (0.0040 mmol) in a Schlenk tube was added 1.0 mL of 1,2-dichloroethane. The resulting mixture was heated to 110 °C. After 2 h, the mixture was cooled to room temperature, diluted with ethyl acetate. The solution was filtered through a plug of celite and concentrated *in vacuo* to afford a mixture of **4.16a**, **4.16b**, **4.59a** and **4.59b**. The resulting residue was dissolved in 0.5 mL of $CDCl_3$ and 7 μL of dibromomethane (0.1 mmol) was added. Analysis of the resulting residue using ^{1}H NMR spectroscopy with CH_2Br_2 as the internal standard revealed that 0.032 mmol of styryl azide **16a**, 0.023 mmol of styryl azide **16c** left in the reaction mixture.



4.16a **4.16c** **4.59a** **4.59c**

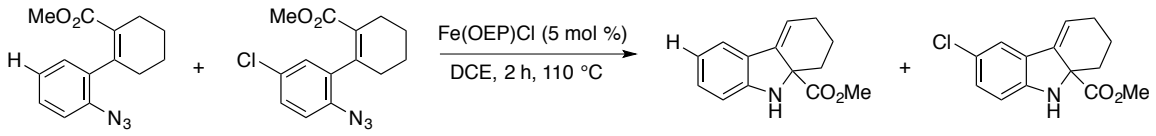
To a mixture of 0.0139 g of styryl azide **4.16a** (0.054 mmol), 0.0144 g of styryl azide **4.16c** (0.054 mmol) and 0.0033 g of Fe(OEP)Cl (0.0054 mmol) in a Schlenk tube was added 1.0 mL of 1,2-dichloroethane. The resulting mixture was heated to 110 °C. After 2 h, the mixture was cooled to room temperature, diluted with ethyl acetate. The solution was filtered through a plug of celite and concentrated *in vacuo* to afford a mixture of **4.16a, 4.16c, 4.59a** and **4.59c**. The resulting residue was dissolved in 0.5 mL of $CDCl_3$ and 7 μL of dibromomethane (0.1 mmol) was added. Analysis of the resulting residue using ^1H NMR spectroscopy with CH_2Br_2 as the internal standard revealed that 0.040 mmol of styryl azide **4.16a**, 0.017 mmol of styryl azide **4.16c** left in the reaction mixture.



4.16a **4.16d** **4.59a** **4.59d**

To a mixture of 0.0135 g of styryl azide **4.16a** (0.052 mmol), 0.0144 g of styryl azide **4.16d** (0.052 mmol) and 0.0032 g of Fe(OEP)Cl (0.0052 mmol) in a Schlenk tube was added 1.0 mL of 1,2-dichloroethane. The resulting mixture was heated to 110 °C. After 2 h, the mixture was cooled to room temperature, diluted with ethyl acetate. The solution was filtered through a plug of celite and concentrated *in vacuo* to afford a mixture of **4.16a**, **4.16d**, **4.59a** and **4.59d**. The resulting residue was dissolved in 0.5 mL of $CDCl_3$ and 7 μL of dibromomethane (0.1 mmol) was added. Analysis of the resulting residue

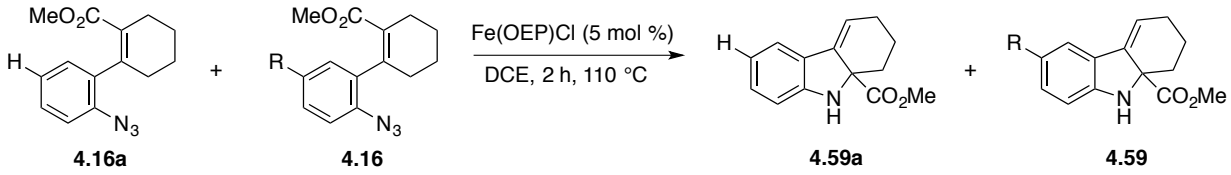
using ^{1}H NMR spectroscopy with CH_2Br_2 as the internal standard revealed that 0.021 mmol of styryl azide **4.16a**, 0.006 mmol of styryl azide **4.16d** left in the reaction mixture.



4.16a **4.16e** **4.59a** **4.59e**

To a mixture of 0.0115 g of styryl azide **4.16a** (0.045 mmol), 0.0131 g of styryl azide **4.16e** (0.045 mmol) and 0.0028 g of Fe(OEP)Cl (0.0045 mmol) in a Schlenk tube was added 1.0 mL of 1,2-dichloroethane. The resulting mixture was heated to 110 °C. After 2 h, the mixture was cooled to room temperature, diluted with ethyl acetate. The solution was filtered through a plug of celite and concentrated *in vacuo* to afford a mixture of **4.16a**, **4.16e**, **4.59a** and **4.59e**. The resulting residue was dissolved in 0.5 mL of $CDCl_3$ and 7 μL of dibromomethane (0.1 mmol) was added. Analysis of the resulting residue using ^{1}H NMR spectroscopy with CH_2Br_2 as the internal standard revealed that 0.025 mmol of styryl azide **4.16a**, 0.010 mmol of styryl azide **4.16e** left in the reaction mixture.

Table s4.5. Effect of changing the electronic environment on the reactivity of the iron *N*-aryl nitrene



entry	#	R	σ_{para} [a]	σ_{mb} [b]	$\sigma_{JJ}^{\bullet}$ [b]	log k_{rel}
1	a	H	0	0	0	0
2	b	OMe	–0.27	–0.77	0.23	0.65
3	c	Me	–0.17	–0.29	0.15	0.42
4	d	F	0.06	–0.24	–0.02	0.17
5	e	Cl	0.23	0.11	0.22	0.24

[a] From ref. [102]. [b] From ref. [103].

Figure s4.11. Correlation of relative rates between substituted styryl azides 16 and 16a with σ_{para}-constants.

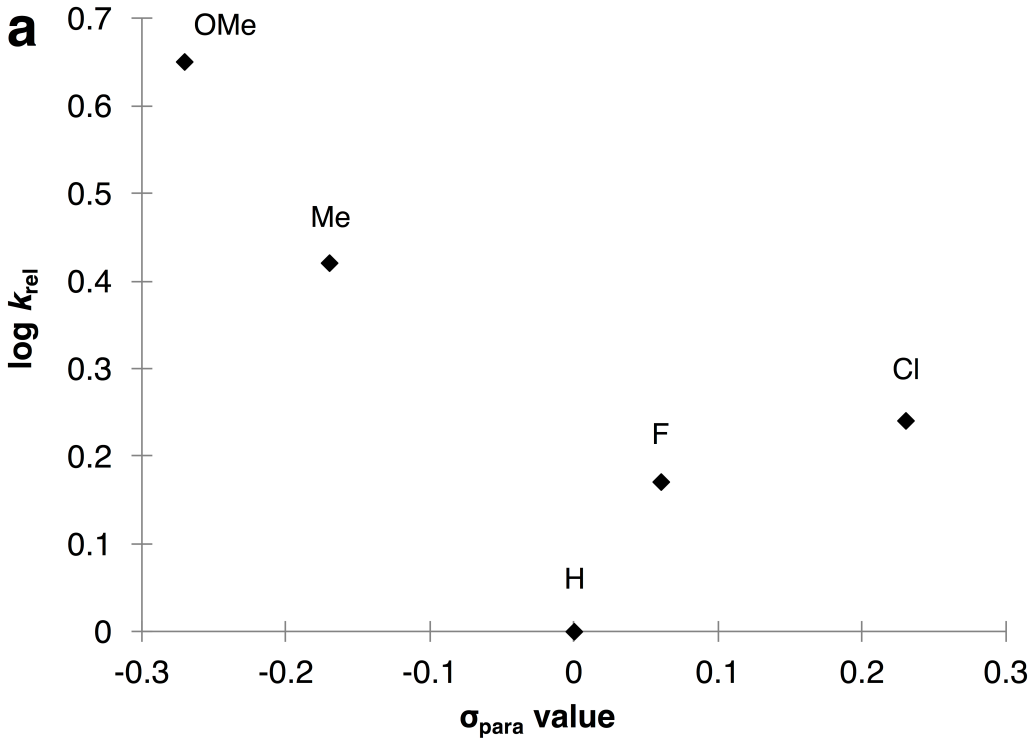
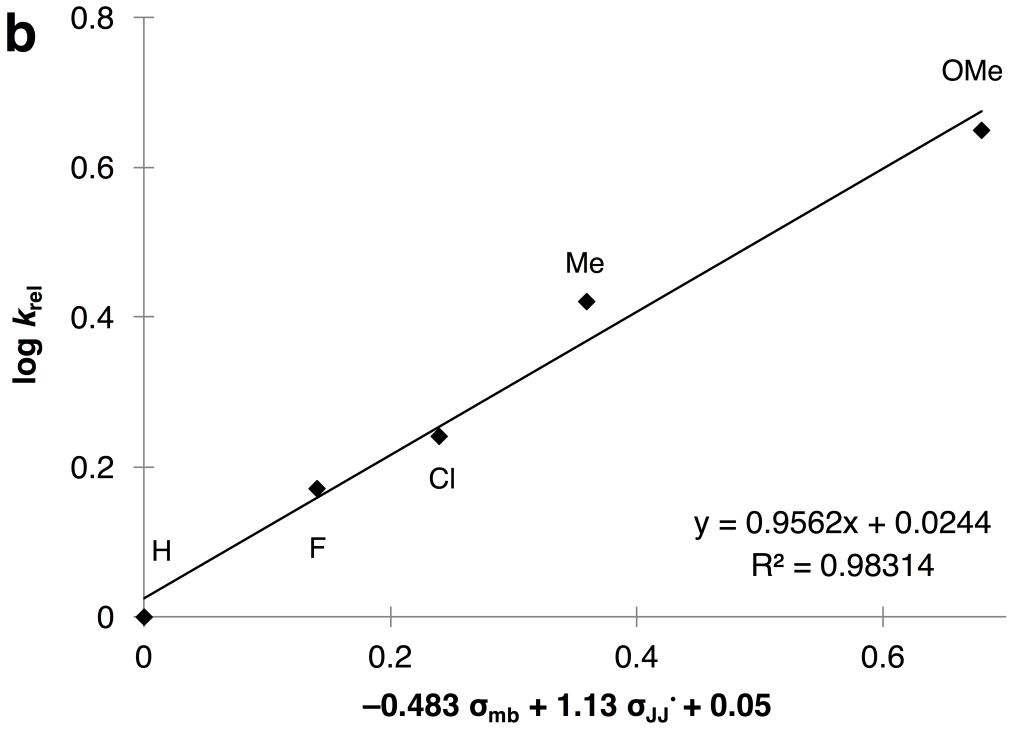
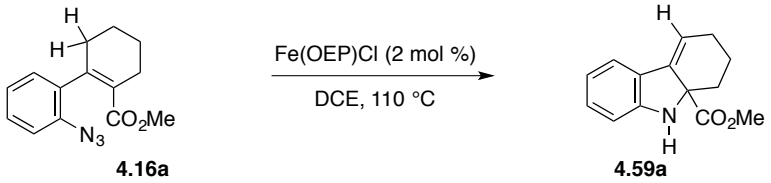


Figure s4.12. Correlation of relative rates between substituted styryl azides 16 and 16a with Jiang and Ji's σ_{mb} and $\sigma_{JJ}^{\bullet}$ values.

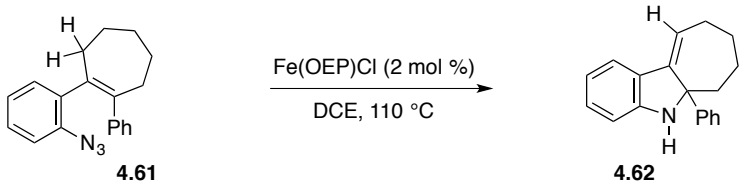


VIII. Fe(OEP)Cl-Catalyzed synthesis of 2*H*-indoles.



Alkylidene indoline 4.59a. To a mixture 0.029 g of styryl azide **4.16a** (0.11 mmol) and Fe(OEP)Cl (2 mol %) was added 1.1 mL of toluene (0.1 M). The resulting mixture was heated at 110 °C. After 16 h, the mixture was cooled to room temperature, diluted with

CH_2Cl_2 and concentrated *in vacuo*. Purification of the residue by MPLC (3:97 – 30:70 EtOAc:hexanes) using silica gel afforded the product as a yellow solid (0.018 g, 70%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (d, *J* = 7.5 Hz, 1H), 7.05 (t, *J* = 8.0 Hz, 1H), 6.76 (t, *J* = 7.5 Hz, 1H), 6.68 (d, *J* = 8.0 Hz, 1H), 6.07 (t, *J* = 4 Hz, 1H), 4.80 (s, 1H), 3.69 (s, 3H), 2.37 – 2.29 (m, 3H), 1.82 – 1.76 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.4 (C), 150.2 (C), 137.0 (C), 128.8 (CH), 127.0 (C), 120.3 (CH), 120.0 (CH), 119.8 (CH), 110.7 (CH), 69.2 (C), 52.7 (CH_3), 32.2 (CH_2), 24.0 (CH_2), 18.1 (CH_2); ATR-FTIR (thin film): 3341, 2936, 2904, 1713, 1603, 1462, 1449, 1255, 1232 cm^{-1}. HRMS (ES) *m/z* calculated for $C_{14}H_{16}NO_2$ $[M + H]^+$: 230.1181, found: 230.1188.



4.61 **4.62**

Alkylidene indoline 4.62. To a mixture of 0.026 g of styryl azide **4.61** (0.088 mmol) and Fe(OEP)Cl (2 mol %) was added 0.9 mL of toluene (0.1 M). The resulting mixture was heated at 110 °C. After 16 h, the mixture was cooled to room temperature, diluted with CH_2Cl_2 and concentrated *in vacuo*. Purification of the residue by MPLC (3:97 – 30:70 EtOAc:hexanes) using silica gel afforded the product as a yellow oil (0.018 g, 77%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (dd, *J* = 8.5 Hz, 1.5 Hz, 2H), 7.37 – 7.33 (m, 3H), 7.27 (m, 1H), 7.00 (dt, *J* = 8.0 Hz, 1.0 Hz, 1H), 6.72 (dt, *J* = 7.5 Hz, 1.0 Hz, 1H), 6.56 (m, 1H), 6.48 (d, *J* = 8.0 Hz, 1H), 3.96 (s, 1H), 2.58 – 2.54 (m, 1H), 2.20 (m, 1H), 2.13 – 2.07 (m, 2H), 1.88 – 1.85 (m, 1H), 1.65 (m, 1H), 1.49 – 1.44 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.1 (C), 146.2 (C), 142.6 (C), 129.0 (CH), 128.9 (CH), 128.6 (C), 127.0 (CH), 126.1

(CH), 120.4 (CH), 119.6 (CH), 118.9 (CH), 110.6 (CH), 72.6 (C), 38.8 (CH_2), 28.2 (CH_2), 27.9 (CH_2), 27.2 (CH_2); ATR-FTIR (thin film): 3342, 3056, 2928, 2859, 1703, 1600, 1445, 1391, 1264 cm^{-1}. HRMS (ES) *m/z* calculated for $C_{19}H_{20}N$ $[M + H]^+$: 262.1596, found: 262.1599.

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Chapter-V

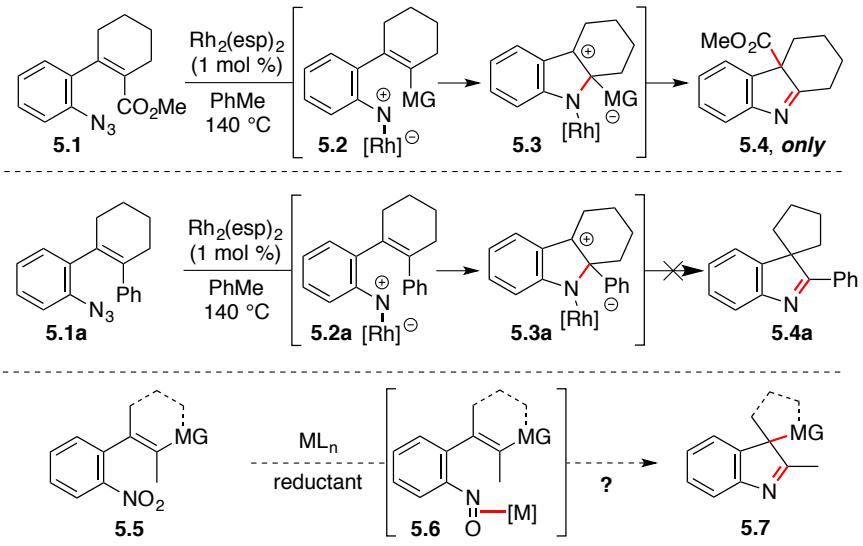
Palladium-Catalyzed Reductive Domino Reaction of Nitrostyrene With $Mo(CO)_6$ to Afford 3*H*-Indoles

(The structure of this chapter followed a published article by me: Promoting reductive tandem reactions of nitrostyrenes with $Mo(CO)_6$ and a palladium catalyst to produce 3*H*-indoles. Jana, N.; Zhou, F.; Driver, T. G. *J. Am. Chem. Soc.* **2015**, *137*, 6738.)

The development of new methods to construct C–N bond continues to be pursued by synthetic organic community in order to streamline the synthesis of important heterocyclic scaffolds. For the last two decades, various nitrogen atom sources were used to trigger C–N bond formation. Out of those, nitro group as a *N*-atom source draws attention, as nitro-functional compounds are easily available and air- and water stable.[1-5] Because of these attributes, reductive cyclization methods were developed to convert the nitrostyrenes into indoles and carbazoles by transforming an sp^2-C–H bond into an sp^2-C–N bond.[6-9] These processes, however, require more than equivalent amount of reductant such as phosphite,[10-13] Grignard reagent[14-17], Zn dust[18-19] or high pressure of poisonous carbon monoxide gas.[20-24] While these methods provide planar unsaturated indoles from nitrostyrenes, generating nonplanar, partially saturated indoles from nitrostyrenes are limited and associated with by-product formation.[25-29]

Our group research is focused on formation of C–N bonds from electrophilic *N*-atom source such as azides and C–H bonds. In attempt to synthesize nonplaner partially saturated indole, my colleague Dr. Chen Kong developed a tandem electrocyclization-1,2-migration reaction of styryl azide **5.1** to afford spirocyclic 3*H*-indole **5.4** via generation of Rh-nitrene intermediate **5.2**.[30-31] While the method developed by Chen, works efficiently for β-ester substituents, its scope was limited. For example, β-phenyl substituted nitrostyrene **5.1a** failed to produce 3*H*-indole **5.4b**. We were curious, if we

could trigger similar reactivity from nitrostyrenes to produce 3*H*-indoles. In this project we describe that trisubstituted nitrostyrene could be converted to 3*H*-indole by using a palladium catalyst and $Mo(CO)_6$ as a reductant.



5.1 5.2 5.3 5.4, *only*

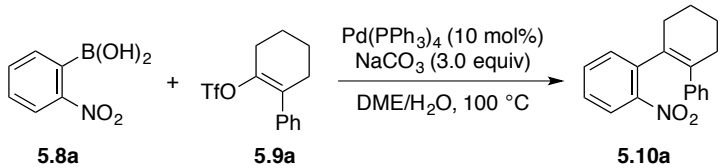
5.1a 5.2a 5.3a 5.4a

5.5 5.6 5.7

Metal nitrosoarenes derived from nitroarenes

Scheme 5.1. Rh(II)-catalyzed domino electrocyclization-1,2-migration reaction

To test our assertion, I prepared model nitrostyrene substrate **5.10a** in one-step by a Suzuki cross-coupling reaction between 2-nitrophenyl boronic acid **5.8a** and cyclohexanone derived vinyl triflate **5.9a**. The starting 2-nitroaryl-boronic acids are commercially available or could be prepared easily in one-step from 1-iodo-2-nitroarenes. The vinyl triflates were easily achieved in one-step from α-substituted cyclohexanones. The desired nitrostyrene substrates were achieved in good yields.



5.8a 5.9a 5.10a

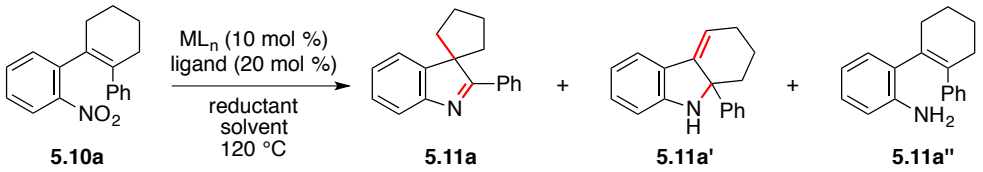
Scheme 5.2. Preparation of the trisubstituted nitrostyrene

5.1. Optimization of the reaction condition

To test our hypothesis, the trisubstituted nitrostyrene **5.10a** was exposed to a variety of metal catalyst with different reductants. In the beginning, we chose 1.5 atm of CO as a reductant. Unfortunately, when commonly used Rh,[32-33] Ru[25,32] or Pt[34] catalyst were used in presence of CO gas, none of them resulted in the formation of desired product—only aniline was obtained. Palladium acetate in combination with phenanthroline ligand and CO gas did trigger the desired cyclization; however, the migration step was prevented by deprotonation and a mixture of **5.11a** and **5.12a** were produced. Changing the nature of the ligand to more the electron-donating 3,4,7,8-tetramethyl-1,10-phenanthroline did not improve the ratio of spirocycle product **5.11a** to **5.12a** (entry 2). The formation of interrupted product **5.12a** could be blocked by using $Pd(TFA)_2$ as catalyst and additional trifluoroacetic acid to facilitate the synthesis of spirocycle (entries 3 – 4). Next, the effect of the pressure of CO gas on the reaction outcome was examined—an increase in the pressure of CO had an adverse effect to lower the yield of the desired spirocycle was observed (entry 5). Since the results from the reaction using CO gas was unsatisfactory, we chose metal carbonyl complexes as an alternative source of CO; which are known to produce CO gas when heated.[35-36] Gratifyingly, use of an equivalent amount of $Mo(CO)_6$ prevented the deprotonation pathway to produce our desired spirocycle along with aniline (entry 6). A screen of solvents revealed that aniline formation was minimized when the reaction was performed in 1,2-DCE and the desired 3*H*-indole was obtained in 80% yield (entries 7–8). In contrast to our investigations using CO gas as the reductant, the addition of trifluoroacetic acid did not have a positive effect on the reaction outcome to generate a

mixture of products (entry 9). Finally, the $Pd(OAc)_2$ catalyst loading could be reduced from 10 mol % to 5 mol % to form only spirocycle 5.11a, albeit reduced in yield (entry-10).

Table 5.1. Optimization of the reaction conditions



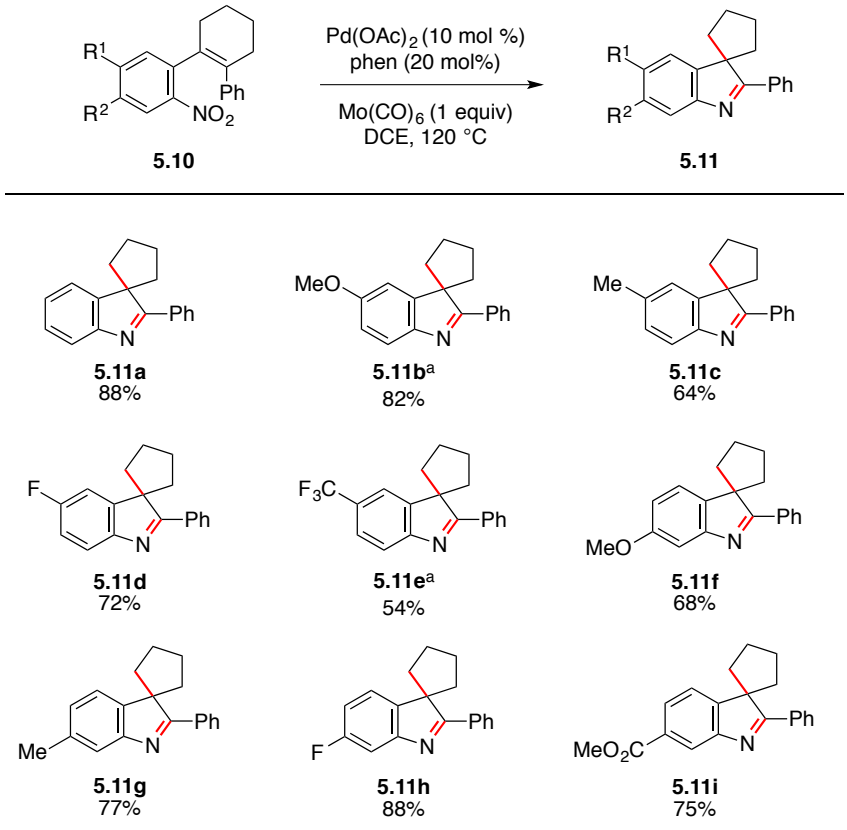
5.10a **5.11a** **5.11a'** **5.11a''**

entry	catalyst	ligand	reductant	solvent	yield, %[a] **5.11a**:**5.11a'**:**5.11a''**
1[b]	$Pd(OAc)_2$	phen	CO(1.5 atm)	DMF	20:40:0
2[b]	$Pd(OAc)_2$	tmphen	CO(1.5 atm)	DMF	12:21:0
3[b]	$Pd(TFA)_2$	phen	CO(1.5 atm)	DMF	44:8:0
4[b,c]	$Pd(TFA)_2$	phen	CO(1.5 atm)	DMF	62:0:0
5[b,c]	$Pd(TFA)_2$	phen	CO(3.0 atm)	DMF	37:0:0
6[d]	$Pd(OAc)_2$	phen	$Mo(CO)_6$	DMF	30:0:35
7	$Pd(OAc)_2$	phen	$Mo(CO)_6$	THF	48:0:50
8	$Pd(OAc)_2$	phen	$Mo(CO)_6$	DCE	80:0:0
9[c]	$Pd(OAc)_2$	phen	$Mo(CO)_6$	DCE	16:15:38
10[f]	$Pd(OAc)_2$	phen	$Mo(CO)_6$	DCE	68:0:0

[a] As determined using ^{1}H NMR spectroscopy using CH_2Br_2 as the internal standard. [b] 20 mol % of $Pd(OAc)_2$ and 40 mol % ligand used. [c] 0.4 equiv of trifluoroacetic acid added. [d] 1.0 equiv of $Mo(CO)_6$ used. [e] 0.5 equiv of $Mo(CO)_6$ used. [f] 5 mol % of $Pd(OAc)_2$ and 10 mol % phen used.

5.2. Examination of the substrate scope by changing the electronic nature of the nitroarene.

Using the standard conditions, Dr. Fei Zhou and I investigated the scope of our cyclization-1,2-migration reaction. First, the effect of *para*-substituents relative to nitro group was examined. We have found that both electron-donating- and -withdrawing *para*-substituents were tolerated equally without significant decrease in yield (**5.11a** – **5.11e**). The effect of changing R^2-substituent was investigated next. Irrespective of the electronic nature of the substituent, the nitroarenes **5.10f** – **5.10i** were converted smoothly to 3*H*-indoles **5.11f** – **5.11i** respectively. These 3*H*-indoles cannot be accessed in a single regioisomer by an inturrepted Fischer-indole-type reaction.[37-39]

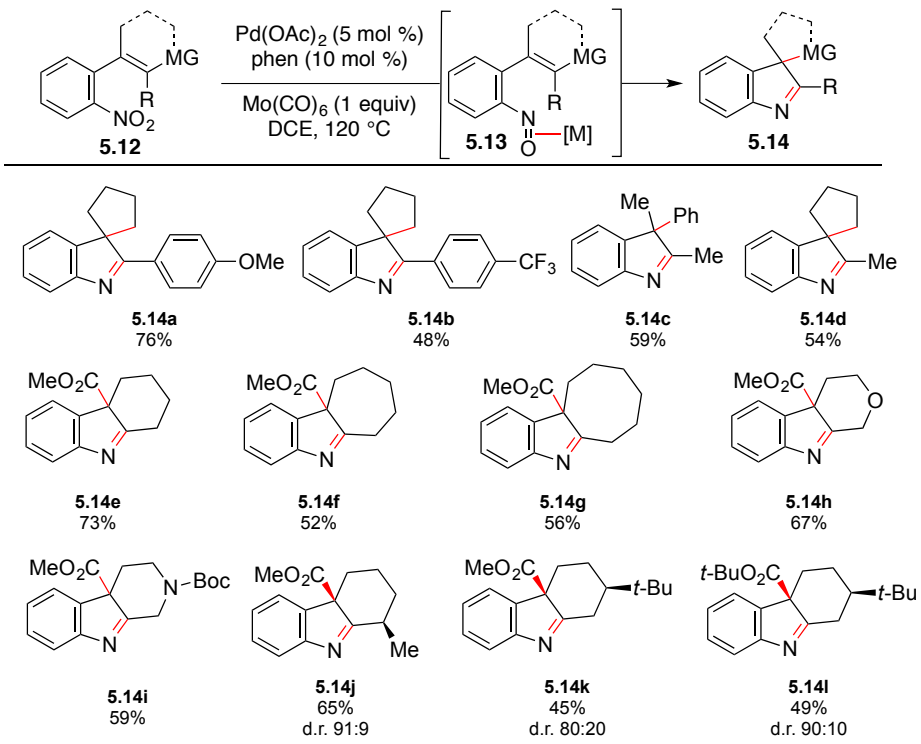


[a] 20 mol % $Pd(OAc)_2$ used.

Scheme 5.3. Survey of substrate scope by changing the electronic nature of the nitroarenes

5.3. Investigation of the substrate scope by changing the identity of the β-substituent

Fei, and I investigated the scope and limitations of 3*H*-indole formation by changing the identity of the β-substituent. We observed a higher yield using electron-rich β-4-methoxyphenyl substituent in comparison to an electron-withdrawing β-4-trifluoromethylphenyl substituent (**5.14a** *cw* **5.14b**). In contrast to 1,2-alkyl group migration shown in the previous example, phenyl group migration was observed using substrate **5.12c**. We attributed the phenyl group migration to the C3 position as a result of reduced steric environment at C2 position in the product. While ring contraction was observed in a substrate bearing β-methyl substituent to give **5.12d**, changing the identity of the R-substituent to ester group provides 3*H*-indole **5.12e**. The 1,2-ester migration was not dependent on the ring size of the tether: six-, seven- and eight-membered ring substituents were converted to the 3*H*-indoles smoothly. Next, the effect of heteroatom substituent on to the tether was investigated. The *ortho*-heterocycles **5.12h** and **5.12i** were converted to 3*H*-indoles **5.14h** and **5.14i** respectively when a higher catalyst loading was used. To probe the diastereoselectivity in our transformation, we prepared nitrostyrene **5.12j**; when exposed to the reaction condition we observed 91:9 mixture of diastereomer of 3*H*-indole **5.14j**. A change in the position of stereocenter from allylic methyl group to homo-allylic *tert*-butyl substituent, however, reduced the diastereoselectivity to 80:20 (**5.14k**). This ratio was improved to 90:10, however, when bulky β-*tert*-butyl ester substituent was used as migrating group (**5.14l**).

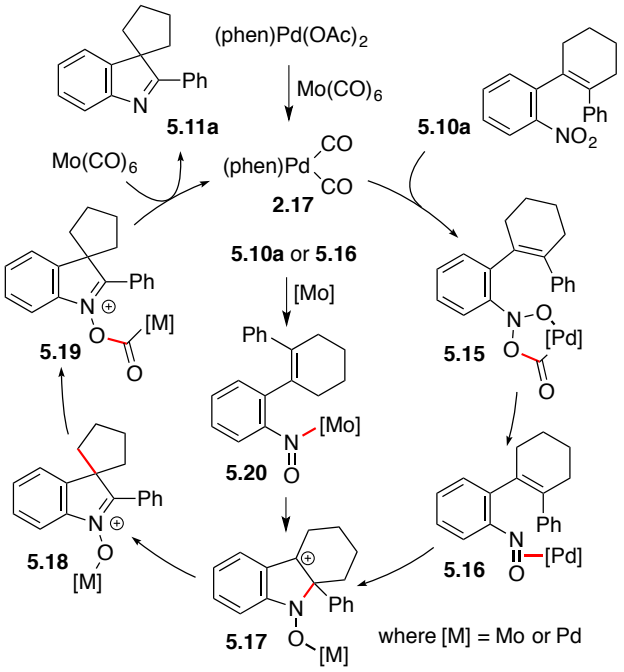


Scheme 5.4. Examination of the scope and limitations of the 3*H*-indole formation

5.4. Mechanistic proposal for the formation of the 3*H*-indole

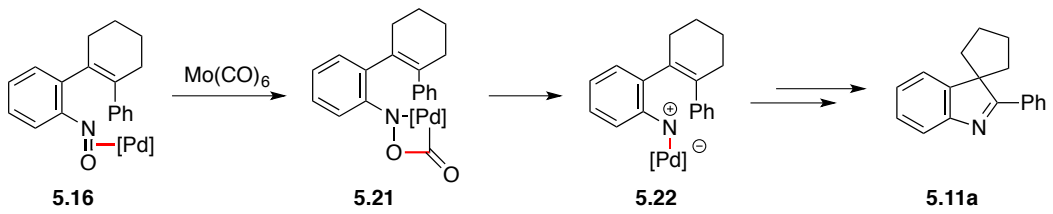
Based on earlier reports of Pd-catalyzed reduction of nitro-compounds, we proposed a catalytic cycle for the transformation.[40-43] Reduction of phenthroline-$Pd(OAc)_2$ complex by $Mo(CO)_6$ would produce palladium-CO complex which might exist as monomer or cluster.[44-47] Oxidative addition of nitroarene **5.10** provides palladacycle **5.15**.[48-49] Exrtrusion of CO_2 gas produces Pd-nitrosoarene intermediate **5.16**. The C–N bond could be formed by electrocyclization or attack of adjacent π-system to give **5.17**.[50-51] The benzyl cation intermediate could undergo ring contraction to afford N-oxide intermediate **5.18**. Reduction of N–O bond by CO produces 3*H*-indole **5.11a** via intermediate **5.19**. A

second possibility arises from reduction of nitroarenes by $Mo(CO)_6$ to give Mo-nitrosoarene intermediate **5.20**,[52-55] which then undergoes cyclization. Molybdenum could also replace Pd in **5.16** to from Mo-nitrosoarene intermediate **5.20**.



Scheme 5.5. Plausible mechanism for the formation of 3*H*-indole

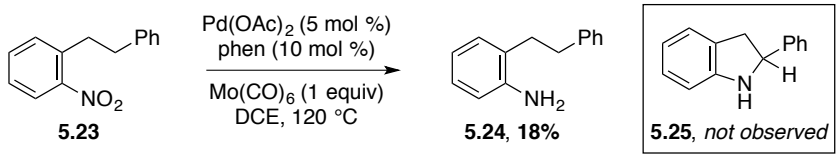
A third possibility of C–N bond formation stems from Pd-nitrene intermediate. Palladium-nitrosoarene complex could be transformed to palladacycle **5.21**,[56] followed be reductive elimination generated Pd-nitrene intermediate **5.22**. This nitrene intermediate could undergo a domino electrocyclization-migration to give 3*H*-indole **5.11a**.



Scheme 5.6. Formation of the potential Pd-nitrene intermediates

5.5. Mechanistic study

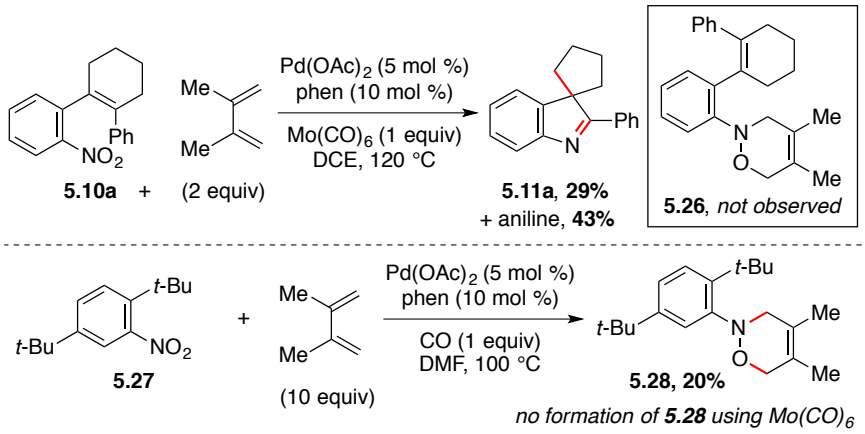
We have performed several experiments to distinguish between these mechanistic possibilities. To test if Pd-nitrene intermediate is involved during the transformation, Fei, exposed nitroarene **5.23** to the standard condition. We expected that if metal-nitrene intermediate were involved during the reaction, 2-phenylindoline **5.24** would be formed as a product,[57-58] however, no C–H bond amination was observed; only aniline was formed as a product. This experiment suggests that, Pd-nitrene species was not the catalytic intermediate.



Scheme 5.7. Test to trap potential Pd-nitrene intermediate

To examine if the metal-nitrosoarene intermediate was formed *in situ*, I added an excess of 2,3-dimethylbutadiene to the reaction of nitroarene **5.10a** (Scheme 5.8). We expected that nitrosoarene intermediate might form a [4+2] cycloaddition product with the diene. When we tested the reactivity of nitroarene **5.10a** toward the reaction conditions, only 3*H*-indole **5.11a** and aniline were observed. We envisioned that this result could be attributed to the enhanced rate of an intramolecular reaction in

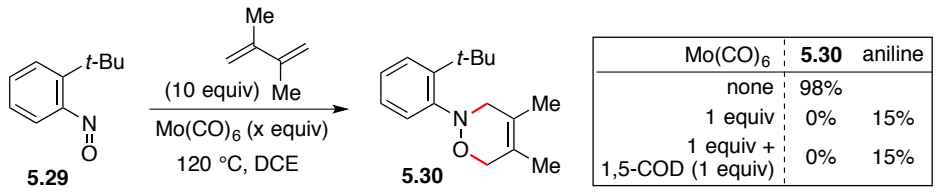
comparison to an intermolecular cycloaddition reaction. To eliminate this competition, we changed the identity of the *ortho*-substituent to an alkyl group and we chose 2,5-di-*tert*-butylnitrobenzene **5.27** to examine the reactivity. Exposure of **5.27** to reaction conditions with excess amount of 2,3-dimethylbutadiene resulted in the formation of only aniline. We found the nitroso-intermediate could be intercepted when $Mo(CO)_6$ was replaced with CO to prduce oxazine **5.28**. Together, these results suggest that $Mo(CO)_6$ plays a more complicated role than just a source of CO.



Scheme 5.8. Attempted interception of the metal-nitrosoarene intermediate

To further investigate the role of $Mo(CO)_6$ towards the trapping of nitrosoarene intermediate, the reactivity of 2-*tert*-butylnitrosobenzene was investigated using 2,3-dimethylbutadiene as a trapping reagent (Scheme 5.9). The cycloadduct oxazine **5.30** was formed in absence of $Mo(CO)_6$, however, use of equivalent amount of $Mo(CO)_6$ completely prevented the cycloadduct formation. Instead, aniline was formed as a by-product. Together with the previous mechanistic experiments, these experiments indicate that $Mo(CO)_6$ has a dual roles: it helps in reduction of the nitroarenes and induces cyclization-migration pathway. As $Pd(OAc)_2$ and phenanthroline are required for high

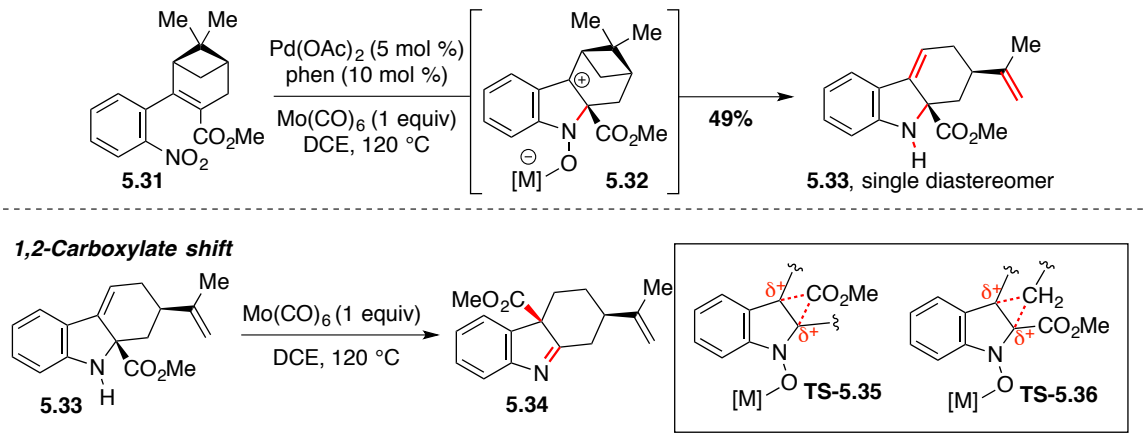
yield, these results suggest that the role of this complex is to catalyze the reduction of nitroarene **5.10a** and N-oxide **5.18**.[59-61]



$Mo(CO)_6$	**5.30**	aniline
none	98%	
1 equiv	0%	15%
1 equiv + 1,5-COD (1 equiv)	0%	15%

Scheme 5.9. Role of $Mo(CO)_6$ towards cycloaddition

Additional insight into the mechanism came from α-pinene derived nitroarene **5.32** (Scheme 5.10). When subjected to the reaction condition, a single diastereomer of **5.33** was formed. This unexpected elimination product was rationalized by the increased steric nature of the gem-dimethyl group in the bridgehead position of **5.32**, which inhibits the expected carboxylate ester migration. Instead fragmentation occurs to produce **5.33**. Ester migration from **5.33**, however, could be triggered without using Pd-catalyst if an equivalent amount of $Mo(CO)_6$ was added. This phenomenon indicates that the Pd-catalyst was not required for the migration process. The chemoselectivity of the migration steps could be rationalized by **TS-5.35**, which generates more stable imminium ion than **TS-5.36**.



Scheme 5.10. Separation of cyclization and migration event

5.6. Conclusion.

In conclusion, we have shown that the reactivity of trisubstituted nitroarenes can be unlocked using $Mo(CO)_6$ and $Pd(OAc)_2$ to trigger cyclization-migration sequence to form 3*H*-indoles. Two different types of 3*H*-indoles were obtained by changing the β-substituent. Our data suggest that $Mo(CO)_6$ plays a dual role in the reaction: it releases CO gas and stabilizes the nitrosoarene intermediate. The major drawback of our reaction is the formation of equivalent amount of molybdenum waste. The future direction of this project is aimed towards unlocking the hidden reactivity in the nitroarenes to trigger other types of C–H bond amination which will be discussed in the next chapter.

5.7. Experimental

(This part was taken from supporting information of my published paper: Jana, N.; Zhou, F.; Driver, T. G. *J. Am. Chem. Soc.* **2015**, *137*, 6738.)

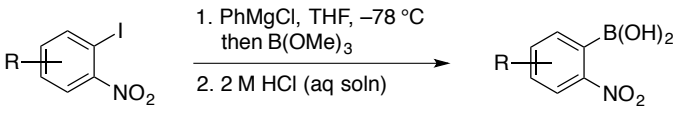
A. General

^{1}H NMR and ^{13}C NMR spectra were recorded at ambient temperature using 500 MHz or 300 MHz spectrometers. The data are reported as follows: chemical shift in ppm from internal tetramethylsilane on the δ scale, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz) and integration. High-resolution mass spectra were obtained by peak matching. Melting points are reported uncorrected. Infrared spectroscopy was obtained using a diamond attenuated total reflectance (ATR) accessory. Analytical thin layer chromatography was performed on 0.25 mm extra hard silica gel plates with UV254 fluorescent indicator. Liquid chromatography was performed using forced flow (flash chromatography) of the indicated solvent system on 60Å (40 – 60 μm) mesh silica gel (SiO_2). Medium pressure liquid chromatography (MPLC) was performed to force flow the indicated solvent system down columns that had been packed with 60Å (40 – 60 μm) mesh silica gel (SiO_2). All reactions were carried out under an atmosphere of nitrogen in glassware, which had been oven-dried. Unless otherwise noted, all reagents were commercially obtained and, where appropriate, purified prior to use. Acetonitrile, Methanol, Toluene, THF, Et_2O, and CH_2Cl_2 were dried by filtration through alumina. Metal salts were stored in a nitrogen atmosphere dry box.

B. Synthesis of 2-Nitroarylboronic acid and 2-Nitroarylboronic Acid Pinacolate Ester.

1. Synthesis of 2-Nitroarylboronic Acids.

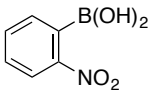
a. General Procedure.



5.8

A dry nitrogen-flushed 25 mL round-bottomed flask equipped with a magnetic stirrer and a septum was charged with aryl iodide (4.0 mmol). Dry THF (6 mL) was added, and the resulting solution was cooled to –78 °C. To the resulting cooled mixture was added dropwise 2.2 mL of a 2 M solution of PhMgCl (4.4 mmol) in THF. After 5 minutes, 0.536 mL of trimethyl borate (4.8 mmol) was added dropwise to the reaction solution. The reaction mixture was stirred for 30 min at –78 °C. The reaction mixture was warmed to –20 °C and was quenched with 4 mL of a 2 M aqueous solution of HCl. The resulting mixture was extracted with 3 × 20 mL of Et_2O. The combined organic layers were washed with 2 × 20 mL of H_2O and 1 × 20 mL of brine. The resulting organic phase was dried over Na_2SO_4, filtered, and concentrated *in vacuo* overnight. The boronic acids were used in subsequent transformations without additional purification.

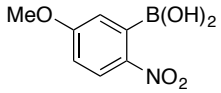
b. Preparation of 2-Nitroarylboronic Acids.



5.8a

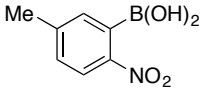
2-Nitrophenylboronic acid 5.8a.[62] The general procedure was followed by using 0.996 g of 2-iodo-1-nitrobenzene (4.0 mmol), PhMgCl (2 M in THF, 2.2 mL, 4.4 mmol), trimethyl borate (4.8 mmol, 0.536 mL) in 6 mL of dry THF at –78 °C to afford the crude

product as a brown solid, which was used in the subsequent transformation without addition purification.



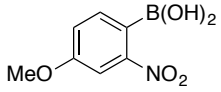
5.8b

2-Nitro-5-methoxyphenylboronic acid 5.8b.[62] The general procedure was followed by using 1.12 g of 2-iodo-4-methoxy-1-nitrobenzene (4.0 mmol), PhMgCl (2 M in THF, 2.2 mL, 4.4 mmol), trimethyl borate (4.8 mmol, 0.536 mL) in 6 mL of dry THF at –78 °C to afford the crude product as a brown solid, which was used in the subsequent transformation without addition purification.



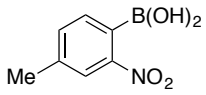
5.8c

2-Nitro-5-methylphenylboronic acid 5.8c.[62] The general procedure was followed by using 1.05 g of 2-iodo-4-methyl-1-nitrobenzene (4.0 mmol), PhMgCl (2 M in THF, 2.2 mL, 4.4 mmol), trimethyl borate (4.8 mmol, 0.536 mL) in 6 mL of dry THF at –78 °C to afford the crude product as a grey solid, which was used in the subsequent transformation without addition purification.



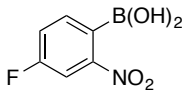
5.8f

2-Nitro-4-methyoxyphenylboronic acid 5.8f.[62] The general procedure was followed by using 1.12 g of 4-iodo-3-nitroanisole (4.0 mmol), PhMgCl (2M in THF, 2.2 mL, 4.4 mmol), trimethyl borate (4.8 mmol, 0.536 mL) in 6 mL of dry THF at –78 °C to afford the crude product as a black solid, which was used in the subsequent transformation without addition purification.



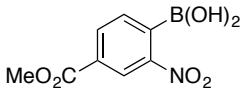
5.8g

2-Nitro-4-methylphenylboronic acid 5.8g.[62] The general procedure was followed by using 1.05 g of 4-iodo-3-nitrotoluene (4.0 mmol), PhMgCl (2M in THF, 2.2 mL, 4.4 mmol), trimethyl borate (4.8 mmol, 0.536 mL) in 6 mL of dry THF at –78 °C to afford the crude product as a black solid, which was used in the subsequent transformation without addition purification.



5.8h

2-Nitro-4-fluorophenylboronic acid 5.8h.[62] The general procedure was followed by using 1.05 g of 5-fluoro-2-iodonitrobenzene (4.0 mmol), PhMgCl (2M in THF, 2.2 mL, 4.4 mmol), trimethyl borate (4.8 mmol, 536 μL) in 6 mL of dry THF at –78 °C to afford the crude product as a black solid, which was used in the subsequent transformation without addition purification.

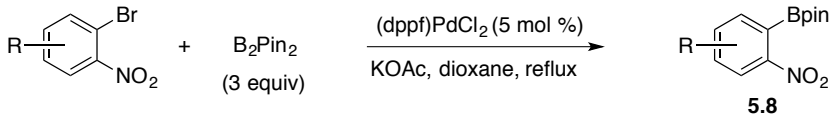


5.8i

2-Nitro-4-methylcarboxylatephenylboronic acid 5.8i.[62] The general procedure was followed by using 1.23 g of methyl-4-iodo-3-nitrobenzoate (4.0 mmol), PhMgCl (2M in THF, 2.2 mL, 4.4 mmol), trimethyl borate (4.8 mmol, 536 μL) in 6 mL of dry THF at –78 °C to afford the crude product as a brown solid, which was used in the subsequent transformation without addition purification.

2. Synthesis of 2-Nitroarylboronic Acid Pinacolate ester..

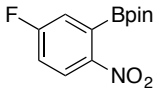
a. General Procedure.



5.8

To a mixture of 2.02 g of 1-bromo-2-nitrobenzene (10.0 mmol, 1 equiv), 3.81 g of bis(pinacolato)diboron (15.0 mmol, 3 equiv), 2.52 g of KOAc (25.7 mmol, 2.57 equiv) and 0.400 g of (dppf)$PdCl_2$ (0.5 mmol, 5 mol %) was added 40 mL of 1,4-dioxane. The resultant mixture was refluxed at 100 °C. After 12 h, the mixture was cooled to room temperature and 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 × 20 mL of EtOAc. The combined organic phases were washed with 1 × 30 mL of brine. The resulting organic phase was dried over Na_2SO_4, filtered, and the filtrate was concentrated *in vacuo*. Purification via MPLC afforded the product.

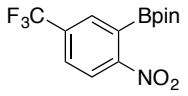
b. Characterization Data for 2-Nitroarylboronic Acid Pinacolate Esters.



5.8d

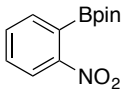
2-Nitro-5-fluorophenylboronic acid pinacolate ester 5.8d.[63] The general procedure was followed using 0.330 g of 1-bromo-2-nitrobenzene (1.50 mmol), 0.571 g of bis(pinacolato)diboron (2.30 mmol), 0.378 g of KOAc (3.86 mmol) and 0.060 g of (dppf)$PdCl_2$ (0.070 mmol) in 8 mL of 1,4-dioxane. Purification by MPLC (2:100 – 10:90 EtOAc: hexanes) afforded the product as a light yellow solid (0.180 g, 45%). The spectral data of **2.12d** matched that reported by Hutchinson and Stevens:[63] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 – 8.19 (m, 1H), 7.19 (d, J = 7.5 Hz, 2H), 1.42 (s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.7 (d, J_{CF} = 257.1 Hz, C), 146.9 (C), 126.0 (d, J_{CF} = 9.4 Hz, CH),

119.5 (d, J_{CF} = 22.1 Hz, CH), 116.9 (d, J_{CF} = 23.7 Hz, CH), 85.0 (C), 24.7 (CH_3), only visible signals; IR (thin film): 2982, 1712, 1577, 1525, 1409, 1337, 1211, 1141, 1049, 946, 841 cm^{-1}.



5.8e

2-Nitro-5-triflouromethylboronic acid pinacolate ester 5.8e.[64] The general procedure was followed using 0.540 g of 1-bromo-2-nitrobenzene (2.00 mmol), 0.762 g of bis(pinacolato)diboron (3.00 mmol), 0.504 g of KOAc (5.14 mmol) and 0.082 g of (dppf)$PdCl_2$ (0.10 mmol) in 10 mL of 1,4-dioxane. Purification by MPLC (2:100 – 10:90 EtOAc: hexanes) afforded the product as a ^{light} yellow solid (0.420 g, 66%). Pinacolate ester **2.12e** was previously reported by Gillespie at Hoffmann-La Roche in 2013:[64] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (d, J = 8.5 Hz, 1H), 7.82 (m, 2H), 1.44 (s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.0 (C), 135.3 (C), 135.1 (C), 130.3 (CH), 127.5 (CH), 125.4 (q, J_{CF} = 313.7 Hz, C), 123.5 (C), 85.2 (C), 24.7 (CH_3); IR (thin film): 2982, 2934, 1525, 1345, 1298, 1172, 1135, 1078, 962, 849 cm^{-1}.



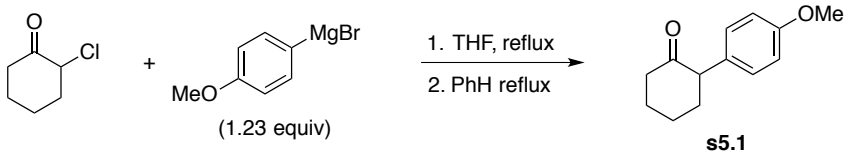
5.8j

2-Nitrophenylboronic acid pinacolate ester 5.8j.[65] The general procedure was followed using 2.02 g of 1-bromo-2-nitrobenzene (10.0 mmol), 3.81 g of bis(pinacolato)diboron (15.0 mmol), 2.52 g of KOAc (25.7 mmol) and 0.400 g of (dppf)$PdCl_2$ (0.5 mmol) in 40 mL of 1,4-dioxane. Purification by MPLC (2:100 – 10:90 EtOAc: hexanes) afforded the product **2.12j** as an orange oil (1.95 g, 80%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (d, J =

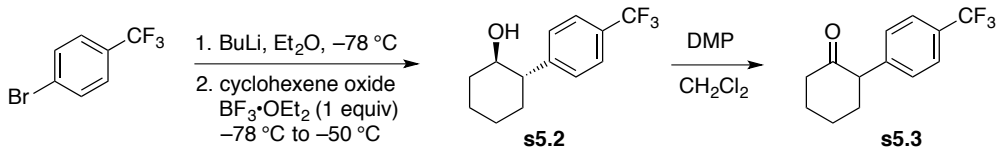
7.9 Hz, 1H), 7.66 (m, 1H), 7.56 (m, 2H), 1.45 (s, 12H); IR (thin film): 2978, 1568, 1524, 1482, 1342, 1317, 1274, 1252, 1142, 1106, 1058, 860, 849 cm^{-1}.

C. Synthesis of Vinyl Triflates.

1. Preparation of 2-Arylcyclohexanones.



2-(4-Methoxy)phenylcyclohexanone s5.1.[66] Following the procedure reported by Nachtsheim and Frahm,[66] to a freshly prepared 4-methoxyphenylmagnesium bromide solution in THF (37 mL, 0.5 M, 18.5 mmol) was added 2-chlorocyclohexanone (1.71 mL, 15.0 mmol) in 8 mL of anhydrous ether via drop funnel under nitrogen at a rate only caused gentle refluxing. After the addition, the THF was removed by distillation and 15 mL of anhydrous benzene was added to the residue. The mixture was refluxed for 8 hours. The reaction mixture was cooled to room temperature, hydrolyzed with water and extracted with 150 mL EtOAc. The extract was concentrated and distilled (106 – 108 °C/1 mmHg) to give 2-(4-methoxy)phenylcyclohexanone as a white solid (0.730 g, 24%). The spectral data matched that reported by Nachtsheim and Frahm:[66] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.06 (d, J = 8.5 Hz, 2H), 6.87 (d, J = 8.5 Hz, 2H), 3.79 (s, 3H), 3.57 (dd, J = 12.5 Hz, 5.5 Hz, 1H), 2.54 – 2.41 (m, 2H), 2.26 – 2.24 (m, 1H), 2.16 – 2.14 (m, 1H), 2.00 – 1.98 (m, 2H), 1.83 – 1.79 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.7 (C), 158.5 (C), 130.9 (C), 129.5 (CH), 113.9 (CH), 56.6 (CH), 55.2 (CH_3), 42.2 (CH_2), 35.3 (CH_2), 27.9 (CH_2), 25.4 (CH_2). ATR-FTIR (thin film): 2927, 2860, 1704, 1614, 1515, 1447, 1552, 1180, 1124, 1092 cm^{-1}.



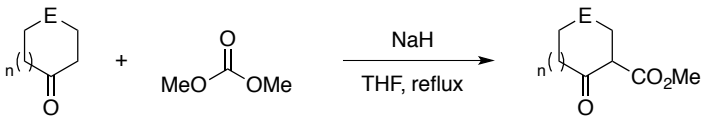
2-(4-Trifluoromethylphenyl)cyclohexanol s5.2.[67] Following the procedure reported by Berti and co-workers,[67] To a solution of 0.47 mL 4-bromotrifluoromethylbenzene (3.34 mmol) in 10 mL of diethylether at –78° C was added 2.56 mL of BuLi (1.6 M, 4.0 mmol) under argon. After 5 min at this temperature, 0.41 mL of cyclohexenoxide (4.0 mmol) was added followed by the addition of 1.07 mL boron trifluoride-diethyletherate (4.0 mmol, 46% BF_3 basis) whereby the temperature increased to approx. –50° C. After 4 h at this temperature the reaction was quenched by the addition of 20 mL saturated ammonium chloride and diluted with water (5 mL). The product was then extracted with diethylether (3 × 20 mL) and the combined organic extracts dried over sodium sulfate. Purification of the residue by MPLC afforded the product (2:100 – 50:50 EtOAc: hexanes) as white solid (0.635 g, 78%). The alcohol product was oxidized without any additional characterization.

2-(4-Trifluoromethyl)phenylcyclohexanone s5.3.[68] To a solution of 0.366 g of 2-(4-trifluoromethyl-phenyl)cyclohexanol (1.5 mmol) in 15 mL of dichloromethane was added 0.763 g of Dess-Martin periodinane (1.8 mmol). After 2 h, the reaction mixture was washed with 10 mL of a 10% aqueous solution of sodium hydrogen carbonate. The organic phase was then separated and washed with 20 mL of a 10% aqueous solution of sodium thiosulfate. The resulting organic phase was dried over sodium sulfate, filtered and concentrated *in vacuo*. Purification of the residue by MPLC afforded the product (2:100 – 30:70 EtOAc: hexanes) as white solid (0.340 g, 94%). The spectral data for s5.3 mathched that reported by Zhou and co-workers.[68] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (d,

J = 8.0 Hz, 2H), 7.25 (d, J = 8.5 Hz, 2H), 3.66 (dd, J = 12.5 Hz, 5.5 Hz, 1H), 2.56 – 2.47 (m, 2H), 2.29 – 2.26 (m, 1H), 2.19 – 2.17 (m, 1H), 2.04 – 1.99 (m, 2H), 1.85 – 1.81 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.4 (C), 142.8 (C), 129.2 (C), 129.0 (CH), 125.2 (q, J = 6.4 Hz, CH), 122.1 (q, J_{CF} = 269.8 Hz, C), 57.3 (CH), 42.2 (CH_2), 35.3 (CH_2), 27.8 (CH_2), 25.4 (CH_2). ATR-FTIR (thin film): 2937, 2863, 1708, 1618, 1324, 1114, 1066, 1019 cm^{-1}.

2. Preparation of β-ketoester.

a. General Procedure.

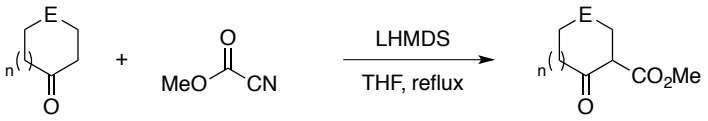


s5.4

Method A: To sodium hydride (60% oil dispersion, 4 equiv) was added a solution of dimethyl carbonate (3 equiv) in dry THF (1M). The mixture was stirred at reflux temperature (75 °C), and then, a solution of ketone (1 equiv) in dry THF (2M) was added dropwise to the mixture using a syringe pump. After 2 – 12 hours, the reaction mixture was cooled using an ice bath. After 20 min, the reaction mixture was diluted with ether. The mixture was hydrolyzed by the slow addition of 1M aqueous solution of HCl, then poured into brine and extracted with diethyl ether (4 × 30 mL). The combined organic layers were dried over Na_2SO_4 and concentration *in vacuo*. Purification of the residue by MPLC afforded the product.

Method B: To a solution of ketone (1 equiv) in dry THF (2M) was slowly added sodium hydride (60% oil dispersion, 2.5 equiv). The mixture was stirred at room temperature for 30 min. Then a solution of dimethyl carbonate (2.5 equiv) in dry THF (1M) was added

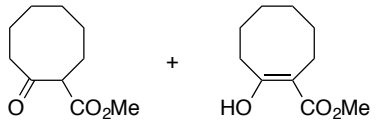
dropwise to the reaction mixture and the solution was stirred at reflux for overnight. The reaction mixture was cooled using an ice bath. After 20 min, the reaction mixture was diluted with ether. The mixture was hydrolyzed by the slow addition of 1M aqueous solution of HCl, then poured into brine and extracted with diethyl ether (4 × 30 mL). The combined organic layers were dried over Na_2SO_4 and concentration *in vacuo*. Purification of the residue by MPLC afforded the product.



s5.4

Method C: To a solution of ketone (1 equiv) in dry THF (2M) was added a solution LHMDS (1.05 equiv) in THF dropwise at –78 °C. After 1.5 hrs, a solution of methyl cyanoformate (1.2 equiv) in dry THF (1M) was added dropwise at –78 °C. The mixture was allowed to warm to room temperature overnight. The reaction mixture was cooled using an ice bath. After 20 min, the reaction mixture was diluted with ether. The mixture was hydrolyzed by the slow addition of 1M aqueous solution of HCl, then poured into brine and extracted with diethyl ether (4 × 30 mL). The combined organic layers were dried over Na_2SO_4 and concentration *in vacuo*. Purification of the residue by MPLC afforded the product.

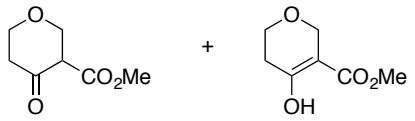
b. Characterization Data.



s5.4a

Methyl-2-oxocyclooctanecarboxylate s5.4a.[69] Method A was followed using 3.20 g of NaH (80 mmol), 5.0 mL of dimethylcarbonate (60 mmol), and 2.53 g of cyclooctanone

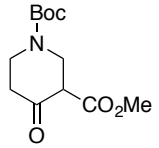
(20 mmol) in 50 mL dioxane reflux at 90 °C. Purification by MPLC (2:98 to 5:95 EtOAc: hexane) afforded the product—a yellow oil—as a mixture of the keto- and enol tautomers (3.70 g, 100%). Cyclooctanecarboxylate **s5.4a** was first reported by Prelog and coworkers:[69] ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.71 (s, 3H), 2.33 (d, *J* = 26.2 Hz, 3H), 1.67 (d, *J* = 3.7Hz, 2H), 1.49 (s, 3H), 1.41 (s, 2H), 0.83 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ mixture of ketone and enol 212.0 (C), 176.1 (C), 173.2 (C), 170.5 (C), 99.0 (C), 56.7 (CH), 52.2 (CH_3), 51.3 (CH_3), 41.8 (CH_2), 32.2 (CH_2), 29.9 (CH_2), 29.0 (CH_2), 28.7 (CH_2), 27.0 (CH_2), 26.5 (CH_2), 26.0 (CH_2), 25.3 (CH_2), 25.2 (CH_2), 24.5 (CH_2), 23.9 (CH_2). ATR-FTIR (thin film): 2923, 2855, 1648, 1609, 1437, 1226 cm^{-1}. The mixture of products was converted to the vinyl triflate without additional purification or characterization.



s5.4b

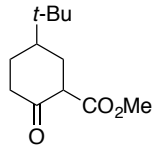
Methyl-4-oxotetrahydro-2*H*-pyran-3-carboxylate s5.4b.[70] Method C was followed using 1.76 g of LHMDS (10.5 mmol), 0.95 mL of methyl cyanoformate (12 mmol), and 1.0 g of tetrahydro-4*H*-pyran-4-one (10 mmol) in 30 mL THF. Purification by MPLC (2:98 to 10:90 EtOAc: hexane) afforded the product—a colorless oil—as a mixture of keto- and enol tautomers (0.31 g, 20%). This carboxylate was first reported by Dowd and Choi:[70] ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.15 (t, *J* = 1.7 Hz, 2H), 3.73 (t, *J* = 5.7 Hz, 2H), 3.66 (s, 1H), 3.65 (s, 3H), 2.27 (tt, *J* = 5.7 Hz, 1.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ mixture of ketone and enol 201.2 (C), 170.3 (C), 168.9 (C), 168.2 (C), 97.2 (C), 69.5 (CH_2), 68.1 (CH_2), 63.8 (CH_2), 62.8 (CH_2), 57.6 (CH), 52.3 (CH_3), 51.2 (CH_3), 41.9 (CH_2), 28.6 (CH_2). ATR-FTIR (thin film): 2957, 2857, 1720, 1649, 1623, 1444, 1308, 1097 cm^{-1}.

The mixture of products was converted to the vinyl triflate without additional purification or characterization.



s5.4c

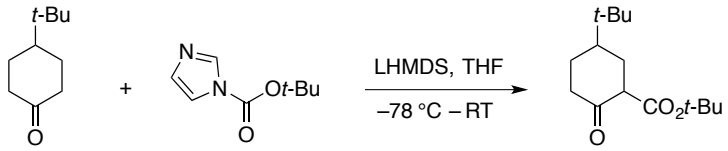
1-*tert*-Butyl-3-methyl-4-oxopiperidine-1,3-dicarboxylate s5.4c.[71] Method B was followed using 1.50 g of NaH (37.5 mmol), 3.2 mL of dimethylcarbonate (37.5 mmol), and 3.0 g of 1-Boc-4-piperidone (15 mmol) in 50 mL THF reflux at 60 °C. Purification by MPLC (2:98 to 10:90 EtOAc: hexane) afforded the product—a colorless oil—as a mixture of rotamers (2.81 g, 74%). The spectral data of **s5.4c** matched that reported by Liu and coworkers:[71] ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.98 (s, 2H), 3.71 (s, 3H), 3.49 (t, J = 5.1 Hz, 2H), 2.29 (s, 2H), 1.40 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.5 (C), 171.0 (C), 154.5 (C), 80.0 (C), 60.3 (CH_2), 56.3 (CH), 53.4 (CH_2), 51.5 (CH_3), 28.8 (CH_2), 28.3 (CH_3). ATR-FTIR (thin film): 2978, 1691, 1661, 1619, 1226 cm^{-1}.



s5.4d

Methyl-5-tert-butyl-2-oxocyclohexanecarboxylate s5.4d.[72] Method A was followed using 2.33 g of NaH (58.3 mmol), 4.2 mL of dimethylcarbonate (50.4 mmol), and 3.0 g of 4-tert-butylcyclohexanone (19.4 mmol) in 60 mL THF. Purification by MPLC (2:98 to 5:95 EtOAc: hexane) afforded the product, a yellow oil, as a mixture of diastereomers (4.2 g, 100%). The spectral data of **s5.4c** matched that reported by Renaud and coworkers:[72] ^{1}H NMR (500 MHz, CDCl3) δ 3.70 (s, 3H), 2.26 (s, 2H), 2.03 (t, J = 4.9 Hz,

1H), 1.80 (s, 2H), 1.21 (s, 4H), 0.86 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.1 (C), 172.0 (C), 97.3 (C), 51.2 (CH_3), 44.1 (CH), 30.1 (CH_2), 27.5 (C), 27.3 (CH_3), 22.8 (CH_2), 23.1 (CH_2). ATR-FTIR (thin film): 2950, 2868, 1657, 1616, 1438, 1277 cm^{-1}. The mixture of products was converted to the vinyl triflate without additional purification or characterization.



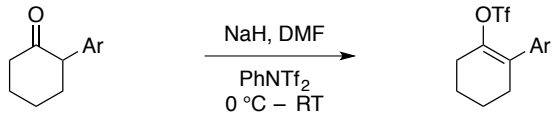
s5.4e

***tert*-Butyl-5-*tert*-butylcyclohexyl-2-oxocyclohexanecarboxylate s5.4e.**[73] To a solution of 4-*tert*-butylcyclo-hexanone (3.25 g, 21.1 mmol) in THF (30 mL) was added a solution of LHMDS (3.88 g, 23.2 mmol) in THF (10 mL) at –78 °C. After 30 min, 1-(*tert*-butoxycarbonyl)imidazole (5.32 g, 31.6 mmol) was added and the resulting mixture was allowed to reach room temperature. After stirring for 30 min, the reaction was quenched by addition of saturated aqueous solution of NH_4Cl (40 mL) and the mixture extracted with CH_2Cl_2 (4 × 50 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated in *vacuo*. Purification of the residue by MPLC (2:98 EtOAc: hexanes) afforded the desired product—a yellow oil—as a mixture of diastereomers (3.33 g, 62%). The spectral data of **s5.4c** matched that reported by Jørgensen and coworkers:[73] ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.25 (d, J = 5.4 Hz, 3H), 2.06 (m, 1H), 1.80 (t, J = 12.5 Hz, 2H), 1.48 (s, 9H), 1.18 (d, J = 10.8 Hz, 1H), 0.87 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.7 (C), 171.2 (C), 98.5 (C), 80.7 (C), 44.2 (CH), 41.3 (CH_2), 30.3 (C), 28.3 (CH_3), 27.6 (CH_3), 27.3 (CH_3), 24.1 (CH_2), 23.2 (CH_2). ATR-FTIR (thin film): 2954, 2868, 1718,

1651, 1365, 1163 cm^{-1}. The mixture of products was converted to the vinyl triflate without additional purification or characterization.

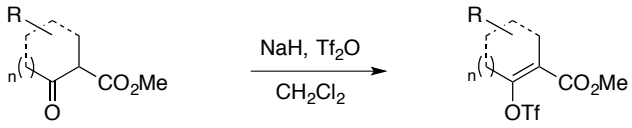
3. Preparation of Vinyl Triflates.

a. General Procedure.



s5.5

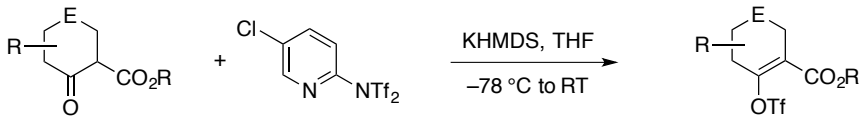
Method A: 2-Arylcyclohexanone (5 mmol, 1.0 equiv) was added to a suspension of NaH (60% dispersed in mineral oil, 9.5 mmol, 1.9 equiv) in 20 mL of DMF at 0 °C. The mixture was warmed to room temperature. After 30 minutes, 1,1,1-trifluoro-N-phenyl-N-(trifluoromethylsulfonyl)methanesulfonamide (5.5 mmol, 1.1 equiv) was added. After an additional 12 hours, the reaction mixture was diluted with 20 mL of water and 50 mL of ethyl acetate. The phases were separated, and the organic phase was washed with 20 mL of brine and 20 mL of water. The resulting organic phase was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude mixture was purified by MPLC (3:97 – 20:80 EtOAc:hexane) to afford the product.



s5.5

Method B: To a solution of β-ketoester (1.0 equiv) in CH_2Cl_2 (0.2 M) was slowly added NaH (60% dispersed in mineral oil, 1.2 equiv) at 0 °C. After stirring for 30 min, trifluoromethanesulfonic anhydride (1.2 equiv) was added dropwise to the reaction. The resulting mixture was then warmed to room temperature. After stirring overnight, the

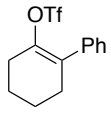
reaction was quenched by adding water. The mixture was then extracted with CH_2Cl_2. The combined organic phases were washed by brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was afforded and was used in the next step without purification.



s5.5

Method C: To a solution of β-ketoester (1.0 equiv) in THF (0.2 M) was slowly added a solution of KHMDS (1.2 equiv) in THF at – 78 °C. After stirring for 1 h, a solution of Comins' reagent (1.2 equiv) in THF was added dropwise to the reaction. The resulting mixture was then gradually warmed to room temperature. After stirring for overnight, the reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl. The mixture was then extracted with EtOAc. The combined organic phases were washed by brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by MPLC (2:98 to 5:95 EtOAc: hexane) afforded the product.

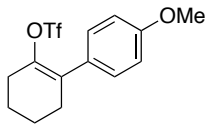
b. Characterization Data.



s5.5a

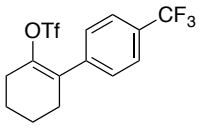
Methanesulfonic acid, 1,1,1-trifluoro-2-phenyl-1-cyclohexenyl ester s5.5a.[74] Method A was followed using 0.871 g of 2-Phenylcyclohexanone (5.0 mmol), 0.380 g of NaH (60% in oil, 9.5 mmol), 1.96 g of 1,1,1-trifluoro-N-phenyl-N-(trifluoromethylsulfonyl)methanesulfonamide (5.5 mmol) in 20 mL of DMF. Purification by MPLC (2:98 to 5:95 EtOAc: hexane) afforded the product as colorless oil (1.25 g, 82%). Triflate **s5.5a** was first reported by Rigby and Qabar:[74] ^{1}H NMR (500 MHz,

$CDCl_3$) δ 7.38 – 7.25 (m, 5H), 2.51 – 2.47 (m, 4H), 1.89 – 1.87 (m, 2H), 1.80 – 1.76 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.8 (C), 137.0 (C), 131.1 (C), 128.3 (CH), 128.1 (CH), 127.9 (CH), 118.1 (q, J_{CF} = 317.7 Hz, C), 31.3 (CH_2), 28.2 (CH_2), 23.1 (CH_2), 22.1 (CH_2). ATR-FTIR (thin film): 2940, 1443, 1413, 1205, 1139, 1028, 889 cm^{-1}.



s5.5b

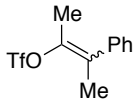
Methanesulfonic acid, 1,1,1-trifluoro-(2-4-methoxyarene)-1-cyclohexenyl ester s5.5b. Method A was followed using 0.204 g of 2-arylcyclohexanone **s5.1** (1.0 mmol), 0.076 g of NaH (60% in oil, 1.9 mmol), 0.393 g of 1,1,1-trifluoro-N-phenyl-N-(trifluoromethylsulfonyl)methanesulfonamide (1.1 mmol) in 5 mL of DMF. Purification by MPLC (2:98 to 5:95 EtOAc: hexane) afforded the product as colorless oil (0.140 g, 42%): ^1H NMR (500 MHz, $CDCl_3$) δ 7.20 (d, J = 9.0 Hz, 2H), 6.89 (d, J = 9.0 Hz, 2H), 3.81 (s, 3H), 2.49 – 2.43 (m, 4H), 1.87 – 1.84 (m, 2H), 1.77 – 1.74 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.2 (C), 143.6 (C), 130.5 (C), 129.3 (CH), 129.1 (C), 118.1 (q, J_{CF} = 317.7 Hz, C), 113.7 (CH), 55.2 (CH_3), 31.3 (CH_2), 28.2 (CH_2), 23.0 (CH_2), 22.1 (CH_2). ATR-FTIR (thin film): 2940, 2863, 2838, 2361, 2338, 1609, 1521, 1409, 1242, 1199, 1179, 1136, 1025, 990, 887, 831 cm^{-1}.



s5.5c

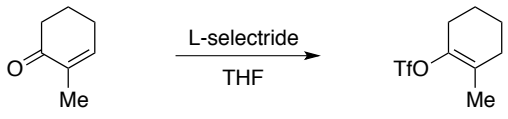
Methanesulfonic acid, 1,1,1-trifluoro-(2-4-methoxyarene)-1-cyclohexenyl ester s5.5c. Method A was followed using 0.242 g of 2-arylcyclohexanone **s5.3** (1.0 mmol), 0.076 g of NaH (60% in oil, 1.9 mmol), 0.393 g of 1,1,1-trifluoro-N-phenyl-N-(trifluoromethylsulfonyl)methanesulfonamide (1.1 mmol) in 5 mL of DMF. Purification

by MPLC (2:98 to 5:95 EtOAc: hexane) afforded the product as colorless oil (0.170 g. 45%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (d, J = 8.0 Hz, 2H), 7.37 (d, J = 8.0 Hz, 2H), 2.52 – 2.45 (m, 4H), 1.90 – 1.87 (m, 2H), 1.82 – 1.78 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.6 (C), 140.7 (C), 130.2 (C), 130.0 (C), 128.5 (CH), 125.3 (CH, J_{CF} = 3.6 Hz), 118.0 (q, J_{CF} = 317.7 Hz, C), 31.1 (CH_2), 28.1 (CH_2), 22.9 (CH_2), 21.9 (CH_2), only peaks visible. ATR-FTIR (thin film): 2947, 2866, 1617, 1410, 1324, 1206, 1125, 1068, 1031, 889, 851 cm^{-1}.



s5.5d

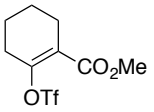
3-Phenylbut-2-en-2-yl trifluoromethanesulfonate s5.5d. Method A was followed using 1.48 g of 3-phenylbutan-2-one (10.0 mmol), 0.760 g of NaH (19.0 mmol) and 3.92 g of 1,1,1-trifluoro-*N*-phenyl-*N*-(trifluoromethylsulfonyl)-methanesulfonamide (11.0 mmol) in 50 mL of DMF. Purification by MPLC (2:98 to 5:95 EtOAc: hexane) afforded the product as colorless oil (1.12 g. 40%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (t, J = 7.5 Hz, 2H), 7.31 (t, J = 7.5 Hz, 1H), 7.24 (d, J = 7.0 Hz, 2H), 2.23 (s, 3H), 2.08 (s, 3H); ^{13}C NMR (125 MHz, CDCl3) δ 163.9 (C), 140.6 (C), 138.0 (C), 128.3 (CH), 128.0 (CH), 127.8 (CH), 118.1 (q, J_{CF} = 317.9 Hz, C), 20.1 (CH_3), 17.2 (CH_3). The crude vinyl triflate was used in the subsequent cross-coupling reaction without additional purification.



s5.5e

2-Methylcyclohex-1-en-1-yl trifluoromethanesulfonate s5.5e.[75] To a solution of 1.11 g of 2-methylcyclohexenone (10.1 mmol) in 25 mL of tetrahydrofuran at –78°C was added 10.5 mL of L-Selectride® (10.5 mmol, 1 M in THF). After stirring at –78°C for 1h, 3.61

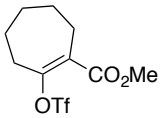
g of 1,1,1-trifluoro-*N*-phenyl-*N*-((trifluoromethyl)sulfonyl)methanesulfonamide (10.1 mmol) in 25 ml of THF was added. The resulting solution was then allowed to warm to room temperature. After 16h, the solution was diluted with 125 mL of pentane and washed with 3 × 50 mL of water. The combined aqueous phases were re-extracted with 2 × 25 mL of pentanes. The combined organic phases are then washed 3 × 50 mL of with 10% sodium hydroxide solution, followed by 2 × 50 mL of brine, and dried with Na_2SO_4, filtered and concentrated *in vacuo*. Purification by MPLC (2:98 EtOAc: hexane) afforded the product as colorless oil (1.87 g, 76%). The spectral data matched that reported by Crisp and Scott:[75] ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.30 (b, 2H), 2.12 (b, 2H), 1.77 – 1.72 (m, 5H), 1.64 – 1.59 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) 143.3 (C), 126.4 (C), 118.3 (q, J_{CF} = 317.7 Hz, C), 30.7 (CH_2), 27.6 (CH_2), 23.3 (CH_2), 21.8 (CH_2), 16.6 (CH_3).



s5.5f

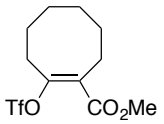
Methyl 2-(trifluoromethylsulfonyloxy)cyclohex-1-enecarboxylate s5.5f.[76] Method B was followed using 2.0 mL of methyl 2-oxocyclohexanecarboxylate (12.7 mmol), 0.608 g of NaH (15.2 mmol) and 2.56 mL of Tf_2O (15.2 mmol) in 60 mL of CH_2Cl_2. The crude product was afforded as brown oil (3.65 g, 100%). The spectral data matched that reported by Bols and co-workers:[76] ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.78 (s, 3H), 2.46 (dt, *J* = 5.6 Hz, 3.0 Hz, 2H), 2.38 (dt, *J* = 5.6 Hz, 3.0 Hz, 2H), 1.77 (dt, *J* = 5.8 Hz, 2.9 Hz, 2H), 1.65 (dt, *J* = 5.8 Hz, 2.9 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.1 (C), 151.8 (C), 122.8 (C), 118.3 (q, J_{CF} = 319.7 Hz, C), 52.1 (CH_3), 28.6 (CH_2), 26.1 (CH_2), 22.2 (CH_2), 21.0 (CH_2). The crude vinyl triflate was used in the subsequent cross-coupling reaction

without additional purification.



s5.5g

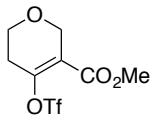
Methyl 2-(trifluoromethylsulfonyloxy)cyclohept-1-enecarboxylate s5.5g.[76] Method B was followed using 1.0 mL of methyl 2-oxocycloheptanecarboxylate (6.4 mmol), 0.307 g of NaH (7.7 mmol) and 1.3 mL of Tf_2O (7.7 mmol) in 30 mL of CH_2Cl_2. The crude product was afforded as brown oil (1.90 g, 98%). The spectral data matched that reported by Bols and co-workers:[76] ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.77 (s, 3H), 2.58 (m, 2H), 2.51 (m, 2H), 1.76 (dt, J = 11.5 Hz, 5.7 Hz, 2H), 1.69 (q, J = 5.4 Hz, 2H), 1.63 (dt, J = 11.0 Hz, 5.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.1 (C), 155.0 (C), 127.8 (C), 118.3 (q, J_{CF} = 320.0, C), 52.2 (CH_3), 34.0 (CH_2), 30.7 (CH_2), 28.0 (CH_2), 25.2 (CH_2), 23.7 (CH_2). The crude vinyl triflate was used in the subsequent cross-coupling reaction without additional purification.



s5.5h

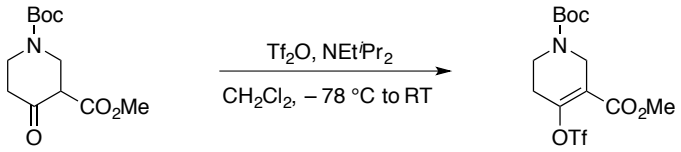
Methyl 2-(trifluoromethylsulfonyloxy)cyclooct-1-enecarboxylate s5.5h.[77] Method B was followed using 1.0 g of methyl 2-oxocyclooctanecarboxylate **s5.4a** (5.4 mmol), 0.260 g of NaH (6.5 mmol) and 1.1 mL of Tf_2O (6.5 mmol) in 30 mL of CH_2Cl_2. The crude product was afforded as brown oil (1.38 g, 80%). The spectral data matched that reported by Tanaka and co-workers:[77] ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.68 (s, 3H), 2.45 (t, J = 6.2 Hz, 2H), 2.34 (t, J = 6.2 Hz, 2H), 1.68 (s, 2H), 1.63 (s, 2H), 0.77 (d, J = 9.0 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.2 (C), 152.5 (C), 125.1 (C), 118.3 (q, J_{CF} = 320.0, C), 51.8 (CH_3), 31.0 (CH_2), 29.4 (CH_2), 28.2 (CH_2), 27.8 (CH_2), 26.0 (CH_2), 25.4

(CH_2). The crude vinyl triflate was used in the subsequent cross-coupling reaction without additional purification.



s5.5i

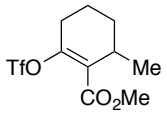
Methyl 4-(trifluoromethylsulfonyloxy)-5,6-dihydro-2H-pyran-3-carboxylate s5.5i.[30] Method C was followed using 0.140 g of β-ketoester **s5.4b** (0.89 mmol), 0.212 g of KHMDS (1.06 mmol) and 0.417 g of Comins' reagent (1.06 mmol) in 10 mL of THF. Purification by MPLC (3:97 to 10:90 EtOAc: hexane) afforded the product as colorless oil (165 mg, 64%). The spectral data of vinyl triflate matched that reported by Kong and Driver:[30] ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.41 (t, J = 2.5 Hz, 2H), 3.86 (t, J = 5.5 Hz, 2H), 3.78 (s, 3H), 2.51 (dt, J = 5.2 Hz, 2.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.4 (C), 149.7 (C), 121.5 (C), 118.3 (q, J_{CF} = 319.4 Hz, C), 64.9 (CH_2), 63.9 (CH_2), 52.2 (CH_3), 28.8 (CH_2). The crude vinyl triflate was used in the subsequent cross-coupling reaction without additional purification.



s5.4c **s5.5j**

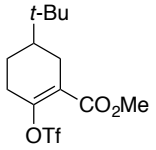
1-*tert*-Butyl 3-methyl 4-(trifluoromethylsulfonyloxy)-5,6-dihydropyridine-1,3(2*H*)-dicarboxylate s5.5j.[78] To a solution of β-ketoester **s5.4c** (0.649 g, 2.52 mmol) in CH_2Cl_2 (10 mL) was slowly added $NEt(^iPr)_2$ (2.2 mL, 12.6 mmol) at – 78 °C. After stirring for 20 min, trifluoromethanesulfonic anhydride (0.51 mL, 3.0 mmol) was added dropwise to the reaction mixture. The resulting mixture was then warmed to rt. After stirring for 2 h, the reaction was quenched by the addition of 20 mL of water. The mixture was then

extracted with CH_2Cl_2. The combined organic phases were washed by brine, dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by MPLC (2:98 to 5:95 EtOAc: hexane) afforded the product as yellow oil (0.750 g, 76%). The spectral data of vinyl triflate matched that reported by Di Fabio and co-workers:[78] ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.16 (s, 2H), 3.71 (s, 3H), 3.52 (t, J = 5.5 Hz, 2H), 2.41 (s, 2H), 1.37 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8 (C), 162.6 (C), 153.8 (C), 120.5 (C), 118.2 (q, J_{CF} = 319.5 Hz, C), 80.7 (C), 60.1 (CH_2), 52.1 (CH_3), 43.0 (CH_2), 28.8 (CH_2), 28.1 (CH_3). ATR-FTIR (thin film): 2980, 2869, 1700, 1419, 1239, 1158, 1078, 821 cm^{-1}. The crude vinyl triflate was used in the subsequent cross-coupling reaction without additional purification.



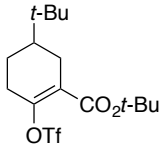
s5.5k

Methyl 6-methyl-2-(((trifluoromethyl)sulfonyl)oxy)cyclohex-1-ene-1-carboxylate s5.5k.[30] Method B was followed using 0.212 g of methyl 2-methyl-6-oxocyclohexane-1-carboxylate (1.25 mmol), 0.060 g of NaH (1.50 mmol) and 0.252 mL of Tf_2O (1.50 mmol) in 5 mL of CH_2Cl_2. The crude product was afforded as brown oil (0.288 g, 67%). The spectral data of vinyl triflate **s5.5k** matched that reported by Kong and Driver:[30] H NMR (500 MHz, $CDCl_3$) δ 3.75 (s, 3H), 2.86 (s, 1H), 2.33 (d, J = 6.2 Hz, 2H), 1.79 (s, 1H), 1.70 (s, 2H), 1.42 (s, 1H), 1.04 (d, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.3 (C), 150.4 (C), 128.4 (C), 118.3 (q, J_{CF} = 319.6 Hz, C), 51.9 (CH_3), 30.9 (CH), 28.7 (CH_2), 28.2 (CH_2), 19.4 (CH_3), 19.1 (CH_2). The crude vinyl triflate was used in the subsequent cross-coupling reaction without additional purification.



s5.5l

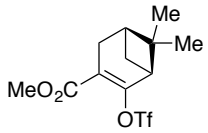
Methyl 5-tert-butyl-2-(trifluoromethylsulfonyloxy)cyclohex-1-enecarboxylate s5.5l.[30] Method B was followed using using 1.26 g of β-ketoester **s5.4d** (5.96 mmol), 0.286 g of NaH (7.15 mmol) and 1.21 mL of Tf_2O (7.15 mmol) in 30 mL of CH_2Cl_2. The crude product was afforded as brown oil (2.05 g, 100%). The spectral data of vinyl triflate **s5.5l** matched that reported by Kong and Driver:[30] ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.79 (s, 3H), 2.59 (d, J = 15.7 Hz, 1H), 2.44 (q, J = 13.5 Hz, 2H), 2.14 (m, 1H), 1.94 (dd, J = 10.2 Hz, 5.3 Hz, 1H), 1.34 (m, 2H), 0.91 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.2 (C), 151.7 (C), 122.8 (C), 118.3 (q, J_{CF} = 320.0 Hz, C), 52.1 (CH_3), 42.9 (CH), 32.1 (C), 29.6 (CH_2), 27.6 (CH_2), 27.1 (CH_3), 23.6 (CH_2). ATR-FTIR (thin film): 2953, 2925, 2855, 1726, 1423, 1205 cm^{-1}. The crude vinyl triflate was used in the subsequent cross-coupling reaction without additional purification.



s5.5m

***tert*-Butyl-5-*tert*-butyl-2-(trifluoromethylsulfonyloxy)cyclohex-1-enecarboxylate s5.5m.**[30] Method C was followed using 0.131 g of β-ketoester **s5.4e** (5.13 mmol), 1.13 g of KHMDS (5.64 mmol) and 2.22 g of Comins' reagent (5.64 mmol) in 50 mL of THF. Purification by MPLC (3:97 to 10:90 EtOAc: hexane) afforded the product as colorless oil (1.49 g, 75%). The spectral data of vinyl triflate **s5.5m** matched that reported by Kong and Driver:[30] ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.52 (d, J = 15.9 Hz, 1H), 2.37 (t, J = 13.1 Hz, 2H), 2.08 (m, 1H), 1.91 (dd, J = 9.9 Hz, 5.1 Hz, 1H), 1.50 (s, 9H), 1.30 (t, J = 5.2 Hz, 2H), 0.89 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.4 (C), 149.2 (C), 124.9 (C), 118.3 (q, J_{CF} = 320.0 Hz, C), 83.0 (C), 42.9 (CH), 32.1 (C), 29.0 (CH_2), 27.9 (CH_2), 27.9

(CH_3), 27.1 (CH_2), 23.7 (CH_2). The crude vinyl triflate was used in the subsequent cross-coupling reaction without additional purification.

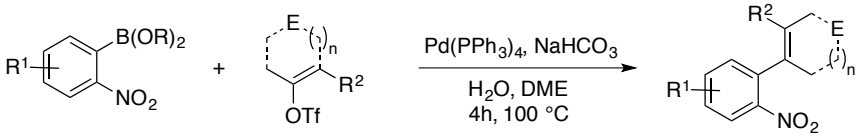


s5.5n

Vinyl triflate s5.5n. Method B was followed using 1.96 g of methyl 6,6-dimethyl-2-oxobicyclo[3.1.1]heptane-3-carboxylate (10.0 mmol), 0.480 g of NaH (12.0 mmol) and 2.02 mL of Tf_2O (12.0 mmol) in 60 mL of CH_2Cl_2. The crude product was afforded as brown oil (0.754 g, 23%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.81 (s, 3H), 2.67 – 2.56 (m, 3H), 2.43 (t, J = 5.5 Hz, 1H), 2.24 (m, 1H), 1.37 (s, 1H), 1.36 (s, 3H), 0.92 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.3 (C), 159.7 (C), 118.3 (q, J_{CF} = 318.7 Hz, C), 116.0 (C), 51.9 (CH_3), 47.3 (CH), 39.9 (C), 39.5 (CH), 30.7 (CH_2), 29.9 (CH_2), 25.3 (CH_3), 20.9 (CH_3). The crude vinyl triflate was used in the subsequent cross-coupling reaction without additional purification.

D. Synthesis of 2-substituted Nitroarenes using Suzuki Cross-Coupling Reaction.

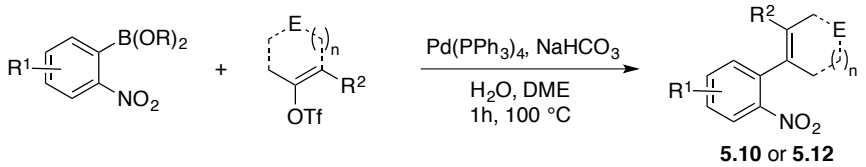
1. General Procedures.



5.10 or **5.12**

Method A: To a mixture of vinyl triflate (1 equiv), 2-nitroarylboronic acid or 2-nitroarylboronic acid pinacolate ester (1.2 equiv), $Pd(PPh_3)_4$ (10 mol %) and sodium carbonate (3.0 equiv) was added a 10:1 v/v mixture of dimethoxyethane and water. The resulting mixture was heated to 100 °C. After 4 h, the mixture was cooled to room

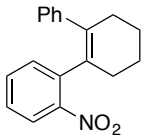
temperature and diluted with 5 mL of cold water. The mixture was extracted with 2 × 10 mL of ethyl acetate. The combined organic phases were washed with 10 mL of brine. The resulting organic phase was dried over Na_2SO_4, filtered and was concentrated *in vacuo*. Purification by MPLC (3:97 to 10:90 EtOAc: hexane) afforded the product.



5.10 or **5.12**

Method B: To a mixture of vinyl triflate (1 equiv), 2-nitroarylboronic acid or 2-nitroarylboronic acid pinacolate ester (1.2 equiv), $Pd(PPh_3)_4$ (10 mol %) in dimethoxyethane (0.1 M) was added a saturated aqueous solution of $NaHCO_3$ (2 mL/mmol of boronic ester). The resulting mixture was heated to 100 °C. After 1h, the mixture was cooled to room temperature and diluted with 5 mL of cold water. The mixture was extracted with 2 × 10 mL of ethyl acetate. The combined organic phases were washed with 10 mL of brine. The resulting organic phase was dried over Na_2SO_4, filtered and was concentrated *in vacuo*. Purification by MPLC (3:97 to 10:90 EtOAc: hexane) afforded the product.

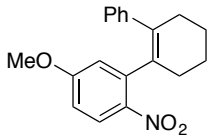
2. Characterization Data.



5.10a

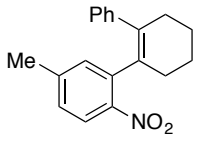
Nitrostyrene 5.10a. General procedure A was followed by using 1.33 g of vinyl triflate **s5.5a** (4.34 mmol), 0.871 g of 2-nitrophenylboronic acid **5.8a** (5.21 mmol), 0.500 g of $Pd(PPh_3)_4$ (0.43 mmol) and 1.38 g of sodium carbonate (13.0 mmol) in a mixture of 43

mL of dimethoxyethane and 4.3 mL of water. Purification by MPLC (3:97 to 10:90 EtOAc: hexane) afforded the product as a yellow solid (1.19 g, 82%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.5 Hz, 1H), 7.33 (t, *J* = 7.5 Hz, 1H), 7.19 (t, *J* = 7.0 Hz, 1H), 7.10 – 7.02 (m, 4H), 6.94 (m, 2H), 2.43 – 2.27 (m, 4H), 1.89 – 1.85 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.6 (C), 142.7 (C), 139.5 (C), 136.1 (C), 132.5 (CH), 132.3 (CH), 132.2 (C), 128.1 (CH), 127.7 (CH), 127.0 (CH), 126.2 (CH), 124.2 (CH), 31.7 (CH_2), 31.5 (CH_2), 23.0 (CH_2), 22.9 (CH_2). ATR-FTIR (thin film): 3057, 2929, 2858, 2831, 1606, 1520, 1347 cm^{-1}. HRMS (ESI) m/z calculated for $C_{18}H_{18}NO_2$ $(M+H)^+$: 280.1338, found: 280.1341.



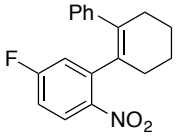
5.10b

Nitrostyrene 5.10b. General procedure A was followed by using 0.250 of vinyl triflate **s5.5a** (0.82 mmol), 0.192 g of 5-methoxy-2-nitrophenylboronic acid **5.8b** (0.98 mmol), 0.094 g of $Pd(PPh_3)_4$ (0.08 mmol) and 0.259 g of sodium carbonate (2.44 mmol) in a mixture of 10 mL of dimethoxyethane and 1 mL of water. Purification by MPLC (3:97 to 10:90 EtOAc: hexane) afforded the product as a yellow solid (0.220 g, 87%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, *J* = 9.0 Hz, 1H), 7.09 – 7.03 (m, 3H), 6.95 (d, *J* = 7.0 Hz, 2H), 6.64 (dd, *J* = 9.0 Hz, 3.0 Hz, 1H), 6.47 (d, *J* = 3.0 Hz, 1H), 3.70 (s, 3H), 2.44 – 2.21 (m, 4H), 1.93 – 1.80 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.7 (C), 142.9 (C), 142.5 (C), 141.8 (C), 135.3 (C), 133.1 (C), 127.9 (CH), 127.8 (CH), 126.9 (CH), 126.2 (CH), 116.8 (CH), 112.4 (CH), 55.7 (CH_3), 31.7 (CH_2), 31.3 (CH_2), 23.1 (CH_2), 22.9 (CH_2). ATR-FTIR (thin film): 2932, 2832, 1602, 1572, 1510, 1335, 1292, 1265, 1245, 1028 cm^{-1}. HRMS (ESI) m/z calculated for $C_{19}H_{20}NO_3$ $(M+H)^+$: 310.1443, found: 310.1445.



5.10c

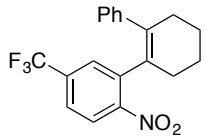
Nitrostyrene 5.10c. General procedure A was followed by using 0.285 of vinyl triflate **s5.5a** (0.93 mmol), 0.200 g of 5-methyl-2-nitrophenylboronic acid **5.8c** (1.11 mmol), 0.537 g of $Pd(PPh_3)_4$ (0.046 mmol) and 0.295 g of sodium carbonate (2.79 mmol) in a mixture of 10 mL of dimethoxyethane and 1 mL of water. Purification by MPLC (3:97 to 10:90 EtOAc: hexane) afforded the product as a yellow liquid (0.226 g, 76%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.0 Hz, 1H), 7.08 – 7.02 (m, 3H), 6.97 – 6.93 (m, 3H), 6.89 (s, 1H), 2.46 – 2.42 (m, 3H), 2.26 (s, 4H), 1.91 – 1.85 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.3 (C), 143.6 (C), 142.9 (CH), 139.6 (C), 135.5 (C), 132.7 (CH), 132.5 (C), 128.1 (CH), 127.7 (CH), 127.6 (CH), 126.1 (CH), 124.3 (CH), 31.7 (CH_2), 31.5 (CH_2), 23.1 (CH_2), 22.9 (CH_2), 21.3 (CH_3). ATR-FTIR (thin film): 2923, 2854, 1582, 1514, 1341, 831 cm^{-1}. HRMS (ESI) m/z calculated for $C_{19}H_{20}NO_2$ $(M+H)^+$: 294.1494, found: 294.1503.



5.10d

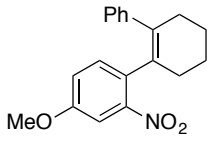
Nitrostyrene 5.10d. General procedure B was followed by using 0.124 g of vinyl triflate **s5.5a** (0.40 mmol), 0.090 g of 5-fluoro-2-nitrophenylboronic acid pinacol ester **5.8d** (0.337 mmol), 0.040 g of $Pd(PPh_3)_4$ (0.034 mmol), 0.7 mL of saturated aq. soln. of $NaHCO_3$ and 5 mL of dimethoxyethane. Purification by MPLC (3:97 to 10:90 EtOAc: hexane) afforded the product as a light yellow liquid (0.054 g, 54%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (dd, *J* = 9.0 Hz, 5.0 Hz, 1H), 7.09 (m, 3H), 6.93 (d, J = 6.5 Hz, 2H), 6.86

(m, 1H), 6.78 (dd, J = 9.0 Hz, 5.0 Hz, 1H), 2.43 – 2.25 (m, 4H), 1.86 (br s, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.2 (d, J_{CF} = 255.0 Hz, C), 142.9 (d, J_{CF} = 9.1 Hz, C), 142.3 (C), 136.7 (C), 131.5 (CH), 128.0 (CH), 127.9 (CH), 127.0 (d, J_{CF} = 14.8 Hz, CH), 126.5 (CH), 119.9 (d, J_{CF} = 34.5 Hz, CH), 114.1 (d, J_{CF} = 23.0 Hz, CH), 31.7 (CH_2), 31.2 (CH_2), 22.9 (CH_2), 22.8 (CH_2), only visible signals; ^{19}F NMR (282 MHz, $CDCl_3$) δ –105.2; ATR-FTIR (thin film): 2931, 2858, 2360, 1617, 1578, 1552, 1345, 1265, 1176, 756 cm^{-1}. HRMS (EI) m/z calculated for $C_{18}H_{16}NO_2F$ $(M)^+$: 298.1165, found: 298.1164.



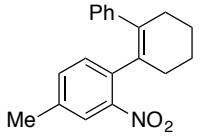
5.10e

Nitrostyrene 5.10e. General procedure B was followed by using 0.235 g of vinyl triflate **s5.5a** (0.77 mmol), 0.292 g of 5-trifluoromethyl-2-nitrophenylboronic acid pinacol ester **5.8e** (0.92 mmol), 0.100 g of $Pd(PPh_3)_4$ (0.086 mmol), 1.8 mL of a saturated aq. soln. of $NaHCO_3$ and 10 mL of dimethoxyethane. Purification by MPLC (3:97 to 10:90 EtOAc: hexane) afforded the product—a 1:1 mixture of rotamers—as a yellow liquid (0.120 g, 45%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, J = 8.5 Hz, 0.49H), 7.44 (d, J = 8.5 Hz, 0.57H), 7.40 – 7.35 (m, 1.43H), 7.32 – 7.30 (m, 0.48 H), 7.27 – 7.25 (m, 1H), 7.10 – 7.05 (m, 1.58H), 6.90 (dd, J = 8.5 Hz, 1.5 Hz, 1H), 2.50 – 2.34 (m, 4H), 1.89 – 1.87 (m, 3H), 1.80 – 1.75 (m, 1H), only visible signals; ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.6 (C), 142.0 (C), 140.1 (C), 137.0 (C), 133.8 (q, J_{CF} = 33.0 Hz, C), 130.8 (C), 129.8 (CH), 128.3 (CH), 128.0 (CH), 126.6 (CH), 124.6 (CH), 124.0 (q, J_{CF} = 4.2 Hz, CH), 118.1 (q, J_{CF} = 317.6 Hz, C), 31.7 (CH_2), 28.2 (CH_2), 23.0 (CH_2), 22.1 (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$) δ –61.6; ATR-FTIR (thin film): 2935, 2860, 2832, 1530, 1412, 1327, 1207, 1132, 1026, 889, 756 cm^{-1}. HRMS (EI) m/z calculated for $C_{19}H_{16}NO_2F_3$ $(M)^+$: 347.1133, found: 347.1129.



5.10f

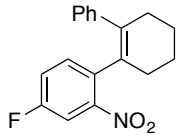
Nitrostyrene 5.10f. General procedure B was followed by using 0.306 g of vinyl triflate **s5.5a** (1.00 mmol), 0.236 g of 4-methoxy-2-nitrophenylboronic acid **5.8f** (1.20 mmol), 0.115 g of $Pd(PPh_3)_4$ (0.100 mmol), 2.0 mL of a saturated aq. soln. of $NaHCO_3$ and 10 mL of dimethoxyethane. Purification by MPLC (3:97 to 10:90 EtOAc: hexane) afforded the product as a yellow liquid (0.151 g, 49%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (d, J = 2.5 Hz, 1H), 7.09 – 7.01 (m, 3H), 6.98 – 6.94 (m, 3H), 6.89 (dd, J = 8.5 Hz, 2.5 Hz, 1H), 3.76 (s, 3H), 2.42 – 2.24 (br m, 4H), 1.81 (br m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.0 (C), 148.9 (C), 143.0 (C), 136.1 (C), 133.1 (CH), 131.9 (C), 131.8 (CH), 128.1 (CH), 127.8 (CH), 126.1 (CH), 119.5 (CH), 108.5 (CH), 55.6 (CH_3), 31.7 (CH_2), 31.6 (CH_2), 23.1 (CH_2), 23.0 (CH_2). ATR-FTIR (thin film): 2928, 2833, 1618, 1523, 1348, 1302, 1034 cm^{-1}. HRMS (EI) m/z calculated for $C_{19}H_{19}NO_3$ $(M)^+$: 309.1365, found: 309.1363.



5.10g

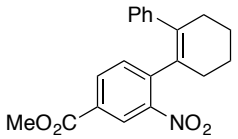
Nitrostyrene 5.10g. General procedure B was followed by using 0.306 g of vinyl triflate **s5.5a** (1.00 mmol), 0.217 g of 4-methoxy-2-nitrophenylboronic acid **5.8g** (1.20 mmol), 0.115 g of $Pd(PPh_3)_4$ (0.100 mmol), 2 mL of a saturated aq. soln. of $NaHCO_3$ and 10 mL of dimethoxyethane. Purification by MPLC (3:97 to 10:90 EtOAc: hexane) afforded the product as a yellow liquid (0.164 g, 56%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (s, 1H), 7.13 (d, J = 8.0 Hz, 1H), 7.08 – 7.02 (m, 3H), 6.97 – 6.93 (m, 3H), 2.44 – 2.34 (m, 3H),

2.29 (s, 3H), 2.24 (br s, 1H), 1.81 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.5 (C), 142.9 (C), 137.2 (C), 136.6 (C), 135.9 (C), 133.4 (CH), 132.1 (CH), 129.1 (C), 128.1 (CH), 127.8 (CH), 126.1 (CH), 124.4 (CH), 31.7 (CH_2), 31.6 (CH_2), 23.1 (CH_2), 23.0 (CH_2), 20.8 (CH_3). ATR-FTIR (thin film): 2927, 2857, 2830, 1522, 1346, 1280, 1146 cm^{-1}. HRMS (EI) m/z calculated for $C_{19}H_{19}NO_2$ $(M)^+$: 293.1416, found: 293.1417.



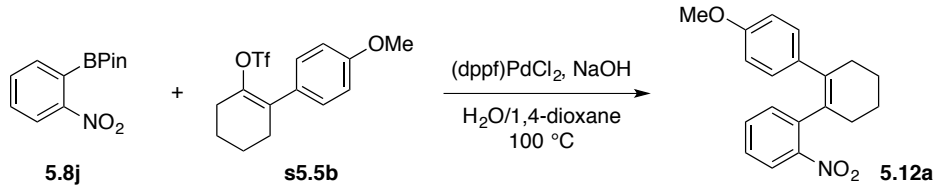
5.10h

Nitrostyrene 5.10h. General procedure A was followed by using 0.178 g of vinyl triflate **s2.5a** (0.58 mmol), 0.129 g of 4-fluoro-2-nitrophenylboronic acid **2.8h** (0.69 mmol), 0.670 g of $Pd(PPh_3)_4$ (0.06 mmol) and 0.184 g of sodium carbonate (1.74 mmol) in a mixture of 6 mL of dimethoxyethane and 0.6 mL of water. Purification by MPLC (3:97 to 10:90 EtOAc: hexane) afforded the product as a yellow liquid (0.119 g, 69%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (d, J = 8.5 Hz, 1H), 7.10 – 7.04 (m, 5H), 6.92 (d, J = 7.0 Hz, 2H), 2.43 – 2.25 (m, 4H), 1.86 (br s, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.3 (d, J = 248.0 Hz, C), 142.6 (C), 136.9 (C), 135.6 (C), 133.8 (d, J = 7.2 Hz, C), 131.3 (C), 128.7 (C), 128.0 (CH), 127.9 (CH), 126.4 (CH), 120.0 (d, J = 8.2 Hz, CH), 111.6 (d, J = 26.0 Hz, C), 31.7 (CH_2), 31.5 (CH_2), 23.0 (CH_2), 22.9 (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$) δ –113.1; ATR-FTIR (thin film): 2929, 2858, 1530, 1489, 1350, 1266, 1202, 874 cm^{-1}. HRMS (ESI) m/z calculated for $C_{18}H_{17}NO_2F$ $(M+H)^+$: 298.1243, found: 298.1252.



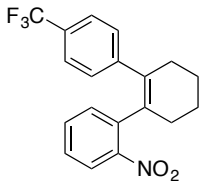
5.10i

Nitrostyrene 5.10i. General procedure B was followed by using 0.306 g of vinyl triflate **s5.5a** (1.00 mmol), 0.270 g of 4-methoxy-2-nitrophenylboronic acid **5.8i** (1.20 mmol), 0.115 g of $Pd(PPh_3)_4$ (0.100 mmol), 2.0 mL of saturated aq. soln. of $NaHCO_3$ and 10 mL of dimethoxyethane. Purification by MPLC (3:97 to 10:90 EtOAc: hexane) afforded the product as a yellow liquid (0.148 g, 44%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.38 (d, *J* = 1.5 Hz, 1H), 7.96 (dd, *J* = 8.0 Hz, 2.0 Hz, 1H), 7.18 (d, *J* = 8.0 Hz, 1H), 7.06 – 7.03 (m, 3H), 6.92 (dd, *J* = 7.5 Hz, 1.5 Hz, 2H), 3.88 (s, 3H), 2.45 – 2.28 (br m, 4H), 1.86 (br s, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.0 (C), 148.7 (C), 144.0 (C), 142.3 (C), 137.1 (C), 133.0 (CH), 132.8 (CH), 131.6 (C), 129.3 (C), 128.0 (CH), 127.9 (CH), 126.6 (CH), 125.5 (CH), 52.5 (CH_3), 31.7 (CH_2), 31.2 (CH_2), 22.9 (CH_2), 22.8 (CH_2). ATR-FTIR (thin film): 2930, 2859, 1725, 1616, 1528, 1434, 1282, 1110 cm^{-1}. HRMS (EI) m/z calculated for $C_{20}H_{19}NO_4$ $(M)^+$: 337.1314, found: 337.1317.



Nitrostyrene 5.12a. To a mixture 0.068 g of vinyl triflate **s5.5b** (0.20 mmol), 0.060 g of 2-nitrophenylboronic acid pinacolate ester **5.8j** (0.24 mml), 0.008 g of $(dppf)PdCl_2$ (0.010 mmol), 0.60 mL of a 0.30 M aq. soln. of NaOH and 4 mL of 1,4-dioxane. The resulting mixture was heated to 100 °C. After 12 h, the mixture was cooled to room temperature and diluted with 5 mL of cold water. The solution was extracted with 2 × 10 mL of ethyl acetate followed by 10 mL of brine. The resulting organic phase was dried over Na_2SO_4, filtered and was concentrated *in vacuo*. Purification by MPLC (3:97 to 10:90 EtOAc: hexane) afforded the product—as a 2:1 mixture of rotamers—as a yellow solid (0.050 g,

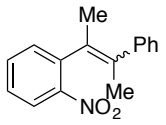
81%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (d, *J* = 7.5 Hz, 0.80H), 7.70 (t, *J* = 7.5 Hz, 0.43H), 7.55 (t, *J* = 7.5 Hz, 0.84H), 7.37 (d, *J* = 8.0 Hz, 0.25H), 7.20 (d, *J* = 8.5 Hz, 2.56H), 6.89 (d, *J* = 9.0 Hz, 2.74H), 3.81 (s, 3H), 2.49 – 2.43 (m, 4H), 1.87 – 1.74 (m, 4H), only visible signals; ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.2 (C), 143.6 (CH), 134.6 (CH), 130.5 (C), 129.3 (CH), 129.1 (C), 123.5 (CH), 119.4 (C), 116.9 (C), 113.7 (CH), 52.2 (CH_3), 31.3 (CH_2), 28.2 (CH_2), 23.1 (CH_2), 22.1 (CH_2), only visible signals. ATR-FTIR (thin film): 2929, 2857, 2832, 1712, 1606, 1520, 1456, 1346, 1241, 1175, 1033, 831, 747 cm^{-1}. HRMS (ESI) m/z calculated for $C_{19}H_{20}NO_3$ $(M+H)^+$: 310.1443, found: 310.1451.



5.12b

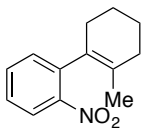
Nitrostyrene 5.12b. The general procedure B was followed by using 0.075 g of vinyl triflate **s5.5c** (0.20 mmol), 0.060 g of 2-nitrophenylboronic acid pinacolate ester **5.8j** (0.24 mmol), 0.023 g of $Pd(PPh_3)_4$ (0.020 mmol), 0.4 mL of a saturated aq. soln. of $NaHCO_3$ and 3 mL of dimethoxyethane. Purification by MPLC (3:97 to 10:90 EtOAc: hexane) afforded the product—a 2:1 mixture of rotamers—as a yellow solid (0.054 g, 79%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.5 Hz, 0.66H), 7.62 (d, *J* = 8.5 Hz, 0.75H), 7.38 – 7.31 (m, 3H), 7.23 (dt, *J* = 7.5 Hz, 1.0 Hz, 1H), 7.07 – 7.04 (m, 2H), 2.52 – 2.27 (m, 4H), 1.91 – 1.78 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.5 (C), 146.5 (C), 144.6 (C), 138.8 (C), 134.9 (C), 133.7 (C), 132.8 (CH), 132.1 (CH), 128.5 (CH), 128.4 (CH), 127.5 (CH), 125.3 (q, J_{CF} = 3.5 Hz, CH), 124.7 (q, J_{CF} = 3.5 Hz, CH), 124.1 (q, J_{CF} = 269.7 Hz, C), 124.4 (CH), 31.5 (CH_2), 28.1 (CH_2), 22.7 (CH_2), 21.9 (CH_2); Diagnostic

data for minor rotamer: ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.7 (C), 130.0 (C), 129.3 (CH), 128.2 (C), 123.5 (CH), 31.0 (CH_2), 22.8 (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$) δ –62.9; ATR-FTIR (thin film): 2935, 2863, 2832, 1615, 1523, 1322, 1163, 1121, 1067, 840 cm^{-1}. HRMS (EI) m/z calculated for $C_{19}H_{16}NO_2F_3$ $(M)^+$: 347.1133, found: 347.1135.



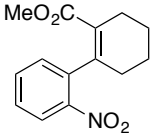
5.12c

Nitrostyrene 5.12c. The general procedure B was followed by using 0.100 g of vinyl triflate **s5.5d** (0.357 mmol), 0.107 g of 2-nitrophenylboronic acid pinacolate ester **5.8j** (0.428 mmol), 0.041 g of $Pd(PPh_3)_4$ (0.036 mmol), 0.7 mL of a saturated aq. soln. of $NaHCO_3$ and 5 mL of dimethoxyethane. Purification by MPLC (3:97 to 10:90 EtOAc: hexane) afforded the product, a brown liquid, as a 87:13 mixture of *E*/*Z* isomers (0.070 g, 78%): ^1H NMR (500 MHz, $CDCl_3$) δ 7.76 (dd, *J* = 8.0 Hz, 1.0 Hz, 1H), 7.36 (m, 0.5H), 7.30 (dq, *J* = 7.5 Hz, 1.0 Hz, 1.5H), 7.18 (dt, *J* = 8.5 Hz, 1.0 Hz, 1H), 7.07 – 7.01 (m, 3H), 6.93 (m, 2H), 2.16 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.5 (C), 143.6 (C), 140.5 (C), 134.3 (C), 132.5 (CH), 132.4 (CH), 129.7 (C), 128.2 (CH), 127.8 (CH), 126.9 (CH), 126.1 (CH), 124.1 (CH), 20.9 (CH_3), 20.7 (CH_3); diagnostic data for minor rotamer: ^1H NMR (500 MHz, $CDCl_3$) δ 7.97 (dd, *J* = 8.0 Hz, 1.0 Hz, 0.15H), 1.90 (s, 0.48H), 1.69 (s, 0.48H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.2 (CH), 130.9 (CH), 128.7 (CH), 126.6 (CH), 124.3 (CH), 22.2 (CH_3), 21.9 (CH_3). ATR-FTIR (thin film): 3057, 2917, 2856, 1606, 1570, 1519, 1490, 1439, 1346, 1293, 1070, 1025 cm^{-1}. HRMS (EI) m/z calculated for $C_{16}H_{15}NO_2$ $(M)^+$: 253.1103, found: 253.1099.



5.12d

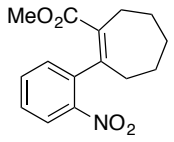
Nitrostyrene 5.12d. General procedure B was followed by using 0.098 g of vinyl triflate **s5.5e** (0.400 mmol), 0.120 g of 2-nitrophenylboronic acid pinacol ester **5.8j** (0.480 mmol), 0.046 g of $Pd(PPh_3)_4$ (0.040 mmol), 0.8 mL of a saturated aq. soln. of $NaHCO_3$ and 4 mL of dimethoxyethane. Purification by MPLC (3:97 to 10:90 EtOAc: hexane) afforded the product as a yellow liquid (0.076 g, 87%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.54 (td, *J* = 7.5, 1.0 Hz, 1H), 7.38 – 7.35 (m, 1H), 7.21 (dd, *J* = 7.5, 1.0 Hz, 1H), 2.30 – 2.27 (m, 1H), 2.13 – 2.03 (m, 3H), 1.73 – 1.67 (m, 4H), 1.34 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.0 (C), 139.2 (C), 132.7 (CH), 131.3 (CH), 130.5 (C), 128.6 (C), 127.2 (CH), 123.9 (CH), 31.4 (CH_2), 31.2 (CH_2), 23.1 (CH_2), 22.9 (CH_2), 20.4 (CH_3); ATR-FTIR (thin film): 2929, 2860, 2830, 1605, 1568, 1524, 1441, 1350 cm^{-1}. HRMS (EI) m/z calculated for $C_{13}H_{15}NO_2$ $(M)^+$: 217.1100, found: 217.1103.



5.12e

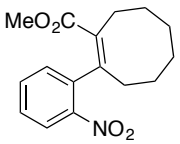
Nitrostyrene 5.12e. General procedure A was followed by using 0.100 g of vinyl triflate **s5.5f** (0.347 mmol), 0.103 g of 2-nitrophenylboronic acid pinacol ester **5.8j** (0.417 mmol), 0.040 g of $Pd(PPh_3)_4$ (0.035 mmol) and 0.60 mL of saturated aq. soln. of $NaHCO_3$ and 3 mL of dimethoxyethane. Purification by MPLC (3:97 to 10:90 EtOAc: hexane) afforded the product as a yellow liquid (0.071 g, 78%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (d, *J*= 8.0 Hz, 1H), 7.56 (t, *J* = 7.5 Hz, 1H), 7.40 (t, *J* = 8.0 Hz, 1H), 7.12 (d, *J* = 7.5 Hz, 1H), 3.40 (s, 3H), 2.54 – 2.49 (m, 2H), 2.36 – 2.22 (m, 2H), 1.88 – 1.65 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.6 (C), 147.0 (C), 146.9 (C), 139.8 (C), 133.2 (CH), 129.1 (CH), 127.5 (CH), 125.9 (C), 124.2 (CH), 51.3 (CH_3), 33.6 (CH_2), 25.8 (CH_2), 22.2 (CH_2), 21.9

(CH_2). ATR-FTIR (thin film): 2975, 2860, 1692, 1521, 1418, 1346, 1293, 1237, 1165, 1114, 1054 cm^{-1}. HRMS (EI) m/z calculated for $C_{14}H_{15}NO_4$ $(M)^+$: 261.1001, found: 261.1009.



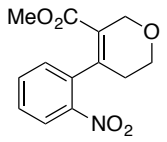
5.12f

Nitrostyrene 5.12f. General procedure A was followed by using 0.115 g of vinyl triflate **s5.5g** (0.380 mmol), 0.064 g of 2-nitrophenylboronic acid **5.8a** (0.380 mmol), 0.231 g of $Pd(PPh_3)_4$ (0.02 mmol) and 0.120 g of sodium carbonate (1.14 mmol) in a mixture of 4 mL of dimethoxyethane and 0.4 mL of water. Purification by MPLC (3:97 to 10:90 EtOAc: hexane) afforded the product as a greenish yellow liquid (0.080 g, 76%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.0 Hz, 1H), 7.55 (t, *J* = 7.5 Hz, 1H), 7.40 (t, *J* = 8.0 Hz, 1H), 7.12 (d, *J* = 7.5 Hz, 1H), 3.34 (s, 3H), 2.82 (dd, *J* = 13.5 Hz, 1.0 Hz, 1H), 2.70 (dd, *J* = 15.0 Hz, 8.5 Hz, 1H), 2.57 (dd, *J* = 14.5 Hz, 10.5 Hz, 1H), 2.38 (dd, *J* = 15.0 Hz, 8.5 Hz, 1H), 1.95 – 1.92 (m, 1H), 1.86 – 1.82 (m, 3H), 1.59 – 1.52 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.8 (C), 151.4 (C), 156.2 (C), 141.0 (C), 133.3 (CH), 132.5 (C), 128.6 (CH), 127.5 (CH), 124.3 (CH), 51.4 (CH_3), 37.5 (CH_2), 32.1 (CH_2), 29.7 (CH_2), 26.3 (CH_2), 25.2 (CH_2). ATR-FTIR (thin film): 2924, 2853, 1706, 1608, 1570, 1523, 1434, 1347, 1262, 1236, 1146 cm^{-1}. HRMS (ESI) m/z calculated for $C_{15}H_{18}NO_4$ $(M+H)^+$: 276.1236, found: 276.1237.



5.12g

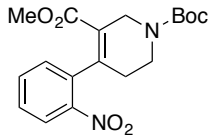
Nitrostyrene 5.12g. General procedure A was followed by using 0.189 g of vinyl triflate **s5.5h** (0.600 mmol), 0.835 g of 2-nitrophenylboronic acid **5.8a** (0.500 mmol), 0.029 g of $Pd(PPh_3)_4$ (0.025 mmol) and 0.158 g of sodium carbonate (1.50 mmol) in a mixture of 5 mL of dimethoxyethane and 0.5 mL of water. Purification by MPLC (3:97 to 10:90 EtOAc: hexane) afforded the product as a brown liquid (0.112 g, 77%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (dd, *J* = 8.5 Hz, 1.0 Hz, 1H), 7.54 (dt, *J* = 7.5 Hz, 1.0 Hz, 1H), 7.41 (dt, *J* = 8.5 Hz, 1.5 Hz, 1H), 7.10 (dd, *J* = 7.5 Hz, 1.5 Hz, 1H), 3.36 (s, 3H), 2.91 (dt, *J* = 26.0 Hz, 3.5 Hz, 1H), 2.63 – 2.50 (m, 2H), 2.28 – 2.23 (m, 1H), 1.80 – 1.52 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.3 (C), 149.0 (C), 146.4 (C), 140.1 (C), 129.3 (C), 133.0 (CH), 129.2 (CH), 127.6 (CH), 124.7 (CH), 51.3 (CH_3), 34.7 (CH_2), 30.2 (CH_2), 28.0 (CH_2), 27.8 (CH_2), 26.9 (CH_2), 26.4 (CH_2). ATR-FTIR (thin film): 2921, 2853, 1710, 1520, 1346, 1320, 1149, 855 cm^{-1}. HRMS (ESI) m/z calculated for $C_{16}H_{20}NO_4$ $(M+H)^+$: 290.1392, found: 290.1405.



5.12h

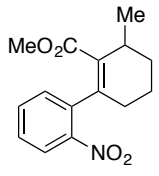
Nitrostyrene 5.12h. General procedure B was followed by using 0.145 g of vinyl triflate **s5.5i** (0.500 mmol), 0.149 g of 2-nitrophenylboronic acid pinacol ester **5.8j** (0.600 mmol), 0.058 g of $Pd(PPh_3)_4$ (0.050 mmol), 1.0 mL of a saturated aq. soln. of $NaHCO_3$ and 5 mL of dimethoxyethane. Purification by MPLC (3:97 to 10:90 EtOAc: hexane) afforded the product as a black liquid (0.091 g, 69%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (dd, *J* = 8.0 Hz, 1.0 Hz, 1H), 7.62 (dt, *J* = 7.5 Hz, 1.0 Hz, 1H), 7.47 (dt, dt, 7.5 Hz, 1.5 Hz, 1H), 7.17 (dd, *J* = 7.5 Hz, 1.5 Hz, 1H), 4.56 (d, *J* = 17.5 Hz, 1H), 4.36 (d, *J* = 17.5 Hz, 1H), 4.03 (br s, 1H), 3.84 (br s, 1H), 3.45 (s, 3H), 2.49 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ

164.7 (C), 146.7 (C), 146.2 (C), 137.7 (C), 133.6 (CH), 128.8 (CH), 128.2 (CH), 124.5 (CH), 124.4 (C), 65.2 (CH_2), 63.7 (CH_2), 51.5 (CH_3), 32.7 (CH_2). ATR-FTIR (thin film): 2952, 2853, 1706, 1520, 1344, 1269, 1232, 1047 cm^{-1}. HRMS (ES) m/z calculated for $C_{13}H_{14}NO_5$ $(M+H)^+$: 264.0872, found: 264.0874.



5.12i

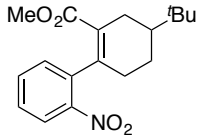
Nitrostyrene 5.12i. General procedure B was followed by using 0.194 g of vinyl triflate **s5.5j** (0.500 mmol), 0.149 g of 2-nitrophenylboronic acid pinacol ester **5.8j** (0.600 mmol), 0.058 g of $Pd(PPh_3)_4$ (0.050 mmol), 1.0 mL of a saturated aq. soln. of $NaHCO_3$ and 5 mL of dimethoxyethane. Purification by MPLC (3:97 to 10:90 EtOAc: hexane) afforded the product as a green solid (0.134 g, 74%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (d, J = 8.0 Hz, 1H), 7.60 (dt, J = 7.5 Hz, 1.0 Hz, 1H), 7.46 (dt, J = 8.5 Hz, 1.5 Hz, 1H), 7.13 (dd, J = 8.0 Hz, 1.5 Hz, 1H), 4.52 (br s, 1H), 3.99 (m, 2H), 3.46 (s, 3H), 3.36 – 3.31 (m, 1H), 2.47 (br s, 2H), 1.51 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.1 (C), 154.6 (C), 146.8 (C), 146.6 (C), 138.2 (C), 133.6 (CH), 128.7 (CH), 128.2 (CH), 124.5 (CH), 123.0 (C), 80.3 (C), 51.6 (CH_3), 43.4 (CH_2), 39.1 (CH_2), 33.2 (CH_2), 28.5 (CH_3). ATR-FTIR (thin film): 2975, 2860, 1692, 1521, 1418, 1356, 1293, 1237, 1165, 1114, 1054, 746 cm^{-1}. HRMS (ES) m/z calculated for $C_{18}H_{23}N_2O_6$ $(M+H)^+$: 363.1556, found: 363.1560.



5.12j

Nitrostyrene 5.12j. General procedure B was followed by using 0.160 g of vinyl triflate **s5.5k** (0.500 mmol), 0.149 g of 2-nitrophenylboronic acid pinacol ester **5.8j** (0.600

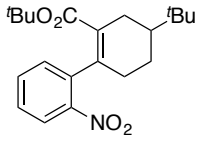
mmol), 0.058 g of $Pd(PPh_3)_4$ (0.050 mmol), 1.0 mL of a saturated aq. soln. of $NaHCO_3$ and 5 mL of dimethoxyethane. Purification by MPLC (3:97 to 10:90 EtOAc: hexane) afforded the product—a 2.7:1 mixture of rotamers—as a yellow liquid (0.115 g, 83%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.5 Hz, 1H), 7.54 (t, *J* = 7.5 Hz, 1H), 7.40 (t, *J* = 7.5 Hz, 1H), 7.09 (d, *J* = 7.5 Hz, 1H), 3.36 (s, 3H), 2.89 (m, 1H), 2.48 (dt, *J* = 18.5, 4.5 Hz, 1H), 2.21 – 2.15 (m, 1H), 1.93 – 1.87 (m, 1H), 1.84 – 1.78 (m, 1H), 1.75 – 1.64 (m, 2H), 1.09 (d, 3H *J* = 6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.2 (C), 144.3 (C), 139.4 (C), 133.2 (CH), 131.4 (C), 130.4 (C), 128.9 (CH), 127.6 (CH), 124.3 (CH), 51.1 (CH_3), 33.4 (CH_2), 29.4 (CH_2), 29.3 (CH_3), 19.8 (CH_3), 18.4 (CH_2); diagnostic data for minor rotamer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.0 Hz, 1H), 7.23 (d, *J* = 8.0 Hz, 1H), 3.42 (s, 3H), 1.13 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 132.8 (CH), 130.2 (CH), 127.6 (CH), 124.1 (CH), 55.0 (CH_3), 33.1 (CH_2), 29.7 (CH_2), 29.6 (CH_3), 20.3 (CH_3), 18.8 (CH_2); ATR-FTIR (thin film): 2934, 2867, 1714, 1523, 1432, 1347, 1238, 1061 cm^{-1}. HRMS (EI) m/z calculated for $C_{15}H_{17}NO_4$ $(M)^+$: 275.1158, found: 275.1158.



5.12k

Nitrostyrene 5.12k. General procedure A was followed by using 0.206g of vinyl triflate **s5.5l** (0.600 mmol), 0.830 g of 2-nitrophenylboronic acid **5.8a** (0.500 mmol), 0.029 g of $Pd(PPh_3)_4$ (0.025 mmol) and 0.158 g of sodium carbonate (1.50 mmol) in a mixture of 5 mL of dimethoxyethane and 0.5 mL of water. Purification by MPLC (3:97 to 10:90 EtOAc: hexane) afforded the product—a 3:2 mixture of rotamers—as a brown liquid (0.125 g, 95%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.0 Hz, 0.61H), 7.99 (d, *J* = 8.0 Hz, 0.39H, minor), 7.56 (t, *J* = 7.5 Hz, 1H), 7.41 (t, *J* = 7.5 Hz, 1H), 7.12 (m, 1H),

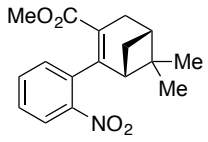
3.41 (s, 3H), 2.74 – 2.50 (m, 2H), 2.35 – 2.26 (m, 1H), 2.08 – 1.92 (m, 2H), 1.60 – 1.33 (m, 2H), 0.95 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.7 (C), 146.9 (C), 145.9 (C), 139.7 (C), 133.2 (CH), 128.9 (CH), 127.6 (CH), 126.1 (C), 124.4 (CH), 51.3 (CH_3), 43.9 (CH), 35.2 (CH_2), 32.4 (C), 27.5 (CH_2), 27.2 (CH_3), 23.6 (CH_2); diagnostic data for minor rotamer ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.9 (C), 133.1 (CH), 129.3 (CH), 127.5 (CH), 126.5 (C), 123.9 (CH), 53.4 (C), 43.1 (CH), 34.8 (CH_2), 27.8 (CH_2), 23.7 (CH_2). ATR-FTIR (thin film): 2961, 2869, 1697, 1524, 1346, 1274, 1136, 851 cm^{-1}. HRMS (ESI) m/z calculated for $C_{18}H_{24}NO_4$ $(M+H)^+$: 318.1705, found: 318.1711.



5.12l

Nitrostyrene 5.12l. General procedure A was followed by using 0.231 g of vinyl triflate **s5.5m** (0.600 mmol), 0.830 g of 2-nitrophenylboronic acid **5.8a** (0.500 mmol), 0.029 g of $Pd(PPh_3)_4$ (0.025 mmol) and 0.158 g of sodium carbonate (1.50 mmol) in a mixture of 5 mL of dimethoxyethane and 0.5 mL of water. Purification by MPLC (3:97 to 10:90 EtOAc: hexane) afforded the product—a 3:2 mixture of rotamers—as a yellow liquid (0.166 g, 93%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.0 Hz, 0.63H), 7.96 (d, *J* = 8.0 Hz, 0.36H, minor), 7.56 (t, *J* = 7.5 Hz, 1H), 7.41 (t, *J* = 8.0 Hz, 1H), 7.15 (m, 1H), 2.68 – 2.64 (m, 1H), 2.50 – 2.46 (m, 1H), 2.28 – 2.09 (m, 2H), 1.99 – 1.89 (m, 1H), 1.39 – 1.30 (m, 2H), 1.04 (s, 4H, minor), 1.02 (s, 5H), 0.94 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.2 (C), 143.9 (C), 140.3 (C), 138.1 (C), 133.2 (CH), 129.4 (CH), 128.1 (C), 127.4 (C), 124.7 (CH), 80.4 (C), 43.9 (CH), 35.1 (CH_2), 32.4 (C), 28.2 (CH_2), 27.6 (CH_3), 27.2 (CH_3), 23.7 (CH_2); diagnostic data for minor rotamer: ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.0 (CH), 129.8 (CH), 128.7 (C), 127.3 (CH), 124.1 (CH), 43.1 (CH), 34.6 (CH_2),

28.0 (CH_2), 23.8 (CH_2). ATR-FTIR (thin film): 2947, 2866, 1715, 1645, 1522, 1433, 1357, 1256, 1230, 1056 cm^{-1}. HRMS (ESI) m/z calculated for $C_{21}H_{30}NO_4$ $(M+H)^+$: 360.2175, found: 360.2180.

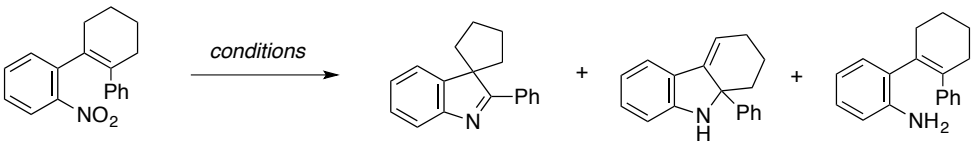


5.12m

Nitrostyrene 5.12m. The general procedure B was followed by using 0.098 g of pinene-derived vinyl triflate **s5.5n** (0.30 mmol), 0.090 g of 2-nitrophenylboronic acid pinacolate ester **5.8j** (0.36 mmol), 0.035 g of $Pd(PPh_3)_4$ (0.03 mmol), 0.6 mL of a saturated aq. soln. of $NaHCO_3$ and 4 mL of dimethoxyethane. Purification by MPLC (3:97 to 10:90 EtOAc: hexane) afforded the product as a brown liquid (0.070 g, 78%): $[\alpha]_D^{25}$: –232.0 (c 0.100, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 8.05 (d, J = 8.0 Hz, 1H), 7.56 (t, J = 7.5 Hz, 1H), 7.40 (t, J = 7.5 Hz, 1H), 7.05 (d, J = 7.5 Hz, 1H), 3.46 (s, 3H), 2.67 (s, 1H), 2.56 (m, 1H), 2.34 (t, J = 5.5 Hz, 1H), 2.28 (m, 1H), 1.70 (d, J = 9.5 Hz, 1H), 1.33 (s, 3H), 1.24 – 1.21 (m, 1H), 1.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.8 (C), 156.8 (C), 146.7 (C), 138.6 (C), 133.2 (CH), 128.2 (CH), 127.7 (CH), 124.2 (CH), 122.1 (C), 51.2 (CH_3), 50.7 (CH), 39.6 (CH), 38.2 (C), 32.1 (CH_2), 31.2 (CH_2), 25.9 (CH_3), 21.6 (CH_3). ATR-FTIR (thin film): 2983, 2947, 2872, 2835, 1709, 1633, 1571, 1524, 1432, 1347, 1250, 1028, 1133, 1068 cm^{-1}. HRMS (ESI) m/z calculated for $C_{17}H_{20}NO_4$ $(M+H)^+$: 302.1392, found: 302.1399.

E. Pd(II)-Catalyzed Formation of 3*H*-Indole.

1. Screening of Reaction Conditions.



5.10a **5.11a** **5.11a'** **5.11a''**

Method using CO gas as the reductant: In a 10 mL Schlenk tube, under a nitrogen atmosphere, was added 0.10 mmol of nitroarene followed by the palladium catalyst and phenanthroline in 1.0 mL of solvent. The Schlenk tube was degased at – 78 °C and refilled with CO. Then the Schlenk tube was sealed and heated. The reaction mixture was then cooled down to room temperature and filtered through a pad of silica gel. The filtrate was concentrated *in vacuo*, and the residue was analyzed using ^{1}H NMR spectroscopy using CH_2Br_2 as the internal standard.

Method using $Mo(CO)_6$ as the reductant: In a 10 mL Schlenk tube, under a nitrogen atmosphere, was added 0.10 mmol of nitroarene followed by the palladium catalyst, phenanthroline and $Mo(CO)_6$ in 1.0 mL of solvent. The Schlenk tube was sealed and heated. The reaction mixture was then cooled down to room temperature and filtered through a pad of silica gel. The filtrate was concentrated *in vacuo*, and the residue was analyzed using ^{1}H NMR spectroscopy using CH_2Br_2 as the internal standard.

Table 2.4 ***Survey of Reaction Conditions for Pd-catalyzd Nitroarene Reduction.***

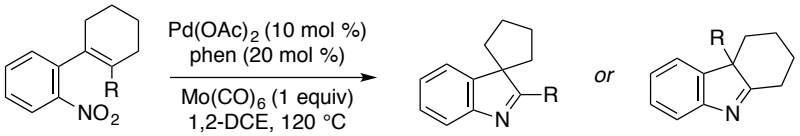
entry	catalyst (mol %)	ligand (mol %)	reductant (equiv)	solvent	T (°C)	yield, %[a] **5.11a** : **5.11a'** : **5.11a''**
1	$Pd(OAc)_2$	phen	CO	DMF	120	20:40:0

	(20 mol %)	(40 mol %)	(1.5 atm)			
2	$Pd(OAc)_2$ (20 mol %)	tmphen (40 mol%)	CO (1.5 atm)	DMF	120	12:21:0
3	$Pd(TFA)_2$ (20 mol %)	phen (40 mol %)	CO (1.5 atm)	DMF	120	44:8:0
4[b]	$Pd(TFA)_2$ (20 mol %)	phen (40 mol %)	CO (1.5 atm)	DMF	120	62:0:0
5[b]	$Pd(TFA)_2$ (20 mol %)	phen (40 mol %)	CO (3.0 atm)	DMF	135	37:0:0
6[b]	$Pd(TFA)_2$ (20 mol %)	tmphen (40 mol %)	CO (1.5 atm)	DMF	120	15:0:0
7	$Pd(OAc)_2$ (10 mol %)	phen (20 mol %)	$Mo(CO)_6$ (1.0 equiv)	DMF	120	30:0:35
8	$Pd(OAc)_2$ (10 mol %)	phen (20 mol %)	$Mo(CO)_6$ (1.0 equiv)	THF	120	48:0:50
9	$Pd(OAc)_2$ (10 mol %)	phen (20 mol %)	$Mo(CO)_6$ (1.0 equiv)	dioxane	120	46:0:18
10	$Pd(OAc)_2$ (10 mol %)	phen (20 mol %)	$Mo(CO)_6$ (1.0 equiv)	DCE	120	80:0:0
11	$Pd(OAc)_2$ (5 mol %)	phen (10 mol %)	$Mo(CO)_6$ (1.0 equiv)	DCE	120	68:0:0
12	$Pd(OAc)_2$ (10 mol %)	phen (20 mol %)	$Mo(CO)_6$ (5 equiv)	THF	120	19:52:0
13	$Pd(OAc)_2$ (10 mol %)	phen (20 mol %)	$Mo(CO)_6$ (0.5 equiv)	THF	120	16:15:38
14	N/A	N/A	$Mo(CO)_6$ (1.0 equiv)	DCE	120	16:0:0
15	N/A	N/A	$Cr(CO)_6$ (1.0 equiv)	DCE	120	15:0:0
16	N/A	N/A	$W(CO)_6$ (1.0 equiv)	DCE	120	6:0:0

[a] As determined using ^1H NMR spectroscopy using CH_2Br_2 as the internal standard. [b] 0.4 equiv of trifluo

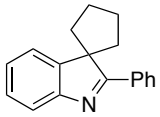
roacetic acid added.

2. Optimized Procedure.



In a 10 mL Schlenk tube, under a nitrogen atmosphere, was added 0.10 mmol of nitroarene followed by 0.01 mmol of $Pd(OAc)_2$ (10 mol %), 0.02 mmol of phenanthroline (20 mol %), 0.10 mmol of $Mo(CO)_6$ (1.0 equiv) in 1.0 mL of 1,2-dichloroethane. The Schlenk tube was sealed and heated at 120 °C for either 24 h, when R = aryl or 16 h, when R = ester. The reaction mixture was then cooled down to room temperature and filtered through a pad of celite. The filtrate was then evaporated and the crude mixture was purified by MPLC (3:97 – 20:80 EtOAc:hexane) to afford the product.

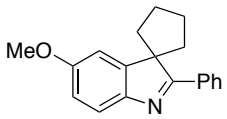
3. Characterization Data.



5.11a

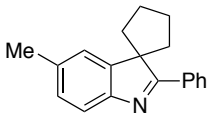
3*H*-Indole 5.11a. The optimized procedure was followed by using 0.028 g of nitroarene **5.10a** (0.10 mmol), 0.0022 g of $Pd(OAc)_2$ (0.010 mmol), 0.0036 g of phenanthroline (0.020 mmol), 0.0264 g of $Mo(CO)_6$ (0.100 mmol) in 1.0 mL of 1,2-dichloroethane. Purification by MPLC (3:97 – 20:80 EtOAc:hexane) afforded the product as a greenish yellow liquid (0.019 g, 77%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (m, 2H), 7.69 (d, J = 7.5 Hz, 1H), 7.49 – 7.47 (m, 3H), 7.39 (d, J = 7.5 Hz, 1H), 7.35 (t, J = 7.5 Hz, 1H), 7.24 (t, J = 7.5 Hz, 1H), 2.54 – 2.41 (m, 2H), 2.25 – 2.10 (m, 4H), 1.96 – 1.91 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.7 (C), 153.0 (C), 150.2 (C), 132.9 (C), 130.4 (CH), 128.6 (CH), 128.3 (CH), 127.4 (CH), 125.9 (CH), 120.9 (CH), 120.7 (CH), 63.3 (C), 36.8

(CH_2), 27.6 (CH_2). ATR-FTIR (thin film): 3057, 2953, 2871, 1519, 1464, 1343, 1018 cm^{-1}. HRMS (ESI) m/z calculated for $C_{18}H_{18}N$ $(M+H)^+$: 248.1439, found: 248.1445.



5.11b

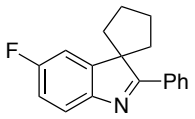
3*H*-Indole 5.11b. The optimized procedure was followed by using 0.031 g of nitroarene **5.10b** (0.10 mmol), 0.0045 g of $Pd(OAc)_2$ (0.020 mmol), 0.0072 g of phenanthroline (0.040 mmol), 0.0264 g of $Mo(CO)_6$ (0.100 mmol) in 1.0 mL of 1,2-dichloroethane. Purification by MPLC (3:97 – 20:80 EtOAc:hexane) afforded the product as a yellow liquid (0.023 g, 82%): ^1H NMR (500 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.0 Hz, 2H), 7.58 (d, *J* = 8.5 Hz, 1H), 7.45 (m, 3H), 6.95 (d, *J* = 2.5 Hz, 1H), 6.86 (dd. *J* = 8.5 Hz, 2.5 Hz, 1H), 3.85 (s, 3H), 2.44 – 2.40 (m, 2H), 2.20 – 2.17 (m, 4H), 1.94 – 1.89 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.7 (C), 158.5 (C), 151.9 (C), 146.9 (C), 133.0 (C), 130.1 (CH), 128.5 (CH), 128.0 (CH), 120.9 (CH), 111.5 (CH), 108.2 (CH), 63.5 (C), 55.8 (CH_3), 37.0 (CH_2), 27.5 (CH_2). ATR-FTIR (thin film): 2952, 2871, 2832, 1589, 1519, 1465, 1438, 1351, 1287, 1270, 1209, 1175, 1117, 1030 cm^{-1}. HRMS (ESI) m/z calculated for $C_{19}H_{20}NO$ $(M+H)^+$: 278.1545, found: 278.1538.



5.11c

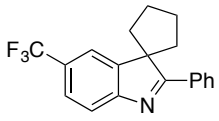
3*H*-Indole 5.11c. The optimized procedure was followed by using 0.029 g of nitroarene **5.10c** (0.10 mmol), 0.0022 g of $Pd(Oac)_2$ (0.010 mmol), 0.0036 g of phenanthroline (0.020 mmol), 0.0264 g of $Mo(CO)_6$ (0.100 mmol) in 1.0 mL of 1,2-dichloroethane. Purification by MPLC (3:97 – 20:80 EtOAc:hexane) afforded the product as a yellow liquid (0.0165 g, 64%): ^1H NMR (500 MHz, $CDCl_3$) δ 8.07 (m, 2H), 7.56 (d, *J* = 8.0 Hz,

1H), 7.46 (m, 3H), 7.20 (s, 1H), 7.15 (d, J = 8.0 Hz, 1H), 2.43 (s, 3H), 2.39 (m, 2H), 2.22 – 2.19 (m, 4H), 1.95 – 1.90 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.8 (C), 150.9 (C), 150.4 (C), 135.7 (C), 133.0 (C), 130.2 (CH), 128.5 (CH), 128.2 (CH), 128.0 (CH), 121.8 (CH), 120.2 (CH), 63.1 (C), 36.9 (CH_2), 27.6 (CH_2), 21.7 (CH_3). ATR-FTIR (thin film): 2918, 2849, 1519, 1462, 1339, 818 cm^{-1}. HRMS (ESI) m/z calculated for $C_{19}H_{20}N$ $(M+H)^+$: 262.1596, found: 262.1591.



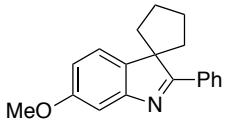
5.11d

***3H*-Indole 5.11d.** The optimized procedure was followed by using 0.030 g of nitroarene **5.10d** (0.10 mmol), 0.0022 g of $Pd(OAc)_2$ (0.010 mmol), 0.0036 g of phenanthroline (0.020 mmol), 0.0264 g of $Mo(CO)_6$ (0.100 mmol) in 1.0 mL of 1,2-dichloroethane. Purification by MPLC (3:97 – 20:80 EtOAc:hexane) afforded the product as a yellow liquid (0.0193 g, 72%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (m, 2H), 7.60 (dd, J = 8.5, 5.0 Hz, 1H), 7.47 (m, 3H), 7.08 (dd, J = 8.0 Hz, 2.0 Hz, 1H), 7.02 (dt, J = 9.0 Hz, 2.0 Hz, 1H), 2.45 – 2.41 (m, 2H), 2.20 (br s, 4H), 1.94 – 1.90 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.5 (C), 161.5 (d, J_{C-F} = 242.4 Hz, C), 151.9 (C), 149.1 (C), 132.6 (C), 130.5 (CH), 128.6 (CH), 128.1 (CH), 121.2 (d, J_{CF} = 8.8 Hz, CH), 113.9 (d, J_{CF} = 23.6 Hz, CH), 108.7 (d, J_{CF} = 25.2 Hz, C), 63.8 (C), 36.8 (CH_2), 27.5 (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$) δ –116.6; ATR-FTIR (thin film): 3057, 2955, 2873, 2361, 2339, 1713, 1594, 1521, 1457, 1344, 1262, 1188, 819 cm^{-1}. HRMS (EI) m/z calculated for $C_{18}H_{16}NF$ $(M)^+$: 265.1267, found: 265.1264.



5.11e

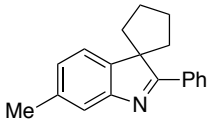
3*H*-Indole 5.11e. The optimized procedure was followed by using 0.035 g of nitroarene **5.10e** (0.10 mmol), 0.0044 g of $Pd(Oac)_2$ (0.020 mmol), 0.0072 g of phenanthroline (0.040 mmol), 0.0264 g of $Mo(CO)_6$ (0.10 mmol) in 1.0 mL of 1,2-dichloroethane. Purification by MPLC (3:97 – 20:80 EtOAc:hexane) afforded the product as a white liquid (0.0170 g, 54%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (m, 2H), 7.74 (d, J = 8.0 Hz, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.60 (s, 1H), 7.52 – 7.48 (m, 3H), 2.47 – 2.43 (m, 2H), 2.26 – 2.23 (m, 4H), 1.97 – 1.93 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.4 (C), 155.8 (C), 150.2 (C), 132.2 (C), 131.1 (CH), 128.7 (CH), 128.5 (CH), 127.5 (CH), 126.7 (q, J_{CF} = 262.6 Hz, C), 125.1 (q, J_{CF} = 3.5 Hz CH), 120.6 (CH), 117.9 (q, J_{CF} = 3.1 Hz, CH), 63.5 (C), 36.9 (CH_2), 27.6 (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$) δ –61.6; ATR-FTIR (thin film): 3051, 2958, 2877, 2360, 1619, 1512, 1436, 1325, 1257, 1152, 1119, 1071, 883 cm^{-1}. HRMS (EI) m/z calculated for $C_{19}H_{16}NF_3$ $(M)^+$: 315.1235, found: 315.1236.



5.11f

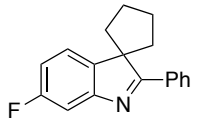
3*H*-Indole 5.11f. The optimized procedure was followed by using 0.031 g of nitroarene **5.10f** (0.10 mmol), 0.0022 g of $Pd(Oac)_2$ (0.010 mmol), 0.0036 g of phenanthroline (0.020 mmol), 0.0264 g of $Mo(CO)_6$ (0.10 mmol) in 1.0 mL of 1,2-dichloroethane. Purification by MPLC (3:97 – 20:80 EtOAc:hexane) afforded the product as a yellow liquid (0.019 g, 68%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (m, 2H), 7.47 (m, 3H), 7.27 (m, 2H), 6.78 (dd, J = 8.0 Hz, 2.0 Hz, 1H), 3.87 (s, 3H), 2.44 – 2.38 (m, 2H), 2.19 – 2.17 (m, 4H), 1.92 – 1.87 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 183.9 (C), 159.6 (C), 154.3 (C), 142.5 (C), 132.8 (C), 130.5 (CH), 128.6 (CH), 128.3 (CH), 121.2 (CH), 112.1(CH), 106.0 (CH), 62.9 (C), 55.6 (CH_3), 37.0 (CH_2), 27.4 (CH_2). ATR-FTIR (thin film): 2954,

2872, 2359, 1617, 1519, 1482, 1442, 1352, 1145, 808 cm^{-1}. HRMS (EI) m/z calculated for $C_{19}H_{19}NO$ $(M)^+$: 277.1467, found: 277.1465.



5.11g

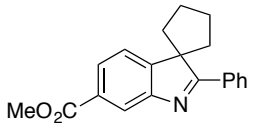
3*H*-Indole 5.11g. The optimized procedure was followed by using 0.029 g of nitroarene **5.10g** (0.10 mmol), 0.0022 g of $Pd(Oac)_2$ (0.010 mmol), 0.0036 g of phenanthroline (0.020 mmol), 0.0264 g of $Mo(CO)_6$ (0.10 mmol) in 1.0 mL of 1,2-dichloroethane. Purification by MPLC (3:97 – 20:80 EtOAc:hexane) afforded the product as a yellow liquid (0.0165 g, 77%): ^1H NMR (500 MHz, $CDCl_3$) δ 8.07 (m, 2H), 7.50 – 7.47 (m, 4H), 7.26 (d, *J* = 7.5 Hz, 1H), 7.05 (d, *J* = 7.5 Hz, 1H), 2.43 (s, 3H), 2.40 (m, 2H), 2.19 (m, 4H), 1.92 – 1.88 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.9 (C), 153.3 (C), 147.3 (C), 137.3 (C), 133.0 (C), 130.3 (CH), 128.5 (CH), 128.3 (CH), 126.5 (CH), 121.3 (CH), 120.6 (CH), 63.0 (C), 36.9 (CH_2), 27.5 (CH_2), 21.5 (CH_3). ATR-FTIR (thin film): 2954, 2872, 2831, 2360, 2340, 1614, 1519, 1478, 1438, 1271, 1150, 1028 cm^{-1}. HRMS (EI) m/z calculated for $C_{19}H_{19}N$ $(M)^+$: 261.1517, found: 261.1516.



5.11h

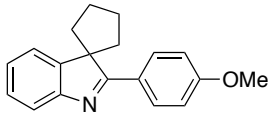
3*H*-Indole 5.11h. The optimized procedure was followed by using 0.030 g of nitroarene **5.10h** (0.10 mmol), 0.0022 g of $Pd(OAc)_2$ (0.010 mmol), 0.0036 g of phenanthroline (0.020 mmol), 0.0264 g of $Mo(CO)_6$ (0.100 mmol) in 1.0 mL of 1,2-dichloroethane. Purification by MPLC (3:97 – 20:80 EtOAc:hexane) afforded the product as a yellow liquid (0.0235 g, 88%): ^1H NMR (500 MHz, $CDCl_3$) δ 8.11 (m, 2H), 7.53 (m, 3H), 7.41 (dd, *J* = 9.0 Hz, 2.5 Hz, 1H), 7.33 (dd, *J* = 8.5 Hz, 5.5 Hz, 1H), 6.96 (dt, *J* = 9.0 Hz, 2.0

Hz, 1H), 2.48 – 2.45 (m, 2H), 2.25 – 2.22 (m, 4H), 1.96 – 1.93 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.8 (C), 162.7 (d, J_{CF} = 240.5 Hz, C), 154.5 (C), 145.8 (C), 132.6 (C), 130.8 (CH), 128.7 (CH), 128.4 (CH), 121.3 (d, J_{CF} = 9.1 Hz, CH), 112.3 (d, J_{CF} = 23.5 Hz, CH), 108.1 (d, J_{CF} = 23.9 Hz, C), 63.0 (C), 37.0 (CH_2), 27.5 (CH_2), ^{19}F NMR (282 MHz, $CDCl_3$) δ –116.1; ATR-FTIR (thin film): 2956, 2874, 1600, 1518, 1470, 1442, 1336, 1257, 1180, 1126, 955, 857 cm^{-1}. HRMS (ESI) m/z calculated for $C_{18}H_{17}NF$ $(M+H)^+$: 266.1345, found: 266.1354.



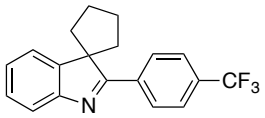
5.11i

3*H*-Indole 5.11i. The optimized procedure was followed by using 0.034 g of nitroarene **5.10i** (0.10 mmol), 0.0022 g of $Pd(OAc)_2$ (0.010 mmol), 0.0036 g of phenanthroline (0.020 mmol), 0.0264 g of $Mo(CO)_6$ (0.100 mmol) in 1.0 mL of 1,2-dichloroethane. Purification by MPLC (3:97 – 20:80 EtOAc:hexane) afforded the product as a yellow solid (0.023 g, 75%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31 (s, 1H), 8.09 (m, 2H), 7.95 (d, *J* = 8.0 Hz, 1H), 7.49 (m, 3H), 7.43 (d, *J* = 7.5 Hz, 1H), 3.94 (s, 3H), 2.46 – 2.42 (m, 2H), 2.27 (t, *J* = 7.5 Hz, 4H), 1.95 – 1.90 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 183.6 (C), 167.1 (C), 155.1 (C), 153.3 (C), 132.5 (C), 130.8 (CH), 129.8 (C), 128.7 (CH), 128.4 (CH), 127.7 (CH), 121.7 (CH), 120.7 (CH), 63.5 (C), 52.2 (C), 36.8 (CH_2), 27.6 (CH_2). ATR-FTIR (thin film): 2950, 2874, 2361, 2338, 1716, 1433, 1280, 1240, 1089 cm^{-1}. HRMS (EI) m/z calculated for $C_{20}H_{19}NO_2$ $(M)^+$: 305.1416, found: 305.1415.



5.14a

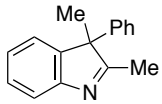
3*H*-Indole 5.14a. The optimized procedure was followed by using 0.031 g of nitroarene **5.12a** (0.10 mmol), 0.0022 g of $Pd(OAc)_2$ (0.010 mmol), 0.0036 g of phenanthroline (0.020 mmol), 0.0264 g of $Mo(CO)_6$ (0.100 mmol) in 1.0 mL of 1,2-dichloroethane. Purification by MPLC (3:97 – 20:80 EtOAc:hexane) afforded the product as a green liquid (0.021 g, 76%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (d, J = 9.0 Hz, 2H), 7.65 (d, J = 7.5 Hz, 1H), 7.37 (d, J = 7.5 Hz, 1H), 7.33 (dt, J = 8.0 Hz, 1.0 Hz, 1H), 7.20 (dt, J = 7.5 Hz, 1.0 Hz, 1H), 7.00 (d, J = 8.5 Hz, 2H), 3.88 (s, 3H), 2.42 – 2.39 (m, 2H), 2.26 – 2.20 (m, 4H), 1.95 – 1.92 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.2 (C), 161.5 (C), 153.0 (C), 150.2 (C), 130.1 (CH), 127.4 (C), 125.4 (CH), 125.3 (C), 120.9 (CH), 120.2 (CH), 114.0 (C), 63.0 (C), 55.4 (CH_3), 37.3 (CH_2), 27.6 (CH_2); ATR-FTIR (thin film): 2953, 2872, 2832, 1602, 1505, 1455, 1416, 1308, 1250, 1167, 1033, 835 cm^{-1}. HRMS (EI) m/z calcd for $C_{19}H_{20}NO$ $[M+H]^+$: 278.1545, found: 278.1547.



5.14b

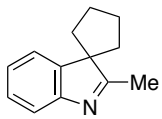
3*H*-Indole 5.14b. The optimized procedure was followed by using 0.035 g of nitroarene **5.12b** (0.10 mmol), 0.0022 g of $Pd(OAc)_2$ (0.010 mmol), 0.0036 g of phenanthroline (0.020 mmol), 0.0264 g of $Mo(CO)_6$ (0.100 mmol) in 1.0 mL of 1,2-dichloroethane. Purification by MPLC (3:97 – 20:80 EtOAc:hexane) afforded the product as a white solid (0.015 g, 48%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (d, J = 8.0 Hz, 2H), 7.73 (d, J = 8.5 Hz, 2H), 7.70 (d, J = 8.0 Hz, 1H), 7.41 (d, J = 7.5 Hz, 1H), 7.37 (dt, J = 8.0 Hz, 1.0 Hz, 1H), 7.27 (dd, J = 7.5 Hz, 1.0 Hz, 1H), 2.41 – 2.36 (m, 2H), 2.26 – 2.18 (m, 4H), 1.97 – 1.92 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.1 (C), 152.7 (C), 150.1 (C), 136.1 (C), 131.8 (q, J_{CF} = 31.7 Hz, C), 128.5 (CH), 127.6 (CH), 126.5 (CH), 125.5 (q, J_{CF} = 3.6 Hz,

CH), 123.9 (q, J_{CF} = 270.0 Hz, C), 121.1 (CH), 121.0 (CH), 63.3 (C), 36.5 (CH_2), 27.5 (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$) δ – 63.3; ATR-FTIR (thin film): 2956, 2874, 1617, 1520, 1407, 1321, 1164, 1128, 1108, 1068, 1014, 846 cm^{-1}. HRMS (EI) m/z calculated for $C_{19}H_{16}NF_3$ $(M)^+$: 315.1235, found: 315.1240.



5.14c

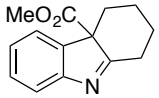
3*H*-Indole 5.14c.[79] The optimized condition was followed by using 0.025 g of nitroarene **5.12c** (0.10 mmol), 0.0022 g of $Pd(OAc)_2$ (0.01 mmol), 0.0036 g of phenanthroline (0.020 mmol), 0.0264 g of $Mo(CO)_6$ (0.10 mmol) in 1.0 mL of 1,2-dichloroethane. Purification by MPLC (3:97 – 20:80 EtOAc:hexane) afforded the product a yellow solid (0.013 g, 59%). The spectral data of vinyl triflate **s5.5l** matched that reported by Dauglis and co-workers:[79] ^1H NMR (500 MHz, $CDCl_3$) δ 7.61 (d, J = 7.5 Hz, 1H), 7.32 (dt, J = 7.5 Hz, 1.5 Hz, 1H), 7.29 – 7.23 (m, 3H), 7.16 (t, J = 8.0 Hz, 1H), 7.10 (d, J = 7.0 Hz, 1H), 7.03 (m, 2H), 2.13 (s, 3H), 1.69 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 187.3 (C), 154.3 (C), 147.0 (C), 139.4 (C), 128.9 (CH), 127.9 (CH), 127.2 (CH), 126.1 (CH), 125.7 (CH), 122.5 (CH), 120.1 (CH), 61.8 (C), 20.3 (CH_3), 15.9 (CH_3). ATR-FTIR (thin film): 3061, 3024, 2967, 2923, 2851, 1578, 1494, 1445, 1374, 1240, 1071, 1014 cm^{-1}. HRMS (EI) m/z calcd for $C_{16}H_{15}N$ $(M)^+$: 221.1204, found 221.1207.



5.14d

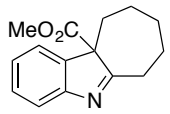
3*H*-Indole 5.14d.[30] The optimal condition was followed by using 0.022 g of nitroarene **5.12d** (0.10 mmol), 0.0044 g of $Pd(OAc)_2$ (0.02 mmol), 0.0072 g of phenanthroline (0.040 mmol), 0.026 g of $Mo(CO)_6$ (0.10 mmol) in 1.0 mL of 1,2-dichloroethane.

Purification by MPLC (3:97 – 20:80 EtOAc:hexane) afforded the product a brown oil (0.010 g, 54%). The spectral data of vinyl triflate **s5.5l** matched that reported by Kong and Driver:[30] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.0 Hz, 1H), 7.29 (t, *J* = 7.5 Hz, 2H), 7.16 (t, *J* = 7.5 Hz, 1H), 2.29 (s, 3H), 2.10 – 1.96 (m, 6H), 1.80 – 1.77 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 187.2 (C), 153.8 (C), 147.3 (C), 127.3 (CH), 125.2 (CH), 121.2 (CH), 119.6 (CH), 63.8 (C), 35.3 (CH_2), 26.9 (CH_2), 16.0 (CH_3). ATR-FTIR (thin film): 2958, 2857, 1715, 1605, 1571, 1455, 1378, 1258, 1201, 1101, 1018 cm^{-1}. HRMS (ES) m/z calcd for $C_{13}H_{16}N$ $(M+H)^+$: 186.1283, found 186.1287.



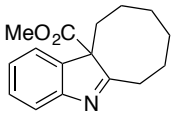
5.14e

3*H*-Indole 5.14e.[30] The optimized procedure was followed by using 0.026 g of nitroarene **5.12e** (0.10 mmol), 0.0022 g of $Pd(OAc)_2$ (0.010 mmol), 0.0036 g of phenanthroline (0.020 mmol), 0.0264 g of $Mo(CO)_6$ (0.100 mmol) in 1.0 mL of 1,2-dichloroethane. Purification by MPLC (3:97 – 20:80 EtOAc:hexane) afforded the product as a yellow solid (0.0166 g, 73%). The spectral data of **2.16e** matched that reported by Kong and Driver:[30] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (d, *J* = 7.5 Hz, 1H), 7.43 (d, *J* = 7.5 Hz, 1H), 7.37 (t, *J* = 7.5 Hz, 1H), 7.20 (t, *J* = 7.5 Hz, 1H), 3.65 (s, 3H), 3.05 – 2.97 (m, 2H), 2.71 (dt, *J* = 13.0 Hz, 5.5 Hz, 1H), 2.21 (br m, 1H), 1.80 (m, 1H), 1.59 – 1.47 (m, 2H), 1.16 (dt, *J* = 13.0 Hz, 3.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 183.9 (C), 170.6 (C), 155.4 (C), 139.5 (C), 128.9 (CH), 125.4 (CH), 122.4 (CH), 120.4 (CH), 64.9 (C), 52.8 (CH_3), 37.2 (CH_2), 31.5 (CH_2), 28.5 (CH_2), 22.9 (CH_2). ATR-FTIR (thin film): 2975, 2890, 2360, 2339, 1692, 1544, 1392, 1217, 1148, 1119, 880 cm^{-1}. HRMS (EI) m/z calcd for $C_{14}H_{15}NO_2$ $(M)^+$: 229.1103, found 229.1101.



5.14f

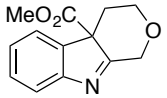
3*H*-Indole 5.14f.[30] The optimized procedure was followed by using 0.028 g of nitroarene **5.12f** (0.10 mmol), 0.0022 g of $Pd(OAc)_2$ (0.010 mmol), 0.0036 g of phenanthroline (0.020 mmol), 0.0264 g of $Mo(CO)_6$ (0.100 mmol) in 1.0 mL of 1,2-dichloroethane. Purification by MPLC (3:97 – 20:80 EtOAc:hexane) afforded the product as a white solid (0.013 g, 52%). The spectral data of **2.16f** matched that reported by Kong and Driver:[30] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (d, *J* = 7.5 Hz, 1H), 7.38 – 7.33 (m, 2H), 7.19 (t, *J* = 7.5 Hz, 1H), 3.65 (s, 3H), 2.99 (t, *J* = 7.0 Hz, 2H), 2.57 (ddd, *J* = 14.0 Hz, 6.0 Hz, 2.0 Hz, 1H), 1.81 – 1.68 (m, 4H), 1.58 – 1.46 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.9 (C), 170.8 (C), 154.8 (CH), 139.6 (CH), 128.9 (CH), 125.7 (CH), 122.1 (CH), 119.9 (CH), 68.1 (C), 52.7 (CH_3), 34.8 (CH_2), 33.6 (CH_2), 29.2 (CH_2), 26.8 (CH_2), 26.2 (CH_2). ATR-FTIR (thin film): 2929, 2858, 1731, 1562, 1456, 1347, 1265, 1238, 1220, 1146, 1076, 1017, 955 cm^{-1}. HRMS (EI) m/z calcd for $C_{15}H_{18}NO_2$ $[M+H]^+$: 244.1338, found 244.1337.



5.14g

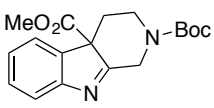
3*H*-Indole 5.14g.[30] The optimized procedure was followed by using 0.029 g of nitroarene **5.12g** (0.10 mmol), 0.0022 g of $Pd(OAc)_2$ (0.010 mmol), 0.0036 g of phenanthroline (0.020 mmol), 0.0264 g of $Mo(CO)_6$ (0.100 mmol) in 1.0 mL of 1,2-dichloroethane. Purification by MPLC (3:97 – 20:80 EtOAc:hexane) afforded the product as a yellow liquid (0.0145 g, 56%). The spectral data for **5.14g** matched that reported by Kong and Driver:[30] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, *J* = 7.5 Hz, 1H), 7.38 – 7.34 (m, 2H),

7.21 (d, J = 7.5 Hz, 1H), 3.58 (s, 3H), 2.98 – 2.93 (m, 1H), 2.79 – 2.67 (m, 2H), 2.44 – 2.39 (m, 1H), 2.07 – 2.01 (m, 1H), 1.95 – 1.88 (m, 1H), 1.61 – 1.39 (m, 4H), 1.13 – 1.09 (m, 1H), 0.96 – 0.91 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 186.9 (C), 171.1 (C), 155.7 (C), 137.9 (C), 128.8 (CH), 125.6 (CH), 122.6 (CH), 120.2 (C), 68.0 (C), 52.9 (CH_3), 31.7 (CH_2), 30.0 (CH_2), 29.2 (CH_2), 25.9 (CH_2), 25.0 (CH_2), 22.6 (CH_2). ATR-FTIR (thin film): 2929, 2857, 1731, 1562, 1456, 1434, 1347, 1312, 1265, 1238, 1220, 1182, 1146, 1116, 1076 cm^{-1}. HRMS (EI) m/z calcd for $C_{15}H_{18}NO_2$ $[M+H]^+$: 244.1338, found 244.1337.



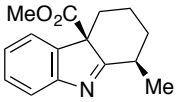
5.14h

3*H*-Indole 5.14h.[30] The optimized procedure was followed by using 0.026 g of nitroarene **5.12h** (0.10 mmol), 0.0044 g of $Pd(OAc)_2$ (0.02 mmol), 0.0072 g of phenanthroline (0.04 mmol), 0.0264 g of $Mo(CO)_6$ (0.10 mmol) in 1.0 mL of 1,2-dichloroethane. Purification by MPLC (3:97 – 20:80 EtOAc:hexane) afforded the product as a white solid (0.022 g, 67%). The spectral data for **5.14h** matched that reported by Kong and Driver:[30] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, J = 7.0 Hz, 1H), 7.50 (d, J = 7.5 Hz, 1H), 7.41 – 7.38 (m, 2H), 4.36 – 4.29 (m, 3H), 3.98 (s, 3H), 7.79 (d, J = 8.0 Hz, 1H), 2.88 – 2.82 (m, 1H), 2.09 – 2.03 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.2 (C), 161.9 (C), 151.9 (C), 146.6 (C), 129.2 (CH), 128.5 (CH), 123.5 (CH), 121.9 (CH), 73.8 (CH_2), 69.1 (CH_2), 64.2 (C), 52.8 (CH_3), 34.7 (CH_2). ATR-FTIR (thin film): 2956, 2854, 1732, 1585, 1454, 1246, 1212, 1166, 1078, 1045, 947, 835, 772, 735 cm^{-1}. HRMS (EI) m/z calcd for $C_{13}H_{13}NO_3$ $(M)^+$: 231.0895, found 231.0897.



5.14i

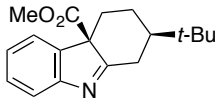
3*H*-Indole 5.14i.[30] The optimized procedure was followed by using 0.036 g of nitroarene **5.12i** (0.10 mmol), 0.0044 g of $Pd(OAc)_2$ (0.020 mmol), 0.0072 g of phenanthroline (0.040 mmol), 0.0264 g of $Mo(CO)_6$ (0.100 mmol) in 1.0 mL of 1,2-dichloroethane. Purification by MPLC (3:97 – 20:80 EtOAc:hexane) afforded the product—a 3:2 mixture of rotamers—as a white solid (0.0135 g, 59%). The spectral data for **5.14i** matched that reported by Kong and Driver:[30] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, *J* = 7.0 Hz, 1H), 7.47 – 7.33 (m, 3H), 4.14 (d, *J* = 10.5 Hz, 1H), 3.98 (s, 3H), 3.94 – 3.82 (m, 2H), 3.52 (d, *J* = 10.5 Hz, 0.40H), 3.41 (d, *J* = 10.5 Hz, 0.60H), 2.93 (m, 1H), 1.81 (br s, 1H), 1.52 (s, 4H), 1.44 (s, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.1 (C), 161.8 (C), 154.6 (C), 151.9 (C), 145.3 (C), 129.3 (CH), 128.8 (CH), 123.8 (CH), 121.7 (CH), 80.0 (C), 62.8 (C), 52.9 (CH_3), 51.3 (CH_2), 45.3 (CH_2), 32.2 (CH_2), 28.4 (CH_3); Diagnostic data for minor rotamer: ^{13}C NMR (125 MHz, $CDCl_3$) δ 129.2 (CH), 121.6 (CH), 50.9 (CH_2), 45.3 (CH_2), 33.2 (CH_2). ATR-FTIR (thin film): 2975, 2890, 1692, 1544, 1392, 1148, 1119 cm^{-1}. HRMS (EI) m/z calcd for $C_{18}H_{22}N_2O_4$ $(M)^+$: 330.1580, found 330.1581.



5.14j

3*H*-Indole 5.14j. The optimized procedure was followed by using 0.028 g of nitroarene **5.12j** (0.10 mmol), 0.0022 g of $Pd(OAc)_2$ (0.010 mmol), 0.0036 g of phenanthroline (0.020 mmol), 0.0264 g of $Mo(CO)_6$ (0.100 mmol) in 1.0 mL of 1,2-dichloroethane. Purification by MPLC (3:97 – 20:80 EtOAc:hexane) afforded the product, a yellow solid, as a 91:9 mixture of diastereomers (0.016 g, 65%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.0 Hz, 1H), 7.41 (d, *J* = 7.0 Hz, 1H), 7.37 (t, *J* = 7.0 Hz, 1H), 7.19 (t, *J* = 7.5 Hz, 1H), 3.63 (s, 3H), 3.03 (dd, *J* = 11.0 Hz, 2.5 Hz, 1H), 2.88 (m, 1H), 2.19 – 2.17 (m, 1H), 1.82

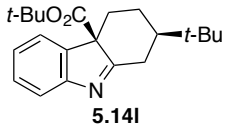
– 1.79 (m, 1H), 1.70 – 1.62 (m, 1H), 1.44 (d, *J* = 9.0 Hz, 3H), 1.21 (dt, J = 4.0 Hz, 13 Hz, 1H), 1.13 (dt, J = 4.0 Hz, 13.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 186.7 (C), 170.8 (C), 164.0 (C), 155.3 (C), 128.8 (CH), 125.3 (CH), 122.2 (CH), 120.6 (CH), 65.2 (C), 52.8 (CH_3), 37.6 (CH_2), 37.2 (CH_2), 36.3 (CH), 23.3 (CH_2), 16.7 (CH_3); diagnostic data for minor diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, *J* = 6.5 Hz, 0.08H), 3.97 (s, 0.21 H), 0.37 (d, *J* = 6.5 Hz, 0.21 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.6 (CH), 123.3 (CH); ATR-FTIR (thin film): 2930, 2857, 1731, 1578, 1455, 1273, 1243, 1213, 1149, 1121, 1003 cm^{-1}. HRMS (ES) m/z calcd for $C_{15}H_{18}NO_2$ $(M+H)^+$: 244.1338, found 244.1339.



5.14k

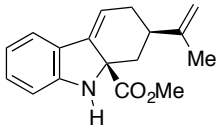
3*H*-Indole 5.14k. The optimized procedure was followed by using 0.032 g of nitroarene **5.12k** (0.10 mmol), 0.0022 g of $Pd(OAc)_2$ (0.010 mmol), 0.0036 g of phenanthroline (0.200 mmol), 0.0264 g of $Mo(CO)_6$ (0.100 mmol) in 1.0 mL of 1,2-dichloroethane. Purification by MPLC (3:97 – 20:80 EtOAc:hexane) afforded the product, a yellow liquid, as an 80:20 mixture of diastereomers (0.013 g, 45%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (d, *J* = 7.5 Hz, 1H), 7.45 (d, *J* = 7.5 Hz, 1H), 7.38 (t, *J* = 7.5 Hz, 1H), 7.20 (t, *J* = 7.5 Hz, 1H), 3.66 (s, 3H), 3.09 – 3.06 (m, 2H), 2.48 (t, *J* = 12.5 Hz, 1H), 1.87 (d, *J* = 13.0 Hz, 1H), 1.45 – 1.35 (m, 2H), 1.12 (dd, *J* = 13.0 Hz, 3.0 Hz, 1H), 0.95 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.1 (C), 170.5 (C), 155.4 (C), 139.5 (C), 128.8 (C), 125.4 (C), 122.5 (C), 120.3 (C), 64.5 (C), 52.8 (CH_3), 51.8 (CH), 36.0 (CH_2), 33.0 (C), 32.9 (CH_2), 27.5 (CH_3), 24.1 (CH_2); diagnostic data for minor diasteriomer: ^{13}C NMR (125 MHz, $CDCl_3$) δ 128.8 (CH), 122.3 (CH), 63.7 (C), 52.9 (CH_3), 28.3 (CH_3). ATR-FTIR (thin film):

2952, 2867, 1731, 1582, 1454, 1217 cm^{-1}. HRMS (ESI) m/z calcd for $C_{18}H_{24}NO_2$ $(M+H)^+$: 286.1807, found 286.1817.



5.14l

3*H*-Indole 5.14l. The optimized procedure was followed by using 0.036 g of nitroarene **5.12l** (0.10 mmol), 0.0022 g of $Pd(OAc)_2$ (0.010 mmol), 0.0036 g of phenanthroline (0.020 mmol), 0.0264 g of $Mo(CO)_6$ (0.100 mmol) in 1.0 mL of 1,2-dichloroethane. Purification by MPLC (3:97–20:80 EtOAc:hexane) afforded the product, a yellow liquid, as a 90:10 mixture of diastereomers (0.016 g, 49%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.0 Hz, 1H), 7.45 (d, *J* = 7.5 Hz, 1H), 7.35 (t, *J* = 7.5 Hz, 1H), 7.18 (t, *J* = 7.5 Hz, 1H), 3.03 (d, *J* = 13.0 Hz, 1H), 2.96 (dt, *J* = 13.0 Hz, 3.0 Hz 1H), 2.54 (t, *J* = 12.0 Hz, 1H), 1.85 (dd, *J* = 10.5 Hz, 2.0 Hz, 1H), 1.46 – 1.41 (m, 2H), 1.37 (s, 9H), 1.08 – 1.01 (m, 1H), 0.96 (s, 8H), 0.93 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.5 (C), 169.0 (C), 155.2 (C), 139.7 (C), 128.6 (CH), 125.2 (CH), 122.3 (CH), 120.1 (CH), 82.3 (C), 65.5 (C), 51.5 (CH), 36.4 (CH_2), 33.0 (C), 32.6 (CH_2), 27.8 (CH_3), 27.5 (CH_3), 24.0 (CH_2); diagnostic data for minor diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.0 Hz, 0.08H), 1.34 (s, 1.20H), 0.91 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 128.5 (CH), 120.0 (CH), 27.8 (CH_3), 27.7 (CH_3). ATR-FTIR (thin film): 2963, 2868, 1725, 1582, 1367, 1256, 1151 cm^{-1}. HRMS (ESI) m/z calcd for $C_{21}H_{30}NO_2$ $(M+H)^+$: 328.2277, found 328.2272.

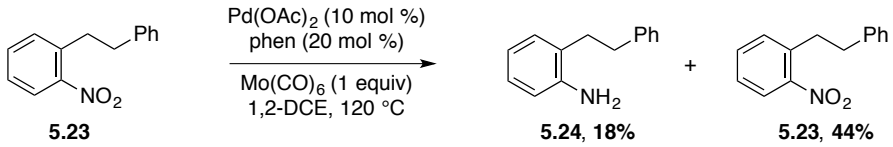


5.33

Indoline 5.33. The optimized procedure was followed by using 0.030 g of nitroarene **5.12m** (0.10 mmol), 0.0022 g of $Pd(OAc)_2$ (0.010 mmol), 0.0036 g of phenanthroline (0.020 mmol), 0.0264 g of $Mo(CO)_6$ (0.100 mmol) in 1.0 mL of 1,2-dichloroethane. Purification by MPLC (3:97 – 20:80 EtOAc:hexane) afforded the product a yellow solid (0.013 g, 49%): $[\alpha]_D^{25}$: –78.0 (c 0.100, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (d, *J* = 7.5 Hz, 1H), 7.06 (t, *J* = 7.5 Hz, 1H), 6.77 (t, *J* = 7.5 Hz, 1H), 6.69 (d, *J* = 8.0 Hz, 1H), 6.08 (t, *J* = 3.5 Hz, 1H), 4.76 (d, *J* = 7.0 Hz, 2H), 4.75 (s, 1H), 3.70 (s, 3H), 2.57 – 2.53 (m, 2H), 2.31 (dd, *J* = 12.5 Hz, 3.5 Hz, 1H), 2.21 – 2.16 (m, 1H), 1.87 (t, *J* = 12.5 Hz, 1H), 1.74 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.2 (C), 150.4 (C), 148.2 (C), 136.9 (C), 128.9 (CH), 126.8 (CH), 120.4 (CH), 120.0 (CH), 119.9 (CH), 110.8 (CH), 109.7 (CH_2), 70.3 (C), 52.8 (CH_3), 37.7 (CH), 36.8 (CH_2), 30.6 (CH_2), 20.2 (CH_3). ATR-FTIR (thin film): 3361, 3038, 2949, 2838, 1721, 1607, 1466, 1247, 1153, 1066, 894 cm^{-1}. HRMS (EI) m/z calcd for $C_{17}H_{20}NO_2$ $[M+H]^+$: 270.1494, found 270.1488.

F. Mechanistic Experiments.

1. Attempted Trap of Potential Metal *N*-aryl Nitrene Intermediate.

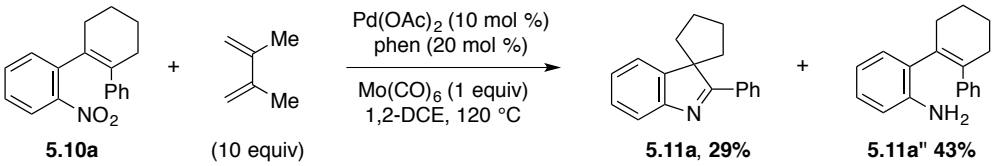


5.23 **5.24**, **18%** **5.23**, **44%**

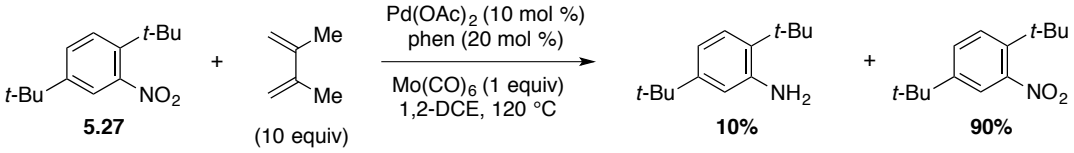
In a 10 mL Schlenk tube, under a nitrogen atmosphere, was added 0.023 g of 1-nitro-2-phenethylbenzene **5.23** (0.10 mmol) followed by 0.0022 g of $Pd(OAc)_2$ (0.01 mmol), 0.0036 g of phenanthroline (0.02 mmol), 0.026 g of $Mo(CO)_6$ (0.10 mmol) and 0.082 g 2,3-dimethyl-1,3-butadiene (1 mmol) in 1.0 mL of 1,2-dichloroethane. The Schlenk tube was sealed and heated at 120 °C for 6 h. The reaction mixture was then cooled down to

room temperature and filtered through a pad of silica gel. The filtrate was concentrated *in vacuo*. The resulting residue was analyzed using ^{1}H NMR spectroscopy using CH_2Br_2 as the internal standard.

2. Attempted Trap of *ortho*-substituted Nitrosoarene Intermediate with 2,3-butadiene.

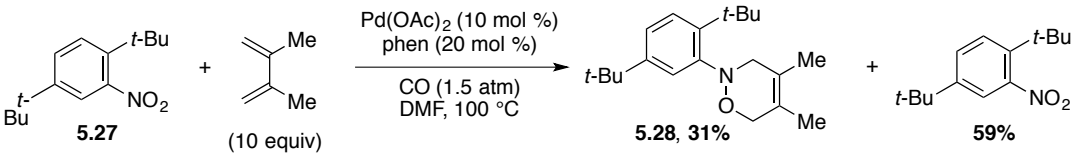


In a 10 mL Schlenk tube, under a nitrogen atmosphere, was added 0.028 g of nitroarene **2.9a** (0.10 mmol) followed by 0.0022 g of $Pd(OAc)_2$ (0.01 mmol), 0.0036 g of phenanthroline (0.02 mmol), 0.026 g of $Mo(CO)_6$ (0.10 mmol) and 0.082 g 2,3-dimethyl-1,3-butadiene (1 mmol) in 1.0 mL of 1,2-dichloroethane. The Schlenk tube was sealed and heated at 120 °C for 6 h. The reaction mixture was then cooled down to room temperature and filtered through a pad of silica gel. The filtrate was concentrated *in vacuo*. The resulting residue was analyzed using ^{1}H NMR spectroscopy using CH_2Br_2 as the internal standard.



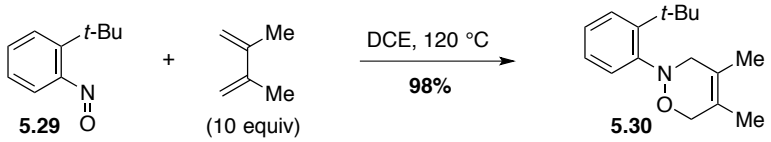
In a 10 mL Schlenk tube, under a nitrogen atmosphere, was added 0.024g of 1,4-di-*tert*-butyl-2-nitrobenzene (0.10 mmol) followed by 0.0022 g of $Pd(OAc)_2$ (0.01 mmol), 0.0036 g of phenanthroline (0.02 mmol), 0.026 g of $Mo(CO)_6$ (0.10 mmol) and 0.082 g 2,3-dimethyl-1,3-butadiene (1 mmol) in 1.0 mL of 1,2-dichloroethane. The Schlenk tube

was sealed and heated at 120 °C for 6 h. The reaction mixture was then cooled down to room temperature and filtered through a pad of silica gel. The filtrate was concentrated *in vacuo*. Analysis of the resulting residue using ^{1}H NMR spectroscopy with CH_2Br_2 as the internal standard revealed only the formation of aniline (10%).



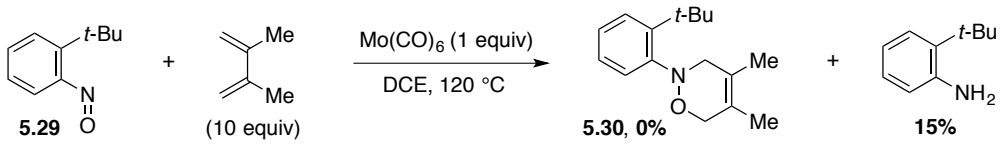
In a 10 mL Schlenk tube, under a nitrogen atmosphere, was added 0.024 g of 1,4-di-*tert*-butyl-2-nitrobenzene (0.10 mmol) followed by 0.0022 g of $Pd(OAc)_2$ (0.01 mmol), 0.0036 g of phenanthroline (0.02 mmol) and 0.082 g 2,3-dimethyl-1,3-butadiene (1 mmol) in 1.0 mL of DMF. The Schlenk tube was filled with CO gas (1.5 atm). The Schlenk tube was sealed and heated at 120 °C for 6 h. The reaction mixture was then cooled down to room temperature and filtered through a pad of silica gel. The filtrate was concentrated *in vacuo*. Analysis of the resulting residue using ^{1}H NMR spectroscopy with CH_2Br_2 as the internal standard revealed 31% formation of the oxazine **2.31**.

3. Reactivity of *o-tert*-butylnitrosobenzene toward 2,3-butadiene and metal complexes

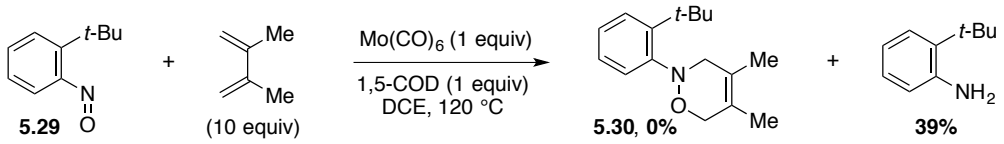


In a 10 mL Schlenk tube, under a nitrogen atmosphere, was added 0.016 g of 1-(*tert*-butyl)-2-nitrosobenzene (0.10 mmol) followed by 0.082 g 2,3-dimethyl-1,3-butadiene (1 mmol) in 1.0 mL of 1,2-dichloroethane. The schlenk tube was sealed and heated at

120 °C for 6 h. The reaction mixture was then cooled down to room temperature and filtered through a pad of silica gel. The filtrate was concentrated *in vacuo*. Analysis of the resulting residue using ^{1}H NMR spectroscopy using CH_2Br_2 as the internal standard revealed quantitative formation of oxazine **2.33**.



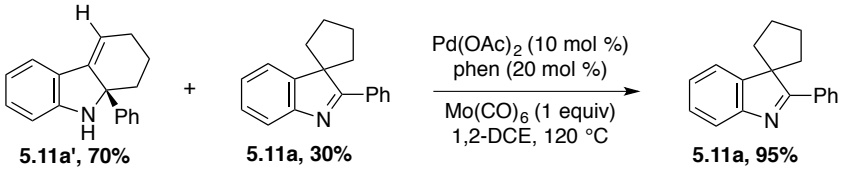
In a 10 mL Schlenk tube, under a nitrogen atmosphere, was added 0.016 g of 1-(*tert*-butyl)-2-nitrosobenzene (0.10 mmol) followed by 0.026 g of $Mo(CO)_6$ (0.10 mmol) and 0.082 g 2,3-dimethyl-1,3-butadiene (1 mmol) in 1.0 mL of 1,2-dichloroethane. The Schlenk tube was sealed and heated at 120 °C for 6 h. The reaction mixture was then cooled down to room temperature and filtered through a pad of silica gel. The filtrate was concentrated *in vacuo*. Analysis of the resulting residue using ^{1}H NMR spectroscopy with CH_2Br_2 as the internal standard revealed no oxazine **2.33**; only the formation of 2-*tert*-butyl aniline in 15%.



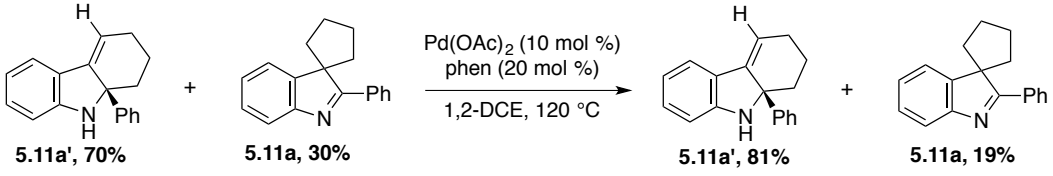
In a 10 mL Schlenk tube, under a nitrogen atmosphere, was added 0.016 g of 1-(*tert*-butyl)-2-nitrosobenzene (0.10 mmol) followed by 0.026 g of $Mo(CO)_6$ (0.10 mmol), 0.082 g 2,3-dimethyl-1,3-butadiene (1 mmol) and 0.011 g of 1,5-cyclooctadiene (0.1 mmol) in 1.0 mL of 1,2-dichloroethane. The Schlenk tube was sealed and heated at 120 °C for 6 h. The reaction mixture was then cooled down to room temperature and filtered through a pad of silica gel. The filtrate was concentrated *in vacuo*. Analysis of

the resulting residue using ^{1}H NMR spectroscopy with CH_2Br_2 as the internal standard mirrored the previous result: no oxazine **2.33** was formed, and 2-*tert*-butyl aniline was observed in 39%.

4. Examination of the mechanism [1,2] shift reaction.

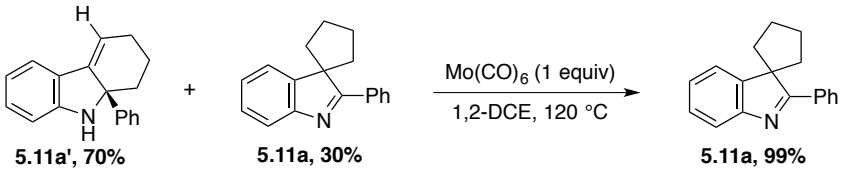


In a 10 mL Schlenk tube, under a nitrogen atmosphere, was added 0.005 g of 1*H*-carbazole **2.10a** (a 70:30 mixture of **2.10a** and **2.9a**, 0.02 mmol), followed by 0.0005 g of $Pd(OAc)_2$ (0.002 mmol), 0.0008 g of phenanthroline (0.004 mmol), 0.005 g of $Mo(CO)_6$ (0.02 mmol) in 0.2 mL of 1,2-dichloroethane. The Schlenk tube was sealed and heated at 120 °C for 12h. The reaction mixture was then cooled down to room temperature and filtered through a pad of silica gel. The filtrate was concentrated *in vacuo*. Analysis of the resulting residue using ^{1}H NMR spectroscopy with CH_2Br_2 as the internal standard revealed formation of **2.9a** in 95%.



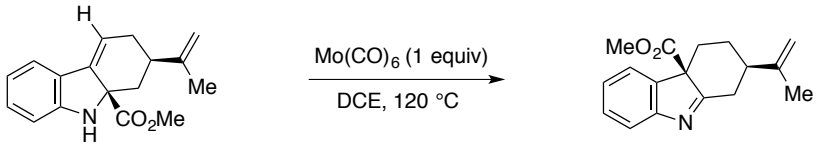
In a 10 mL Schlenk tube, under a nitrogen atmosphere, was added 0.005 g of 1*H*-carbazole **2.10a** (a 70:30 mixture of **2.10a** and **2.9a**, 0.02 mmol), followed by 0.005 g of $Mo(CO)_6$ (0.02 mmol) in 0.2 mL of 1,2-dichloroethane. The Schlenk tube was sealed and heated at 120 °C for 12h. The reaction mixture was then cooled down to room temperature and filtered through a pad of silica gel. The filtrate was concentrated *in*

vacuo. Analysis of the resulting residue using ^{1}H NMR spectroscopy with CH_2Br_2 as the internal standard revealed formation of **2.9a** in 99%.



5.11a', 70% **5.11a, 30%** **5.11a, 99%**

In a 10 mL Schlenk tube, under a nitrogen atmosphere, was added 0.005 g of 1*H*-carbazole **2.10a** (a 70:30 mixture of **2.10a** and **2.9a**, 0.02 mmol), followed by 0.005 g of $Mo(CO)_6$ (0.02 mmol) in 0.2 mL of 1,2-dichloroethane. The Schlenk tube was sealed and heated at 120 °C for 12h. The reaction mixture was then cooled down to room temperature and filtered through a pad of silica gel. The filtrate was concentrated *in vacuo*. Analysis of the resulting residue using ^{1}H NMR spectroscopy with CH_2Br_2 as the internal standard revealed formation of **2.9a** in 99%.



5.33 **5.34**

In a 10 mL Schlenk tube, under a nitrogen atmosphere, was added 0.0045 g of **2.35** (0.017 mmol), followed by 0.0045 g of $Mo(CO)_6$ (0.017 mmol) in 0.2 mL of 1,2-dichloroethane. The Schlenk tube was sealed and heated at 120 °C for 12h. The reaction mixture was then cooled down to room temperature and filtered through a pad of silica gel. The filtrate was concentrated *in vacuo*. Analysis of the resulting residue using ^{1}H NMR spectroscopy with CH_2Br_2 as the internal standard revealed formation of **2.16m** in 59%.

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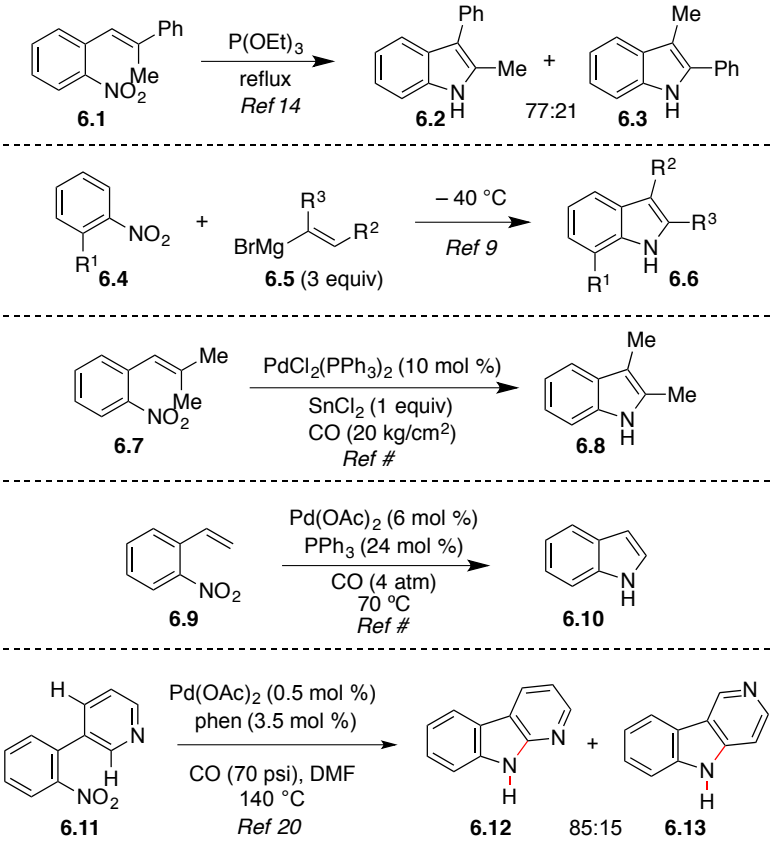
Chapter-VI
Promoting Reductive Cyclization of Nitroarenes by A Palladium Catalyst and Carbon Monoxide to Afford Indoline Heterocycles

Nitroarenes have the potential to construct carbon–nitrogen bond because of their widespread availability.[1-4] As such, significant research efforts have been directed toward developing transformationa to convert nitroarenes into important heterocycles such as indoles and carbazoles by forming C–N bonds from sp^2-C–H bonds.[5-7] Traditionally, these processes involve stoichiometric amount of reductants such as Grignard reagent,[8-11] triethyl phosphite,[12-15] zinc dust[16-17] or high pressure of carbon monoxide gas,[18-22] which limit their generality. For example, Sundberg and co-workers reported that nitrostyrene **6.1** produces mixture of regiosomers of indoles when refluxed with $P(OEt)_3$ (Scheme 6.1).[14] Bartoli and co-workers also reported that indoles could be formed from nitroarenes by using excess vinyl magnesium bromide **6.5**.[9] More recently catalytic transformations have emerged to access *N*-heterocycles from 2-substituted nitroarenes. The very first report by Watanabe, who developed palladium catalyzed and tin-mediated transformations of nitrostyrenes **6.7** to indoles **6.8**.[18] Following this report, Söderberg and Shriver developed a milder protocol using a palladium catalyst in the presence of carbon monoxide to synthesize indoles **6.10** and their method avoides the use of stoichiometric reagents.[19] Although these catalytic methods provided useful indoles, regioselective mixture of products was observed when 1,2-disubstituted nitrostyrenes were exposed to reaction conditions. For example, Smitrovich and Davies reported formation of regioisomeric mixture of carbolines from nitroarene **6.11** when exposed to a Pd-catalyst and a high pressure of CO gas.[20-21] While all these methods provide unsaturated *N*-

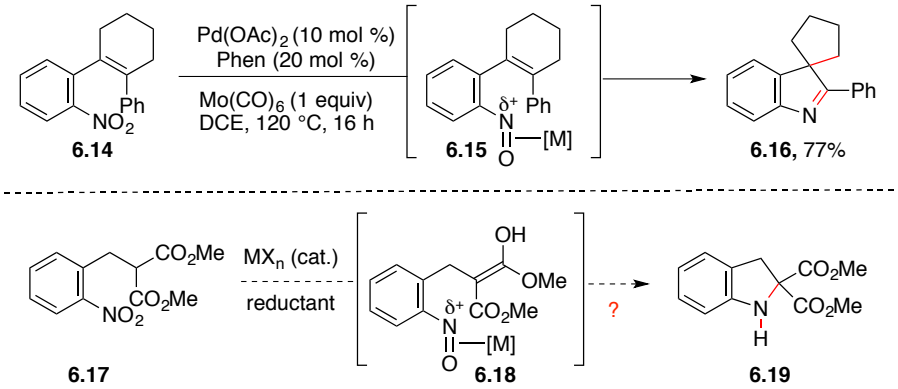
heterocycles, creating saturated heterocycles has been slow to emerge, and often associated with low yields and by-product formation.



Scheme 6.1. Reduction of nitrostyrenes using stoichiometric reagents

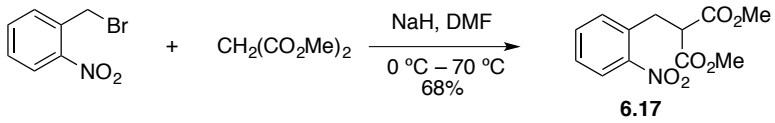
Our group research is centered on making C–N bonds by exploiting the reactivity of electrophilic metal–*N*-aryl intermediates.[23-33] We have used aryl azides as a source of *N*-atom and more recently we explored the reactivity of nitroarenes as an alternative source of *N*-atom.[34-36] Our recent results reveals that, spirocyclic 3*H*-indole **6.16** could be accessed from nitrostyrene **6.14** using 5 – 10 mol % of $Pd(OAc)_2$, phenanthroline as a ligand and stoichiometric amount of molybdenum hexacarbonyl (Scheme 6.2).[34] Our mechanism study suggested that the C–N bond was formed by either an electrocyclization[37-38] or a nucleophilic attack by adjacent π-electrons of the double bond

onto the metal-nitrosoarene intermediate. If it was the latter mechanism, we were interested if we could trap this electrophilic intermediate with a nucleophile, such as an enol or enolate, to create a new sp^3-C–NAr bond. Within this chapter, I describe my development of a new method for the formation of an sp^3-C–NAr bond from nitroarenes by exposure to a Pd(II)-catalyst and CO gas to produce indolines.



Scheme 6.2. Palladium catalyzed tandem cyclization-migration reaction

To test our assertion we chose nitroarene **6.17** as the model substrate, which which contained an *ortho*-malonate group. The designed nitroarene was prepared in one step by a nucleophilic substitution reaction of 2-nitrobenzyl bromide and dimethylmalonate (Scheme 6.3). Both the starting materials were obtained from commercial sources and the product was synthesized in high yields.

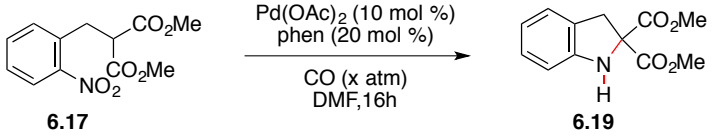


Scheme 6.3. Preparation of *ortho*-substituted nitroarenes

6.1. Development of optimal conditions

To determine if the nitrosoarene could be generated and intercepted with an enol, the reactivity of nitroarene **6.17** was examined toward a range of potential transition-metal catalysts and reductants (Table 6.1). First, a variety of transition metal catalysts were surveyed using 1 atm pressure of CO as the reductant. To our dismay, survey of common nitro-reduction catalysts such as Rh-,[39-40] Ru-[41] and Pt-complexes[42] produced only aniline, which cyclized with the adjacent ester substituent to produce amide. In contrast, $Pd(OAc)_2$ in combination with phenanthroline and CO as reductant did trigger the desired indoline with 69% yield. Increasing the pressure of CO gas had positive effect on the reaction outcome (entry 2). The reaction time was reduced to 3 hours without decrease in the yield (entry 3). The best result was obtained by decreasing the catalyst loading to 5 mol % (entry 4). Changing the identity of phenanthroline ligand or Pd-counter ion did not improve the reaction outcome: a reduced yield of indoline was obtained if tetramethlphenanthroline or $Pd(TFA)_2$ was used in place of phenanthroline or palladium acetate (entries 5 and 6). Next, different reductants were surveyed. To avoid the use of CO gas, $Mo(CO)_6$ was chosen which upon heating releases CO gas. Complete decomposition of the substrate was observed in presence of an equivalent amount of $Mo(CO)_6$ (entry 7). We attributed this outcome as a result of coordination between the β-keto ester and metal carbonyl complex, and decomposition of the β-keto ester occurs at high temperature. Finally, the effect of the temperature on the reaction outcome was examined: reducing the reaction temperature proved detrimental to this result (entry 8).

Table 1. Development of optimal conditions



6.17 6.19

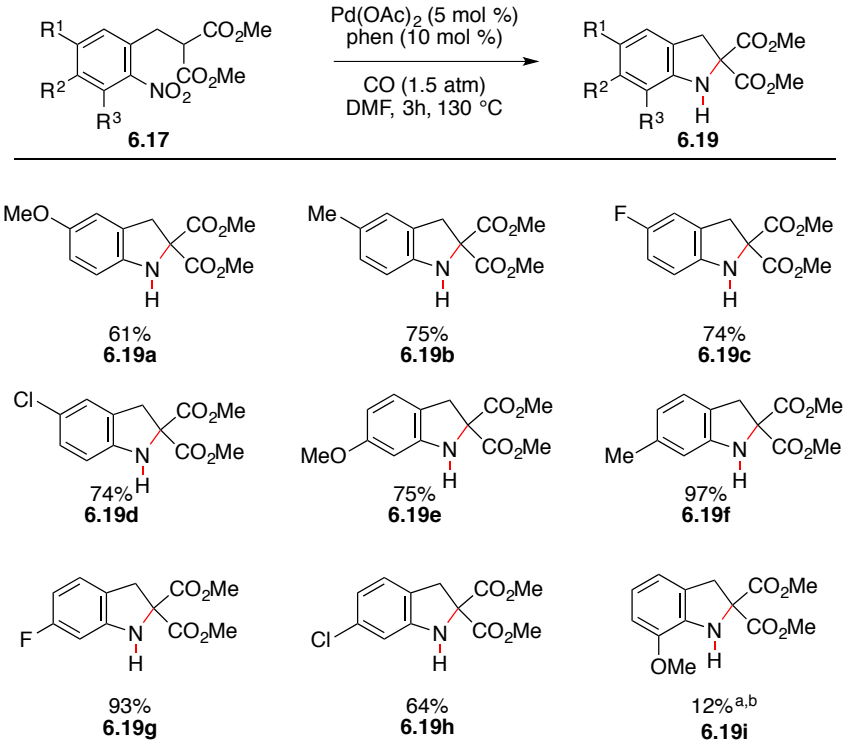
entry	catalyst	ligand (mol %)	reductant (atm)	T, °C	yield, %[a] 6.14
1	$Pd(OAc)_2$	phen	CO (1.0)	130	69
2	$Pd(OAc)_2$	phen	CO (1.5)	130	87
3[b]	$Pd(OAc)_2$	phen	CO (1.5)	130	87
4[b,c]	$Pd(OAc)_2$	phen	CO (1.5)	130	89
5[b]	$Pd(OAc)_2$	tmphen	CO (1.5)	130	65
6[b]	$Pd(TFA)_2$	phen	CO (1.5)	130	72
7	$Pd(OAc)_2$	phen	$Mo(CO)_6$	130	dec
8[b,c,d]	$Pd(OAc)_2$	phen	CO (1.5)	110	55

[a] As determined using ^{1}H NMR spectroscopy using CH_2Br_2 as the internal standard. [b] the reaction was run for 3 h. [c] 5 mol % $Pd(OAc)_2$ used. [d] 42% SM recovered. dec = decomposition products observed.

6.2. Examination of the electronic nature of nitroarenes

Using the optimal conditions, we explored the scope and limitations of the reductive cyclization reaction (Table 6.2). First, the effect of changing the substituents on the nitroarene was examined. To our delight, we found that our reaction tolerated a range of both electron-donating and -withdrawing R^1- and R^2-substituents (**6.19a** – **6.19h**). In contrast, increasing the steric environment around the nitro group by adding an *ortho*-methoxy substituent had an adverse effect on the reaction outcome to provide the indoline in a lower yield (**6.19i**).

Table 6.2. Examination of the electronic nature of nitroarenes



Yield represents isolated yield after silica gel chromatography.

[a] 10 mol % $Pd(OAc)_2$ used. [b.] 80% SM left.

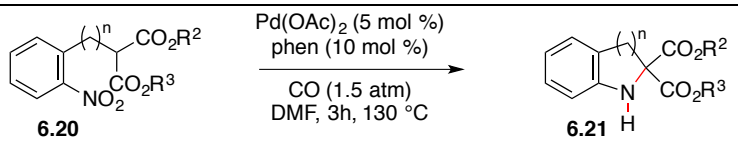
6.3. Scope and limitations of indoline formation

Next, the scope of the reaction was surveyed by changing the identity of C–H reaction site of the nitroarenes (Table 6.3). First, the ring size of the reductive cyclization was examined: while tetrahydroquinoline **6.21a** was formed smoothly, benzoazepine **6.21b** heterocycles was produced in only 12% (entries 1 and 2). Benzoazepine **6.21b** was accompanied with the formation of several by-products including a partially saturated benzoazepine where elimination of one methylcarboxylate group had occurred. Second, the effect of adding an additional α-methyl substituent to the *ortho*-alkyl substituent of the nitroarenes was investigated: both indoline and tetrahydroquinolines were formed

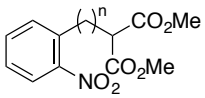
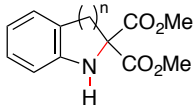
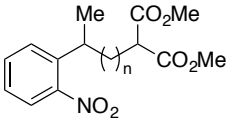
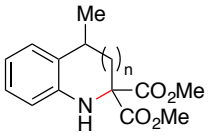
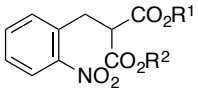
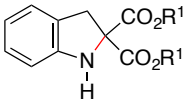
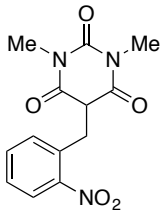
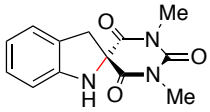
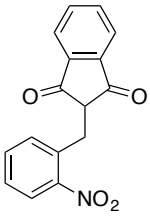
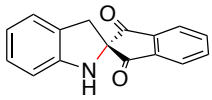
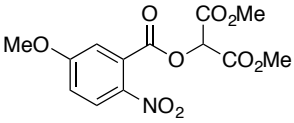
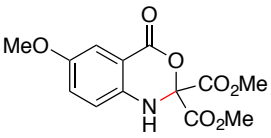
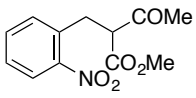
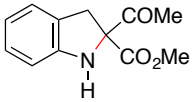
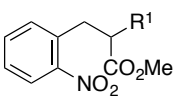
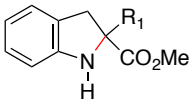
smoothly (entries 3 and 4). Third, the identity of the carboxylate R^1- and R^2-substituents in nitroarene substrates were changed in order to examine the effect toward reductive cyclization reaction. While diisopropyl malonate-derived nitroarene underwent the reaction smoothly, di-*tert*-butyl malonate- or *tert*-butyl ethyl malonate-derived nitroarenes produced indolines in attenuated yield (entries 5 – 7). Fourth, we anticipated that changing identity of the malonate to a cyclic 1,3-diamide- or -diketo-substituent in the nitroarene substrates could provide spirocyclic indolines. In line with our hypothesis, exposure of barbituric acid-derived **6.20h** or 1,3-indanone-derived **6.20i** to the reaction conditions furnished corresponding indolines **6.21h** or **6.21i** in moderate yield. Fifth, the effect of changing the atom-composition of the tether of the nitroarene was investigated: 2-nitrobenzoic acid derived **6.20j** afforded oxazine **6.21j**, albeit in reduced yield. The effect of changing pK_a of the C–H reaction center was investigated next. Towards this end, we synthesized substrates where one of the ester-substituents was replaced with a different electron-withdrawing group. We observed that exposure of methyl acetoacetate derived nitroarene **6.20k** under reaction conditions provided the indoline in reduced yield (entry 11). To our dismay, replacing one of the esters with a nitro- or cyano substituent proved detrimental, and only decomposition of the starting materials was observed (entry 12). We explained this outcome as a result of decrease in pK_a of the reaction center facilitating generation of the stable enolate nucleophile, which decomposes under reaction conditions. Finally, to test if C–N bond formation could be triggered by other nucleophiles, a nitroarene containing a furan nucleophile was examined (entry 13). Gratifyingly, furan-derived nitroarene **6.20m** underwent reductive cyclization reaction

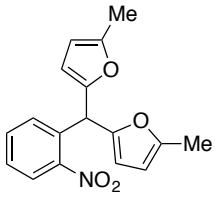
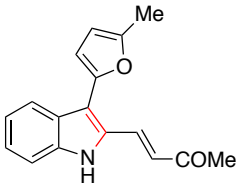
under the reaction conditions followed by furan ring-opening occured to afford 2,3-disubstituted indole **6.21m**.

Table 6.3. Scope and limitations of indoline formation



6.20 **6.21**

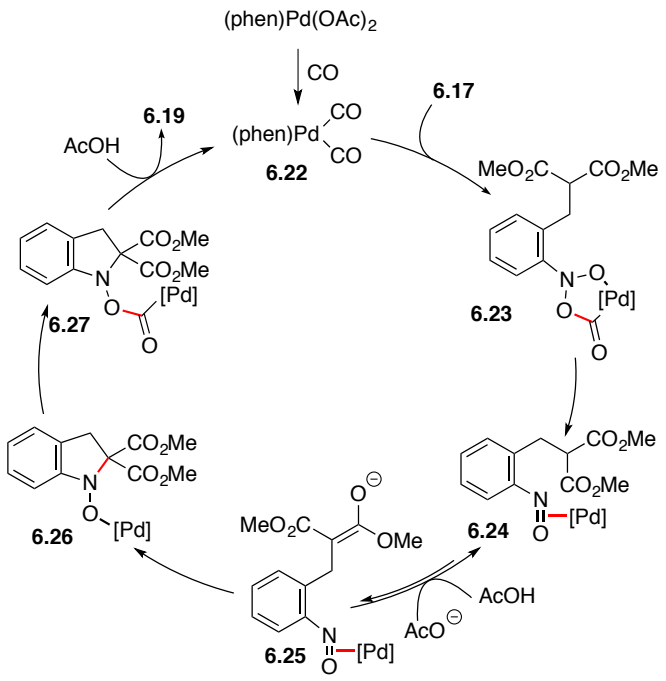
entry	#	nitroarene	indoline	yield, %[a]
1	a			91, n = 2
2	b			12, n = 3[b]
3	c			93, n = 0
4	d			89, n = 1
5	e			90, $R^1 = R^2 = i$Pr
6	f			56, $R^1 = R^2 = t$Bu[c]
7	g			59, $R^1 = t$Bu, R^2 = Et
8	h			54
9	i			59
10	j			46
11	k			35[d]
12	l			R^1 = -CN, -NO_2 dec[e]

13	m			52

[a] Isolated after silica gel chromatography. [b] 20 mol % $Pd(OAc)_2$ used. [c] 8% of *tert*-butylindole-2-carboxylate was observed. [d] 35% quinolone *N*-oxidede was formed. [e] dec = decomposition occurred upon heating.

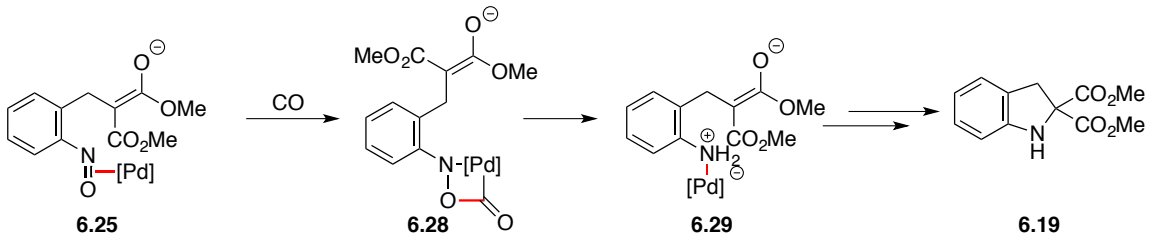
6.4. Possible mechanism for the indoline formation

Based on the reactivity trend of our substrates and literature precedence, we have proposed a plausible mechanism for the reductive C–N bond forming reaction (Scheme 6.4).[43-45] Reduction of phenanthroline-palladium complex by CO would produce palladium-carbon monoxide complex **6.22**, which, which could exist as a monomer or cluster.[47-49] The active complex **6.22** could form five-membered paladacycle **6.23** with nitroarene **6.17** by oxidative addition.[50-51] Extrusion of CO_2 produces palladium-nitrosoarene intermediate **6.24**. The difference in pK_a between acetic acid (4.75) and malonate (13.0) suggest that enolate (**6.25**) formation occurs after the generation of nitrosoarene intermediate. Cyclization of **6.25** could occur through nucleophilic attack of the enolate to the electrophilic palladium-nitrosoarene complex to produce **6.26**.[52-53] Reduction of N–O bond in **6.26** generates CO_2 and indoline **6.19**.



Scheme 6.4. Possible mechanism for indoline formation

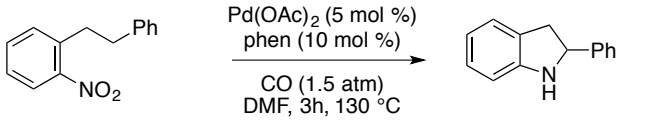
We have also proposed an alternative pathway for the reductive cyclization reaction involving a metal-nitrene intermediate (Scheme 6.5). We envisioned that CO could undergo an oxidative insertion to palladium-nitrosoarene intermediate to produce **6.26**.[54] Extrusion of CO_2 generates palladium-nitrene intermediate **6.27**. Nucleophilic attack by the enolate in **6.27** or C–H bond amination of the methine proton would produce indoline **6.19**.



Scheme 6.5. Formation of metal-nitrene intermediate

6.5. Mechanistic investigation

A mechanistic experiment was performed to see if the metal-nitrene reactive intermediate was involved in the reductive cyclization reaction. We prepare nitroarene **6.30**, which has a benzylic C–H bond and exposed the nitroarene to the optimal conditions (Scheme 6.6). We expected that if metal-nitrene intermediate was involved during the reaction, indoline **6.31** would be formed as a product,[55-56] however, no C–H bond amination was observed; only decomposition of the starting material was observed. This data suggests that, Pd-nitrene species was not involved in the reductive cyclization reaction.

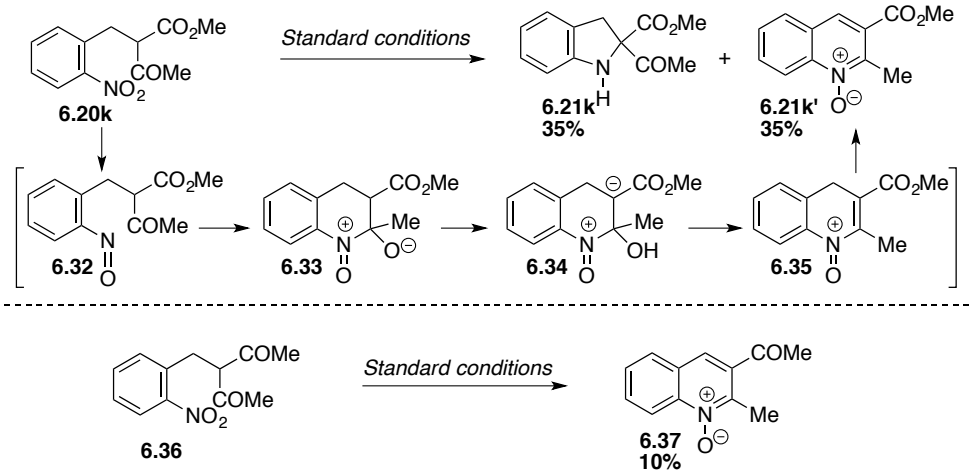


6.30 **6.31, *not observed***

Scheme 6.6. Test to intercept potential nitrene intermediate

Next, we want to investigate if our reductive cyclization reaction involves generation of a nitrosoarene intermediate. The intermediate was confirmed serendipitously while studying the reactivity of methyl acetoacetate-derived nitroarene **6.20k**: exposure of it to the optimal conditions produced indoline **6.21k** and quinoline *N*-oxide **6.21k'** in 1:1 ratio (Scheme 6.7). We attribute the formation of quinoline *N*-oxide to a palladium-nitrosoarene intermediate. Because of mismatching reactivity between the electrophilic- and nucleophilic components (or low pK_a of the reaction site), the palladium complex is released. The resulting free nitrosoarene then acts as a nucleophile to undergo reaction with electrophilic ketone partner to produce the tetrahedral intermediate (**6.33**).[57-61] Aromatization occurs through elimination of hydroxide produces **6.34** followed by deprotonation to produce quinoline *N*-oxide. Cyclization of the nitroso group onto a pendant methyl ketone was not an isolated phenomenon: exposure of nitroarene **6.36**, which contains a 1,3-dione *ortho*-substituent to reaction conditions,

produced quinoline *N*-oxide **6.37** albeit in low yield. It is still unknown whether palladium is involved during the reduction of *N*-oxide intermediate. Further mechanistic investigation is underway in our laboratory.



Schene 6.7. Formation of quinoline *N*-oxide from methyl ketone-containing substrates

6.6. Conclusion:

In this project, we demonstrated that sp^3-C–N bonds can be produced through a Pd-catalyzed a reductive cyclization of nitroarenes to furnish indolines. Our data suggests that the cyclization is going through a nitrosoarene intermediate. Our future studies are focused on exploring the reactivity of the metal-nitrosoarene intermediate to streamline complex functionalized *N*-heterocycles from readily available *ortho*-substituted nitroarenes.

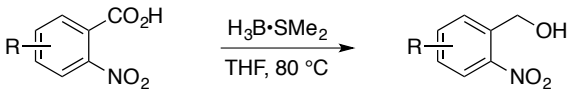
6.7. Experimental

General. ^{1}H NMR and ^{13}C NMR spectra were recorded at ambient temperature using 500 MHz or 300 MHz spectrometers. The data are reported as follows: chemical shift in ppm from internal tetramethylsilane on the δ scale, multiplicity (br = broad, s = singlet, d =

doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz) and integration. High-resolution mass spectra were obtained by peak matching. Melting points are reported uncorrected. Infrared spectroscopy was obtained using a diamond attenuated total reflectance (ATR) accessory. Analytical thin layer chromatography was performed on 0.25 mm extra hard silica gel plates with UV254 fluorescent indicator. Liquid chromatography was performed using forced flow (flash chromatography) of the indicated solvent system on 60Å (40 – 60 μm) mesh silica gel (SiO_2). Medium pressure liquid chromatography (MPLC) was performed to force flow the indicated solvent system down columns that had been packed with 60Å (40 – 60 μm) mesh silica gel (SiO_2). All reactions were carried out under an atmosphere of nitrogen in glassware, which had been oven-dried. Unless otherwise noted, all reagents were commercially obtained and, where appropriate, purified prior to use. Acetonitrile, Methanol, Toluene, THF, Et_2O, and CH_2Cl_2 were dried by filtration through alumina according to the procedure of Grubbs.[62] Metal salts were stored in a nitrogen atmosphere dry box.

2.7.1 Preparation of substituted 2-Nitrobenzyl alcohols

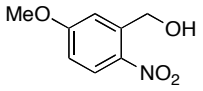
A. General Procedure.



To a 2M solution of the substituted 2-nitrobenzoic acid in dried THF was added drop wise a 10 M solution of borane dimethylsulfide complex (1.1– 1.3 equiv). The resulting solution was heated to 80 °C. After 3 hours, a 3 M aqueous solution of hydrochloric acid was added drop wise into this reaction system until effervescence was no longer observed.

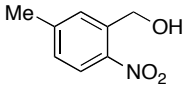
The resulting mixture was then extracted with 3 × 30 mL of ethyl acetate. The combined organic phases were washed with a saturated aqueous solution of Na_2CO_3 followed by brine. The resulting organic phase was dried over Na_2SO_4 and filtered. The filtrate was concentrated in *vacuo* to afford the product.

B. Synthesis of Substituted 2-Nitrobenzyl alcohol



s6.1a

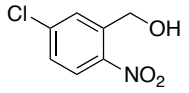
(5-Methoxy-2-nitrophenyl)methanol s6.1a.[63] The general procedure was followed using 3.67 g of 5-methoxy-2-nitrobenzoic acid (18 mmol) in 100 mL THF and 2.3 mL of BH_3-Me_2S (23 mmol, 1.3 equiv). Purification by extraction afforded the product as a white solid (2.97 g, 90%). The spectral data for **s6.1** matched that reported by Kanjilal and co-workers:[63] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (d, J = 9.1 Hz, 1H), 7.22 (s, 1H), 6.88 (d, J = 8.7 Hz, 1H), 4.99 (s, 2H), 3.91 (s, 3H), 2.73 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.2 (C), 140.3 (C), 128.0 (CH), 114.2 (CH), 113.2 (CH), 62.9 (CH_2), 56.0 (CH_3) only visible signals. ATR-FTIR (thin film): 3390, 2983, 1511, 1239, 1025 cm^{-1}.



s6.1b

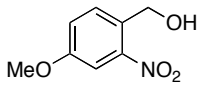
(5-Methyl-2-nitrophenyl)methanol s6.1b.[64] The general procedure was followed using 4.36 g of 5-methyl-2-nitrobenzoic acid (22.9 mmol) in 150 mL THF and 3.0 mL of BH_3-Me_2S (30 mmol, 1.3 equiv). Purification by extraction afforded the product as a white solid (3.82 g, 100%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, J = 8.3 Hz, 1H), 7.51 (s, 1H), 7.24 (d, J = 8.6 Hz, 1H), 4.93 (s, 2H), 2.69 (s, 1H), 2.45 (s, 3H); ^{13}C NMR (125 MHz,

$CDCl_3$) δ 145.7 (C), 145.4 (C), 136.8 (C), 130.6 (CH), 129.0 (CH), 125.3 (CH), 62.8 (CH_2), 21.6 (CH_3). ATR-FTIR (thin film): 3291, 2942, 1512, 1334, 1035 cm^{-1}.



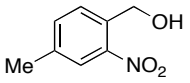
s6.1c

(5-Chloro-2-nitrophenyl)methanol s6.1c.[65] The general procedure was followed using 5.8 g of 5-methoxy-2-nitrobenzoic acid (28.5 mmol) in 150 mL of of THF and 3.2 mL of BH_3-Me_2S (32 mmol, 1.1 equiv). Purification by extraction afforded the product as a white solid (5.34 g, 100%). The spectral data matched that reported by Naganawa and co-workers:[65] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, J = 9.0 Hz, 1H), 7.81 (d, J = 2.0 Hz, 1H), 7.42 (dd, J = 8.5, 2.5 Hz, 1H), 5.01 (s, 2H), 2.49 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.4 (C), 140.9 (C), 139.2 (C), 129.4 (CH), 128.3 (CH), 126.6 (CH), 62.0 (CH_2). ATR-FTIR (thin film): 3100–3450, 1604, 1502 cm^{-1}.



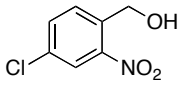
s6.1d

(4-Methoxy-2-nitrophenyl)methanol s6.1e.[66] The general procedure was followed using 3.91 g of 4-methoxy-2-nitrobenzoic acid (19.2 mmol) in 150 mL THF and 2.5 mL of BH_3-Me_2S (25 mmol, 1.3 equiv). Purification by extraction afforded the product as a white solid (3.52 g, 100%). The spectral data for **s6.4** matched that reported by Katitzky and co-workers:[66] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (d, J = 2.9 Hz, 1H), 7.56 (s, 1H), 7.18 (dd, J = 8.6, 2.5 Hz, 1H), 4.85 (s, 2H), 3.87 (s, 3H), 2.73 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.4 (C), 148.5 (C), 131.5 (CH), 128.8 (C), 120.4 (CH), 109.7 (CH), 62.3 (CH_2), 55.9 (CH_3). ATR-FTIR (thin film): 3253, 2836, 1512, 1303 cm^{-1}.



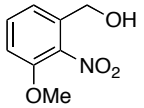
s6.1e

(4-Methyl-2-nitrophenyl)methanol s6.1e.[67] The general procedure was followed using 2.9210 g of 5-methoxy-2-nitrobenzoic acid (15.6 mmol) in 100 mL THF and 2.1 mL of BH_3-Me_2S (21 mmol, 1.3 equiv). Purification by extraction afforded the product as a white solid (2.39 g, 91%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.57 (d, J = 7.0 Hz, 1H), 7.45 (d, J = 6.3 Hz, 1H), 4.88 (s, 2H), 2.75 (s, 1H), 2.43 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.6 (C), 139.1 (C), 134.9 (CH), 133.8 (C), 130.0 (CH), 125.3 (CH), 62.4 (CH_2), 20.8 (CH_3). ATR-FTIR (thin film): 3181–3406, 3080, 1516, 1347 cm^{-1}. HRMS (EI) *m/z* calculated for $C_8H_8O_3N$ $(M–H)^+$: 166.05042, found: 166.05021.



s6.1f

(4-Chloro-2-nitrophenyl)methanol s6.1f.[68] The general procedure was followed using 6.50 g of 4-chloro-2-nitrobenzoic acid (31.3 mmol) in 150 mL THF and 4.2 mL of BH_3-Me_2S (42 mmol, 1.3 equiv). Purification by extraction afforded the product as a yellow solid (5.86 g, 100%). The spectral data for **s6.6f** matched that reported by Blanc and Bochet:[68] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, J = 1.6 Hz, 1H), 7.72 (d, J = 8.3 Hz, 1H), 7.63 (dd, J = 8.2, 1.7 Hz, 1H), 4.96 (s, 2H), 2.63 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.7 (C), 135.4 (C), 134.2 (C), 134.1 (CH), 130.9 (CH), 125.0 (CH), 61.9 (CH_2). ATR-FTIR (thin film): 3279, 1512, 1341, 1031 cm^{-1}.

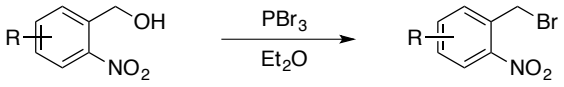


s6.1g

(3-Methoxy-2-nitrophenyl)methanol s6.1g. The general procedure was followed using 5.02 g of 5-methoxy-2-nitrobenzoic acid (24.4 mmol) in 150 mL THF and 2.9 mL of BH_3-Me_2S (29 mmol, 1.2 equiv). Purification by extraction afforded the product as a white solid (4.47 g, 100%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (t, J = 8.1 Hz, 1H), 7.09 (d, J = 7.6 Hz, 1H), 6.99 (d, J = 8.4 Hz, 1H), 4.61 (s, 2H), 3.88 (s, 3H), 2.54 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.1 (C), 140.1 (C), 134.4 (C), 131.7 (CH), 120.5 (CH), 112.2 (CH), 60.9 (CH_2), 56.5 (CH_3). ATR-FTIR (thin film): 3372, 1526, 1369, 1275, 1035 cm^{-1}.

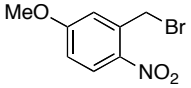
2.7.2 Preparation of Substituted 1-(Bromomethyl)-2-nitrobenzenes

A. General Procedure



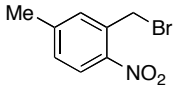
To a solution of substituted (2-nitrophenyl) methanol in Et_2O (0.1 M) was added PBr_3 (2 equiv). After 3 hours, a saturated aqueous solution of $NaHCO_3$ was added dropwise to the reaction mixture until a neutral pH was obtained. The resulting mixture was extracted with 1 × 30 mL of ethyl acetate, and the resulting organic phase washed with brine. The resulting organic phase was dried over Na_2SO_4, filtered and concentrated in *vacuo* to afford the product.

B. Synthesis of Substituted 1-(Bromomethyl)-2-nitrobenzenes



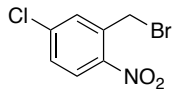
s6.2

2-(Bromomethyl)-4-methoxy-1-nitrobenzene s6.2a.[69] The general procedure was followed by using 2.75 g of **s6.1a** (15 mmol) in 150 mL of diethyl ether and 2.8 mL of PBr_3 (30 mmol). Purification by extraction afforded the product as a yellow oil (3.65 g, 99%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (d, J = 9.1 Hz, 1H), 7.02 (d, J = 2.7 Hz, 1H), 6.92 (dd, J = 9.1, 2.7 Hz, 1H), 4.86 (s, 2H), 3.91 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 6 δ 135.7 (C), 128.4 (CH), 117.6 (CH), 114.0 (CH), 56.1 (CH_3), 29.9 (CH_2) only visible signals. ATR-FTIR (thin film): 2982, 2936, 2909, 1513, 1259, 1022 cm^{-1}.



s6.2b

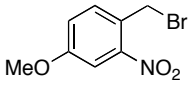
2-(Bromomethyl)-4-methyl-1-nitrobenzene s6.2b.[70] The general procedure was followed by using 3.89 g of **s6.2a** (23.2 mmol) in 180 mL of ethyl ether and 4.4 mL of PBr_3 (46 mmol). Purification by extraction afforded the product as a yellow solid (4.7 g, 88%). The spectral data of **s6.2b** matched that reported by McAllister and co-workers:[70] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (d, J = 8.3 Hz, 1H), 7.32 (s, 1H), 7.23 (d, J = 8.3 Hz, 1H), 4.77 (s, 2H), 2.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.5 (C), 145.3 (C), 133.1 (CH), 132.8 (C), 130.2 (CH), 125.7 (CH), 29.5 (CH_2), 21.4 (CH_3). ATR-FTIR (thin film): 3068.2, 1511.9, 1313.3, 826.3 cm^{-1}.



s6.2c

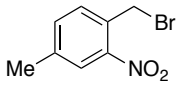
2-(Bromomethyl)-4-chloro-1-nitrobenzene s6.2c.[70] The general procedure was followed by using 5.32 g of **s6.1c** (28.3 mmol) in 100 mL of ethyl ether and 5.35 mL of

PBr_3 (56.6 mmol). Purification by extraction afforded the product as a yellow oil (6.98 g, 99%). The spectral data of **s6.2c** matched that reported by McAllister and co-workers:[70] ^{1}H NMR (500MHz, $CDCl_3$) 8.01 (d, J = 7.5 Hz, 1H), 7.57 (d, J = 2.0 Hz, 1H), 7.45 (dd, J = 8.5, 2.0 Hz, 1H), 4.78 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.1 (C), 140.1 (C), 134.8 (C), 132.5 (CH), 129.7 (CH), 127.1 (CH), 28.2 (CH_2). ATR-FTIR (thin film): 3107, 3070, 1519, 1333 cm^{-1}.



s6.2d

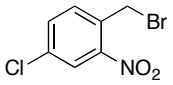
1-(Bromomethyl)-4-methoxy-2-nitrobenzene s6.2d.[70] The general procedure was followed by using 3.40 g of **s6.1d** (18.6 mmol) in 150 mL of diethyl ether and 3.5 mL of PBr_3 (37.2 mmol). Purification by extraction afforded the product as a yellow oil (4.51 g, 99%). The spectral data of **s6.2d** matched that reported by McAllister and co-workers:[70] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, J = 2.4 Hz, 1H), 7.43 (d, J = 8.6 Hz, 1H), 7.10 (dd, J = 8.5, 2.4 Hz, 1H), 4.77 (s, 2H), 3.86 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.1 (C), 148.6 (C), 133.6 (CH), 124.7 (C), 119.9 (CH), 110.5 (CH), 56.0 (CH_3), 29.3 (CH_2). ATR-FTIR (thin film): 2952, 1515, 1363, 1282 cm^{-1}.



s6.2e

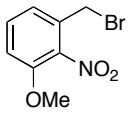
1-(Bromomethyl)-4-methyl-2-nitrobenzene s6.2e.[70] The general procedure was followed by using 2.30 g of **s6.1e** (13.7 mmol) in 50 mL of diethyl ether and 2.60 mL of PBr_3 (27.5 mmol). Purification by extraction afforded the product as yellow oil (3.12 g, 99%). The spectral data of **s6.2e** matched that reported by McAllister and co-workers:[70]

^{1}H NMR (500MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.44 – 7.39 (m, 2H), 4.79 (s, 2H), 3.29 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.8 (C), 140.5 (C), 134.5 (CH), 132.4 (CH), 129.9 (C), 125.9 (CH), 29.1 (CH_2), 21.0 (CH_3). ATR-FTIR (thin film): 3056, 2924, 2870, 1523, 1343 cm^{-1}. HRMS (EI) *m/z* calculated for $C_8H_8O_2NBr$ $(M)^+$: 228.97383, found: 228.97442.



s6.2f

1-(Bromomethyl)-4-chloro-2-nitrobenzene s6.2f.[70] The general procedure was followed by using 6.51 g of **s6.f** (34.7 mmol) in 150 mL of diethyl ether and 6.5 mL of PBr_3 (69 mmol). Purification by extraction afforded the product as yellow oil (8.25 g, 95%). The spectral data matched of **s6.2f** that reported by McAllister and co-workers:[70] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, *J* = 1.8 Hz, 1H), 7.56 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.52 (d, *J* = 8.3 Hz, 1H), 4.76 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.2 (C), 135.4 (C), 133.8 (CH), 133.7 (CH), 131.4 (C), 125.6 (CH), 28.1 (CH_2). ATR-FTIR (thin film): 3086, 2866, 1526, 1343 cm^{-1}.



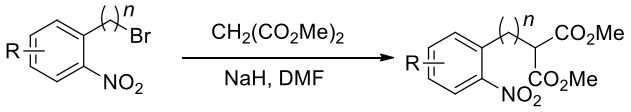
s6.2g

1-(Bromomethyl)-3-methoxy-2-nitrobenzene s6.2g. The general procedure was followed by using 4.85 g of **s6.1g** (26.5 mmol) in 150 mL of diethyl ether and 5.0 mL of PBr_3 (53 mmol). Purification by extraction afforded the product as a white solid (5.27 g, 81%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (t, *J* = 8.1 Hz, 1H), 7.08 (d, *J* = 7.8 Hz, 1H), 7.01 (d, *J* = 8.1 Hz, 1H), 4.42 (s, 2H), 3.90 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.2

(C), 140.7 (C), 131.7 (CH), 130.8 (C), 122.5 (CH), 113.1 (CH), 56.7 (CH_3), 26.3 (CH_2). ATR-FTIR (thin film): 2952, 1515, 1362, 1282, 1075 cm^{-1}.

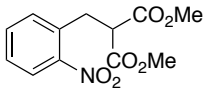
C. Preparation of Malonate Ester Substrate.

I. General Procedure.



To a solution of 0.17 mL dimethyl malonate (1.1 mmol) in DMF (4 mL) was slowly added 0.044 g of sodium hydride (1.1 mmol, 60% in oil) and the mixture stirred for 15 min at 40 ºC. The mixture was then cooled to 0 ºC. 2-Nitrobenzyl bromide (0.216 g, 1.0 mmol) was added at 0 ºC. The reaction mixture was warmed to 70 ºC and stirred for a further 3 h, then poured into 10% HCl. The solution was extracted with 2 × 10 mL of ethyl acetate followed by 10 mL of brine. The resulting organic phase was dried over Na_2SO_4 and was concentrated *in vacuo*. Purification by MPLC (3:97 to 10:90 EtOAc: hexane) afforded the product.

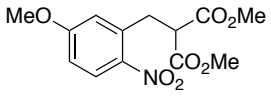
II. Preparation of the substrate



6.17

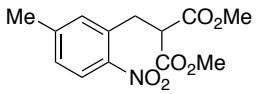
Malonate 6.17. The general procedure was followed by using 0.17 mL of dimethyl malonate (1.1 mmol), 0.044 g of sodium hydride (1.1 mmol, 60% in oil), 0.216 g of 2-nitrobenzyl bromide (1.0 mmol) in 4 mL of DMF. Purification by MPLC (3:97 to 10:90 EtOAc: hexane) afforded the product as a light yellow solid (0.182 g, 68%) ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, J = 8.0 Hz, 1H), 7.53 (t, J = 7.5 Hz, 1H), 7.43 – 7.38 (m,

2H), 3.92 (t, J = 7.5 Hz, 1H), 3.70 (s, 6H), 3.51 (d, J = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.9 (C), 142.2 (C), 140.9 (C), 133.3 (CH), 133.0 (CH), 128.3 (CH), 125.3 (CH), 52.7 (CH_3), 52.2 (CH), 32.2 (CH_2). ATR-FTIR (thin film): 3001, 2956, 1740, 1715, 1522, 1435, 1344, 1216, 1142, 858, 787 cm^{-1}. HRMS (ESI) m/z calculated for $C_{13}H_{13}NO_6Na$ $(M+H)^+$: 291.0641, found: 298.0647.



6.17a

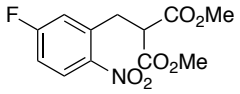
Malonate 6.17a. The general procedure was followed by using 0.17 mL of dimethyl malonate (1.1 mmol), 0.044 g of sodium hydride (1.1 mmol, 60% in oil), 0.246 g of 4-methoxy-2-nitrobenzyl bromide (1.0 mmol) in 4 mL of DMF. Purification by MPLC (3:97 to 10:90 EtOAc: hexane) afforded the product as a white solid (0.154 g, 52%) ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (d, J = 9.0 Hz, 1H), 6.85 (d, J = 9.0 Hz, 1H), 6.82 (s, 1H), 3.92 (t, J = 7.5 Hz, 1H), 3.86 (s, 3H), 3.71 (s, 3H), 3.52 (d, J = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.0 (C), 163.2 (C), 141.9 (C), 136.2 (C), 128.2 (CH), 117.9 (CH), 113.2 (CH), 55.9 (CH_3), 52.7 (CH_3), 51.9 (CH), 33.2 (CH_2). ATR-FTIR (thin film): 2952, 2848, 1733, 1608, 1580, 1514, 1435, 1338, 1259, 1155, 1083, 908 cm^{-1}. HRMS (ESI) m/z calculated for $C_{13}H_{16}NO_7$ $(M+H)^+$: 298.0927, found: 298.0926.



6.17b

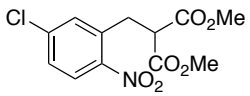
Malonate 6.17b. The general procedure was followed by using 0.17 mL of dimethyl malonate (1.1 mmol), 0.044 g of sodium hydride (1.1 mmol, 60% in oil), 0.230 g of 4-methyl-2-nitrobenzyl bromide (1.0 mmol) in 4 mL of DMF. Purification by MPLC (3:97 to 10:90 EtOAc: hexane) afforded the product as a yellow liquid (0.258 g, 92%). ^{1}H

NMR (500 MHz, $CDCl_3$) δ 7.94 (d, *J* = 10.5 Hz, 1H), 7.18 (d, *J* = 10.5 Hz, 1H), 7.15 (s, 1H), 3.90 (t, *J* = 9.5 Hz, 1H), 3.70 (s, 6H), 3.48 (d, *J* = 9.0 Hz, 2H), 2.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.0 (C), 144.8 (C), 144.6 (C), 133.5 (CH), 133.1 (C), 128.9 (CH), 125.5 (CH), 52.6 (CH_3), 52.1 (CH), 32.4 (CH_2), 21.4 (CH_3). ATR-FTIR (thin film): 3004, 2952, 2852, 1746, 1728, 1519, 1436, 1335, 1301, 1227, 1153, 839 cm^{-1}. HRMS (ESI) m/z calculated for $C_{13}H_{16}NO_6$ $(M+H)^+$: 282.0978, found: 282.0972.



6.17c

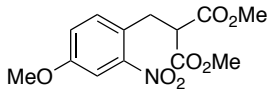
Malonate 6.17c. The general procedure was followed by using 0.17 mL of dimethyl malonate (1.1 mmol), 0.044 g of sodium hydride (1.1 mmol, 60% in oil), 0.234 g of 4-fluoro-2-nitrobenzyl bromide (1.0 mmol) in 4 mL of DMF. Purification by MPLC (3:97 to 10:90 EtOAc: hexane) afforded the product as a yellow liquid (0.119 g, 42%). ^1H NMR (500 MHz, $CDCl_3$) δ 8.08 (m, 1H), 7.08 (m, 2H), 3.89 (t, *J* = 7.5 Hz, 1H), 3.71 (s, 6H), 3.49 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.6 (C), 164.4 (d, *J* = 255.1 Hz, C-F), 145.2 (C), 136.8 (C), 128.2 (d, *J* = 9.25 Hz, CH), 119.8 (d, *J* = 23.8 Hz, CH), 115.4 (d, *J* = 22.1 Hz. CH), 52.8 (CH_3), 51.8 (CH), 32.4 (CH_2). ATR-FTIR (thin film): cm^{-1}. HRMS (ESI) m/z calculated for $C_{16}H_{20}NO_4$ $(M+H)^+$: 286.0727, found: 286.0729.



6.17d

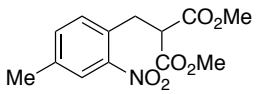
Malonate 6.17d. The general procedure was followed by using 0.17 mL of dimethyl malonate (1.1 mmol), 0.044 g of sodium hydride (1.1 mmol, 60% in oil), 0.250 g of 4-chloro-2-nitrobenzyl bromide (1.0 mmol) in 4 mL of DMF. Purification by MPLC (3:97 to 10:90 EtOAc: hexane) afforded the product as a yellow solid (0.138 g, 46%). ^1H NMR

(500 MHz, $CDCl_3$) δ 7.98 (d, J = 9.5 Hz, 1H), 7.39 (m, 2H), 3.88 (t, J = 7.5 Hz, 1H), 3.72 (s, 6H), 3.48 (d, J = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.6 (C), 147.4 (C), 139.7 (C), 135.1 (C), 125.9 (CH), 128.5 (CH), 126.8 (CH), 52.8 (CH_3), 51.9 (CH), 32.1 (CH_2). ATR-FTIR (thin film): 3004, 2956, 2852, 1745, 1725, 1567, 1521, 1437, 1334, 1296, 1230, 1155, 1113, 889 cm^{-1}. HRMS (ESI) m/z calculated for $C_{12}H_{13}NO_6Cl$ $(M+H)^+$: 302.0431, found: 302.0436.



6.17e

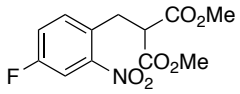
Malonate 6.17e. The general procedure was followed by using 0.17 mL of dimethyl malonate (1.1 mmol), 0.044 g of sodium hydride (1.1 mmol, 60% in oil), 0.246 g of 5-methoxy-2-nitrobenzyl bromide (1.0 mmol)in 4 mL of DMF. Purification by MPLC (3:97 to 10:90 EtOAc: hexane) afforded the product as a yellow solid (0.124 g, 42%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (d, J = 2.5 Hz, 1H), 7.26 (d, J = 8.5 Hz, 1H), 7.06 (d, J = 9.0 Hz, 1H), 3.87 (t, J = 7.5 Hz, 1H), 3.84 (s, 3H), 3.69 (s, 6H), 3.42 (d, J = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.0 (C), 159.1 (C), 149.6 (C), 133.9 (CH), 124.7 (C), 119.9 (CH), 109.8 (CH), 55.8 (CH_3), 52.7 (CH_3), 52.3 (CH), 31.7 (CH_2). ATR-FTIR (thin film): 2946, 2852, 1752, 1731, 1522, 1433, 1319, 1261, 1232, 1157, 1030, 862 cm^{-1}. HRMS (ESI) m/z calculated for $C_{13}H_{16}NO_7$ $(M+H)^+$: 298.0927, found: 298.0924.



6.17f

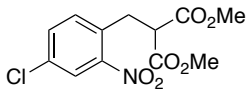
Malonate 6.17f. The general procedure was followed by using 0.17 mL of dimethyl malonate (1.1 mmol), 0.044 g of sodium hydride (1.1 mmol, 60% in oil), 0.230 g of 5-methyl-2-nitrobenzyl bromide (1.0 mmol) in 4 mL of DMF. Purification by MPLC (3:97 to 10:90 EtOAc: hexane) afforded the product as a yellow solid (0.202 g, 72%). ^{1}H NMR

(500 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.32 (d, J = 9.0 Hz, 1H), 7.24 (d, J = 7.5 Hz, 1H), 3.90 (t, J = 7.5 Hz, 1H), 3.70 (s, 6H), 3.45 (d, J = 8.0 Hz, 2H), 2.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.0 (C), 148.9 (C), 138.8 (C), 134.1 (CH), 132.8 (CH), 129.9 (C), 125.5 (CH), 52.7 (CH_3), 52.2 (CH), 31.9 (CH_2), 20.8 (CH_3). ATR-FTIR (thin film): 2962, 2925, 2851, 1742, 1726, 1523, 1496, 1434, 1530, 1034, 1258, 1162, 1078, 1071 cm^{-1}. HRMS (ESI) m/z calculated for $C_{13}H_{16}NO_6$ $(M+H)^+$: 290.0978, found: 290.0975.



6.17g

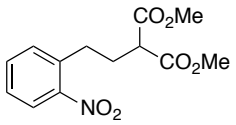
Malonate 6.17g. The general procedure was followed by using 0.17 mL of dimethyl malonate (1.1 mmol), 0.044 g of sodium hydride (1.1 mmol, 60% in oil), 0.234 g of 5-fluoro-2-nitrobenzyl bromide (1.0 mmol) in 4 mL of DMF. Purification by MPLC (3:97 to 10:90 EtOAc: hexane) afforded the product as a yellow solid (0.159 g, 56%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (dd, J = 8.0 Hz, 2.5 Hz, 1H), 7.40 (d, J = 8.5 Hz, 5.5 Hz, 1H), 7.26 (m, 1H), 3.88 (t, J = 8.0 Hz, 1H, 3.71 (s, 6H), 3.48 (d, J = 7.5 Hz, 2H)); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.8 (C), 161.2 (d, J = 250 Hz, C-F), 149.6 (C), 134.6 (d, J = 8.1 Hz, CH), 128.9 (C), 120.6 (d, J = 20.2 Hz, CH), 112.8 (d, J = 27.2 Hz, CH), 52.8 (CH_3), 52.1 (CH), 31.7 (CH_2). ATR-FTIR (thin film): 2962, 2921, 2851, 1719, 1528, 1496, 1434, 1356, 1232, 1198, 1165, 1078 cm^{-1}. HRMS (ESI) m/z calculated for $C_{12}H_{13}NO_6F$ $(M+H)^+$: 286.0727, found: 286.0729.



6.17h

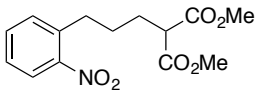
Malonate 6.17h. The general procedure was followed by using 0.17 mL of dimethyl malonate (1.1 mmol), 0.044 g of sodium hydride (1.1 mmol, 60% in oil), 0.250 g of 5-chloro-2-nitrobenzyl bromide (1.0 mmol) in 4 mL of DMF. Purification by MPLC (3:97

to 10:90 EtOAc: hexane) afforded the product as a yellow solid (0.163 g, 54%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, *J* = 2.0 Hz, 1H), 7.50 (dd, *J* = 8.0 Hz, 2.0 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 1H), 3.86 (t, *J* = 7.5 Hz, 1H), 3.70 (s, 6H), 3.46 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.7 (C), 149.5 (C), 134.2 (CH), 133.4 (CH), 131.4 (C), 125.3 (CH), 52.8 (CH_3), 52.0 (CH), 31.7 (CH_2). ATR-FTIR (thin film): 3094, 2959, 2845, 1731, 1528, 1434, 1346, 1149, 1111, 1024, 889 cm^{-1}. HRMS (ESI) m/z calculated for $C_{12}H_{13}NO_6Cl$ $(M+H)^+$: 302.0431, found: 302.0434.



6.20a

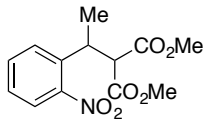
Malonate 6.20a. The general procedure was followed by using 0.17 mL of dimethyl malonate (1.1 mmol), 0.044 g of sodium hydride (1.1 mmol, 60% in oil), 0.230 g of 2-nitrophenethyl bromide (1.0 mmol) in 4 mL of DMF. Purification by MPLC (3:97 to 10:90 EtOAc: hexane) afforded the product as a yellow liquid (0.211 g, 75%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.5 Hz, 1H), 7.53 (t, *J* = 7.5 Hz), 7.36 (m, 2H), 3.75 (s, 6H), 3.45 (t, *J* = 7.5 Hz, 1H), 2.93 (t, *J* = 8.0 Hz, 2H), 2.26 (q, *J* = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.4 (C), 149.2 (C), 135.8 (C), 133.2 (CH), 132.1 (CH), 127.5 (CH), 124.9 (CH), 52.6 (CH_3), 51.2 (CH), 30.5 (CH_2), 29.6 (CH_2). ATR-FTIR (thin film): 2952, 2921, 2854, 1729, 1609, 1523, 1434, 1345, 1224, 1197, 1153, 859 cm^{-1}. HRMS (ESI) m/z calculated for $C_{13}H_{16}NO_6$ $(M+H)^+$: 282.0978, found: 282.0974.



6.20b

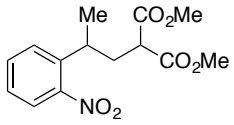
Malonate 6.20b. The general procedure was followed by using 0.083g of dimethyl malonate (0.52 mmol), 0.021 g of sodium hydride (0.52 mmol, 60% in oil), 0.125 g of 1-

(3-iodopropyl)-2-nitrobenzene (0.432 mmol) in 2 mL of DMF. Purification by MPLC (3:97 to 10:90 EtOAc: hexane) afforded the product as a brown liquid (0.120 g, 95%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (d, *J* = 7.5 Hz, 1H), 7.50 (t, *J* = 7.5 Hz, 1H), 7.34 (t, *J* = 8.0 Hz, 2H), 3.73 (s, 6H), 3.40 (t, *J* = 7.5 Hz, 1H), 2.90 (t, *J* = 8.0 Hz, 2H), 2.00 (q, *J* = 7.5 Hz, 2H), 1.70 – 1.67 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.6 (C), 149.3 (C), 136.6 (C), 132.9 (CH), 131.9 (CH), 121.2 (CH), 124.8 (CH), 52.6 (CH_3), 51.4 (CH), 32.6 (CH_2), 28.6 (CH_2), 28.3 (CH_2). ATR-FTIR (thin film): 2954, 2869, 1731, 1609, 1576, 1434, 1345, 1151, cm^{-1}. HRMS (ESI) m/z calculated for $C_{14}H_{18}NO_6$ $(M+H)^+$: 296.1134, found: 296.1130.



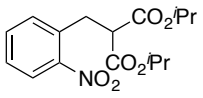
6.20c

Malonate 6.20c. The general procedure was followed by using 0.13 mL of dimethyl malonate (1.1 mmol), 0.044 g of sodium hydride (1.1 mmol, 60% in oil), 0.231 g of 1-(1-bromoethyl)-2-nitrobenzene (1.0 mmol) in 4 mL of DMF. Purification by MPLC (3:97 to 10:90 EtOAc: hexane) afforded the product as a white solid (0.157 g, 56%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.0 Hz, 1H), 7.48 (t, *J* = 7.5 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.28 (t, *J* = 7.5 Hz, 1H), 3.99 (m, 1H), 3.70 (d, *J* = 10.5 Hz, 1H), 3.67 (s, 3H), 3.40 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.5 (C), 132.6 (CH), 128.1 (CH), 127.6 (CH), 124.1 (CH), 58.0 (CH), 52.6 (CH_3), 52.5 (CH_3), 33.8 (CH), 19.3 (CH_3), only visible peaks. ATR-FTIR (thin film): 2985, 2954, 1752, 1732, 1518, 1345, 1318, 1301, 1258, 1198, 1148, 991, 854, 787 cm^{-1}. HRMS (ESI) m/z calculated for $C_{13}H_{16}NO_6$ $(M+H)^+$: 282.0978, found: 282.0977.



6.20d

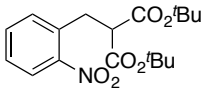
Malonate 6.20d. The general procedure was followed by using 0.13 mL of dimethyl malonate (1.1 mmol), 0.044 g of sodium hydride (1.1 mmol, 60% in oil), 0.244 g of 1-(1-bromopropan-2-yl)-2-nitrobenzene (1.0 mmol) in 4 mL of DMF. Purification by MPLC (3:97 to 10:90 EtOAc: hexane) afforded the product as a white solid (0.203 g, 69%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, J = 8.0 Hz, 1H), 7.53 (t, J = 7.5 Hz, 1H), 7.42 (d, J = 8.0 Hz, 1H), 7.32 (t, J = 7.0 Hz, 1H), 3.69 (s, 3H), 3.63 (s, 3H), 3.30 (m, 1H), 3.15 (dd, J = 6.5 Hz, 9.0 Hz, 1H), 2.25 (m, 2H), 1.30 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.5 (C), 150.3 (C), 139.4 (C), 132.8 (CH), 127.8 (CH), 127.2 (CH), 124.1 (CH), 52.6 (CH), 49.8 (CH_3), 36.3 (CH), 31.5 (CH_2), 22.5 (CH_3). ATR-FTIR (thin film): 2951, 2924, 1730, 1523, 1434, 1351, 1233, 1201, 1152, 1024, 852, 784, 751 cm^{-1}. HRMS (ESI) m/z calculated for $C_{14}H_{18}NO_6$ $(M+H)^+$: 296.1134, found: 296.1133.



6.20e

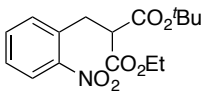
Malonate 6.20e. The general procedure was followed by using 0.182 g of diisopropyl malonate (1.1 mmol), 0.044 g of sodium hydride (1.1 mmol, 60% in oil), 0.216 g of 2-nitrobenzyl bromide (1.0 mmol) in 4 mL of DMF. Purification by MPLC (3:97 to 10:90 EtOAc: hexane) afforded the product as a yellow solid (0.180 g, 56%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (dd, J = 8.5 Hz, 1Hz, 1H), 7.51 (dt, J = 7.5 Hz, 1.0 Hz, 1H), 7.41 – 7.38 (m, 2H), 5.00 (sep, J = 6.5 Hz, 2H), 3.79 (t, J = 7.5 Hz, 1H), 3.48 (d, J = 7.5 Hz, 2H),

1.21 (d, J = 6.5 Hz, 6H), 1.15 (d, J = 6.5 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.1 (C), 149.2 (C), 133.2 (C), 133.1 (CH), 128.1 (CH), 125.2 (CH), 69.2 (C), 52.6 (CH), 32.1 (CH_2), 21.6 (CH_3), 21.5 (CH_3). ATR-FTIR (thin film): 2982, 2935, 2878, 1725, 1525, 1467, 1452, 1346, 1293, 1229, 1164, 1099, 1001, 909, 859, 824, 786 cm^{-1}. HRMS (ESI) m/z calculated for $C_{16}H_{22}NO_6$ $(M+H)^+$: 324.1447, found: 324.1443.



6.20f

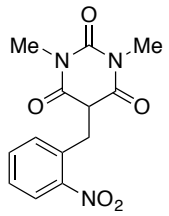
Malonate 6.20f. The general procedure was followed by using 0.216 g of di-*tert*-butyl malonate (1.1 mmol), 0.044 g of sodium hydride (1.1 mmol, 60% in oil), 0.216 g of 2-nitrobenzyl bromide (1.0 mmol) in 4 mL of DMF. Purification by MPLC (3:97 to 10:90 EtOAc: hexane) afforded the product as a yellow solid (0.249 g, 71%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, J = 8.0 Hz, 1H), 7.50 (t, J = 7.5 Hz, 1H), 7.41 – 7.39 (m, 2H), 3.65 (t, J = 7.5 Hz, 1H), 3.42 (d, J = 8.0 Hz, 2H), 1.39 (s, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.9 (C), 149.3 (C), 133.6 (C), 133.2 (CH), 133.0 (CH), 128.0 (CH), 125.1 (CH), 81.9 (C), 53.8 (CH), 32.1 (CH_2), 27.9 (CH_3). ATR-FTIR (thin film): 2974, 2935, 2874, 1742, 1718, 1523, 1393, 1368, 1350, 1295, 1247, 1222, 1148, 1135, 1063, 991, 965, 845, 789, 704 cm^{-1}. HRMS (ESI) m/z calculated for $C_{18}H_{25}NO_6Na$ $(M+Na)^+$: 374.1580, found: 374.1577.



6.20g

Malonate 6.20g. The general procedure was followed by using 0.188g of *tert*-butyl ethyl malonate (1.1 mmol), 0.044 g of sodium hydride (1.1 mmol, 60% in oil), 0.216 g of 2-

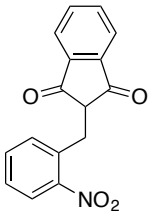
nitrobenzyl bromide (1.0 mmol) in 4 mL of DMF. Purification by MPLC (3:97 to 10:90 EtOAc: hexane) afforded the product as a yellow solid (0.203 g, 63%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, J = 8.0 Hz, 1H), 7.51 (t, J = 7.5 Hz, 1H), 7.40 – 7.38 (m, 2H), 4.20 – 4.08 (m, 2H), 3.75 (t, J = 7.5 Hz, 1H), 3.46 (t, J = 7.5 Hz, 2H), 1.38 (s, 9H), 1.20 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.9 (C), 167.6 (C), 149.2 (C), 133.4 (C), 1331.1 (CH), 128.1 (CH), 125.1 (CH), 82.2 (C), 61.4 (CH_2), 53.1 (CH), 32.1 (CH_2), 27.8 (CH_3), 14.1 (CH_3). ATR-FTIR (thin film): 2979, 1725, 1525, 1451, 1345, 1295, 1233, 1137, 1063, 1024, 845, 786, 740 cm^{-1}. HRMS (ESI) m/z calculated for $C_{16}H_{21}NO_6Na$ $(M+Na)^+$: 346.1267, found: 346.1265.



6.20h

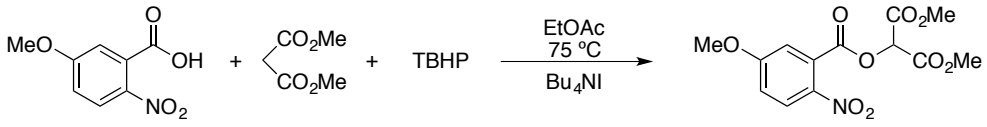
Malonate 6.20b. To a stirring mixture of 0.604 g of 2-nitrobenzaldehyde (4.0 mmol) in 10 mL of ethanol was added 0.624 g of 1,3-dimethylbarbituric acid (4.0 mmol). The mixture was refluxed for 10 minutes, and then cooled down to room temperature. To the mixture 0.304 g of sodium borohydride (8.0 mmol) was added and stirred for 1 hour. Solvent was removed *in vacuo* followed by purification using MPLC (3:97 to 10:90 EtOAc: hexane) afforded the product as a yellow solid (0.885 g, 76%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, J = 8.0 Hz, 1.0 Hz, 1H), 7.58 (dt, J = 8.0 Hz, 1.5 Hz, 1H), 7.46 – 7.42 (m, 2H), 3.84 (t, J = 7.0 Hz, 1H), 3.72 (d, J = 7.0 Hz, 2H), 3.26 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.4 (C), 151.4 (C), 149.4 (C), 133.2 (CH), 132.9 (CH), 132.1 (C), 128.6 (CH), 125.2 (CH), 50.3 (CH), 33.0 (CH_2), 28.8 (CH_3). ATR-FTIR (thin film):

2864, 1745, 1694, 1660, 1518, 1447, 1415, 1378, 1332, 1273, 1089, 1042 cm^{-1}. HRMS (ESI) m/z calculated for $C_{13}H_{14}N_3O_5$ $(M+H)^+$: 292.0933, found: 292.0925.



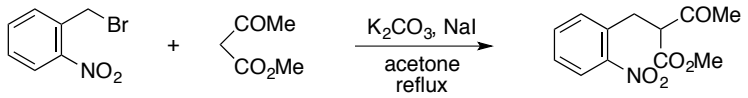
6.20i

Malonate 6.20b. In a clean and dry round bottom flask was taken 0.100 g of 2-nitrobenzaldehyde (0.66 mmol), 0.096 g of 1,3-indanedione (0.66 mmol), 0.167 g of Hantzsh ester (0.66 mmol) in 0.20 mL of ethanol. To this mixture, 0.015 g of L-proline (0.13 mmol) was added and stirred for 3 h at room temperature. Solvent was removed *in vacuo* followed by purification using MPLC (3:97 to 10:90 EtOAc: hexane) afforded the product as a yellow solid (0.133 g, 72%). ^1H NMR (500 MHz, $CDCl_3$) δ 8.02 (dd, J = 8.0 Hz, 1.0 Hz, 1H), 7.97 – 7.95 (m, 2H), 7.85 – 7.83 (m, 2H), 7.56 (dt, J = 7.5 Hz, 1.0 Hz, 1H), 7.50 (dd, J = 8.0 Hz, 1.5 Hz, 1H), 7.42 (dt, J = 8.5 Hz, 1.0 Hz, 1H), 3.52 (d, J = 7.5 Hz, 2H), 3.46 (dd, J = 8.5 Hz, 7.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.9 (C), 141.9 (CH), 135.8 (CH), 133.2 (C), 133.1 (CH), 128.1 (CH), 125.1 (CH), 123.4 (CH), 53.4 (CH), 30.0 (CH_2). ATR-FTIR (thin film): 3072, 2848, 1743, 1698, 1590, 1577, 1522, 1403, 1353, 1332, 1298, 1271, 1208, 1183, 1054 cm^{-1}. HRMS (ESI) m/z calculated for $C_{16}H_{12}NO_4$ $(M+H)^+$: 282.0766, found: 282.0758.



6.20j

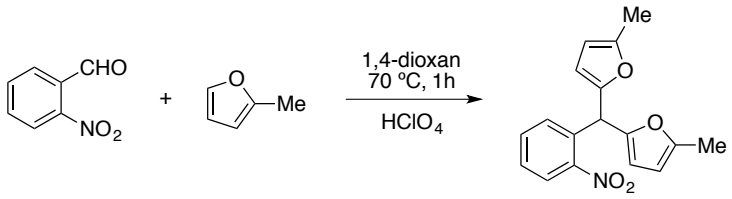
Malonate 6.20b. To a stirring mixture of 0.197 g 4-methoxy-2-nitrobenzoic acid (1.0 mmol), 0.132 g of dimethyl malonate (1.0 mmol) and 0.037 g of Bu_4NI (0.1 mmol) in 5 mL of EtOAc was added 0.36 mL of *t*-butyl hydroperoxide (5.5M in decane, 2.0 mmol) at room temperature. The resulting mixture was heated to 75 °C for 10 h. After the reaction was completed, the reaction mixture was cooled to room temperature and poured into $Na_2S_2O_3$ (5 mL) and $NaHCO_3$ (5 mL). The solution was extracted with 2 × 10 mL of ethyl acetate followed by 10 mL of brine. The resulting organic phase was dried over Na_2SO_4 and was concentrated *in vacuo*. Purification by MPLC (3:97 to 10:90 EtOAc: hexane) afforded the product as a yellow solid (0.216 g, 54%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, *J* = 9.0 Hz, 1H), 7.16 (d, *J* = 3.0 Hz, 1H), 7.04 (dd, *J* = 9.0 Hz, 3.0 Hz, 1H), 5.81 (s, 1H), 3.92 (s, 3H), 3.86 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.5 (C), 164.2 (C), 163.6 (C), 139.6 (C), 129.6 (C), 126.8 (CH), 116.3 (CH), 114.6 (CH), 72.5 (CH), 56.3 (CH_3), 53.5 (CH_3). ATR-FTIR (thin film): 3285, 2918, 1744, 1639, 1605, 1582, 1520, 1485, cm^{-1}. HRMS (ESI) m/z calculated for $C_{13}H_{13}NO_9Na$ $(M+Na)^+$: 350.0488, found: 350.0493.



6.20j

Malonate 6.20b. A solution of 0.268 g of methyl acetoacetate (2.31 mmol) was added dropwise to a stirred suspension of 0.350 g potassium carbonate (2.54 mmol) and 0.415 g of NaI (1.20 mmol) in 10 mL of dry acetone. A solution of 0.500 g of 2-nitrobenzyl bromide (2.31 mmol) in 5 mL of acetone was added dropwise to this solution at room temperature. The reaction was stirred under reflux for 6 hours. The reaction mixture was

vacuum filtered through a pad of Celite and concentrated under reduced pressure. The solution was extracted with 2 × 10 mL of ether followed by 10 mL of brine. The resulting organic phase was dried over Na_2SO_4 and was concentrated *in vacuo*. Purification by MPLC (3:97 to 10:90 EtOAc: hexane) afforded the product as a light yellow solid (0.384g, 66%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.5 Hz, 1H), 7.52 (t, *J* = 7.5 Hz, 1H), 7.41 (d, *J* = 7.5 Hz, 2H), 4.02 (dd, *J* = 8.5 Hz, 6.5 Hz, 1H), 3.68 (s, 3H), 3.47 (dd, *J* = 14.5 Hz, 6.5 Hz, 1H), 3.35 (dd, *J* = 14.5 Hz, 8.5 Hz, 1H), 2.72 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.8 (C), 169.2 (C), 133.6 (C), 133.5 (CH), 133.4 (CH), 128.2 (CH), 125.2 (CH), 59.6 (CH), 52.6 (CH_3), 31.4 (CH_2), 29.8 (CH_3). ATR-FTIR (thin film): 2985, 1731, 1714, 1610, 1577, 1521, 1450, 1431, 1343, 1315, 1262, 1212, 1146, 1067 cm^{-1}. HRMS (ESI) m/z calculated for $C_{12}H_{14}NO_5$ $(M+H)^+$: 252.0872, found: 252.0873.



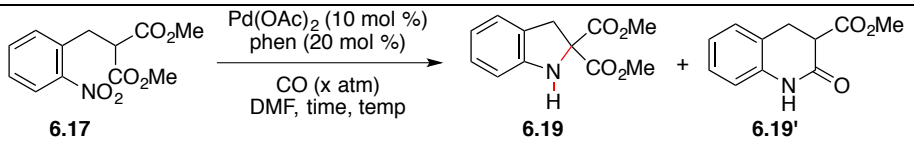
6.20j

Malonate 6.20b. Aq. HClO4 (70%, 0.06 mL) was added to solution of 0.151 g of 2-nitrobenzaldehyde (1.0 mmol) and 0.164 g of 2-methylfuran (2.0 mmol) in 4 mL of 1,4-dioxane. The reaction mixture was stirred at 70 C for 1 h, and then poured into 20 mL of cold water. The solution was extracted with 2 × 10 mL of ethyl acetate followed by 10 mL of brine. The resulting organic phase was dried over Na_2SO_4 and was concentrated *in vacuo*. Purification by MPLC (3:97 to 10:90 EtOAc: hexane) afforded the product as a brown solid (0.214 g, 72%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (dd, *J* = 8.0Hz, 1.0 Hz,

1H), 7.53 (dt, J = 8.0 Hz, 1.0 Hz, 1H), 7.39 (dt, J = 8.0 Hz, 1.5 Hz, 1H), 7.35 (dd, J = 8.0 Hz, 1.0 Hz, 1H), 6.21 (s, 1H), 5.91 (d, J = 3.0 Hz, 2H), 5.88 (d, J = 3.0 Hz, 2H), 2.23 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ. 151.9 (C), 150.8 (C), 148.8 (C), 134.5 (C), 132.9 (CH), 131.0 (CH), 127.9 (CH), 124.8 (CH), 109.1 (CH), 106.2 (CH), 39.9 (CH), 13.6 (CH_3). ATR-FTIR (thin film): 2919, 1604, 1562, 1520, 1476, 1446, 1348, 1216, 1021, 1004, 968 cm^{-1}. HRMS (ESI) m/z calculated for $C_{17}H_{16}NO_4$ $(M+H)^+$: 288.1079, found: 288.1090.

2.7.3 Pd(II) catalyzed formation of the indoline

A. Optimization of reaction conditions



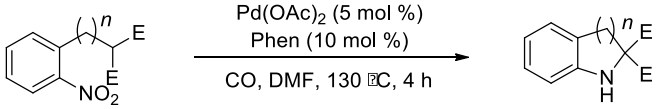
6.17 **6.19** **6.19'**

entry	catalyst	ligand (mol %)	reductant (atm)	T, °C	yield, %[a] **6.19:6.19'**
1[b]	$Pd(OAc)_2$	phen	$Mo(CO)_6$	130	nd
2[b]	$Pd(OAc)_2$	phen	CO (1.0)	130	69:0
3[b]	$Pd(OAc)_2$	phen	CO (1.5)	130	87:0
4[c]	$Pd(OAc)_2$	phen	CO (1.5)	130	87:0
5[c,d]	$Pd(OAc)_2$	phen	CO (1.5)	130	89:0
6[c,d,e]	$Pd(OAc)_2$	phen	CO (1.5)	110	55:0
7[c]	$Pd(OAc)_2$	tmphen	CO (1.5)	130	0:0

8[c]	$Pd(TFA)_2$	phen	CO (1.5)	130	0:0
8[c]	$Ru_3CO)_{12}$	Phen	CO (1.5)	130	12:28
9[c,f]	$PtCl_2(PPh_3)_2$	Phen	CO (1.5)	130	0:0
10[c,g]	Pd/C	–	HCO_2NH_4	rt	0:100
11[c,g]	Rh/C	–	H_2 (1.0)	rt	0:100

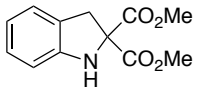
[a] As determined using ^{1}H NMR spectroscopy using CH_2Br_2 as the internal standard. [b] the reaction was run for 16 h. [c] the reaction was run for 3 h. [d] 5 mol % Pd(OAc)2 used. [e] 42% SM recovered. [f] 90% SM recovered. [g] MeOH was used as solvent.

B. Optimal condition



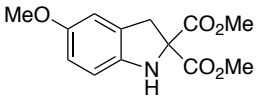
In a clean and dry shlenk tube, 0.027 g of **6.13** (0.10 mmol, 1 equiv) was taken followed by the addition of 0.0011 g of $Pd(OAc)_2$ (0.005 mmol, 5 mol %), 0.002 g of phenanthroline (0.010 mmol, 10 mol %) in 1.0 mL of DMF solvent under nitrogen atmosphere. The mixture was then degassed using freeze-pump-though technique and CO gas was then added from cylinder. The mixture was shaken for 1 minute to saturate the mixture with CO gas. A characteristic dark brown color indicates saturation of CO gas in the mixture. The shlenk tube was then closed and heated for 3 hours at 130 ºC. The solution was then cooled to room temperature and and diluted with 5 mL of cold water. The solution was extracted with 2 × 10 mL of ethyl acetate followed by 10 mL of brine. The resulting organic phase was dried over Na_2SO_4 and was concentrated in vacuo. Purification by MPLC (3:97 to 10:90 EtOAc: hexane) afforded the product.

C. Preparation of indoleines.



6.19

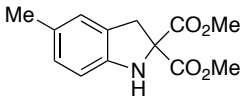
Indoline 6.19. The general procedure was followed by using 0.027 g of **6.17** (0.10 mmol), 0.0011 g of $Pd(OAc)_2$ (0.005 mmol), 0.002 g of phenanthroline (0.010 mmol) in 1.0 mL of DMF solvent. Purification by MPLC (3:97 to 10:90 EtOAc: hexane) afforded the product as a yellow solid (0.021 g, 88%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.07 (m, 2H), 6.78 (t, J = 7.5 Hz, 1H), 6.73 (d, J = 7.5 Hz, 1H), 5.02 (s, 1H), 3.80 (s, 6H), 3.69 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9 (C), 148.3 (C), 127.9 (CH), 125.6 (C), 124.4 (CH), 120.3 (CH), 72.8 (C), 53.4 (CH_3), 18.9 (CH_2). ATR-FTIR (thin film): 3366, 3053, 2949, 2855, 1725, 1609, 1432, 1236, 1163, 1076, 1042 cm^{-1}. HRMS (ESI) m/z calculated for $C_{12}H_{14}NO_4$ $(M+H)^+$: 236.0923, found: 236.0917.



6.19a

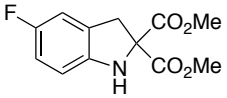
Indoline 6.19a. The general procedure was followed by using 0.030 g of **6.17a** (0.10 mmol), 0.0011 g of $Pd(OAc)_2$ (0.005 mmol), 0.002 g of phenanthroline (0.010 mmol) in 1.0 mL of DMF solvent. The reaction mixture was stirred for 24 h at 130 ºC. Purification by MPLC (3:97 to 10:90 EtOAc: hexane) afforded the product as a white solid (0.0165 g, 62%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.65 (m, 3H), 4.85 (s, 1H), 3.80 (s, 6H), 3.72 (s, 3H), 3.66 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9 (C), 154.6 (C), 141.9 (C), 127.2 (C), 113.2 (CH), 111.1 (CH), 110.9 (CH), 73.3 (C), 55.9 (CH_3), 53.4 (CH_3), 37.6 (CH_2). ATR-FTIR (thin film): 3362, 2956, 2920, 2848, 1756, 1725, 1499, 1433, 1225, 1220,

1165, 1073, 1027, 809 cm^{-1}. HRMS (ESI) m/z calculated for $C_{13}H_{16}NO_5$ $(M+H)^+$: 266.1028, found: 266.1031.



6.19b

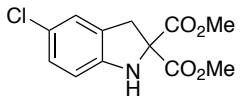
Indoline 6.19b. The general procedure was followed by using 0.028 g of **6.17b** (0.10 mmol), 0.0011 g of $Pd(OAc)_2$ (0.005 mmol), 0.002 g of phenanthroline (0.010 mmol) in 1.0 mL of DMF solvent. Purification by MPLC (3:97 to 10:90 EtOAc: hexane) afforded the product as a yellow solid (0.0186 g, 75%). ^1H NMR (500 MHz, $CDCl_3$) δ 6.91 (s, 1H), 6.88 (d, J = 10.0 Hz, 1H), 6.64 (d, J = 9.5 Hz), 4.93 (s, 1H), 3.79 (s, 6H), 3.65 (s, 2H), 2.24 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.0 (C), 145.9 (C), 129.7 (C), 128.3 (CH), 125.8 (C), 125.1 (CH), 110.3 (CH), 73.1 (C), 53.4 (CH_3), 37.3 (CH_2), 20.8 (CH_3). ATR-FTIR (thin film): 3366, 2952, 2916, 2848, 1752, 1729, 1498, 1428, 1250, 1234, 1037, 805 cm^{-1}. HRMS (ESI) m/z calculated for $C_{13}H_{16}NO_4$ $(M+H)^+$: 250.1079, found: 250.1084.



6.19c

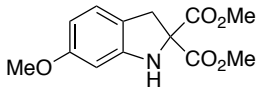
Indoline 6.19c. The general procedure was followed by using 0.028 g of **6.17c** (0.10 mmol), 0.0011 g of $Pd(OAc)_2$ (0.005 mmol), 0.002 g of phenanthroline (0.010 mmol) in 1.0 mL of DMF solvent. Purification by MPLC (3:97 to 10:90 EtOAc: hexane) afforded the product as a yellow liquid (0.0190 g, 75%). ^1H NMR (500 MHz, $CDCl_3$) δ 6.76 (m, 2H), 6.63 (m, 1H), 4.92 (s, 1H), 3.80 (s, 3H), 3.67 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7 (C), 157.9 (d, J = 235 Hz, C-F), 144.2 (C), 127.3 (C), 114.2 (d, J = 23.75 Hz, CH), 111.7 (d, J = 24.0 Hz, CH), 110.8 (d, J = 7.2 Hz, CH), 73.4 (C), 53.5 (CH_3), 37.4

(CH_2). ATR-FTIR (thin film): 3411, 2956, 2920, 2845, 1735, 1483, 1429, 1259, 1192, 1171, 1119, 1075, 1035, 949 cm^{-1}. HRMS (ESI) m/z calculated for $C_{12}H_{13}NO_4F$ $(M+H)^+$: 254.0829, found: 254.0826.



6.19d

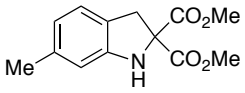
Indoline 6.19d. The general procedure was followed by using 0.030 g of **6.17d** (0.10 mmol), 0.0011 g of $Pd(OAc)_2$ (0.005 mmol), 0.002 g of phenanthroline (0.010 mmol) in 1.0 mL of DMF solvent. Purification by MPLC (3:97 to 10:90 EtOAc: hexane) afforded the product as a yellow solid (0.020 g, 74%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.03 (m, 2H), 6.63 (d, J = 8.5 Hz, 1H), 4.99 (s, 1H), 3.80 (s, 6H), 3.65 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5 (C), 149.9 (C), 127.8 (CH), 127.5 (C), 124.6 (CH), 111.1 (CH), 73.1 (C), 53.52 (CH_3), 37.0 (CH_2). ATR-FTIR (thin film): 3352, 2952, 2845, 1730, 1482, 1433, 1248, 1165, 1103, 1075, 1036, 808 cm^{-1}. HRMS (ESI) m/z calculated for $C_{12}H_{13}NO_4Cl$ $(M+H)^+$: 270.0533, found: 270.0538.



6.19e

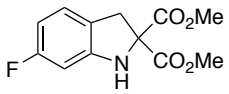
Indoline 6.19e. The general procedure was followed by using 0.030 g of **6.17e** (0.10 mmol), 0.0011 g of $Pd(OAc)_2$ (0.005 mmol), 0.002 g of phenanthroline (0.010 mmol) in 1.0 mL of DMF solvent. The reaction mixture was stirred for 24 h at 130 ºC. Purification by MPLC (3:97 to 10:90 EtOAc: hexane) afforded the product as a white solid (0.020 g, 75%). ^1H NMR (500 MHz, $CDCl_3$) δ 6.95 (d, J = 8.0 Hz, 1H), 6.33 (m, 2H), 4.99 (s, 1H), 3.80 (s, 6H), 3.74 (s, 3H), 3.60 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8 (C), 160.3 (C), 149.6 (C), 124.7 (CH), 117.7 (C), 105.5 (CH), 97.0 (CH), 73.5 (C), 55.4 (CH_3), 53.4 (CH_3), 36.6 (CH_2). ATR-FTIR (thin film): 3387, 2949, 2926, 2845, 1730, 1613, 1597,

1500, 1434, 1241, 1193, 1153, 1094, 1028, 820 cm^{-1}. HRMS (ESI) m/z calculated for $C_{13}H_{16}NO_5$ $(M+H)^+$: 266.1028, found: 266.1030.



6.19f

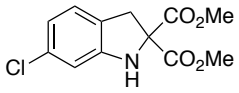
Indoline 6.19f. The general procedure was followed by using 0.028 g of **6.17f** (0.10 mmol), 0.0011 g of $Pd(OAc)_2$ (0.005 mmol), 0.002 g of phenanthroline (0.010 mmol) in 1.0 mL of DMF solvent. Purification by MPLC (3:97 to 10:90 EtOAc: hexane) afforded the product as a yellow solid (0.0241 g, 97%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.96 (d, 7.5 Hz, 1H), 6.60 (d, J = 7.5 Hz, 1H), 6.56 (s, 1H), 4.94 (s, 1H), 3.79 (s, 6H), 3.63 (s, 2H), 2.26 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.0 (C), 148.5 (C), 137.9 (C), 124.0 (CH), 122.6 (C), 121.0 (CH), 11.2 (CH), 73.1 (C), 53.4 (CH_3), 37.0 (CH_2), 21.5 (CH_3). ATR-FTIR (thin film): 3366, 2956, 2920, 2845, 1728, 1619, 1431, 1235, 1159, 1139, 1070, 1041, 960, 934, 802 cm^{-1}. HRMS (ESI) m/z calculated for $C_{13}H_{16}NO_4$ $(M+H)^+$: 250.1079, found: 250.1077.



6.19g

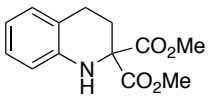
Indoline 6.19g. The general procedure was followed by using 0.028 g of **6.17g** (0.10 mmol), 0.0011 g of $Pd(OAc)_2$ (0.005 mmol), 0.002 g of phenanthroline (0.010 mmol) in 1.0 mL of DMF solvent. Purification by MPLC (3:97 to 10:90 EtOAc: hexane) afforded the product as a white solid (0.0235 g, 93%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.97 (t, J = 6.5 Hz, 1H), 6.43 (m, 2H), 5.05 (s, 1H), 3.80 (s, 6H), 3.61 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5 (C), 163.3 (d, J = 241.4 Hz, C-F), 149.8 (C), 124.8 (d, J = 9.1 Hz, CH), 120.9 (C), 106.4 (d, J_{CF} = 19.5 Hz, 1H), 98.1 (d, J = 27.5 Hz, CH), 73.6 (C), 53.5 (CH_3), 36.4 (CH_2). ATR-FTIR (thin film): 3421, 2955, 2921, 2852, 1725, 1618, 1606, 1496,

1430, 1252, 1223, 1202, 1135, 1090, 1038, 943 cm^{-1}. HRMS (ESI) m/z calculated for $C_{12}H_{13}NO_4F$ $(M+H)^+$: 254.0829, found: 254.0832.



6.19h

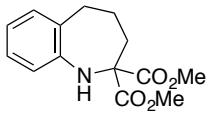
Indoline 6.19h. The general procedure was followed by using 0.030 g of **6.17h** (0.10 mmol), 0.0011 g of $Pd(OAc)_2$ (0.005 mmol), 0.002 g of phenanthroline (0.010 mmol) in 1.0 mL of DMF solvent. Purification by MPLC (3:97 to 10:90 EtOAc: hexane) afforded the product as a white solid (0.0172 g, 64%). ^1H NMR (500 MHz, $CDCl_3$) δ 6.96 (d, J = 8.0 Hz, 1H), 6.74 (d, J = 8.0 Hz, 1H), 6.69 (s, 1H), 5.02 (s, 1H), 3.80 (s, 6H), 3.62 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5 (C), 149.5 (C), 133.5 (C), 125.1 (CH), 124.1 (C), 120.1 (CH), 110.5 (CH), 73.2 (C), 53.5 (CH_3), 36.6 (CH_2). ATR-FTIR (thin film): 3352, 3011, 2959, 2845, 1729, 1603, 1485, 1435, 1292, 1251, 1166, 1079, 1051, 913 cm^{-1}. HRMS (ESI) m/z calculated for $C_{12}H_{13}NO_4Cl$ $(M+H)^+$: 270.0533, found: 270.0527.



6.21a

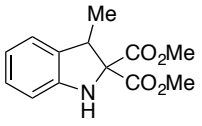
Tetrahydroquinoline 6.21a. The general procedure was followed by using 0.028 g of **6.20a** (0.10 mmol), 0.0011 g of $Pd(OAc)_2$ (0.005 mmol), 0.002 g of phenanthroline (0.010 mmol) in 1.0 mL of DMF solvent. Purification by MPLC (3:97 to 10:90 EtOAc: hexane) afforded the product as a red solid (0.0226 g, 91%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.02 (t, J = 7.5 Hz, 1H), 6.95 (d, J = 7.0 Hz, 1H), 6.68 (t, J = 7.0 Hz, 1H), 6.65 (d, J = 8.5 Hz, 1H), 4.83 (s, 1H), 3.79 (s, 6H), 2.80 (t, J = 6.5 Hz, 2H), 2.37 (t, J = 6.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5 (C), 141.6 (C), 128.9 (CH), 127.2 (CH), 120.3 (C), 118.5 (CH), 114.8 (CH), 64.8 (C), 53.2 (CH_3), 26.8 (CH_2), 23.8 (CH_2). ATR-FTIR (thin

film): 3398, 2949, 2920, 2845, 1739, 1722, 1588, 1488, 1432, 1293, 1220, 1161, 1122, 1053, 749 cm^{-1}. HRMS (ESI) m/z calculated for $C_{13}H_{16}NO_4$ $(M+H)^+$: 250.1079, found: 250.1085.



6.21b

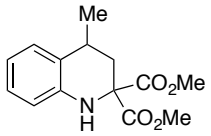
Indoline 6.21b. The general procedure was followed by using 0.029 g of **6.20c** (0.10 mmol), 0.0011 g of $Pd(OAc)_2$ (0.005 mmol), 0.002 g of phenanthroline (0.010 mmol) in 1.0 mL of DMF solvent. Purification by MPLC (3:97 to 10:90 EtOAc: hexane) afforded the product as a white solid (0.0030 g, 12%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.06 (m, 2H), 6.89 (dt, *J* = 7.5 Hz, 1Hz, 1H), 6.85 (d, *J* = 7.5 Hz, 1H), 4.68 (s, 1H), 3.69 (s, 6H), 2.75 (m, 2H), 2.25 (t, *J* = 6.0 Hz, 2H), 1.86 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) 170.19 (C), 143.5 (C), 135.0 (C), 129.6 (CH), 126.7 (CH), 122.8 (CH), 122.5 (CH), 68.5 (C), 52.9 (CH_3), 34.8 (CH_2), 33.9 (CH_2), 22.3 (CH_2). ATR-FTIR (thin film): 3381, 2951, 1735, 1613, 1487, 1465, 1431, 1270, 1223, 1098, 906, 730 cm^{-1}. HRMS (ESI) m/z calculated for $C_{14}H_{18}NO_4$ $(M+H)^+$: 264.1236, found: 264.1233.



6.21c

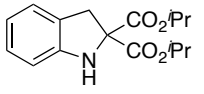
Indoline 6.21c. The general procedure was followed by using 0.028 g of **6.20c** (0.10 mmol), 0.0011 g of $Pd(OAc)_2$ (0.005 mmol), 0.002 g of phenanthroline (0.010 mmol) in 1.0 mL of DMF solvent. Purification by MPLC (3:97 to 10:90 EtOAc: hexane) afforded the product as a white solid (0.0230 g, 93%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.08 –7.03

(m, 2H), 6.80 (t, J = 7.5 Hz, 1H), 6.70 (d, J = 8.0 Hz, 1H), 4.81 (s, 1H), 4.14 (q, J = 7.5 Hz, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 1.30 (d, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.3 (C), 170.0 (C), 147.5 (C), 131.2 (C), 128.0 (CH), 123.4 (CH), 120.1 (CH), 110.0 (CH), 77.6 (C), 53.2 (CH_3), 52.7 (CH_3), 42.9 (CH), 16.3 (CH_3). ATR-FTIR (thin film): 3381, 2951, 1735, 1613, 1487, 1465, 1431, 1270, 1223, 1098, 906, 730 cm^{-1}. HRMS (ESI) m/z calculated for $C_{13}H_{16}NO_4$ $(M+H)^+$: 250.1079, found: 250.1077.



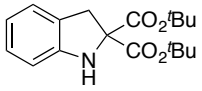
6.21d

Tetrahydroquinoline 6.21d. The general procedure was followed by using 0.029 g of **6.20d** (0.10 mmol), 0.0011 g of $Pd(OAc)_2$ (0.005 mmol), 0.002 g of phenanthroline (0.010 mmol) in 1.0 mL of DMF solvent. Purification by MPLC (3:97 to 10:90 EtOAc: hexane) afforded the product as a white solid (0.0230 g, 89%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.11 (d, J = 7.5 Hz, 1H), 7.04 (t, J = 7.5 Hz, 1H), 6.74 (t, J = 7.5 Hz, 1H), 6.65 (d, J = 8.0 Hz, 1H), 4.82 (s, 1H), 3.81 (s, 3H), 3.75 (s, 3H), 2.93 – 2.86 (m, 1H), 2.67 (dd, J = 13.0 Hz, 5.0 Hz, 1H), 1.85 (m, 1H), 1.35 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.0 (C), 170.4 (C), 141.4 (C), 127.1 (CH), 126.3 (CH), 125.6 (C), 118.7 (CH), 114.8 (CH), 64.9 (C), 53.3 (CH_3), 53.2 (CH_3), 35.4 (CH_2), 27.6 (CH), 19.6 (CH_3). ATR-FTIR (thin film): 3394, 2951, 1744, 1607, 1482, 1434, 1265, 1235, 909, 727 cm^{-1}. HRMS (ESI) m/z calculated for $C_{14}H_{18}NO_4$ $(M+H)^+$: 264.1236, found: 264.1237.



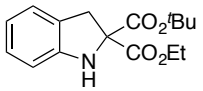
6.21e

Indoline 6.21e. The general procedure was followed by using 0.032 g of **6.20e** (0.10 mmol), 0.0011 g of $Pd(OAc)_2$ (0.005 mmol), 0.002 g of phenanthroline (0.010 mmol) in 1.0 mL of DMF solvent. Purification by MPLC (3:97 to 10:90 EtOAc: hexane) afforded the product as a white solid (0.0260 g, 90%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.08 – 7.04 (m, 2H), 6.77 (t, *J* = 7.5 Hz, 1H), 6.73 (d, *J* = 8.0 Hz, 1H), 5.08 (sep, *J* = 6.5 Hz, 2H), 4.99 (s, 1H), 3.64 (s, 2H), 1.26 (d, *J* = 2.0 Hz, 6H), 1.25 (d, *J* = 2.0 Hz), 6H; ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.0 (C), 148.6 (C), 127.8 (CH), 125.9 (C), 124.4 (CH), 120.0 (CH), 110.3 (CH), 72.9 (C), 70.0 (CH), 36.9 (CH_2), 21.5 (CH_3). ATR-FTIR (thin film): 3385, 2979, 2924, 2864, 1725, 1611, 1469, 1415, 1371, 1256, 1248, 1174, 1087, 1044, 910, 733 cm^{-1}. HRMS (ESI) m/z calculated for $C_{16}H_{22}NO_4$ $(M+H)^+$: 292.1549, found: 292.1546.



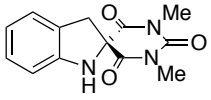
6.21f

Indoline 6.21f. The general procedure was followed by using 0.035 g of **6.20f** (0.10 mmol), 0.0011 g of $Pd(OAc)_2$ (0.005 mmol), 0.002 g of phenanthroline (0.010 mmol) in 1.0 mL of DMF solvent. Purification by MPLC (3:97 to 10:90 EtOAc: hexane) afforded the product as a white solid (0.0170 g, 53%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.07 – 7.03 (m, 2H), 6.75 (t, *J* = 7.5 Hz, 1H), 6.71 (d, *J* = 7.5 Hz, 1H), 4.90 (s, 1H), 3.57 (s, 2H), 1.47 (s, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.6 (C), 148.7 (C), 127.7 (CH), 126.1 (C), 124.3 (CH), 119.8 (CH), 110.2 (CH), 82.5 (C), 73.6 (C), 36.7 (CH_2), 27.9 (CH_3). ATR-FTIR (thin film): 3362, 2978, 2931, 1731, 1611, 1486, 1467, 1368, 1036, 1251, 1138, 1087, 842, 738 cm^{-1}. HRMS (ESI) m/z calculated for $C_{18}H_{26}NO_4$ $(M+H)^+$: 320.1862, found: 320.1862.



6.21g

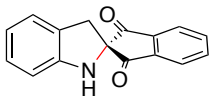
Indoline 6.21g. The general procedure was followed by using 0.032 g of **6.20g** (0.10 mmol), 0.0011 g of $Pd(OAc)_2$ (0.005 mmol), 0.002 g of phenanthroline (0.010 mmol) in 1.0 mL of DMF solvent. Purification by MPLC (3:97 to 10:90 EtOAc: hexane) afforded the product as a white solid (0.0170 g, 59%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.08 – 7.04 (m, 2H), 6.78 (t, *J* = 7.5 Hz, 1H), 6.72 (d, *J* = 8.0 Hz, 1H), 4.96 (s, 1H), 4.24 (q, *J* = 7.0 Hz, 2H), 3.61 (d, *J* = 16.5 Hz, 1H), 3.59 (d, *J* = 16.5 Hz, 1H), 1.47 (s, 9H), 1.29 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7 (C), 169.4 (C), 148.6 (C), 127.8 (CH), 126.0 (C), 124.3 (CH), 120.0 (CH), 110.3 (CH), 83.0 (C), 62.1 (CH_2), 36.9 (CH_2), 27.8 (CH_3), 14.1 (CH_3). ATR-FTIR (thin film): 3369, 2978, 2913, 1731, 1611, 1585, 1467, 1368, 1303, 1249, 1231, 1145, 1078, 842, 744 cm^{-1}. HRMS (ESI) m/z calculated for $C_{16}H_{22}NO_4$ $(M+H)^+$: 292.1549, found: 292.1548.



6.21h

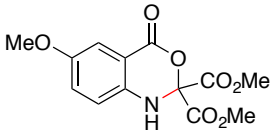
Indoline 6.21h. The general procedure was followed by using 0.029 g of **6.20h** (0.10 mmol), 0.0011 g of $Pd(OAc)_2$ (0.005 mmol), 0.002 g of phenanthroline (0.010 mmol) in 1.0 mL of DMF solvent. Purification by MPLC (3:97 to 10:90 EtOAc: hexane) afforded the product as a white solid (0.0140 g, 54%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13 (t, *J* = 7.5 Hz, 1H), 7.02 (d, *J* = 7.5 Hz, 1H), 6.83 (m, 2H), 4.59 (s, 1H), 3.56 (s, 2H), 3.35 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6 (C), 150.9 (C), 149.6 (C), 128.6 (CH), 124.2 (CH), 123.8 (C), 121.1 (CH), 111.6 (CH), 69.8 (C), 44.8 (CH_2), 29.5 (CH_3). ATR-FTIR

(thin film): 3332, 2958, 2924, 1752, 1682, 1605, 1486, 1445, 1375, 1063, 909, 730 cm^{-1}. HRMS (ESI) m/z calculated for $C_{13}H_{14}N_3O_3$ $(M+H)^+$: 260.1035, found: 260.1037.



6.21i

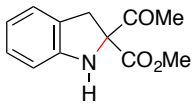
Indoline 6.21i. The general procedure was followed by using 0.028 g of **6.20i** (0.10 mmol), 0.0011 g of $Pd(OAc)_2$ (0.005 mmol), 0.002 g of phenanthroline (0.010 mmol) in 1.0 mL of DMF solvent. Purification by MPLC (3:97 to 10:90 EtOAc: hexane) afforded the product as a brown solid (0.0150 g, 59%). ^1H NMR (500 MHz, $CDCl_3$) δ 8.05 (m, 2H), 7.92 (m, 2H), 7.11 (J = 7.5 Hz, 1H), 7.03 (d, J = 7.5 Hz, 6.82 (t, J = 7.5 Hz, 1H), 6.78 (d, J = 8.0 Hz, 1H), 4.33 (s, 1H), 3.40 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.6 (C), 150.2 (C), 140.6 (C), 136.5 (CH), 128.3 (CH), 125.3 (C), 124.2 (CH), 124.1 (CH), 120.5 (CH), 110.8 (CH), 40.5 (CH_2). ATR-FTIR (thin film): 3351, 2919, 1743, 1698, 1589, 1485, 1466, 1330, 1241, 1050 cm^{-1}. HRMS (ESI) m/z calculated for $C_{16}H_{12}NO_2$ $(M+H)^+$: 250.0868, found: 250.0876.



6.21j

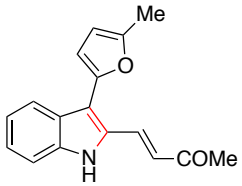
Indoline 6.21j. The general procedure was followed by using 0.030 g of **6.20j** (0.10 mmol), 0.0011 g of $Pd(OAc)_2$ (0.005 mmol), 0.002 g of phenanthroline (0.010 mmol) in 1.0 mL of DMF solvent. Purification by MPLC (3:97 to 10:90 EtOAc: hexane) afforded the product as a white solid (0.0120 g, 46%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, J = 3.0 Hz, 1H), 7.10 (dd, J = 9.0 Hz, 3.0 Hz, 1H), 6.87 (d, J = 9.0 Hz, 1H), 5.48 (s, 1H), 3.85 (s, 6H), 3.79 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.4 (C), 155.1 (C), 136.6 (C),

125.1 (CH), 119.3 (CH), 114.5 (C), 111.5 (CH), 87.0 (C), 55.8 (CH_3), 54.3 (CH_3), only visible peaks. ATR-FTIR (thin film): 3366, 3017, 2962, 1772, 1746, 1722, 1626, 1514, 1435, 1354, 1284, 1246, 1215, 1030 cm^{-1}. HRMS (ESI) m/z calculated for $C_{13}H_{14}NO_7$ $(M+H)^+$: 296.0770, found: 296.0770.



6.21k

Indoline 6.21k. The general procedure was followed by using 0.025 g of **6.20k** (0.10 mmol), 0.0011 g of $Pd(OAc)_2$ (0.005 mmol), 0.002 g of phenanthroline (0.010 mmol) in 1.0 mL of DMF solvent. Purification by MPLC (3:97 to 10:90 EtOAc: hexane) afforded the product as a brown oil (0.0075 g, 35%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.07 (t, J = 7.0 Hz, 2H), 6.79 (t, J = 7.5 Hz, 1H), 6.75 (d, J = 8.5 Hz, 1H), 5.06 (s, 1H), 3.80 (s, 3H), 3.76 (d, J = 16.5 Hz, 1H), 3.50 (d, J = 16.5 Hz, 1H), 2.29 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.3 (C), 171.7 (C), 148.6 (C), 128.0 (CH), 125.7 (C), 124.5 (CH), 120.4 (CH), 110.7 (CH), 78.4 (C), 53.4 (CH_3), 36.3 (CH_2), 24.8 (CH_3). ATR-FTIR (thin film): 3343, 2952, 1715, 1608, 1529, 1486, 1437, 1244, 1203, 1148, 1087 cm^{-1}. HRMS (ESI) m/z calculated for $C_{12}H_{14}NO_3$ $(M+H)^+$: 220.0974, found: 220.0969.



6.21m

Indoline 6.21k. The general procedure was followed by using 0.030 g of **6.20m** (0.10 mmol), 0.0011 g of $Pd(OAc)_2$ (0.005 mmol), 0.002 g of phenanthroline (0.010 mmol) in 1.0 mL of DMF solvent. Purification by MPLC (3:97 to 10:90 EtOAc: hexane) afforded the product as a brown solid (0.0140 g, 52%). ^1H NMR (500 MHz, MeOD) δ 7.95 (d, J =

16.0 Hz, 1H), 7.83 (d, J = 7.0 Hz, 1H), 7.39 (d, J = 8.5 Hz, 1H), 7.27 (dt, J = 8.0 Hz, 1.0 Hz, 1H), 7.10 (dt, J = 8.0 Hz, 1.0 Hz, 1H), 6.80 (d, 16.0 Hz, 1H), 6.69 (d, J = 3.5 Hz, 1H), 6.26 (dd, J = 3.0 Hz, 1.0 Hz, 1H), 2.39 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (125 MHz, MeOD) δ 197.8 (C), 151.8 (C), 147.8 (C), 138.3 (C), 132.2 (CH), 130.0 (C), 126.2 (CH), 125.5 (CH), 125.3 (C), 121.3 (CH), 120.9 (CH), 112.4 (C), 112.1 (CH), 109.3 (CH), 108.4 (CH), 27.7 (CH_3), 13.9 (CH_3). ATR-FTIR (thin film): 3286, 2920, 2851, 1714, 1667, 1639, 1603, 1487, 1443, 1357, 1262, 1234, 1150, 1046, 1029 cm^{-1}. HRMS (ESI) m/z calculated for $C_{17}H_{16}NO_2$ $(M+H)^+$: 266.1181, found: 266.1188.

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Appendix

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3. ''Rh_2(II) catalyzed selective aminomethylene migration from styryl azides.'' Kong, C.; Jana, N.; Driver, T. G. *Org. Lett.* **2013**, *15,* 824. Copyright 2013 American Chemical Society.
4. ''Development of a Suzuki cross-coupling reaction between 2-azidoarylboronic pinacolate esters and vinyl triflates to enable synthesis of [2,3] fused indole heterocycles.'' Jana, N.; Nguyen, Q.; Driver, T. G. *J. Org. Chem.* **2014**, *79*, 2781. Copyright 2014 American Chemical Society.
5. ''Control of the Chemoselectivity of Metal *N*-Aryl Nitrene Reactivity: C–H Bond Amination versus Electrocyclization.'' Kong, C.[†]; Jana, N.[†]; Jones, C.; Driver, T. G.*J. Am. Chem. Soc.* **2016**, *138*, 13721. Copyright 2016 American Chemical Society. ([†]equal contribution)
6. ''Promoting reductive tandem reactions of nitrostyrenes with $Mo(CO)_6$ and a palladium catalyst to produce 3*H*-indoles.'' Jana, N.; Zhou, F.; Driver, T. G. *J. Am. Chem. Soc.* **2015**, *137*, 6738. Copyright 2015 American Chemical Society.

Assembly of functionalized carbocycles or N-heterocycles through a domino electrocyclization–[1,2] migration reaction sequence

N. Jana and T. G. Driver, *Org. Biomol. Chem.*, 2015, **13**, 9720
DOI: 10.1039/C5OB01334H

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Title: Mechanism of Rh2(II)-Catalyzed Indole Formation: The Catalyst Does Not Control Product Selectivity

Author: Jason G. Harrison, Osvaldo Gutierrez, Navendu Jana, et al

Publication: Journal of the American Chemical Society

Publisher: American Chemical Society

Date: Jan 1, 2016

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Development of a Suzuki Cross-Coupling Reaction between 2-Azidoarylboronic Pinacolate Esters and Vinyl Triflates To Enable the Synthesis of [2,3]-Fused Indole Heterocycles

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J. Org. Chem., **2014**, *79* (6), pp 2781–2791
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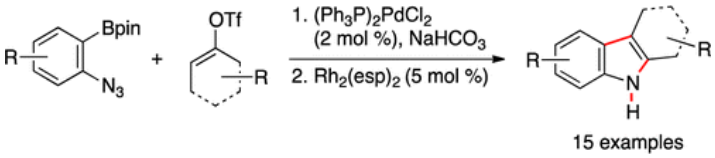
Abstract



The scope and limitations of a Suzuki reaction between 2-azidoarylboronic acid pinacolate esters and vinyl triflates are reported. This cross-coupling reaction enables the regioselective synthesis of indoles after a subsequent Rh^{II}_2-catalyzed sp^2-C–H bond amination reaction.

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Publications

1. Kong, C.[†]; **Jana**, **N**.[†]; Jones, C.; Driver, T. G. Control of the Chemoselectivity of Metal *N*-Aryl Nitrene Reactivity: C–H Bond Amination versus Electrocyclization. *J. Am. Chem. Soc*. **2016**, *138*, 13721. ([†]equal contribution)
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Undergraduate Publication:

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Manuscript in preparation:

11. Mazumdar, W. **Jana**, **N**. Driver, T. G. New reactivity pattern of Rh_2(II)–*N*-aryl nitrenes: Ring expansion of *ortho*-cyclobutanol aryl azides to access benzazipinones.
12. **Jana**, **N**.; Ekhomu, O.; Driver, T. G. Promoting reductive cyclization of nitroarenes by a palladium catalyst and carbon monoxide to afford indoline heterocycles.

Presentations

Jana, **N**.; Zhou, F.; Driver, T. G. Promoting reductive tandem reactions of nitrostyrenes with $Mo(CO)_6$ and a palladium catalyst to produce 3*H*-Indoles. Presented at the 4th Chicago Organic Symposium, Chicago, Illinois, July 2015 (Poster).

Jana, **N**.; Driver, T. G. Shifting reaction pathways by controlling the reactivity of metal-nitrene intermediate. ACS Philadelphia, August 2016 (Oral).

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