The Development of New Methods to Streamline Heterocycle Synthesis

BY

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THESIS

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Contributions of Authors

Chapter I represents a published manuscript for which I was the first author. Chapter II represents a published manuscript for which I was the second author. The first author was Navendu Jana. Chapter III includes two parts. The part 1 represents a published manuscript for which I was the first author. The second author, Dr. Duo-sheng Wang, contributed equally to this project. The part 2 represents an unpublished manuscript for which I was the second author. I assisted the first author, Kai Yang, in the mechanistic study. Chapter IV represents an unpublished manuscript for which I was the first author. The second author Dr. Duo-sheng Wang played a large role in finishing this project. Chapter V represents an unpublished manuscript for which I was the first author. The second author, Dr. Sheng Liu, assisted me in finishing the preliminary study. Chapter VI represents my synthesis of potential small molecule therapeutics in the collaboration with College of Pharmacy, UIC. I am the only researcher in this synthetic work.

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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
BOM	benzyloxymethyl
Bpin	pinacolborane borate
BQ	1,4-benzoquinone
Bz	benzoyl
n-Bu	butyl
t-Bu	*tert*-butyl
Calcd	calculated
cat.	catalytic amount
Cbz	carboxybenyl
COD	1,5-cyclooctadiene
Cond.	condition
Cy	cyclohexyl
δ	chemical shifts in parts per million downfield from tetramethylsilane (NMR)
d	doublet

LIST OF ABBREVIATIONS (continued)

dba	dibenzylidene acetone
DABCO	1,4-diazabicyclo[2.2.2]octane
DCM	dichloromethane
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
DMP	Dess–Martin periodinane
dppf	1,1'-bis(diphenylphosphino)ferrocene
EDG	electron-donating group
EE	ethoxyethyl
EI	electron impact ionization (in mass spectrometry)
Et	ethyl
equiv.	molar equivalent
EWG	electron withdrawing group
esp	α, α, α', α'-tetramethyl-1,3-benzenedipropionic acid
G	group, Gibbs free energy

LIST OF ABBREVIATIONS (continued)

g	gram
GC	gas chromatography
h, hrs	hour(s)
HR	high resolution (mass spectrometry)
Hz	Hertz
J	spin-spin coupling constant (NMR)
L	ligand
LDA	lithium diisopropyl amide
LHMDS	lithium bis(trimethylsilyl)amide
m	multiplet (NMR)
mp	melting point
μ	micro
[M]	metal
M	molar
MS	mass spectrometry
MS	molecular sieves
Me	methyl
Mes	Mesityl
mg	milligram
min	minute
mL	milliliter
mm	millimeter

LIST OF ABBREVIATIONS (continued)

mmol	millimole
mol	mole
MOM	methoxymethyl
MHz	megahertz
m/z	mass to charge ratio
NBS	N-bromosuccinimide
NMP	*N*-methyl-2-pyrrolidinone
NMR	nuclear magnetic resonance
pfb	perfluorobutyrate, heptafluorobutyrate
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)

LIST OF ABBREVIATIONS (continued)

SEM	2-(trimethylsilyl)ethoxymethyl
sept	septet (NMR)
SFC	supercritical fluid chromoatography
t	triplet (NMR)
TBS	*tert*-butyldimethylsilyl
tf	trifluoromethanesulfonyl
TFA	trifluoro acetate
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
tmphen	3,4,7,8-tetramethyl-1,10-phenanthroline
Tol, tol	tolyl
Ts	*p*-toluenesulfonyl
χ_c	mentholate
X-Ray	X-radiation

SUMMARY

The structure motifs of *N*-hetercycles obtain the ubiquity in bioactive and organoelectronic molecules. Their syntheses always motivate synthetic groups to develop new efficient processes. In Driver group, our research interest focus on new method developments of transition metal catalyzed C–N bond formation from aryl azides and nitroarenes to construct *N*-heterocycles. Under this topic, there are six chapters, which contain my contributions to new method developments of C–N, bond formation, studies of organic *N*-heteroheptacenes for organic field-effect transistor and synthesis of FTY-720 phosphonate for a potential small molecule therapeutic.

Part one was divided into three chapters. In first chapter, an efficient synthesis of 3*H*-indoles from aryl azides was discussed. In second chapter, two new reductive methods for the transformation from nitroarenes to *N*-heterocycles were investigated. In third chapter, an intermolecular C–H bond aminocarbonylation using nitroarenes was explored.

In part two, syntheses of a series of *N*-heteroheptacenes were presented. Their photochemical properties, crystal structures and electronic properties were studied.

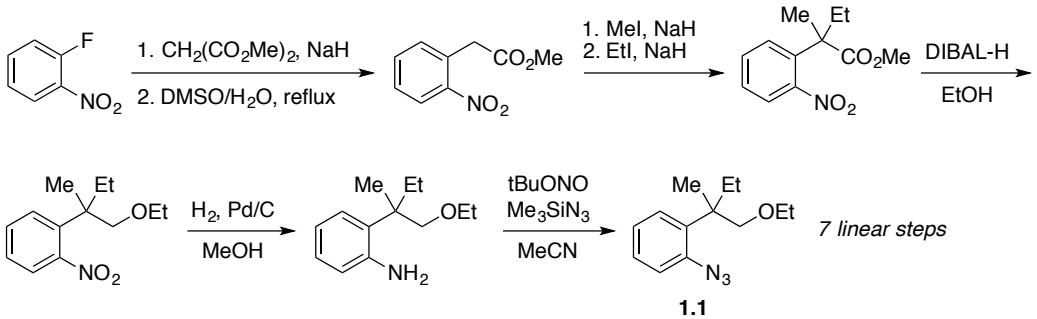
Part three is about the design and accomplishment of a new synthetic route to FTY-720 phosphonate. In this synthesis, an enzyme-enabled desymmetrization reaction was applied and SFC was used to determine the enantioselectivity.

Chapter I

Lead-mediated α-arylation of β-ketoesters or γ-lactams using Aryl Azide

Synthetic chemists have pursued the development of new pathways to construct *N*-heterocycles due to their wide existence in bioactive and organoelectronic molecules.[1-5] Our group has been working on transition-metal-catalyzed C–N bond formation using aryl azides as the nitrogen source for the last 10 years because we believed that C–H bond amination was an efficient way to introduce the nitrogen atom.[6-12]. However, during our development of C–H bond amination, the efficiency of our method were diminished by the multi-step synthesis of the aryl azide substrates. In our study of intramolecular sp^3-C–H bond amination reaction,[12] seven linear steps were required to synthesize the *o*-alkyl substituted aryl azide **1.1** (Scheme 1.1). This study suggested us that a new efficient synthetic pathway to *o*-alkyl substituted aryl azide was needed to streamline our *N*-heterocycle synthesis.

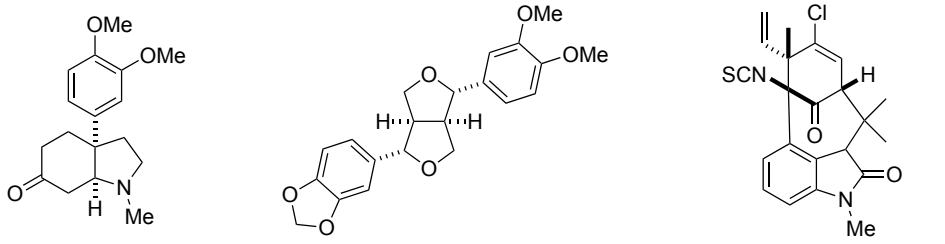
Scheme 1.1 ***Previous synthesis of o-alkyl substituted aryl azide***



To solve this problem, we anticipated a more step-economical synthesis would result if the *o*-azido aryl moiety could be installed to a carbonyl compound through an α-arylation reaction.[13-

[15] To our surprise, however, no aryl azide—and few *ortho*-heteroatom—examples had been reported in the reaction of α-arylation.[16,17] To address this gap, our study started with reaction screen with many catalyzed and non-catalyzed α-arylation reaction carbonyl compounds. Unfortunately, we found the *o*-azido moiety was not compatible with those popular methods or other environmentally friendly arylation reagents.[18-24] These results turned our attention to the α-arylation of β-ketoester using the aryllead reagent. Pinhey and co-workers firstly prepared the aryllead tricarboxylate reagents from arylstannanes[25] or arylboronic acid[26] through metal-lead exchange. Recently, the method has been employed in the total synthesis of (±)-mesembrine,[27] (±)-methyl piperitol,[28] and N-methylwelwitindolinone C isothiocyanate (Figure 1.1).[29] Although the use of the aryllead reagent has been well-established, there are no examples of this reagent which contained an azide substituent.

Figure 1.1 ***Totally synthesis using α-arylation with aryllead reagent***

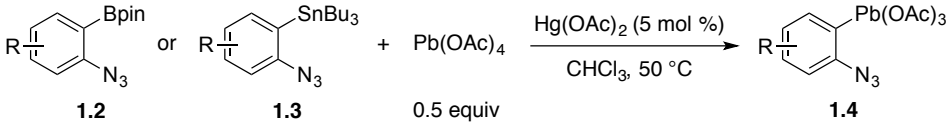


(±)-mesembrine (±)-methyl piperitol *N*-methylwelwitindolinone C Isothiocyanate

Our desired 2-azidoaryllead acetate was readily prepared from either the 2-azidoarylboronic acid pinacolate ester[30] or analogous arylstannane without any decomposition of the azido group (Scheme 1.2).[25,26] With the *o*-azidoaryllead reagent in hand, the α-arylation of β-ketoester **1.5a** was screened to find the optimal conditions (Table 1.1). For the initial screen, excess

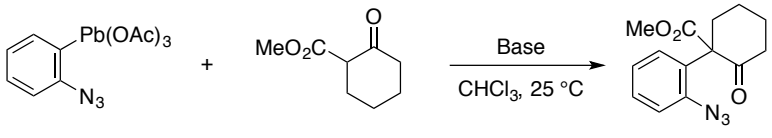
amount of **1.5a** was used (entries 1–3). While the equivalents of **1.5a** could be reduced from five to three without diminishing the yield, a significant reduction in conversion was found when the equivalent of **1.5a** was dropped to 1.05 equivalent. To further improve the conversion, a variety of amine bases were tested (entries 4–6). Among different bases, pyridine gave the highest yield over DABCO and phenanthraline. Using pyridine, yield could be improved to 87% when the reaction temperature was increased to 50 °C (entry 7). Next, in order to enable the utility of our method in more valuable carbonyl compounds, we explored the stoichiometry of our α-arylation reaction (entries 8 and 9). We were delighted to see reversing the stoichiometry only diminished the yield slightly: 88% yield was obtained when three equivalents of **1.4a** was used. We also tested the feasibility of one-pot synthesis of **1.6a** from 2-azidophenylboronic acid pinacolate ester **1.2a** (entry 10). Despite our best efforts, we found the yield of **1.6a** dropped from 87% to 45% when using **1.2a** as starting material.

Scheme 1.2 ***Preparation of o-azidoaryllead triacetate***



1.2 **1.3** **1.4**

Table 1.1 ***Optimization of α-arylation condition***



1.4a **1.5a** ***conditions*** **1.6a**

entry	base (equiv)	**1.4a** (equiv)	**1.5a** (equiv)	T, °C	%, yield **1.6a**[a]
1	none	1	5	25	90
2	none	1	3	25	89

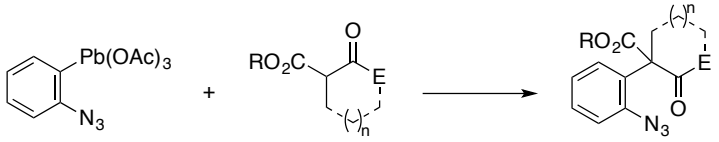
3	none	1	1.05	25	59
4	DABCO (3)	1	1.05	25	44
5	phenanthraline (3)	1	1.05	25	62
6	pyridine (3)	1	1.05	25	78
7	pyridine (3)	1	1.05	50	87[b]
8	pyridine (3)	1.05	1	50	83[b]
9	pyridine (3)	3	1	50	88[b]
10	pyridine (3)	1	1.05	50	45[c]

[a] As determined using ^{1}H NMR spectroscopy using CH_2Br_2 as an internal standard. [b] Reaction performed at 50 °C [c] Two-step yield from **1.2a**.

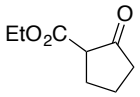
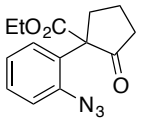
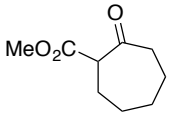
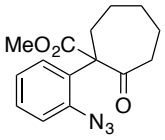
With the optimized condition in hand, a variety of β-ketoesters were screened to explore the scope and limitations of our α-arylation method (Table 1.2). We first examined the β-ketoesters with different ring sizes (entries 1–3). The desired functionalized aryl azide **1.6b–d** were formed with excellent yield. Next, the conversion of **1.5e** to product with good yield demonstrated that our method tolerated acyclic β-ketoester substrates. To further investigate the scope of the β-ketoester (entries 5–7), indanone **1.5f**, 4-tetrahydropyranone **1.5g**, and 4-amino-cyclohexanone **1.5h** were submitted to our reaction condition. The formation of the products with good yields indicated that our method worked well with substrates that contained heteroatom substitution. To our surprise, although the α-arylation of amides has been significantly studied,[31-33] no example was found with γ-lactam despite the potential synthetic utility of its product. We were delighted to see that they could be efficiently arylated to generate lactams, such as **1.6i** in good yield (entry 8). Next, we wanted to study the stereoselectivity of our α-arylation method. We anticipated that simple 4-substituted β-ketoesters would provide this insight. Submitting 4-*tert*-butyl-substituted β-ketoester **1.5j** to our optimized conditions yielded **1.6j** with 10:1 diastereoselectivity (entry 9). No reduction in diastereoselectivity was observed when the bulky *tert*-butyl group was replaced with a smaller 4-phenyl group (entry 10) to indicate that our method was not affected by the size of the 4-

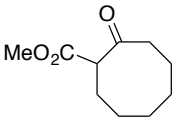
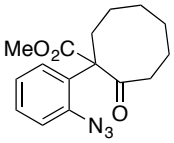
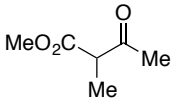
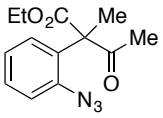
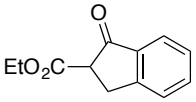
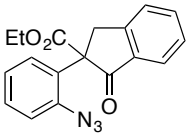
substituent. Lastly, β-ketoester with different carboxylate groups were examined in our reaction (entries 11–13). Replacing the ethyl group with an allyl group still afforded the desired product. While the desired product was still formed, no diastereoselectivity was observed with menthol-substituted **1.5m**. The lack of reaction observed using β-ketoamide **1.5n** demonstrates the limitation of our reaction (entry 13). Upon the recovery of the β-ketoamide, we believed no reaction was due to the difficulty of the depronation.

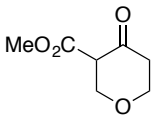
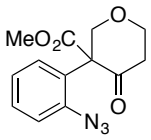
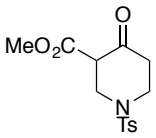
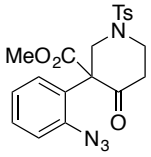
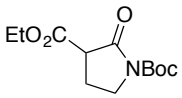
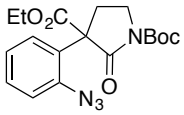
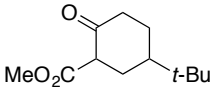
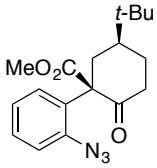
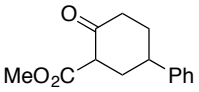
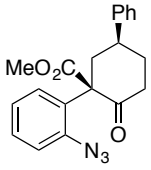
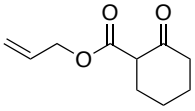
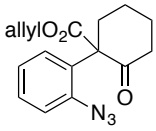
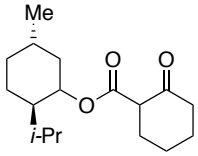
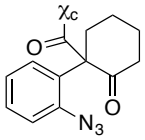
Table 1.2 ***Effect of changing the identity of the β-ketoester***

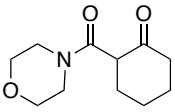
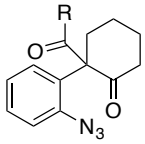


1.4a **1.5** **1.6**

entry[a]	#	β-ketoester **1.5**	aryl azide **1.6**	%, yield **1.6**[b]
1	b			89
2	c			97

entry[a]	#	β-ketoester **1.5**	aryl azide **1.6**	%, yield **1.6**[b]
3	d			97
4	e			79
5	f			75

6	g			53
7	h			86
8	i			79
9	j			79 d.r. 91:9
10	k			63 d.r. 91:9
11	l			89
12	m			54 d.r. 50:50

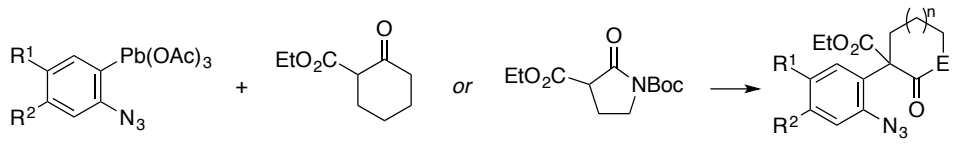
entry[a]	#	β-ketoester **1.5**	aryl azide **1.6**	%, yield **1.6**[b]
13	n			n.r.

[a] Reaction performed using 1 equiv of **1.4a**, 1.05 equiv of **1.5**, and 3 equiv of pyridine in $CHCl_3$ at 50 °C. [b] Isolated yield of **1.6** after silica gel chromatography; only product obtained.

Next, our method's scope was tested toward modifications to the 2-azidoaryllead reagent was examined. Towards this end, a variety of substituted 2-azidoaryllead triacetate was screened

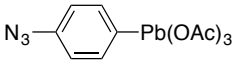
in the α-arylation of β-ketoester **1.5a** and γ-lactam **1.5i** (Table 1.3). For the α-arylation of β-ketoester **1.5a**, the 2-azidoaryllead reagent could be substituted with a halide or alkyl group at R^1 position (entries 1–3). The yield, however, depended on the electronic nature of substituents at aryllead reagent. The yield of the arylated product dropped when electron-poor aryllead reagents, **1.4b** and **1.4c** were used. This trend remained true with different substituents at R^2 position (entries 4–6): both the electron-rich (**1.4e**) and electron-neutral (**1.4f**) arylleads offered the excellent yields, but the yield dropped precipitously when an electron-withdrawing fluorine substituent was present. While the preparation of *m*-azidoaryllead reagent failed, the *p*-azidoaryllead acetate could be employed to provide the azide product without much diminishment of the yield (entry 7). To further explore the scope of our reaction, we examined the α-arylation of γ-lactam **1.5i**, which had never been used as nucleophile in the α-arylation reaction before our study (entries 8–12). We found that a variety of substituted 2-azidoaryllead acetates could be employed to arylate γ-lactam **1.5i** as well. Compared with β-ketoester **1.5a**, however, the reactivity was diminished in the α-arylation of γ-lactam **1.5i**. 3 equivalent of **1.4a** was often necessary to obtain the azide products with comparable yields (entry 10–12).

Table 1.3 ***Effect of changing the identity of 2-azidoaryllead acetate***



1.4 **1.5a** **1.5i** **1.6**

entry[a]	**1.4**	R^1	R^2	**1.5**	**1.6**	%, yield **1.6**[b]
1	b	F	H	a	o	67
2	c	Cl	H	a	p	67

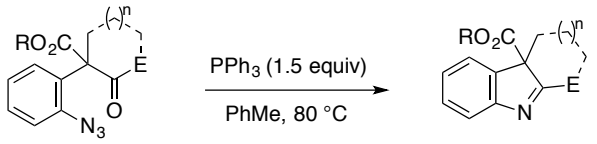
3	d	Me	H	a	q	77
4	e	H	OMe	a	r	94
5	f	H	Me	a	s	94
6	g	H	F	a	t	58[c]
7	h			a	u	67
8	b	F	H	i	v	75
9	c	Cl	H	i	w	56
10	d	Me	H	i	x	52[c]
11	f	H	Me	i	y	89[c]
12	g	H	F	i	z	42[c]

[a] Reaction performed using 1 equiv of **1.4**, 1.05 equiv of **1.5**, 3 equiv of pyridine in $CHCl_3$ at 50 °C. [b] Isolated yield of **1.6** after silica gel chromatography; only product obtained. [c] 3 equiv of **1.4** used.

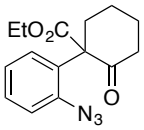
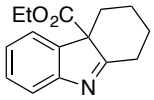
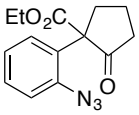
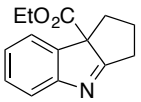
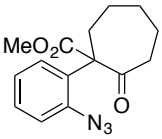
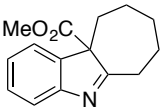
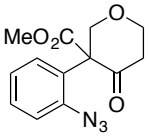
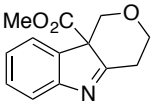
To demonstrate the utility of our α-arylation method, aryl azide **1.6** was submitted to a Staudinger reduction reaction (Table 1.4). Quantitative yield of 3*H*-indole **1.7** formation were observed when aryl azide **1.6** were exposed to triphenylphospine. We found the ring size of the β-ketoester didn't effect the Staudinger reaction (entries 1–3). While 3*H*-indole **1.7** with 5- to 7-membered ring could be formed, **1.7b** rapidly decomposed when exposed to air. The formation of 3*H*-indoles, **1.7g** and **1.7h**, demonstrated this Staugdinger reaction tolerated with heteroatoms as well (entries 4–5). It is notable that the Staudinger reaction could even be applied to γ-lactam to readily form 3*H*-pyrroloindole **1.7i**, whose structure is ubiquitous in bioactive alkaloids. Finally, the stereoselectivity of Staudinger reaction was examined by exposing the aryl azide **1.6k** to the reaction condition (entry 7). To our delight, we found 3*H*-indole **1.7k** was formed without loss of any diastereoselectivity. Base on these results, it is reasonable to conclude that when paired with

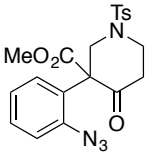
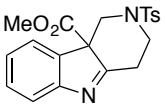
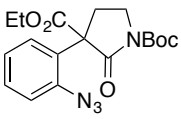
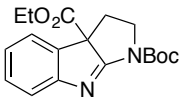
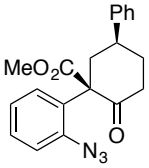
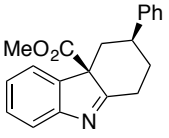
Staudinger reduction our α-arylation reaction offered a diastereoselective synthetic pathway to a range of 3*H*-indoles.

Table 1.4 ***Conversion of Azides to 3H-indoles***



1.6 **1.7**

entry	#	aryl aizde **1.6**	3*H*-indole **1.7**	%, yield **1.7**[a]
1	a			96
2	b			>95[b]
3	c			84
4	g			90

entry	#	aryl aizde **1.6**	3*H*-indole **1.7**	%, yield **1.7**[a]
5	h			95
6	i			92
7	k			91

[a] Isolated yield of **1.7** after silica gel chromatography. [b] As determined using 1H NMR spectroscopy; 3*H*-indole **1.7b** rapidly decomposed upon exposure to air

In conclusion, an α-arylation reaction of β-ketoester and γ-lactam using 2-azidoaryllead triacetates was developed to access a variety of complex aryl azides bearing a tetrasubstituted benzylic carbon. When paired with Staudinger reduction, the synthetic utility of our reaction was demonstrated to streamline the synthesis of 3*H*-indoles from aryl azides.

Experiment

A. General

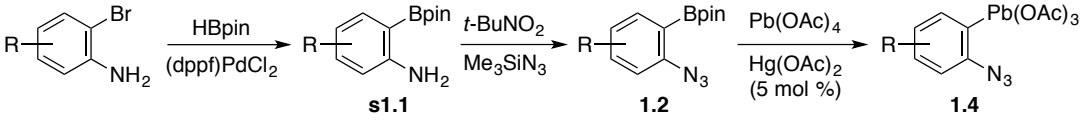
^{1}H NMR and ^{13}C NMR spectra were recorded at ambient temperature using 500 MHz or 300 MHz spectrometers. The data are reported as follows: chemical shift in ppm from internal tetramethylsilane on the δ scale, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), 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 according to the procedure of Grubbs. Metal salts were stored in a nitrogen atmosphere dry box.

B. Preparation of Substituted 2-Azidoarylead Acetates

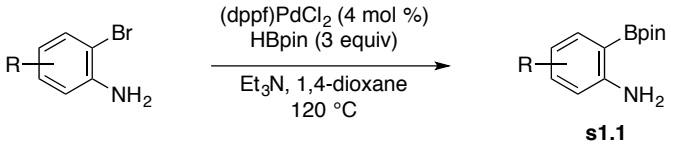
1. Substrate Synthesis Overview

The 2-azidoaryllead acatate 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. Azidation of **s1.1** 2-iodoaniline using trimethylsilyl azide following the conditions reported by Zhang and Moses produced 2-azidoarylboronic acid pinacolate ester **1.2**. Transmetallation to lead produces the requisite 2-azidoaryllead acetate **1.4** for our method development.



2. Synthesis of 2-Aminoarylboronic Acid Pinacolate Esters.

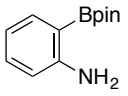
a. General Procedure



To a mixture of 2-bromoaniline (10.0 mmol), 5.60 mL of Et_3N (40.0 mmol), 0.701 g of $(PPh_3)_2PdCl_2$ (1.00 mmol) in 20 mL of 1,4-dioxane, was added dropwise 4.33 mL of 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (30.0s 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

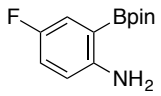
organic phases were washed with 1 × 30 mL of brine. The resulting organic phase was dried over Na_2SO_4, filtered, and the filtrate was concentrated *in vacuo*. Purification via MPLC afforded the product.

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



s1.1a

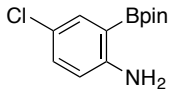
Aniline s1.1a. The general procedure was followed using 3.40 g of 2-bromoaniline (20.0 mmol), 8.7 mL of 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (60.0 mmol), 0.82 g of $(PPh_3)_2PdCl_2$ (1.0 mmol), and 8.4 mL of Et_3N (80.0 mmol) in 100 mL of 1, 4-dioxane. Purification by MPLC (2:100 – 10:90 EtOAc: hexanes) afforded the product as a light yellow solid (3.02 g, 69%): mp 62 – 64 °C; ^{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}.



s1.1b

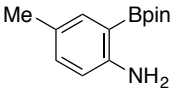
Aniline s1.1b. The general procedure was followed using 1.72 g of 2-bromo-4-fluoroaniline (10.0 mmol), 4.33 mL of 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (30.0 mmol), 0.701 g of $(PPh_3)_2PdCl_2$ (1.00 mmol), and 5.60 mL of Et_3N (40.0 mmol) in 20 mL of 1,4-dioxane. Purification by MPLC (0:100 – 20:80 EtOAc: hexanes) afforded the product as a light yellow solid (1.97 g, 83%); mp 50 – 52 °C; ^{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}.



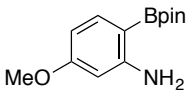
s1.1c

Aniline s1.1c. The general procedure was followed using 2.06 g of 2-bromo-4-chloroaniline (10.0 mmol), 4.33 mL of 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (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%): mp 62 – 64 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, J = 2.5 Hz, 1H), 7.13 (dd, J = 7.5, 2.5 Hz, 1H), 6.52 (d, J = 7.5 Hz, 1H), 4.65 (br, 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 peaks visible; ATR-FTIR (thin film): 3485, 3388, 2978, 1619, 1482, 1416, 1351, 1141, 963, 850 cm^{-1}.



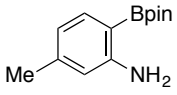
s1.1d

Aniline s1.1d. The general procedure was followed using 1.86 g of 2-bromo-4-methylaniline (10.0 mmol), 4.33 mL of 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (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 20 mL of 1,4-dioxane. Purification by MPLC (0:100 – 10:90 EtOAc: hexanes) afforded the product as a white solid (2.07 g, 89%): mp 60 °C; ^1H 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) only peaks visible; IR (thin film): 3500, 2980, 2244, 1618, 1576, 1496 cm^{-1}.



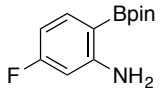
s1.1e

Aniline s1.1e. The general procedure was followed using 2.02 g of 2-bromo-5-methoxyaniline (10.0 mmol), 4.33 mL of 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (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 20 mL of 1,4-dioxane. Purification by MPLC (0:100 – 15:85 EtOAc: hexanes) afforded the product as a light yellow oil (2.31g, 93%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, J = 8.0 Hz, 1H), 6.28 (dd, J = 8.0, 2.0 Hz, 1H), 6.12 (d, J = 2.0 Hz, 1H), 4.82 (br, 2H), 3.76 (s, 3H), 1,34 (s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.7 (C), 155.6 (C), 138.3 (CH), 103.8 (CH), 99.3 (CH), 83.3 (C), 54.9 (CH_3), 24.9 (CH_3) only peaks visible; ATR-FTIR (thin film): 2976, 2934, 2832, 2101, 1601, 1565, 1345, 1035, 836 cm^{-1}; HRMS (EI) m/z calcd for $C_{13}H_{20}BNO_3$ $[M]^+$: 249.1536, found 249.1539.



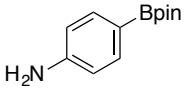
s1.1f

Aniline s1.1f. The general procedure was followed using 1.86 g of 2-bromo-5-methylaniline (10.0 mmol), 4.33 mL of 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (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 20 mL of 1,4-dioxane. Purification by MPLC (0:100 – 10:90 EtOAc: hexanes) afforded the product as a white solid (1.96 g, 84%): mp 68 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, J = 7.5 Hz, 1H), 6.52 (d, J = 7.5 Hz, 1H), 6.44 (s, 1H), 4.16 (br, 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 (C), 118.2 (CH), 115.4 (CH), 83.4 (C), 24.9 (CH_3), 21.7 (CH_3) only peaks visible; ATR-FTIR (thin film): 3473, 3370, 2972, 1617, 1563, 1507, 1435, 1357, 1305, 1247, 1143, 1305, 1247, 1143, 1098, 1052, 857 cm^{-1}.



s1.1g

Aniline s1.1g. The general procedure was followed using 1.90 g of 2-bromo-5-fluoroaniline (10.0 mmol), 4.33 mL of 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (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 20 mL of 1,4-dioxane. Purification by MPLC (0:100 – 20:80 EtOAc: hexanes) afforded the product as a white solid (1.92 g, 81%): mp 44 – 46 °C; this compound is commercially available: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (t, J = 7.5 Hz, 1H), 6.36 (td, J = 7.5, 2.5 Hz, 1H), 6.26 (dd, J = 6.5, 2.5 Hz, 1H), 4.86 (br, 2H), 1.33 (s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.4 (d, J_{CF} = 246.0 Hz, C), 155.7 (d, J_{CF} = 11.1 Hz, C), 139.0 (d, J_{CF} = 9.6 Hz, CH), 104.3 (d, J_{CF} = 20.4 Hz, CH), 101.0 (d, J_{CF} = 23.9 Hz, CH), 83.6 (C), 24.9 (CH_3) only peaks visible; ^{19}F NMR (282 MHz, $CDCl_3$) δ –108.5; ATR-FTIR (thin film): 3488, 3388, 2978, 1611, 1579, 1355, 1249, 1083, 960, 856 cm^{-1}.

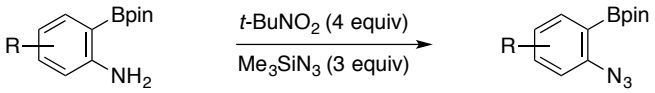


s1.1h

Aniline s1.1h. The general procedure was followed using 1.72 g of 2-bromo-5-fluoroaniline (10.0 mmol), 5.60 mL of 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (40.0 mmol), 0.701 g of $(PPh_3)_2PdCl_2$ (1.00 mmol), and 5.60 mL of Et_3N (40.0 mmol) in 20 mL of 1,4-dioxane. Purification by MPLC (0:100 – 15:85 EtOAc: hexanes) afforded the product as a white solid (1.95 g, 89%): mp 156 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, J = 8.5 Hz, 2H), 6.65 (d, J = 8.5 Hz, 2H), 3.79 (br, 2H), 1.34 (s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.4 (C), 136.4 (CH), 114.1 (C), 83.8 (C), 24.9 (CH_3) only peaks visible; ATR-FTIR (thin film): 3486, 3382, 2976, 1605, 1454, 1351, 1136, 1085, 846, 757, 654 cm^{-1}.

3. Synthesis of 2-Azidoarylboronic Acid Pinacolate Esters.

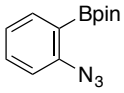
a. General Procedure.



s1.1 **1.2**

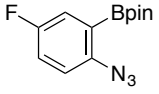
To a cooled solution (0 °C) of aniline **s1.1** in MeCN (0.2 M) was added dropwise *t*-$BuNO_2$ (4.0 equiv) and Me_3SiN_3 (3.0 equiv). The resulting solution was warmed to room temperature. After 1.5 h, the reaction mixture was concentrated *in vacuo*. Purification of the residue by MPLC (0:100 – 5:95 EtOAc: hexanes) afforded the 2-azidoarylboronic acid pinacolate ester **1.2**.

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



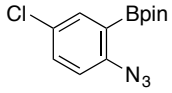
1.2a

2-Azidophenylboronic acid pinacolate ester 1.2a. The general procedure was followed by using 1.60 g of aniline **s1.1a** (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 (0.930 g, 52%); ^{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 peaks visible. ATR-FTIR (thin film): 2976, 2112, 2076, 1594, 1572, 1487, 1432, 1351, 1316, 1279, 1143, 1110, 1058, 1036, 836, 747 cm^{-1}.



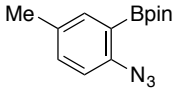
1.2b

2-Azido-5-fluorophenylboronic acid pinacolate ester 1.2b. The general procedure was followed by using 1.18 g of aniline **s1.1b** (5.00 mmol), 2.40 mL of *t*-$BuNO_2$ (20.0 mmol) and 2.00 mL of Me_3SiN_3 (15.00 mmol) in 20 mL of MeCN. Purification by MPLC (0:100 – 15:85 EtOAc:hexanes) afforded the product, a brown oil (0.447 g, 34%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (dd, *J* = 7.5, 3.0 Hz, 1H), 7.12 – 7.04 (m, 2H), 1.34 (s, 12H); ^{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; ^{19}F NMR (282 MHz, $CDCl_3$) δ –119.4; ATR-FTIR (thin film): 2989, 2121, 2092, 1485, 1416, 1319, 1200, 1143, 1126, 966, 916, 807, 763 cm^{-1}.



1.2c

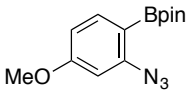
2-Azido-5-chlorophenylboronic acid pinacolate ester 1.2c. The general procedure was followed by using 1.26 g of aniline **s1.1c** (5.00 mmol), 2.40 mL of *t*-$BuNO_2$ (20.0 mmol) and 2.00 mL of Me_3SiN_3 (15.0 mmol) in 20 mL of MeCN. Purification by MPLC (0:100 – 15:85 EtOAc:hexanes) afforded the product, a brown oil (0.753 g, 54%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (s, 1H), 7.38 (d, *J* = 7.5 Hz, 1H), 7.06 (d, *J* = 7.5 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 peaks visible; ATR-FTIR (thin film): 2978, 2116, 2083, 1590. 1479, 1334, 1140, 1105, 963, 869, 847, 812 cm^{-1}.



1.2d

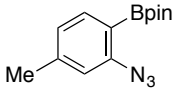
2-Azido-5-methylphenylboronic acid pinacolate ester 1.2d. The general procedure was followed by using 1.16 g of aniline **s1.1d** (5.00 mmol), 2.40 mL of *t*-$BuNO_2$ (20.0 mmol) and 2.00 mL of Me_3SiN_3 (15.0 mmol) in 20 mL of MeCN. Purification by MPLC (0:100 – 15:85

EtOAc:hexanes) afforded the product, a brown oil (0.622 g, 48%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (s, 1H), 7.18 (d, *J* = 8.0 Hz, 1H), 6.97 (d, *J* = 8.0 Hz, 1H), 2.26 (s, 3H), 1.32 (s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.1 (C), 137.4 (CH), 133.6 (C), 133.0 (CH), 118.0 (CH), 83.8 (C), 24.8 (CH_3), 20.6 (CH_3) only peaks visible; ATR-FTIR (thin film): 2979, 2924, 2118, 2092, 1579, 1487, 1400, 1345, 1312, 1269, 1146, 906, 730 cm^{-1}.



1.2e

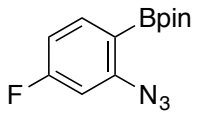
2-Azido-4-methoxyphenylboronic acid pinacolate ester 1.2e. The general procedure was followed by using 1.24 g of aniline **s1.1e** (5.00 mmol), 2.40 mL of *t*-$BuNO_2$ (20.0 mmol) and 2.00 mL of Me_3SiN_3 (15.0 mmol) in 20 mL of MeCN. Purification by MPLC (0:100 – 15:85 EtOAc:hexanes) afforded the product, a brown oil (0.893 g, 65%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.5 Hz, 1H), 6.67 – 6.64 (m, 2H), 3.82 (s, 3H), 1.34 (s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.1 (C), 146.6 (C), 138.8 (CH), 110.0 (C), 104.3 (CH), 83.7 (C), 55.3 (CH_3), 24.8 (CH_3) only peaks visible; ATR-FTIR (thin film): 2979, 2973, 2101, 1601, 1565, 136, 1228, 1151, 1111, 1035, 837, 649 cm^{-1}.



1.2f

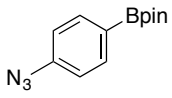
2-Azido-4-methylphenylboronic acid pinacolate ester 1.2f. The general procedure was followed by using 1.16 g of aniline **s1.1f** (5.00 mmol), 2.40 mL of *t*-$BuNO_2$ (20.0 mmol) and 2.00 mL of Me_3SiN_3 (15.0 mmol) in 20 mL of MeCN. Purification by MPLC (0:100 – 15:85 EtOAc:hexanes) afforded the product, a brown oil (0.595 g, 46%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (d, *J* = 7.5 Hz, 1H), 6.95 – 6.93 (m, 2H), 2,36 (s, 3H), 1.36 (s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.8 (C), 143.0 (C), 137.1 (CH), 125.2 (CH), 118.8 (CH), 83.8 (C), 24.8 (CH_3), 21.6

(CH_3) only peaks visible; ATR-FTIR (thin film): 2979, 2931, 2102, 1615, 1556, 1341, 1257, 1153, 1120, 1055, 961, 863, 815 cm^{-1}.



1.2g

2-Azido-4-fluorophenylboronic acid pinacolate ester 1.2g. The general procedure was followed by using 1.18 g of aniline **s1.1g** (5.00 mmol), 2.40 mL of *t*-$BuNO_2$ (20.0 mmol) and 2.00 mL of Me_3SiN_3 (15.0 mmol) in 20 mL of MeCN. Purification by MPLC (0:100 – 15:85 EtOAc:hexanes) afforded the product, a brown oil (0.447 g, 34%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (t, J = 7.5 Hz, 1H), 6.84 – 6.79 (m, 2H), 1.34 (s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.3 (d, J_{CF} = 249.7 Hz, C), 147.1 (d, J_{CF} = 7.6 Hz, C), 139.1 (d, J_{CF} = 9.1 Hz, CH), 111.6 (d, J_{CF} = 20.1 Hz, CH), 105.7 (d, J_{CF} = 21.1, CH), 84.0 (C), 24.8 (CH_3) only peaks visible; ^{19}F NMR (282 MHz, $CDCl_3$) δ –107.0; ATR-FTIR (thin film): 2979, 2106, 1585, 1406, 1347, 1205, 1143, 1100, 1054, 955, 858, 650 cm^{-1}.

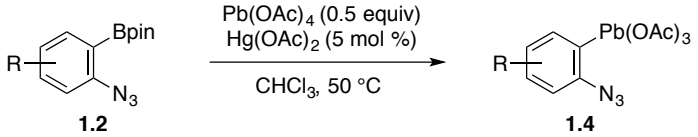


1.2h

4-Azidophenylboronic acid pinacolate ester 1.2h. The general procedure was followed by using 1.09 g of aniline **s1.1h** (5.00 mmol), 2.40 mL of *t*-$BuNO_2$ (20.0 mmol) and 2.00 mL of Me_3SiN_3 (15.0 mmol) in 20 mL of MeCN. Purification by MPLC (0:100 – 15:85 EtOAc:hexanes) afforded the product, a brown oil (0.585 g, 45%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, J = 7.5 Hz, 2H), 7.01 (d, J = 7.5 Hz, 2H), 1.34 (s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.9 (C), 136.4 (CH), 118.3 (CH), 83.9 (C), 14.1 (CH_3) only peaks visible; ATR-FTIR (thin film): 2978, 2127, 2106, 1600, 1355, 1286, 1143, 1085, 962, 858, 832, 731 cm^{-1}.

4. Synthesis of 2-Azidoaryllead Acetates.

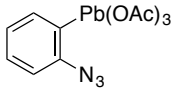
a. General Procedure.



1.2 **1.4**

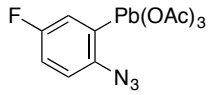
To a flame-dried round bottom flask—evacuated and back filled three times with nitrogen—was added $Pb(OAc)_4$ (0.5 equiv) and 5 mol % of $Hg(OAc)_2$. To this mixture was added a solution of 2-azidoarylboronic acid pinacolate ester **1.2** in chloroform. The resulting mixture was heated to 50 °C. After 16 h, the reaction was cooled to room temperature, filtered with a plug of celite and filtrate was concentrated in vacuo. Then the residue was washed with hexane to afforded 2-azidoaryllead acetate **1.4**. Attempts to analyze the aryllead products by a variety of HRMS techniques were not successful; LRMS data is included instead.

b. Characterization Data for 2-Azidoaryllead Acetates.



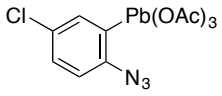
1.4a

2-Azidophenyllead acetate 1.4a. The general procedure was followed using 0.490 g of 2-azidophenylboronic acid pinacolate ester **1.2a** (2.00 mmol), 0.443 g of $Pb(OAc)_4$ (1.00 mmol)$_4$ and 0.033 g of $Hg(OAc)_2$ (0.1 mmol) in 10 mL of chloroform. Purification afforded the product as as a light yellow solid (0.342 g, 68%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, J = 8.0 Hz, 1H), 7.54 (t, J = 8.0 Hz, 1H), 7.38 (t, J = 8.0 Hz, 1H), 7.31 (d, J = 8.0 Hz, 1H), 2.12 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.3 (C), 152.1 (C), 141.3 (C), 133.1 (CH), 132.4 (CH), 127.6 (CH), 119.5 (CH), 20.2 (CH_3). ATR-FTIR (thin film): 2935, 2131, 1581, 1557, 1461, 1369, 1338, 1304, 1006, 949, 753 cm^{-1}. LRMS (EI) m/z calcd for $C_{10}H_{10}N_3O_4Pb$ $[M - OAc]^+$: 444.0, found 444.0.



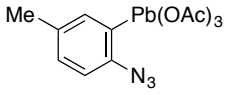
1.4b

2-Azido-5-fluorophenyllead acetate 1,4b. The general procedure was followed using 0.395 g of 2-azido-5-fluorophenylboronic acid pinacolate ester **1.2b** (1.50 mmol), 0.332 g of $Pb(OAc)_4$ $(0.750\ mmol)_4$ and 0.025 g of $Hg(OAc)_2$ (0.080 mmol) in 10 mL of chloroform. Purification afforded the product as a brown solid (0.132 g, 34%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (s, 1H), 7.27 – 7.23 (m, 2H), 2.11 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.4 (C), 160.7 (d, J_{CF} = 253.5 Hz, C), 137.3 (d, J_{CF} = 3.5 Hz, C), 120.4 (d, J_{CF} = 23.8 Hz, CH), 120.1 (d, J_{CF} = 7.1 Hz, CH), 119.8 (d, J_{CF} = 25.5 Hz, CH), 20.0 (CH_3) only peaks visible; ^{19}F NMR (282 MHz, $CDCl_3$) δ – 112.1. ATR-FTIR (thin film): 3088, 2123, 1560, 1473, 1374, 1340, 1265, 1205, 1016, 879, 693 cm^{-1}. LRMS (EI) m/z calcd for $C_{10}H_9FN_3O_4Pb$ $[M - OAc]^+$: 462.0, found 462.0.



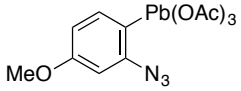
1.4c

2-Azido-5-chlorophenyllead acetate 1.4c. The general procedure was followed using 0.558 g of 2-azido-5-fluorophenylboronic acid pinacolate ester **1.2c** (2.00 mmol), 0.443 g of $Pb(OAc)_4$ (1.00 $mmol)_4$ and 0.033 g of $Hg(OAc)_2$ (0.10 mmol) in 10 mL of chloroform. Purification afforded the product as a brown solid (0.226 g, 41%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.46 (s, 1H), 7.24 (s, 1H), 2.10 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.4 (C), 152.5 (C), 139.8 (C), 133.2 (CH), 133.0 (C), 132.2 (CH), 120.1 (C), 20.0 (CH_3). ATR-FTIR (thin film): 3077, 2132, 2106, 1558, 1459, 1376, 1296, 1103, 1017, 814, 694 cm^{-1}. LRMS (EI) m/z calcd for $C_{10}H_9ClN_3O_4Pb$ $[M - OAc]^+$: 478.0, found 477.9.



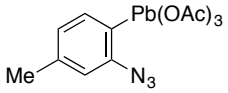
1.4d

2-Azido-5-methylphenyllead acetate 1.4d. The general procedure was followed using 0.555 g of 2-azido-5-methylphenylboronic acid pinacolate ester **1.2d** (2.14 mmol), 0.474 g of $Pb(OAc)_4$ $(1.07\ mmol)_4$ and 0.035 g of $Hg(OAc)_2$ (0.11 mmol) in 10 mL of chloroform. Purification afforded the product as a yellow solid (0.242 g, 45%): ^1H NMR (500 MHz, $CDCl_3$) δ 7.61 (s, 1H), 7.31 (d, J = 8.0 Hz, 1H), 7.19 (d, J = 8.0 Hz, 1H), 2.39 (s, 3H), 2.10 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.2 (C), 151.7 (C), 138.3 (C), 138.2 (CH), 133.8 (C), 132.2 (CH), 119.1 (C), 21.3 (CH_3), 20.3 (CH_3). ATR-FTIR (thin film): 2970, 2120, 1559, 1480, 1396, 1305, 1017, 692 cm^{-1}. LRMS (EI) m/z calcd for $C_7H_7N_3Pb$ $[M - 3\ OAc + H]^+$: 341.0, found 340.9.



1.4e

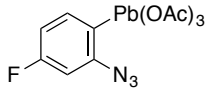
2-Azido-4-methoxyphenyllead acetate 1.4e. The general procedure was followed using 0.605 g of 2-azido-4-methoxyphenylboronic acid pinacolate ester **1.2e** (2.20 mmol), 0.487 g of $Pb(OAc)_4$ $(1.10\ mmol)_4$ and 0.036 g of $Hg(OAc)_2$ (0.11 mmol) in 10 mL of chloroform. Purification afforded the product as a yellow solid (0.309 g, 56%): ^1H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, J = 9.0 Hz, 1H), 6.86 (dd, J = 9.0, 2.5 Hz, 1H), 6.76 (d, J = 2.5 Hz, 1H), 3.85 (s, 3H), 2.10 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.1 (C), 163.4 (C), 144.0 (C), 142.6 (C), 133.4 (CH), 112.6 (CH), 105.2 (CH), 56.0 (CH_3), 20.4 (CH_3). ATR-FTIR (thin film): 2941, 2117, 1568, 1476, 1375, 1323, 1225, 1042, 839, 692 cm^{-1}. LRMS (EI) m/z calcd for $C_{11}H_{12}N_3O_5Pb$ $[M - OAc]^+$: 474.0, found 474.0.



1.4f

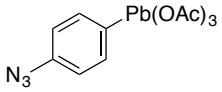
2-Azido-4-methylphenyllead acetate 1.4f. The general procedure was followed using 0.388 g of 2-azido-4-methylphenylboronic acid pinacolate ester **1.2f** (1.50 mmol), 0.332 g of $Pb(OAc)_4$ $(0.750\ mmol)_4$ and 0.026 g of $Hg(OAc)_2$ (0.080 mmol) in 10 mL of chloroform. Purification

afforded the product as a yellow solid (0.151 g, 40%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, J = 8.0 Hz, 1H), 7.17 (d, J = 8.0 Hz, 1H), 7.10 (s, 1H), 2.42 (s, 3H), 2.10 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.2 (C), 149.4 (C), 144.2 (C), 134.8 (C), 132.0 (CH), 128.3 (CH), 119.9 (CH), 21.5 (CH_3), 20.3 (CH_3). ATR-FTIR (thin film): 2923, 2113, 1573, 1392, 1297, 1007, 809, 692 cm^{-1}. LRMS (EI) m/z calcd for $C_7H_7N_3Pb$ [M – 3 OAc + H]$^+$: 341.0, found 340.9.



1.4g

2-Azido-4-fluorophenyllead acetate 1.4g. The general procedure was followed using 0.394 g of 2-azido-4-fluorophenylboronic acid pinacolate ester **1.2g** (1.50 mmol), 0.332 g of $Pb(OAc)_4$ (0.750 mmol)$_4$ and 0.026 g of $Hg(OAc)_2$ (0.080 mmol) in 10 mL of chloroform. Purification afforded the product as a brown solid (0.121 g, 32%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.07 – 7.02 (m, 2H), 2.11 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.1 (C), 165.2 (d, J_{CF} = 252.3 Hz, C), 143.4 (d, J_{CF} = 8.9 Hz, C), 134.3 (d, J_{CF} = 9.3 Hz, CH), 114.7 (d, J_{CF} = 22.1 Hz, CH), 107.0 (d, J_{CF} = 25.8 Hz, CH), 20.2 (CH_3) only peaks visible; ^{19}F NMR (282 MHz, $CDCl_3$) δ –104.6. ATR-FTIR (thin film): 2931, 2121, 1568, 1399, 1471, 1399, 1295, 1201, 1014, 952, 842, 693 cm^{-1}. LRMS (EI) m/z calcd for $C_6H_3FN_3Pb$ [M – 3 OAc + H]$^+$: 345.0, found 344.9.



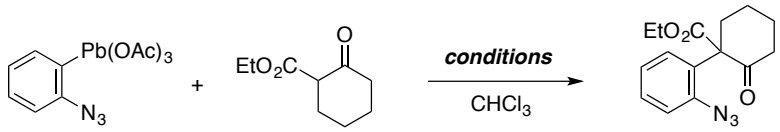
1.4h

4-Azidophenyllead acetate 1.4h. The general procedure was followed using 0.490 g of 4-azidophenylboronic acid pinacolate ester **1.2h** (2.00 mmol), 0.443 g of $Pb(OAc)_4$ (1.00 mmol)$_4$ and 0.033 g of $Hg(OAc)_2$ (0.10 mmol) in 10 mL of chloroform. Purification afforded the product as a light yellow solid (0.326 g, 65%): ^{1}H NMR (500 MHz, $CDCl_3$) 7.64 (d, J = 8.5 Hz, 2H), 7.19 (d, J = 8.5 Hz, 2H), 1.18 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.6 (C), 157.4 (C), 144.1 (C),

132.7 (CH), 121.2 (CH), 24.6 (CH_3); ATR-FTIR (thin film): 2931, 2124, 1557, 1479, 1395, 1291, 1274, 1182, 1000, 810, 691 cm^{-1}. LRMS (EI) m/z calcd for $C_{10}H_{10}N_3O_4Pb$ $[M - OAc]^+$: 444.0, found 444.0.

C. α-Arylation of β-Ketoesters using 2-Azidoaryllead Acetates.

1. Screening of Reaction Conditions.



1.4a **1.5a** **1.6a**

A flame-dried 10 mL round bottom flask was evacuated and back filled three times with nitrogen. To this flask was added a solution of β-ketoester **1.5a** and a Lewis base in 1.5 mL of chloroform. To this mixture was added dropwise a solution of 2-azidophenyllead acetate **1.4a** in 1.5 mL of chloroform. The resulting mixture was heated. After 12h, the reaction mixture was cooled to room temperature and poured into 5 mL of a saturated aqueous solution of NH_4Cl. The mixture was extracted with 2 × 5 mL of dichloromethane. 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 (0:100 – 20:80 EtOAc:hexanes) afforded α-aryl-β-ketoester **1.6a**.

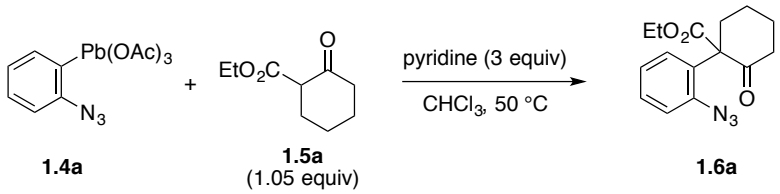
Table 1.5 ***Survey of reaction conditions for α-arylation of β-keto-ester 1.5a using 2-azidophenyllead acetate 1.4a.***

entry	base (equiv)	equiv **1.4a**	equiv **1.5a**	T (°C)	**1.6a** %, yield[a]
1	none	1	5	25	90
2	none	1	3	25	89

3	none	1	1.05	25	59
4	dabco (3)	1	3	25	78
5[b]	phenanthroline (3)	1	3	25	83
6	pyridine (3)	1	3	25	90
7	dabco (3)	1	1.05	25	44
8	phenanthroline (3)	1	1.05	25	62
9	pyridine (3)	1	1.05	25	78
10	pyridine (3)	1	1.05	25	78
11	pyridine (3)	1	1.05	50	87
12	pyridine (3)	1.05	1	50	83
13	pyridine (3)	3	1	50	88
14	pyridine (3)	1	1.05	50	45[b]

[a] as determined using ^{1}H NMR spectroscopy using CH_2Br_2 as the internal standard. [b] Two-step yield from **1.2a**.

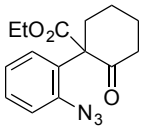
2. Optimal Conditions.



1.4a + **1.5a** (1.05 equiv) → **1.6a**

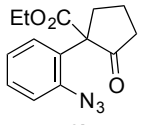
A flame-dried 10 mL round bottom flask was evacuated and back filled three times with nitrogen. To this flask was added a solution of β-ketoester **1.5a** (1.05 equiv) and pyridine (3 equiv) in 1.5 mL of chloroform. To this mixture was added dropwise a solution of 2-azidophenyllead acetate **1.4a** (1.00 equiv) in 1.5 mL of chloroform. The resulting mixture was heated to 50 °C. After 12h, the reaction mixture was cooled to room temperature and poured into 5 mL of a saturated aqueous solution of NH_4Cl. The mixture was extracted with 2 × 5 mL of dichloromethane. 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 (0:100 – 20:80 EtOAc:hexanes) afforded α-aryl-β-ketoester **1.6a**.

3. Characterization Data for α-aryl-β-ketoesters 1.6.



1.6a

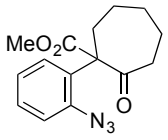
α-Aryl-β-ketoester 1.6a. The optimal procedure was followed by using 0.0460 g of β-ketoester **1.5a** (0.260 mmol), 0.126 g of 2-azidophenyllead acetate **1.4a** (0.250 mmol), 0.0590 g of pyridine (0.750 mmol) in 3 mL total of chloroform. Purification by MPLC (3:97 – 20:80 EtOAc:hexane) afforded the product as a yellow solid (0.0620 g, 87%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.33 (m, 1H), 7.18 (d, *J* = 8.0 Hz, 1H), 7.15 – 7.10 (m, 2H), 4.30 – 4.18 (m, 1H), 2.75 – 2.69 (m, 2H), 2.63 – 2.51 (m, 3H), 2.00 – 1.96 (m, 1H), 1.91 – 1.84 (m, 1H), 1.84 – 1.66 (m, 2H), 1.24 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.2 (C), 170.8 (C), 138.6 (C), 130.2 (C), 128.9 (CH), 128.3 (CH), 125.0 (CH), 119.3 (CH), 65.6 (C), 61.7 (CH_2), 40.9 (CH_2), 35.7 (CH_2), 26.9 (CH_2), 22.0 (CH_2), 14.0 (CH_3); ATR-FTIR (thin film): 2937, 2865, 2128, 2095, 1715, 1293, 1234, 1208, 1127, 747 cm^{-1}. HRMS (EI) m/z calcd for $C_{15}H_{17}N_3O_3Na$ $[M+Na]^+$: 310.1168, found 310.1167.



1.6b

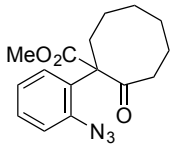
α-Aryl-β-ketoester 1.6b. The optimal procedure was followed by using 0.0410 g of β-ketoester **1.5b** (0.260 mmol), 0.126 g of 2-azidophenyllead acetate **1.4a** (0.250 mmol), 0.0590 g of pyridine (0.750 mmol) in 3 mL total of chloroform. Purification by MPLC (3:97 – 20:80 EtOAc:hexane) afforded the product as a yellow solid (0.0610 g, 89%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (td, *J* = 7.0, 1.5 Hz, 1H), 7.18 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.09 (td, *J* = 8.0, 1.0 Hz, 1H), 7.00 (dd, *J* = 8.0, 1.0 Hz, 1H), 4.30 – 4.16 (m, 2H), 3.02 – 2.97 (m, 1H), 2.51 (td, *J* = 8.0, 1.0 Hz, 2H), 2.35 – 2.30

(m, 1H), 2.10 – 2.01 (m, 1H), 1.89 – 1.80 (m, 1H), 1.23 (t, J = 7.0, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.2 (C), 169.8 (C), 137.9 (C), 130.7 (C), 128.8 (CH), 128.3 (CH), 124.9 (CH), 119.2 (CH), 65.1 (C), 62.0 (CH_2), 38.3 (CH_2), 35.7 (CH_2), 19.7 (CH_2), 14.1 (CH_3); ATR-FTIR (thin film): 2980, 2125, 1752, 1721, 1488, 1291, 1230, 1156, 1021, 752 cm^{-1}. HRMS (EI) m/z calcd for $C_{14}H_{15}N_3O_3Na$ $[M+Na]^+$: 296.1011, found 296.1013.



1.6c

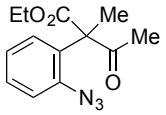
α-Aryl-β-ketoester 1.6c. The optimal procedure was followed by using 0.0450 g of β-ketoester **1.5c** (0.260 mmol), 0.126 g of 2-azidophenyllead acetate **1.4a** (0.250 mmol), 0.0590 g of pyridine (0.750 mmol) in 3 mL total of chloroform. Purification by MPLC (3:97 – 20:80 EtOAc:hexane) afforded the product as a yellow solid (0.0700 g, 97%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.32 (m, 1H), 7.17 (d, J = 8.0 Hz, 1H), 7.14 – 7.09 (m, 2H), 3.32 (s, 3H), 2.89 – 2.83 (m, 2H), 2.73 – 2.68 (m, 1H), 2.16 – 2.11 (m, 1H), 1.77 – 1.69 (m, 5H), 1.55 – 1.51 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.3 (C), 172.2 (C), 138.4 (C), 131.5 (C), 128.8 (CH), 128.6 (CH), 124.8 (CH), 119.2 (CH), 67.2 (C), 52.7 (CH_3), 42.9 (CH_2), 34.0 (CH_2), 30.6 (CH_2), 26.7 (CH_2), 25.6 (CH_2); ATR-FTIR (thin film): 2934, 2861, 2124, 2094, 1736, 1706, 1488, 1444, 1289, 1229, 1155, 1005, 753 cm^{-1}. HRMS (EI) m/z calcd for $C_{15}H_{17}N_3O_3Na$ $[M+Na]^+$: 310.1168, found 310.1163.



1.6d

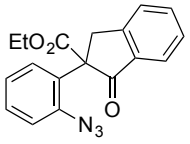
α-Aryl-β-ketoester 1.6d. The optimal procedure was followed by using 0.0480 g of β-ketoester **1.5d** (0.260 mmol), 0.126 g of 2-azidophenyllead acetate **1.4a** (0.250 mmol), 0.0590 g of pyridine

(0.750 mmol) in 3 mL total of chloroform. Purification by MPLC (3:97 – 20:80 EtOAc:hexane) afforded the product as a yellow solid (0.0730 g, 97%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.35 (td, *J* = 7.5, 1.0 Hz, 1H), 7.18 – 7.15 (m, 2H), 3.69 (s, 3H), 2.88 – 2.76 (m, 2H), 2.45 – 2.39 (m, 2H), 1.94 – 1.87 (m, 1H), 1.80 – 1.74 (m, 1H), 1.66 – 1.53 (m, 4H), 1.37 – 1.25 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.1 (C), 171.1 (C), 138.4 (C), 129.7 (CH), 129.1 (C), 128.8 (CH), 124.7 (CH), 119.1 (CH), 66.5 (C), 52.8 (CH_3), 38.6 (CH_2), 31.2 (CH_2), 28.8 (CH_2), 25.7 (CH_2), 25.4 (CH_2), 24.0 (CH_2); ATR-FTIR (thin film): 2928, 2857, 2124, 2092, 1733, 1705, 1485, 1443, 1289, 1218, 1156, 751 cm^{-1}. HRMS (EI) m/z calcd for $C_{16}H_{19}N_3O_3Na$ $[M+Na]^+$: 324.1324, found 324.1321.



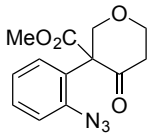
1.6e

α-Aryl-β-ketoester 1.6e. The optimal procedure was followed by using 0.0360 g of β-ketoester **1.5e** (0.260 mmol), 0.126 g of 2-azidophenyllead acetate **1.4a** (0.250 mmol), 0.0590 g of pyridine (0.750 mmol) in 3 mL total of chloroform. Purification by MPLC (3:97 – 20:80 EtOAc:hexane) afforded the product as a yellow oil (0.0680 g, 79%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.35 (m, 1H), 7.19 (d, *J* = 8.0 Hz, 1H), 7.17 – 7.13 (m, 2H), 4.26 (dq, *J* = 7.0, 2.0 Hz, 2H), 2.26 (s, 3H), 1.72 (s, 3H), 1.28 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.6 (C), 171.4 (C), 137.8 (C), 131.8 (C), 129.1 (CH), 128.4 (CH), 125.2 (CH), 119.2 (CH), 63.6 (C), 61.8 (CH_2), 27.8 (CH_3), 21.3 (CH_3), 14.0 (CH_3); ATR-FTIR (thin film): 2983, 2125, 2094, 1711, 1488, 1444, 1288, 1239, 1103, 1018, 853, 751 cm^{-1}. HRMS (EI) m/z calcd for $C_{13}H_{15}N_3O_3Na$ $[M+Na]^+$: 284.1011, found 284.1002.



1.6f

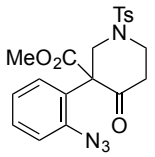
α-Aryl-β-ketoester 1.6f. The optimal procedure was followed by using 0.0480 g of β-ketoester **1.5f** (0.260 mmol), 0.126 g of 2-azidophenyllead acetate **1.4a** (0.250 mmol), 0.0590 g of pyridine (0.750 mmol) in 3 mL total of chloroform. Purification by MPLC (3:97 – 20:80 EtOAc:hexane) afforded the product as a yellow oil (0.0800 g, 75%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.0 Hz, 1H), 7.65 (t, *J* = 8.0 Hz, 1H), 7.46 (d, *J* = 7.5 Hz, 1H), 7.42 (t, *J* = 8.0 Hz, 1H), 7.34 (td, *J* = 7.5, 1.5 Hz, 1H), 7.20 (td, *J* = 8.0, 1.5 Hz, 2H), 7.08 (td, *J* = 8.0, 1.0 Hz, 1H), 4.46 (d, *J* = 17.5 Hz, 2H), 3.75 (s, 3H), 3.22 – 3.19 (d, *J* = 17.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.4 (C), 170.1 (C), 153.1 (C), 138.4 (C), 136.1 (CH), 134.9 (C), 131.5 (C), 128.9 (CH), 128.3 (CH), 127.9 (CH), 126.4 (CH), 125.0 (CH), 118.8 (CH), 64.7 (C), 53.5 (CH_3), 41.1 (CH_2) only peaks visible; ATR-FTIR (thin film): 2950, 2123, 1710, 1606, 1486, 1275, 1211. 1155, 1006, 886, 752 cm^{-1}. HRMS (EI) m/z calcd for $C_{17}H_{13}N_3O_3Na$ $[M+Na]^+$: 330.0855, found 330.0854.



1.6g

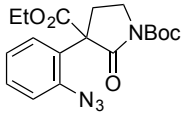
α-Aryl-β-ketoester 1.6g. The optimal procedure was followed by using 0.0420 g of β-ketoester **1.5g** (0.260 mmol), 0.126 g of 2-azidophenyllead acetate **1.4a** (0.250 mmol), 0.0590 g of pyridine (0.750 mmol) in 3 mL total of chloroform. Purification by MPLC (3:97 – 20:80 EtOAc:hexane) afforded the product as a yellow oil (0.0360 g, 75%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (t, *J* = 8.0 Hz, 1H), 7.20 (d, *J* = 8.0 Hz, 1H), 7.14 (t, *J* = 8.0 Hz, 1H), 7.10 (d, *J* = 8.0 Hz, 1H), 4.57 (d, *J* = 11.5 Hz, 1H), 4.36 (d, *J* = 11.5 Hz, 1H), 4.24 – 4.21 (m, 1H), 4.01 (td, *J* = 11.0, 1.0 Hz, 1H), 3.85 (s, 3H), 2.94 – 2.87 (m, 1H), 2.65 (td, *J* = 15.0, 3.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ

200.3 (C), 169.8 (C), 138.2 (C), 129.6 (CH), 129.3 (CH), 126.2 (C), 125.2 (CH), 119.4 (CH), 73.5 (CH_2), 67.9 (CH_2), 67.2 (C), 53.3 (CH_3), 40.9 (CH_2); ATR-FTIR (thin film): 2954, 2127, 1725, 1489, 1358, 1290, 1238, 1162, 1091, 1004, 946, 754, 736 cm^{-1}. HRMS (EI) m/z calcd for $C_{13}H_{13}N_3O_3Na$ $[M+Na]^+$: 298.0804, found 298.0803.



1.6h

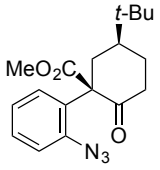
α-Aryl-β-ketoester 1.6h. The optimal procedure was followed by using 0.0780 g of β-ketoester **1.5h** (0.260 mmol), 0.126 g of 2-azidophenyllead acetate **1.4a** (0.250 mmol), 0.0590 g of pyridine (0.750 mmol) in 3 mL total of chloroform. Purification by MPLC (3:97 – 20:80 EtOAc:hexane) afforded the product as a white solid (0.0910 g, 86%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, J = 8.0 Hz, 2H), 7.39 (td, J = 7.5, 1.5 Hz, 1H), 7.34 (d, J = 8.0 Hz, 2H), 7.18 – 7.12 (m, 3H), 4.14 – 4.11 (m, 1H), 3.83 (s, 3H), 3.79 (d, J = 12.0 Hz, 1H), 3.67 – 3.65 (m, 1H), 3.25 – 3.21 (m, 1H), 2.89 – 2.84 (m, 1H), 2.78 – 2.74 (m, 1H), 2.45 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.7 (C), 169.0 (C), 144.2 (C), 138.0 (C), 133.4 (C), 130.0 (CH), 129.8 (CH), 129.5 (CH), 127.6 (CH), 126.4 (C), 125.4 (CH), 119.3 (CH), 65.7 (C), 53.5 (CH_3), 52.6 (CH_2), 46.1 (CH_2), 39.4 (CH_2), 21.6 (CH_3); ATR-FTIR (thin film): 2954, 2129, 1489, 1358, 1239, 1163, 1092, 1004, 946, 755, 736 cm^{-1}. HRMS (EI) m/z calcd for $C_{20}H_{20}N_4O_5NaS$ $[M+Na]^+$: 451.1052, found 451.1049.



1.6i

α-Aryl-β-ketoester 1.6i. The optimal procedure was followed by using 0.0640 g of β-ketoester **1.5i** (0.260 mmol), 0.126 g of 2-azidophenyllead acetate **1.4a** (0.250 mmol), 0.0590 g of pyridine (0.750 mmol) in 3 mL total of chloroform. Purification by MPLC (3:97 – 20:80 EtOAc:hexane)

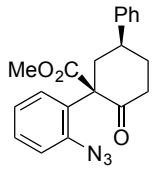
afforded the product as a yellow oil (0.0710 g, 79%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (td, *J* = 8.0, 1.0 Hz, 1H), 7.26 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.18 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.13 (td, *J* = 8.0, 1.0 Hz, 1H), 4.33 – 4.15 (m, 2H), 3.89 – 3.84 (m, 1H), 3.53 – 3.48 (m, 1H), 3.18 – 3.13 (m, 1H), 2.20 – 2.15 (m, 1H), 1.55 (s, 9H), 1.22 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.6 (C), 169.3 (C), 150.0 (C), 137.8 (C), 129.6 (C), 129.2 (CH), 128.3 (CH), 125.1 (CH), 118.9 (CH), 83.6 (C), 62.4 (CH_2), 61.9 (C), 43.6 (CH_2), 30.1 (CH_2), 28.0 (CH_3), 14.0 (CH_3); ATR-FTIR (thin film): 2982, 2124, 2095, 1783, 1723, 1488, 1367, 1288, 1232, 1147, 1105, 1010, 942, 853, 751, 732 cm^{-1}. HRMS (EI) m/z calcd for $C_{18}H_{22}N_4O_5Na$ $[M+Na]^+$: 397.1488, found 397.1488.



1.6j

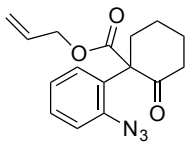
α-Aryl-β-ketoester 1.6j. The optimal procedure was followed by using 0.0240 g of β-ketoester **1.5j** (0.105 mmol), 0.051 g of 2-azidophenyllead acetate **1.4a** (0.100 mmol), 0.024 g of pyridine (0.300 mmol) in 3 mL total of chloroform. Purification by MPLC (3:97 – 20:80 EtOAc:hexane) afforded the product as a yellow oil, as an inseparable 10:1 mixture of diastereomers (0.0270 g, 79%). Diagnostic peaks for major diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (td, *J* = 7.5, 2.0 Hz, 1H), 7.24 – 7.17 (m, 3H), 2.96 (s, 3H), 2.99 (td, *J* = 15.0, 2.5 Hz, 1H), 2.59 (td, *J* = 13.0, 6.5 Hz, 1H), 2.53 – 2.49 (m, 1H), 2.18 (t, *J* = 12.5 Hz, 1H), 1.98 – 1.94 (m, 1H), 1.57 (qd, *J* = 12.5, 4.5, 1H), 1.38 (tt, *J* = 12.5, 2.5 Hz, 1H), 0.90 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.6 (C), 171.3 (C), 139.1 (C), 129.3 (CH), 129.1 (C), 129.0 (CH), 125.2 (CH), 119.8 (CH), 65.3 (C), 52.8 (CH_3), 41.8 (CH_3), 39.8 (CH_2), 36.4 (CH_2), 32.5 (C), 29.6 (CH_2), 27.4 (CH_3); diagnostic peaks for minor diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.81 (s, 3H), 0.94 (s, 9H); ATR-FTIR (thin

film of mixture): 2954, 2870, 2124, 1736, 1712, 1487, 1443, 1292, 1240, 1053, 752, 735 cm^{-1}. HRMS (EI) m/z calcd for $C_{18}H_{23}N_3O_3Na$ $[M+Na]^+$: 352.1637, found 352.1639.



1.6k

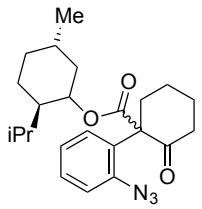
α-Aryl-β-ketoester 1.6k. The optimal procedure was followed by using 0.0250 g of β-ketoester **1.5k** (0.105 mmol), 0.051 g of 2-azidophenyllead acetate **1.4a** (0.100 mmol), 0.0240 g of pyridine (0.300 mmol) in 3 mL total of chloroform. Purification by MPLC (3:97 – 20:80 EtOAc:hexane) afforded the product as a yellow oil, 80 EtOAc:hexane) afforded the product as a yellow oil, as an inseparable 10:1 mixture of diastereomers (0.0230 g, 63%). Diagnostic peaks for major diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ major product: 7.44 (t, J = 8.0 Hz, 1H), 7.35 – 7.21 (m, 8H), 3.70 (s, 3H), 3.18 (d, J = 15.0 Hz, 1H), 2.95 (t, J = 12.5 Hz, 1H), 2.85 – 2.72 (m, 2H), 2.64 – 2.60 (m, 1H), 2.16 – 2.11 (m, 1H), 2.03 (qd, J = 13.0, 4.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.7 (C), 170.8 (C), 143.7 (C), 139.3 (C), 129.5 (CH), 128.7 (CH), 126.9 (CH), 126.8 (CH), 125.4 (CH), 120.0 (CH), 65.5 (C), 52.9 (CH_3), 41.7 (CH_2), 40.2 (CH_2), 38.6 (CH_3), 36.2 (CH_2) only visible peaks; diagnostic peaks for minor diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.88 (s, 3H); ATR-FTIR (thin film): 2948, 2125, 1737, 1714, 1488, 1444, 1293, 1242, 1142, 1048, 758, 700 cm^{-1}. HRMS (EI) m/z calcd for $C_{20}H_{19}N_3O_3Na$ $[M+Na]^+$: 372.1324, found 372.1318.



1.6l

α-Aryl-β-ketoester 1.6l. The optimal procedure was followed by using 0.0480 g of β-ketoester **1.5j** (0.260 mmol), 0.126 g of 2-azidophenyllead acetate **1.4a** (0.250 mmol), 0.0590 g of pyridine

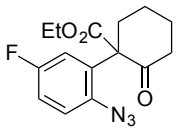
(0.750 mmol) in 3 mL total of chloroform. Purification by MPLC (3:97 – 20:80 EtOAc:hexane) afforded the product as a yellow oil (0.0890 g, 89%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.34 (m, 1H), 7.19 (d, *J* = 8.0 Hz, 1H), 7.15 – 7.14 (m, 2H), 5.91 – 5.83 (m, 1H), 5.24 – 5.19 (m, 2H), 4.71 – 4.63 (m, 2H), 2.77 – 2.71 (m, 1H), 2.64 – 2.52 (m, 3H), 2.01 – 1.96 (m, 1H), 1.90 – 1.85 (m, 1H), 1.78 – 1.68 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.4 (C), 170.6 (C), 138.7 (C), 131.5 (C), 130.0 (CH), 129.0 (CH), 128.3 (CH), 125.0 (CH), 119.3 (CH), 118.7 (CH_2), 66.2 (CH_2), 65.6 (C), 40.9 (CH_2), 35.8 (CH_2), 27.2 (CH_2), 22.0 (CH_2); ATR-FTIR (thin film): 2943, 2868, 2125, 2099, 1717, 1579, 1488, 1448, 1293, 1211, 1132, 1073, 752 cm^{-1}. HRMS (EI) m/z calcd for $C_{16}H_{17}N_3O_3Na$ $[M+Na]^+$: 322.1168, found 322.1164.



1.6m

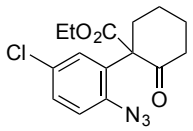
α-Aryl-β-ketoester 1.6m. The optimal procedure was followed by using 0.0740 g of β-ketoester **1.5k** (0.260 mmol), 0.126 g of 2-azidophenyllead acetate **1.4a** (0.250 mmol), 0.0590 g of pyridine (0.750 mmol) in 3 mL total of chloroform. Purification by MPLC (3:97 – 20:80 EtOAc:hexane) afforded the product, a yellow oil, as an inseparable 50:50 mixture of diastereomers (0.0530 g, 54%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (t, *J* = 7.0 Hz, 2H), 7.20 – 7.11 (m, 6H), 4.74 – 4.68 (m, 2H), 2.90 – 2.70 (m, 2H), 2.64 – 2.45 (m, 6H), 2.15 – 2.05 (m, 2H), 2.02 – 1.95 (m, 2H), 1.89 – 1.86 (m, 2H), 1.78 – 1.74 (m, 4H), 1.67 – 1.49 (m, 10H), 1.29 – 1.24 (m, 2H), 1.05 – 1.00 (m, 2H), 0.90 (dd, *J* = 9.0, 6.5 Hz, 6H), 0.86 – 0.82 (m, 2H), 0.78 (d, *J* = 7.0 Hz, 3H), 0.74 (t, *J* = 7.0 Hz, 6H), 0.67 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.5 (C), 205.4 (C), 170.4 (C), 170.3 (C), 138.7 (C), 138.7 (C), 130.3 (C), 130.3 (C), 128.9 (CH), 128.8 (CH), 128.3 (CH), 128.1

(CH), 124.9 (CH), 124.9 (CH), 119.3 (CH), 119.0 (CH), 76.0 (CH), 76.0 (CH), 65.8 (C), 65.5 (C), 46.7 (CH), 41.0 (CH_2), 41.0 (CH_2), 40.3 (CH_2), 40.2 (CH_2), 35.9 (CH_2), 35.8 (CH_2), 34.1 (CH_2), 31.4 (CH), 27.3 (CH_2), 27.3 (CH_2), 25.6 (CH), 25.6 (CH), 23.0 (CH_2), 22.8 (CH_2), 22.0 (CH_2), 20.8 (CH_3), 20.8 (CH_3), 15.7 (CH_3), 15.6 (CH_3) only peaks visible. ATR-FTIR (thin film): 2951, 2868, 2125, 2096, 1717, 1579, 1488, 1450, 1292, 1239, 1213, 1135, 750 cm^{-1}. HRMS (EI) m/z calcd for $C_{23}H_{31}N_3O_3Na$ $[M+Na]^+$: 420.2263, found 420.2249.



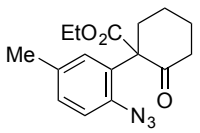
1.6o

α-Aryl-β-ketoester 1.6o. The optimal procedure was followed by using 0.0130 g of β-ketoester **1.5a** (0.0790 mmol), 0.0390 g of 2-azido-5-fluorophenyllead acetate **1.4b** (0.0750 mmol), 0.0180 g of pyridine (0.230 mmol) in 3 mL total of chloroform. Purification by MPLC (3:97 – 20:80 EtOAc:hexane) afforded the product as a yellow oil (0.015 g, 67%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 – 7.13 (m, 1H), 7.08 – 7.04 (m, 1H), 6.88 (dd, J = 10.0, 2.5 Hz, 1H), 4.30 – 4.22 (m, 2H), 2.84 – 2.78 (m, 1H), 2.61 – 2.42 (m, 3H), 2.04 – 2.01 (m, 1H), 1.88 – 1.70 (m, 3H), 1.26 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.6 (C), 170.4 (C), 160.0 (d, J_{CF} = 243.0 Hz, C), 134.6 (C), 126.4 (C), 120.4 (d, J_{CF} = 8.5 Hz, CH), 115.7 (d, J_{CF} = 25.6 Hz, CH), 115.5 (d, J_{CF} = 23.9 Hz, CH), 65.4 (C), 62.0 (CH_2), 40.9 (CH_2), 35.8 (CH_2), 26.9 (CH_2), 22.0 (CH_2), 14.0 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ –117.3. ATR-FTIR (thin film): 2942, 2124, 1717, 1490, 1277, 1229, 1174, 1137, 1023, 810 cm^{-1}. HRMS (EI) m/z calcd for $C_{15}H_{16}N_3O_3NaF$ $[M+Na]^+$: 328.1073, found 328.1071.



1.6p

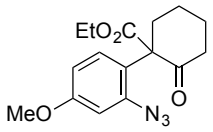
α-Aryl-β-ketoester 1.6p. The optimal procedure was followed by using 0.0360 g of β-ketoester **1.5a** (0.201 mmol), 0.0540 g of 2-azido-5-chlorophenyllead acetate **1.4c** (0.104 mmol), 0.0190 g of pyridine (0.110 mmol) in 3 mL total of chloroform. Purification by MPLC (3:97 – 20:80 EtOAc:hexane) afforded the product as a yellow oil (0.039 g, 67%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (dd, J = 8.5, 2.0 Hz, 1H), 7.12 – 7.10 (m, 2H), 4.30 – 4.22 (m, 2H), 2.85 – 2.79 (m, 1H), 2.61 – 2.54 (m, 2H), 2.48 – 2.44 (m, 1H), 2.03 – 2.00 (m, 1H), 1.86 – 1.79 (m, 2H), 1.72 – 1.70 (m, 1H), 1.25 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.5 (C), 170.4 (C), 137.4 (C), 132.0 (C), 130.4 (C), 128.8 (CH), 128.6 (CH), 120.3 (CH), 65.3 (C), 62.0 (CH_2), 40.9 (CH_2), 35.8 (CH_2), 26.9 (CH_2), 22.0 (CH_2), 14.0 (CH_3); ATR-FTIR (thin film): 2941, 2868, 2108, 1716, 1483, 1299, 1238, 1210, 1126, 1021, 811 cm^{-1}. HRMS (EI) m/z calcd for $C_{15}H_{16}N_3O_3NaCl$ $[M+Na]^+$: 344.0778, found 344.0779.



1.6q

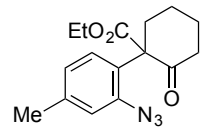
α-Aryl-β-ketoester 1.6q. The optimal procedure was followed by using 0.0190 g of β-ketoester **1.5a** (0.110 mmol), 0.108 g of 2-azido-5-methylphenyllead acetate **1.4d** (0.201 mmol), 0.0480 g of pyridine (0.603 mmol) in 3 mL total of chloroform. Purification by MPLC (3:97 – 20:80 EtOAc:hexane) afforded the product as a yellow oil (0.024 g, 77%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 (d, J = 8.0 Hz, 1H), 7.08 (d, J = 8.0 Hz, 1H), 6.90 (s, 1H), 4.32 – 4.20 (m, 2H), 2.73 – 2.67 (m, 1H), 2.64 – 2.50 (m, 3H), 2.31 (s, 3H), 2.01 – 1.96 (m, 1H), 1.92 – 1.85 (m, 1H), 1.81 – 1.76 (m, 1H), 1.74 – 1.66 (m, 1H), 1.26 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.4 (C),

170.9 (C), 135.7 (C), 134.6 (C), 130.0 (C), 129.5 (CH), 129.0 (CH), 119.3 (CH), 65.7 (C), 61.8 (CH_2), 41.0 (CH_2), 35.8 (CH_2), 26.9 (CH_2), 22.1 (CH_2), 21.1 (CH_3), 14.1 (CH_3); ATR-FTIR (thin film): 2942, 2865, 2117, 1717, 1496, 1451, 1302, 1232, 1207, 1136, 810 cm^{-1}. HRMS (EI) m/z calcd for $C_{16}H_{19}N_3O_3Na$ $[M+Na]^+$: 324.1324, found 324.1328.



1.6r

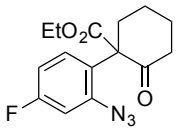
α-Aryl-β-ketoester 1.6r. The optimal procedure was followed by using 0.0180 g of β-ketoester **1.5a** (0.107 mmol), 0.0540 g of 2-azido-4-methoxyphenyllead acetate **1.4e** (0.101 mmol), 0.0240 g of pyridine (0.303 mmol) in 3 mL total of chloroform. Purification by MPLC (3:97 – 20:80 EtOAc:hexane) afforded the product as a yellow solid (0.030 g, 94%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.03 (d, *J* = 8.5 Hz, 1H), 6.72 (d, *J* = 2.5 Hz, 1H), 6.67 (dd, *J* = 8.0, 2.5 Hz 1H), 4.29 – 4.17 (m, 2H), 3.82 (s, 3H), 2.74 – 2.68 (m, 1H), 2.62 – 2.48 (m, 3H), 1.99 – 1.94 (m, 1H), 1.89 – 1.84 (m, 1H), 1.78 – 1.75 (m, 1H), 1.71 – 1.66 (m, 1H), 1.24 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.8 (C), 171.1 (C), 159.9 (C), 140.0 (C), 129.1 (CH), 122.5 (C), 110.1 (CH), 105.5 (CH), 65.1 (C), 61.7 (CH_2), 55.5 (CH_3), 40.9 (CH_2), 35.9 (CH_2), 27.2 (CH_2), 22.0 (CH_2), 14.1 (CH_3); ATR-FTIR (thin film): 2941, 2114, 1717, 1609, 1577, 1506, 1445, 1295, 1230, 1133, 840 cm^{-1}. HRMS (EI) m/z calcd for $C_{16}H_{19}N_3O_4Na$ $[M+Na]^+$: 340.1273, found 340.1263.



1.6s

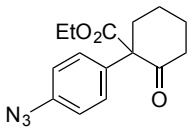
α-Aryl-β-ketoester 1.6s. The optimal procedure was followed by using 0.0180 g of β-ketoester **1.5a** (0.107 mmol), 0.0520 g of 2-azido-4-methylphenyllead acetate **1.4e** (0.101 mmol), 0.0240 g of pyridine (0.303 mmol) in 3 mL total of chloroform. Purification by MPLC (3:97 – 20:80

EtOAc:hexane) afforded the product as a yellow oil (0.030 g, 94%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.01 – 6.99 (m, 1H), 6.94 (d, *J* = 8.5 Hz, 1H), 4.30 – 4.18 (m, 2H), 2.74 – 2.68 (m, 1H), 2.63 – 2.49 (m, 3H), 2.36 (s, 3H), 2.01 – 1.95 (m, 1H), 1.91 – 1.83 (m, 1H), 1.79 – 1.75 (m, 1H), 1.79 – 1.65 (m, 2H), 1.24 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.6 (C), 171.0 (C), 139.2 (C), 138.3 (C), 128.1 (CH), 127.2 (C), 125.9 (CH), 120.0 (CH), 65.4 (C), 61.7 (CH_2), 40.9 (CH_2), 35.8 (CH_2), 27.1 (CH_2), 22.1 (CH_2), 21.0 (CH_3), 14.1 (CH_3); ATR-FTIR (thin film): 2940, 2866, 2109, 1716, 1505, 1451, 1296, 1237, 1213, 1133, 805 cm^{-1}. HRMS (EI) m/z calcd for $C_{16}H_{19}N_3O_3Na$ $[M+Na]^+$: 324.1324, found 324.1321.



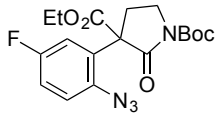
1.6t

α-Aryl-β-ketoester 1.6t. The optimal procedure was followed by using 0.0080 g of β-ketoester **1.5a** (0.045 mmol), 0.0700 g of 2-azido-4-fluorophenyllead acetate **1.4f** (0.134 mmol), 0.0110 g of pyridine (0.134 mmol) in 3 mL total of chloroform. Purification by MPLC (3:97 – 20:80 EtOAc:hexane) afforded the product as a yellow oil (0.0080 g, 58%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.08 (dd, *J* = 8.5, 6.0 Hz, 1H), 6.91 (dd, *J* = 8.5, 2.5 1H), 6.84 (td, *J* = 7.5, 2.5 Hz, 1H), 4.31 – 4.19 (m, 2H), 2.81 – 2.74 (m, 1H), 2.62 – 2.45 (m, 3H), 2.04 – 1.98 (m, 1H), 1.90 – 1.67 (m, 3H), 1.25 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.0 (C), 170.8 (C), 162.5 (d, J_{CF} = 246.1 Hz, C), 140.4 (d, J_{CF} = 9.2 Hz, C), 129.6 (d, J_{CF} = 9.1 Hz, CH), 126.1 (d, J_{CF} = 2.5 Hz, C), 111.8 (d, J_{CF} = 22.0 Hz, CH), 106.7 (d, J_{CF} = 24.4 Hz, CH), 65.1 (C), 61.9 (CH_2), 40.9 (CH_2), 35.9 (CH_2), 27.0 (CH_2), 22.1 (CH_2), 14.1 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ –112.7. ATR-FTIR (thin film): 2941, 2867, 2114, 1715, 1593, 1500, 1450, 1414, 1298, 1238, 1207, 1133, 966, 843 cm^{-1}. HRMS (EI) m/z calcd for $C_{15}H_{16}N_3O_3NaF$ $[M+Na]^+$: 328.1073, found 328.1069.



1.6u

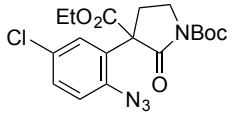
α-Aryl-β-ketoester 1.6u. The optimal procedure was followed by using 0.0890 g of β-ketoester **1.5a** (0.500 mmol), 0.2520 g of 4-azido-phenyllead acetate **1.4g** (0.5000 mmol), 0.119 g of pyridine (1.500 mmol) in 3 mL total of chloroform. Purification by MPLC (3:97 – 20:80 EtOAc:hexane) afforded the product as a yellow oil (0.098 g, 67%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 – 7.22 (m, 1H), 7.03 – 7.01 (m, 1H), 4.25 – 4.19 (m, 2H), 2.80 – 2.77 (m, 1H), 2.60 – 2.52 (m, 2H), 2.29 – 2.24 (m, 1H), 2.02 – 2.00 (m, 1H), 1.86 – 1.75 (m, 3H), 1.24 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.4 (C), 170.9 (C), 135.7 (C), 134.6 (C), 130.0 (C), 129.5 (CH), 129.1 (CH), 119.3 (CH), 65.7 (C), 61.7 (CH_2), 41.0 (CH_2), 35.8 (CH_2), 26.9 (CH_2), 22.1 (CH_2), 14.1 (CH_3); ATR-FTIR (thin film): 2940, 2866, 2123, 2093, 1713, 1604, 1713, 1285, 1128, 1019, 807 cm^{-1}. HRMS (EI) m/z calcd for $C_{15}H_{17}N_3O_3Na$ $[M+Na]^+$: 310.1168, found 310.1165.



1.6v

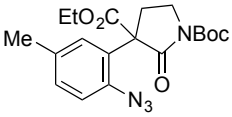
α-Aryl-γ-lactam 1.6v. The optimal procedure was followed by using 0.0170 g of γ-lactam **1.5i** (0.0660 mmol), 0.0330 g of 2-azido-5-fluorophenyllead acetate **1.4b** (0.0630 mmol), 0.0150 g of pyridine (0.150 mmol) in 3 mL total of chloroform. Purification by MPLC (3:97 – 20:80 EtOAc:hexane) afforded the product as a yellow oil (0.019 g, 75%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 – 7.05 (m, 3H), 4.33 – 4.16 (m, 2H), 3.91 – 3.86 (m, 1H), 3.59 – 3.55 (m, 1H), 3.20 – 3.14 (m, 1H), 2.17 – 2.12 (m, 1H), 1.56 (s, 9H), 1.23 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.9 (C), 168.8 (C), 159.6 (d, J_{CF} = 244.1 Hz, C), 149.8 (C), 133.7 (C), 131.5 (d, J_{CF} = 8.0 Hz, C), 120.5 (d, J_{CF} = 9.1 Hz, CH), 116.1 (d, J_{CF} = 25.4 Hz, CH), 115.8 (d, J_{CF} = 22.3 Hz, CH), 83.8

(C), 62.6 (CH_2), 60.7 (C), 43.7 (CH_2), 29.9 (CH_2), 28.0 (CH_3), 14.0 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ –116.5; ATR-FTIR (thin film): 2980, 2124, 1784, 1725, 1489, 1367, 1294, 1240, 1150, 1106, 943, 850 cm^{-1}. HRMS (EI) m/z calcd for $C_{18}H_{21}N_4O_5FNa$ $[M+Na]^+$: 415.1394, found 415.1388.



1.6w

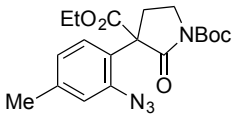
α-Aryl-γ-lactam 1.6w. The optimal procedure was followed by using 0.0270 g of γ-lactam **1.5i** (0.105 mmol), 0.0540 g of 2-azido-5-chlorophenyllead acetate **1.4c** (0.100 mmol), 0.0240 g of pyridine (0.300 mmol) in 3 mL total of chloroform. Purification by MPLC (3:97 – 20:80 EtOAc:hexane) afforded the product as a yellow oil (0.023 g, 56%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.32 (m, 2H), 7.10 (d, J = 9.5 Hz, 1H), 4.33 – 4.16 (m, 2H), 3.91 – 3.86 (m, 1H), 3.60 – 3.55 (m, 1H), 3.18 – 3.13 (m, 1H), 2.15 – 2.10 (m, 1H), 1.56 (s, 9H), 1.23 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.9 (C), 168.8 (C), 149.8 (C), 136.5 (C), 131.3 (C), 130.6 (C), 129.2 (CH), 128.7 (CH), 120.0 (CH), 83.8 (C), 62.7 (CH_2), 61.5 (C), 43.7 (CH_2), 29.9 (CH_2), 28.0 (CH_3), 14.0 (CH_3); ATR-FTIR (thin film): 2981, 2111, 1784, 1368, 1296, 1232, 1151, 1014, 938, 842 cm^{-1}. HRMS (EI) m/z calcd for $C_{18}H_{21}N_4O_5Na$ $[M+Na]^+$: 431.1098, found 431.1086.



1.6x

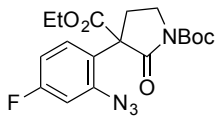
α-Aryl-γ-lactam 1.6x. The optimal procedure was followed by using 0.0290 g of γ-lactam **1.5i** (0.113 mmol), 0.1750 g of 2-azido-5-methylphenyllead acetate **1.4d** (0.338 mmol), 0.0270 g of pyridine (0.338 mmol) in 3 mL total of chloroform. Purification by MPLC (3:97 – 20:80 EtOAc:hexane) afforded the product as a yellow oil (0.039 g, 89%): ^1H NMR (500 MHz, $CDCl_3$)

δ 7.15 (d, J = 8.0 Hz, 1H), 7.07 – 7.06 (m, 2H), 4.33 – 4.17 (m, 2H), 3.88 – 3.84 (m, 1H), 3.55 – 3.51 (m, 1H), 3.18 – 3.12 (m, 1H), 2.31 (s, 3H), 2.17 – 2.13 (m, 1H), 1.56 (s, 9H), 1.23 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.7 (C), 169.3 (C), 150.0 (C), 135.0 (C), 135.0 (C), 129.7 (C), 129.4 (CH), 128.9 (CH), 118.8 (CH), 83.6 (C), 62.4 (CH_2), 61.8 (C), 43.7 (CH_2), 30.2 (CH_2), 28.0 (CH_3), 21.1 (CH), 14.0 (CH_3); ATR-FTIR (thin film): 2981, 2121, 1785, 1725, 1495, 1367, 1297, 1244, 1152, 941 cm^{-1}. HRMS (EI) m/z calcd for $C_{19}H_{24}N_4O_5Na$ $[M+Na]^+$: 411.1644, found 411.1645.



1.6y

α-Aryl-γ-lactam 1.6y. The optimal procedure was followed by using 0.0260 g of γ-lactam **1.5i** (0.100 mmol), 0.1560 g of 2-azido-4-methylphenyllead acetate **1.4f** (0.302 mmol), 0.0240 g of pyridine (0.300 mmol) in 3 mL total of chloroform. Purification by MPLC (3:97 – 20:80 EtOAc:hexane) afforded the product as a yellow oil (0.020 g, 52%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13 (d, J = 8.0 Hz, 1H), 6.98 (s, 1H), 6.93 (d, J = 8.0 Hz, 1H), 4.33 – 4.15 (m, 2H), 3.87 – 3.83 (m, 1H), 3.52 – 3.46 (m, 1H), 3.16 – 3.10 (m, 1H), 2.36 (s, 3H), 2.19 – 2.14 (m, 1H), 1.55 (s, 9H), 1.23 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.7 (C), 169.4 (C), 150.0 (C), 139.0 (C), 137.5 (C), 128.1 (C), 126.6 (CH), 125.9 (CH), 119.6 (CH), 83.5 (C), 62.4 (CH_2), 61.6 (C), 43.6 (CH_2), 30.2 (CH_2), 28.1 (CH_3), 21.1 (CH), 14.0 (CH_3); ATR-FTIR (thin film): 2978, 2112, 1784, 1724, 1505, 1367, 1291, 1236, 1149, 1105, 1011, 943, 730 cm^{-1}. HRMS (EI) m/z calcd for $C_{19}H_{24}N_4O_5Na$ $[M+Na]^+$: 411.1644, found 411.1642.

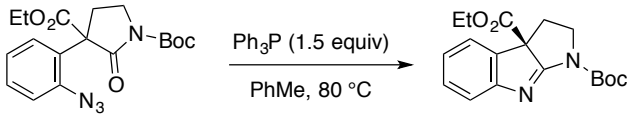


1.6z

α-Aryl-γ-lactam 1.6z. The optimal procedure was followed by using 0.0120 g of γ-lactam **1.5i** (0.0450 mmol), 0.0700 g of 2-azido-4-fluorophenyllead acetate **1.4g** (0.134 mmol), 0.0110 g of pyridine (0.134 mmol) in 3 mL total of chloroform. Purification by MPLC (3:97 – 20:80 EtOAc:hexane) afforded the product as a yellow solid (0.007 g, 42%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (dd, J = 8.5, 6.0 Hz, 1H), 6.91 (dd, J = 8.5, 2.5 Hz, 1H), 6.84 (td, J = 8.5, 2.5 Hz, 1H), 4.33 – 4.16 (m, 2H), 3.90 – 3.85 (m, 1H), 3.55 – 3.50 (m, 1H), 3.18 – 3.12 (m, 1H), 2.17 – 2.12 (m, 1H), 1.55 (s, 9H), 1.23 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.4 (C), 169.1 (C), 162.6 (d, J_{CF} = 248.4 Hz, C), 149.9 (C), 139.6 (d, J_{CF} = 7.4 Hz, C), 129.8 (d, J_{CF} = 9.1 Hz, CH), 125.6 (d, J_{CF} = 3.8 Hz, C), 112.1 (d, J_{CF} = 20.5 Hz, CH), 106.5 (d, J_{CF} = 25.6 Hz, CH), 83.8 (C), 62.6 (CH_2), 61.3 (C), 43.7 (CH_2), 30.1 (CH_2), 28.0 (CH_3), 14.0 (CH_3), ^{19}F NMR (282 MHz, $CDCl_3$) δ –111.8; ATR-FTIR (thin film): 2979, 2118, 1783, 1723, 1594, 1501, 1367, 1293, 1232, 1148, 1097, 963, 842 cm^{-1}. HRMS (EI) m/z calcd for $C_{18}H_{21}N_4O_5NaF$ $[M+Na]^+$: 415.1394, found 415.1397.

D. Synthesis of 3*H*-Indoles by Staudinger Reduction

1. General Procedure.

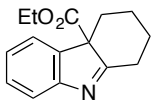


1.6i **1.7i**

To a round bottom flask was added α-aryl-γ-lactam **1.6i** (1 equiv) and triphenylphosphine (1.5 equiv). To this mixture was added toluene. The reaction mixture was heated to 80 °C. After 2h, the reaction mixture was cooled to room temperature, and the volatiles were removed *in vacuo*. The residue was dissolved in ethyl acetate and poured into water. The resulting mixture was extracted by 2 × 5 mL of ethyl acetate. The combined organic phases were washed with brine. The

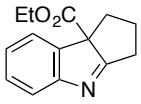
resulting organic phase was dried over Na_2SO_4, filtered, and the filtrate was concentrated *in vacuo*. Purification of the residue by MPLC afforded 3*H*-pyrroloindoline **1.7i**.

2. Characterization Data for 3*H*-indoles 1.7.



1.6a

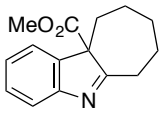
3*H*-Indole 1.7a. The general procedure was followed by using 0.146 g of β-ketoester **1.6a** (0.525 mmol), 0.206 g of triphenylphosphine (0.788 mmol) and 3 mL toluene. Purification by MPLC (0:100 – 30:70 EtOAc: hexanes) afforded the product as a yellow oil (0.123 g, 96%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.0 Hz, 1H), 7.41 (d, *J* = 7.5 Hz, 1 H), 7.34 (t, *J* = 8.0 Hz, 1H), 7.17 (t, *J* = 7.5 Hz, 1H), 4.20 – 3.99 (m, 2H), 3.03 – 2.95 (m, 2H), 2.72 (td, *J* = 8.5, 6.0 Hz, 1H), 2.18 – 2.16 (m, 1H), 1.80 – 1.77 (m, 1H), 1.60 – 1.45 (m, 2H), 1.16 – 1.10 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 183.9 (C), 170.0 (C), 155.4 (C), 139.6 (C), 128.9 (CH), 125.3 (CH), 122.3 (CH), 120.3 (CH), 65.0 (C), 61.6 (CH_2), 37.2 (CH_2), 31.4 (CH_2), 28.4 (CH_2), 22.9 (CH_2), 14.0 (CH_3); ATR-FTIR (thin film): 2936, 2859, 1725, 1584, 1454, 1246, 1207, 1089, 1021, 766, 753, 657 cm^{-1}. HRMS (EI) m/z calcd for $C_{15}H_{18}NO_2$ $[M+H]^+$: 244.1338, found 244.1335.



1.6b

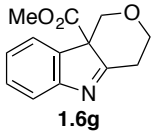
3*H*-Indole 1.7b. The general procedure was followed by using 0.0390 g of β-ketoester **1.6b** (0.143 mmol), 0.0560 g of triphenylphosphine (0.214 mmol) and 3 mL toluene. Purification by MPLC (0:100 – 30:70 EtOAc: hexanes) afforded the product as a yellow oil (0.031 g, 96%), which decomposed upon exposure to air: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.08 – 7.04 (m, 2H), 6.71 (t, *J* = 7.5 Hz, 1H), 6.55 (d, *J* = 8.0 Hz, 1H), 4.25 – 4.20 (m, 2H), 2.64 – 2.58 (m, 1H), 2.17 – 2.06 (m,

3H), 1.79 – 1.76 (m, 1H), 1.52 – 1.45 (m, 1H), 1.27 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.7 (C), 173.1 (C), 148.6 (C), 130.0 (C), 128.8 (CH), 124.2 (CH), 119.0 (CH), 108.4 (CH), 64.0 (C), 61.4 (CH_2), 42.4 (CH_2), 30.4 (CH_2), 22.8 (CH_2), 14.2 (CH_3); ATR-FTIR (thin film): 3364, 2960, 2871, 1712, 1607, 1486, 1257, 1230, 1099, 1021, 743 cm^{-1}. HRMS (EI) m/z calcd for $C_{14}H_{16}NO_2$ $[M+H]^+$: 230.1181, found 230.1178.



1.6c

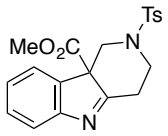
3*H*-Indole 1.7c. The general procedure was followed by using 0.037 g of β-ketoester **1.6c** (0.129 mmol), 0.050 g of triphenylphosphine (0.190 mmol) and 2 mL toluene. Purification by MPLC (0:100 – 30:70 EtOAc: hexanes) afforded the product as a yellow solid (0.026 g, 84%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (d, J = 8.0 Hz, 1H), 6.91 (m, 1H), 7.19 (t, J = 7.5 Hz, 1H), 3.65(s, 3H), 2.99 (t, J = 7.0 Hz, 2H), 2.57 (dd, J = 9.0, 4.5 Hz, 1H), 1.84 – 1.46 (m, 7H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 186.0 (C), 170.1 (C), 154.8 (C), 139.6 (C), 128.9 (CH), 125.7 (CH), 122.1 (CH), 119.9 (CH), 68.2 (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): 2931, 2857, 1730, 1697, 1455, 1226, 1013, 767, 748 cm^{-1}. HRMS (EI) m/z calcd for $C_{15}H_{18}NO_2$ $[M+H]^+$: 244.1338, found 244.1337.



1.6g

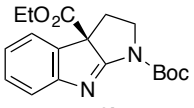
3*H*-Indole 1.7g. The general procedure was followed by using 0.024 g of β-ketoester **1.6g** (0.086 mmol), 0.034 g of triphenylphosphine (0.258 mmol) and 2 mL toluene. Purification by MPLC (0:100 – 30:70 EtOAc: hexanes) afforded the product as a yellow solid (0.018 g, 90%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (t, J = 8.0 Hz, 1H), 7.20 (d, J = 8.0 Hz, 1H), 7.14 (t, J = 8.0 Hz, 1H), 7.10 (d, J = 8.0 Hz, 1H), 4.57 (d, J = 11.5 Hz, 1H), 4.36 (d, J = 11.5 Hz, 1H), 4.24 – 4.21 (m, 1H),

4.01 (td, J = 11.0, 1.0 Hz, 1H), 3.85 (s, 3H), 2.94 – 2.87 (m, 1H), 2.65 (td, J = 15.0, 3.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.3 (C), 169.8 (C), 138.2 (C), 129.6 (CH), 129.3 (CH), 126.2 (C), 125.2 (CH), 119.4 (CH), 73.5 (CH_2), 67.9 (CH_2), 67.2 (C), 53.3 (CH_3), 40.9 (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 $C_{13}H_{14}NO_3$ $[M+H]^+$: 232.0974, found 232.0972.



1.6h

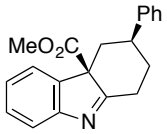
3*H*-Indole 1.7h. The general procedure was followed by using 0.044 g of β-ketoester **1.6h** (0.100 mmol), 0.039 g of triphenylphosphine (0.15 mmol) and 2 mL toluene. Purification by MPLC (0:100 – 30:70 EtOAc: hexanes) afforded the product as a yellow oil (0.038 g, 95%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, J = 8.0 Hz, 2H), 7.39 (td, J = 7.5, 1.5 Hz, 1H), 7.34 (d, J = 8.0 Hz, 2H), 7.18 – 7.12 (m, 3H), 4.14 – 4.11 (m, 1H), 3.83 (s, 3H), 3.79 (d, J = 12.0 Hz, 1H), 3.67 – 3.65 (m, 1H), 3.25 – 3.21 (m, 1H), 2.89 – 2.84 (m, 1H), 2.78 – 2.74 (m, 1H), 2.45 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.7 (C), 169.0 (C), 144.2 (C), 138.0 (C), 133.4 (C), 130.0 (CH), 129.8 (CH), 129.5 (CH), 127.6 (CH), 126.4 (C), 125.4 (CH), 119.3 (CH), 65.7 (C), 53.5 (CH_3), 52.6 (CH_2), 46.1 (CH_2), 39.4 (CH_2), 21.6 (CH_3); ATR-FTIR (thin film): 3342, 2948, 1733, 1688, 1542, 1335, 1267, 1191, 1156, 1117, 1086, 1017, 937, 812, 788, 731, 699, 657 cm^{-1}. HRMS (EI) m/z calcd for $C_{20}H_{21}N_2O_4S$ $[M+H]^+$: 385.1222, found 385.1219.



1.6i

3*H*-Indole 1.7i. The general procedure was followed by using 0.124 g of α-aryl-γ-lactam **1.6i** (0.332 mmol), 0.130 g of triphenylphosphine (0.496 mmol) and 3 mL toluene. Purification by

MPLC (0:100 – 30:70 EtOAc: hexanes) afforded the product as a white solid (0.100 g, 92%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (d, *J* = 7.5 Hz, 1H), 7.28 (t, *J* = 7.0 Hz, 1H), 7.19 (d, *J* = 7.5 Hz, 1H), 7.07 (t, *J* = 7.5 Hz, 1H), 4.48 (q, *J* = 7.0, 2H), 4.06 – 3.97 (m, 2H), 2.58 – 2.52 (m, 1H), 2.37 – 2.31 (m, 1H), 1.54 (s, 9H), 1.40 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.5 (C), 169.1 (C), 153.8 (C), 150.2 (C), 136.6 (C), 129.4 (CH), 124.1 (CH), 121.6 (CH), 118.8 (CH), 83.7 (C), 66.2 (CH_2), 62.4 (C), 44.1 (CH_2), 28.0 (CH_3), 27.2 (CH_2), 14.3 (CH_3); ATR-FTIR (thin film): 3247, 2980, 1702, 1579, 1457, 1321, 1274, 1169, 1018, 758, 668 cm^{-1}. HRMS (EI) m/z calcd for $C_{18}H_{23}N_2O_4$ $[M+H]^+$: 331.1658, found 331.1656.



1.6k

3*H*-Indole 1.7k. The general procedure was followed by using 0.020 g of β-ketoester **1.6k** (0.055 mmol), 0.043 g of triphenylphosphine (0.083 mmol) and 3 mL toluene. Purification by MPLC (0:100 – 30:70 EtOAc: hexanes) afforded the product as a yellow oil (0.016 g, 91%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.5 Hz, 1H), 7.46 (d, *J* = 7.5 Hz, 3H), 7.37 (t, *J* = 7.0 Hz, 3H), 7.23 (t, *J* = 7.5 Hz, 1H), 7.19 (t, *J* = 7.5 Hz, 1H), 3.48 – 3.38 (m, 2H), 3.16 – 3.15 (m, 1H), 3.15 (s, 3H), 3.09 – 3.04 (m, 1H), 2.69 – 2.66 (m, 1H), 2.07 – 2.00 (m, 1H), 1.84 (dd, *J* = 14.0, 6.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.0 (C), 170.2 (C), 155.2 (C), 142.0 (C), 140.0 (C), 128.9 (CH), 128.3 (CH), 127.5 (CH), 126.4 (CH), 125.5 (CH), 122.9 (CH), 120.4 (CH), 62.3 (C), 52.3 (CH_3), 42.1 (CH_2), 36.6 (CH), 30.2 (CH_2), 28.7 (CH_2); ATR-FTIR (thin film): 2948, 1731, 1584, 1455, 1223, 1174, 757, 699 cm^{-1}. HRMS (EI) m/z calcd for $C_{20}H_{20}NO_2$ $[M+H]^+$: 306.1494, found 306.1484.

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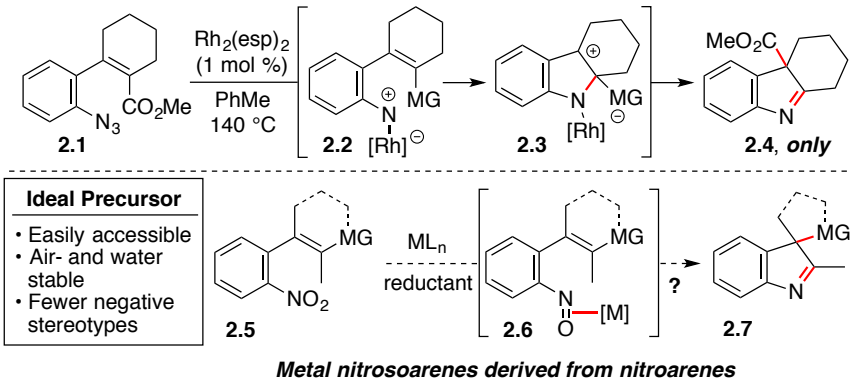
Chapter II

Palladium-catalyzed Reductive Tandem Reaction of Nitrostyrenes with $Mo(CO)_6$ to Produce 3*H*-indoles

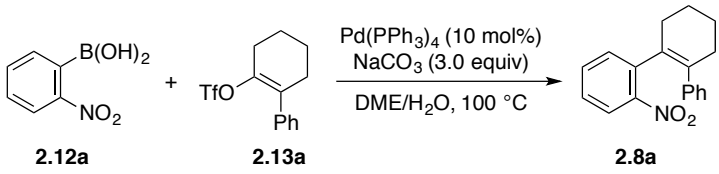
The development of new methods to trigger carbon–nitrogen bond formation continues to be one of the most active areas of organic research. Among the sources of nitrogen-atom, the nitro group inspires numerous studies due to its widespread availability.[1-3] Due to these efforts, the formation of *N*-heterocyles scaffold, such as indoles and carbazoles, have been significantly facilitated. The reductive sp^2-C–H amination of nitroarenes was often employed to generate C–N bond.[4,5] Traditionally, superstoichiometric quantities of the reductant, such as Zinc dust,[6] phosphite,[7-10] high pressures of carbon monoxide gas,[11-15] or Grignard reagent,[16-19] was required to reduce the nitro-group into electrophilic nitrogen species. Generating partially saturated, non-planar *N*-heterocycles, however, still remains unsolved. While some methods have emerged,[20,21] they are limited by the low yield and significant by-product formation that occurs instead of *N*-heterocycle formation.[22,23] Our group has been working on transition-metal-catalyzed C–N bond formation using aryl azides as the source of nitrogen for the last 10 years. Our group discovered that complex and functionalized *N*-heterocycles could be formed through a electrocylization-migration tandem reaction of rhodium-stabilized *N*-aryl nitrene **2.2** (Scheme 2.1).[24-29] However, the possible spirocycle product, which could be resulted from alkyl migration, was inaccessible from aryl azide using our method. As a consequence, we were curious if this spirocyclic heterocycle could be

formed using an alternative nitrogen-atom source: a nitro group. Besides the potential access to the novel structure motif, using the nitro group could also avoid explosive nature and multiple-step synthesis of azide substrate.

Scheme 2.1 ***Observation of a Rh_2(II)-catalyzed tandem reaction***



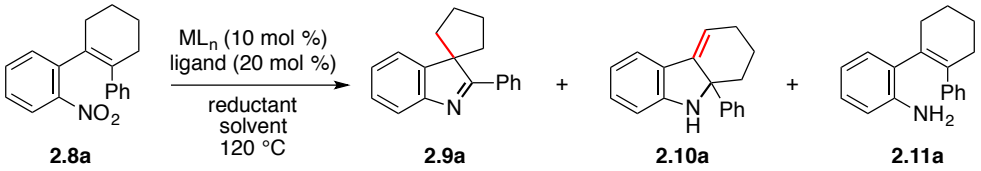
To test this hypothesis, my colleague, Navendu Jana, prepared nitroarene **2.8a** by Suzuki cross-coupling between the commercially available 2-nitrophenylboronic acid and the vinyl triflate derived from 2-phenylcyclohexanone. The desired *o*-nitrostyrenes could be formed with good yields.



The nitrostyrene **2.8a** was submitted to a number of conditions including transition-metal catalysts and reductants (Table 2.1). To start, we screened a variety of metal catalysts using carbon monoxide gas (1.5 atm) as reductant. Unfortunately, no desired product but aniline **2.11a** was yielded by using common Rh-,[30,31] Ru-,[20,30] and Pt-catalysts.[32] To our delight, formation of the desired spirocycle product was observed by

using phenanthroline palladium(II) complexes (entry 1), which was *in situ* generated through the combination of $Pd(OAc)_2$ and phenanthroline. Further optimization was performed to improve the yield and eliminate the byproduct **2.10a** formation. While changing the ligand to tetramethyl phenanthroline did not improve the ratio of spirocycle **2.9a** to **2.10a** (entry 2),[31,33] we found using $Pd(TFA)_2$ as the pre-catalyst (entry 3) and the addition of trifluoroacetic acid (entry 4) could improve both the yield and the ratio. We believed that the increased yield was due to inhibition of the deprotonation process, which leads to the byproduct **2.10a**. To our dismay, our attempts to further improve the outcome of the reaction by changing the pressure of CO failed (entry 5). Since the result of the transition-metal catalyst screen was unsatisfactory, we decided to screen alternative sources of CO. Metal carbonyl complexes are well known to release CO gas upon thermolysis,[34] and molybdenum hexacarbonyl is a demonstrated CO equivalent in palladium-catalyzed carbonylation reactions.[35-38] To our surprise, when switching the CO source to $Mo(CO)_6$, neither the deprotonation byproduct **2.10a** nor oligomerization was observed (entries 6). Screen of solvent was performed to further develop the yield. While using THF only slightly improved the yield (entry 7), the optimized condition was obtained by using dichloroethane (entry 8). The yield was improved to 80% without formation of byproduct **2.10a** or aniline **2.11a**. Reducing the equivalent of $Mo(CO)_6$ to 0.5 diminished the yield dramatically (entry 9). In contrast, reducing the catalyst loading affected this transformation slightly (entry 10). The yield of spirocycle **2.9a** was attenuated to 68% without the formation of byproduct.

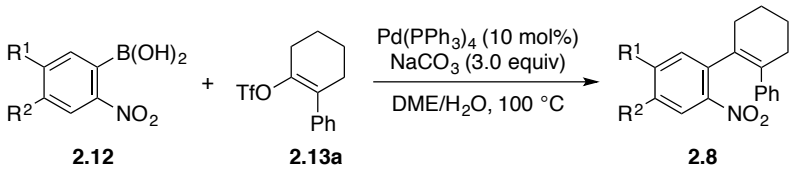
Table 2.1 ***Development of optimal conditions***



entry	catalyst	ligand	reductant	solvent	yield, %[a] **2.9a**:**2.10a**:**2.11a**
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

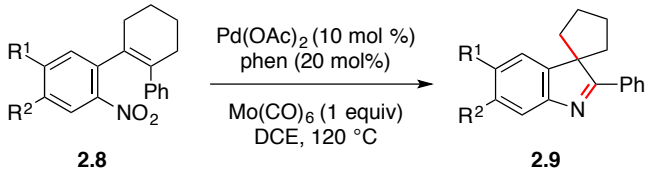
With the optimized condition in hand, Navendu and I examined the scope and limitations of our reaction. We firstly varied the identity of aryl substituents of the *o*-nitrostyrenes (Table 2.2). In comparison with our azide research, this part of our studies was significantly facilitated because our substrates **2.8** were more easily accessible than the analogous styryl azides. The requisite nitrostyrenes could be readily prepared from a Suzuki coupling between substituted 2-nitroarylboronic acids **2.12** with vinyl triflate **2.13a**.



2.12 **2.13a** **2.8** (eq. 2.2)

The effect of para-substituents, R^1, was examined firstly (entries 1–5). We found our reaction tolerated a range of electron-donating and electron-withdrawing R^1-substituents to form the desired spirocyclic products **2.9** in modest- to good yields. To our delight, the identity of meta-substituents, R^2, also showed no effect on our reaction (entries 6–9). The product was formed smoothly irrespective of the electronic nature of the R^2 substituent. These results demonstrated that our reaction enables access to 3*H*-indoles, which cannot be formed as single isomers through Fisher indole synthesis.[39]

Table 2.2 ***Examintion of the electronic nature of the 2-nitrostyrene.***



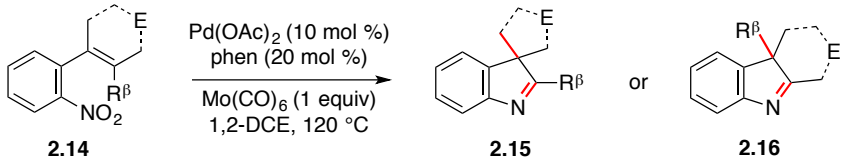
2.8 **2.9**

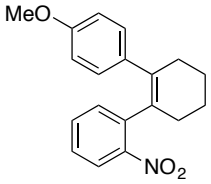
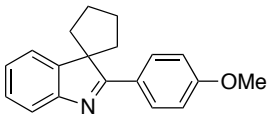
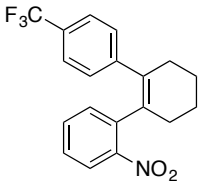
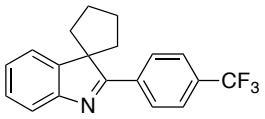
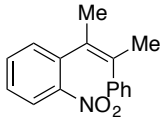
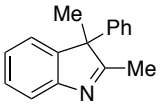
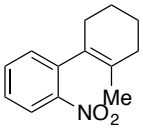
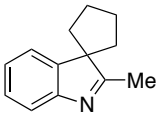
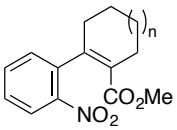
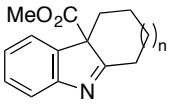
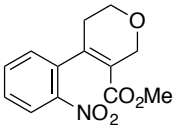
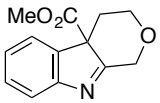
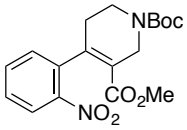
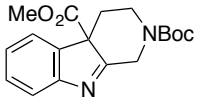
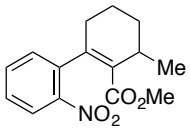
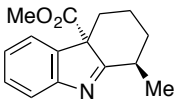
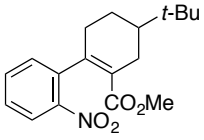
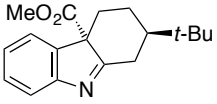
entry	#	R^1	R^2	**2.9**, yield, %[a,b]
1	a	H	H	88
2	b	MeO	H	60 (82)[c]
3	c	Me	H	64
4	d	F	H	72
5	e	F_3C	H	54[c]
6	f	H	MeO	68
7	g	H	Me	77
8	h	H	F	88
9	i	H	CO_2Me	75

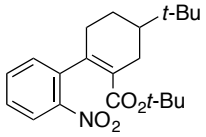
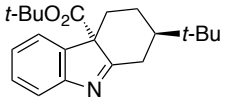
[a] Conditions: 10 mol % $Pd(OAc)_2$ 20 mol % phenanthroline, $Mo(CO)_6$ (1 equiv), DCE, 120 °C, 16 h. [b] Isolated after silica gel chromatography. [c] 20 mol % $Pd(OAc)_2$ used.

Next, the scope of our reaction was further investigated by changing the identity of the *o*-substituent of the nitroarene (Table 2.3). Upon the synthesis of substrates **2.14a** and **2.15a**, the effect of the electronic identity of R^{β}-aryl substituent was studies (entries 1 and 2). A higher yield was obtained when the substrate was substituted with an electron-rich 4-methoxylphenyl substituent. Instead of alkyl migration, aryl group migration was observed with acyclic substrate **2.14c**. This result may arise from the reduced steric environment of β-position in **2.14c**. Next, the scope of our reaction was further examined by changing the R^{β}-substituent from aryl group to other types of functional group (entries 2–4). While the ring construction remains with R^{β}-methyl substituent (entry 4), changing to a carboxylate group yielded 3*H*-indole **2.16** through an ester migration process (entry 5). We believe this ester migration is favored because the ester group will destabilize the positive charge, which could be resulted from ring construction.[28] This ester migration reactivity was irrespective to the ring size. 3*H*-indoles **2.16e**, **2.16f** and **2.16g** were formed from six-, seven- and even eight-membered cycloalkenyl substrates respectively (entries 5–7). Heteroatom-containing R^{β}-cycloalkenyl substituted nitrostryrenes could be employed in our reaction as long as the catalyst loading was increased to 20 mol % (entries 8–9). Next, the diastereoselectivity of our reaction was studied (entries 10–12). To our delight, our reaction showed a good diastereoselectivity of 91:9 by adding a methyl group at allylic position (entry 10). When the stereocenter was moved to the homoallylic position, the diastereoselectivity reduced slightly to 80:20 (entry 11). The diastereoselectivity was improved with a *tert*-butyl carboxylate migrating group, which has an increased size (entry 12).

Table 2.3 ***Examination of the o-substituent of the nitroarene.***



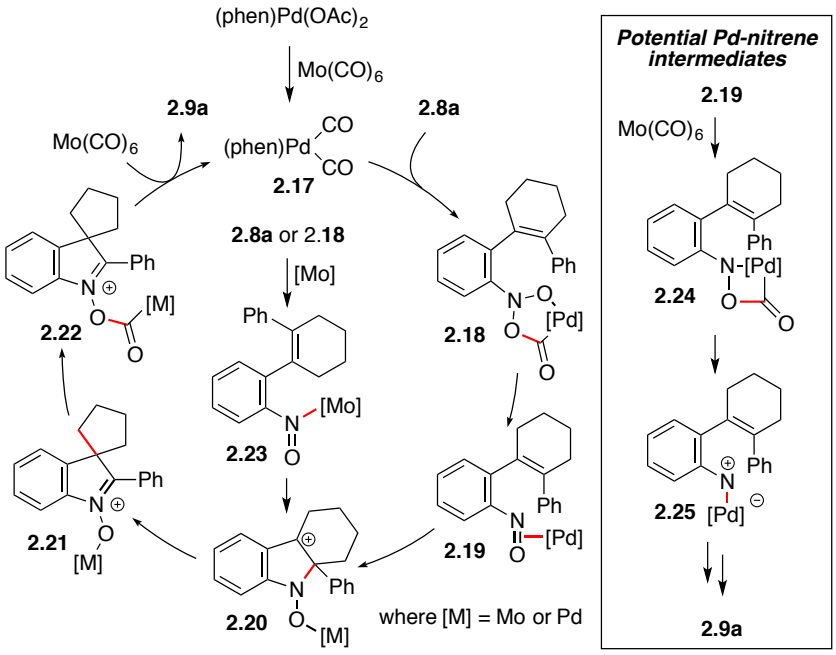
entry	#	nitroarene	3*H*-indole	yield, %[a]
1	a			76
2	b			48
3	c			59
4	d			49(54)[b]
5	e			73, n = 1
6	f			52, n = 2
7	g			56, n = 3
8	h			67[b]
9	i			59[b]
10	j			65 d.r. 91:9
11	k			45 d.r. 80:20

entry	#	nitroarene	3*H*-indole	yield, %[a]
12	l			49 d.r. 90:10

[a] Isolated after silica gel chromatography. [b] 20 mol % $Pd(OAc)_2$ used.

We proposed a mechanism for our 3*H*-indole formation based on the reported investigations into the catalytic cycle of palladium-catalyzed nitroarene reduction reaction, (Scheme 2.2).[33,40-46] The complex (phen)$Pd(OAc)_2$ could be *in situ* formed from the combination of $Pd(OAc)_2$ and phenanthroline. Then it could be reduced by $Mo(CO)_6$ to form the palladium CO complex **2.17**. Palladacycle **2.18** could be generated from oxidative addition of nitroarene **8a**,[47,48] which would undergo reductive elimination of CO_2 to produce palladium-nitrosoarene **2.19**. Cyclization of **2.19** occurs through electrocyclization or attack by the adjacent π-system.[49,50] The resulting carbocation at benzylic position then causes a ring contraction to generate spirocycle *N*-oxide **2.21**. Deoxygenation occurs through carbonyl insertion, followed by reduction elimination of **2.22**, to produce 3*H*-indole product and regenerate the palladium CO complex. We recognized that an alternative pathway is possible if $Mo(CO)_6$ has multiple roles: in addition to supplying CO for palladium-catalyzed reduction, it could also coordinate nitrosoarene **2.23** to trigger the attack by the pendant olefin to form **2.20**.[51-53] A third possible mechanistic pathway is that a metal nitrene intermediate initiates the cyclization. Upon the formation of palladium-nitrosoarene **2.19**, oxidative addition could occur to generate palladacycle **2.24**,[54] followed by reductive elimination of CO_2 to produce palladium nitrene **2.25**. A 4π-electron-5-atom-electrocyclization could trigger the cyclization to generate the benzylic carbon cation, which could undergo a ring contraction to produce the 3*H*-indole product.

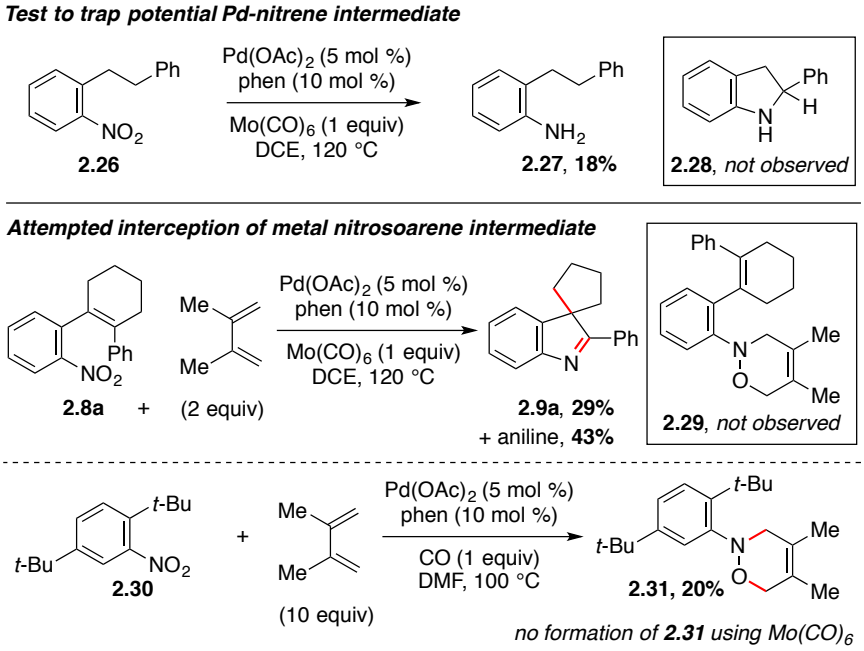
Scheme 2.2 ***Proposed mechanism for Pd-catalyzed 3H-indole formation***



Next, Navendu and I designed and performed a series of control experiments to distinguish between these possible mechanisms (Scheme 3). The palladium nitrene pathway was firstly examined by exposing nitroarene **2.26** to reaction conditions. If the reaction went through the nitrene intermediate, we expected that 2-phenylindoline would be formed.[55,56] In contrast, only aniline formation was observed. We interpreted this result to suggest that metal nitrene are not involved in the catalytic cycle. Next, to intercept the nitrosoarene intermediate, 2,3-dimethylbutadiene was added to the reaction mixture. A cycloaddition of putative nitrosoarene intermediate was expected to generate **2.29**. Only 3*H*-indole product **2.9a** and aniline were observed. We anticipated that this result could be attributed to the enhanced rate of an intramolecular reaction in comparison to an intermolecular reaction. To eliminate this competition, we tested the 2,5-di-*tert*-butylnitrobenzene **2.30**. To our surprise, exposure of **2.30** to reaction

conditions and 2,3-dimethylbutadiene produced only aniline. We found the nitrosointermediate could be intercepted when $Mo(CO)_6$ was replaced with CO. We interpret this result to suggest that $Mo(CO)_6$ plays a more complex role than simply acting as a source of CO.

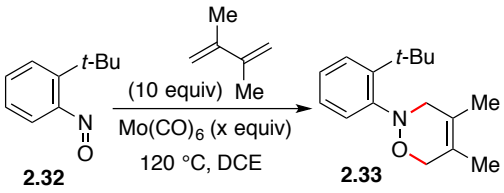
Scheme 2.3 ***Attempted interception of potential intermediates***



To further understand the effect of $Mo(CO)_6$, 2-*tert*-butylnitrosobenzene **2.32** was prepared and tested. As expected, exposure of **2.32** to 2,3-dimethylbutadiene afforded oxazine **2.33** with 98% yield. The addition of $Mo(CO)_6$, however, completely inhibited cycloaddition to produce only trace amounts of aniline. Adding 1,5-cyclooctadiene did not affect this result in an effort to trap a potential coordinatively unsaturated molybdenum carbonyl complex. These results suggested that $Mo(CO)_6$ is not simply supplying CO source in our reaction, and suggests that it also coordinates the

nitrosoarene to trigger cyclization and subsequent migration. Since $Pd(OAc)_2$ is necessary for high yields, our data does not exclude a catalytic cycle involving a heterobimetallic Pd-$Mo(CO)_n$ complex.[57-59] It does imply, however, that role of the palladium phenanthroline complex is to catalyze the N–O bond reduction in both nitroarene **2.8a** and spirocycle *N*-oxide **2.21**.

Scheme 2.4 ***Effect of $Mo(CO)_6$ on the cycloaddition of nitrosoarene***

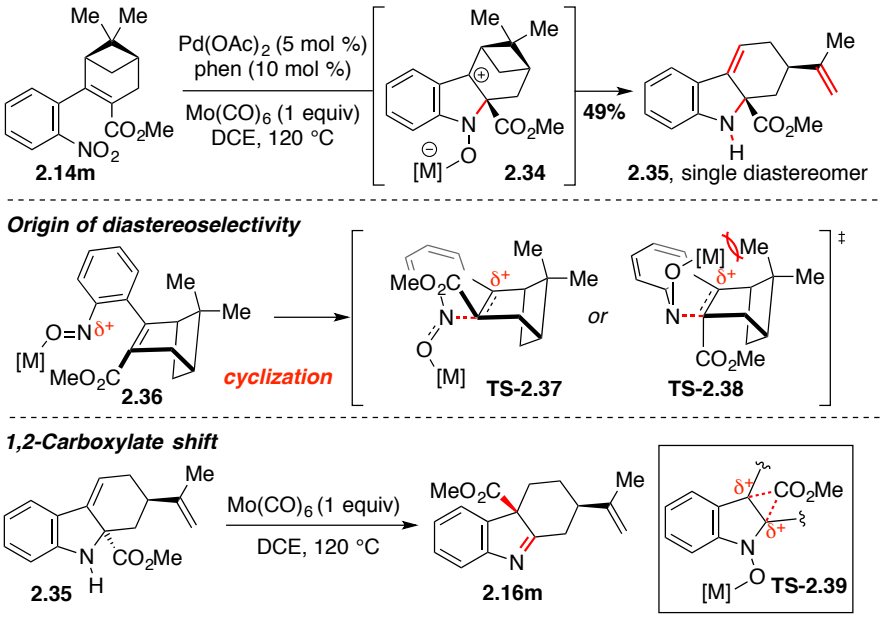


$Mo(CO)_6$	**2.33**	aniline
none	98%	
1 equiv	0%	15%
1 equiv + 1,5-COD (1 equiv)	0%	15%

Next, the origin of the diastereoselectivity of our reaction was investigated using α-pinene-derived nitroarene **2.14m**. Exposing **2.14m** to reaction conditions did not form the expected spirocycle product. Instead, 2*H*-indole **2.35** was obtained as a single diastereomer. We rationalized that this *N*-heterocycle was formed from deprotonation of one of the bridgehead methyl groups present in benzylic cation intermediate **2.34**. This deprotonation triggers a fragmentation to produce 2*H*-indole **2.35** as single diastereomer. The stereochemistry embedded in **2.35** provides insight into the diastereoselectivity of the cyclization step. Two possible transition states **2.37** and **2.38** potentially explain the electrocyclization step of metal nitrososarene **2.36**. The torqueselectivity appears to result from minimizing the steric interactions between the metal complex and the bridgehead methyl group, which are present in **TS-2.38**.[60-62] Next, we found that the migration of the methyl carboxylate did not require the presence of palladium. Exposing indoline **2.35** to

$Mo(CO)_6$ induced 1,2-migration of the methyl carboxylate group to yield 3*H*-indole **2.16m** as a single diastereomer.[63] The chemoselectivity appears to arise from the transition state or intermediate with more stable iminium ion (e.g. **TS-2.39**).

Scheme 2.5 ***Origin of cyclization-migration selectivity***



In conclusion, the reactivity of 2-alkenyl-substituted nitroarenes was unlocked by the combination of palladium acetate and $Mo(CO)_6$. A range of spirocyclic 3*H*-indoles was achieved through the cyclization-migration reaction. Our mechanistic studies provided insights into the multiple roles of $Mo(CO)_6$ as well as the diastereoselectivity. Our studies opened access to use nitroarenes as nitrogen atom source by taking advantage of the reactivity of palladium nitrosoarene complexes, which will be demonstrated in the next two chapters of my thesis.

Experiment

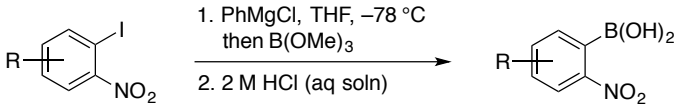
A. General

^{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.

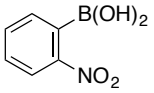
a. General Procedure.



2.12

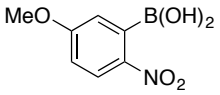
A dry nitrogen-flushed 25 mL round-bottomed flask equipped with a magnetic stirrer and a septum was charged with aryl iodide (4.0 mmol). Dry THF (6 mL) was added, and the resulting solution was cooled to −78 °C. To the resulting cooled mixture was added dropwise 2.2 mL of a 2 M solution of PhMgCl (4.4 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.



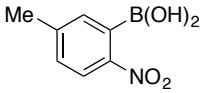
2.12a

2-Nitrophenylboronic acid 2.12a. 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.



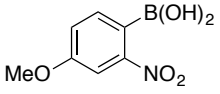
2.12b

2-Nitro-5-methoxyphenylboronic acid 2.12b. 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.



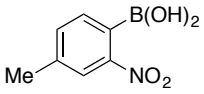
2.12c

2-Nitro-5-methylphenylboronic acid 2.12c. 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.



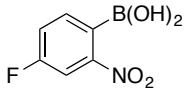
2.12f

2-Nitro-4-methyoxyphenylboronic acid 2.12f. 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.



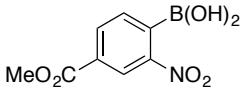
2.12g

2-Nitro-4-methylphenylboronic acid 2.12g. 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.



2.12h

2-Nitro-4-fluorophenylboronic acid 2.12h. 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.

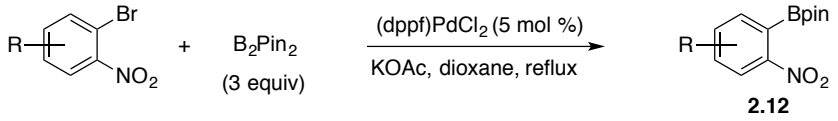


2.12l

2-Nitro-4-methylcarboxylatephenylboronic acid 2.12i. 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..

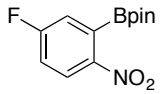
a. General Procedure.



2.12

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.

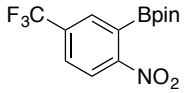
b. Characterization Data for 2-Nitroarylboronic Acid Pinacolate Esters.



2.12d

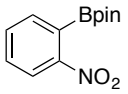
2-Nitro-5-fluorophenylboronic acid pinacolate ester 2.12d. The general procedure was followed using 0.330 g of 1-bromo-2-nitrobenzene (1.50 mmol), 0.571 g of bis(pinacolato)diboron (2.30 mmol), 0.378 g of KOAc (3.86 mmol) and 0.060 g of (dppf)$PdCl_2$ (0.070 mmol) in 8 mL of 1,4-dioxane. Purification 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:[4] ^{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}.



2.12e

2-Nitro-5-triflouromethylboronic acid pinacolate ester 2.12e. 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:[5] ^{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}.

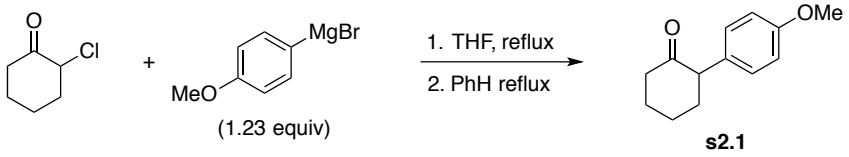


2.12j

2-Nitrophenylboronic acid pinacolate ester 2.12j. 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}.

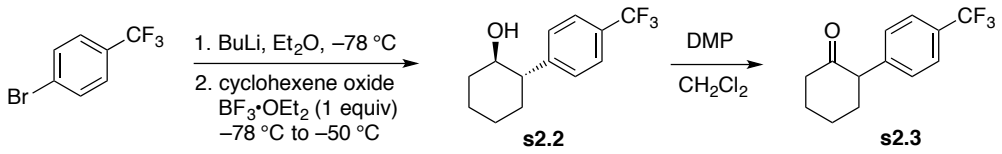
C. Synthesis of Vinyl Triflates.

1. Preparation of 2-Arylcyclohexanones.



s2.1

2-(4-Methoxy)phenylcyclohexanone s2.1. Following the procedure reported by Nachtsheim and Frahm, 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: ^{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}.



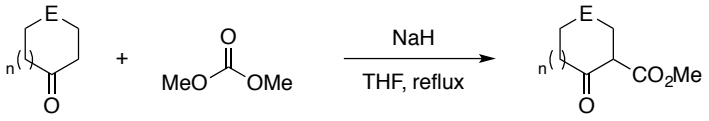
2-(4-Trifluoromethylphenyl)cyclohexanol s2.2. To a solution of 0.47 mL 4-bromotrifluoromethylbenzene (3.34 mmol) in 10 mL of diethylether at −78° C was added 2.56 mL of BuLi (1.6 M, 4.0 mmol) under argon. After 5 min at this temperature, 0.41 mL of cyclohexenoxide (4.0 mmol) was added followed by the 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 s2.3. 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%). ^{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.

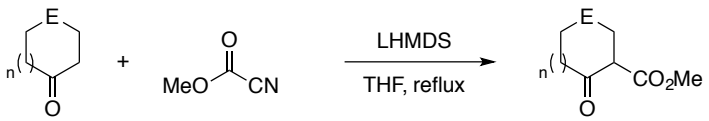


s2.4

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

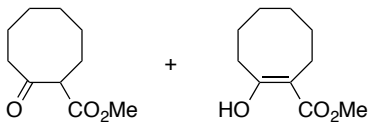
diluted with ether. The mixture was hydrolyzed by the slow addition of 1M aqueous solution of HCl, then poured into brine and extracted with diethyl ether (4 × 30 mL). The combined organic layers were dried over Na_2SO_4 and concentration *in vacuo*. Purification of the residue by MPLC afforded the product.



s2.4

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.

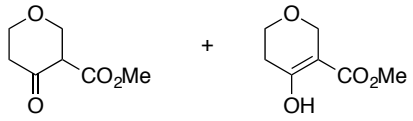
b. Characterization Data.



s2.4a

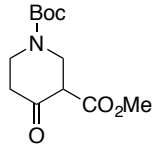
Methyl-2-oxocyclooctanecarboxylate s2.4a. Method A was followed using 3.20 g of NaH (80 mmol), 5.0 mL of dimethylcarbonate (60 mmol), and 2.53 g of cyclooctanone (20 mmol) in 50 mL dioxane reflux at 90 °C. Purification by MPLC (2:98 to 5:95 EtOAc: hexane) afforded the product—a yellow oil—as a mixture of the keto- and enol tautomers (3.70 g, 100%). ^{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.



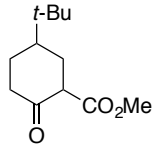
s2.4h

Methyl-4-oxotetrahydro-2*H*-pyran-3-carboxylate s2.4b. 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:[10] ^{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.



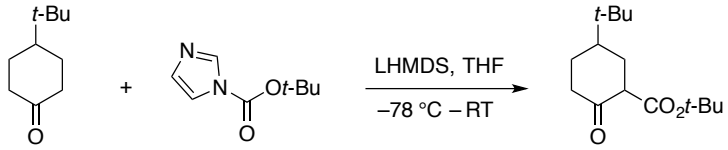
s2.4c

1-*tert*-Butyl-3-methyl-4-oxopiperidine-1,3-dicarboxylate s2.4c. 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%). ^{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}.



s2.4d

Methyl-5-tert-butyl-2-oxocyclohexanecarboxylate s2.4d. 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%). ^{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.

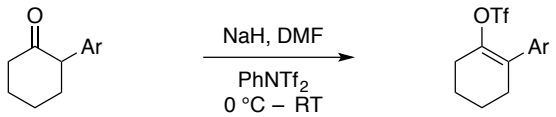


s2.4e

***tert*-Butyl-5-*tert*-butylcyclohexyl-2-oxocyclohexanecarboxylate s2.4e.** 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%). ^{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.

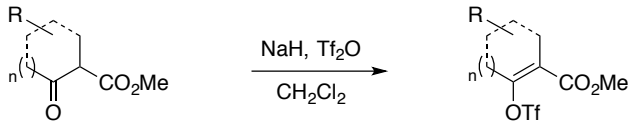
3. Preparation of Vinyl Triflates.

a. General Procedure.



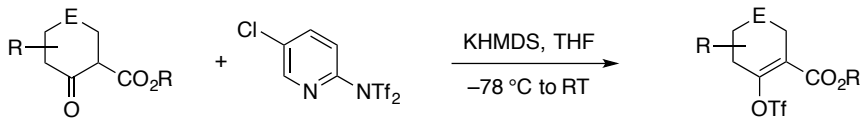
s2.5

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.



s2.5

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.

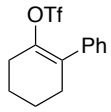


s2.5

Method C: To a solution of β-ketoester (1.0 equiv) in THF (0.2 M) was slowly added a

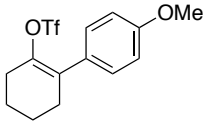
solution of KHMDS (1.2 equiv) in THF at – 78 °C. After stirring for 1 h, a solution of Comins' reagent (1.2 equiv) in THF was added dropwise to the reaction. The resulting mixture was then gradually warmed to room temperature. After stirring for overnight, the reaction was quenched by the addition of 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.



s2.5a

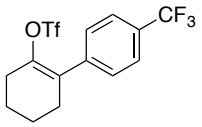
Methanesulfonic acid, 1,1,1-trifluoro-2-phenyl-1-cyclohexenyl ester s2.5a. Method A was followed using 0.871 g of 2-Phenylcyclohexanone (5.0 mmol), 0.380 g of NaH (60% in oil, 9.5 mmol), 1.96 g of 1,1,1-trifluoro-N-phenyl-N-(trifluoromethylsulfonyl)methanesulfonamide (5.5 mmol) in 20 mL of DMF. Purification by MPLC (2:98 to 5:95 EtOAc: hexane) afforded the product as colorless oil (1.25 g, 82%). Triflate s5a was first reported by Rigby and Qabar: ^{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}.



s2.5b

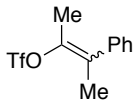
Methanesulfonic acid, 1,1,1-trifluoro-(2-4-methoxyarene)-1-cyclohexenyl ester s2.5b.

Method A was followed using 0.204 g of 2-arylcyclohexanone **s2.1** (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%): ^{1}H 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}.



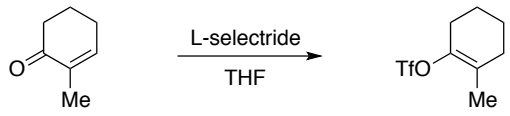
s2.5c

Methanesulfonic acid, 1,1,1-trifluoro-(2-4-methoxyarene)-1-cyclohexenyl ester s2.5c. Method A was followed using 0.242 g of 2-arylcyclohexanone **s2.3** (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}.



s2.5d

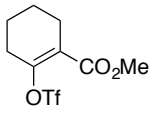
3-Phenylbut-2-en-2-yl trifluoromethanesulfonate s2.5d. Method A was followed using 1.48 g of 3-phenylbutan-2-one (10.0 mmol), 0.760 g of NaH (19.0 mmol) and 3.92 g of 1,1,1-trifluoro-*N*-phenyl-*N*-(trifluoromethylsulfonyl)-methanesulfonamide (11.0 mmol) in 50 mL of DMF. Purification by MPLC (2:98 to 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.



s2.5e

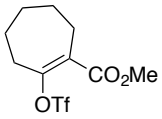
2-Methylcyclohex-1-en-1-yl trifluoromethanesulfonate s2.5e. To a solution of 1.11 g of 2-methylcyclohexenone (10.1 mmol) in 25 mL of tetrahydrofuran at –78°C was added 10.5 mL of L-Selectride® (10.5 mmol, 1 M in THF). After stirring at –78°C for 1h, 3.61 g of 1,1,1-trifluoro-*N*-phenyl-*N*-((trifluoromethyl)sulfonyl)methanesulfonamide (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: ^{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).



s2.5f

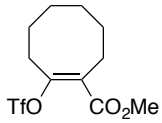
Methyl 2-(trifluoromethylsulfonyloxy)cyclohex-1-enecarboxylate s2.5f. Method B was followed using 2.0 mL of methyl 2-oxocyclohexanecarboxylate (12.7 mmol), 0.608 g of NaH (15.2 mmol) and 2.56 mL of Tf_2O (15.2 mmol) in 60 mL of CH_2Cl_2. The crude product was afforded as brown oil (3.65 g, 100%). ^{1}H 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.



s2.5g

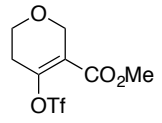
Methyl 2-(trifluoromethylsulfonyloxy)cyclohept-1-enecarboxylate s2.5g. Method B was followed using 1.0 mL of methyl 2-oxocycloheptanecarboxylate (6.4 mmol), 0.307 g of NaH (7.7 mmol) and 1.3 mL of Tf_2O (7.7 mmol) in 30 mL of CH_2Cl_2. The crude product was afforded as brown oil (1.90 g, 98%). ^{1}H 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.



s2.5h

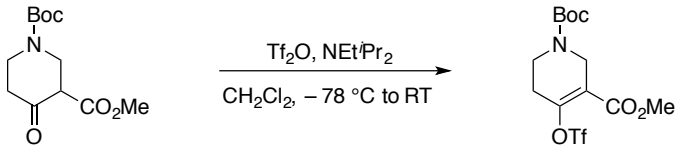
Methyl 2-(trifluoromethylsulfonyloxy)cyclooct-1-enecarboxylate s2.5h. Method B was followed using 1.0 g of methyl 2-oxocyclooctanecarboxylate **s2.4a** (5.4 mmol), 0.260 g of NaH (6.5 mmol) and 1.1 mL of Tf_2O (6.5 mmol) in 30 mL of CH_2Cl_2. The crude product was afforded as brown oil (1.38 g, 80%). ^{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.



s2.5i

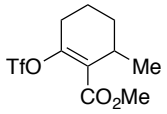
Methyl 4-(trifluoromethylsulfonyloxy)-5,6-dihydro-2H-pyran-3-carboxylate s2.5i. Method C was followed using 0.140 g of β-ketoester **s2.4b** (0.89 mmol), 0.212 g of KHMDS (1.06 mmol) and 0.417 g of Comins' reagent (1.06 mmol) in 10 mL of THF. Purification by MPLC (3:97 to 10:90 EtOAc: hexane) afforded the product as colorless oil (165 mg, 64%). The spectral data of vinyl triflate matched that reported by Kong and Driver:[19] ^{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.



s2.4c **s2.5j**

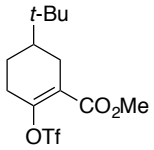
1-*tert*-Butyl 3-methyl 4-(trifluoromethylsulfonyloxy)-5,6-dihydropyridine-1,3(2*H*)-dicarboxylate s2.5j. To a solution of β-ketoester **s2.4c** (0.649 g, 2.52 mmol) in CH_2Cl_2 (10 mL) was slowly added $NEt(^iPr)_2$ (2.2 mL, 12.6 mmol) at – 78 °C. After stirring for 20 min, trifluoromethanesulfonic 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%). ^{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.



s2.5k

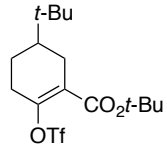
Methyl 6-methyl-2-(((trifluoromethyl)sulfonyl)oxy)cyclohex-1-ene-1-carboxylate

s2.5k. 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 **s2.5k** matched that reported by Kong and Driver: 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.



s2.5l

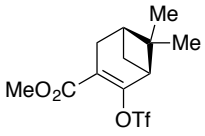
Methyl 5-tert-butyl-2-(trifluoromethylsulfonyloxy)cyclohex-1-enecarboxylate s2.5l. Method B was followed using using 1.26 g of β-ketoester **s2.4d** (5.96 mmol), 0.286 g of NaH (7.15 mmol) and 1.21 mL of Tf_2O (7.15 mmol) in 30 mL of CH_2Cl_2. The crude product was afforded as brown oil (2.05 g, 100%). The spectral data of vinyl triflate **s2.5l** matched that reported by Kong and Driver: ^{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.



s2.5m

***tert*-Butyl-5-*tert*-butyl-2-(trifluoromethylsulfonyloxy)cyclohex-1-enecarboxylate**

s2.5m. Method C was followed using 0.131 g of β-ketoester **s2.4e** (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 **s5m** matched that reported by Kong and Driver: ^{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.



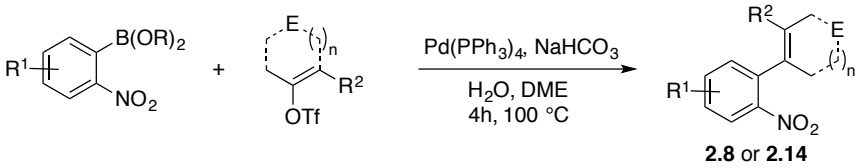
s2.5n

Vinyl triflate s2.5n. 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.

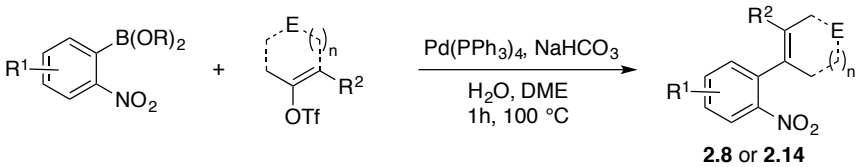
D. Synthesis of 2-substituted Nitroarenes using Suzuki Cross-Coupling Reaction.

1. General Procedures.



2.8 or **2.14**

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.

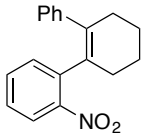


2.8 or **2.14**

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

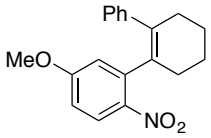
mixture was cooled to room temperature and diluted with 5 mL of cold water. The mixture was extracted with 2 × 10 mL of ethyl acetate. The combined organic phases were washed with 10 mL of brine. The resulting organic phase was dried over Na_2SO_4, filtered and was concentrated *in vacuo*. Purification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

2. Characterization Data.



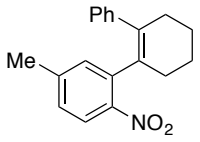
2.8a

Nitrostyrene 2.8a. General procedure A was followed by using 1.33 g of vinyl triflate **s2.5a** (4.34 mmol), 0.871 g of 2-nitrophenylboronic acid **2.12a** (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.



2.8b

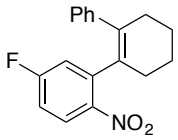
Nitrostyrene 2.8b. General procedure A was followed by using 0.250 of vinyl triflate **s2.5a** (0.82 mmol), 0.192 g of 5-methoxy-2-nitrophenylboronic acid **2.12b** (0.98 mmol), 0.094 g of $Pd(PPh_3)_4$ (0.08 mmol) and 0.259 g of sodium carbonate (2.44 mmol) in a mixture of 10 mL of dimethoxyethane and 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.



2.8c

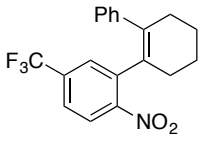
Nitrostyrene 2.8c. General procedure A was followed by using 0.285 of vinyl triflate **s2.5a** (0.93 mmol), 0.200 g of 5-methyl-2-nitrophenylboronic acid **2.12c** (1.11 mmol), 0.537 g of $Pd(PPh_3)_4$ (0.046 mmol) and 0.295 g of sodium carbonate (2.79 mmol) in a mixture of 10 mL of dimethoxyethane and 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.



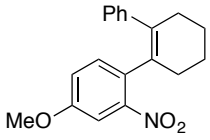
2.8d

Nitrostyrene 2.8d. General procedure B was followed by using 0.124 g of vinyl triflate **s2.5a** (0.40 mmol), 0.090 g of 5-fluoro-2-nitrophenylboronic acid pinacol ester **2.12d** (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.



2.8e

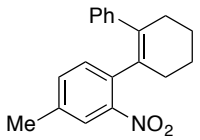
Nitrostyrene 2.8e. General procedure B was followed by using 0.235 g of vinyl triflate **s2.5a** (0.77 mmol), 0.292 g of 5-trifluoromethyl-2-nitrophenylboronic acid pinacol ester **2.12e** (0.92 mmol), 0.100 g of $Pd(PPh_3)_4$ (0.086 mmol), 1.8 mL of a saturated aq. soln. of $NaHCO_3$ and 10 mL of dimethoxyethane. 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.



2.8f

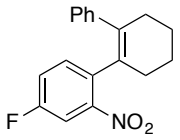
Nitrostyrene 2.8f. General procedure B was followed by using 0.306 g of vinyl triflate **s2.5a** (1.00 mmol), 0.236 g of 4-methoxy-2-nitrophenylboronic acid **2.12f** (1.20 mmol), 0.115 g of $Pd(PPh_3)_4$ (0.100 mmol), 2.0 mL of a saturated aq. soln. of $NaHCO_3$ and 10 mL of dimethoxyethane. Purification 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.



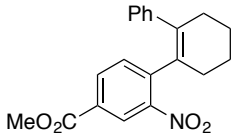
2.8g

Nitrostyrene 2.8g. General procedure B was followed by using 0.306 g of vinyl triflate **s2.5a** (1.00 mmol), 0.217 g of 4-methoxy-2-nitrophenylboronic acid **2.12g** (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.



2.8h

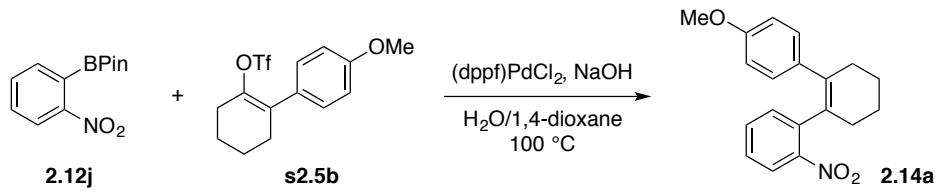
Nitrostyrene 2.8h. General procedure A was followed by using 0.178 g of vinyl triflate **s2.5a** (0.58 mmol), 0.129 g of 4-fluoro-2-nitrophenylboronic acid **2.12h** (0.69 mmol), 0.670 g of $Pd(PPh_3)_4$ (0.06 mmol) and 0.184 g of sodium carbonate (1.74 mmol) in a mixture of 6 mL of dimethoxyethane and 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.



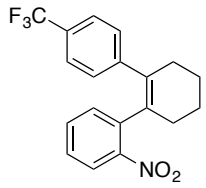
2.8i

Nitrostyrene 2.8i. General procedure B was followed by using 0.306 g of vinyl triflate **s2.5a** (1.00 mmol), 0.270 g of 4-methoxy-2-nitrophenylboronic acid **2.12i** (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.

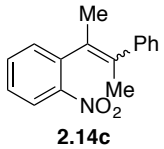


Nitrostyrene 2.14a. To a mixture 0.068 g of vinyl triflate **s2.5b** (0.20 mmol), 0.060 g of 2-nitrophenylboronic acid pinacolate ester **2.12j** (0.24 mml), 0.008 g of (dppf)$PdCl_2$ (0.010 mmol), 0.60 mL of a 0.30 M aq. soln. of NaOH and 4 mL of 1,4-dioxane. The resulting mixture was heated to 100 °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.



2.14b

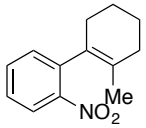
Nitrostyrene 2.14b. The general procedure B was followed by using 0.075 g of vinyl triflate **s2.5c** (0.20 mmol), 0.060 g of 2-nitrophenylboronic acid pinacolate ester **2.12j** (0.24 mmol), 0.023 g of $Pd(PPh_3)_4$ (0.020 mmol), 0.4 mL of a saturated aq. soln. of $NaHCO_3$ and 3 mL of dimethoxyethane. 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.



2.14c

Nitrostyrene 2.14c. The general procedure B was followed by using 0.100 g of vinyl triflate **s2.5d** (0.357 mmol), 0.107 g of 2-nitrophenylboronic acid pinacolate ester **2.12j** (0.428 mmol), 0.041 g of $Pd(PPh_3)_4$ (0.036 mmol), 0.7 mL of a saturated aq. soln. of

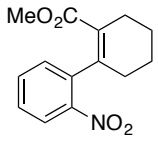
$NaHCO_3$ and 5 mL of dimethoxyethane. Purification by MPLC (3:97 to 10:90 EtOAc: hexane) afforded the product, a brown liquid, as a 87:13 mixture of *E/Z* isomers (0.070 g, 78%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (dd, *J* = 8.0 Hz, 1.0 Hz, 1H), 7.36 (m, 0.5H), 7.30 (dq, *J* = 7.5 Hz, 1.0 Hz, 1.5H), 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: ^{1}H 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.



2.14d

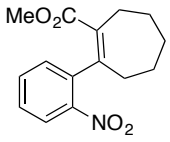
Nitrostyrene 2.14d. General procedure B was followed by using 0.098 g of vinyl triflate **s2.5e** (0.400 mmol), 0.120 g of 2-nitrophenylboronic acid pinacol ester **2.12j** (0.480 mmol), 0.046 g of $Pd(PPh_3)_4$ (0.040 mmol), 0.8 mL of a saturated aq. soln. of $NaHCO_3$ and 4 mL of dimethoxyethane. Purification 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.



2.14e

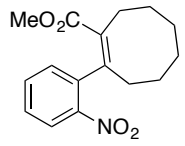
Nitrostyrene 2.14e. General procedure A was followed by using 0.100 g of vinyl triflate **s2.5f** (0.347 mmol), 0.103 g of 2-nitrophenylboronic acid pinacol ester **2.12j** (0.417 mmol), 0.040 g of $Pd(PPh_3)_4$ (0.035 mmol) and 0.60 mL of saturated aq. soln. of $NaHCO_3$ and 3 mL of dimethoxyethane.. Purification by MPLC (3:97 to 10:90 EtOAc: hexane) afforded the product as a yellow liquid (0.071 g, 78%): ^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* = 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.



2.14f

Nitrostyrene 2.14f. General procedure A was followed by using 0.115 g of vinyl triflate **s2.5g** (0.380 mmol), 0.064 g of 2-nitrophenylboronic acid **2.12a** (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

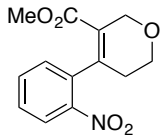
mL of dimethoxyethane and 0.4 mL of water. Purification by MPLC (3:97 to 10:90 EtOAc: hexane) afforded the product as a greenish yellow liquid (0.080 g, 76%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.0 Hz, 1H), 7.55 (t, *J* = 7.5 Hz, 1H), 7.40 (t, *J* = 8.0 Hz, 1H), 7.12 (d, *J* = 7.5 Hz, 1H), 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.



2.14g

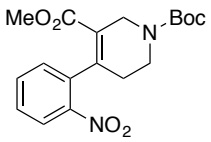
Nitrostyrene 2.14g. General procedure A was followed by using 0.189 g of vinyl triflate **s2.5h** (0.600 mmol), 0.835 g of 2-nitrophenylboronic acid **2.12a** (0.500 mmol), 0.029 g of $Pd(PPh_3)_4$ (0.025 mmol) and 0.158 g of sodium carbonate (1.50 mmol) in a mixture of 5 mL of dimethoxyethane and 0.5 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.



2.14h

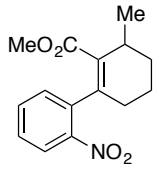
Nitrostyrene 2.14h. General procedure B was followed by using 0.145 g of vinyl triflate **s2.5i** (0.500 mmol), 0.149 g of 2-nitrophenylboronic acid pinacol ester **2.12j** (0.600 mmol), 0.058 g of $Pd(PPh_3)_4$ (0.050 mmol), 1.0 mL of a saturated aq. soln. of $NaHCO_3$ and 5 mL of dimethoxyethane. Purification 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.



2.14i

Nitrostyrene 2.14i. General procedure B was followed by using 0.194 g of vinyl triflate **s2.5j** (0.500 mmol), 0.149 g of 2-nitrophenylboronic acid pinacol ester **2.12j** (0.600 mmol), 0.058 g of $Pd(PPh_3)_4$ (0.050 mmol), 1.0 mL of a saturated aq. soln. of $NaHCO_3$

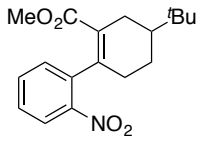
and 5 mL of dimethoxyethane. Purification by MPLC (3:97 to 10:90 EtOAc: hexane) afforded the product as a green solid (0.134 g, 74%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.0 Hz, 1H), 7.60 (dt, *J* = 7.5 Hz, 1.0 Hz, 1H), 7.46 (dt, *J* = 8.5 Hz, 1.5 Hz, 1H), 7.13 (dd, *J* = 8.0 Hz, 1.5 Hz, 1H), 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.



2.14j

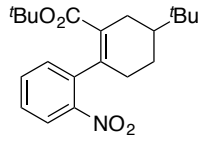
Nitrostyrene 2.14j. General procedure B was followed by using 0.160 g of vinyl triflate **s2.5k** (0.500 mmol), 0.149 g of 2-nitrophenylboronic acid pinacol ester **2.12j** (0.600 mmol), 0.058 g of $Pd(PPh_3)_4$ (0.050 mmol), 1.0 mL of a saturated aq. soln. of $NaHCO_3$ and 5 mL of dimethoxyethane. Purification 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); δ 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.



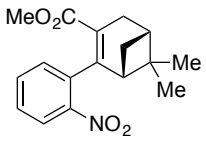
2.14k

Nitrostyrene 2.14k. General procedure A was followed by using 0.206g of vinyl triflate **s2.5l** (0.600 mmol), 0.830 g of 2-nitrophenylboronic acid **2.12a** (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.



2.14l

Nitrostyrene 2.14l. General procedure A was followed by using 0.231 g of vinyl triflate **s2.5m** (0.600 mmol), 0.830 g of 2-nitrophenylboronic acid **2.12a** (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.



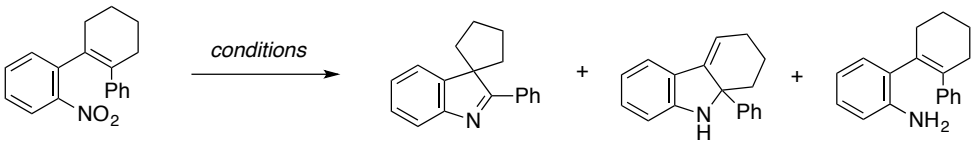
2.14m

Nitrostyrene 2.14m. The general procedure B was followed by using 0.098 g of pinene-derived vinyl triflate **s2.5n** (0.30 mmol), 0.090 g of 2-nitrophenylboronic acid pinacolate

ester **2.12a** (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.



2.8a **2.9a** **2.10a** **2.11a**

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.

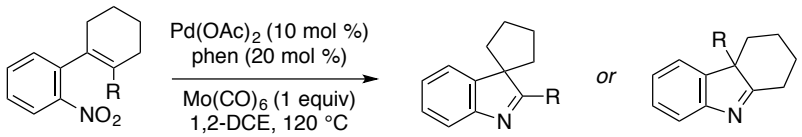
Table 2.4 ***Survey of Reaction Conditions for Pd-catalyzd Nitroarene Reduction.***

entry	catalyst (mol %)	ligand (mol %)	reductant (equiv)	solvent	T (°C)	yield, %[a] **2.9a** : **2.10a** : **2.11a**
1	$Pd(OAc)_2$ (20 mol %)	phen (40 mol %)	CO (1.5 atm)	DMF	120	20:40:0
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	$Pd(OAc)_2$	phen	$Mo(CO)_6$	DCE	120	80:0:0

	(10 mol %)	(20 mol %)	(1.0 equiv)			
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

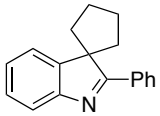
[a] As determined using ^1H NMR spectroscopy using CH_2Br_2 as the internal standard. [b] 0.4 equiv of trifluoroacetic acid added.

2. Optimized Procedure.



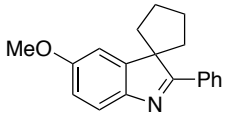
In a 10 mL Schlenk tube, under a nitrogen atmosphere, was added 0.10 mmol of nitroarene followed by 0.01 mmol of $Pd(OAc)_2$ (10 mol %), 0.02 mmol of phenanthroline (20 mol %), 0.10 mmol of $Mo(CO)_6$ (1.0 equiv) in 1.0 mL of 1,2-dichloroethane. The Schlenk tube was sealed and heated at 120 °C for either 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.



2.9a

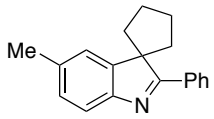
3*H*-Indole 2.9a. The optimized procedure was followed by using 0.028 g of nitroarene **2.8a** (0.10 mmol), 0.0022 g of $Pd(OAc)_2$ (0.010 mmol), 0.0036 g of phenanthroline (0.020 mmol), 0.0264 g of $Mo(CO)_6$ (0.100 mmol) in 1.0 mL of 1,2-dichloroethane. Purification by MPLC (3:97 – 20:80 EtOAc:hexane) 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.



2.9b

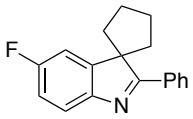
3*H*-Indole 2.9b. The optimized procedure was followed by using 0.031 g of nitroarene **2.8b** (0.10 mmol), 0.0045 g of $Pd(OAc)_2$ (0.020 mmol), 0.0072 g of phenanthroline (0.040 mmol), 0.0264 g of $Mo(CO)_6$ (0.100 mmol) in 1.0 mL of 1,2-dichloroethane. Purification by MPLC (3:97 – 20:80 EtOAc:hexane) afforded the product as a yellow liquid (0.023 g, 82%): ^{1}H 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.



2.9c

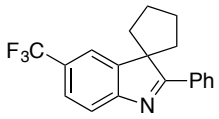
3*H*-Indole 2.9c. The optimized procedure was followed by using 0.029 g of nitroarene **2.8c** (0.10 mmol), 0.0022 g of $Pd(Oac)_2$ (0.010 mmol), 0.0036 g of phenanthroline (0.020 mmol), 0.0264 g of $Mo(CO)_6$ (0.100 mmol) in 1.0 mL of 1,2-dichloroethane. Purification by MPLC (3:97 – 20:80 EtOAc:hexane) 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.



2.9d

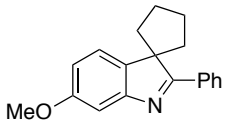
3*H*-Indole 2.9d. The optimized procedure was followed by using 0.030 g of nitroarene **2.8d** (0.10 mmol), 0.0022 g of $Pd(Oac)_2$ (0.010 mmol), 0.0036 g of phenanthroline (0.020 mmol), 0.0264 g of $Mo(CO)_6$ (0.100 mmol) in 1.0 mL of 1,2-dichloroethane. Purification by MPLC (3:97 – 20:80 EtOAc:hexane) 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.



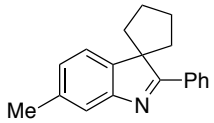
2.9e

3*H*-Indole 2.9e. The optimized procedure was followed by using 0.035 g of nitroarene **2.8e** (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.



2.9f

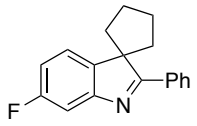
3*H*-Indole 2.9f. The optimized procedure was followed by using 0.031 g of nitroarene **2.8f** (0.10 mmol), 0.0022 g of $Pd(Oac)_2$ (0.010 mmol), 0.0036 g of phenanthroline (0.020 mmol), 0.0264 g of $Mo(CO)_6$ (0.10 mmol) in 1.0 mL of 1,2-dichloroethane. Purification by MPLC (3:97 – 20:80 EtOAc:hexane) 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.



2.9g

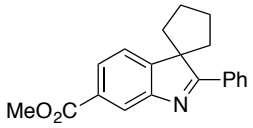
3*H*-Indole 2.9g. The optimized procedure was followed by using 0.029 g of nitroarene **2.8g** (0.10 mmol), 0.0022 g of $Pd(Oac)_2$ (0.010 mmol), 0.0036 g of phenanthroline (0.020 mmol), 0.0264 g of $Mo(CO)_6$ (0.10 mmol) in 1.0 mL of 1,2-dichloroethane. Purification by MPLC (3:97 – 20:80 EtOAc:hexane) afforded the product as a yellow liquid (0.0165 g, 77%): ^{1}H 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.



2.9h

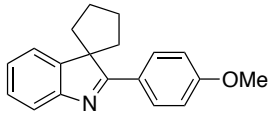
3*H*-Indole 2.9h. The optimized procedure was followed by using 0.030 g of nitroarene **2.8h** (0.10 mmol), 0.0022 g of $Pd(Oac)_2$ (0.010 mmol), 0.0036 g of phenanthroline (0.020 mmol), 0.0264 g of $Mo(CO)_6$ (0.100 mmol) in 1.0 mL of 1,2-dichloroethane. Purification by MPLC (3:97 – 20:80 EtOAc:hexane) afforded the product as a yellow liquid (0.0235 g, 88%): ^{1}H 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.



2.9i

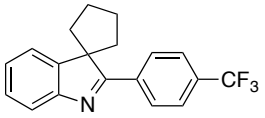
3*H*-Indole 2.9i. The optimized procedure was followed by using 0.034 g of nitroarene **2.8b** (0.10 mmol), 0.0022 g of $Pd(OAc)_2$ (0.010 mmol), 0.0036 g of phenanthroline (0.020 mmol), 0.0264 g of $Mo(CO)_6$ (0.100 mmol) in 1.0 mL of 1,2-dichloroethane.

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.



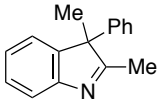
2.15a

3*H*-Indole 2.15a. The optimized procedure was followed by using 0.031 g of nitroarene **2.14a** (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.



2.15b

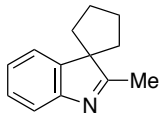
3*H*-Indole 2.15b. The optimized procedure was followed by using 0.035 g of nitroarene **2.14b** (0.10 mmol), 0.0022 g of $Pd(OAc)_2$ (0.010 mmol), 0.0036 g of phenanthroline (0.020 mmol), 0.0264 g of $Mo(CO)_6$ (0.100 mmol) in 1.0 mL of 1,2-dichloroethane. Purification by MPLC (3:97 – 20:80 EtOAc:hexane) 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.



2.15c

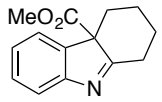
3*H*-Indole 2.15c. The optimized condition was followed by using 0.025 g of nitroarene **2.14c** (0.10 mmol), 0.0022 g of $Pd(OAc)_2$ (0.01 mmol), 0.0036 g of phenanthroline (0.020 mmol), 0.0264 g of $Mo(CO)_6$ (0.10 mmol) in 1.0 mL of 1,2-dichloroethane. Purification by MPLC (3:97 – 20:80 EtOAc:hexane) afforded the product a yellow solid (0.013 g, 59%). ^{1}H 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.



2.15d

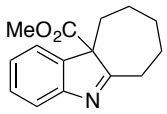
3*H*-Indole 2.15d. The optimal condition was followed by using 0.022 g of nitroarene **2.14d** (0.10 mmol), 0.0044 g of $Pd(OAc)_2$ (0.02 mmol), 0.0072 g of phenanthroline (0.040 mmol), 0.026 g of $Mo(CO)_6$ (0.10 mmol) in 1.0 mL of 1,2-dichloroethane. Purification by MPLC (3:97 – 20:80 EtOAc:hexane) afforded the product a brown oil (0.010 g, 54%): ^{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.



2.16e

3*H*-Indole 2.16e. The optimized procedure was followed by using 0.026 g of nitroarene **2.14e** (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

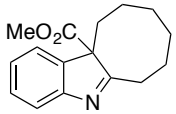
solid (0.0166 g, 73%). The spectral data of **2.16e** matched that reported by Kong and Driver:[19] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (d, *J* = 7.5 Hz, 1H), 7.43 (d, *J* = 7.5 Hz, 1H), 7.37 (t, *J* = 7.5 Hz, 1H), 7.20 (t, *J* = 7.5 Hz, 1H), 3.65 (s, 3H), 3.05 – 2.97 (m, 2H), 2.71 (dt, *J* = 13.0 Hz, 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.



2.16f

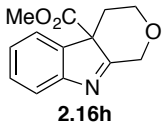
3*H*-Indole 2.16f. The optimized procedure was followed by using 0.028 g of nitroarene **2.14f** (0.10 mmol), 0.0022 g of $Pd(OAc)_2$ (0.010 mmol), 0.0036 g of phenanthroline (0.020 mmol), 0.0264 g of $Mo(CO)_6$ (0.100 mmol) in 1.0 mL of 1,2-dichloroethane. Purification by MPLC (3:97 – 20:80 EtOAc:hexane) afforded the product as a white solid (0.013 g, 52%). The spectral data of **2.16f** matched that reported by Kong and Driver. ^{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.



2.16g

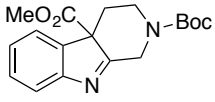
3*H*-Indole 2.16g. The optimized procedure was followed by using 0.029 g of nitroarene **2.14g** (0.10 mmol), 0.0022 g of $Pd(OAc)_2$ (0.010 mmol), 0.0036 g of phenanthroline (0.020 mmol), 0.0264 g of $Mo(CO)_6$ (0.100 mmol) in 1.0 mL of 1,2-dichloroethane. Purification by MPLC (3:97 – 20:80 EtOAc:hexane) afforded the product as a yellow liquid (0.0145 g, 56%). The spectral data for **2.16g** matched that reported by Kong and Driver: ^{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.



2.16h

3*H*-Indole 2.16h. The optimized procedure was followed by using 0.026 g of nitroarene **2.14h** (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

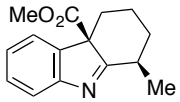
by MPLC (3:97 – 20:80 EtOAc:hexane) afforded the product as a white solid (0.022 g, 67%). The spectral data for **2.16h** matched that reported by Kong and Driver:[19] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, *J* = 7.0 Hz, 1H), 7.50 (d, *J* = 7.5 Hz, 1H), 7.41 – 7.38 (m, 2H), 4.36 – 4.29 (m, 3H), 3.98 (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.



2.16i

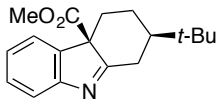
3*H*-Indole 2.16i. The optimized procedure was followed by using 0.036 g of nitroarene **2.14i** (0.10 mmol), 0.0044 g of $Pd(OAc)_2$ (0.020 mmol), 0.0072 g of phenanthroline (0.040 mmol), 0.0264 g of $Mo(CO)_6$ (0.100 mmol) in 1.0 mL of 1,2-dichloroethane. Purification by MPLC (3:97 – 20:80 EtOAc:hexane) afforded the product—a 3:2 mixture of rotamers—as a white solid (0.0135 g, 59%). The spectral data for **2.16i** matched that reported by Kong and Driver:[19] ^{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.



2.16j

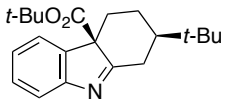
3*H*-Indole 2.16j. The optimized procedure was followed by using 0.028 g of nitroarene **2.14j** (0.10 mmol), 0.0022 g of $Pd(OAc)_2$ (0.010 mmol), 0.0036 g of phenanthroline (0.020 mmol), 0.0264 g of $Mo(CO)_6$ (0.100 mmol) in 1.0 mL of 1,2-dichloroethane. Purification by MPLC (3:97 – 20:80 EtOAc:hexane) 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.



2.16k

3*H*-Indole 2.16k. The optimized procedure was followed by using 0.032 g of nitroarene

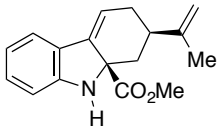
2.14k (0.10 mmol), 0.0022 g of $Pd(OAc)_2$ (0.010 mmol), 0.0036 g of phenanthroline (0.200 mmol), 0.0264 g of $Mo(CO)_6$ (0.100 mmol) in 1.0 mL of 1,2-dichloroethane. Purification by MPLC (3:97 – 20:80 EtOAc:hexane) afforded the product, a yellow liquid, as an 80:20 mixture of diastereomers (0.013 g, 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.



2.16l

3*H*-Indole 2.16l. The optimized procedure was followed by using 0.036 g of nitroarene **2.14l** (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.

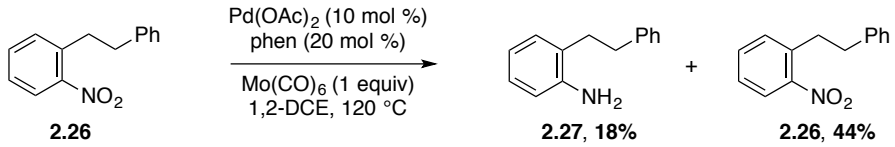


2.35

Indoline 2.35. The optimized procedure was followed by using 0.030 g of nitroarene **2.14m** (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.

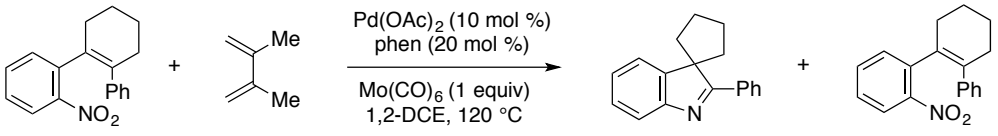
1. Attempted Trap of Potential Metal *N*-aryl Nitrene Intermediate.



2.26 **2.27**, **18%** **2.26**, **44%**

In a 10 mL Schlenk tube, under a nitrogen atmosphere, was added 0.023 g of 1-nitro-2-phenethylbenzene (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 ^1H NMR spectroscopy using CH_2Br_2 as the internal standard.

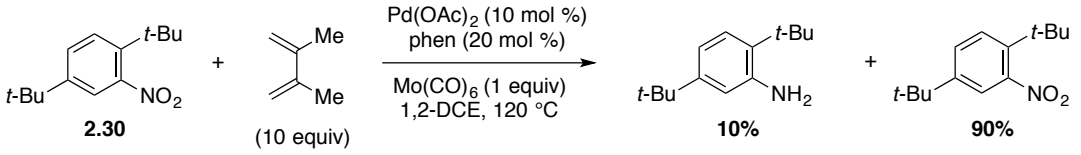
2. Attempted Trap of *ortho*-substituted Nitrosoarene Intermediate with 2,3-butadiene.



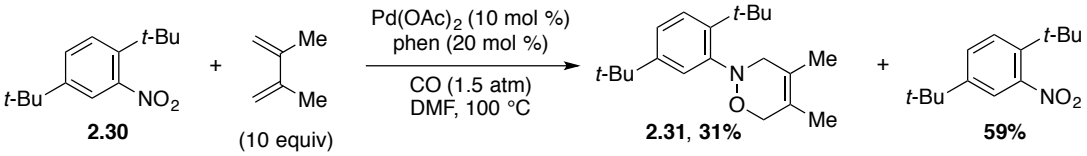
2.8a (10 equiv) **2.9a**, **29%** **2.8a**, **43%**

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.



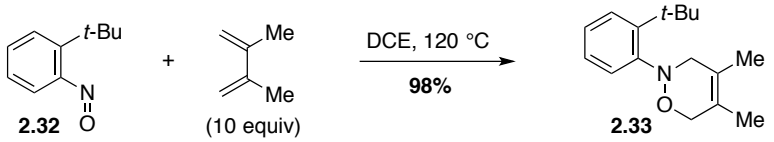
In a 10 mL Schlenk tube, under a nitrogen atmosphere, was added 0.024g of 1,4-di-*tert*-butyl-2-nitrobenzene (0.10 mmol) followed by 0.0022 g of $Pd(OAc)_2$ (0.01 mmol), 0.0036 g of phenanthroline (0.02 mmol), 0.026 g of $Mo(CO)_6$ (0.10 mmol) and 0.082 g 2,3-dimethyl-1,3-butadiene (1 mmol) in 1.0 mL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



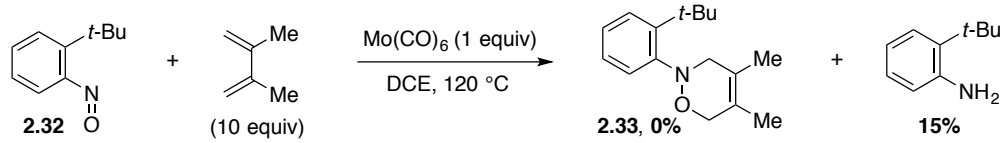
In a 10 mL Schlenk tube, under a nitrogen atmosphere, was added 0.024 g of 1,4-di-*tert*-butyl-2-nitrobenzene (0.10 mmol) followed by 0.0022 g of $Pd(OAc)_2$ (0.01 mmol), 0.0036 g of phenanthroline (0.02 mmol) and 0.082 g 2,3-dimethyl-1,3-butadiene (1 mmol) in 1.0 mL of DMF. The Schlenk tube was filled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

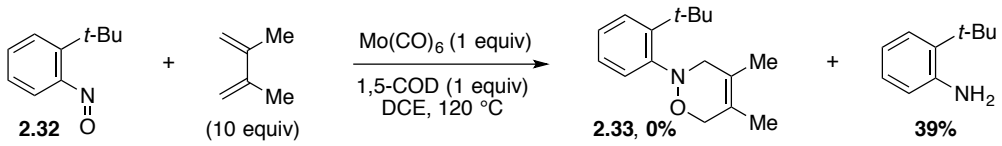


In a 10 mL Schlenk tube, under a nitrogen atmosphere, was added 0.016 g of 1-(*tert*-butyl)-2-nitrosobenzene (0.10 mmol) followed by 0.082 g 2,3-dimethyl-1,3-butadiene (1 mmol) in 1.0 mL of 1,2-dichloroethane. The schlenk tube was sealed and heated at 120 °C for 6 h. The reaction mixture was then cooled 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**.



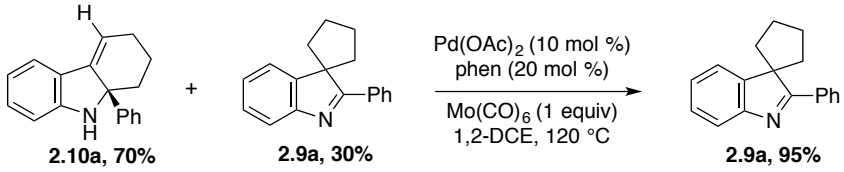
In a 10 mL Schlenk tube, under a nitrogen atmosphere, was added 0.016 g of 1-(*tert*-butyl)-2-nitrosobenzene (0.10 mmol) followed by 0.026 g of $Mo(CO)_6$ (0.10 mmol) and 0.082 g 2,3-dimethyl-1,3-butadiene (1 mmol) in 1.0 mL of 1,2-dichloroethane. The Schlenk tube was sealed and heated at 120 °C for 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%.



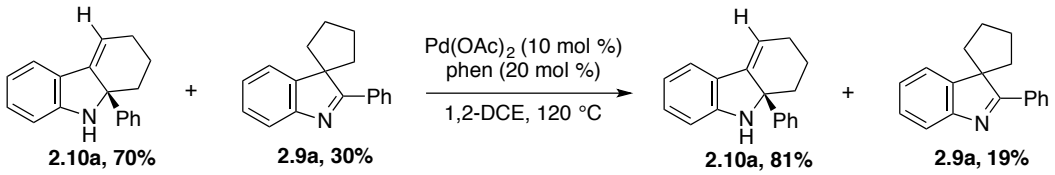
In a 10 mL Schlenk tube, under a nitrogen atmosphere, was added 0.016 g of 1-(*tert*-butyl)-2-nitrosobenzene (0.10 mmol) followed by 0.026 g of $Mo(CO)_6$ (0.10 mmol), 0.082 g 2,3-dimethyl-1,3-butadiene (1 mmol) and 0.011 g of 1,5-cyclooctadiene (0.1 mmol) in 1.0 mL of 1,2-dichloroethane. The Schlenk 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 ^1H 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.



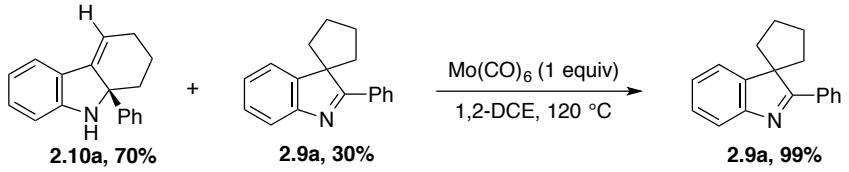
In a 10 mL Schlenk tube, under a nitrogen atmosphere, was added 0.005 g of 1*H*-carbazole **2.10a** (a 70:30 mixture of **2.10a** and **2.9a**, 0.02 mmol), followed by 0.0005 g of $Pd(OAc)_2$ (0.002 mmol), 0.0008 g of phenanthroline (0.004 mmol), 0.005 g of $Mo(CO)_6$ (0.02 mmol) in 0.2 mL of 1,2-dichloroethane. 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%.



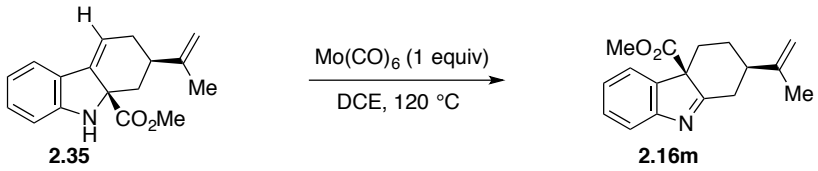
2.10a, 70% **2.9a, 30%** **2.10a, 81%** **2.9a, 19%**

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%.



2.10a, 70% **2.9a, 30%** **2.9a, 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%.



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 ^1H NMR spectroscopy with CH_2Br_2 as the internal standard revealed formation of **2.16m** in 59%.

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(63) The combination $Pd(OAc)_2$, phenanthroline and $Mo(CO)_6$ also promoted the formation of spirocycle **2.9a** from **2.10a**. No 1,2 migration was observed when $Mo(CO)_6$ was omitted from the reaction mixture.

Chapter III

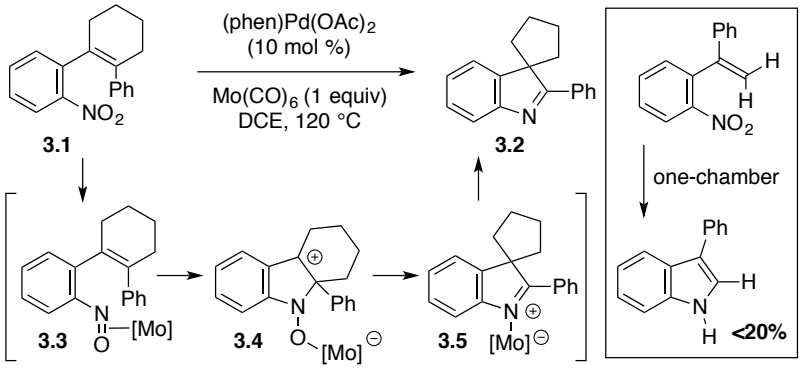
The Development of New Reductive Methods for the Transformation of Nitroarenes into *N*-Heterocycles

1. Palladium-catalyzed Formation of *N*-heteroarenes from Nitroarenes using $Mo(CO)_6$ as the Source of Carbon Monoxide

The pervasive presence of the indole scaffold in compounds that exhibit biological activities continues to motivate organic chemists to develop new synthetic methods to ease its synthesis. [1-14] Our group has developed methods, which used azide as the nitrogen-atom source to construct *N*-hetercycles via transition-metal-catalyzed C–N bond formation.[15-18] Because of the difficulties of substrate preparation and safety concerns with introducing the azide group,[19-21] we expanded our research interest to developing new methods using an alternative electrophilic nitrogen-atom source to form *N*-hetercycles. We recently reported a method development to synthesize spirocyclic 3*H*-indoles from *ortho*-nitrostyrenes (Scheme 3.1).[22] We found that the combination of $Mo(CO)_6$, phenanthroline and $Pd(OAc)_2$ could trigger a domino cyclization-migration process of α,β,β-trisubstituted *o*-nitrostyrenes. At the conclusion of these studies we wanted to investigate the generality of using $Mo(CO)_6$ as a reductant to access other N-heterocycles. Although the synthesis of N-heterocycles from nitroarenes or nitroalkenes has been reported, most of these studies employ high pressures of CO or other toxic or flammable reductants.[23-32] In comparison with these methods, we believed that using $Mo(CO)_6$ as a reductant would be easier and safer to handle.[33-39] However, when we

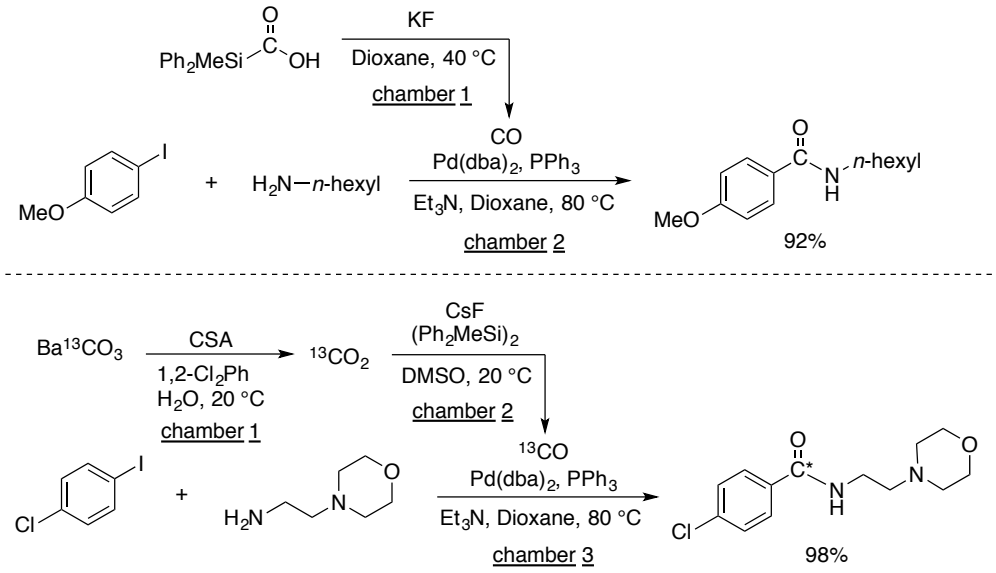
tested our hypothesis by exposing α-phenylnitrostyrene to $Mo(CO)_6$, $Pd(OAc)_2$ and phenanthroline, we observed only traces amount of the 3-phenylindole product. On the basis of our mechanistic studies,[22] which indicated that molybdenum played a more complex role than just serving as the source of carbon monoxide, we anticipated that *N*-heterocycles could be formed from nitrostyrenes using the $Mo(CO)_6$ if the molybdenum complex was segregated from the nitroarene.

Scheme 3.1 ***Use of $Mo(CO)_6$ in Palladium-catalyzed 3H-indole formation***



Skrydstrup and co-workers recently reported the development of two- or three-chamber reaction vessels for palladium-catalyzed carbonylation reaction (Scheme 3.2).[40-42] In their studies, CO is generated in one chamber, and the Pd-catalyzed process occurs in a separate chamber. Inspired by their work, we designed our two-chamber reactor, a so-called H-cell, and proceeded to examine our Pd-catalyzed C–H amination forming *N*-heterocycle from *o*-nitrostyrene.

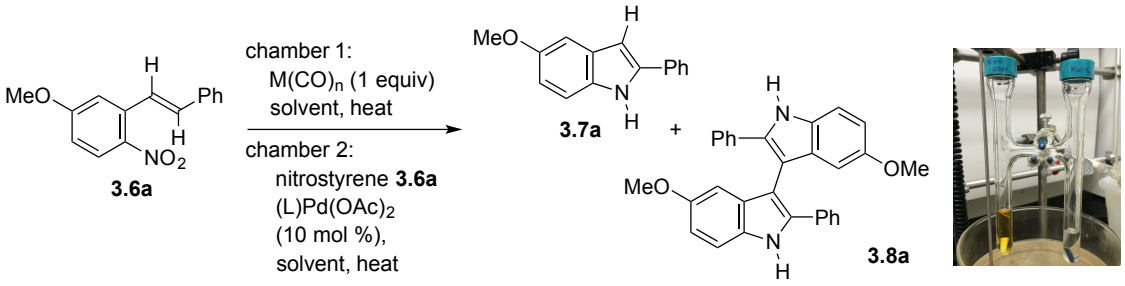
Scheme 3.2 ***Pd-catalyzed carbonylation with two- or three- chamber reactor***



β-Phenylnitrostyrene **3.6a** was chosen to test our hypothesis with the H-cell with Teflon-lined screw caps pictured in Table 1. No reaction was observed in the absence of a palladium catalyst (entry 1). Then we applied the optimal condition for the formation of 3*H*-indole, which was the combination of $Pd(OAc)_2$ and phenanthroline. We found that 1:1 mixture of the desired indole **3.7a** and bisindole **3.8a** was produced (entry 2). The formation of **8a** was previously observed by Sundberg and co-workers when ethyl phosphite was employed as the reductant,[43] and by Cenini and co-workers in their studies of palladium-catalyzed carbonylation of *ortho*-substituted nitroarenes.[44] Besides $Mo(CO)_6$, other d^6-metal carbonyl complex, such as $Cr(CO)_6$ and $W(CO)_6$, were also tested in our reaction (entries 3 and 4). However, the only a reduced yield of indole was observed. To our delight, altering the identitiy of the phenanthroline ligand had a significant effect on indole formation (entries 5 and 6). While using diazafluorenone leaded to no reaction, tetramethylphenanthroline resulted in the generation of indole **3.7a** in 77%. Next, in the screen of the solvent, both DMF and DMA resulted 95% yield

(entries 7–9). We found that the catalyst loading could be reduced to 5 mol % without impacting the reaction conversion (entry 10). To improve the ratio, the reaction solution was diluted from 0.1 mM to 0.05 mM (entry 11). Further improvement in the ratio of indole **3.7a** to bisindole **3.8a** was achieved by running the reaction in a lower temperature (entry 12).

Table 3.1 ***Determination of the optimal conditions***

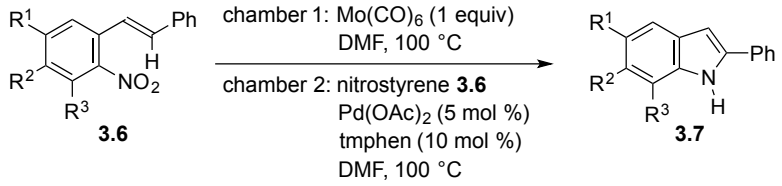


entry	$M(CO)_6$	ligand	solvent	T, °C	% yield (**3.7a**:**3.8a**)
1[b]	$Mo(CO)_6$	n.a.	DMF	120	n.r.
2	$Mo(CO)_6$	phen	DMF	120	66 (50:50)
3	$Cr(CO)_6$	phen	DMF	120	36 (50:50)
4	$W(CO)_6$	phen	DMF	120	16 (25:75)
5	$Mo(CO)_6$	azafluor	DMF	120	n.r
6	$Mo(CO)_6$	tmphen	DMF	120	95 (81:19)
7	$Mo(CO)_6$	tmphen	DMA	120	95 (81:19)
8	$Mo(CO)_6$	tmphen	DMSO	120	69 (91:9)
9	$Mo(CO)_6$	tmphen	DCE	120	n.r.
10[c]	$Mo(CO)_6$	tmphen	DMF	120	95 (77:23)
11[c,d]	$Mo(CO)_6$	tmphen	DMF	120	91 (82:18)
12[c,d]	$Mo(CO)_6$	tmphen	DMF	100	84 (96:4)

[a] As determined using ^{1}H NMR spectroscopy with Br_2CH_2 as the internal standard [b] No $Pd(OAc)_2$ was added to the reaction mixture [c] 5 mol % $Pd(OAc)_2$, 10 mol% tmphen added [d] Diluted from 0.1 mM to 0.05 mM; azafluor = 4,5-diazafluoren-9-one; tmphen = 3,4,7,8-tetramethyl-1,10-phenanthroline

With the optimized conditions in hand, the scope and limitations of our reaction were examined. Initially, we focused on the formation of indole from β-phenyl-substituted nitrostyrene by investigating the effect of varying the electronic- and steric nature of the *o*-nitrostyrene (Table 2). In terms of R^1-substituent, our reaction tolerated both electron-withdrawing and electron-releasing without reduction of the yield (entries 1–4). Since the traditional Fischer indole synthesis does not generate 6-substituted indoles as single regioisomers,[45] we examined the 5-substituted *o*-nitrostyrenes with our reaction (entries 5–10). To our delight, our reaction was not affected by changing the electronic identity of R^2-substituent. Finally, to investigate the effect of increased steric environment around the nitro group, we prepared **3.6k** and submitted to reaction conditions (entry 11). In contrast to our experiences with C–H amination of 2,6-disubstituted aryl azides, **3.6k** could be converted to 7-methyl-substituted indole with an acceptable yield.

Table 3.2 ***Examination of the electronic and steric nature of the 2-nitrostyrene***



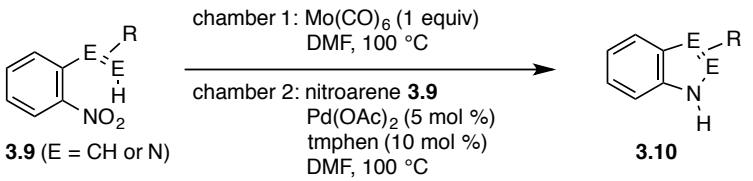
entry	#	R^1	R^2	R^3	**3.7**, %, yield[a]
1	a	MeO	H	H	80
2	b	Me	H	H	82
3	c	H	H	H	85
4	d	CF_3	H	H	75
5	e	H	Me	H	77
6	f	H	MeO	H	54
7	g	H	F	H	80

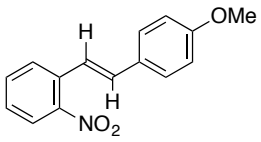
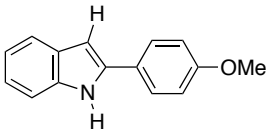
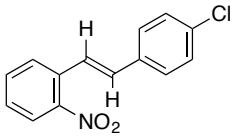
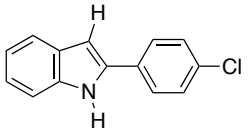
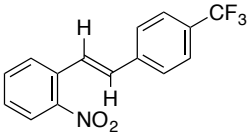
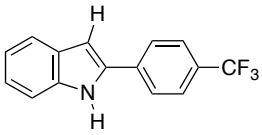
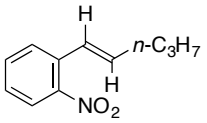
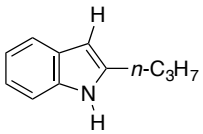
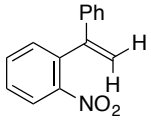
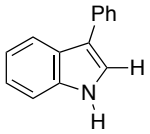
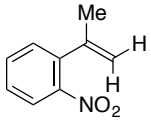
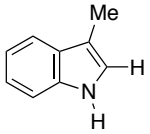
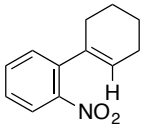
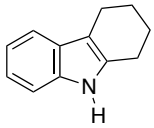
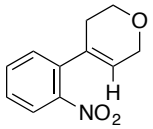
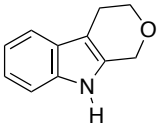
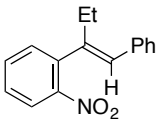
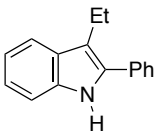
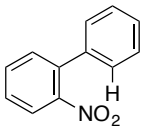
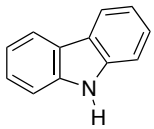
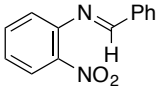
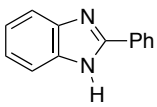
entry	#	R^1	R^2	R^3	**3.7**, %, yield[a]
8	h	H	Cl	H	67
9	i	H	CO_2Et	H	87
10	j	H	CF_3	H	55
11	k	H	H	Me	48

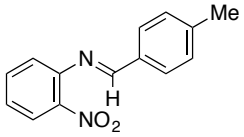
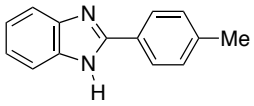
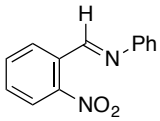
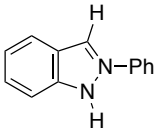
[a] After silica gel chromatography

Next, the scope of our reaction was further investigated by changing the identity of the *o*-substituent of the nitroarene (Table 2.4). Upon the formation of **3.10a**, **3.10b**, and **3.10c**, the effect of the electronic identity of R^{β}-aryl substituent was studied (entries 1–3). We found that the reaction outcome did trend with the electron-nature of the R^{β}-aryl substituent: higher yields was obtained with the more electron-rich 4-methoxylphenyl substituent. Our reaction also tolerated with β-alkyl substituent (entry 4), α-phenyl substituent (entry 5) and α-alkyl substituent (entry 6). The corresponding indole could be synthesized with good yield. We also found 2,3-disubstituted styrenes could be smoothly converted to indoles with our reaction (entries 7–9). Besides indole, we also attempted to access other *N*-hetercycles using our reaction. The carbazole could be formed with reduced yield (entry 10). While indazole could not be prepared with our method (entry 13), *N*-arylimines **3.9k** and **3.9l** were transformed into benzimidazoles **3.10k** and **3.10l** respectively (entries 11 and 12).

Table 3.3 ***Examination of the o-substituent of the nitrostyrene***



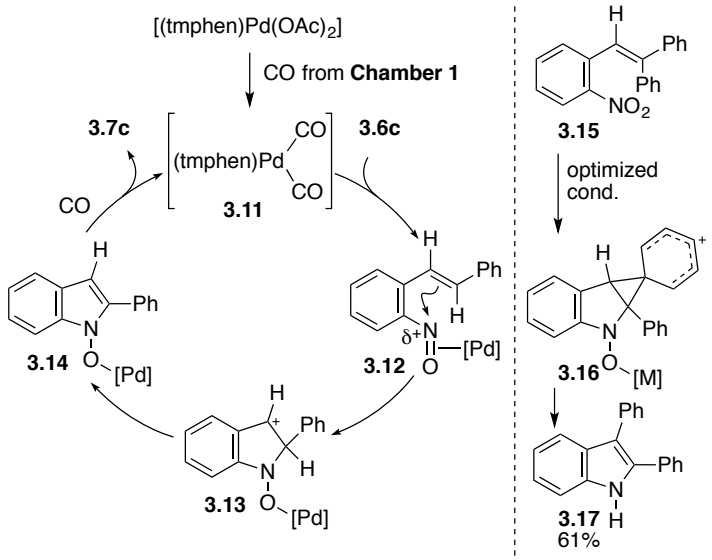
entry	#	Nitroarene **3.9**	*N*-heterocycle **3.10**	**3.10**, % yield[a]
1	a			94
2	b			57
3	c			50
4	d			77
5	e			95
6	f			85
7	g			65
8	h			70
9	i			91
10	j			40
11	k			62

entry	#	Nitroarene **3.9**	*N*-heterocycle **3.10**	**3.10**, % yield[a]
12	l			52
13	m			n.r.

[a] After silica gel chromatography.

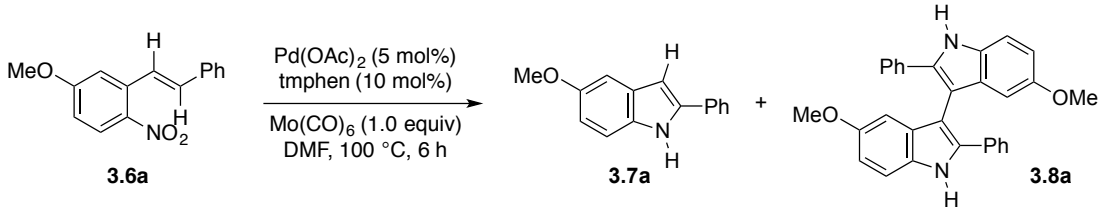
While detailed mechanistic studies are ongoing, we propose mechanism for indole formation that is centered on the formation of palladium-coordinated nitrosoarene **3.12** (Scheme 3.3).[46-52] Thermolysis of $Mo(CO)_6$ generated CO from chamber one. In chamber two, upon the formation of palladium-carbonyl complex **3.11**, reduction of nitroarene **3.6c** could occur to generate palladium nitrosoarene **3.12**. (6π?)Electrocyclization with *ortho*-alkenyl substituent could generate **3.13**.[53,54] Deprotonation could afford indole-*N*-oxide **3.14**. Further reduction with CO could produce indole **3.7c** and regenerate the palladium-carbonyl complex **3.11**. To support this stepwise C–H amination, exposing β,β-diphenyl nitrostyrene **3.15** to the reaction reactions generated 2,3-diphenylindole in 61% yield. We believed that this reaction could occur via phenonium ion **3.16**.[55-62]

Scheme 3.3 ***Potential mechanism***

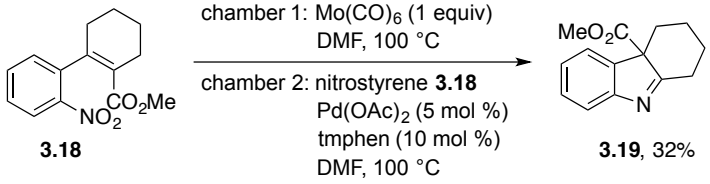


A series of control experiments were performed to investigate the role of Mo complex in our reaction (Scheme 3.4). First, we studied the effect of Mo complex on the rate of the reaction. The formation of indole **3.7a** was performed in both one-chamber and two-chamber reactors. The reactions were stopped after 6 hours stirring at 100 °C. By comparing the conversions of these two reactions, we found that the reaction in two-chamber reactor had gone to 45% completion while the reaction in one-chamber reactor had only gone to 19% completion. When using two-chamber reactor, however, the formation of 3*H*-indole **3.19** only resulted in 32% yield, compared with 73% with a one-chamber reactor.[22]

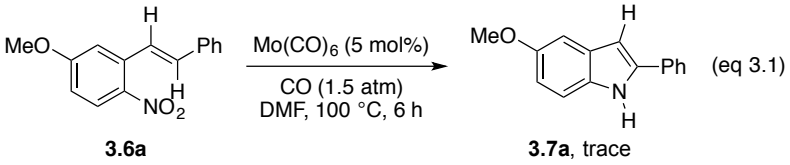
Scheme 3.4 ***Examination of the role of Molybdenum complexes***



reactor	% conversion 3.6a	3.7a	3.8a
one-chamber	81	19	0
two-chamber	55	36	6



Next, we were curious if molybdenum carbonyl complex traversed from chamber one to chamber two to catalyze the indole formation because of the well-established volatility of $Mo(CO)_6$.[63] To study this question, nitrostyrene **3.6a** was submitted to 5 mol % of $Mo(CO)_6$ and 1.5 atm of CO in one-chamber reactor. Only trace amounts of indole **3.7a** were observed. Based on these results, we believe that producing CO is the primary role of $Mo(CO)_6$ in our reaction.



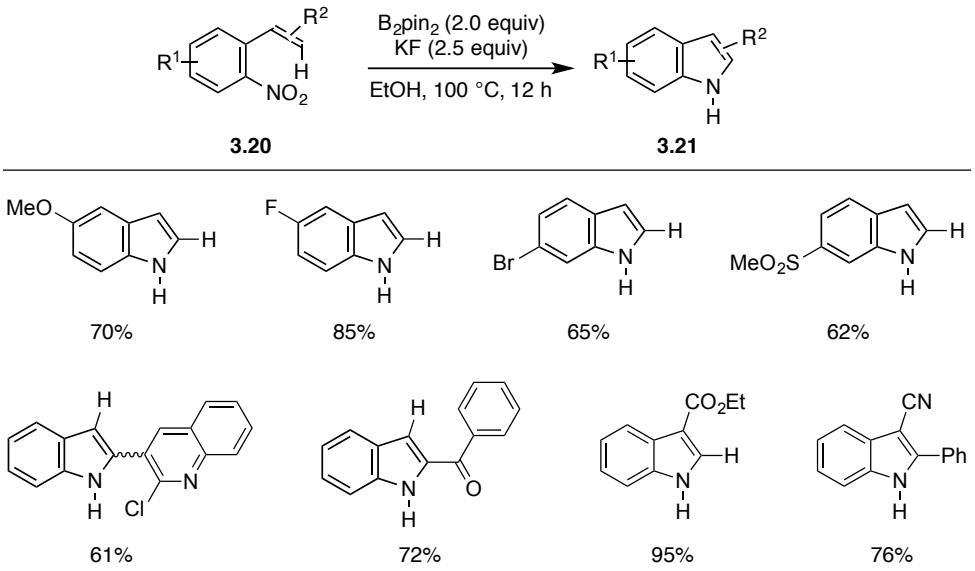
In conclusion, a new synthetic method of *N*-heterocycles via Pd-catalyzed nitro reductive C–H amination was developed. We demonstrated that $Mo(CO)_6$ could be used as a reductant in this synthesis when a two-chamber reactor was employed to segregate the molybdenum carbonyl complex from the nitroarene. Detailed mechanistic study is

ongoing. Further experiments are also aimed at applying two-chamber reactor to more synthesise.

2. Mechanistic Study of Diborane-mediated Deoxygenation of *ortho*-Nitrostyrenes to form Indoles

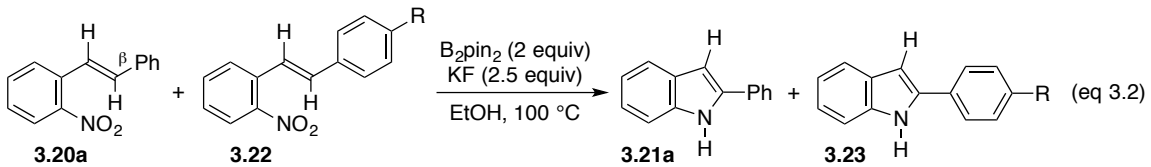
In addition to examining alternative CO sources, I have been interested in employing other less toxic reductants, such as disilane and diborane, to trigger reductive C–N bond formation from nitroarenes. Recently, in collaboration with Prof. Qiuling Song's group in Huaqiao University, I was involved in the project of diborane-mediated deoxygenation of *ortho*-nitrostyrenes to form indoles. Kai Yang, a third-year graduate student in Prof. Song's group, developed a new method of a mild, transition metal-free, diborane-mediated deoxygenation of nitro group. In the presence of bis(pinacolato)diboron and potassium fluoride, the *ortho*-nitrostyrene was smoothly transformed to indole (Scheme 3.5). Kai also explored the scope and limitations of this reaction. When I traveled to Huaqiao, I joined this project, validated the results and pursued designing experiments to study the mechanism of this unusual transformation.

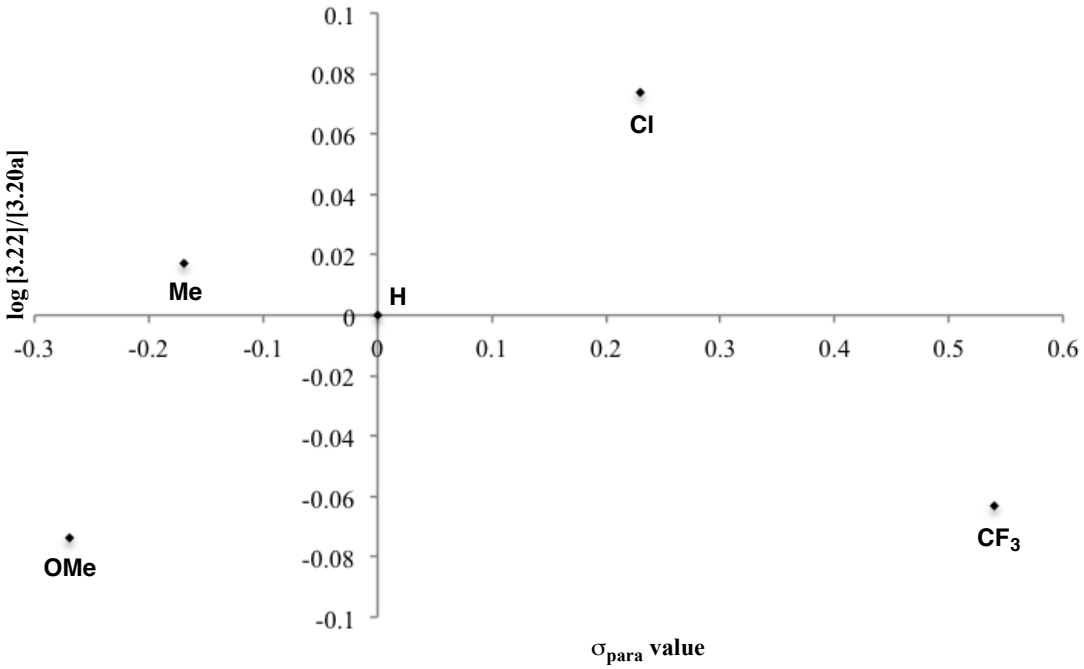
Scheme 3.5 ***Diborane-mediated deoxygenation of o-nitrostyrenes to form indoles***



Towards this end, I performed a series of intermolecular competition experiments to provide insight into the mechanism of indole formation. The results of the reactions were correlated to the Hammett equation. First, the effect of changing the electronic nature of the β-aryl group on the *ortho*-nitrostyrene was examined (eq 3.2, Figure 3.1). A 1:1 mixture of substrates was exposed to the standard conditions. The reaction was stopped at approximately 40% and the consumptions of 3.20a and 3.22 were measured using ^{1}H NMR spectroscopy. When the ratio of the consumption was correlated to the Hammett equation, however, no linear trend was observed. The lack of correlation suggests that no charge build up occurs at the β-position occurs during the rate-determining step.

Figure 3.1 ***Intermolecular Hammett analysis of B_2pin_2-mediated indole formation: the effect of the electronic nature of the β-aryl group***

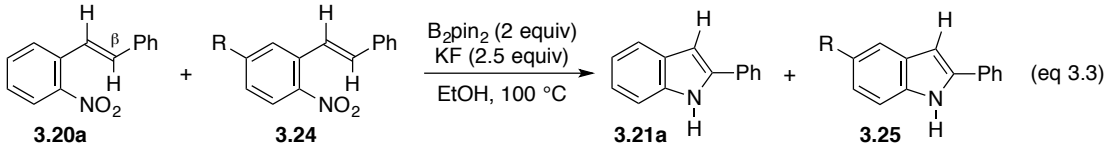


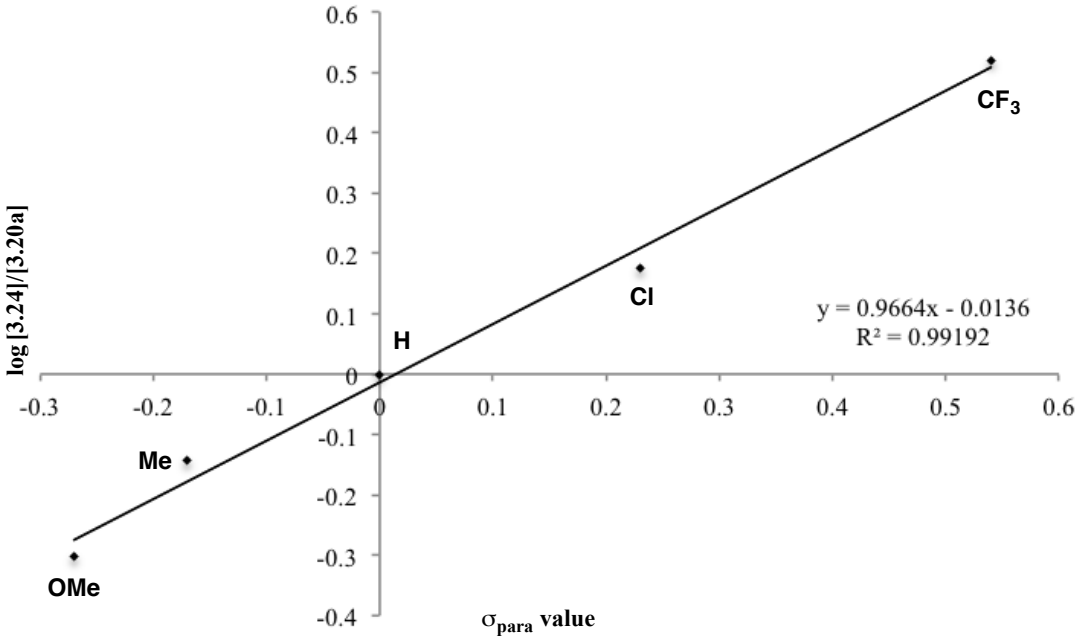


Next, the effect of the electronic nature of the substituent in nitroarene **3.20** was examined (eq 3.3, Figure 3.2). We found that electron-deficient substrates reacted faster than electron-rich substrates. In contrast, studies of other common reductive-cyclization reactions of nitroarenes showed electron-rich substrates react faster.[43,62,64] Compare with those studies, we believe that a differently charged reactive intermediate is being formed in our reaction. We further examined the difference in rate of **3.24** using the Hammett equation and the best linear correlation was obtained using σ_{para} values.[65,66] The positive ρ-value of 0.96 indicates that a negative charge could build up during or before the rate-limiting step of *N*-heterocycle formation.[67] This data, together with inability of the β-aryl

group to impact the rate of the reaction, suggests that our reaction occurs first at the nitro-group of nitroarene and not at the *ortho*-alkenyl substituent.

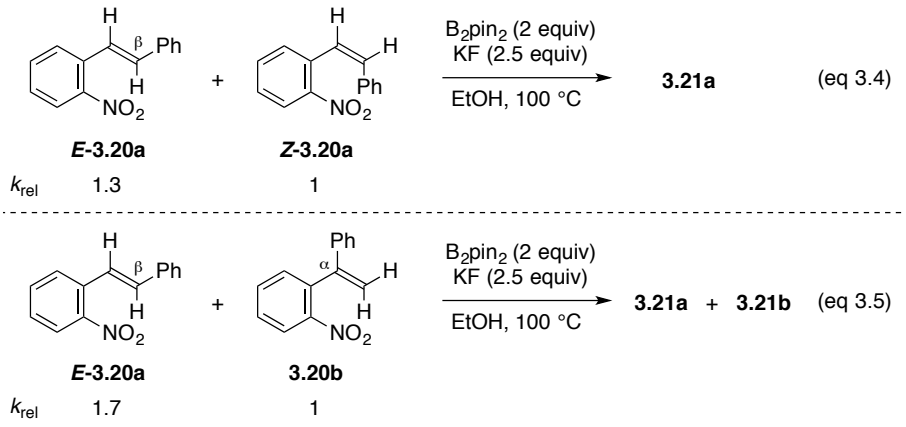
Figure 3.2 ***Intermolecular Hammett analysis of B_2pin_2-mediated indole formation: the effect of the electronic nature of the nitroarene***





Two other competition experiments were performed to get the insight into the role of the *ortho*-alkenyl substituent in our reaction (eqs 3.4 and 3.5). While the electronic nature of the β-aryl group did not impact the rate of the reaction, changing the steric environment at the β-position affected the rate. While submitting β,β-disubstituted nitrostyrene to standard conditions yielded only aniline, *E*-nitrostilbene ***E*-3.20a** was

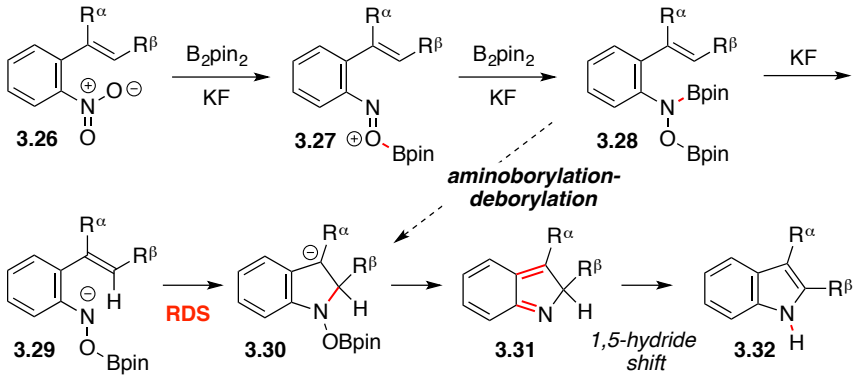
found to react 1.3-times faster than *Z*-nitrostilbene ***Z*-3.20a** (eq 3.4). The position of the phenyl group on the ortho-alkenyl substituent also affected the rate of the reaction. *E*-nitrostilbene ***E*-3.20a** was found to react 1.7-times faster than α-phenylnitrostyrene **3.20b** (eq 3.5). These data, together with the Hammett correlation study, suggest that *ortho*-alkenyl substituent is involved in the rate-determining step. The generated negative- or partial negative charge could delocalize into the π-system of the nitroarene portion of the substrate.



Based on these data, we propose the mechanism that the indole formation goes through negatively charged intermediates (Scheme 3.6). Diborane-mediated deoxygenation of *o*-nitrostyrene **3.26** affords nitrosoarene borane **3.27** and a borate anion.[68] The nitrosoarene intermediate **3.27** reacts with a second equivalent of B_2pin_2 to generate **3.28**. KF-mediated deboronation generates nitrosylanion **3.29**.[69-71] Cyclization with the *o*-alkenyl substituent forms benzyl anion **3.30**,[53,54] followed by the elimination of OBpin to afford 2*H*-indole **3.32**. A 1,5-hydride shift then generates the indole product.[72-75] Alternatively, aminoboration of the *ortho*-alkenyl group could also form **3.30** after deborylation of the Bpin at C3-position. However, aminoboration has only been observed for polarized carbon–heteroatom π-bonds or carbon–carbon triple bonds.[76-79] In our

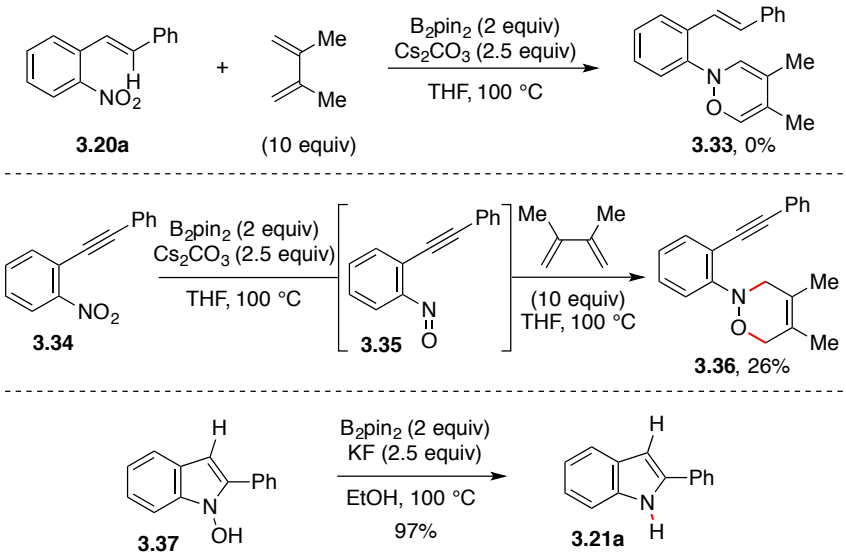
competition experiments, the substrates, which were either less sterically congested at the β-position or contained electron-withdrawing substituents on the nitroarene, reacted faster. Based on these observations, we believed the rate-determining step is the cyclization step.

Scheme 3.6 ***Proposed Mechanism for Diborane-mediation Nitroarene Reduction.***



To get more insight into the identity of the reactive intermediates (Scheme 3.7), Kai Yang and I performed additional experiments. Firstly, Kai attempted to trap the putative nitrosoarene intermediate by adding 2,3-dimethylbutadiene. The cycloaddition product, an oxazine, however was not observed from the reaction with *o*-nitrostyrene **3.20a**. The nitrososarene intermediate, however, could be intercepted from nitroarene **3.34** to form oxazirine **3.36** in 26% with aprotic reduction conditions. Next, I prepared *N*-hydroxyindole **3.37** and submitted it to protic conditions. Deoxygenation occurred to generate 2-phenylindole **3.21a** in almost quantitive yield. Only partial deoxygenation was observed in the absence of the diborane.

Scheme 3.7 ***Interception of potential reactive intermediates***



Together in collaboration with our colleagues at Huaqiao University, we developed a mild, transition-metal free transformation of *o*-nitrostyrenes to afford indoles using the combination of B_2pin_2 and KF. My role in this project, was to design and execute experiments to elucidate the mechanism of this reductive cyclization. The mechanism that emerged from this study was distinct from our metal-mediated ones. Instead of positively charged intermediates, our data suggest that negatively charged reactive intermediates are generated.

In this Chapter, two methods of indole synthesis were introduced and their mechanistic studies were described. While *ortho*-nitrostyrene was chosen as the starting material in both methods, different reductants was employed in two methods. In the palladium-catalyzed method, while using $Mo(CO)_6$ is easier and safer than CO gas, the special-designed reactor, H-cell, is required to segregate the $Mo(CO)_6$. The diborane-mediated deoxygenation reaction provids a mild, transition-metal free method to form indole. Further mechanistic study is desired to expand the application of this method.

Experiment

1. Palladium-catalyzed formation of *N*-heteroarenes from nitroarenes using $Mo(CO)_6$ as the source of carbon monoxide

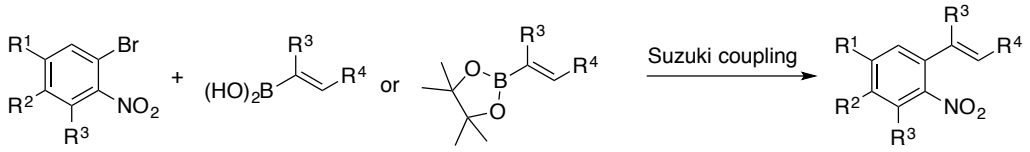
A. General

^{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 according to the procedure of Grubbs. Metal salts were stored in a nitrogen atmosphere dry box.

B. Synthesis of 2-Substituted Nitroarene.

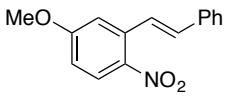
1. General Procedure.



3.6

To a solution of vinylboronic acid (1.5 equiv), $Pd(PPh_3)_4$ (10 mol %) and K_2CO_3 (4.0 equiv) in a 5/2/1 ratio of PhMe, EtOH, and H_2O was added 2-bromonitrobenzene (1.0 equiv). The resultant mixture was then purged with N_2 and refluxed. After 24 h, the mixture was cooled to room temperature and diluted with 30 mL of water and 30 mL of CH_2Cl_2. The phases were separated and the resulting aqueous phase was extracted with an additional 2 × 30 mL of CH_2Cl_2. The combined organic phases were washed with 1 × 20 mL of distilled water and 1 × 20 mL of brine. The resulting organic phase was dried over Na_2SO_4, and the heterogeneous mixture was filtered. The filtrate was concentrated in vacuo. Purification via MPLC (0:100 – 15:85 EtOAc:hexanes) afforded the product.

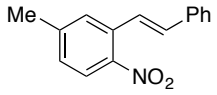
2. Preparation of 2-Substituted Nitroarene.



3.6a

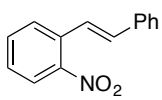
Nitroarene (3.6a). The general procedure was followed using 0.279 g of 3-iodo-4-nitroanisole (1.00 mmol), 0.207 g of trans-2-phenyl-vinylboronic acid (1.40 mmol), 0.115

g of $Pd(PPh_3)_4$ (0.100 mmol) and 0.553 g of K_2CO_3 (4.00 mmol) in 6 mL of toluene, 2.4 mL of EtOH and 1.2 mL of water. Purification via MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **3.6a** as a yellow solid (0.239 g, 93%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.03 (d, *J* = 9.0 Hz, 1H), 7.71 (d, *J* = 16.5 Hz, 1H), 7.53 (d, *J* = 7.5 Hz, 2H), 7.38 (t, *J* = 7.5 Hz, 2H), 7.31 (t, *J* = 7.5 Hz, 1H), 7.11 (d, *J* = 3.0 Hz, 1H), 6.99 (d, *J* = 16.0 Hz, 1H), 6.82 (dd, *J* = 9.0, 2.5 Hz, 1H), 3.89 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 163.3 (C), 141.0 (C), 136.6 (C), 136.3 (C), 133.6 (CH), 128.8 (CH), 128.6 (CH), 127.7 (CH), 127.2 (CH), 124.8 (CH), 113.2 (CH), 112.9 (CH), 55.9 (CH_3); IR (thin film): 1600, 1579, 1506, 1477, 1336, 1290, 1235 cm^{-1}.



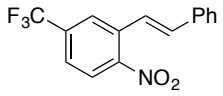
3.6b

Nitroarene (3.6b). The general procedure was followed using 0.263 g of 3-iodo-4-nitrotoluene (1.00 mmol), 0.207 g of trans-2-phenyl-vinylboronic acid (1.40 mmol), 0.115 g of $Pd(PPh_3)_4$ (0.100 mmol) and 0.553 g of K_2CO_3 (4.00 mmol) in 6 mL of toluene, 2.4 mL of EtOH and 1.2 mL of water. Purification via MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **3.6b** as a yellow liquid (0.053 g, 22%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.91 (d, *J* = 8.5 Hz, 1H), 7.64 (d, *J* = 16.5 Hz, 1H), 7.56 – 7.54 (m, 3H), 7.39 (t, *J* = 7.5 Hz, 2H), 7.32 (t, *J* = 7.5 Hz, 1H), 7.18 (d, *J* = 7.5 Hz, 1H), 7.06 (d, *J* = 16.0 Hz, 1H), 2.47 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 163.3 (C), 141.0 (C), 136.6 (C), 136.3 (C), 133.6 (CH), 128.8 (CH), 128.6 (CH), 127.2 (CH), 124.8 (CH), 113.2 (CH), 112.9 (CH), 55.9 (CH_3), only peaks visible; IR (thin film): 1605, 1580, 1510, 1447, 1337, 961 cm^{-1}.



3.6c

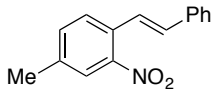
Nitroarene (3.6c). The general procedure was followed using 1.010 g of 3 1-bromo-2-nitrobenzene (5.00 mmol), 1.04 g of trans-2-phenyl-vinylboronic acid (7.00 mmol), 0.578 g of $Pd(PPh_3)_4$ (0.500 mmol) and 2.764 g of K_2CO_3 (20.0 mmol) in 30 mL of toluene, 12 mL of EtOH and 6 mL of water. Purification via MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **3.6c** as a yellow solid (0.835 g, 74%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.97 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.77 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.65 – 7.57 (m, 2H), 7.58 – 7.52 (m, 2H), 7.40 (dt, *J* = 9.3, 8.2 Hz, 3H), 7.34 – 7.29 (m, 1H), 7.09 (d, *J* = 16.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 148.1 (C), 136.5 (C), 133.9 (CH), 133.1 (CH), 128.8 (CH), 128.6 (CH), 128.2 (CH), 128.0 (CH), 127.1 (CH), 124.8 (CH), 123.5 (CH), only peaks visible; IR (thin film): 1602, 1570, 1517, 1494, 1342, 968 cm^{-1}.



3.6d

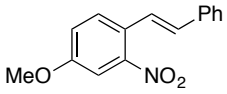
Nitroarene (3.6d). The general procedure was followed using 0.270 g of 3-bromo-4-nitrobenzotrifluoride (1.00 mmol), 0.207 g of trans-2-phenyl-vinylboronic acid (1.40 mmol), 0.115 g of $Pd(PPh_3)_4$ (0.100 mmol) and 0.553 g of K_2CO_3 (4.00 mmol) in 6 mL of toluene, 2.4 mL of EtOH and 1.2 mL of water. Purification via MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **3.6d** as a yellow solid (0.101 g, 34%): ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.09 – 7.96 (m, 2H), 7.64 (dd, *J* = 8.6, 1.9 Hz, 1H), 7.56 (d, *J* = 7.8 Hz, 3H), 7.46 – 7.30 (m, 3H), 7.17 (d, *J* = 16.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 149.7 (C), 135.9 (C), 135.7 (CH), 134.6 (q, J_{CF} = 33.5 Hz, C), 133.6 (C), 129.2 (CH), 128.9 (CH), 128.1 (q, J_{CF} = 135 Hz, CH), 127.3 (CH), 125.3 (q, J_{CF} = 8.9 Hz, CH), 124.6 (CH), 123.1 (q, J_{CF} = 270.9, C), 121.7 (CH); ^{19}F NMR ($CDCl_3$, 282 MHz) δ –62.8; IR (thin

film): 1617, 1589, 1524, 1497, 1323, 1256, 1173 cm^{-1}. HRMS (EI) m/z calcd for $C_{15}H_{10}F_3NO_2$ $[M]^+$: 293.0664, found 293.0655.



3.6e

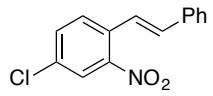
Nitroarene (3.6e). The general procedure was followed using 0.216 g of 4-bromo-3-nitrotoluene (1.00 mmol), 0.207 g of trans-2-phenyl-vinylboronic acid (1.40 mmol), 0.115 g of $Pd(PPh_3)_4$ (0.100 mmol) and 0.553 g of K_2CO_3 (4.00 mmol) in 6 mL of toluene, 2.4 mL of EtOH and 1.2 mL of water. Purification via MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **3.6e** as a yellow solid (0.239 g, 99%). ^1H NMR ($CDCl_3$, 500 MHz) δ 7.77 (d, *J* = 1.8 Hz, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.61 – 7.49 (m, 3H), 7.43 – 7.34 (m, 3H), 7.34 – 7.27 (m, 1H), 7.05 (d, *J* = 16.1 Hz, 1H), 2.44 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 147.9 (C), 138.6 (C), 136.7 (C), 133.9 (CH), 133.0 (CH), 130.2 (C), 128.8 (CH), 128.4 (CH), 127.9 (CH), 127.0 (CH), 125.0 (CH), 123.5 (CH), 20.9 (CH_3); IR (thin film): 1557, 1521, 1448, 1342, 1260, 959 cm^{-1}.



3.6f

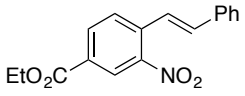
Nitroarene (3.6f). The general procedure was followed using 0.232 g of 4-bromo-3-nitroanisole (1.00 mmol), 0.207 g of trans-2-phenyl-vinylboronic acid (1.40 mmol), 0.115 g of $Pd(PPh_3)_4$ (0.100 mmol) and 0.553 g of K_2CO_3 (4.00 mmol) in 6 mL of toluene, 2.4 mL of EtOH and 1.2 mL of water. Purification via MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **3.6f** as a yellow solid (0.233 g, 91%). ^1H NMR ($CDCl_3$, 500 MHz) δ 7.69 (d, *J* = 9.0 Hz, 1H), 7.56 – 7.51 (m, 3H), 7.47 (d, *J* = 3.0 Hz, 1H), 7.38 (t, *J* = 7.5 Hz, 2H), 7.30 (t, *J* = 7.5 Hz, 1H), 7.17 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.99 (d, *J* = 16.0 Hz, 1H), 3.90 (s, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.1 (C), 148.5 (C), 136.8 (C), 132.2 (CH), 129.1 (CH), 128.8 (CH), 128.3 (CH), 126.9 (CH), 125.6 (C), 123.3 (CH), 120.3 (CH), 108.9 (CH), 55.9 (CH_3); IR (thin film): 1616, 1522, 1497, 1343, 1248, 1063, 1031, 959 cm^{-1}.



3.6g

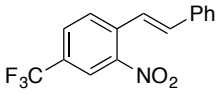
Nitroarene (3.6g). The general procedure was followed using 0.235 g of 1-bromo-4-chloro-2-nitrobenzene (1.00 mmol), 0.207 g of trans-2-phenyl-vinylboronic acid (1.40 mmol), 0.115 g of $Pd(PPh_3)_4$ (0.100 mmol) and 0.553 g of K_2CO_3 (4.00 mmol) in 6 mL of toluene, 2.4 mL of EtOH and 1.2 mL of water. Purification via MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **3.6g** as a yellow solid (0.220 g, 85%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.95 (d, J = 2.5 Hz, 1H), 7.71 (d, J = 8.5 Hz, 1H), 7.57 (d, J = 2.5 Hz, 1H), 7.52 – 7.55 (m, 3H), 7.38 – 7.41 (m, 2H), 7.32 – 7.35 (m, 1H), 7.08 (d, J = 16 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 148.0 (C), 136.2 (C), 134.5 (CH), 133.5 (C), 133.3 (CH), 131.6 (C), 129.3 (CH), 128.9 (CH), 127.2 (CH), 124.9 (CH), 122.3 (CH), only peaks visible; IR (thin film): 1628, 1526, 1449, 1346, 1256, 1151, 1110, 962, 891, 819, 764, 694, 533 cm^{-1}.



3.6h

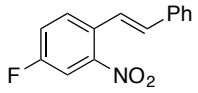
Nitroarene (3.6h). The general procedure was followed using 0.321 g of ethyl 4-iodo-3-nitrobenzoate (1.00 mmol), 0.207 g of trans-2-phenyl-vinylboronic acid (1.40 mmol), 0.115 g of $Pd(PPh_3)_4$ (0.100 mmol) and 0.553 g of K_2CO_3 (4.00 mmol) in 6 mL of toluene, 2.4 mL of EtOH and 1.2 mL of water. Purification via MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **3.6h** as a yellow solid (0.060 g, 20%). Nitroarene **3.6h** was

previously reported by Pfeiffer and Matton:[6] ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.56 (d, *J* = 2.0 Hz, 1H), 8.21 (d, *J* = 8.0, 2.0 Hz, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.58 (d, *J* = 16.0 Hz, 1H), 7.55 – 7.54 (m, 2H), 7.40 – 7.37 (m, 2H), 7.35 – 7.32 (m, 1H), 7.19 (d, *J* = 16.0 Hz, 1H), 4.43 (q, *J* = 7.0 Hz, 2H), 1.43 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.4 (C), 147.8 (C), 136.7 (C), 136.0 (C), 135.9 (CH), 133.4 (CH), 130.2 (C), 129.2 (CH), 128.9 (CH), 128.0 (CH), 127.4 (CH), 126.0 (CH), 122.4 (CH), 61.8 (CH_2), 14.3 (CH_3); IR (thin film): 1720, 1613, 1558, 1529, 1349, 1291, 1263, 1113 cm^{-1}.



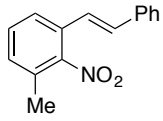
3.6i

Nitroarene (3.6i). The general procedure was followed using 0.270 g of 1-bromo-2-nitro-4-(trifluoromethyl)benzene (1.00 mmol), 0.207 g of trans-2-phenyl-vinylboronic acid (1.40 mmol), 0.115 g of $Pd(PPh_3)_4$ (0.100 mmol) and 0.553 g of K_2CO_3 (4.00 mmol) in 6 mL of toluene, 2.4 mL of EtOH and 1.2 mL of water. Purification via MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **3.6i** as a yellow solid (0.226 g, 77%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.23 (s, 1H), 7.90 (d, *J* = 8.0 Hz, 1H), 7.82 (d, *J* = 9.0 Hz, 1H), 7.46 (d, *J* = 16 Hz, 1H), 7.55 – 7.57 (m, 2H), 7.35 – 7.42 (m, 3H), 7.18 (d, *J* = 16.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 147.6 (C), 136.4 (C), 136.3 (CH), 135.9 (C), 130.1 (q, J_{CF} = 34.8 Hz, C), 129.4 (CH), 129.3 (CH), 128.9 (CH), 127.4 (CH), 122.9 (q, J_{CF} = 271.0 Hz, C), 122.3 (CH), 122.1 (CH), only peaks visible; ^{19}F NMR ($CDCl_3$, 282 MHz) δ –62.6; IR (thin film): 1623, 1566, 1530, 1490, 1328, 1122, 961, 902, 827, 764, 689, 525 cm^{-1}.



3.6j

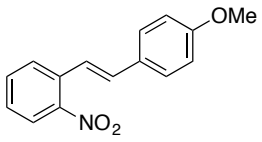
Nitroarene (3.6j). The general procedure was followed using 0.267 g of 1-bromo-4-flouoro-2-nitrobenzene (1.00 mmol), 0.207 g of trans-2-phenyl-vinylboronic acid (1.40 mmol), 0.115 g of $Pd(PPh_3)_4$ (0.100 mmol) and 0.553 g of K_2CO_3 (4.00 mmol) in 6 mL of toluene, 2.4 mL of EtOH and 1.2 mL of water. Purification via MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **3.6j** as a yellow solid (0.078 g, 32%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.74 (dd, *J* = 8.8, 5.5 Hz, 1H), 7.70 (dd, *J* = 8.3, 2.7 Hz, 1H), 7.58 – 7.49 (m, 3H), 7.42 – 7.36 (m, 2H), 7.36 – 7.30 (m, 2H), 7.02 (d, *J* = 16.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 161.1 (C, d, *J* = 253.2 Hz), 148.0 (C, d, *J* = 6.3 Hz), 136.3 (C), 134.0 (CH), 129.9 (CH, d, *J* = 7.0 Hz), 129.5 (C), 128.9 (CH), 128.7 (CH), 127.1 (CH), 122.6 (CH), 120.8 (CH, d, *J* = 22.8 Hz), 112.2 (CH, d, *J* = 26.8 Hz); ^{19}F NMR ($CDCl_3$, 282 MHz) δ –110.8; IR (thin film): 1615, 1580, 1523, 1496, 1344, 1291, 1242 cm^{-1}. HRMS (EI) m/z calcd for $C_{14}H_{10}FNO_2$ $[M]^+$: 243.0696, found 243.0695.



3.6k

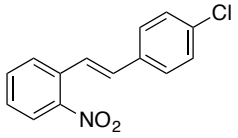
Nitroarene (3.6k). The general procedure was followed using 0.216 g of 3-bromo-2-nitrotoluene (1.00 mmol), 0.207 g of trans-2-phenyl-vinylboronic acid (1.40 mmol), 0.115 g of $Pd(PPh_3)_4$ (0.100 mmol) and 0.553 g of K_2CO_3 (4.00 mmol) in 6 mL of toluene, 2.4 mL of EtOH and 1.2 mL of water. Purification via MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **3.6k** as a yellow liquid (0.025 g, 11%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.60 (d, *J* = 7.9 Hz, 1H), 7.52 – 7.46 (m, 2H), 7.41 – 7.27 (m, 4H), 7.20 (d, *J* = 7.6 Hz, 1H), 7.14 (d, *J* = 16.1 Hz, 1H), 6.97 (d, *J* = 16.1 Hz, 1H), 2.34 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 150.6 (C), 136.3 (C), 133.8 (CH), 130.1 (CH), 129.7 (C), 129.6 (C),

128.8 (CH), 128.6 (CH), 127.0 (CH), 124.1 (CH), 121.0 (CH), 17.4 (CH_3), only peaks visible; IR (thin film): 1524, 1367, 1260, 1031, 797 cm^{-1}.



3.9a

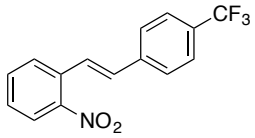
Nitroarene (3.9a). The general procedure was followed using 0.202 g of 1-bromo-2-nitrobenzene (1.00 mmol), 0.249 g of *trans*-2-(4-methoxyphenyl)vinylboronic acid (1.40 mmol), 0.115 g of $Pd(PPh_3)_4$ (0.100 mmol) and 0.553 g of K_2CO_3 (4.00 mmol) in 6 mL of toluene, 2.4 mL of EtOH and 1.2 mL of water. Purification via MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **3.9a** as a yellow solid (0.249 g, 84%). ^1H NMR ($CDCl_3$, 500 MHz) δ 7.92 (d, J = 8.0 Hz, 1H), 7.73 (d, J = 7.5 Hz, 1H), 7.56 (t, J = 7.5 Hz, 1H), 7.48 – 7.44 (m, 3H), 7.35 (t, J = 8.0 Hz, 1H), 7.04 (d, J = 16.0 Hz, 1H), 6.92 – 6.90 (m, 2H), 3.83 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 160.1 (C), 147.9 (C), 133.5 (CH), 133.3 (C), 133.0 (CH), 129.3 (C), 128.5 (CH), 127.9 (CH), 127.5 (CH), 124.8 (CH), 121.1 (CH), 114.3 (CH), 55.4 (CH_3); IR (thin film): 1599, 1569, 1509, 1463, 1340, 1248, 1173 cm^{-1}.



3.9b

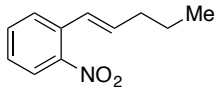
Nitroarene (3.9b). The general procedure was followed using 0.202 g of 1-bromo-2-nitrobenzene (1.00 mmol), 0.253 g of trans-2-(4-chlorophenyl)vinylboronic acid (1.40 mmol), 0.115 g of $Pd(PPh_3)_4$ (0.100 mmol) and 0.553 g of K_2CO_3 (4.00 mmol) in 6 mL of toluene, 2.4 mL of EtOH and 1.2 mL of water. Purification via MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **3.9b** as a yellow solid (0.046 g, 18%). Nitroarene **3.9b** has previously been reported by Kendurkar and Tewari: ^1H NMR ($CDCl_3$, 500 MHz): δ 7.96

(d, J = 8.0 Hz, 1H), 7.73 (d, J = 7.5 Hz, 1H), 7.61 – 7.54 (m, 2H), 7.45 (d, J = 8.0 Hz, 2H), 7.41 (t, J = 8.0 Hz, 1H), 7.33 (d, J = 8.5 Hz, 2H), 7.01 (d, J = 16.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 148.0 (C), 135.0 (C), 134.3 (C), 133.2 (CH), 132.7 (C), 132.5 (CH), 129.0 (CH), 128.3 (CH), 128.2 (CH), 124.9 (CH), 124.2 (CH), only peaks visible; IR (thin film): 1520, 1491, 1343, 1093, 961, 811 cm^{-1}.



3.9c

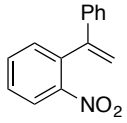
Nitroarene (3.9c). The general procedure was followed using 0.202 g of 1-bromo-2-nitrobenzene (1.00 mmol), 0.302 g of trans-2-[4-(trifluoromethyl)phenyl]vinylboronic acid (1.40 mmol), 0.115 g of $Pd(PPh_3)_4$ (0.100 mmol) and 0.553 g of K_2CO_3 (4.00 mmol) in 6 mL of toluene, 2.4 mL of EtOH and 1.2 mL of water. Purification via MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **3.9c** as a yellow solid (0.195 g, 67%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.95 (d, J = 8.0 Hz, 1H), 7.71 (d, J = 8.0 Hz, 1H), 7.64 (d, J = 16.0 Hz, 1H), 7.60 – 7.58 (m, 5H), 7.41 (t, J = 8.0 Hz, 1H), 7.04 (d, J = 16.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 147.8 (C), 139.9 (C), 133.3 (CH), 132.4 (C), 132.0 (CH), 130.0 (q, J_{CF} = 32.8 Hz, C), 128.6 (CH), 128.3 (CH), 127.2 (CH), 126.2 (CH), 125.7 (CH), 124.8 (CH); 124.1 (q, J_{CF} = 270.9 Hz, C); ^{19}F NMR ($CDCl_3$, 282 MHz) δ –62.2; IR (thin film): 1614, 1527, 1345, 1325, 1107, 1066, 822 cm^{-1}.



3.9d

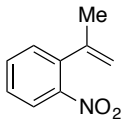
Nitroarene (3.9d). The general procedure was followed using 0.202 g of 1-bromo-2-nitrobenzene (1.00 mmol), 0.159 g of 1-penten-1-ylboronic acid (1.40 mmol), 0.115 g of $Pd(PPh_3)_4$ (0.100 mmol) and 0.553 g of K_2CO_3 (4.00 mmol) in 6 mL of toluene, 2.4 mL

of EtOH and 1.2 mL of water. Purification via MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **3.9d** as a brown liquid (0.191 g, 99%). The spectral data for **3.9d** matched that reported by Kacprzynski and Hoveyda: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.84 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.57 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.50 (td, *J* = 7.6, 1.3 Hz, 1H), 7.31 (ddd, *J* = 8.5, 7.3, 1.5 Hz, 1H), 6.82 (dd, *J* = 15.7, 1.7 Hz, 1H), 6.22 (dt, *J* = 15.7, 6.9 Hz, 1H), 2.23 (qd, *J* = 7.1, 1.6 Hz, 2H), 1.52 (h, *J* = 7.4 Hz, 2H), 0.96 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 147.7 (C), 136.7 (CH), 133.4 (C), 132.8 (CH), 128.4 (CH), 127.3 (CH), 125.1 (CH), 124.3 (CH), 35.2 (CH_2), 22.2 (CH_2), 13.7 (CH_3); IR (thin film): 1605, 1570, 1519, 1343, 962, 856 cm^{-1}.



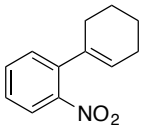
3.9e

Nitroarene (3.9e). The general procedure was followed using 0.202 g of 2-bromonitrobenzene (1.00 mmol), 0.159 g of (1-phenylvinyl)boronic acid (1.40 mmol), 0.115 g of $Pd(PPh_3)_4$ (0.100 mmol) and 0.553 g of K_2CO_3 (4.00 mmol) in 6 mL of toluene, 2.4 mL of EtOH and 1.2 mL of water. Purification via MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **3.9e** as a brown solid (0.167 g, 74%). Nitroarene **3.9e** was previously reported by Creech and Kwon: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.94 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.63 (td, *J* = 7.5, 1.5 Hz, 1H), 7.51 (td, *J* = 8.0, 1.5 Hz, 1H), 7.47 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.31 – 7.24 (m, 5H), 5.75 (s, 1H), 5.32 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 148.9 (C), 146.5 (C), 139.1 (C), 137.0 (C), 132.8 (CH), 132.5 (CH), 128.7 (CH), 128.4 (CH), 128.2 (CH), 126.5 (CH), 124.4 (CH), 115.5 (CH_2); IR (thin film): 2921, 2851, 1605, 1571, 1522, 1494, 1346, 1026 cm^{-1}.



3.9f

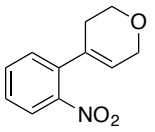
Nitroarene (3.9f). The general procedure was followed using 0.202 g of 1-bromo-2-nitrobenzene (1.00 mmol), 0.235 g of isopropenylboronic acid pinacol ester (1.40 mmol), 0.115 g of $Pd(PPh_3)_4$ (0.100 mmol) and 0.553 g of K_2CO_3 (4.00 mmol) in 6 mL of toluene, 2.4 mL of EtOH and 1.2 mL of water. Purification via MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **3.9f** as a brown liquid (0.148 g, 91%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.82 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.52 (td, *J* = 7.5, 1.4 Hz, 1H), 7.38 (td, *J* = 7.8, 1.6 Hz, 1H), 7.31 (dd, *J* = 7.7, 1.6 Hz, 1H), 5.15 (dp, *J* = 3.1, 1.8 Hz, 1H), 4.92 (d, *J* = 6.9 Hz, 1H), 2.21 – 1.91 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 148.2 (C), 142.8 (C), 139.0 (C), 132.7 (CH), 130.5 (CH), 127.9 (CH), 124.0(CH), 115.4 (CH_2), 23.2 (CH_3); IR (thin film): 1608, 1570, 1522, 1482, 1349, 1309, 903 cm^{-1}.



3.9g

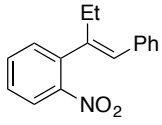
Nitroarene (3.9g). The general procedure was followed using 0.202 g of 1-bromo-2-nitrobenzene (1.00 mmol), 0.291 g of 1-cyclohexen-1-yl-boronic acid pinacol ester (1.40 mmol), 0.115 g of $Pd(PPh_3)_4$ (0.100 mmol) and 0.553 g of K_2CO_3 (4.00 mmol) in 6 mL of toluene, 2.4 mL of EtOH and 1.2 mL of water. Purification via MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **3.9g** as a yellow liquid (0.059 g, 29%). Nitroarene **3.9g** was previously reported by Creech and Kwon: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.78 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.50 (td, *J* = 7.5, 1.3 Hz, 1H), 7.34 (td, *J* = 7.9, 1.5 Hz, 1H), 7.27 (dd, *J* = 7.7, 1.5 Hz, 1H), 5.62 (tt, *J* = 3.7, 1.7 Hz, 1H), 2.22 (ddt, *J* = 6.1, 3.9, 2.2 Hz, 2H), 2.14 (tq, *J* = 6.1, 2.8 Hz, 2H), 1.79 – 1.73 (m, 2H), 1.71 – 1.62 (m, 2H); ^{13}C NMR ($CDCl_3$,

125 MHz): δ 148.7 (C), 139.5 (C), 135.9 (C), 132.4 (CH), 130.8 (CH), 127.4 (CH), 126.7 (CH), 123.9 (CH), 29.3 (CH_2), 25.4 (CH_2), 22.8 (CH_2), 21.7 (CH_2); IR (thin film): 1606, 1570, 1521, 1436, 1345, 921, 857 cm^{-1}.



3.9h

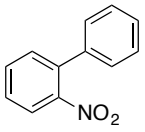
Nitroarene (3.9h). The general procedure was followed using 0.202 g of 1-bromo-2-nitrobenzene (1.00 mmol), 0.294 g of 3,6-dihydro-2H-pyran-4-boronic acid pinacol ester (1.40 mmol), 0.115 g of $Pd(PPh_3)_4$ (0.100 mmol) and 0.553 g of K_2CO_3 (4.00 mmol) in 6 mL of toluene, 2.4 mL of EtOH and 1.2 mL of water. Purification via MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **3.9h** as a yellow liquid (0.089 g, 43%): ^1H NMR ($CDCl_3$, 500 MHz) δ 7.86 – 7.79 (m, 1H), 7.52 (t, J = 7.7 Hz, 1H), 7.41 – 7.34 (m, 1H), 7.30 – 7.24 (m, 1H), 5.61 (t, J = 2.5 Hz, 1H), 4.20 – 4.22 (m, 2H), 3.86 (dd, J = 6.8, 3.8 Hz, 2H), 2.29 (dp, J = 5.4, 2.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 148.2 (C), 137.4 (C), 133.8 (C), 132.9 (CH), 130.8 (CH) 128.1 (CH), 124.8 (CH), 124.2 (CH), 65.4 (CH_2), 64.2 (CH_2), 29.1 (CH_2), IR (thin film): 1571, 1523, 1383, 1347, 1128, 853 cm^{-1}. HRMS (EI) m/z calcd for $C_{11}H_{10}NO_3$ $[M - H]^-$: 204.0661, found 204.0662.



3.9i

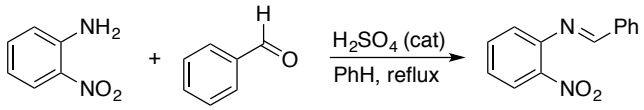
Nitroarene (3.9i). The general procedure was followed using 0.202 g of 1-bromo-2-nitrobenzene (1.00 mmol), 0.246 g of (Z)-(1-phenylbut-1-en-2-yl)boronic acid (1.40 mmol), 0.115 g of $Pd(PPh_3)_4$ (0.100 mmol) and 0.553 g of K_2CO_3 (4.00 mmol) in 6 mL of toluene, 2.4 mL of EtOH and 1.2 mL of water. Purification via MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **3.9i** as a yellow liquid (0.250 g, 99%): ^1H NMR ($CDCl_3$, 500

MHz) δ 7.94 (dd, J = 7.9, 1.8 Hz, 1H), 7.60 (td, J = 7.5, 1.4 Hz, 1H), 7.50 – 7.34 (m, 6H), 7.34 – 7.27 (m, 1H), 6.43 (s, 1H), 2.70 (q, J = 7.5 Hz, 2H), 1.03 (t, J = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 149.0 (C), 141.8 (C), 138.9 (C), 137.2 (C), 132.5 (CH), 131.4 (CH), 129.2 (CH), 128.8 (CH), 128.4 (CH), 127.9 (CH), 127.1 (CH), 124.3 (CH), 25.2 (CH_2), 13.0 (CH_3); IR (thin film): 1605, 1570, 1522, 1494, 1344, 1072 cm^{-1}. HRMS (EI) m/z calcd for $C_{16}H_{15}NO_2$ $[M]^+$: 253.1103, found 253.1105.



3.9j

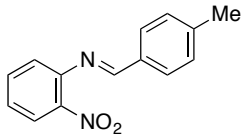
Nitroarene (3.9j). The general procedure was followed using 0.202 g of 2-bromonitrobenzene (1.00 mmol), 0.171 g of phenylboronic acid (1.40 mmol), 0.115 g of $Pd(PPh_3)_4$ (0.100 mmol) and 0.553 g of K_2CO_3 (4.00 mmol) in 6 mL of toluene, 2.4 mL of EtOH and 1.2 mL of water. Purification via MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **3.9j** as a light yellow solid (0.160 g, 80%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.85 (d, J = 8 Hz, 1H), 7.61 (t, J = 7.5 Hz, 1H), 7.50 – 7.49 (m, 5H), 7.33 – 7.31 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 149.4 (C), 137.4 (C), 136.4 (C), 132.3 (CH), 132.0 (CH), 128.7 (CH), 128.3 (CH), 128.2 (CH), 127.9 (CH), 124.1 (CH); IR (thin film): 2921, 2852, 1523, 1467, 1351, 852 cm^{-1}.



3.9k

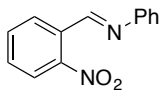
Nitroarene (3.9k). A round-bottom flask with a reflux condenser was charged with 20 mL of dry benzene and 1.66 g of 2-nitroaniline (12.0 mmol), 1.06 g of benzaldehyde (10.0 mmol), 10 g of the freshly baked molecular sieves. The reaction was heating to 80 °C under an atmosphere of argon. After 12 h, the mixture was cooled to room

temperature and filtered through a pad of celite. The filtrate was concentrated *in vacuo*. Purification via MPLC (0:100 – 1:6 EtOAc:hexanes with 2% Et_3N) afforded **3.9k** as a yellow solid (0.768 g, 34%). ^1H NMR ($CDCl_3$, 500 MHz) δ 8.41 (s, 1H), 7.96 (dd, J = 8.0, 1.0 Hz, 1H), 7.91 (d, J = 6.5 Hz, 2H), 7.59 (td, J = 8.0, 1.5 Hz, 1H), 7.55 – 7.48 (m, 3H), 7.03 (td, J = 7.0, 1.5 Hz, 1H), 7.05 (d, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 162.0 (CH), 147.0 (C), 135.5 (C), 133.9 (CH), 132.2 (CH), 129.3 (CH), 128.9 (CH), 125.3 (CH), 124.7 (CH), 121.1 (CH), only peaks visible; IR (thin film): 3378, 3063, 2891, 1630, 1596, 1574, 1514, 1451, 1343, 1301, 1261, 1192 cm^{-1}.



3.9l

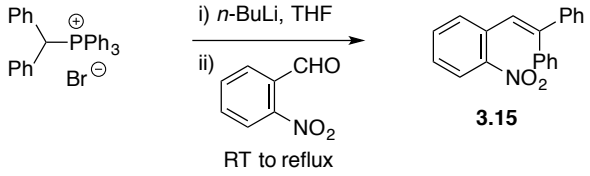
Nitroarene (3.9l). The procedure for **3.9k** was followed using 1.658 g of 2-nitroaniline (12.0 mmol), 1.202 g of p-tolualdehyde of (10.0 mmol). Purification via MPLC (0:100 – 1:6 EtOAc:hexanes with 2% Et_3N) and then recrystallization with hexanes afforded **3.9l** as a yellow solid (0.329 g, 14%). ^1H NMR ($CDCl_3$, 500 MHz) δ 8.36 (s, 1H), 7.94 (dd, J = 8.2, 1.5 Hz, 1H), 7.80 (d, J = 7.9 Hz, 2H), 7.58 (td, J = 7.7, 1.5 Hz, 1H), 7.29 (dd, J = 8.7, 1.8 Hz, 3H), 7.05 (dd, J = 7.9, 1.3 Hz, 1H), 2.43 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 161.8 (CH), 147.1 (C), 142.9 (C), 133.8 (CH), 133.1 (C), 129.6 (CH), 129.3 (CH), 125.1 (CH), 124.7 (CH), 121.2 (CH), 111.0 (C), 21.7 (CH_3); IR (thin film): 1628, 1597, 1571, 1517, 1475, 1345, 1308, 1260 cm^{-1}.



3.9m

Nitroarene (3.9m). A mixture of 2-nitrobenzaldenhyde (2.30 g, 15.0 mmol) and aniline (1.2 equiv.) was stirred at 90 ^oC for 3 h, and then cooled to room temperature. Ethanol

(10 ml) was added into the reaction mixture, and the solution was set in the refrigerator for overnight. After filtration, the resulting solid was washed with 4 × 3 mL cold ethanol. Then the solid was dried to obtain the product **3.9m** as a yellow solid (1.896 g, 55%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.94 (s, 1H), 8.31 (d, *J* = 7.8 Hz, 1H), 8.07 (d, *J* = 8.2 Hz, 1H), 7.74 (t, *J* = 7.9 Hz, 1H), 7.67 – 7.56 (m, 1H), 7.47 – 7.38 (m, 2H), 7.35 – 7.26 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.9 (CH), 151.1 (C), 149.4 (C), 133.6 (CH), 131.2 (CH), 131.1 (C) 129.8 (CH), 129.3 (CH), 127.0 (CH), 124.6 (CH), 121.2 (CH); IR (thin film): 1617, 1570, 1519, 1486, 1442, 1340, 1306, 1189, cm^{-1}.

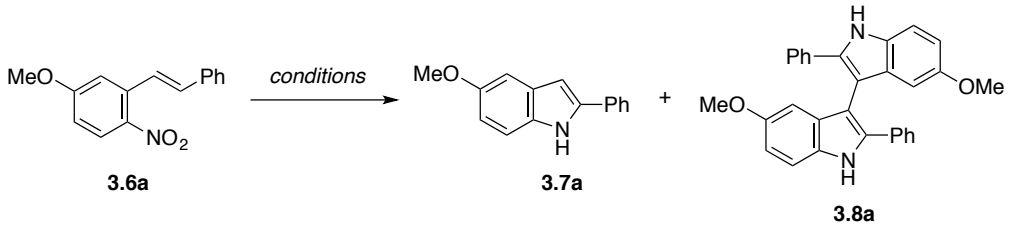


Styrene (3.15). Diphenylmethylene(triphenyl)phosphonium bromide (6.4 mmol) was obtained by refuxing triphenyl-phosphine and bromodiphenyl methane in toluene for 48 h. The resulting solid was dissolved in 32 mL of THF, and 2.8 mL of *n*-BuLi (2.5 M in hexanes, 7.10 mmol) was added dropwise. After 2 h, the reaction solution was deep red. Then 0.876 g of 2-nitrobenzaldehyde (5.80 mmol) was added and the mixture was stirred for 1 h at room temperature. Then the mixture was heated to reflux. After 12 h, the crude mixture was cooled to room temperature and 40 mL ethyl ether was added. The resulting mixture was filtered through a pad of SiO_2. The filtrate was concentrated *in vacuo*. Purification via MPLC (0:100 – 2:98 EtOAc:hexanes) afforded only **3.15** as a bright yellow oil (0.384 g, 25%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.96 – 7.98 (m, 1H), 7.36 – 7.39 (m, 6H), 7.24 – 7.26 (m, 5H), 7.13 – 7.15 (m, 2H), 7.04 – 7.06 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 149.0 (C), 145.6 (C), 142.3 (C), 139.3 (C), 133.8 (C), 132.7 (CH),

132.4 (CH), 130.8 (CH), 128.3 (CH), 128.2 (CH), 127.8 (CH), 127.5 (CH), 124.3 (CH), 123.8 (CH), only peaks visible; IR (thin film): 1628, 1597, 1571, 1517, 1475, 1345, 1308, 1260 cm^{-1}.

C. Pd(II)-Catalyzed Formation of *N*-Heterocycles.

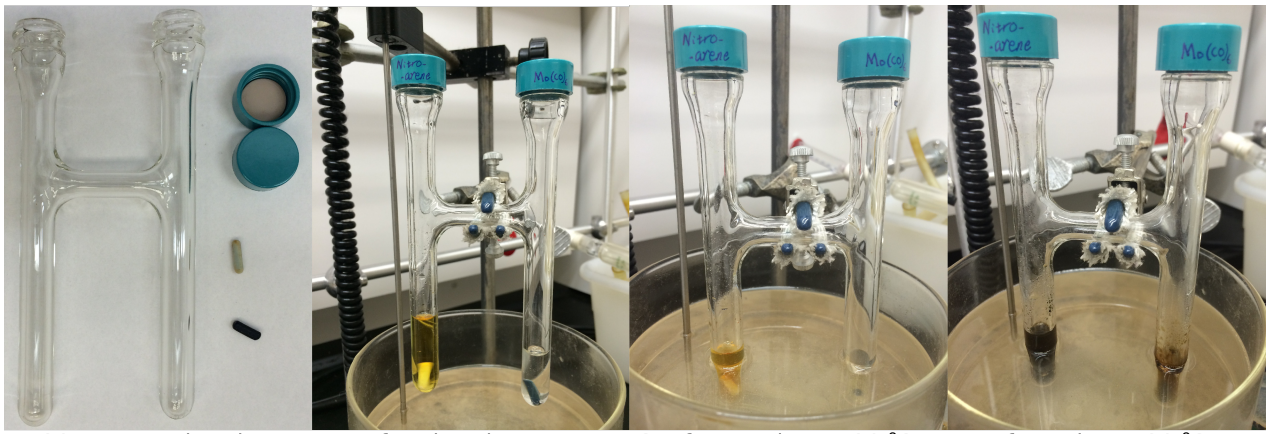
1. Screening of Reaction Conditions.



3.6a **3.7a** **3.8a**

To a 20 mL H-cell (Figure 3.3), under a nitrogen atmosphere, $Mo(CO)_6$ and 1 mL of solvent was added to chamber 1, 0.10 mmol of nitroarene, palladium catalyst, ligand and solvent was added to chamber 2. The H-cell 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 ^1H NMR spectroscopy using CH_2Br_2 as the internal standard.

Figure 3.3. ***Reaction progress in 20 mL two chamber glass H-shaped reactor.***



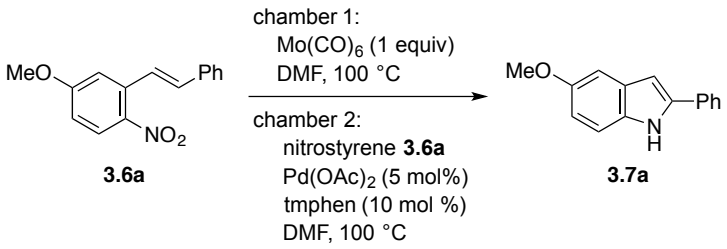
A. 20 mL two chamber reactor **B**. Before heating **C**. After 5 min at 120 °C **D**. After 1 h at 120 °C

Table 3.4. ***Development of Optimized Conditions.***

entry	catalyst (mol %)	ligand (mol %)	Reductant (equiv)	solvent (mL)	T (°C)	yield, %[a] **3.7a** : **3.8a**
1	N/A	N/A	$Mo(CO)_6$ (1.0 equiv)	DMF (1.0 mL)	120	n.r.
2	$Pd(OAc)_2$ (10 mol%)	phen (20 mol%)	$Mo(CO)_6$ (1.0 equiv)	DMF (1.0 mL)	120	66 (50:50)
3	$Pd(OAc)_2$ (10 mol%)	phen (20 mol%)	$Cr(CO)_6$ (1.0 equiv)	DMF (1.0 mL)	120	36 (50:50)
4	$Pd(OAc)_2$ (10 mol%)	phen (20 mol%)	$W(CO)_6$ (1.0 equiv)	DMF (1.0 mL)	120	16 (25:75)
5	$Pd(OAc)_2$ (10 mol%)	azafluor (20 mol%)	$Mo(CO)_6$ (1.0 equiv)	DMF (1.0 mL)	120	n.r.
6	$Pd(OAc)_2$ (10 mol%)	tmphen (20 mol%)	$Mo(CO)_6$ (1.0 equiv)	DMF (1.0 mL)	120	95 (81:19)
7	$Pd(OAc)_2$ (10 mol%)	tmphen (20 mol%)	$Mo(CO)_6$ (1.0 equiv)	DMA (1.0 mL)	120	95 (81:19)
8	$Pd(OAc)_2$ (10 mol%)	tmphen (20 mol%)	$Mo(CO)_6$ (1.0 equiv)	DMSO (1.0 mL)	120	69 (91:9)
9	$Pd(OAc)_2$ (10 mol%)	tmphen (20 mol%)	$Mo(CO)_6$ (1.0 equiv)	DCE (1.0 mL)	120	n.r.
10	$Pd(OAc)_2$ (5 mol%)	tmphen (10 mol%)	$Mo(CO)_6$ (1.0 equiv)	DMF (1.0 mL)	120	95 (77:23)
11	$Pd(OAc)_2$ (5 mol%)	tmphen (10 mol%)	$Mo(CO)_6$ (1.0 equiv)	DMF (2.0 mL)	120	91 (82:18)
12	$Pd(OAc)_2$ (5 mol%)	tmphen (10 mol%)	$Mo(CO)_6$ (1.0 equiv)	DMF (2.0 mL)	100	84 (96:4)

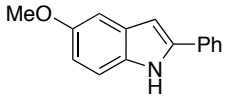
[a] As determined using ^1H NMR spectroscopy using CH_2Br_2 as the internal standard; phen = 1,10-phenanthroline; tmphen = 3,4,7,8-tetramethyl-1,10-phenanthroline; azafluor = 4,5-diazafluoren-9-one; DMF = dimethyformamide; DCE = 1,2-dichloroethane; DMA = dimethylacetamide; DMSO = dimethylsulfoxide.

2. Optimized Conditions.



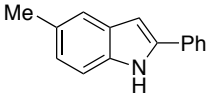
To a 20 mL H-cell, under a nitrogen atmosphere, 0.10 mmol $Mo(CO)_6$ (1.0 equiv) and 1 mL of DMF was added to chamber 1, 0.10 mmol of nitroarene, 0.005 mmol of $Pd(OAc)_2$ (5 mol %), 0.01 mmol of 3,4,7,8-tetramethyl-1,10-phenanthroline and 2 mL of DMF was added to chamber 2. The H-cell was sealed and heated at 100 °C for 10 hours. The H-cell was then cooled down to room temperature and the reaction mixture of chamber 1 was filtered through a pad of silica gel. 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.



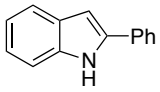
3.7a

Indole (3.7a). The general procedure was followed adding 0.0255 g of nitroarene **3.6a** (0.10 mmol), 0.0011 g of $Pd(OAc)_2$ (0.005 mmol), 0.0024 g of 3,4,7,8-tetramethyl-1,10-phenanthroline (0.01 mmol) and 2 mL of DMF to chamber 2, 0.0264 g of $Mo(CO)_6$ (0.10 mmol) and 1 mL of DMF to chamber 1. Purification via MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **3.7a** as a yellow solid (0.0178 g, 80%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.23 (br, 1H), 7.65 (d, J = 7.0 Hz, 2H), 7.44 (t, J = 7.5 Hz, 2H), 7.34 – 7.28 (m, 2H), 7.10 (d, J = 2.5 Hz, 1H), 6.87 (dd, J = 9.0, 2.5 Hz, 1H), 6.77 (d, J = 1.5 Hz, 1H), 3.87 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 154.5 (C), 138.6 (C), 132.5 (C), 132.1 (C), 129.8 (C), 129.0 (CH), 127.7 (CH), 125.1 (CH), 112.7 (CH), 111.7 (CH), 102.3 (CH), 99.9 (CH), 55.9 (CH_3); IR (thin film): 3426, 2999, 2919, 2842, 1619, 1539, 1476, 1456, 1215, 1150, 1028 cm^{-1}.



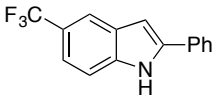
3.7b

Indole (3.7b). The general procedure was followed adding 0.0239 g of nitroarene **3.6b** (0.10 mmol), 0.0011 g of $Pd(OAc)_2$ (0.005 mmol), 0.0024 g of 3,4,7,8-tetramethyl-1,10-phenanthroline (0.01 mmol) and 2 mL of DMF to chamber 2, 0.0264 g of $Mo(CO)_6$ (0.10 mmol) and 1 mL of DMF to chamber 1. Purification via MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **3.7b** as a yellow solid (0.0170 g, 82%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.23 (br s, 1H), 7.65 (d, *J* = 10.0 Hz, 2H), 7.46 – 7.43 (m, 3H), 7.34 – 7.29 (m, 2H), 7.03 (d, *J* = 8.5 Hz, 1H), 6.77 (s, 1H), 2.47 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 138.0 (C), 135.2 (C), 132.6 (C), 129.6 (C), 129.5 (C), 129.0 (CH), 127.6 (CH), 125.1 (CH), 124.0 (CH), 120.3 (CH), 110.6 (CH), 99.6 (CH), 21.5 (CH_3); IR (thin film): 3405, 2918, 2852, 1457, 1317, 1299, 1203, 1072 cm^{-1}.



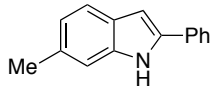
3.7c

Indole (3.7c). The general procedure was followed adding 0.025 g of nitroarene **3.6c** (0.10 mmol), 0.0011 g of $Pd(OAc)_2$ (0.005 mmol), 0.0024 g of 3,4,7,8-tetramethyl-1,10-phenanthroline (0.01 mmol) and 2 mL of DMF to chamber 2, 0.0264 g of $Mo(CO)_6$ (0.10 mmol) and 1 mL of DMF to chamber 1. Purification via MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **3.7c** as a light brown solid (0.0164 g, 85%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.32 (s, 1H), 7.66 (t, *J* = 8.5 Hz, 3H), 7.46 (t, *J* = 7.6 Hz, 2H), 7.41 (d, *J* = 8.1 Hz, 1H), 7.34 (t, *J* = 7.4 Hz, 1H), 7.22 (t, *J* = 7.5 Hz, 1H), 7.15 (t, *J* = 7.4 Hz, 1H), 6.85 (d, *J* = 2.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 137.9(C), 136.9(C), 132.4(C), 129.3(C), 129.1(CH), 127.7(CH), 125.2(CH), 122.4(CH), 120.7(CH), 120.3(CH), 110.9(CH), 100.1(CH); IR (thin film): 3446, 1457, 1403, 1352, 798, 763, 741, 688 cm^{-1}.



3.7d

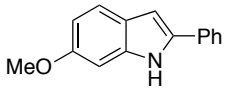
Indole (3.7d). The general procedure was followed adding 0.0293 g of nitroarene **3.6d** (0.10 mmol), 0.0011 g of $Pd(OAc)_2$ (0.005 mmol), 0.0024 g of 3,4,7,8-tetramethyl-1,10-phenanthroline (0.01 mmol) and 2 mL of DMF to chamber 2, 0.0264 g of $Mo(CO)_6$ (0.10 mmol) and 1 mL of DMF to chamber 1. Purification via MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **3.7d** as a light brown solid (0.0196 g, 75%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.51 (s, 1H), 7.93 (s, 1H), 7.68 (d, J = 7.3 Hz, 2H), 7.52 – 7.41 (m, 4H), 7.38 (t, J = 7.4 Hz, 1H), 6.90 (d, J = 2.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 139.7 (C), 138.1 (C), 131.7 (C), 129.2 (CH), 128.6 (C), 128.3 (CH), 125.3 (CH), 125.3 (q, J_{CF} = 266.3 Hz, C), 122.8 (q, J_{CF} = 30.3 Hz, C), 119.0 (CH), 118.3 (CH), 111.1 (CH), 100.6 (CH); ^{19}F NMR ($CDCl_3$, 282 MHz) δ –60.1; IR (thin film): 3432, 1496, 1449,1355,1338,1130, 1102 cm^{-1}.



3.7e

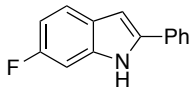
Indole (3.7e). The general procedure was followed adding 0.0239 g of nitroarene **3.6e** (0.10 mmol), 0.0011 g of $Pd(OAc)_2$ (0.005 mmol), 0.0024 g of 3,4,7,8-tetramethyl-1,10-phenanthroline (0.01 mmol) and 2 mL of DMF to chamber 2, 0.0264 g of $Mo(CO)_6$ (0.10 mmol) and 1 mL of DMF to chamber 1. Purification via MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **3.7e** as a white solid (0.016 g, 77%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.20 (s, 1H), 7.67 (d, J = 7.4 Hz, 2H), 7.55 (d, J = 8.0 Hz, 1H), 7.46 (t, J = 7.7 Hz, 2H), 7.34 (t, J = 7.4 Hz, 1H), 7.21 (s, 1H), 7.00 (d, J = 8.0 Hz, 1H), 6.81 (s, 1H), 2.51 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 137.3(C), 137.3(C), 132.6(C), 132.3(C),

129.0(CH), 127.5(CH), 127.1(C), 125.0(CH), 122.1(CH), 120.3(CH), 110.9(CH), 99.9(CH), 21.8(CH_3); IR (thin film): 3429, 1454, 1350, 1232, 814, 760, 740, 686 cm^{-1}.



3.7f

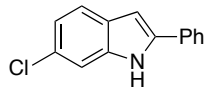
Indole (3.7f). The general procedure was followed adding 0.0255 g of nitroarene **3.6f** (0.10 mmol), 0.0011 g of $Pd(OAc)_2$ (0.005 mmol), 0.0024 g of 3,4,7,8-tetramethyl-1,10-phenanthroline (0.01 mmol) and 2 mL of DMF to chamber 2, 0.0264 g of $Mo(CO)_6$ (0.10 mmol) and 1 mL of DMF to chamber 1. Purification via MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **3.7f** as a white solid (0.0120 g, 54%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.24 (br s, 1H), 7.62 (d, *J* = 7.5 Hz, 2H), 7.50 (d, *J* = 8.5 Hz, 1H), 7.43 (t, *J* = 7.5 Hz, 2H), 7.30 (t, *J* = 7.5 Hz, 1H), 6.89 (s, 1H), 6.80 (dd, J = 6.5, 2.0 Hz, 1H), 6.76 (s, 1H), 3.87 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) 156.8 (C), 137.7 (C), 136.8 (C), 132.6 (C), 129.0 (CH), 127.3 (CH), 124.7 (CH), 123.6 (C), 121.3 (CH), 110.2 (CH), 99.8 (CH), 94.6 (CH), 55.7 (CH_3); IR (thin film): 3387, 2922, 2852, 1622, 1598, 1452, 1259, 1203, 1159, 1116, 1019 cm^{-1}.



3.7g

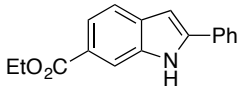
Indole (3.7g). The general procedure was followed by adding 0.0243 g of nitroarene **3.6g** (0.10 mmol), 0.0011 g of $Pd(OAc)_2$ (0.005 mmol), 0.0024 g of 3,4,7,8-tetramethyl-1,10-phenanthroline (0.01 mmol) and 2 mL of DMF to chamber 2, 0.0264 g of $Mo(CO)_6$ (0.10 mmol) and 1 mL of DMF to chamber 1. Purification via MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **3.7g** as a light brown solid (0.0169 g, 80%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.31 (s, 1H), 7.63 (d, *J* = 7.6 Hz, 2H), 7.54 (dd, *J* = 8.6, 5.3 Hz, 1H), 7.45 (t, *J* = 7.7 Hz, 2H), 7.33 (t, *J* = 7.4 Hz, 1H), 7.08 (dd, *J* = 9.5, 2.2 Hz, 1H), 6.90 (td, *J* = 9.2,

2.3 Hz, 1H), 6.80 (d, J = 2.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 160.1 (C, d, J = 238.0 Hz), 138.4 (C), 136.8 (C, d, J = 12.4 Hz), 132.1 (C), 129.1 (CH), 127.8 (CH), 125.8 (C), 125.0 (CH), 121.4 (CH, d, J = 10.1 Hz), 109.1 (CH, d, J = 24.1 Hz), 99.9 (CH), 97.3 (CH, d, J = 26.8 Hz); ^{19}F NMR ($CDCl_3$, 282 MHz) δ –119.9, IR (thin film): 3434, 1499, 1446, 1356, 1254, 1142, 813, 757 cm^{-1}.



3.7h

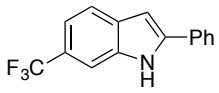
Indole (3.7h). The general procedure was followed by adding 0.0259 g of nitroarene **3.6h** (0.10 mmol), 0.0011 g of $Pd(OAc)_2$ (0.005 mmol), 0.0024 g of 3,4,7,8-tetramethyl-1,10-phenanthroline (0.01 mmol) and 2 mL of DMF to chamber 2, 0.0264 g of $Mo(CO)_6$ (0.10 mmol) and 1 mL of DMF to chamber 1. Purification via MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **3.7h** as a white solid (0.0153 g, 67%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.32 (s, 1H), 7.68 – 7.60 (m, 2H), 7.53 (d, J = 8.4 Hz, 1H), 7.45 (dd, J = 8.6, 7.0 Hz, 2H), 7.41 – 7.37 (m, 1H), 7.37 – 7.32 (m, 1H), 7.09 (dd, J = 8.4, 1.8 Hz, 1H), 6.80 (d, J = 2.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 138.7(C), 137.1(C), 132.0(C), 129.1(CH), 128.0(CH), 127.9(C), 125.2(CH), 121.5(CH), 121.1(CH), 110.8(CH), 100.0(CH), only peaks visible; IR (thin film): 3432, 1614, 1536, 1485, 1450, 1346, 1230, 1065 cm^{-1}.



3.7i

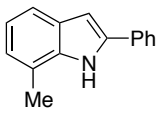
Indole (3.7i). The general procedure was followed by adding 0.0299 g of nitroarene **3.6i** (0.10 mmol), 0.0011 g of $Pd(OAc)_2$ (0.005 mmol), 0.0024 g of 3,4,7,8-tetramethyl-1,10-phenanthroline (0.01 mmol) and 2 mL of DMF to chamber 2, 0.0264 g of $Mo(CO)_6$ (0.10 mmol) and 1 mL of DMF to chamber 1. Purification via MPLC (0:100 – 5:95

EtOAc:hexanes) afforded **3.7i** as a yellow solid (0.0230 g, 87%). Indole **3.7i** was previously reported by Izumi and Yokota: ^{1}H NMR (DMSO-d_6, 500 MHz) δ 11.9 (br, 1H), 8.06 (s, 1H), 7.88 (d, J = 7.0 Hz, 2H), 7.63 – 7.59 (m, 2H), 7.49 (t, J = 8.0 Hz, 2H), 7.36 (d, J = 7.0 Hz, 1H), 6.99 (d, J = 1.5 Hz, 1H), 4.30 (q, J = 7.5 Hz, 2H), 1.33 (t, J = 7.5 Hz, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 167.1 (C), 141.8 (C), 136.8 (C), 132.8 (C), 132.0 (C), 129.5 (CH), 128.7 (CH), 125.9 (CH), 123.1 (C), 120.6 (CH), 120.2 (CH), 113.6 (CH), 99.6 (CH), 60.7 (CH_2), 14.8 (CH_3); IR (thin film): 3353, 2922, 2853, 1691, 1619, 1452, 1367, 1319, 1283, 1260, 1217 cm^{-1}, HRMS (EI) m/z calcd for $C_{17}H_{16}NO_2$ $[M+H]^+$: 266.1181, found 266.1185.



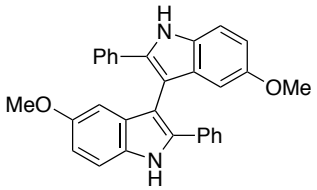
3.7j

Indole (3.7j). The general procedure was followed by adding 0.0293 g of nitroarene **3.6j** (0.10 mmol), 0.0011 g of $Pd(OAc)_2$ (0.005 mmol), 0.0024 g of 3,4,7,8-tetramethyl-1,10-phenanthroline (0.01 mmol) and 2 mL of DMF to chamber 2, 0.0264 g of $Mo(CO)_6$ (0.10 mmol) and 1 mL of DMF to chamber 1. Purification via MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **3.7j** as a light brown (0.0144 g, 55%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.54 (s, 1H), 7.77 – 7.62 (m, 4H), 7.48 (dd, J = 8.4, 7.0 Hz, 2H), 7.43 – 7.32 (m, 2H), 6.87 (d, J = 2.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 140.6(C), 135.6(C), 131.6(C), 129.2(CH), 128.5(CH), 125.4(CH), 124.1(q, J_{CF} = 268.8 Hz, C), 120.9(CH), 117.0(CH), 111.0(C), 108.4(CH), 100.1(CH), only peaks visible; ^{19}F NMR ($CDCl_3$, 282 MHz) δ –60.1, IR (thin film): 3444, 1456, 1342, 1155, 1105, 829, 766, 690 cm^{-1}.



3.7k

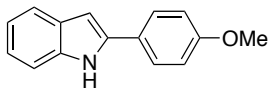
Indole (3.7k). The general procedure was followed by adding 0.0239 g of nitroarene **3.6k** (0.10 mmol), 0.0011 g of $Pd(OAc)_2$ (0.005 mmol), 0.0024 g of 3,4,7,8-tetramethyl-1,10-phenanthroline (0.01 mmol) and 2 mL of DMF to chamber 2, 0.0264 g of $Mo(CO)_6$ (0.10 mmol) and 1 mL of DMF to chamber 1. Purification via MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **3.7k** as a light yellow solid (0.0099 g, 48%). The spectral data of **3.7k** matched that reported by Fang and Lautens: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.20 (s, 1H), 7.76 – 7.66 (m, 2H), 7.48 (dt, *J* = 15.7, 7.8 Hz, 3H), 7.34 (t, *J* = 7.5 Hz, 1H), 7.10 – 7.03 (m, 1H), 7.01 (d, *J* = 7.2 Hz, 1H), 6.85 (d, *J* = 1.9 Hz, 1H), 2.56 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 137.7(C), 136.4(C), 132.6(C), 128.8(CH), 128.8(C), 127.7(CH), 125.2(CH), 123.0(CH), 120.5(CH), 120.1(C), 118.4(CH), 100.6(CH), 16.7(CH_3); IR (thin film): 3451, 1604, 1484, 1449, 1356, 1330, 1301, 799 cm^{-1}.



3.8a

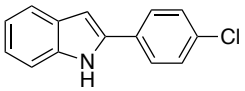
Indole (3.8a). The general procedure was followed adding 0.0255 g of nitroarene **3.6a** (0.10 mmol), 0.0022 g of $Pd(OAc)_2$ (0.010 mmol), 0.0036 g of 1,10-phenanthroline (0.020 mmol) and 1 mL of DMF to chamber 2, 0.0264 g of $Mo(CO)_6$ (0.10 mmol) and 1 mL of DMF to chamber 1. Purification via MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **3.8a** as a yellow solid (0.0073 g, 33%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.22 (s, 2H), 7.40 – 7.29 (m, 6H), 7.20 – 7.06 (m, 6H), 6.85 (dd, *J* = 8.6, 2.4 Hz, 2H), 6.67 (d, *J* = 2.4 Hz, 2H), 3.57 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 154.3 (C), 135.9 (C), 133.3 (C), 131.4 (C), 130.0 (C), 128.5 (CH), 127.1 (CH), 126.9 (CH), 113.0 (CH), 111.5 (CH),

107.3 (C), 102.0 (CH), 55.6 (CH_3); IR (thin film): 3407, 1621, 1577, 1476, 1455, 1405, 1279 cm^{-1}. HRMS (EI) m/z calcd for $C_{30}H_{24}N_2O_2$ $[M]^+$: 444.1838, found 444.1834.



3.10a

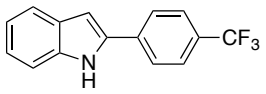
Indole (3.10a). The general procedure was followed by adding 0.0255 g of nitroarene **3.9a** (0.10 mmol), 0.0011 g of $Pd(OAc)_2$ (0.005 mmol), 0.0024 g of 3,4,7,8-tetramethyl-1,10-phenanthroline (0.01 mmol) and 2 mL of DMF to chamber 2, 0.0264 g of $Mo(CO)_6$ (0.10 mmol) and 1 mL of DMF to chamber 1. Purification via MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **3.10a** as a yellow solid (0.0210 g, 94%). The spectral data of **3.10a** matched that reported by Fang and Lautens: ^{1}H NMR (DMSO-d_6, 500 MHz) δ 8.25 (br, 1H), 7.61 – 7.59 (m, 3H), 7.38 (d, J = 8.0 Hz, 1H), 7.17 (t, J = 7.5 Hz, 1H), 7.11 (t, J = 7.5 Hz, 1H), 6.98 (d, J = 9.0 Hz, 2H), 6.72 (s, 1H), 3.86 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 159.3 (C), 138.3 (C), 137.4 (C), 129.3 (C), 126.8 (CH), 125.4 (C), 121.5 (CH), 120.1 (CH), 120.0 (CH), 114.8 (CH), 111.5 (CH), 97.8 (CH), 55.7 (CH_3); IR (thin film): 3427, 1606, 1500, 1452, 1430, 1286, 1248, 1179, 1113, 1048, 1024 cm^{-1}.



3.10b

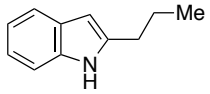
Indole (3.10b). The general procedure was followed by adding 0.0259 g of nitroarene **3.9b** (0.10 mmol), 0.0011 g of $Pd(OAc)_2$ (0.005 mmol), 0.0024 g of 3,4,7,8-tetramethyl-1,10-phenanthroline (0.01 mmol) and 2 mL of DMF to chamber 2, 0.0264 g of $Mo(CO)_6$ (0.10 mmol) and 1 mL of DMF to chamber 1. Purification via MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **3.10b** as a yellow solid (0.0129 g, 57%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.28 (br, 1H), 7.63 (d, J = 7.5 Hz, 1H), 7.58 (d, J = 8.5 Hz, 2H), 7.42 – 7.39 (m, 3H), 7.22 (t, J = 7.5 Hz, 1H), 7.14 (t, J = 7.5 Hz, 1H), 6.81 (d, J = 1.5 Hz, 1H); ^{13}C NMR

($CDCl_3$, 125 MHz) δ 136.9 (C), 136.7 (C), 133.5 (C), 130.9 (C), 129.2 (CH), 126.3 (CH), 122.7 (CH), 120.8 (CH), 120.5 (CH), 111.0 (CH), 100.5 (CH), only peaks visible; IR (thin film): 3432, 2922, 2852, 1728, 1480, 1452, 1425, 1348, 1298, 1260, 1094 cm^{-1}.



3.10c

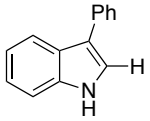
Indole (3.10c). The general procedure was followed by adding 0.0293 g of nitroarene **3.9c** (0.10 mmol), 0.0011 g of $Pd(OAc)_2$ (0.005 mmol), 0.0024 g of 3,4,7,8-tetramethyl-1,10-phenanthroline (0.01 mmol) and 2 mL of DMF to chamber 2, 0.0264 g of $Mo(CO)_6$ (0.10 mmol) and 1 mL of DMF to chamber 1. Purification via MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **3.10c** as a light yellow solid (0.0130 g, 50%). ^{1}H NMR ($CDCl_3$, 500 MHz) 8.38 (br, 1H), 7.76 (d, J = 8.0 Hz, 2H), 7.69 (d, J = 8.0 Hz, 2H), 7.65 (d, J = 7.5 Hz, 1H), 7.42 (d, J = 8.0 Hz, 1H), 7.24 (t, J = 8.0 Hz, 1H), 7.15 (t, J = 8.0 Hz, 1H), 6.93 (d, J = 1.5 Hz, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 138.0 (C), 136.6 (C), 128.9 (C), 127.9 (C), 126.3 (q, J_{CF} = 3.5 Hz, C), 125.8 (CH), 124.8 (q, J_{CF} = 270.0 Hz, C), 122.9 (CH), 121.0 (CH), 120.2 (CH), 112.0 (CH), 101.2 (CH); only peaks visible, ^{19}F NMR ($CDCl_3$, 282 MHz) δ –62.6, IR (thin film): 3421, 2929, 2852, 1612, 1427, 1326, 1168, 1111, 1073, 1012 cm^{-1}.



3.10d

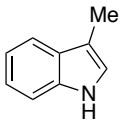
Indole (3.10d). The general procedure was followed by adding 0.0191 g of nitroarene **3.9d** (0.10 mmol), 0.0011 g of $Pd(OAc)_2$ (0.005 mmol), 0.0024 g of 3,4,7,8-tetramethyl-1,10-phenanthroline (0.01 mmol) and 2 mL of DMF to chamber 2, 0.0264 g of $Mo(CO)_6$ (0.10 mmol) and 1 mL of DMF to chamber 1. Purification via MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **3.10d** as a brown oil (0.0122 g, 77%). ^{1}H NMR ($CDCl_3$, 500

MHz) δ 7.84 (s, 1H), 7.54 (d, J = 7.7 Hz, 1H), 7.30 (d, J = 7.9 Hz, 1H), 7.10 (dtd, J = 22.6, 7.2, 1.2 Hz, 2H), 6.25 (s, 1H), 2.74 (t, J = 7.5 Hz, 2H), 1.76 (h, J = 7.4 Hz, 2H), 1.02 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 139.8(C), 135.8(C), 128.9(C), 120.9(CH), 119.8(CH), 110.3(CH), 99.6(CH), 30.3(CH_2), 22.5(CH_2), 13.9(CH_3), only peaks visible; IR (thin film): 3404, 1457, 1415, 1289, 781, 750 cm^{-1}.



3.10e

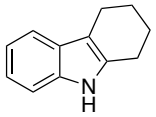
Indole (3.10e). The general procedure was followed by adding 0.0225 g of nitroarene **3.9e** (0.10 mmol), 0.0011 g of $Pd(OAc)_2$ (0.005 mmol), 0.0024 g of 3,4,7,8-tetramethyl-1,10-phenanthroline (0.01 mmol) and 2 mL of DMF to chamber 2, 0.0264 g of $Mo(CO)_6$ (0.10 mmol) and 1 mL of DMF to chamber 1. Purification via MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **3.10e** as a yellow solid (0.0183 g, 95%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.17 (br, 1H), 7.99 (d, J = 8.0 Hz, 1H), 7.72 – 7.71 (m, 2H), 7.49 (t, J = 8.0 Hz, 2H), 7.43 (d, J = 8.5 Hz, 1H), 7.36 – 7.32 (m, 2H), 7.29 (td, J = 7.0, 1.0 Hz, 1H), 7.24 (td, J = 7.0, 1.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 136.7 (C), 135.6 (C), 128.8 (CH), 127.5 (CH), 126.0 (CH), 125.8 (C), 122.5 (CH), 121.8 (CH), 120.4 (CH), 119.9 (CH), 118.4 (CH), 111.5 (C); IR (thin film): 3414, 3054, 1601, 1544, 1486, 1455, 1415, 1336, 1263, 1238, 1111, 1098 cm^{-1}.



3.10f

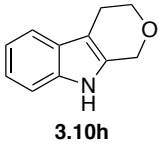
Indole (3.10f). The general procedure was followed by adding 0.0163 g of nitroarene **3.9f** (0.10 mmol), 0.0011 g of $Pd(OAc)_2$ (0.005 mmol), 0.0024 g of 3,4,7,8-tetramethyl-1,10-phenanthroline (0.01 mmol) and 2 mL of DMF to chamber 2, 0.0264 g of $Mo(CO)_6$

(0.10 mmol) and 1 mL of DMF to chamber 1. Purification via MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **3.10f** as a light yellow solid (0.0111 g, 85%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.86 (s, 1H), 7.60 (d, *J* = 7.8 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.23 – 7.17 (m, 1H), 7.17 – 7.09 (m, 1H), 7.02 – 6.93 (m, 1H), 2.35 (d, *J* = 1.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 136.4(C), 128.3(C), 121.9(CH), 121.6(CH), 119.1(CH), 118.8(CH), 111.8(C), 110.9(CH), 9.6(CH_3); IR (thin film): 3417, 1455, 1418, 1334, 1264, 1247, 10876, 1009, 733 cm^{-1}.



3.10g

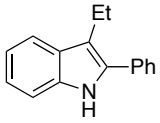
Indole (3.10g). The general procedure was followed by adding 0.0203 g of nitroarene **3.9g** (0.10 mmol), 0.0011 g of $Pd(OAc)_2$ (0.005 mmol), 0.0024 g of 3,4,7,8-tetramethyl-1,10-phenanthroline (0.01 mmol) and 2 mL of DMF to chamber 2, 0.0264 g of $Mo(CO)_6$ (0.10 mmol) and 1 mL of DMF to chamber 1. Purification via MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **3.10g** as a yellow solid (0.0111 g, 65%). The spectral data matched that reported by Leogane and Lebel: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.63 (s, 1H), 7.48 (d, *J* = 7.6 Hz, 1H), 7.28 (d, *J* = 7.9 Hz, 1H), 7.18 – 7.05 (m, 2H), 2.73 (br, 4H), 2.00 – 1.84 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 135.7(C), 134.1(C), 127.8(C), 121.0(CH), 119.1(CH), 117.7(CH), 110.3(CH), 110.2(C), 23.3(CH_2), 20.9(CH_2), only peaks visible; IR (thin film): 3398, 1469, 1450, 1440, 1303, 1234, 1143 cm^{-1}.



3.10h

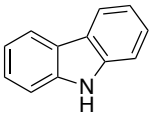
Indole (3.10h). The general procedure was followed by adding 0.0205 g of nitroarene **3.9h** (0.10 mmol), 0.0011 g of $Pd(OAc)_2$ (0.005 mmol), 0.0024 g of 3,4,7,8-tetramethyl-

1,10-phenanthroline (0.01 mmol) and 2 mL of DMF to chamber 2, 0.0264 g of $Mo(CO)_6$ (0.10 mmol) and 1 mL of DMF to chamber 1. Purification via MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **3.10h** as a yellow solid (0.012 g, 70%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.71 (s, 1H), 7.51 (d, *J* = 7.6 Hz, 1H), 7.32 (d, *J* = 7.9 Hz, 1H), 7.22 – 7.08 (m, 2H), 4.82 (t, *J* = 1.7 Hz, 2H), 4.04 (t, *J* = 5.5 Hz, 2H), 2.86 (tt, *J* = 5.5, 1.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 136.0(C), 131.5(C), 127.2(C), 121.7(CH), 119.6(CH), 118.0(CH), 111.0(C), 110.9(CH), 65.8(CH_2), 63.7(CH_2), 22.2(CH_2); IR (thin film): 3392, 1449, 1240, 1088, 1065, 740 cm^{-1}.



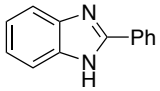
3.10i

Indole (3.10i). The general procedure was followed by adding 0.0253 g of nitroarene **3.9i** (0.10 mmol), 0.0011 g of $Pd(OAc)_2$ (0.005 mmol), 0.0024 g of 3,4,7,8-tetramethyl-1,10-phenanthroline (0.01 mmol) and 2 mL of DMF to chamber 2, 0.0264 g of $Mo(CO)_6$ (0.10 mmol) and 1 mL of DMF to chamber 1. Purification via MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **3.10i** as a light yellow solid (0.0201 g, 91%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.98 (s, 1H), 7.66 – 7.11 (m, 9H), 2.93 (q, *J* = 7.5 Hz, 2H), 1.36 (t, *J* = 7.6 Hz, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 136.0(C), 133.7(C), 133.4(C), 129.1(C), 128.8(CH), 127.9(CH), 127.5(CH), 122.2(CH), 119.5(CH), 119.2(CH), 115.5(C), 110.8(CH), 17.8(CH_2), 15.6(CH_3); IR (thin film): 3411, 1603, 1525, 1486, 1457, 1448, 1370, 1340, 1306, 1228, 759 cm^{-1}.



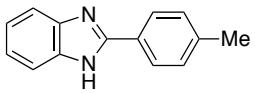
3.10j

Indole (3.10j). The general procedure was followed by adding 0.0199 g of nitroarene **3.9j** (0.10 mmol), 0.0011 g of $Pd(OAc)_2$ (0.005 mmol), 0.0024 g of 3,4,7,8-tetramethyl-1,10-phenanthroline (0.01 mmol) and 2 mL of DMF to chamber 2, 0.0264 g of $Mo(CO)_6$ (0.10 mmol) and 1 mL of DMF to chamber 1. Purification via MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **3.10j** as a light yellow solid (0.0067 g, 40%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.09 (d, *J* = 7.5 Hz, 2H), 8.04 (br, 1H), 7.43 – 7.41 (m, 4H), 7.27 – 7.23 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 139.5 (C), 125.9 (CH), 123.4 (C), 120.3 (CH), 119.5 (CH), 110.6 (CH); IR (thin film): 3416, 3047, 1624, 1599, 1448, 1394, 1323, 1235, 1204 cm^{-1}.



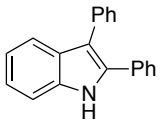
3.10k

Indole (3.10k). The general procedure was followed by adding 0.0260 g of nitroarene **3.9k** (0.10 mmol), 0.0011 g of $Pd(OAc)_2$ (0.005 mmol), 0.0024 g of 3,4,7,8-tetramethyl-1,10-phenanthroline (0.01 mmol) and 2 mL of DMF to chamber 2, 0.0264 g of $Mo(CO)_6$ (0.10 mmol) and 1 mL of DMF to chamber 1. Purification via MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **3.10k** as a light yellow solid (0.0120 g, 62%). The spectral data of **3.10k** matched that reported by Shen and Driver: ^{1}H NMR (DMSO-d_6, 500 MHz) δ 8.17 (d, *J* = 7.5 Hz, 2H), 7.66 (d, *J* = 5.0 Hz, 1H), 7.55 – 7.46 (m, 4H), 7.19 (br, 2H), only peaks visible; ^{13}C NMR (DMSO-d_6, 125 MHz) δ 151.7 (C), 144.3 (C), 135.5 (C), 130.6 (C), 130.3 (CH), 129.4 (CH), 126.9 (CH), 123.0 (CH), 122.2 (CH), 119.4 (CH), 111.8 (CH); IR (thin film): 2923, 2852, 1719, 1541, 1460, 1443, 1408, 1314, 1275, 1225, 1118, 1027, 1004, 970 cm^{-1}.



3.10l

Indole (3.10k). The general procedure was followed by adding 0.0260 g of nitroarene **3.9k** (0.10 mmol), 0.0011 g of $Pd(OAc)_2$ (0.005 mmol), 0.0024 g of 3,4,7,8-tetramethyl-1,10-phenanthroline (0.01 mmol) and 2 mL of DMF to chamber 2, 0.0264 g of $Mo(CO)_6$ (0.10 mmol) and 1 mL of DMF to chamber 1. Purification via MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **3.10k** as a light yellow solid (0.0120 g, 62%). The spectral data of **3.10k** matched that reported by Shen and Driver: ^{1}H NMR (DMSO-d_6, 500 MHz) δ 8.17 (d, J = 7.5 Hz, 2H), 7.66 (d, J = 5.0 Hz, 1H), 7.55 – 7.46 (m, 4H), 7.19 (br, 2H), only peaks visible; ^{13}C NMR (DMSO-d_6, 125 MHz) δ 151.7 (C), 144.3 (C), 135.5 (C), 130.6 (C), 130.3 (CH), 129.4 (CH), 126.9 (CH), 123.0 (CH), 122.2 (CH), 119.4 (CH), 111.8 (CH); IR (thin film): 2923, 2852, 1719, 1541, 1460, 1443, 1408, 1314, 1275, 1225, 1118, 1027, 1004, 970 cm^{-1}.

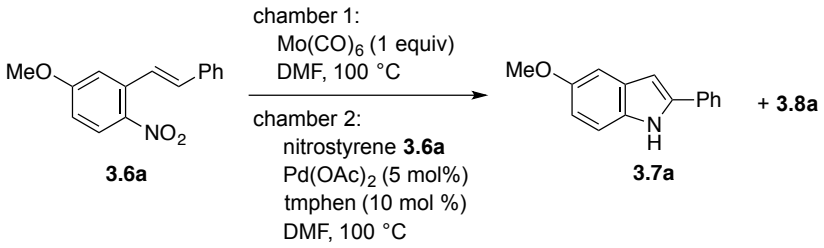


3.17

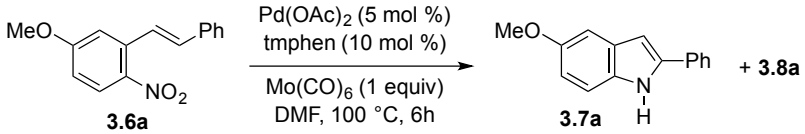
Indole (3.17). The general procedure was followed adding 0.0301 g of nitroarene **3.15** (0.10 mmol), 0.0011 g of $Pd(OAc)_2$ (0.005 mmol), 0.0024 g of 3,4,7,8-tetramethyl-1,10-phenanthroline (0.01 mmol) and 2 mL of DMF to chamber 2, 0.0264 g of $Mo(CO)_6$ (0.10 mmol) and 1 mL of DMF to chamber 1. Purification via MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **3.17** as a light yellow solid (0.0163 g, 61%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.23 (s, 1H), 7.70 (d, J = 7.9 Hz, 1H), 7.45 (t, J = 8.1 Hz, 5H), 7.39 (t, J = 7.6 Hz, 2H), 7.37 – 7.22 (m, 5H), 7.17 (t, J = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 135.9(C), 135.1(C), 134.1(C), 132.7(C), 130.2(CH), 128.8(C), 128.7(CH), 128.5(CH), 128.2(CH), 127.7(CH), 126.3(CH), 122.7(CH), 120.5(CH), 119.7(CH), 115.1(C),

110.9(CH); IR (thin film): 3404, 3055, 1601, 1455, 1440, 1304, 1251, 1071, 742, 698 cm^{-1}.

D. Control Experiments.

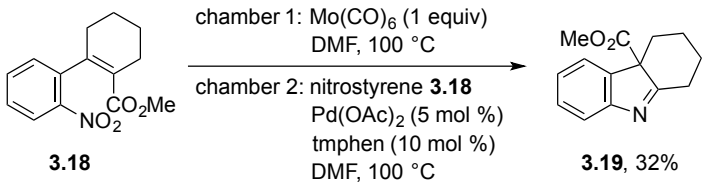


To a 20 mL H-cell, under a nitrogen atmosphere, 0.0255 g of nitroarene **3.6a** (0.10 mmol), 0.0011 g of $Pd(OAc)_2$ (0.005 mmol), 0.0024 g of 3,4,7,8-tetramethyl-1,10-phenanthroline (0.01 mmol) and 2 mL of DMF to chamber 2, 0.0264 g of $Mo(CO)_6$ (0.10 mmol) and 1 mL of DMF to chamber 1. The H-cell was sealed and heated at 100 °C for 6 hours. The H-cell was then cooled down to room temperature and the reaction mixture of chamber 1 was filtered through a pad of silica gel. The filtrate was concentrated in vacuo. Analysis of the resulting residue using ^1H NMR spectroscopy with CH_2Br_2 as the internal standard revealed 36% formation of the indole **3.7a**.



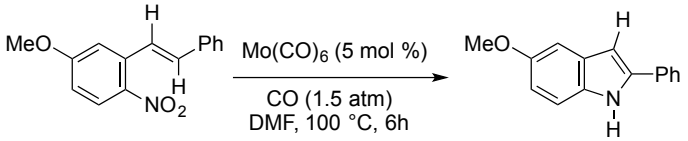
To a 20 mL Schlenk tube, under a nitrogen atmosphere, 0.0255 g of nitroarene **3.6a** (0.10 mmol), 0.0011 g of $Pd(OAc)_2$ (0.005 mmol), 0.0024 g of 3,4,7,8-tetramethyl-1,10-phenanthroline (0.01 mmol), 0.0264 g of $Mo(CO)_6$ (0.10 mmol) and 2 mL of DMF was added. The Schlenk tube was sealed and heated at 100 °C for 6 hours. The Schlenk tube was then cooled down to room temperature and the reaction mixture was 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 19% formation of the indole **3.7a**.



3.18 **3.19**, 32%

To a 20 mL H-cell, under a nitrogen atmosphere, 0.0260 g of nitrostyrene **3.18** (0.10 mmol), 0.0011 g of $Pd(OAc)_2$ (0.005 mmol), 0.0024 g of 3,4,7,8-tetramethyl-1,10-phenanthroline (0.01 mmol) and 2 mL of DMF to chamber 2, 0.0264 g of $Mo(CO)_6$ (0.10 mmol) and 1 mL of DMF to chamber 1. The H-cell was sealed and heated at 100 °C for 10 hours. The H-cell was then cooled down to room temperature and the reaction mixture of chamber 1 was 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 36% formation of the indole **3.19**.



3.6a **3.7a**, trace

To a 20 mL Schlenk tube, under a nitrogen atmosphere, 0.0255 g of nitroarene **3.6a** (0.10 mmol), 0.0013 g of $Mo(CO)_6$ (0.005 mmol) and 2 mL of DMF was added. Then the Schlenk tube was degased and refilled with CO gas (1.5 atm). The Schlenk tube was sealed and heated at 100 °C for 6 hours. The Schlenk tube was then cooled down to room temperature and the reaction mixture was 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 trace of the indole **3.7a**.

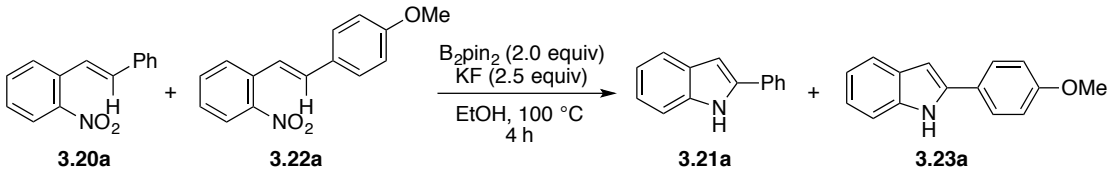
2. Mechanistic study of diborane-mediated deoxygenation of *ortho*-nitrostyrenes to form indoles

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 according to the procedure of Grubbs. Metal salts were stored in a nitrogen atmosphere dry box.

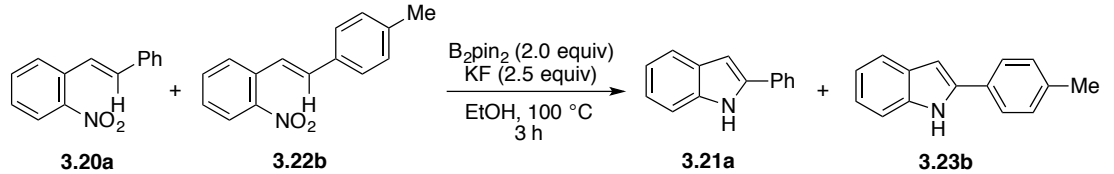
B. Mechanism Experiments.

1. Hammett Competition Experiment—β-aryl substituent.



3.20a **3.22a** **3.21a** **3.23a**

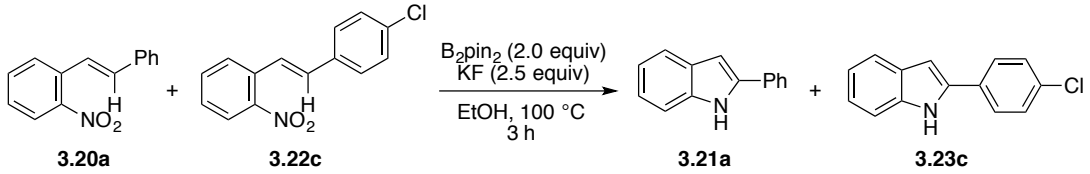
To a 10 mL Schlenk tube, under a nitrogen atmosphere, was added 0.0112 g of *o*-nitrostyrene **3.20a** (0.0500 mmol), 0.0127 g of *o*-nitrostyrene **3.22a** (0.0500 mmol), 0.051 g of bis(pinacolato)diboron (0.20 mmol), and 0.0145 g of potassium fluoride (0.25 mmol) in 1.00 mL of ethanol. The Schlenk tube was sealed and heated at 100 °C. After 3 h, the reaction mixture was cooled to room temperature and diluted with 3 mL of water. The resulting mixture was extracted with 3 × 3 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 the filtrate was concentrated *in vacuo*. Analysis of the resulting residue using ^1H NMR spectroscopy with CH_2Br_2 as the internal standard revealed 0.012 mmol of *o*-nitrostyrene **3.20a**, 0.018 mmol of *o*-nitrostyrene **3.22a**, 0.029 mmol of indole **3.21a**, 0.024 mmol of indole **3.23a**.



3.20a **3.22b** **3.21a** **3.23b**

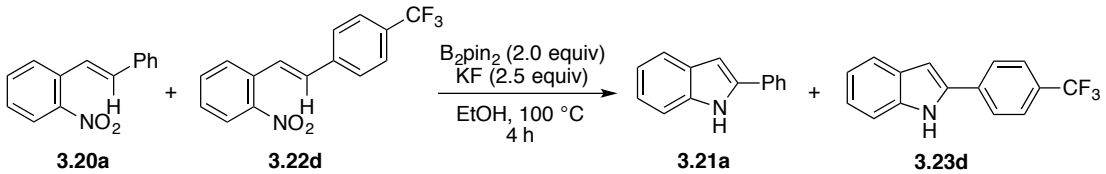
To a 10 mL Schlenk tube, under a nitrogen atmosphere, 0.0112 g of *o*-nitrostyrene **3.20a** (0.050 mmol), 0.0120 g of *o*-nitrostyrene **3.22b** (0.050 mmol), 0.051 g of bis(pinacolato)diboron (0.200 mmol), 0.0145 g of potassium fluoride (0.25 mmol) in 1.00 mL of ethanol. The Schlenk tube was sealed and heated at 100 °C. After 3 h, the reaction mixture was cooled to room temperature and diluted with 3 mL of water. The resulting mixture was extracted with 3 × 3 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 the filtrate was concentrated *in vacuo*. Analysis of the resulting residue using ^1H NMR spectroscopy with CH_2Br_2 as the internal standard revealed 0.025 mmol of *o*-nitrostyrene **3.20a**, 0.024 mmol of *o*-nitrostyrene **3.22b**, 0.023 mmol of indole **3.21a**, 0.021 mmol of indole **3.23b**.



3.20a **3.22c** **3.21a** **3.23c**

To a 10 mL Schlenk tube, under a nitrogen atmosphere, was added 0.0112 g of *o*-nitrostyrene **3.20a** (0.050 mmol), 0.0130 g of *o*-nitrostyrene **3.22c** (0.050 mmol), 0.051 g of bis(pinacolato)diboron (0.200 mmol), 0.0145 g of potassium fluoride (0.25 mmol) in 1.00 mL of ethanol. The Schlenk tube was sealed and heated at 100 °C. After 3 h, the reaction mixture was cooled to room temperature and diluted with 3 mL of water. The resulting mixture was extracted with 3 × 3 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 the filtrate was concentrated *in vacuo*. Analysis of the resulting residue using ^1H NMR spectroscopy with CH_2Br_2 as the internal standard revealed 0.023 mmol of *o*-nitrostyrene **3.20a**, 0.018 mmol of *o*-nitrostyrene **3.22c**, 0.026 mmol of indole **3.21a**, 0.027 mmol of indole **3.23c**.



3.20a **3.22d** **3.21a** **3.23d**

To a 10 mL Schlenk tube, under a nitrogen atmosphere, was added 0.0112 g of *o*-nitrostyrene **3.20a** (0.050 mmol), 0.0146 g of *o*-nitrostyrene **3.22d** (0.050 mmol), 0.051 g

of bis(pinacolato)diboron (0.200 mmol), 0.0145 g of potassium fluoride (0.25 mmol) in 1.00 mL of ethanol. The Schlenk tube was sealed and heated at 100 °C. After 3 h, the reaction mixture was cooled to room temperature and diluted with 3 mL of water. The resulting mixture was extracted with 3 × 3 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 the filtrate was concentrated *in vacuo*. Analysis of the resulting residue using ^1H NMR spectroscopy with CH_2Br_2 as the internal standard revealed 0.013 mmol of *o*-nitrostyrene **3.20a**, 0.018 mmol of *o*-nitrostyrene **3.22d**, 0.025 mmol of indole **3.21a**.

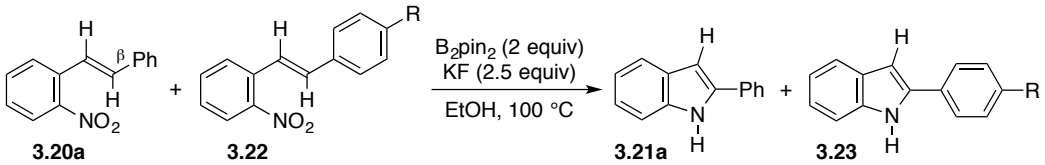


Table 3.5. ***Hammett Competition Experiment Summary.***

entry	log([**3.22**]/[**3.20a**])	R	σ_{para} [a]	σ_{meta} [a]	σ^+ [b]
1	–0.075	OMe	–0.27	0.12	–0.778
2	0.017	Me	–0.17	–0.07	–0.311
3	0.015	Cl	0.23	0.37	0.114
4	–0.051	CF_3	0.54	0.43	0.612

[a] σ_{para}- and σ_{meta}-values taken from ref. 26. [b] σ^+-values taken from ref. 27.

Figure 3.4 ***Hammett Correlation with σ_{para}-values.***

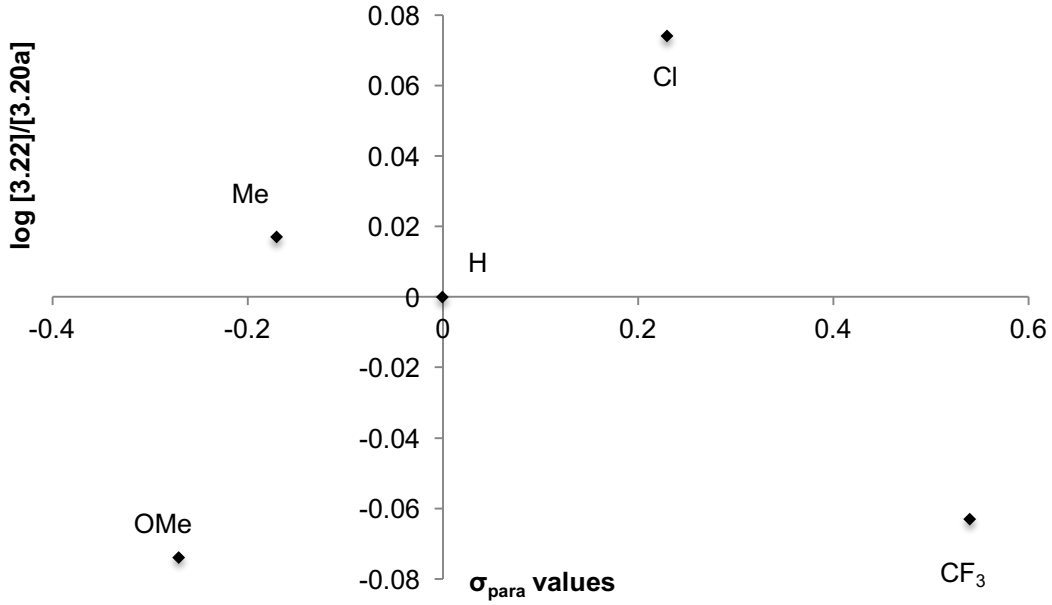


Figure 3.5 ***Hammett Correlation with σ_{meta}-values.***

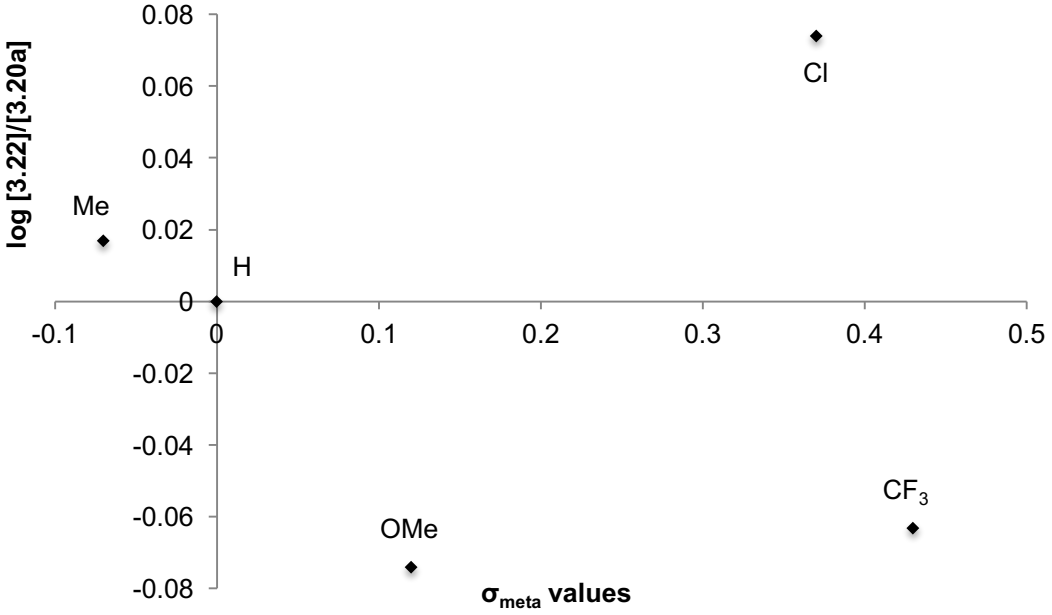
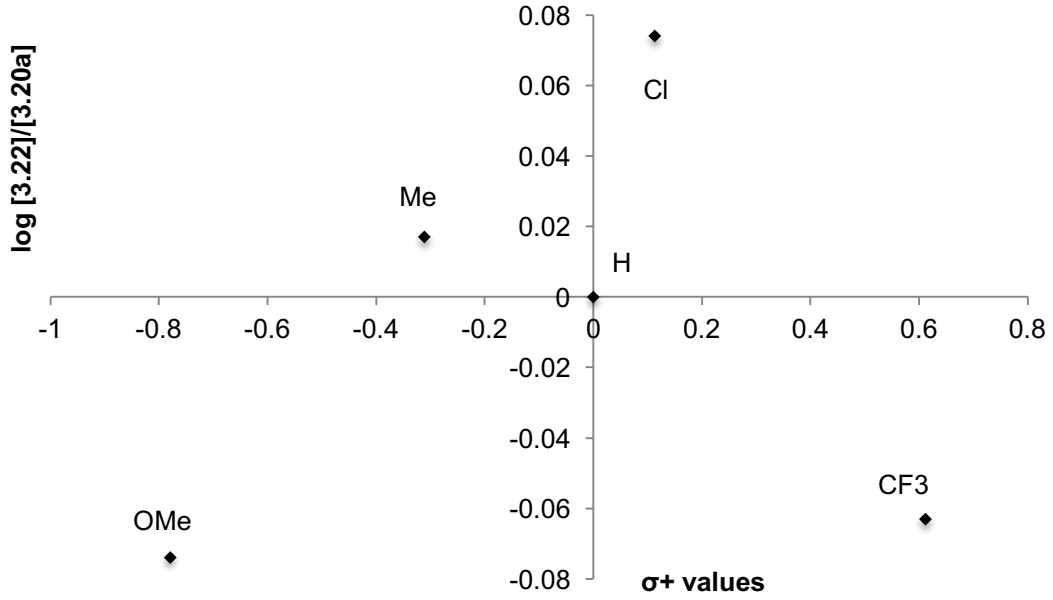
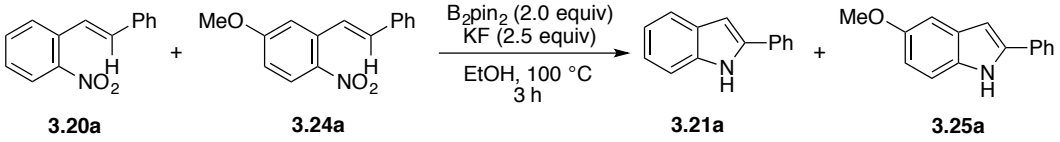


Figure 3.6 ***Hammett Correlation with σ^{+}-values.***

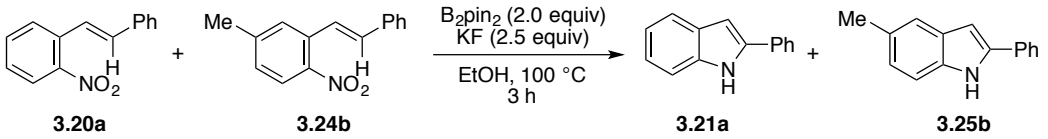


2. Hammett Competition Experiment—nitroarene.



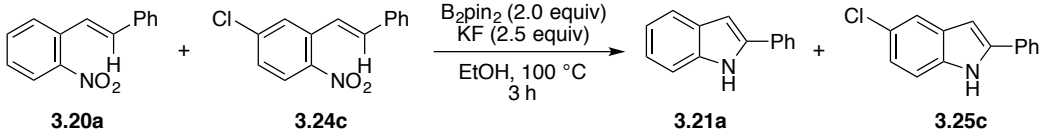
To a 10 mL Schlenk tube, under a nitrogen atmosphere, was added 0.0074 g of *o*-nitrostyrene **3.20a** (0.033 mmol), 0.0083 g of *o*-nitrostyrene **3.24a** (0.033 mmol), 0.034 g of bis(pinacolato)diboron (0.132 mmol), and 0.0097 g of potassium fluoride (0.167 mmol) in 0.66 mL of ethanol. The Schlenk tube was sealed and heated to 100 °C. After 3 h, the reaction mixture was cooled to room temperature and diluted with 3 mL of water. The resulting mixture was extracted with 3 × 3 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 the resulting filtrate was concentrated *in vacuo*. Analysis of the resulting residue using ^1H NMR spectroscopy with CH_2Br_2 as the internal standard

revealed 0.011 mmol of *o*-nitrostyrene **3.20a**, 0.022 mmol of *o*-nitrostyrene **3.24a**, 0.013 mmol of indole **3.21a** and 0.011 mmol of indole **3.25a**.



3.20a **3.24b** **3.21a** **3.25b**

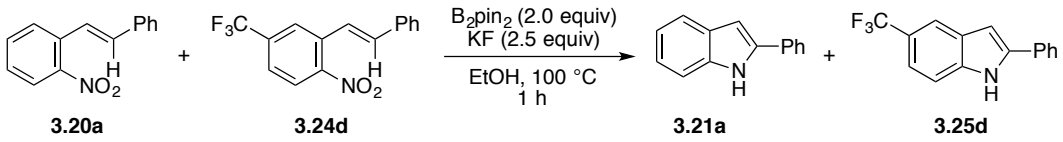
To a 10 mL Schlenk tube, under a nitrogen atmosphere, was added 0.0112 g of *o*-nitrostyrene **3.20a** (0.050 mmol), 0.0120 g of *o*-nitrostyrene **3.24b** (0.050 mmol), 0.051 g of bis(pinacolato)diboron (0.200 mmol), and 0.0145 g of potassium fluoride (0.25 mmol) in 1.00 mL of ethanol. The Schlenk tube was sealed and heated to 100 °C. After 3 h, the reaction mixture was cooled to room temperature and diluted with 3 mL of water. The resulting mixture was extracted with 3 × 3 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 the filtrate was concentrated *in vacuo*. Analysis of the resulting residue using ^1H NMR spectroscopy with CH_2Br_2 as the internal standard revealed 0.011 mmol of *o*-nitrostyrene **3.20a**, 0.022 mmol of *o*-nitrostyrene **3.24b**, 0.015 mmol of indole **3.21a** and 0.018 mmol of indole **3.25b**.



3.20a **3.24c** **3.21a** **3.25c**

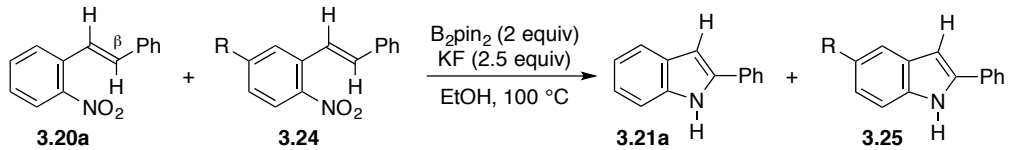
To a 10 mL Schlenk tube, under a nitrogen atmosphere, was added 0.0135 g of *o*-nitrostyrene **3.20a** (0.060 mmol), 0.0104 g of *o*-nitrostyrene **3.24c** (0.040 mmol), 0.051 g of bis(pinacolato)diboron (0.200 mmol), and 0.0145 g of potassium fluoride (0.25 mmol) in 1.00 mL of ethanol. The Schlenk tube was sealed and heated to 100 °C. After 3 h, the reaction mixture was cooled to room temperature and diluted with 3 mL of water. The resulting mixture was extracted with 3 × 3 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 the filtrate was concentrated *in vacuo*. Analysis of the resulting residue using ^1H NMR spectroscopy with CH_2Br_2 as the internal standard revealed 0.031 mmol of *o*-nitrostyrene **3.20a**, 0.011 mmol of *o*-nitrostyrene **3.24c**, 0.026 mmol of indole **3.21a** and 0.007 mmol of indole **3.25c**.



3.20a **3.24d** **3.21a** **3.25d**

To a 10 mL Schlenk tube, under a nitrogen atmosphere, was added 0.0112 g of *o*-nitrostyrene **3.20a** (0.050 mmol), 0.0147 g of *o*-nitrostyrene **3.24d** (0.050 mmol), 0.051 g of bis(pinacolato)diboron (0.200 mmol), and 0.0145 g of potassium fluoride (0.25 mmol) in 1.00 mL of ethanol. The Schlenk tube was sealed and heated to 100 °C. After 1 h, the reaction mixture was cooled to room temperature and diluted with 3 mL of water. The resulting mixture was extracted with 3 × 3 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 the filtrate was concentrated *in vacuo*. Analysis of the resulting residue using ^1H NMR spectroscopy with CH_2Br_2 as the internal standard revealed 0.037 mmol of *o*-nitrostyrene **3.20a**, 0.007 mmol of *o*-nitrostyrene **3.24d**, 0.012 mmol of indole **3.21a** and 0.031 mmol of indole **3.25d**.



3.20a **3.24** **3.21a** **3.25**

Table 3.6. ***Hammett Competition Experiment Summary.***

entry	log([**3.24**]/[**3.20a**])	R	σ_{para}	σ_{meta}	σ^+
1	–0.301	OMe	–0.27	0.12	–0.778

2	–0.144	Me	–0.17	–0.07	–0.311
3	0.176	Cl	0.23	0.37	0.114
4	0.520	CF_3	0.54	0.43	0.612

Figure 3.7 ***Hammett Correlation with σ_{para}-values.***

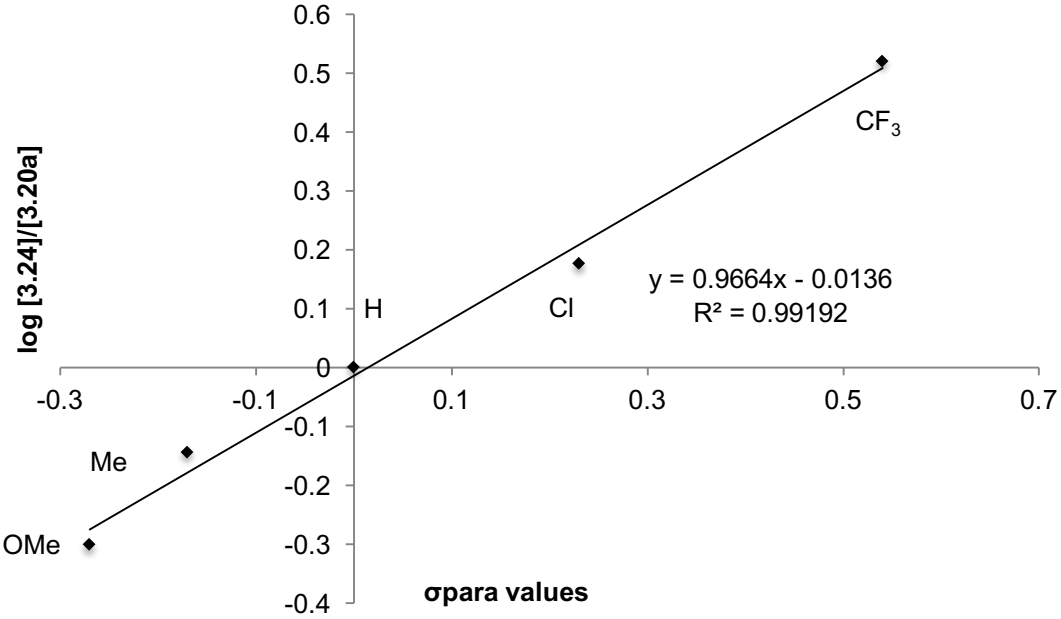


Figure 3.8 ***Hammett Correlation with σ_{meta}-values.***

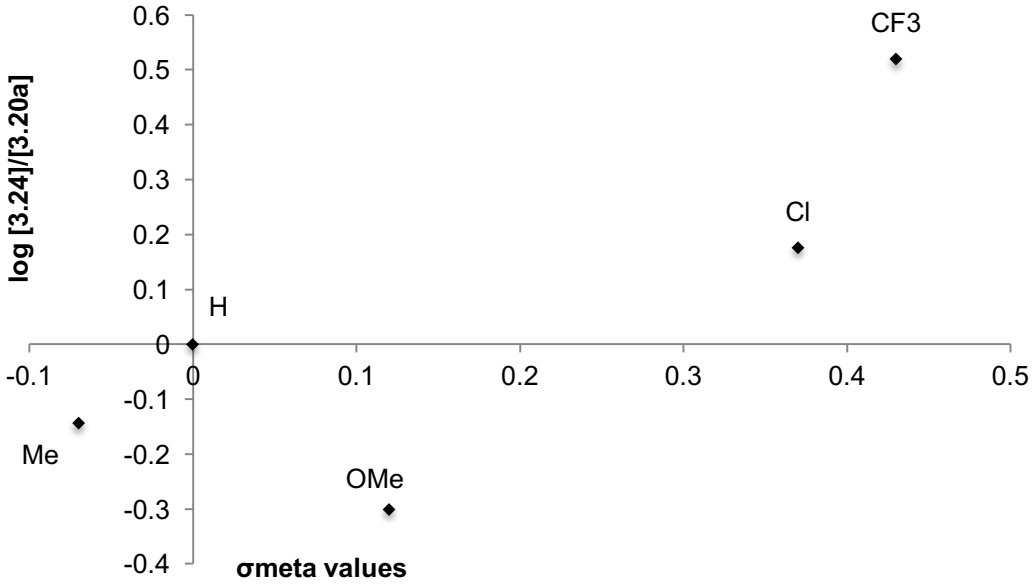
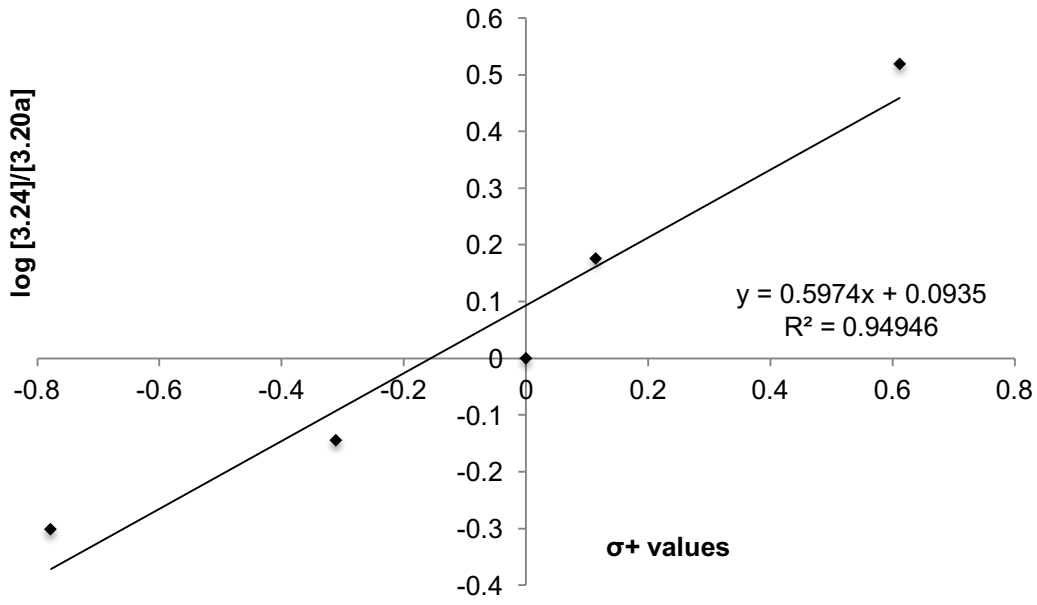
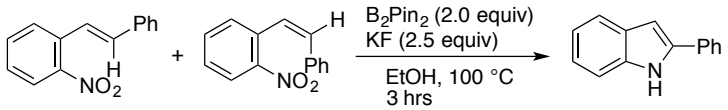


Figure 3.9 ***Hammett Correlation with σ^{+}-values.***

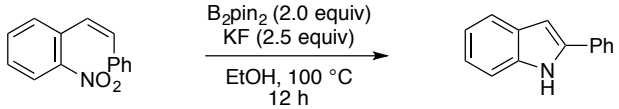


3. Investigation of the Reactivity of *Z*-*o*-Nitrostilbene.



***E*-3.20a** ***Z*-3.20a** **3.21a**

In a 10 mL Schlenk tube, under a nitrogen atmosphere, was added 0.0112 g of *o*-nitrostyrene ***E*-3.20a** (0.050 mmol), 0.0112 g of *o*-nitrostyrene ***Z*-3.20a** (0.050 mmol), 0.051 g of Bis(pinacolato)diboron (0.200 mmol), 0.0145 g of potassium fluoride (0.25 mmol) in 1.00 mL of ethanol. The Schlenk tube was sealed and heated at 100 °C for 3 hours. Then, the reaction mixture was cooled to room temperature and diluted with 3 mL of water. The solution was extracted with 3 × 3 mL of ethyl acetate. The combined organic phase was washed with 10 mL of brine. The resulting organic phase was dried over Na_2SO_4, filtered and was concentrated *in vacuo*. Analysis of the resulting residue using ^1H NMR spectroscopy with CH_2Br_2 as the internal standard revealed 0.014 mmol of *o*-nitrostyrene ***E*-3.20a**, 0.022 mmol of *o*-nitrostyrene ***Z*-3.20a**, 0.032 mmol of indole **3.21a**.

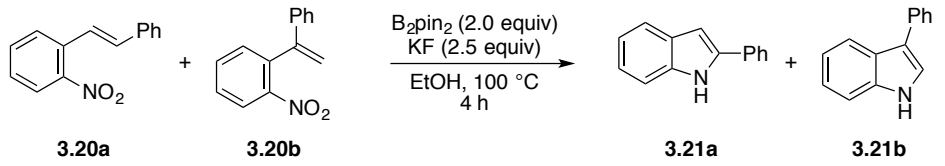


***Z*-3.20a** **3.21a**

To a 10 mL Schlenk tube, under a nitrogen atmosphere, was added 0.009 g of o-nitrostyrene ***Z*-3.20a** (0.040 mmol), 0.020 g of bis(pinacolato)diboron (0.080 mmol), and 0.006 g of potassium fluoride (0.100 mmol) in 0.40 mL of ethanol. The Schlenk tube was sealed and heated at 100 °C. After 12 hours, the reaction mixture was cooled to room temperature and diluted with 3 mL of water. The solution was extracted with 3 × 3 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 the filtrate was concentrated *in vacuo*. Analysis of the resulting residue using ^1H NMR spectroscopy

with CH_2Br_2 as the internal standard revealed 0.009 mmol of *o*-nitrostyrene ***Z*-3.20a** and 0.009 mmol of indole **3.21a**.

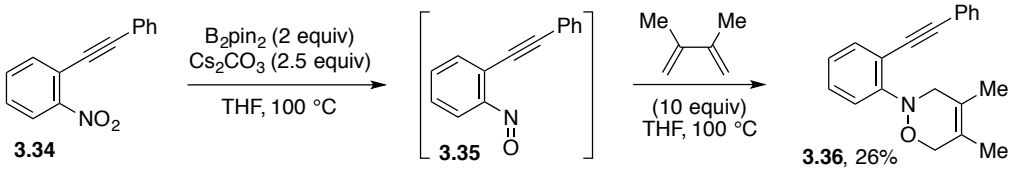
4. Competition Experiments.



3.20a **3.20b** **3.21a** **3.21b**

To a 10 mL Schlenk tube, under a nitrogen atmosphere, was added 0.0112 g of *o*-nitrostyrene **3.20a** (0.050 mmol), 0.0112 g of *o*-nitrostyrene **3.20b** (0.050 mmol), 0.051 g of bis(pinacolato)diboron (0.200 mmol), and 0.0145 g of potassium fluoride (0.25 mmol) in 1.00 mL of ethanol. The Schlenk tube was sealed and heated at 100 °C. After 4 hours, the reaction mixture was cooled to room temperature and diluted with 3 mL of water. The solution was extracted with 3 × 3 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 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 0.016 mmol of *o*-nitrostyrene **3.20a**, 0.030 mmol of *o*-nitrostyrene **3.20b**, 0.028 mmol of indole **3.21a** and 0.019 mmol of indole **3.21b**.

5. Trapping of Nitrosoarene with 2,3-dimethylbutadiene.

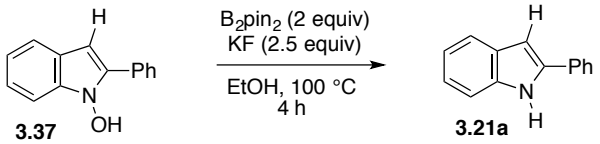


3.34 **3.35** **3.36**, 26%

To a 25 mL Schlenk tube, under a nitrogen atmosphere, was added 0.045 g of 1-nitro-2-(phenylethynyl)benzene (0.20 mmol) followed by 0.102 g of B_2pin_2 (0.400 mmol), 0.163 g of Cs_2CO_3 (0.50 mmol) in 3.0 mL of dry THF. The Schlenk tube was sealed and heated

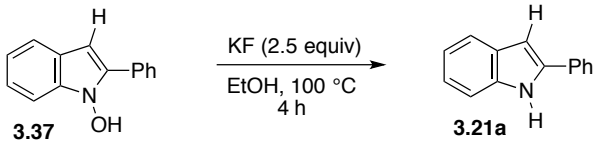
to 100 °C. After 12 h, the reaction mixture was cooled to room temperature and filtered through a plug of silica gel. The resulting filtrate was concentrated *in vacuo*. A portion of the resulting residue was submitted for HMRS analysis: HMRS (EI) calcd for $C_{14}H_9NO$: 207.0684, found 207.0688. The remainder of the residue was dissolved in 3.0 mL of dry THF and then transferred to a 25 mL Schlenk tube containing 2.00 mmol of 2,3-dimethylbutadiene. The Schlenk tube was sealed and heated to 100 °C. After 12 h, the reaction mixture was then cooled down to room temperature and filtered through a silica gel plug. The filtrate was then evaporated and the crude mixture was purified using silica gel chromatography (15:1 petroleum ether:EtOAc) to afford the product: 0.015 g of **3.36** as yellow oil (26%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (dd, J = 7.7, 0.5 Hz, 1H), 7.54 – 7.49 (m, 1H), 7.37 – 7.30 (m, 4H), 7.28 – 7.23 (m, 1H), 6.85 (d, J = 8.4 Hz, 1H), 6.75 – 6.71 (m, 1H), 4.00 (d, J = 16.8 Hz, 1H), 3.75 (d, J = 16.8 Hz, 1H), 2.86 (d, J = 16.7 Hz, 1H), 2.35 (dd, J = 16.7, 1.0 Hz, 1H), 1.69 (s, 3H), 1.59 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.5 (C), 137.5 (CH), 137.1 (C), 128.7 (CH), 127.6 (CH), 125.9 (CH), 125.8 (CH), 123.0 (C), 122.7 (C), 117.8 (C), 117.2 (CH), 108.4 (CH), 69.6 (C), 46.2 (CH_2), 35.8 (CH_2), 19.4 (CH_3), 15.9 (CH_3). HRMS (EI) m/z calcd for $C_{20}H_{19}NO$: 289.1467, found 289.1472.

6. Deoxygenation of *N*-Hydroxyindole 3.37.



To a 10 mL Schlenk tube, under a nitrogen atmosphere, was added 0.0063 g of 2-phenyl-1*H*-indol-1-ol **3.37** (0.030 mmol), 0.015 g of bis(pinacolato)diboron (0.060 mmol), and 0.0044 g of potassium fluoride (0.075 mmol) in 0.30 mL of ethanol. The Schlenk tube

was sealed and heated at 100 °C. After for 4 hours, the reaction mixture was cooled to room temperature and diluted with 3 mL of water. The solution was extracted with 3 × 3 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 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 0.029 mmol of indole **3.21a**.



3.37 **3.21a**

To a 10 mL Schlenk tube, under a nitrogen atmosphere, was added 0.0063 g of 2-phenyl-1*H*-1-ol **3.37** (0.030 mmol), and 0.0044 g of potassium fluoride (0.075 mmol) in 0.30 mL of ethanol. The Schlenk tube was sealed and heated at 100 °C. After 4 hours, the reaction mixture was cooled to room temperature and diluted with 3 mL of water. The solution was extracted with 3 × 3 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 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 0.005 mmol of indole **3.21a**.

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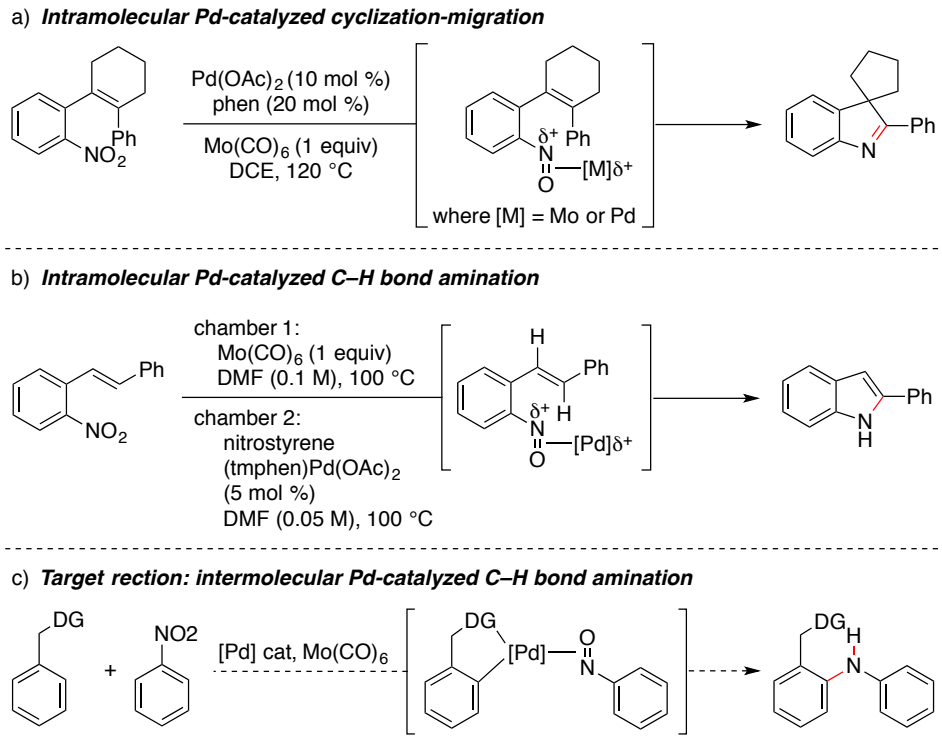
Chapter IV

Intermolecular Pd-catalyzed Aryl C–H bond Aminocarbonylation using Nitroarenes and $Mo(CO)_6$

In the first three chapters, I have talked about my investigations about the formation of *N*-hetercycles from aryl azide or nitroarene. In this chapter, my investigation into intermolecular C–H bond functionalization using nitroarenes will be discussed. Our investigations into the reactivity of nitroarenes towards $Mo(CO)_6$ and palladium catalyst[1,2] suggested that a nitrososarene was formed as a reactive intermediate in these reactions (Scheme 4.1a and 4.1b). Based on this assumption, I was curious if intermolecular C–H bond amination reactions could be achieved by taking advantage of the electrophilicity of the nitrosoarene intermediate.

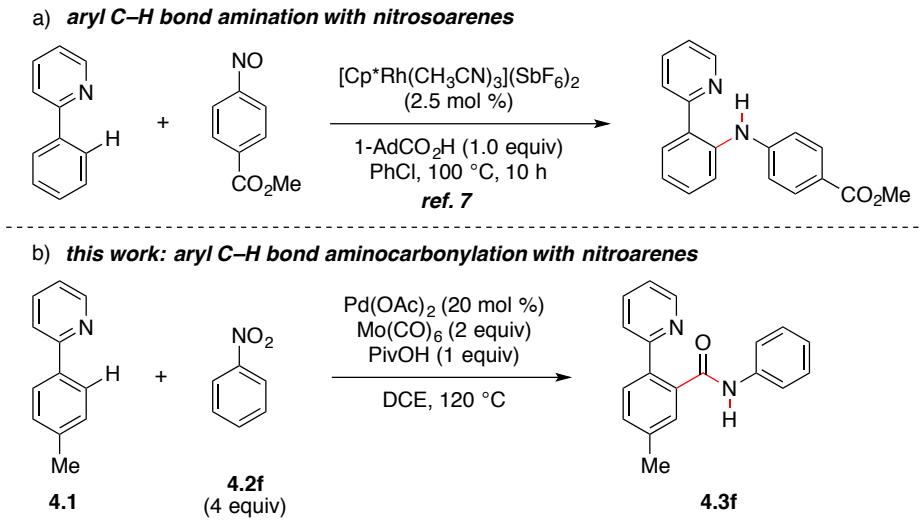
Scheme 4.1 ***Formation of the reactive nitrosoarene intermediate***



While the reactivity of nitrosoarene in the nitroso aldol reaction has been well studied,[3-5] the C–H bond functionalization process using nitrosoarene was rare. Recently, Li and co-workers reported a rhodium-catalyzed direct amination of arenes with nitrosobenzenes to form diarylamines (Scheme 4.2a).[6,7] This work inspired me that the same transformation may be achieved by replacing the reactive, hard to handle nitrosoarene might be replaced with a benchtop stable nitroarene using the conditions we developed to access 3*H*-indoles from trisubstituted nitrostyrenes. To test my idea, a mixture of 2-(*p*-tolyl)pyridine and nitrobenzene was exposed to pivalic acid, $Mo(CO)_6$ and palladium acetate (Scheme 4.2b). To my surprise, an amide produce was generated through the aminocarbonylation reaction. While the directed aryl C–H bond aminocarbonylation has been reported, pre-activated nitrogen atom sources, such as carbamoyl chloride,[8] isocynate,[9-12] acyl azide,[13,14] are required. Using nitro-substituted

arenes, however, provide a broader and easier accessibility to this transformation. Given the ubiquitous existence of amides in bioactive molecules and drugs, this aryl C–H bond aminocarbonylation with nitroarene represents a worthwhile pursuit.

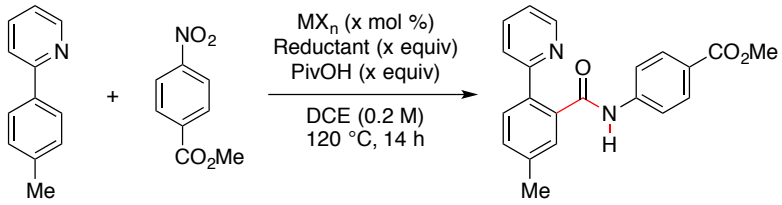
Scheme 4.2 ***Intermolecular C–H bond functionalization using nitroarenes.***



Development of the optimal conditions was performed by using 2-(*p*-tolyl)pyridine and methyl 4-nitrobenzoate as standard substrates (table 4.1). Only trace amount of product was observed in the absence of catalyst (entry 1). A series transition metal complexes were screened (entry 2 – 8) and only rhodium(III)- or rhodium(II) complexes gave a trace amount of desired product (entry 2 and 3). To our delight, palladium(II) salts and palladium(0) complexes were competent catalysts for this transformation (entries 9 – 12). Reaction with $Pd(dba)_2$ afforded product in the yield of 42% (entry 11). Among the several Pd(II) salts examined, palladium acetate gave the highest yield of 76%—*in the absence of an added ligand* (entry 9, 10, and 12). No reaction was observed using 1.5 atm of CO gas (entry 13). This result is consistent with

our previous mechanism study which indicated that $Mo(CO)_6$ serves as more than the source of CO in our reactions. While changing the pivalic acid to 1-adamantanecarboxylic acid impacted the yield only slightly (entry 14), the yield was reduced when no acid was added (entry 15). Further improvement was achieved by decreasing the amount of acid (entry 16). To our delight, either lower catalyst loading (entry 17 and 18) or performing the reaction under air atmosphere (entry 19) only gave a trivial attenuation of the yield.

Table 4.1 ***Development of Optimal Conditions.***



4.1 **4.2a** **4.3a**

entry	MX_n (mol%)	reductant (equiv)	additive (equiv)	**4.3a**, yield, %[a]
1[b]	N/A	$Mo(CO)_6$ (2.0 equiv)	PivOH (1.5 equiv)	5%
2[b]	$[Cp^*Rh(CH_3CN)_3](SbF_5)_2$ (10 mol%)	$Mo(CO)_6$ (2.0 equiv)	PivOH (1.5 equiv)	11%
3[b]	$Rh_2(esp)_2$ (10 mol%)	$Mo(CO)_6$ (2.0 equiv)	PivOH (1.5 equiv)	5%
4[b]	$[Ir(COD)Cl]_2$ (10 mol%)	$Mo(CO)_6$ (2.0 equiv)	PivOH (1.5 equiv)	n. r.[c]
5[b]	$Ni(COD)_2$ (20 mol%)	$Mo(CO)_6$ (2.0 equiv)	PivOH (1.5 equiv)	n. r.[c]
6[b]	$RuBr_3$ (20 mol%)	$Mo(CO)_6$ (2.0 equiv)	PivOH (1.5 equiv)	n. r.[c]
7[b]	$Cu(OAc)_2$ (20 mol%)	$Mo(CO)_6$ (2.0 equiv)	PivOH (1.5 equiv)	n. r.[c]
8[b]	$PtCl_2$ (10 mol%)	$Mo(CO)_6$ (2.0 equiv)	PivOH (1.5 equiv)	n. r.[c]

entry	MX_n (mol%)	reductant (equiv)	additive (equiv)	**4.3a**, yield, %[a]
9[b]	$PdCl_2$ (20 mol%)	$Mo(CO)_6$ (2.0 equiv)	PivOH (1.5 equiv)	26%
10[b]	$Pd(TFA)_2$ (20 mol%)	$Mo(CO)_6$ (2.0 equiv)	PivOH (1.5 equiv)	52%
11[b]	$Pd(dba)_2$ (20 mol%)	$Mo(CO)_6$ (2.0 equiv)	PivOH (1.5 equiv)	42%
12[b]	$Pd(OAc)_2$ (20 mol%)	$Mo(CO)_6$ (2.0 equiv)	PivOH (1.5 equiv)	76%
13[b]	$Pd(OAc)_2$ (20 mol%)	CO (1.5 atm)	PivOH (1.5 equiv)	n. r.[c]
14[b]	$Pd(OAc)_2$ (20 mol%)	$Mo(CO)_6$ (2.0 equiv)	1-AdCOOH (1.5 equiv)	74%
15[b]	$Pd(OAc)_2$ (20 mol%)	$Mo(CO)_6$ (2.0 equiv)	N/A	65%
16[b]	$Pd(OAc)_2$ (20 mol%)	$Mo(CO)_6$ (2.0 equiv)	PivOH (0.5 equiv)	82%
17[b]	$Pd(OAc)_2$ (10 mol%)	$Mo(CO)_6$ (2.0 equiv)	PivOH (0.5 equiv)	78%
18[b]	$Pd(OAc)_2$ (5 mol%)	$Mo(CO)_6$ (2.0 equiv)	PivOH (0.5 equiv)	74%
19[b,d]	$Pd(OAc)_2$ (10 mol%)	$Mo(CO)_6$ (2.0 equiv)	PivOH (0.5 equiv)	80%

[a] As determined using ^1H NMR spectroscopy using CH_2Br_2 as the internal standard. [b] 1.0 equiv of 2-(*p*-tolyl)pridine and 4.0 equiv of methyl 4-nitrobenzoate used. [c] no reaction. [d] This experiment was performed under air atmosphere.

Next, the scope and the limitation of this reaction were investigated with the help of my colleague, Dr. Duosheng Wang. First, using these optimal conditions, the effect of changing the nitroarene and directing group on the Pd-catalyzed aminocarbonylation reaction was examined (Table 4.2). We found that the electronic nature of the nitroarene did impact the success of the reaction. The higher yields were observed with electron-deficient R^1-substituents on the nitroarene (entries 1 and 2). Halogen-substituents—including bromide—were even tolerated without any competing dehalogenation

decomposition products (entries 3–5). While electron-neutral (entry 6) and weak electron-donating (entry 7) R^1-substituents only resulted a slight drop of the yields, a significant attenuation of the yield was observed when an electron-donating methoxy R^1-substituent was present (entry 8). Increasing the steric environment around the nitro-group by adding an R^2-methyl group inhibited the reaction (entry 9).

Table 4.2 ***Investigation of the effect of changing the nitroarene.***

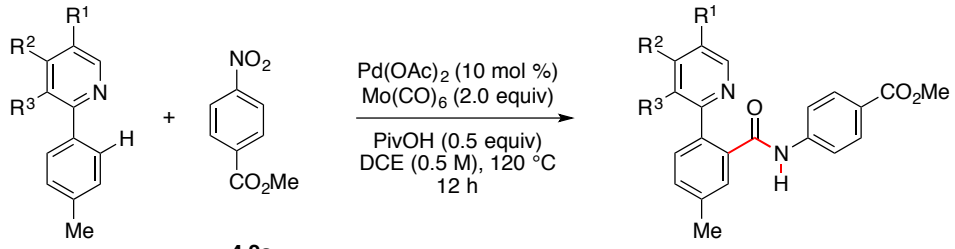
entry	#	R^1	R^2	**4.3**, yield, %[a]
1	a	CO_2Me	H	80
2	b	CF_3	H	70
3	c	Br	H	68
4	d	Cl	H	81
5	e	F	H	72
6	f	H	H	63
7	g	Me	H	66
8	h	OMe	H	30
9	i	H	Me	n. r.[b]

[a] Isolated after silica gel chromatography. [b] no reaction.

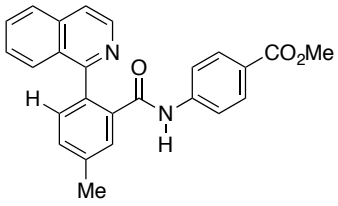
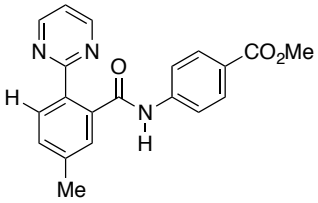
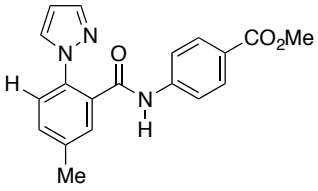
The reaction was much less sensitive to changes to the pyridine-directing group (Table 4.3). While no reaction was observed if a C6 substituent was present on the pyridine, adding substituents to the other positions did not have a negative impact on amide formation. An R^1-trifluoromethyl group attenuated the yield (entry 1); higher yields were obtained with R^1-methyl- or methoxy groups relative to the unsubstituted

pyridine (entries 2 and 3). Besides methyl R^2-subsituent (entry 4), electron-deficient trifluoromethyl R^2-substituent was also tolerated with 62% of yield (entry 5). Much to our surprise, adding an R^5-substituent did not negatively impact the reaction (entries 6–9). Both electron-deficient and electron-donating groups were tolerated with our reaction. In addition to these pyridines, other potential directing groups were examined. Using the optimal conditions, amide formation could not be triggered using oxazoline-, oxazole- or Yu's amide-directing groups. In contrast, aminocarbonylation was observed using quinoline-, pyridazine- and indazole as directing groups although the yield of **4.5** was diminished in comparison to pyridine (entries 10–12).

Table 4.3 ***Investigation of the effect of changing the pyridine group.***



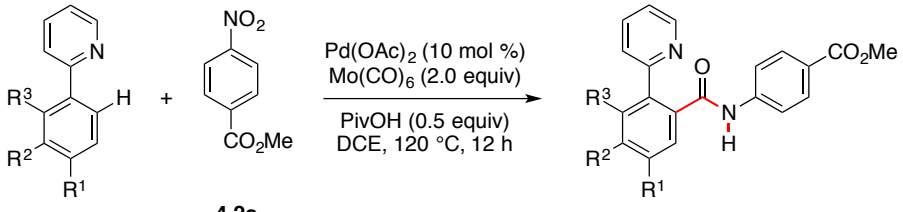
entry	#	R^1	R^2	R^3	**4.5**, yield, %[a]
1	a	CF_3	H	H	64
2	b	Me	H	H	89
3	c	OMe	H	H	84
4	d	H	CF_3	H	62
5	e	H	Me	H	89
6	f	H	H	CF_3	90
7	g	H	H	F	83
8	h	H	H	Me	90
9	i	H	H	OMe	65

entry	#	R^1	R^2	R^3	**4.5**, yield, %[a]
10	j				75
11	k				58
12	l				45

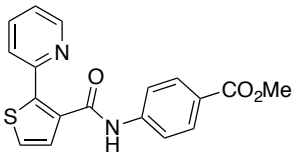
[a] Isolated after silica gel chromatography.

Next, the scope of the reaction was surveyed by varying the identity of the arene portion of the substrate (Table 4.4). While electron-deficient R^1-substituents also cause dimished yields in other pyridine-directed aryl C–H bond aminocarbonylation reactions, it completely inhibited our reaction.[8,9,13] The yield was largely unaffected by either electron-neutral (entry 1) or electron-donating R^1-substituents (entry 2–5). Notably, the thioether functionality, which is rarely tolerated in Pd-catalyzed processes, did not negatively impact the efficiency of our aminocarbonylation reaction (entry 3). A substrate bearing a hydroxyl group was effectively transformed into the amide product (entry 5). Both alkyl substituents (entry 6) and halogens—including bromide—were tolerated as R^2-substituents (entry 7 and 8). In contrast with pyridine portion which tolerated methyl substituent at C6 position, adding methyl group at *ortho*-position of the phenyl ring inhibited our reaction (entry 9). In contrast, aminocarbonylation could be achieved when the 2-phenyl ring was changed to an 2-thiophene (entry 10).

Table 4.4 ***Investigation of the effect of changing the phenyl group.***



4.6 **4.2a** (4 equiv) **4.7**

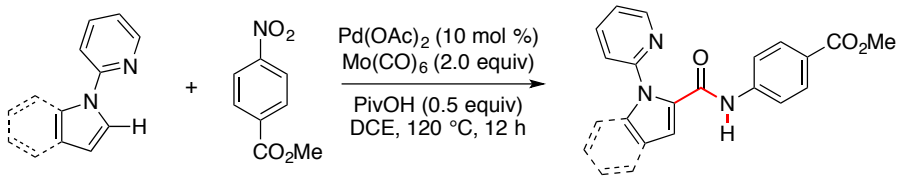
entry	#	R^1	R^2	R^3	**4.7**, yield, %[a]
1[b]	a	H	H	H	66
2[b]	b	OMe	H	H	62
3	c	SMe	H	H	69
4	d	NMe_2	H	H	46
5[b]	e	OH	H	H	55
6	f	H	Me	H	79
7	g	H	Br	H	51
8	h	H	Cl	H	50
9	i	H	H	Me	n. r.[c]
10	j				83

[a] Isolated after silica gel chromatography. [b] 1.0 equiv of pivalid acid added [c] no reaction.

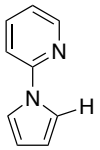
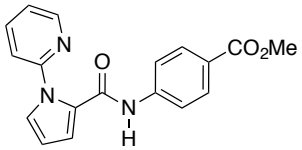
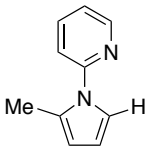
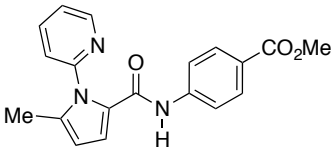
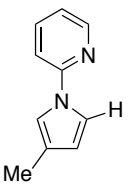
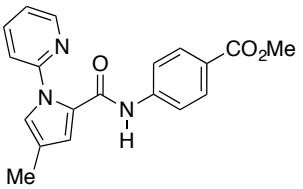
Finally, *N*-pyridyl-substituted heteroarenes were examined as potential substrates for the palladium-catalyzed aminocarbonylation because the pyridine could be easily removed[10,15,16] from the aminocarbonylation product (Table 4.5). To our delight, these *N*-heterocycles proved to be competent substrates in our transformation. In contrast with our results in C–H bond functionalization of a phenyl ring, the presence of an additional methyl substituent at the C2 position did not negatively impact the reaction (entry 2). To examine the regioselectivity, 3-methyl substituted substrate was submitted to the standard condition. The observation of only C5-aminocarbonylation product suggests that the

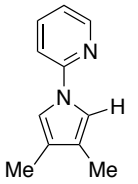
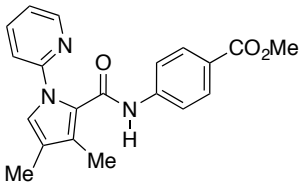
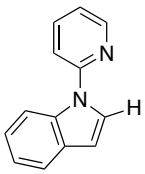
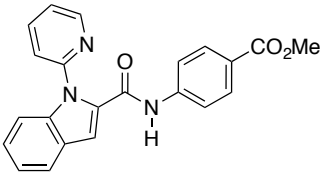
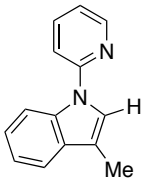
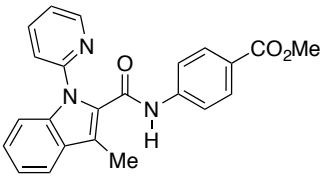
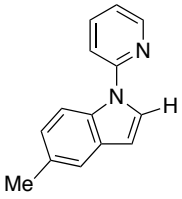
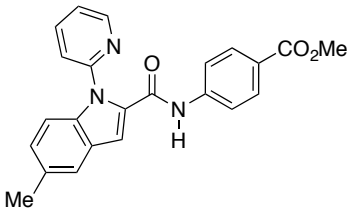
selectivity of our C–H bond functionalization can be controlled by steric interactions (entry 3). Further, the steric environment around the reaction center could be increased by adding an adjacent methyl substituent without adversely affecting the aminocarbonylation reaction (entry 4). Next, indole was examined with our aminocarbonylation reaction and aminocarbonylation only occurred at C2 position (entries 5–7). Installing methyl substituent to C3 (entry 6) or C5 (entry 7) position did not impact our reaction. To demonstrate that the pyridyl directing group could be easily removed, pyrrole **4.9a** was subjected to methyl triflate followed by sodium thiophenolate to produce pyrrole **4.10a** in 75% (eq 4.1).

Table 4.5 ***Investigation of N-heteroacenes.***

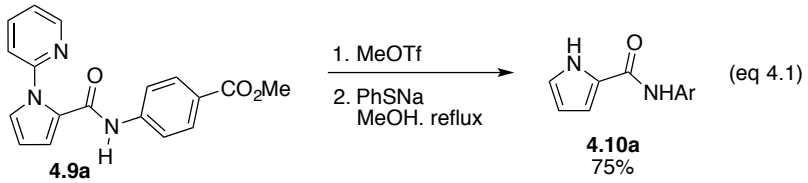


4.8 **4.2a** (4 equiv) **4.9**

entry	#	**4.8**	**4.9**	**4.9**, yield, %[a]
1	a			58
2	b			70
3	c			61

entry	#	**4.8**	**4.9**	**4.9**, yield, %[a]
4	d			60
5	e			62
6	f			91
7	g			62

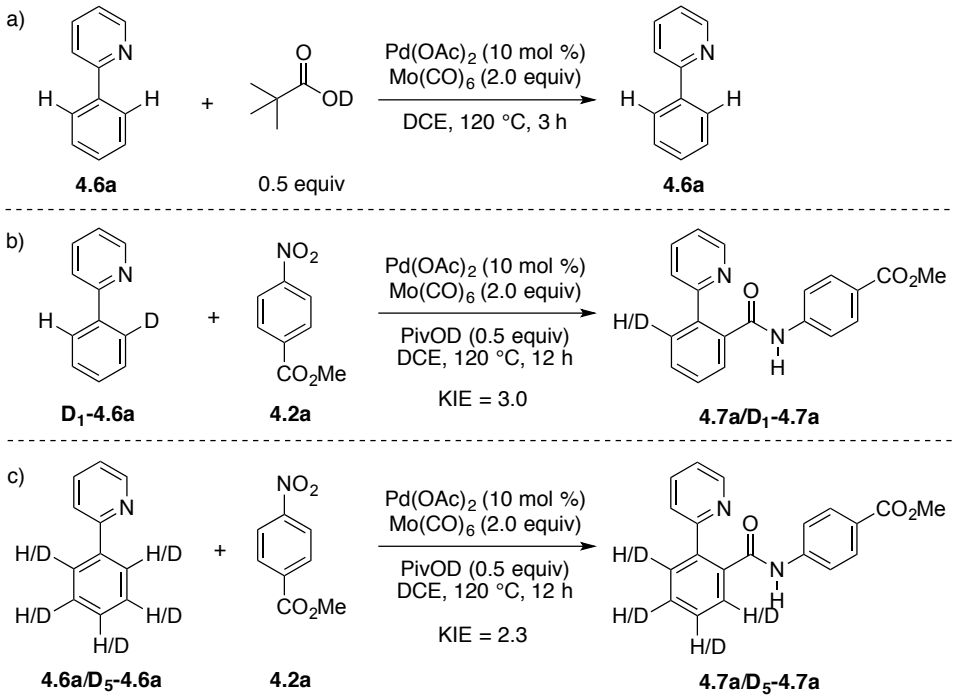
[a] Isolated after silica gel chromatography.



Several experiments were performed to provide insight into the mechanism of the transformation. To study the C–H activation step, we performed the aminocarbonylation reaction with isotopically-labeled additives and substrates (Scheme 4.3). First, pivalic acid-d_1 was used in the absence of the nitroarene (Scheme 4.3a), and no deuterium was exchanged into the 2-phenyl pyridine substrate (Scheme 4.3a). A primary kinetic isotope effect (KIE) of 3 was measured when 2-phenyl pyridine-d_1 was submitted to the reaction (Scheme 4.3b). Third, an intermolecular competition experiment between 2-phenylpyridine-d_0 and 2-phenylpyridine-d_5 exhibited a KIE of 2.3 (Scheme 4.3c).

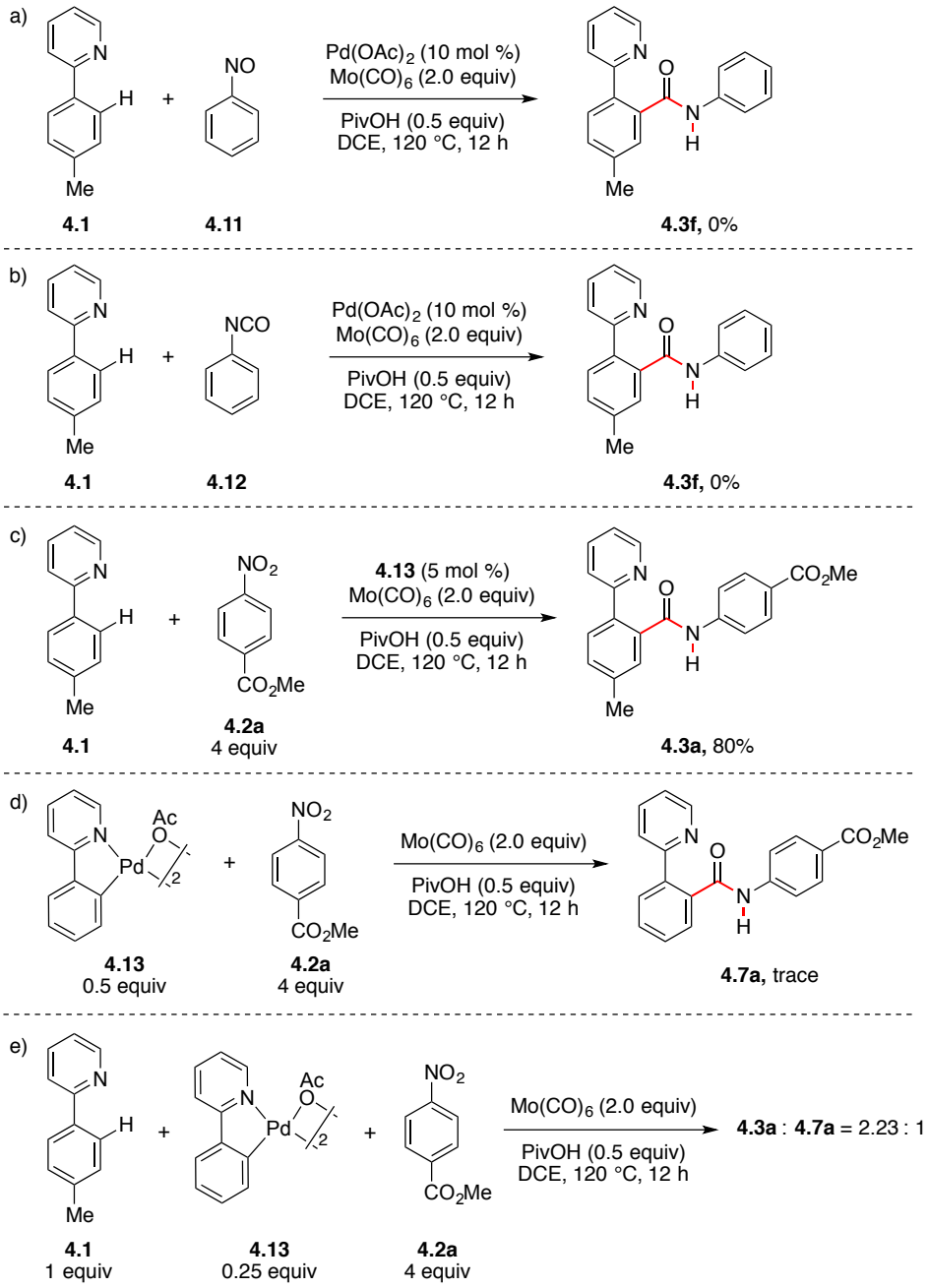
Together with the intramolecular competition experiment, this suggests that the C–H bond activation step is both the product determining- and the turnover-limiting step.

Scheme 4.3 ***Studies with isotope-labeled stubstrates***



To gain more insight into the identity of the nitrogen reactive intermediate, more control experiments were performed (Scheme 4.4). For the aminocarbonylation to be successful, we thought that either a nitrosoarene or an isocyanate might be formed from the reaction of $Mo(CO)_6$ with the nitroarene. To test these hypotheses, we replaced the nitroarene with nitrosobenzene **4.11** (Scheme 4.4a) or isocyanatobenzene **4.12** (Scheme 4.4b). No amide product, however, was observed from these two reactions. We interpret these results to suggest that their concentrations do not build up over the course of the reaction.

Scheme 4.4 ***Mechanistic studies***

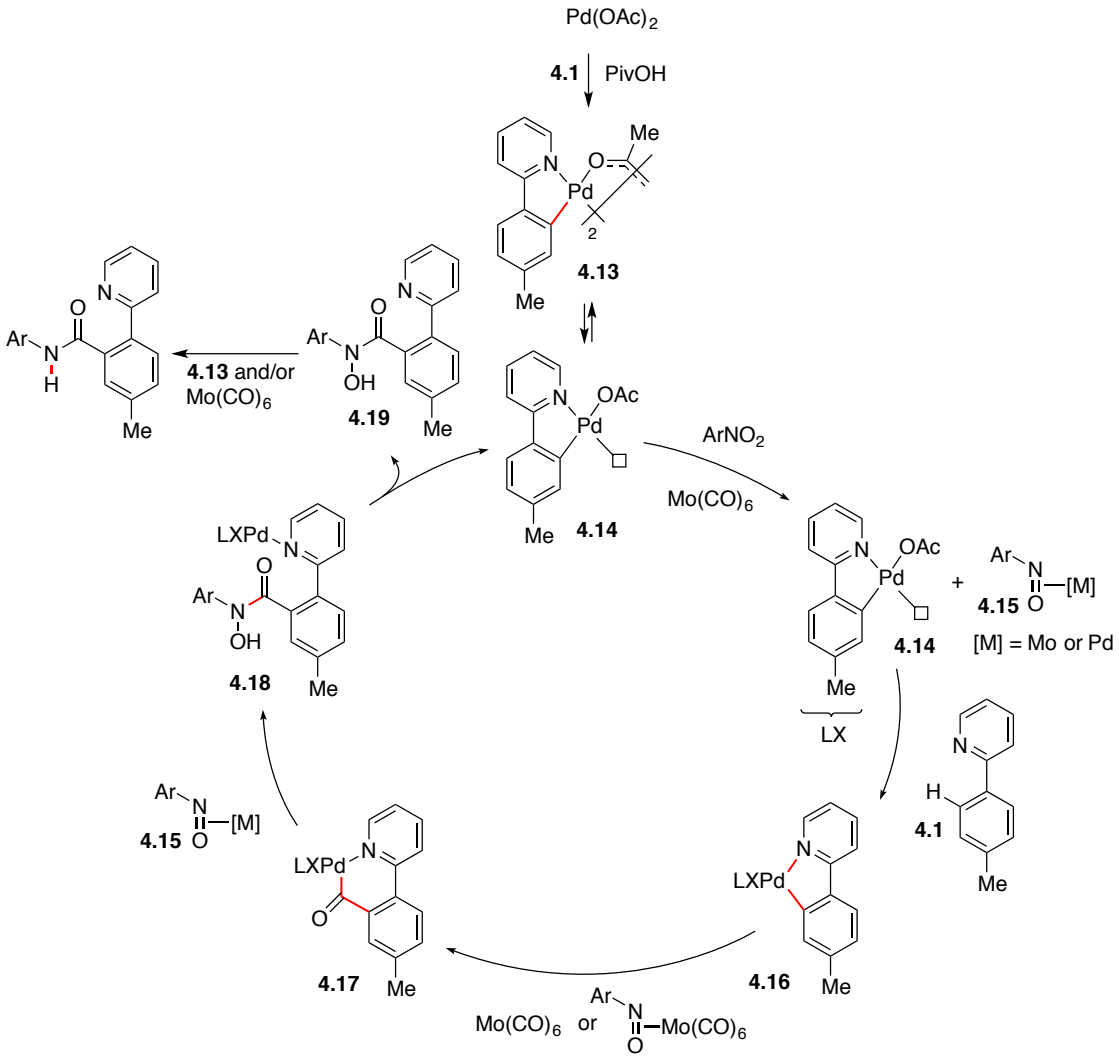


Next, several experiments were performed to determine the identity of the palladium catalyst in the aminocarbonylation reaction (Scheme 4.5). First, palladacycle

4.13 was prepared by Dr. Duosheng Wang following the report by Shen and co-workers.[17] With the palladacycle in hand, its reactivity was examined. First, we found palladacycle **4.13** to be a competent catalyst: 5mol % of **4.13** effectively catalyzed aminocarbonylation to produce **4.3a** in 80% (scheme 4.4d). However, a stoichiometric amount of **4.13** was submitted to the reaction conditions (Scheme 4.4d) and only trace amount of **4.7a** was found. While no aminocarbonylation product was observed, the palladacycle did reduce the nitroarene to hydrazine. Adding 1 equiv of 2-(*p*-tolyl)pyridine to the reaction with **4.13** turned on the formation of **4.7a**. Together with previous result, this finding suggests that the 2-arylpyridine serves as the ligand in addition to the substrate and that the catalytic cycle involves formation on an intermediate in which more than one 2-arylpyridine is attached to palladium.

A mechanism was proposed based on these results (Scheme 4.5). Palladium acetate reacted with 2-(*p*-tolyl)pyridine **4.1** to generate palladacycle **4.14**, which would reduce nitroarene to nitrosoarene. Then **4.14** would then trigger a C–H bond activation with a second 2-(*p*-tolyl)pyridine to produce **4.16**. Carbonyl insertion into palladium–carbon bond then forms **4.17**. While the exact details of C–N bond formation currently remain murky, its generation may benefit from the coordination between palladium and nitrosoarene. Dissociation of palladium would deliver hydroxyl amide **4.19** and regenerate palladacycle **4.14**. Further reduction of **4.19** with $Mo(CO)_6$ would afford the amide product.

Scheme 4.5 ***Possible Mechanism for Amide Formation*****.**



In conclusion, a new method of intermolecular Pd-catalyzed aryl C–H bond aminocarbonylation using nitroarenes and $Mo(CO)_6$ was developed. A wide substrate scope was explored including *N*-heterarenes in which pyridyl directing group could be readily removed. A series of control experiments were performed to provide insight into the mechanism. Further investigation will focus on the detailed mechanistic study.

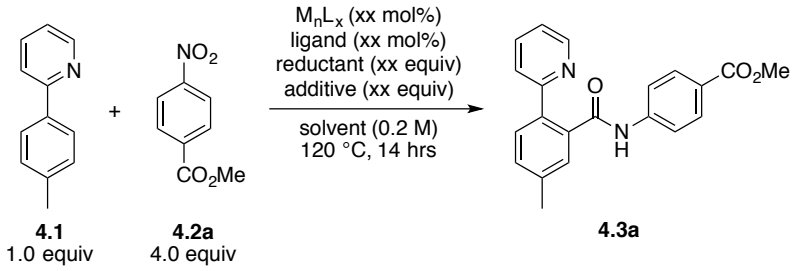
Experiment

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. Pd-catalyzed Directed C–H Amidation

1. Screening of Reaction Conditions.



General Method: Under a nitrogen atmosphere, a 10 mL Schlenk tube was charged with 0.40 mmol of methyl 4-nitrobenzoate **4.2a**, catalyst, ligand and reductant. Then a solution of 0.10 mmol of 2-(*p*-tolyl)pyridine **4.1** and additive in 0.5 mL of solvent was added to the Schlenk tube. The Schlenk tube was sealed. The reaction mixture was stirred at ambient temperature for 30 minutes and heated at 120 °C for 14 hours. 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.

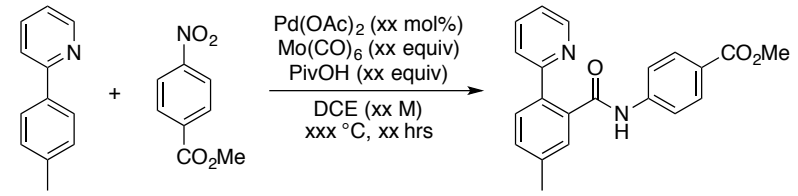
Table 4.6 ***Screen of Catalyst, Ligand, Reductant, Additive and Solvent.***

entry	catalyst (mol%)	ligand (mol%)	reductant (equiv)	additive (equiv)	solvent (mL)	**4.3a**, yield, %[a]
1	N/A	N/A	$Mo(CO)_6$ (2.0 equiv)	PivOH (1.5 equiv)	DCE (0.5 mL)	5%
2	$Ni(COD)_2$ (20 mol%)	N/A	$Mo(CO)_6$ (2.0 equiv)	PivOH (1.5 equiv)	DCE (0.5 mL)	n. r.[b]
3	NiI_2 (20 mol%)	N/A	$Mo(CO)_6$ (2.0 equiv)	PivOH (1.5 equiv)	DCE (0.5 mL)	n. r.[b]
4	$[Rh(COD)_2](BF_4)$ (10 mol%)	N/A	$Mo(CO)_6$ (2.0 equiv)	PivOH (1.5 equiv)	DCE (0.5 mL)	decomp[c]
5	$Rh_2(esp)_2$ (10 mol%)	N/A	$Mo(CO)_6$ (2.0 equiv)	PivOH (1.5 equiv)	DCE (0.5 mL)	11%
6	$[Cp^*Rh(CH_3CN)_3](SbF_5)_2$ (10 mol%)	N/A	$Mo(CO)_6$ (2.0 equiv)	PivOH (1.5 equiv)	DCE (0.5 mL)	< 5%
7	$[Ir(COD)Cl]_2$ (10 mol%)	N/A	$Mo(CO)_6$ (2.0 equiv)	PivOH (1.5 equiv)	DCE (0.5 mL)	n. r.[b]

entry	catalyst (mol%)	ligand (mol%)	reductant (equiv)	additive (equiv)	solvent (mL)	**4.3a**, yield, %[a]
8	$RuBr_3$ (20 mol%)	N/A	$Mo(CO)_6$ (2.0 equiv)	PivOH (1.5 equiv)	DCE (0.5 mL)	n. r.[b]
9	$Cu(OAc)_2$ (20 mol%)	N/A	$Mo(CO)_6$ (2.0 equiv)	PivOH (1.5 equiv)	DCE (0.5 mL)	n. r.[b]
10	$PtCl_2$ (10 mol%)	N/A	$Mo(CO)_6$ (2.0 equiv)	PivOH (1.5 equiv)	DCE (0.5 mL)	n. r.[b]
11	$PdCl_2$ (20 mol%)	N/A	$Mo(CO)_6$ (2.0 equiv)	PivOH (1.5 equiv)	DCE (0.5 mL)	26%
12	$PdCl_2(PPh_3)_2$ (20 mol%)	N/A	$Mo(CO)_6$ (2.0 equiv)	PivOH (1.5 equiv)	DCE (0.5 mL)	6%
13	$Pd(TFA)_2$ (20 mol%)	N/A	$Mo(CO)_6$ (2.0 equiv)	PivOH (1.5 equiv)	DCE (0.5 mL)	52%
14	$Pd(dba)_2$ (20 mol%)	N/A	$Mo(CO)_6$ (2.0 equiv)	PivOH (1.5 equiv)	DCE (0.5 mL)	42%
15	$Pd_2(dba)_3$ (20 mol%)	N/A	$Mo(CO)_6$ (2.0 equiv)	PivOH (1.5 equiv)	DCE (0.5 mL)	38%
16	$Pd(OAc)_2$ (20 mol%)	N/A	$Mo(CO)_6$ (2.0 equiv)	PivOH (1.5 equiv)	DCE (0.5 mL)	76%
17	$Pd(OAc)_2$ (20 mol%)	phen (20 mol%)	$Mo(CO)_6$ (2.0 equiv)	PivOH (1.5 equiv)	DCE (0.5 mL)	12%
18	$Pd(OAc)_2$ (20 mol%)	DPPE (20 mol%)	$Mo(CO)_6$ (2.0 equiv)	PivOH (1.5 equiv)	DCE (0.5 mL)	24%
19	$Pd(OAc)_2$ (20 mol%)	PPh_3 (20 mol%)	$Mo(CO)_6$ (2.0 equiv)	PivOH (1.5 equiv)	DCE (0.5 mL)	36%
20	$Pd(OAc)_2$ (20 mol%)	Pyridine (20 mol%)	$Mo(CO)_6$ (2.0 equiv)	PivOH (1.5 equiv)	DCE (0.5 mL)	18%
21	$Pd(OAc)_2$ (20 mol%)	N/A	CO (1.5 atm)	PivOH (1.5 equiv)	DMF (0.5 mL)	n. r.[b]
22	$Pd(OAc)_2$ (20 mol%)	N/A	$Cr(CO)_6$ (2.0 equiv)	PivOH (1.5 equiv)	DCE (0.5 mL)	< 5%
23	$Pd(OAc)_2$ (20 mol%)	N/A	$W(CO)_6$ (2.0 equiv)	PivOH (1.5 equiv)	DCE (0.5 mL)	24%
24	$Pd(OAc)_2$ (20 mol%)	N/A	$Mo(CO)_6$ (2.0 equiv)	PivOH (1.5 equiv)	Toluene (0.5 mL)	31%
25	$Pd(OAc)_2$ (20 mol%)	N/A	$Mo(CO)_6$ (2.0 equiv)	PivOH (1.5 equiv)	DMF (0.5 mL)	14%
26	$Pd(OAc)_2$ (20 mol%)	N/A	$Mo(CO)_6$ (2.0 equiv)	PivOH (1.5 equiv)	PhCl (0.5 mL)	36%

entry	catalyst (mol%)	ligand (mol%)	reductant (equiv)	additive (equiv)	solvent (mL)	**4.3a**, yield, %[a]
27	$Pd(OAc)_2$ (20 mol%)	N/A	$Mo(CO)_6$ (2.0 equiv)	PivOH (1.5 equiv)	dioxane (0.5 mL)	52%
28	$Pd(OAc)_2$ (20 mol%)	N/A	$Mo(CO)_6$ (2.0 equiv)	PivOH (1.5 equiv)	C_6F_6 (0.5 mL)	15%
29	$Pd(OAc)_2$ (20 mol%)	N/A	$Mo(CO)_6$ (2.0 equiv)	1-AdCOOH (1.5 equiv)	DCE (0.5 mL)	74%
30	$Pd(OAc)_2$ (20 mol%)	N/A	$Mo(CO)_6$ (2.0 equiv)	AcOH (1.5 equiv)	DCE (0.5 mL)	43%
31	$Pd(OAc)_2$ (20 mol%)	N/A	$Mo(CO)_6$ (2.0 equiv)	CF_3COOH (1.5 equiv)	DCE (0.5 mL)	48%
32	$Pd(OAc)_2$ (20 mol%)	N/A	$Mo(CO)_6$ (2.0 equiv)	H_2O (1.5 equiv)	DCE (0.5 mL)	10%
33	$Pd(OAc)_2$ (20 mol%)	N/A	$Mo(CO)_6$ (2.0 equiv)	N/A	DCE (0.5 mL)	65%
34	$Pd(OAc)_2$ (20 mol%)	N/A	$Mo(CO)_6$ (2.0 equiv)	K_2CO_3 (2.0 equiv)	DCE (0.5 mL)	11%
35	$Pd(OAc)_2$ (20 mol%)	N/A	$Mo(CO)_6$ (2.0 equiv)	PivOH (1.5 equiv) + K_2CO_3 (2.0 equiv)	DCE (0.5 mL)	18%
36	$Pd(OAc)_2$ (20 mol%)	N/A	$Mo(CO)_6$ (2.0 equiv)	PivOH (1.5 equiv) + AgOAc (1.0 equiv)	DCE (0.5 mL)	55%
37	$Pd(OAc)_2$ (20 mol%)	N/A	$Mo(CO)_6$ (2.0 equiv)	PivOH (1.5 equiv) + $Cu(OAc)_2$ (1.0 equiv)	DCE (0.5 mL)	56%
38	$Pd(OAc)_2$ (20 mol%)	N/A	$Mo(CO)_6$ (2.0 equiv)	PivOH (1.5 equiv) + BQ (1.0 equiv)	DCE (0.5 mL)	35%

[a] As determined using ^1H NMR spectroscopy using CH_2Br_2 as the internal standard. [b] No reaction. [c] Decomposition.



4.1 1.0 equiv + **4.2a** xx equiv → **4.3a**

General Method: A 10 mL Schlenk tube was charged with methyl 4-nitrobenzoate **4.1**, palladium acetate, molybdenumhexacarbonyl. Then a solution of 0.1 mmol of 2-(*p*-tolyl)pyridine **4.2a** and 2,2-dimethylpropionic acid in DCE was added to the Schlenk tube. The Schlenk tube was sealed, stirred at ambient temperature for 30 minute and then 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.

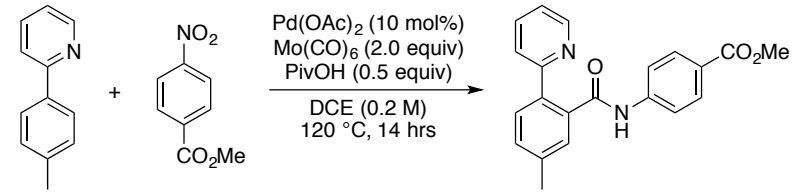
Table 4.7 ***Development of Optimized Condition.***

entry	**4.2a** (equiv)	catalyst (mol%)	reductant (equiv)	additive (equiv)	solvent (mL)	T (°C)	Time (hrs)	**4.3a**, yield, %[a]
1	4.0 equiv	$Pd(OAc)_2$ (20 mol%)	$Mo(CO)_6$ (2.0 equiv)	PivOH (1.5 equiv)	DCE (0.5 mL)	120 °C	14 hrs	76%
2	4.0 equiv	$Pd(OAc)_2$ (20 mol%)	$Mo(CO)_6$ (2.0 equiv)	PivOH (1.5 equiv)	DCE (1.0 mL)	120 °C	14 hrs	57%
3	4.0 equiv	$Pd(OAc)_2$ (20 mol%)	$Mo(CO)_6$ (2.0 equiv)	PivOH (1.5 equiv)	DCE (0.5 mL)	100 °C	14 hrs	27%
4	4.0 equiv	$Pd(OAc)_2$ (20 mol%)	$Mo(CO)_6$ (2.0 equiv)	PivOH (1.5 equiv)	DCE (0.5 mL)	140 °C	14 hrs	31%
5	4.0 equiv	$Pd(OAc)_2$ (20 mol%)	$Mo(CO)_6$ (2.0 equiv)	PivOH (1.5 equiv)	DCE (0.5 mL)	120 °C	12 hrs	63%
6	4.0 equiv	$Pd(OAc)_2$ (20 mol%)	$Mo(CO)_6$ (2.0 equiv)	PivOH (1.5 equiv)	DCE (0.5 mL)	120 °C	16 hrs	68%
7	4.0 equiv	$Pd(OAc)_2$ (20 mol%)	$Mo(CO)_6$ (2.0 equiv)	PivOH (0.2 equiv)	DCE (0.5 mL)	120 °C	14 hrs	78%
8	4.0 equiv	$Pd(OAc)_2$ (20 mol%)	$Mo(CO)_6$ (2.0 equiv)	PivOH (0.5 equiv)	DCE (0.5 mL)	120 °C	14 hrs	82%

entry	**4.2a** (equiv)	catalyst (mol%)	reductant (equiv)	additive (equiv)	solvent (mL)	T (°C)	Time (hrs)	**4.3a**, yield, %[a]
9	4.0 equiv	$Pd(OAc)_2$ (20 mol%)	$Mo(CO)_6$ (2.0 equiv)	PivOH (1.0 equiv)	DCE (0.5 mL)	120 °C	14 hrs	78%
10	4.0 equiv	$Pd(OAc)_2$ (20 mol%)	$Mo(CO)_6$ (2.0 equiv)	PivOH (2.5 equiv)	DCE (0.5 mL)	120 °C	14 hrs	45%
11	4.0 equiv	$Pd(OAc)_2$ (20 mol%)	$Mo(CO)_6$ (2.0 equiv)	PivOH (5.0 equiv)	DCE (0.5 mL)	120 °C	14 hrs	55%
12	4.0 equiv	$Pd(OAc)_2$ (20 mol%)	$Mo(CO)_6$ (1.0 equiv)	PivOH (0.5 equiv)	DCE (0.5 mL)	120 °C	14 hrs	44%
13	4.0 equiv	$Pd(OAc)_2$ (20 mol%)	$Mo(CO)_6$ (3.0 equiv)	PivOH (0.5 equiv)	DCE (0.5 mL)	120 °C	14 hrs	44%
14	3.0 equiv	$Pd(OAc)_2$ (20 mol%)	$Mo(CO)_6$ (2.0 equiv)	PivOH (0.5 equiv)	DCE (0.5 mL)	120 °C	14 hrs	79%
15	3.0 equiv	$Pd(OAc)_2$ (10 mol%)	$Mo(CO)_6$ (2.0 equiv)	PivOH (0.5 equiv)	DCE (0.5 mL)	120 °C	14 hrs	65%
16	4.0 equiv	$Pd(OAc)_2$ (10 mol%)	$Mo(CO)_6$ (2.0 equiv)	PivOH (0.5 equiv)	DCE (0.5 mL)	120 °C	14 hrs	78%
17[b]	4.0 equiv	$Pd(OAc)_2$ (10 mol%)	$Mo(CO)_6$ (2.0 equiv)	PivOH (0.5 equiv)	DCE (0.5 mL)	120 °C	14 hrs	80%
18	4.0 equiv	$Pd(OAc)_2$ (5 mol%)	$Mo(CO)_6$ (2.0 equiv)	PivOH (0.5 equiv)	DCE (0.5 mL)	120 °C	14 hrs	74%
19[b]	4.0 equiv	$Pd(OAc)_2$ (5 mol%)	$Mo(CO)_6$ (2.0 equiv)	PivOH (0.5 equiv)	DCE (0.5 mL)	120 °C	14 hrs	74%

[a] As determined using ^{1}H NMR spectroscopy using CH_2Br_2 as the internal standard. [b] The experiment was performed under air atmosphere.

2. Optimized Conditions.

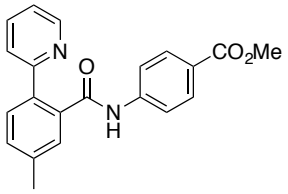


4.1 1.0 equiv **4.2a** 4.0 equiv **4.3a**

General Method: A 10 mL Schlenk tube was charged with methyl 4-nitrobenzoate **4.1** (0.4 mmol), palladium acetate (0.01 mmol), molybdenumhexacarbonyl (0.2 mmol). Then 0.4 mL of solution of 2-(*p*-tolyl)pyridine **4.2a** (0.1 mmol) in DCE (0.25M), and 0.1 mL

of solution of 2,2-dimethylpropionic acid (0.05 mmol) in DCE (0.50 M) were added to the Schlenk tube. The Schlenk tube was sealed, stirred at ambient temperature for 5 to 7 minutes and heated at 120 °C for 14 hours. The entire procedure was performed under air atmosphere. 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 crude mixture was purified by MPLC (3:97 – 35:65 EtOAc:hexane) to afford the product.

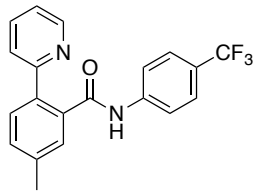
3. Characterization Data.



4.3a

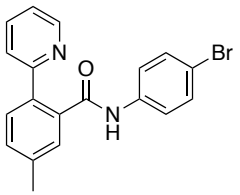
Amide (4.3a). The general method was followed adding 0.0169 g of 2-(*p*-tolyl)pyridine **4.1** (0.10 mmol), 0.072 g of methyl 4-nitrobenzoate (0.40 mmol), 0.052 g of molybdenumhexacarbonyl (0.2 mmol), 0.0051 g of 2,2-dimethylpropionic acid (0.05 mmol), 0.0023 g of $Pd(OAc)_2$ (0.01 mmol) and 0.5 mL of DCE. Purification via MPLC (0:100 – 35:65 EtOAc:hexanes) afforded **4.3a** as a white solid (0.0275 g, 80%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.63 (b, 1H), 8.58 (d, J = 4.5 Hz, 1H), 7.88 (d, J = 8.5 Hz, 2H), 7.73 (td, J = 8.0, 1.0 Hz, 1H), 7.53 (b, 3H), 7.46 (d, J = 8.0 Hz, 1H), 7.31 (d, J = 8.0 Hz, 1H), 7.27 — 7.22 (m, 2H), 3.86 (s, 3H), 2.34 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.1 (C), 166.6 (C), 158.4 (C), 148.4 (CH), 142.7 (C), 138.8 (C), 137.2 (CH), 135.6 (C), 135.5 (C), 131.3 (CH), 130.6 (CH), 130.4 (CH), 130.1 (CH), 125.3 (C), 124.2 (CH), 122.5 (CH), 118.9 (CH), 51.9 (CH_3), 21.0 (CH_3); IR (thin film): 3053, 1715, 1674, 1593, 1531,

1435, 1408, 1322, 1278, 1264, 1175, 1103, 1026 cm^{-1}; HRMS: (ES+) m/z calcd for $C_{21}H_{19}N_2O_3$ $[M+H]^+$: 347.1396, found 347.1396.



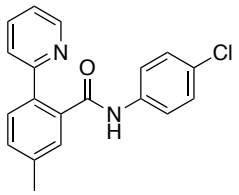
4.3b

Amide (4.3b). The general method was followed adding 0.0169 g of 2-(*p*-tolyl)pyridine **4.1** (0.10 mmol), 0.077 g of 4-nitrobenzotrifluoride **4.2b** (0.40 mmol), 0.052 g of molybdenumhexacarbonyl (0.2 mmol), 0.0051 g of 2,2-dimethylpropionic acid (0.05 mmol), 0.0023 g of $Pd(OAc)_2$ (0.01 mmol) and 0.5 mL of DCE. Purification via MPLC (0:100 – 35:65 EtOAc:hexanes) afforded **4.3b** as a yellow solid (0.025 g, 70%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.59 (br, 1H), 8.61 (d, *J* = 4.5 Hz, 1H), 7.76 (td, *J* = 8.0, 1.0 Hz, 1H), 7.59 — 7.58 (m, 3H), 7.50 — 7.47 (m, 3H), 7.35 — 7.27 (m, 3H), 2.38 (s, 3H) ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.0 (C), 158.5 (C), 148.3 (CH), 141.5 (C), 138.9 (C), 137.3 (CH), 135.5 (C), 135.4 (C), 131.4 (CH), 130.4 (CH), 130.2 (CH), 126.0 (q, *J* = 3.5 Hz, CH), 125.4 (q, *J* = 51.3 Hz, C), 124.4 (CH), 124.2 (q, *J* = 288.4 Hz, C), 122.6 (CH), 119.4 (CH), 21.1 (CH_3) ; IR (thin film): 3259, 2925, 1667, 1602, 1531, 1464, 1411, 1321, 1263, 1114, 1066 cm^{-1}; HRMS: (ES+) m/z calcd for $C_{20}H_{16}N_2OF_3$ $[M+H]^+$: 357.1215, found 357.1211.



4.3c

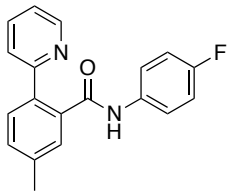
Amide (4.3c). The general method was followed adding 0.0169 g of 2-(*p*-tolyl)pyridine **4.1** (0.10 mmol), 0.081 g of 1-bromo-4-nitrobenzene **4.2c** (0.40 mmol), 0.052 g of molybdenumhexacarbonyl (0.2 mmol), 0.0051 g of 2,2-dimethylpropionic acid (0.05 mmol), 0.0023 g of $Pd(OAc)_2$ (0.01 mmol) and 0.5 mL of DCE. Purification via MPLC (0:100 – 35:65 EtOAc:hexanes) afforded **4.3c** as a yellow solid (0.025 g, 68%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.23 (br, 1H), 8.59 (d, *J* = 4.0 Hz, 1H), 7.74 (t, *J* = 7.5 Hz, 1H), 7.56 (s, 1H), 7.47 (d, *J* = 8.0 Hz, 1H), 7.35 (br, 5H), 7.29 (d, *J* = 8.0 Hz, 1H), 7.27 — 7.24 (m, 1H), 2.38 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.8 (C), 158.5 (C), 148.4 (CH), 138.9 (C), 137.5 (C), 137.2 (CH), 135.8 (C), 135.3 (C), 131.8 (CH), 131.2 (CH), 130.4 (CH), 130.0 (CH), 124.4 (CH), 122.5 (CH), 121.4 (CH), 116.6 (C), 21.1 (CH_3); IR (thin film): 3240, 2922, 2852, 1659, 1590, 1560, 1532, 1466, 1393, 1314, 1258, 1025 cm^{-1}; HRMS: (ES+) m/z calcd for $C_{19}H_{16}N_2OBr$ $[M+H]^+$: 367.0446, found 367.0438.



4.3d

Amide (4.3d). The general method was followed adding 0.0169 g of 2-(*p*-tolyl)pyridine **4.1** (0.10 mmol), 0.068 g of 1-chloro-4-nitrobenzene **4.2d** (0.40 mmol), 0.052 g of molybdenumhexacarbonyl (0.2 mmol), 0.0051 g of 2,2-dimethylpropionic acid (0.05 mmol), 0.0023 g of $Pd(OAc)_2$ (0.01 mmol) and 0.5 mL of DCE. Purification via MPLC (0:100 – 35:65 EtOAc:hexanes) afforded **4.3d** as a yellow solid (0.026 g, 81%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.33 (br, 1H), 8.58 (d, *J* = 4.5 Hz, 1H), 7.74 (td, *J* = 8.0, 1.5 Hz,

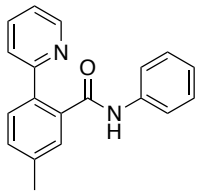
1H), 7.53 (s, 1H), 7.47 (d, J = 8.0 Hz, 1H), 7.39 (d, J = 8.5 Hz, 2H), 7.32 (d, J = 8.0 Hz, 1H), 7.28 — 7.24 (m, 2H), 7.18 (d, J = 8.5 Hz, 2H), 2.36 (s, 3H) ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.8 (C), 158.5 (C), 148.4 (CH), 138.8 (C), 137.2 (CH), 137.0 (C), 135.7 (C), 135.4 (C), 131.2 (CH), 130.3 (CH), 130.1 (CH), 129.0 (C), 128.8 (CH), 124.3 (CH), 122.5 (CH), 121.1 (CH), 21.1 (CH_3) ; IR (thin film): 3234, 3024, 2921, 1658, 1592, 1532, 1490, 1428, 1398, 1292, 1253, 1092, 1012 cm^{-1}; HRMS: (ES+) m/z calcd for $C_{19}H_{16}N_2OCl$ $[M+H]^+$: 323.0951, found 323.0950.



4.3e

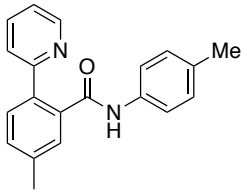
Amide (4.3e). The general method was followed adding 0.0169 g of 2-(*p*-tolyl)pyridine **4.1** (0.10 mmol), 0.056 g of methyl 1-fluoro-4-nitrobenzene **4.2e** (0.40 mmol), 0.052 g of molybdenumhexacarbonyl (0.2 mmol), 0.0051 g of 2,2-dimethylpropionic acid (0.05 mmol), 0.0023 g of $Pd(OAc)_2$ (0.01 mmol) and 0.5 mL of DCE. Purification via MPLC (0:100 – 35:65 EtOAc:hexanes) afforded **4.3e** as a brown solid (0.022 g, 72%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.11 (b, 1H), 8.58 (d, J = 4.5 Hz, 1H), 7.73 (t, J = 7.5 Hz, 1H), 7.55 (s, 1H), 7.48 (d, J = 8.0 Hz, 1H), 7.39 (dd, J = 9.0, 5.0 Hz, 2H), 7.35 (d, J = 7.5 Hz, 1H), 7.29 — 7.23 (m, 2H), 6.93 (t, J = 8.0 Hz, 2H), 2.38 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.8 (C), 158.5 (C), 158.3 (C), 148.5 (CH), 138.8 (C), 137.1 (CH), 135.9 (C), 135.4 (C), 134.4 (C), 131.1 (CH), 130.2 (CH), 129.9 (CH), 124.2 (CH), 122.4 (CH), 121.7 (d, J = 8.6, CH), 115.4 (d, J = 22.5, CH), 21.1 (CH_3); IR (thin film): 3215, 3040, 2924, 1644,

1617, 1547, 1507, 1459, 1407, 1281, 1151, 1025, 1014 cm^{-1}; HRMS: (ES+) m/z calcd for $C_{19}H_{16}N_2OF$ $[M+H]^+$: 307.1247, found 307.1239.



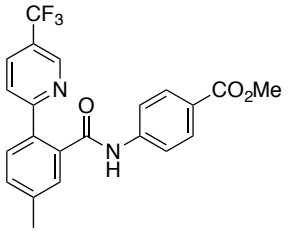
4.3f

Amide (4.3f). The general method was followed adding 0.0169 g of 2-(*p*-tolyl)pyridine **4.1** (0.10 mmol), 0.049 g of nitrobenzene **4.2f** (0.40 mmol), 0.052 g of molybdenumhexacarbonyl (0.2 mmol), 0.0102 g of 2,2-dimethylpropionic acid (0.10 mmol), 0.0023 g of $Pd(OAc)_2$ (0.01 mmol) and 0.5 mL of DCE. Purification via MPLC (0:100 – 35:65 EtOAc:hexanes) afforded **4.3f** as a yellow solid (0.018 g, 63%). ^1H NMR ($CDCl_3$, 500 MHz) δ 8.87 (b, 1H), 8.61 (d, *J* = 4.0 Hz, 1H), 7.71 (t, *J* = 7.5 Hz, 1H), 7.60 (s, 1H), 7.49 (d, *J* = 7.5 Hz, 1H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.39 (d, *J* = 7.5 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.27 — 7.22 (m, 3H), 7.06 (t, *J* = 7.5 Hz, 1H), 2.41 (s, 3H) ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.8 (C), 158.5 (C), 148.7 (CH), 138.9 (C), 138.3 (C), 137.0 (CH), 136.1 (C), 135.4 (C), 131.1 (CH), 130.3 (CH), 130.0 (CH), 128.9 (CH), 124.3 (CH), 124.2 (CH), 122.4 (CH), 119.9 (CH), 21.1 (CH_3); IR (thin film): 2924, 2853, 1660, 1593, 1538, 1493 1466, 1442, 1317, 1258, 1201, 1025 cm^{-1}; HRMS: (ES+) m/z calcd for $C_{19}H_{17}N_2O$ $[M+H]^+$: 289.1341, found 289.1345.



4.3g

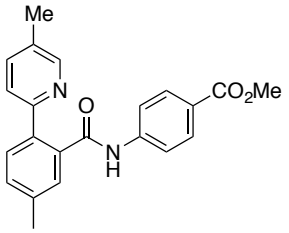
Amide (4.3g). The general method was followed adding 0.0169 g of 2-(*p*-tolyl)pyridine **4.1** (0.10 mmol), 0.055 g of 4-nitrotoluene **4.2g** (0.40 mmol), 0.052 g of molybdenumhexacarbonyl (0.2 mmol), 0.0051 g of 2,2-dimethylpropionic acid (0.05 mmol), 0.0023 g of $Pd(OAc)_2$ (0.01 mmol) and 0.5 mL of DCE. Purification via MPLC (0:100 – 35:65 EtOAc:hexanes) afforded **4.3g** as a brown solid (0.020 g, 66%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.66 (br, 1H), 8.61 (d, *J* = 4.0 Hz, 1H), 7.70 (td, *J* = 7.5, 2.0 Hz, 1H), 7.60 (s, 1H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.32 — 7.30 (m, 3H), 7.24 — 7.21 (m, 1H), 7.06 (d, *J* = 7.5 Hz, 2H), 2.42 (s, 3H), 2.29 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.6 (C), 158.4 (C), 148.7 (CH), 138.9 (C), 136.9 (CH), 136.2 (C), 135.7 (C), 135.3 (C), 133.8 (C), 131.0 (CH), 130.2 (CH), 129.9 (CH), 129.4 (CH), 124.3 (CH), 122.4 (CH), 120.0 (CH), 21.1 (CH_3), 20.9 (CH_3) ; IR (thin film): 3242, 2920, 1652, 1594, 1513, 1464, 1428, 1404, 1319, 1299, 1091 cm^{-1}; HRMS: (ES+) m/z calcd for $C_{20}H_{19}N_2O$ $[M+H]^+$: 303.1497, found 303.1497.



4.5a

Amide (4.5a). The general method was followed adding 0.0237 g of 2-(*p*-tolyl)-5-(trifluoromethyl)pyridine **4.4a** (0.10 mmol), 0.072 g of methyl 4-nitrobenzoate **4.2a** (0.40 mmol), 0.052 g of molybdenumhexacarbonyl (0.2 mmol), 0.0051 g of 2,2-dimethylpropionic acid (0.05 mmol), 0.0023 g of $Pd(OAc)_2$ (0.01 mmol) and 0.5 mL of

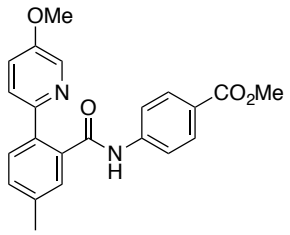
DCE. Purification via MPLC (0:100 – 35:65, EtOAc:hexanes) afforded **4.5a** as a white solid (0.0265 g, 64%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.81 (s, 1H), 8.52 (s, 1H), 7.96 (d, *J* = 8.2 Hz, 3H), 7.65 (d, *J* = 8.3 Hz, 1H), 7.54 (d, *J* = 8.5 Hz, 3H), 7.46 (d, *J* = 7.9 Hz, 1H), 7.36 (d, *J* = 7.9 Hz, 1H), 3.89 (s, 3H), 2.42 (s, 3H); IR (thin film): 1709, 1662, 1601, 1406, 1326, 1280, 1258, 1174, 1130, 1080, 1014, 830, 768 cm^{-1}; HRMS: (EI) m/z calcd for $C_{22}H_{16}N_2O_3F_3$ $[M-H]^-$: 413.1113, found 413.1110.



4.5b

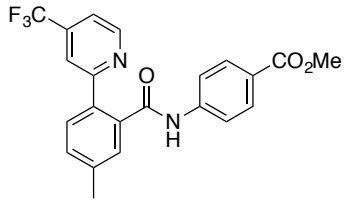
Amide (4.5b). The general method was followed adding 0.0183 g of 5-methyl-2-(*p*-tolyl)pyridine **4.4b** (0.10 mmol), 0.072 g of methyl 4-nitrobenzoate **4.2a** (0.40 mmol), 0.052 g of molybdenumhexacarbonyl (0.2 mmol), 0.0051 g of 2,2-dimethylpropionic acid (0.05 mmol), 0.0023 g of $Pd(OAc)_2$ (0.01 mmol) and 0.5 mL of DCE. Purification via MPLC (0:100 – 35:65, EtOAc:hexanes) afforded **4.5b** as a yellow solid (0.032 g, 89%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.81 (s, 1H), 8.40 (s, 1H), 7.91 (d, *J* = 8.3 Hz, 2H), 7.73 (d, *J* = 8.1 Hz, 1H), 7.68 – 7.55 (m, 3H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.39 – 7.26 (m, 2H), 3.87 (s, 3H), 2.39 (s, 3H), 2.37 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.7 (C), 166.7 (C), 153.8 (C), 145.6 (CH), 142.6 (C), 140.8 (CH), 140.0 (C), 136.2 (C), 133.7 (C), 132.1 (C), 131.4 (CH), 130.6 (CH), 130.4 (CH), 130.0 (CH), 125.4 (C), 125.0 (CH), 119.2 (CH), 51.9 (CH_3), 21.2 (CH_3), 18.2 (CH_3); IR (thin film): 1714, 1675, 1599, 1530, 1435,

1408, 1323, 1277, 1257, 1175, 1111, 828, 771 cm^{-1}; HRMS: (EI) m/z calcd for $C_{22}H_{21}N_2O_3$ $[M+H]^+$: 361.1552, found 361.1543.



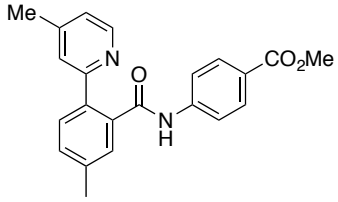
4.5c

Amide (4.5c). The general method was followed adding 0.0199 g of 5-methoxy-2-(*p*-tolyl)pyridine **4.4c** (0.10 mmol), 0.072 g of methyl 4-nitrobenzoate **4.2a** (0.40 mmol), 0.052 g of molybdenumhexacarbonyl (0.2 mmol), 0.0051 g of 2,2-dimethylpropionic acid (0.05 mmol), 0.0023 g of $Pd(OAc)_2$ (0.01 mmol) and 0.5 mL of DCE. Purification via MPLC (0:100 – 35:65, EtOAc:hexanes) afforded **4.5c** as a yellow solid (0.0316 g, 84%). ^1H NMR ($CDCl_3$, 500 MHz) δ 9.25 (s, 1H), 8.30 (d, *J* = 2.9 Hz, 1H), 7.96 (d, *J* = 8.3 Hz, 2H), 7.64 – 7.52 (m, 3H), 7.41 (d, *J* = 8.6 Hz, 1H), 7.38 – 7.30 (m, 2H), 7.24 (dd, *J* = 8.7, 3.0 Hz, 1H), 3.89 (s, 3H), 3.85 (s, 3H), 2.41 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.2 (C), 166.7 (C), 155.0 (C), 150.5 (C), 142.6 (C), 138.5 (C), 136.2 (CH), 135.5 (C), 135.0 (C), 131.4 (CH), 130.8 (CH), 130.4 (CH), 130.2 (CH), 125.4 (C), 124.7 (CH), 121.5 (CH), 118.8 (CH), 55.7 (CH_3), 52.0 (CH_3), 21.1 (CH_3); IR (thin film): 1716, 1682, 1594, 1528, 1476, 1435, 1408, 1322, 1276, 1174, 1112, 1017, 770 cm^{-1}; HRMS: (EI) m/z calcd for $C_{22}H_{21}N_2O4$ $[M+H]^+$: 377.1501, found 377.1498.



4.5d

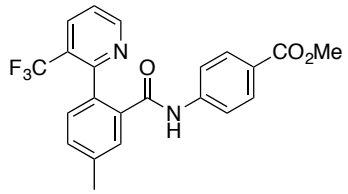
Amide (4.5d). The general method was followed adding 0.0237 g of 2-(*p*-tolyl)-4-(trifluoromethyl)pyridine **4.4d** (0.10 mmol), 0.072 g of methyl 4-nitrobenzoate **4.2a** (0.40 mmol), 0.052 g of molybdenumhexacarbonyl (0.2 mmol), 0.0051 g of 2,2-dimethylpropionic acid(0.05 mmol), 0.0023 g of $Pd(OAc)_2$ (0.01 mmol) and 0.5 mL of DCE. Purification via MPLC (0:100 – 35:65, EtOAc:hexanes) afforded **4.5d** as a yellow solid (0.0257 g, 62%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.74 (d, *J* = 5.1 Hz, 1H), 8.69 (s, 1H), 7.94 (d, *J* = 8.2 Hz, 2H), 7.74 (s, 1H), 7.58 – 7.48 (m, 3H), 7.48 – 7.40 (m, 2H), 7.36 (d, *J* = 7.9 Hz, 1H), 3.88 (s, 2H), 2.41 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.8 (C), 166.6 (C), 159.4 (C), 149.7 (CH), 142.3 (C), 139.8 (C), 139.5 (C), 136.2 (C), 134.5 (C), 131.4 (CH), 131.0 (C), 130.8 (CH), 130.2 (CH), 129.6 (CH), 125.6 (C), 119.2 (CH), 118.9 (CH), 118.0 (CH), 111.0, 52.0 (CH_3), 21.1 (CH_3); IR (thin film): 1719, 1684, 1596, 1529, 1436, 1406, 1336, 1279, 1256, 1174, 1137, 1112, 771, 667 cm^{-1}; HRMS: (EI) m/z calcd for $C_{22}H_{16}N_2O_3F_3$ $[M-H]^-$: 413.1113, found 413.1109.



4.5e

Amide (4.5e). The general method was followed adding 0.0183 g of 4-methyl-2-(*p*-tolyl)pyridine **4.4e** (0.10 mmol), 0.072 g of methyl 4-nitrobenzoate **4.2a** (0.40 mmol),

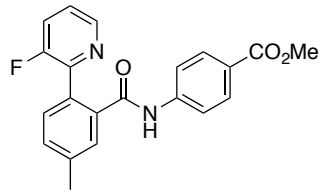
0.052 g of molybdenumhexacarbonyl (0.2 mmol), 0.0051 g of 2,2-dimethylpropionic acid (0.05 mmol), 0.0023 g of $Pd(OAc)_2$ (0.01 mmol) and 0.5 mL of DCE. Purification via MPLC (0:100 – 35:65, EtOAc:hexanes) afforded **4.5e** as a yellow solid (0.032 g, 89%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.76 (s, 1H), 8.47 (d, J = 5.1 Hz, 1H), 7.92 (d, J = 8.5 Hz, 2H), 7.62 (s, 1H), 7.56 (d, J = 8.2 Hz, 2H), 7.37 – 7.27 (m, 3H), 7.08 (dd, J = 5.1, 1.6 Hz, 1H), 3.88 (s, 3H), 2.40 (s, 3H), 2.35 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.9 (C), 166.7 (C), 158.5 (C), 148.8 (C), 147.9 (CH), 142.7 (C), 138.8 (C), 135.5 (C), 131.3 (CH), 130.7 (CH), 130.5 (CH), 130.4 (CH), 125.4 (CH), 125.3 (C), 123.7 (CH), 118.9 (CH), 111.0(CH), 51.9 (CH_3), 21.2 (CH_3), 21.1 (CH_3); IR (thin film): 1716, 1682, 1599, 1530, 1435, 1408, 1322, 1277, 1259, 1174, 1111, 820, 770 cm^{-1}; HRMS: (EI) m/z calcd for $C_{22}H_{21}N_2O_3$ $[M+H]^+$: 361.1552, found 361.1544.



4.5f

Amide (4.5f). The general method was followed adding 0.0237 g of 2-(*p*-tolyl)-3-(trifluoromethyl)pyridine **4.4f** (0.10 mmol), 0.072 g of methyl 4-nitrobenzoate **4.2a** (0.40 mmol), 0.052 g of molybdenumhexacarbonyl (0.2 mmol), 0.0051 g of 2,2-dimethylpropionic acid (0.05 mmol), 0.0023 g of $Pd(OAc)_2$ (0.01 mmol) and 0.5 mL of DCE. Purification via MPLC (0:100 – 35:65, EtOAc:hexanes) afforded **4.5f** as a white solid (0.0373 g, 90%).^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.79 (d, J = 4.9 Hz, 1H), 8.23 (s, 1H), 8.07 (dd, J = 8.1, 1.6 Hz, 1H), 7.90 (d, J = 8.8 Hz, 2H), 7.63 (d, J = 1.7 Hz, 1H), 7.49 – 7.39 (m, 3H), 7.36 (dd, J = 7.8, 1.8 Hz, 1H), 7.24 (d, J = 7.8 Hz, 1H), 3.87 (s, 3H),

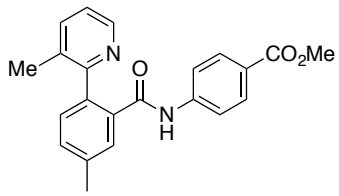
2.45 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.5 (C), 166.4 (C), 157.8 (C), 151.3 (CH), 142.1 (C), 139.5 (C), 135.2 (C), 135.1 (CH), 134.1 (C), 131.1 (CH), 130.7 (CH), 130.1 (CH), 128.9 (CH), 125.8 (C), 125.6 (C), 122.5 (CH), 122.1 (C), 118.7 (CH), 52.0 (CH_3), 21.2 (CH_3); IR (thin film): 1717, 1655, 1598, 1534, 1439, 1407, 1322, 1277, 1160, 1130, 1117, 1031, 769 cm^{-1}; HRMS: (EI) m/z calcd for $C_{22}H_{16}N_2F_3O_3$ $[M-H]^-$: 413.1113, found 413.1103.



4.5g

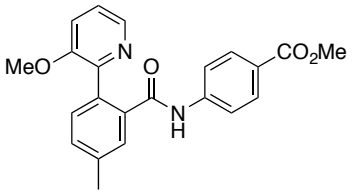
Amide (4.5g). The general method was followed adding 0.0187 g of 3-fluoro-2-(*p*-tolyl)pyridine **4.4g** (0.10 mmol), 0.072 g of methyl 4-nitrobenzoate **4.2a** (0.40 mmol), 0.052 g of molybdenumhexacarbonyl (0.2 mmol), 0.0051 g of 2,2-dimethylpropionic acid (0.05 mmol), 0.0023 g of $Pd(OAc)_2$ (0.01 mmol) and 0.5 mL of DCE. Purification via MPLC (0:100 – 35:65, EtOAc:hexanes) afforded **4.5g** as a yellow solid (0.0302 g, 83%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.62 (s, 1H), 8.46 (d, *J* = 4.6 Hz, 1H), 7.93 (d, *J* = 8.4 Hz, 2H), 7.63 (s, 1H), 7.52 (d, *J* = 8.3 Hz, 2H), 7.45 (d, *J* = 8.1 Hz, 2H), 7.38 (d, *J* = 7.9 Hz, 1H), 7.35 – 7.26 (m, 1H), 3.88 (s, 3H), 2.44 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.2 (C), 166.6 (C), 157.3 (C, d, *J* = 260.9 Hz), 146.8 (C, d, *J* = 14.9 Hz), 144.7 (CH), 142.3 (C), 139.7 (C), 136.0 (C), 131.4 (CH) , 131.0 (CH), 130.8 (CH), 130.2 , 129.6 (CH), 125.6 (C), 124.4 (CH), 124.1 (CH, d, *J* = 19.2 Hz), 118.9 (CH), 52.0 2 (CH_3), 21.2 (CH_3); IR (thin film): 1715, 1680, 1594, 1525, 1437, 1407, 1321, 1276, 1250, 1187,

1174, 1104, 799, 769, 734, 698 cm^{-1}; HRMS: (EI) m/z calcd for $C_{21}H_{17}N_2FO_3$ $[M+H]^+$: 365.1301, found 365.1298.



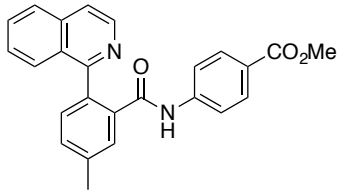
4.5h

Amide (4.5h). The general method was followed adding 0.0183 g of 3-methyl-2-(*p*-tolyl)pyridine **4.4h** (0.10 mmol), 0.072 g of methyl 4-nitrobenzoate **4.2a** (0.40 mmol), 0.052 g of molybdenumhexacarbonyl (0.2 mmol), 0.0051 g of 2,2-dimethylpropionic acid (0.05 mmol), 0.0023 g of $Pd(OAc)_2$ (0.01 mmol) and 0.5 mL of DCE. Purification via MPLC (0:100 – 35:65, EtOAc:hexanes) afforded **4.5h** as a white solid (0.0324 g, 90%). ^1H NMR ($CDCl_3$, 500 MHz) δ 8.87 (s, 1H), 8.56 (dd, J = 5.0, 1.6 Hz, 1H), 7.91 (d, J = 8.7 Hz, 2H), 7.78 – 7.68 (m, 2H), 7.59 (d, J = 7.7 Hz, 1H), 7.44 (d, J = 8.7 Hz, 1H), 7.37 (dd, J = 7.8, 1.8 Hz, 1H), 7.23 (dd, J = 7.8, 4.8 Hz, 1H), 7.17 (d, J = 7.8 Hz, 1H), 3.87 (s, 3H), 2.46 (s, 3H), 2.10 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.1 (C), 166.6 (C), 158.5 (C), 146.1 (CH), 142.3 (C), 139.1 (CH), 138.8 (C), 135.0 (C), 134.8 (C), 133.2 (C), 131.6 (CH), 130.7 (CH), 130.3 (CH), 129.9 (CH), 125.4 (C), 123.2 (CH), 118.6 (CH), 51.9 (CH_3), 21.2 (CH_3), 19.5 (CH_3); IR (thin film): 1717, 1681, 1597, 1529, 1435, 1408, 1321, 1278, 1257, 1175, 1113, 770 cm^{-1}; HRMS: (EI) m/z calcd for $C_{22}H_{21}N_2O_3$ $[M+H]^+$: 361.1552, found 361.1545.



4.5i

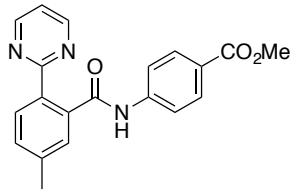
Amide (4.5i). The general method was followed adding 0.0199 g of 3-methoxy-2-(*p*-tolyl)pyridine **4.4i** (0.10 mmol), 0.072 g of methyl 4-nitrobenzoate **4.2a** (0.40 mmol), 0.052 g of molybdenumhexacarbonyl (0.2 mmol), 0.0051 g of 2,2-dimethylpropionic acid (0.05 mmol), 0.0023 g of $Pd(OAc)_2$ (0.01 mmol) and 0.5 mL of DCE. Purification via MPLC (0:100 – 35:65, EtOAc:hexanes) afforded **4.5i** as a yellow solid (0.0244 g, 65%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.31 (d, J = 4.7 Hz, 1H), 8.21 (s, 1H), 7.92 (d, J = 8.4 Hz, 2H), 7.65 (s, 1H), 7.43 (d, J = 8.1 Hz, 2H), 7.38 (d, J = 7.9 Hz, 1H), 7.26 (q, J = 4.6 Hz, 2H), 7.16 (d, J = 8.2 Hz, 1H), 3.88 (s, 3H), 3.64 (s, 3H), 2.45 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.4 (C), 166.6 (C), 153.8 (C), 148.2 (C), 142.4 (C), 140.9 (CH), 138.9 (C), 135.6 (C), 132.4 (C), 131.7 (CH), 131.1 (CH), 130.8 (CH), 129.3 (CH), 125.3 (C), 123.9 (CH), 118.4 (CH), 118.3 (CH), 55.4 (CH_3), 52.0 (CH_3), 21.2 (CH_3); IR (thin film): 1716, 1683, 1595, 1526, 1431, 1407, 1322, 1278, 1253, 1175, 1113, 771 cm^{-1}; HRMS: (EI) m/z calcd for $C_{22}H_{21}N_2O_4$ $[M+H]^+$: 377.1501, found 377.1490.



4.5j

Amide (4.5j). The general method was followed adding 0.0219 g of 1-(*p*-tolyl)isoquinoline **4.4j** (0.10 mmol), 0.072 g of methyl 4-nitrobenzoate **4.2a** (0.40 mmol),

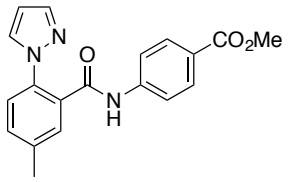
0.052 g of molybdenumhexacarbonyl (0.2 mmol), 0.0051 g of 2,2-dimethylpropionic acid (0.05 mmol), 0.0023 g of $Pd(OAc)_2$ (0.01 mmol) and 0.5 mL of DCE. Purification via MPLC (0:100 – 35:65, EtOAc:hexanes) afforded **4.5j** as a yellow solid (0.0297 g, 75%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.21 (s, 1H), 8.62 (d, J = 5.7 Hz, 1H), 7.91 – 7.77 (m, 4H), 7.73 – 7.61 (m, 3H), 7.49 (ddd, J = 8.2, 6.8, 1.3 Hz, 1H), 7.43 (dd, J = 7.8, 1.8 Hz, 1H), 7.36 (d, J = 8.5 Hz, 2H), 7.32 (d, J = 7.8 Hz, 1H), 3.85 (s, 3H), 2.51 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.0 (C), 166.6 (C), 160.4 (C), 142.1 (C), 140.9 (CH), 139.3 (C), 136.7 (C), 135.9 (C), 133.5 (C), 131.3 (CH), 131.1 (CH), 130.9 (CH), 130.6 (CH), 130.5 (CH), 128.1 (C), 128.0 (CH), 127.4 (CH), 127.0 (CH), 125.4 (C), 121.2 (CH), 118.6 (CH), 51.9 (CH_3), 21.3 (CH_3); IR (thin film): 1717, 1682, 1596, 1530, 1435, 1408, 1320, 1278, 1175, 1111, 826, 769 cm^{-1}; HRMS: (EI) m/z calcd for $C_{25}H_{21}N_2O_3$ $[M+H]^+$: 397.1552, found 397.1545.



4.5k

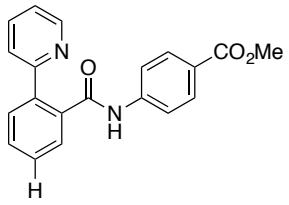
Amide (4.5k). The general method was followed adding 0.0170 g of 2-(*p*-tolyl)pyrimidine **4.4k** (0.10 mmol), 0.072 g of methyl 4-nitrobenzoate **4.2a** (0.40 mmol), 0.052 g of molybdenumhexacarbonyl (0.2 mmol), 0.0051 g of 2,2-dimethylpropionic acid (0.05 mmol), 0.0023 g of $Pd(OAc)_2$ (0.01 mmol) and 0.5 mL of DCE. Purification via MPLC (0:100 – 35:65 EtOAc:hexanes) afforded **4.5k** as a yellow solid (0.020 g, 58%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.69 (d, J = 4.5 Hz, 2H), 8.25 (br, 1H), 8.01 (d, J = 8.0 Hz, 1H), 7.96 (d, J = 8.0 Hz, 2H), 7.59 (d, J = 8.0 Hz, 2H), 7.43 (s, 1H), 7.34 (d, J = 8.0 Hz,

1H), 7.13 (t, *J* = 5.0 Hz, 1H), 3.89 (s, 3H), 2.41 (s, 3H) ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.7 (C), 164.8 (C), 157.0 (CH), 142.7 (C), 140.7 (C), 137.0 (C), 133.4 (C), 131.1 (CH), 130.8 (CH), 130.5 (CH), 129.0 (CH), 125.4 (C), 119.1 (CH), 118.9 (CH), 52.0 (CH_3), 21.1 (CH_3), only peaks visible ; IR (thin film): 3169, 2923, 2852, 1720, 1690, 1594, 1535, 1419, 1409, 1319, 1279, 1261, 1197, 1179, 1110 cm^{-1}; HRMS: (ES+) m/z calcd for $C_{20}H_{18}N_3O_3$ $[M+H]^+$: 348.1348, found 348.1342.



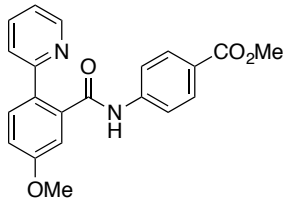
4.5l

Amide (4.5l). The general method was followed adding 0.0158 g of 1-(*p*-tolyl)-1*H*-pyrazole **4.4l** (0.10 mmol), 0.072 g of methyl 4-nitrobenzoate **4.2a** (0.40 mmol), 0.052 g of molybdenumhexacarbonyl (0.2 mmol), 0.0051 g of 2,2-dimethylpropionic acid (0.05 mmol), 0.0023 g of $Pd(OAc)_2$ (0.01 mmol) and 0.5 mL of DCE. Purification via MPLC (0:100 – 35:65 EtOAc:hexanes) afforded **4.5l** as a brown solid (0.015 g, 45%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.93 (br, 1H), 7.94 (d, *J* = 8.5 Hz, 2H), 7.81 (s, 1H), 7.76 (s, 1H), 7.66 (s, 1H), 7.53 (d, *J* = 8.0 Hz, 2H), 7.37 (d, *J* = 7.0 Hz, 1H), 7.27 (d, *J* = 8.0 Hz, 1H), 6.46 (s, 1H), 3.88 (s, 3H), 2.46 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.6 (C), 164.7 (C), 142.2 (C), 141.3 (CH), 139.8 (C), 134.9 (C), 132.5 (C), 132.4 (CH), 131.5 (CH), 130.7 (CH), 127.1 (CH), 125.7 (C), 119.0 (CH), 107.8 (CH), 52.0 (CH_3), 21.1 (CH_3), only peaks visible; IR (thin film): 3249, 3110, 2923, 2853, 1716, 1661, 1596, 1522, 1432, 1406, 1309, 1276, 1256, 1173, 1110, 1016 cm^{-1}; HRMS: (ES+) m/z calcd for $C_{19}H_{18}N_3O_3$ $[M+H]^+$: 336.1348, found 336.1342.



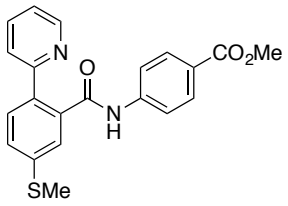
4.7a

Amide (4.7a). The general method was followed adding 0.0155 g of 2-phenylpyridine **4.6a** (0.10 mmol), 0.072 g of methyl 4-nitrobenzoate **4.2a** (0.40 mmol), 0.052 g of molybdenumhexacarbonyl (0.2 mmol), 0.0051 g of 2,2-dimethylpropionic acid (0.05 mmol), 0.0023 g of $Pd(OAc)_2$ (0.01 mmol) and 0.5 mL of DCE. Purification via MPLC (0:100 – 35:65 EtOAc:hexanes) afforded **4.7a** as a yellow solid (0.022 g, 66%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.30 (br, 1H), 8.63 (d, *J* = 3.0 Hz, 1H), 7.93 (d, *J* = 8.0 Hz, 2H), 7.81 — 7.75 (m, 2H), 7.55 — 7.47 (m, 6H), 7.28 (t, *J* = 6.0 Hz, 1H), 3.88 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.7 (C), 166.6 (C), 158.4 (C), 148.5 (CH), 142.5 (C), 138.2 (C), 137.3 (CH), 135.8 (C), 130.7 (CH), 130.7 (CH), 130.5 (CH), 129.6 (CH), 128.9 (CH), 125.4 (C), 124.4 (CH), 122.8 (CH), 118.9 (CH), 52.0 (CH_3); IR (thin film): 3336, 2923, 2852, 1682, 1588, 1520, 1470, 1438, 1404, 1321, 1285, 1250, 1174, 1117, 1099, 1085, 1046, 1022 cm^{-1}; HRMS: (ES+) m/z calcd for $C_{20}H_{17}N_2O_3$ $[M+H]^+$: 333.1239, found 333.1234.



4.7b

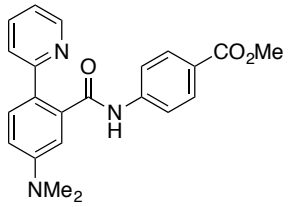
Amide (4.7b). The general method was followed adding 0.0185 g of 2-(4-methoxyphenyl)pyridine **4.6b** (0.10 mmol), 0.072 g of methyl 4-nitrobenzoate **4.2a** (0.40 mmol), 0.052 g of molybdenumhexacarbonyl (0.2 mmol), 0.0102 g of 2,2-dimethylpropionic acid (0.10 mmol), 0.0023 g of $Pd(OAc)_2$ (0.01 mmol) and 0.5 mL of DCE. Purification via MPLC (0:100 – 35:65 EtOAc:hexanes) afforded **4.7b** as a yellow solid (0.022 g, 62%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.38 — 9.36 (m, 1H), 8.60 — 8.59 (m, 1H), 7.93 (td, *J* = 8.0, 2.0 Hz, 1H), 7.89 (d, *J* = 9.0 Hz, 2H), 7.55 (d, *J* = 9.0 Hz, 2H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.45 — 7.43 (m, 1H), 7.38 — 7.32 (m, 2H), 7.27 — 7.24 (m, 1H), 7.12 — 7.09 (m, 2H), 3.88 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.6 (C), 159.5 (C), 151.2 (C), 149.1 (CH), 142.2 (C), 138.8 (C), 138.8 (CH), 133.3 (C), 130.6 (CH), 126.7 (C), 125.5 (CH), 122.9 (CH), 122.2 (CH), 122.0 (CH), 121.4 (CH), 119.4 (CH), 110.8 (CH), 110.8 (C), 109.4 (CH), 52.0 (CH_3); IR (thin film): 3227, 2922, 2852, 1715, 1660, 1591, 1530, 1511, 1463, 1429, 1408, 1328, 1260, 1227, 1174, 1103, 1040, 1016 cm^{-1}; HRMS: (ES+) m/z calcd for $C_{21}H_{19}N_2O_4$ $[M+H]^+$: 363.1345, found 363.1339.



4.7c

Amide (4.7c). The general method was followed adding 0.0201 g of 2-(4-(methylthio)phenyl)pyridine **4.6c** (0.10 mmol), 0.072 g of methyl 4-nitrobenzoate **4.2a** (0.40 mmol), 0.052 g of molybdenumhexacarbonyl (0.2 mmol), 0.0051 g of 2,2-dimethylpropionic acid (0.05 mmol), 0.0023 g of $Pd(OAc)_2$ (0.01 mmol) and 0.5 mL of DCE. Purification via MPLC (0:100 – 35:65 EtOAc:hexanes) afforded **4.7c** as a yellow

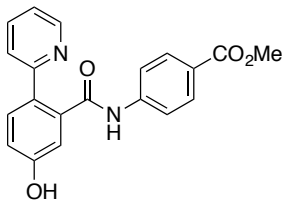
solid (0.026 g, 69%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.99 (br, 1H), 8.59 (d, *J* = 4.0 Hz, 1H), 7.84 (d, *J* = 8.5 Hz, 2H), 7.77 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.53 — 7.49 (m, 3H), 7.46 (s, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.28 — 7.26 (m, 2H), 3.87 (s, 3H), 2.36 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.5 (C), 166.6 (C), 158.0 (C), 148.3 (CH), 142.7 (C), 140.1 (C), 137.5 (CH), 136.2 (C), 134.6 (C), 130.7 (CH), 130.6 (CH), 128.1 (CH), 126.1 (CH), 125.4 (C), 124.2 (CH), 122.7 (CH), 119.0 (CH), 51.9 (CH_3), 15.0 (CH_3); IR (thin film): 3236, 2950, 1715, 1679, 1591, 1531, 1466, 1429, 1407, 1321, 1274, 1258, 1191, 1174, 1104, 1021 cm^{-1}; HRMS: (ES+) m/z calcd for $C_{21}H_{19}N_2O_3S$ $[M+H]^+$: 379.1116, found 379.1115.



4.7d

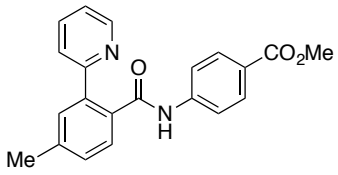
Amide (4.7d). The general method was followed adding 0.0198 g of *N*,*N*-dimethyl-4-(pyridin-2-yl)aniline **4.6d** (0.10 mmol), 0.072 g of methyl 4-nitrobenzoate **4.2a** (0.40 mmol), 0.052 g of molybdenumhexacarbonyl (0.2 mmol), 0.0051 g of 2,2-dimethylpropionic acid (0.05 mmol), 0.0023 g of $Pd(OAc)_2$ (0.01 mmol) and 0.5 mL of DCE. Purification via MPLC (0:100 – 35:65 EtOAc:hexanes) afforded **4.7d** as a yellow solid (0.017 g, 46%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.69 (br, 1H), 8.56 (d, *J* = 4.5 Hz, 1H), 7.92 (d, *J* = 8.0 Hz, 2H), 7.68 (t, *J* = 7.5 Hz, 1H), 7.57 (d, *J* = 8.0 Hz, 2H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.35 (d, *J* = 8.5 Hz, 1H), 7.17 (t, *J* = 6.0 Hz, 1H), 7.07 (s, 1H), 6.79 (d, *J* = 8.5 Hz, 1H), 3.88 (s, 3H), 2.99 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.6 (C), 166.7 (C), 158.8 (C), 150.3 (C), 148.2 (CH), 142.9 (C), 137.0 (CH), 136.5 (C), 131.7 (CH),

130.7 (CH), 125.5 (C), 125.2 (C), 124 (CH), 121.7 (CH), 118.9 (CH), 113.9 (CH), 112.9 (CH), 51.9 (CH_3), 40.2 (CH_3); IR (thin film): 2922, 2852, 1714, 1677, 1591, 1515, 1468, 1428, 1407, 1363, 1307, 1274, 1173, 1101, 1023 cm^1; HRMS: (ES+) m/z calcd for $C_{22}H_{22}N_3O_3$ $[M+H]^+$: 376.1661, found 376.1655.



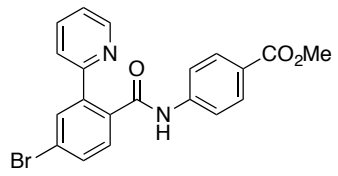
4.7e

Amide (4.7e). The general method was followed adding 0.0172 g of 4-(pyridin-2-yl)phenol **4.6e** (0.10 mmol), 0.072 g of methyl 4-nitrobenzoate **4.2a** (0.40 mmol), 0.052 g of molybdenumhexacarbonyl (0.2 mmol), 0.0102 g of 2,2-dimethylpropionic acid (0.10 mmol), 0.0023 g of $Pd(OAc)_2$ (0.01 mmol) and 0.5 mL of DCE. Purification via MPLC (0:100 – 35:65 EtOAc:hexanes) afforded **4.7e** as a yellow solid (0.019 g, 55%). ^{1}H NMR (DMSO-d_6, 500 MHz) δ 10.53 (s, 1H), 10.03 (br, 1H), 8.40 (d, *J* = 4.0 Hz, 1H), 7.87 (d, *J* = 8.5 Hz, 2H), 7.73 (td, *J* = 8.0, 1.0 Hz, 1H), 7.69 (d, *J* = 8.5 Hz, 2H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.17 (dd, *J* = 7.5, 4.5 Hz, 1H), 6.98 — 6.94 (m, 2H), 3.80 (s, 3H); ^{13}C NMR (DMSO-d_3, 125 MHz) δ 168.9 (C), 166.4 (C), 158.0 (C), 157.4 (C), 149.2 (CH), 144.4 (C), 138.6 (C), 137.0 (CH), 131.5 (CH), 130.6 (CH), 129.9 (C), 124.3 (C), 122.5 (CH), 122.0 (CH), 119.2 (CH), 117.0 (CH), 115.4 (CH), 52.3 (CH_3); IR (thin film): 3326, 2923, 2853, 1716, 1683, 1594, 1562, 1527, 1467, 1432, 1406, 1276, 1252, 1216, 1174, 1110, 1083, cm^{-1}; HRMS: (ES+) m/z calcd for $C_{20}H_{17}N_2O_4$ $[M+H]^+$: 349.1188, found 349.1186.



4,7f

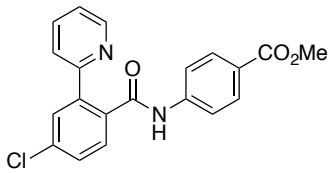
Amide (4.7f). The general method was followed adding 0.0170 g of 2-(m-tolyl)pyridine **4.6f** (0.10 mmol), 0.072 g of methyl 4-nitrobenzoate **4.2a** (0.40 mmol), 0.052 g of molybdenumhexacarbonyl (0.2 mmol), 0.0051 g of 2,2-dimethylpropionic acid (0.05 mmol), 0.0023 g of $Pd(OAc)_2$ (0.01 mmol) and 0.5 mL of DCE. Purification via MPLC (0:100 – 35:65 EtOAc:hexanes) afforded **4.7f** as a yellow solid (0.027 g, 79%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.53 (br, 1H), 8.60 (d, *J* = 4.5 Hz, 1H), 7.88 (d, *J* = 8.5 Hz, 2H), 7.73 (t, *J* = 8.0 Hz, 1H), 7.64 (d, *J* = 7.5 Hz, 1H), 7.51 (d, *J* = 8.0 Hz, 2H), 7.47 (d, *J* = 7.5 Hz, 1H), 7.27 — 7.21 (m, 3H), 3.86 (s, 3H), 2.40 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.2 (C), 166.6 (C), 158.6 (C), 148.4 (CH), 142.7 (C), 140.9 (C), 138.3 (C), 137.2 (CH), 133.0 (C), 131.1 (CH), 130.6 (CH), 129.7 (CH), 129.4 (CH), 125.2 (C), 124.4 (CH), 122.7 (CH), 118.9 (CH), 51.9 (CH_3), 21.4 (CH_3); IR (thin film): 2923, 2852, 1713, 1669, 1598, 1553, 1510, 1473, 1435, 1410, 1370, 1323, 1271, 1172, 1109, 1013 cm^{-1}; HRMS: (ES+) m/z calcd for $C_{21}H_{19}N_2O_3$ $[M+H]^+$: 347.1396, found 347.1391.



4.7g

Amide (4.7g). The general method was followed adding 0.0234 g of 2-(3-bromophenyl)pyridine **4.6g** (0.10 mmol), 0.072 g of methyl 4-nitrobenzoate **4.2a** (0.40 mmol), 0.052 g of molybdenumhexacarbonyl (0.2 mmol), 0.0051 g of 2,2-

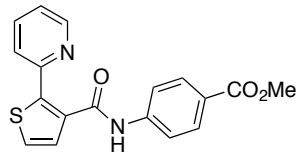
dimethylpropionic acid (0.05 mmol), 0.0023 g of $Pd(OAc)_2$ (0.01 mmol) and 0.5 mL of DCE. Purification via MPLC (0:100 – 35:65 EtOAc:hexanes) afforded **4.7g** as a yellow solid (0.020 g, 50%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.59 (br, 1H), 8.61 (d, *J* = 4.5 Hz, 1H), 7.89 (d, *J* = 8.5 Hz, 2H), 7.79 (t, *J* = 7.5 Hz, 1H), 7.62 — 7.60 (m, 2H), 7.55 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.51 (d, *J* = 8.0 Hz, 3H), 7.31 (dd, *J* = 7.5, 2.5 Hz, 1H), 3.87 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.8 (C), 166.5 (C), 156.9 (C), 148.6 (CH), 142.4 (C), 139.9 (C), 137.6 (CH), 134.6 (C), 133.2 (CH), 131.8 (CH), 131.2 (CH), 130.7 (CH), 125.6 (C), 124.9 (C), 124.4 (CH), 123.3 (CH), 119.0 (CH), 52.0 (CH_3); IR (thin film): 2923, 2853, 1715, 1683, 1595, 1529, 1462, 1434, 1407, 1321, 1274, 1175, 1102, 1033 cm^{-1}; HRMS: (ES+) m/z calcd for $C_{20}H_{16}N_2O_3Br$ $[M+H]^+$: 411.0344, found 411.0336.



4.7h

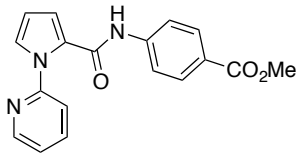
Amide (4.7h). The general method was followed adding 0.0190 g of 2-(3-chlorophenyl)pyridine **4.6h** (0.10 mmol), 0.072 g of methyl 4-nitrobenzoate **4.2a** (0.40 mmol), 0.052 g of molybdenumhexacarbonyl (0.2 mmol), 0.0051 g of 2,2-dimethylpropionic acid (0.05 mmol), 0.0023 g of $Pd(OAc)_2$ (0.01 mmol) and 0.5 mL of DCE. Purification via MPLC (0:100 – 35:65 EtOAc:hexanes) afforded **4.7h** as a yellow solid (0.019 g, 51%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.70 (br, 1H), 8.61 (d, *J* = 4.0 Hz, 1H), 7.87 (d, *J* = 8.5 Hz, 2H), 7.79 (t, *J* = 7.5 Hz, 1H), 7.65 (d, *J* = 8.5 Hz, 1H), 7.50 (d, *J* = 7.5 Hz, 3H), 7.41 (d, *J* = 1.5 Hz, 1H), 7.36 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.31 (t, *J* = 6.0 Hz, 1H), 3.87 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.8 (C), 166.5 (C), 157.0 (C), 148.5

(CH), 142.4 (C), 139.8 (C), 137.6 (CH), 136.6 (C), 134.2 (C), 131.0 (CH), 130.6 (CH), 130.3 (CH), 128.7 (CH), 125.5 (C), 124.4 (CH), 123.3 (CH), 119.0 (CH), 52.0 (CH_3); IR (thin film): 2956, 2922, 2852, 1715, 1668, 1591, 1531, 1462, 1435, 1406, 1274, 1175, 1100, 1035, 1018 cm^{-1}; HRMS: (ES+) m/z calcd for $C_{20}H_{16}N_2O_3Cl$ $[M+H]^+$: 367.0849, found 367.0844.



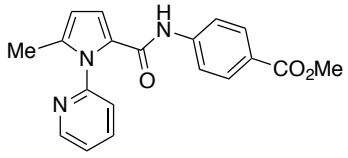
4.7j

Amide (4.7j). The general method was followed adding 0.0161 g of 2-(thiophen-2-yl)pyridine **4.6j** (0.10 mmol), 0.072 g of methyl 4-nitrobenzoate **4.2a** (0.40 mmol), 0.052 g of molybdenumhexacarbonyl (0.2 mmol), 0.0051 g of 2,2-dimethylpropionic acid (0.05 mmol), 0.0023 g of $Pd(OAc)_2$ (0.01 mmol) and 0.5 mL of DCE. Purification via MPLC (0:100 – 35:65 EtOAc:hexanes) afforded **4.7j** as a yellow solid (0.028 g, 83%). ^1H NMR ($CDCl_3$, 500 MHz) δ 8.75 (d, *J* = 4.5 Hz, 1H), 8.04 (d, *J* = 8.5 Hz, 2H), 7.87 — 7.82 (m, 4H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.40 (t, *J* = 6.0 Hz, 1H), 7.37 (d. *J* = 5.5 Hz, 1H), 3.90 (s, 3H), 3.70 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.8 (C), 161.5 (C), 152.0 (C), 147.4 (CH), 143.4 (C), 140.8 (C), 138.4 (CH), 136.4 (C), 133.8 (CH), 130.9 (CH), 125.2 (CH), 125.0 (CH), 123.4 (CH), 119.2 (CH), 52.0 (CH_3), only peaks visible; IR (thin film): 3225, 3039, 2923, 2852, 1710, 1656, 1590, 1533, 1512, 1475, 1438, 1407, 1327, 1307, 1275, 1189, 1174, 1153, 1101, 1014 cm^{-1}; HRMS: (ES+) m/z calcd for $C_{18}H_{15}N_2O_3S$ $[M+H]^+$: 339.0803, found 339.0802.



4.9a

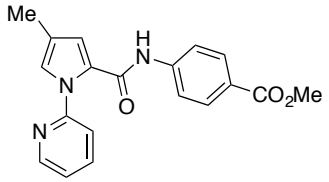
Amide (4.9a). The general method was followed adding 0.0144 g of 2-(1*H*-pyrrol-1-yl)pyridine **4.8a** (0.10 mmol), 0.072 g of methyl 4-nitrobenzoate **4.2a** (0.40 mmol), 0.052 g of molybdenumhexacarbonyl (0.2 mmol), 0.0051 g of 2,2-dimethylpropionic acid (0.05 mmol), 0.0023 g of $Pd(OAc)_2$ (0.01 mmol) and 0.5 mL of DCE. Purification via MPLC (0:100 – 35:65, EtOAc:hexanes) afforded **4.9a** as a yellow solid (0.0186 g, 58%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.14 (s, 1H), 8.53 (dd, *J* = 4.9, 1.9 Hz, 1H), 8.01 – 7.93 (m, 2H), 7.83 (td, *J* = 7.8, 1.9 Hz, 1H), 7.67 – 7.56 (m, 2H), 7.36 (d, *J* = 8.0 Hz, 1H), 7.32 (dd, *J* = 7.4, 5.0 Hz, 1H), 7.23 – 7.14 (m, 1H), 6.99 (dd, *J* = 3.8, 1.7 Hz, 1H), 6.33 (t, *J* = 3.3 Hz, 1H), 3.88 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.7 (C), 159.1 (C), 152.2 (C), 148.2 (CH), 142.6 (C), 138.8 (CH), 130.8 (CH), 127.8 (CH), 127.7 (C), 125.2 (C), 122.8 (CH), 119.4 (CH), 118.9 (CH), 117.3 (CH), 110.0 (CH), 52.0 (CH_3); IR (thin film): 1716, 1673, 1592, 1533, 1474, 1447, 1280, 1175, 1113, 770 cm^{-1}; HRMS: (EI) m/z calcd for $C_{18}H_{16}N_3O_3$ $[M+H]^+$: 322.1192, found 322.1185.



4.9b

Amide (4.9b). The general method was followed adding 0.0158 g of 2-(2-methyl-1*H*-pyrrol-1-yl)pyridine **4.8b** (0.10 mmol), 0.072 g of methyl 4-nitrobenzoate **4.2a** (0.40 mmol), 0.052 g of molybdenumhexacarbonyl (0.2 mmol), 0.0051 g of 2,2-

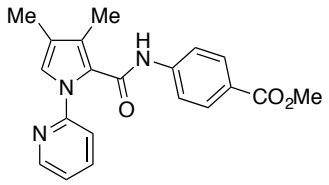
dimethylpropionic acid (0.05 mmol), 0.0023 g of $Pd(OAc)_2$ (0.01 mmol) and 0.5 mL of DCE. Purification via MPLC (0:100 – 35:65, EtOAc:hexanes) afforded **4.9b** as a white solid (0.0235 g, 70%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.60 (d, *J* = 4.2 Hz, 1H), 7.97 (s, 1H), 7.92 (d, *J* = 8.7 Hz, 2H), 7.86 (td, *J* = 7.7, 1.9 Hz, 1H), 7.50 (d, *J* = 8.8 Hz, 2H), 7.38 (dd, *J* = 7.5, 4.8 Hz, 1H), 7.33 (d, *J* = 7.8 Hz, 1H), 6.82 (d, *J* = 3.9 Hz, 1H), 6.07 (d, *J* = 3.9 Hz, 1H), 3.87 (s, 2H), 2.10 (s, 2H); IR (thin film): 1716, 1656, 1591, 1525, 1473, 1438, 1403, 1280, 1248, 1175, 1110, 769 cm^{-1}; HRMS: (EI) m/z calcd for $C_{19}H_{18}N_3O_3$ $[M+H]^+$: 336.1348, found 336.1343.



4.9c

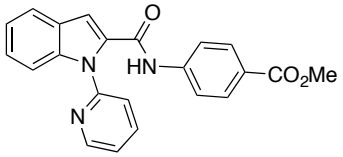
Amide (4.9c). The general method was followed adding 0.0158 g of 2-(3-methyl-1*H*-pyrrol-1-yl)pyridine **4.8c** (0.10 mmol), 0.072 g of methyl 4-nitrobenzoate **4.2a** (0.40 mmol), 0.052 g of molybdenumhexacarbonyl (0.2 mmol), 0.0051 g of 2,2-dimethylpropionic acid (0.05 mmol), 0.0023 g of $Pd(OAc)_2$ (0.01 mmol) and 0.5 mL of DCE. Purification via MPLC (0:100 – 35:65, EtOAc:hexanes) afforded **4.9c** as a yellow solid (0.0204 g, 61%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.62 (s, 1H), 8.52 – 8.44 (m, 1H), 7.97 (d, *J* = 8.5 Hz, 2H), 7.79 (td, *J* = 7.8, 1.9 Hz, 1H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.32 – 7.19 (m, 2H), 7.07 (d, *J* = 2.8 Hz, 1H), 6.20 (d, *J* = 2.9 Hz, 1H), 3.89 (s, 3H), 2.41 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.7 (C), 160.2 (C), 152.3 (C), 148.4 (CH), 142.5 (C), 138.8 (CH), 130.9 (CH), 128.3 (C), 125.6 (CH), 125.3 (C), 124.7 (C), 122.3 (CH), 118.7 (CH), 118.6 (CH), 113.0 (CH), 52.0 (CH_3), 13.1 (CH_3); IR (thin film): 1715, 1667,

1592, 1522, 1474, 1417, 1347, 1278, 1252, 1175, 1102, 771, 738 cm^{-1}; HRMS: (EI) m/z calcd for $C_{19}H_{18}N_3O_3$ $[M+H]^+$: 336.1348, found 336.1344.



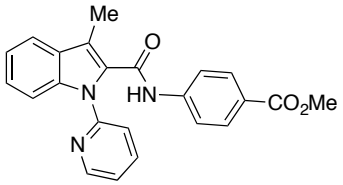
4.9d

Amide (4.9d). The general method was followed adding 0.0172 g of 2-(3,4-dimethyl-1*H*-pyrrol-1-yl)pyridine **4.8d** (0.10 mmol), 0.072 g of methyl 4-nitrobenzoate **4.2a** (0.40 mmol), 0.052 g of molybdenumhexacarbonyl (0.2 mmol), 0.0051 g of 2,2-dimethylpropionic acid (0.05 mmol), 0.0023 g of $Pd(OAc)_2$ (0.01 mmol) and 0.5 mL of DCE. Purification via MPLC (0:100 – 35:65, EtOAc:hexanes) afforded **4.9d** as a yellow solid (0.021 g, 60%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.80 (s, 1H), 8.44 (dd, *J* = 4.8, 1.9 Hz, 1H), 7.94 (d, *J* = 8.7 Hz, 2H), 7.75 (td, *J* = 7.8, 1.9 Hz, 1H), 7.56 (d, *J* = 8.3 Hz, 2H), 7.25 – 7.14 (m, 2H), 6.91 (s, 1H), 3.88 (s, 3H), 2.26 (s, 3H), 2.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.7(C), 160.5(C), 152.2(C), 148.2(CH), 142.6(C), 138.8(CH), 130.8(CH), 127.8(C), 125.2(C), 124.7(C), 123.6(CH), 121.9(CH), 121.1(C), 118.7(CH), 118.2(CH), 51.9(CH_3), 10.6(CH_3), 10.0(CH_3); IR (thin film): 1713, 1668, 1592, 1522, 1474, 1439, 1411, 1393, 1364, 1309, 1278, 1255, 1175, 1110, 770 cm^{-1}; HRMS: (EI) m/z calcd for $C_{20}H_{20}N_3O_3$ $[M+H]^+$: 350.1505, found 350.1496.



4.9e

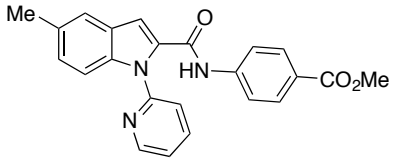
Amide (4.9e). The general method was followed adding 0.0194 g of 1-(pyridine-2-yl)-1*H*-indole **4.8e** (0.10 mmol), 0.072 g of methyl 4-nitrobenzoate **4.2a** (0.40 mmol), 0.052 g of molybdenumhexacarbonyl (0.2 mmol), 0.0051 g of 2,2-dimethylpropionic acid (0.05 mmol), 0.0023 g of $Pd(OAc)_2$ (0.01 mmol) and 0.5 mL of DCE. Purification via MPLC (0:100 – 35:65 EtOAc:hexanes) afforded **4.9e** as a white solid (0.023 g, 62%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.38 — 9.36 (m, 1H), 8.60 — 8.59 (m, 1H), 7.93 (td, *J* = 8.0, 2.0 Hz, 1H), 7.89 (d, *J* = 9.0 Hz, 2H), 7.55 (d, *J* = 9.0 Hz, 2H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.45 — 7.43 (m, 1H), 7.38 — 7.32 (m, 2H), 7.27 — 7.24 (m, 1H), 7.12 — 7.09 (m, 2H), 3.88 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.6 (C), 159.5 (C), 151.2 (C), 149.1 (CH), 142.2 (C), 138.8 (C), 138.8 (CH), 133.3 (C), 130.6 (CH), 126.7 (C), 125.5 (CH), 122.9 (CH), 122.2 (CH), 122.0 (CH), 121.4 (CH), 119.4 (CH), 110.8 (CH), 110.8 (C), 109.4 (CH), 52.0 (CH_3); IR (thin film): 3230, 3034, 1721, 1705, 1679, 1593, 1536, 1477, 1445, 1407, 1388, 1316, 1289, 1269, 1248, 1187, 1145, 1012 cm^{-1}; HRMS: (ES+) m/z calcd for $C_{22}H_{18}N_3O_3$ $[M+H]^+$: 372.1348, found 372.1342.



4,9f

Amide (4.9f). The general method was followed adding 0.0208 g of 3-methyl-1-(pyridin-2-yl)-1*H*-indole **4.8f** (0.10 mmol), 0.072 g of methyl 4-nitrobenzoate **4.2a** (0.40 mmol), 0.052 g of molybdenumhexacarbonyl (0.2 mmol), 0.0051 g of 2,2-dimethylpropionic acid (0.05 mmol), 0.0023 g of $Pd(OAc)_2$ (0.01 mmol) and 0.5 mL of DCE. Purification via MPLC (0:100 – 35:65, EtOAc:hexanes) afforded **4.9f** as a white solid (0.035 g, 91%).^{1}H

NMR ($CDCl_3$, 500 MHz) δ 8.78 (s, 1H), 8.56 (dd, *J* = 4.9, 1.9 Hz, 1H), 7.93 (d, *J* = 8.4 Hz, 2H), 7.86 (td, *J* = 7.7, 1.9 Hz, 1H), 7.56 (t, *J* = 9.0 Hz, 3H), 7.42 (dd, *J* = 8.2, 5.0 Hz, 2H), 7.35 – 7.26 (m, 2H), 7.20 (t, *J* = 7.5 Hz, 1H), 3.88 (s, 3H), 2.54 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.6 (C), 160.7 (C), 151.6 (C), 149.1 (CH), 142.1 (C), 138.8 (CH), 137.7 (C), 130.8 (CH), 130.2 (C), 128.6 (C), 125.8 (CH), 125.6 (C), 122.4 (CH), 121.6 (CH), 120.8 (CH), 120.5 (CH), 119.6 (C), 119.0 (CH), 111.0 (CH), 52.0 (CH_3), 9.9 (CH_3); IR (thin film): 1718, 1660, 1592, 1525, 1470, 1450, 1309, 1280, 1175, 1112, 771, 737 cm^{-1}; HRMS: (EI) m/z calcd for $C_{23}H_{20}N_3O_3$ $[M+H]^+$: 386.1505, found 386.1499.

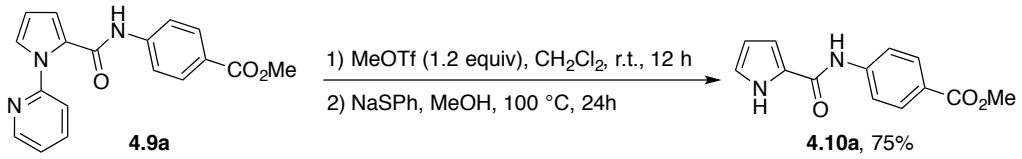


4.9g

Amide (4.9g). The general method was followed adding 0.0208 g of 5-methyl-1-(pyridin-2-yl)-1*H*-indole **4.8g** (0.10 mmol), 0.072 g of methyl 4-nitrobenzoate **4.2a** (0.40 mmol), 0.052 g of molybdenumhexacarbonyl (0.2 mmol), 0.0051 g of 2,2-dimethylpropionic acid (0.05 mmol), 0.0023 g of $Pd(OAc)_2$ (0.01 mmol) and 0.5 mL of DCE. Purification via MPLC (0:100 – 35:65 EtOAc:hexanes) afforded **4.9g** as a yellow solid (0.024 g, 62%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.69 (br, 1H), 8.57 (d, *J* = 4.0 Hz, 1H), 7.95 (t, *J* = 7.5 Hz, 1H), 7.84 (d, *J* = 8.5 Hz, 2H), 7.53 — 7.51 (m, 3H), 7.35 (t, *J* = 6.0 Hz, 1H), 7.19 (d, *J* = 8.5 Hz, 1H), 7.07 — 7.05 (m, 2H), 6.95 (s, 1H), 3.87 (s, 3H), 2.36 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.6 (C), 160.2 (C), 151.4 (C), 149.0 (CH), 142.4 (C), 138.8 (CH), 137.2 (C), 133.2 (C), 131.1 (C), 130.5 (CH), 127.1 (CH), 126.9 (C), 125.4 (C), 122.7 (CH), 121.8 (CH), 121.1 (CH), 119.6 (CH), 110.3 (CH), 109.2 (CH), 51.9 (CH_3), 21.3

(CH_3); IR (thin film): 2921, 2852, 1720, 1673, 1594, 1531, 1471, 1435, 1408, 1388, 1310, 1277, 1248, 1175, 1157, 1111, 1015 cm^{-1}; HRMS: (ES+) m/z calcd for $C_{23}H_{20}N_3O_3$ $[M+H]^+$: 386.1505, found 386.1498.

C. Removal of Directing Group.

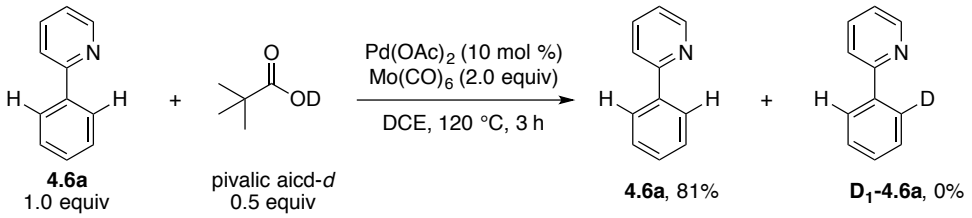


4.9a **4.10a**, 75%

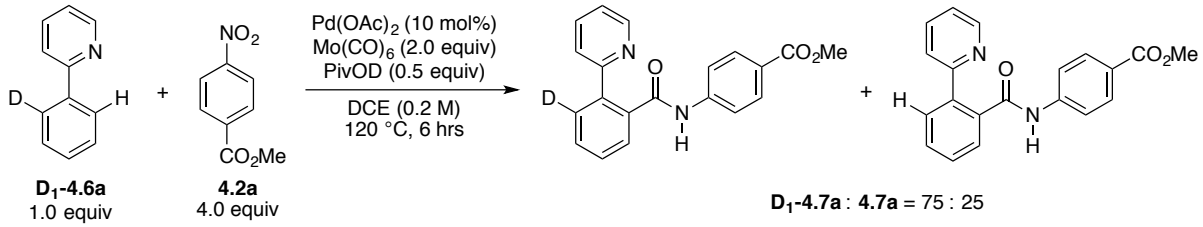
Methyl trifluoromethanesulfonate (0.24 mmol, 1.2 equiv) was added dropwise to a solution of **4.9a** (0.20 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL) at 0 °C, and the resulting solution was stirred for 12 h at ambient temperature. The solvent was removed *under vacuo*. Then, PhSNa (132 mg, 5.0 equiv) and MeOH (3.0 mL) were added and the resulting mixture was stirred at 100 °C for 24 h with a reflux condenser. The solvents were removed, and the resulting residue was acidified to pH = 7 by using HCl (1.0 M), then extracted with CH_2Cl_2 (4 × 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography to afford **4.10a** as a white solid (0.034 g, 75%). ^{1}H NMR (DMSO-d_6, 500 MHz) δ 11.72 (s, 1H), 10.02 (s, 1H), 7.97 – 7.80 (m, 4H), 7.11 (d, J = 3.0 Hz, 1H), 6.99 (d, J = 2.9 Hz, 1H), 6.17 (t, J = 3.0 Hz, 1H), 3.81 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 166.4 (C), 159.8 (C), 144.5 (C), 130.6 (CH), 126.1 (C), 124.0 (C), 123.7 (CH), 119.5 (CH), 112.6 (CH), 109.6 (CH), 52.3 (CH_3); IR (thin film): 3352, 3278, 1697, 1656, 1587, 1550, 1523, 1439, 1411, 1328, 1280, 1248, 1172, 1125, 1112, 889, 853, 768, 736,

696, 606 cm^{-1}. HRMS: (EI) m/z calcd for $C_{13}H_{13}N_2O_3$ $[M+H]^+$: 245.0926, found 245.0923.

D. Mechanistic Study.

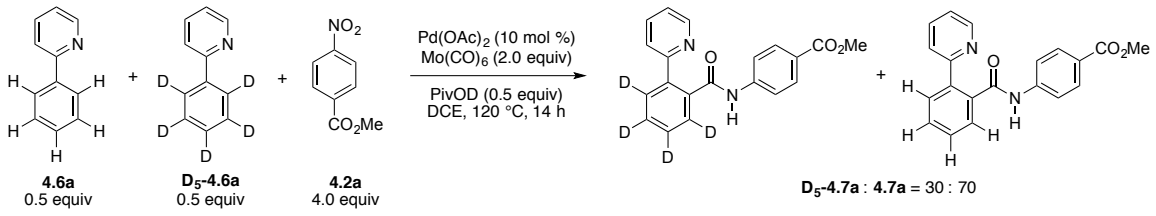


A 10 mL Schlenk tube was charged with 0.0023g of palladium acetate (0.01 mmol), 0.052g of molybdenumhexacarbonyl (0.2 mmol). Then 0.4 mL of solution of 2-phenylpyridine **4.6a** (0.1 mmol) in DCE (0.25M), and 0.1 mL of solution of pivalic acid-*d* in DCE (0.50 M) were added to the Schlenk tube. The Schlenk tube was sealed, stirred at ambient temperature for 5 to 7 minutes and heated at 120 °C for 3 hours. The entire procedure was performed under air atmosphere. 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 ^1H NMR spectroscopy with CH_2Br_2 as the internal standard revealed 0.081 mmol of **4.6a**.



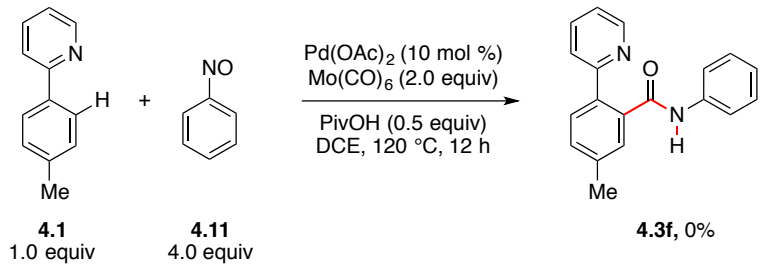
A 10 mL Schlenk tube was charged with 0.072 g of methyl 4-nitrobenzoate **4.2a** (0.4 mmol), 0.0023g of palladium acetate (0.01 mmol), 0.052g of molybdenumhexacarbonyl

(0.2 mmol). Then 0.4 mL of solution of **D_1-4.6a** (0.1 mmol) in DCE (0.25M), and 0.1 mL of solution of pivalic acid-*d* in DCE (0.50 M) were added to the Schlenk tube. The Schlenk tube was sealed, stirred at ambient temperature for 5 to 7 minutes and heated at 120 °C for 6 hours. The entire procedure was performed under air atmosphere. 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 crude mixture was purified by MPLC (3:97 – 35:65 EtOAc:hexane) to afford the mixture of **D_1-4.7a** and **4.7a**. Analysis of the mixture using ^{1}H NMR spectroscopy revealed the ratio of **D_1-4.7a** and **4.7a** was 75 : 25.



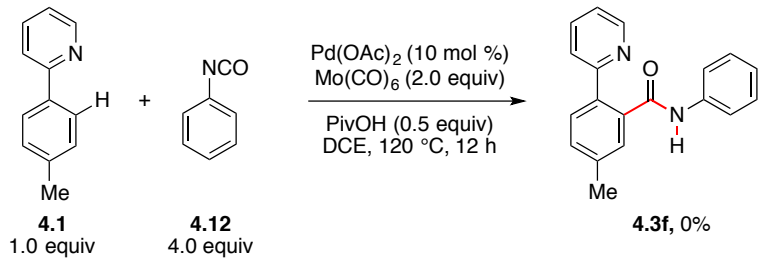
A 10 mL Schlenk tube was charged with 0.072 g of methyl 4-nitrobenzoate **4.2a** (0.4 mmol), 0.0023g of palladium acetate (0.01 mmol), 0.052g of molybdenumhexacarbonyl (0.2 mmol). Then 0.4 mL of solution of 2-phenylpyridine **4.6a** (0.05 mmol) and **D_5-4.6a** (0.05 mmol) in DCE and 0.1 mL of solution of pivalic acid-*d* in DCE (0.50 M) were added to the Schlenk tube. The Schlenk tube was sealed, stirred at ambient temperature for 5 to 7 minutes and heated at 120 °C for 14 hours. The entire procedure was performed under air atmosphere. 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 crude mixture was purified by MPLC (3:97 – 35:65 EtOAc:hexane) to

afford the mixture of **D_5-4.7a** and **4.7a**. Analysis of the mixture using ^{1}H NMR spectroscopy revealed the ratio of **D_5-4.7a** and **4.7a** was 30 : 70.



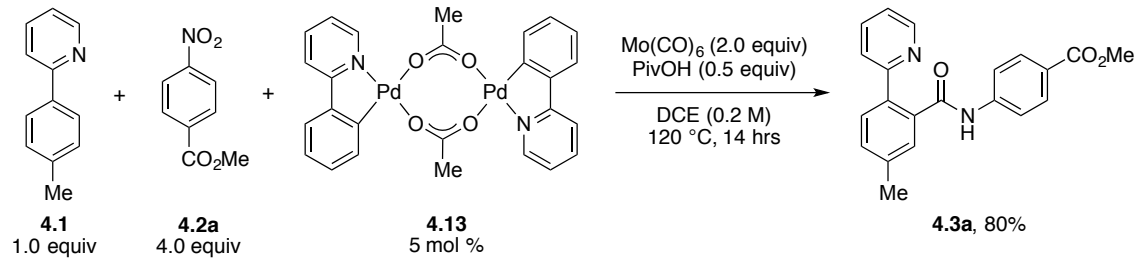
4.1 1.0 equiv **4.11** 4.0 equiv **4.3f,** 0%

A 10 mL Schlenk tube was charged with 0.043 g of nitrosobenzene **4.11** (0.4 mmol), 0.0023g of palladium acetate (0.01 mmol), 0.052g of molybdenumhexacarbonyl (0.2 mmol). Then 0.4 mL of solution of 2-(*p*-tolyl)pyridine **4.1** (0.1 mmol) in DCE (0.25M), and 0.1 mL of solution of pivalic acid in DCE (0.50 M) were added to the Schlenk tube. The Schlenk tube was sealed, stirred at ambient temperature for 5 to 7 minutes and heated at 120 °C for 12 hours. The entire procedure was performed under air atmosphere. 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 formation of **4.3f**.



4.1 1.0 equiv **4.12** 4.0 equiv **4.3f,** 0%

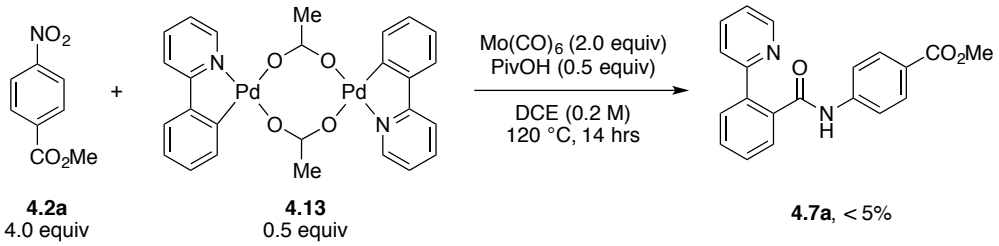
A 10 mL Schlenk tube was charged with 0.048 g of phenyl isocyanate **4.12** (0.4 mmol), 0.0023g of palladium acetate (0.01 mmol), 0.052g of molybdenumhexacarbonyl (0.2 mmol). Then 0.4 mL of solution of 2-(*p*-tolyl)pyridine **4.1** (0.1 mmol) in DCE (0.25M), and 0.1 mL of solution of pivalic acid in DCE (0.50 M) were added to the Schlenk tube. The Schlenk tube was sealed, stirred at ambient temperature for 5 to 7 minutes and heated at 120 °C for 12 hours. The entire procedure was performed under air atmosphere. 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 formation of **4.3f**.



4.1 1.0 equiv | **4.2a** 4.0 equiv | **4.13** 5 mol % | **4.3a**, 80%

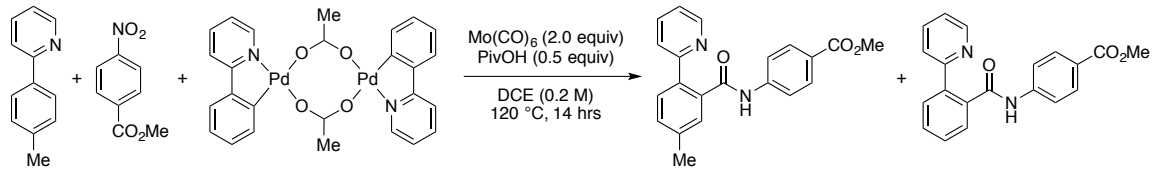
A 10 mL Schlenk tube was charged with 0.072 g of methyl 4-nitrobenzoate **4.2a** (0.4 mmol), 0.0032g of **4.13** (0.005 mmol), 0.052g of molybdenumhexacarbonyl (0.2 mmol). Then 0.4 mL of solution of 2-(*p*-tolyl)pyridine **4.1** (0.1 mmol) in DCE (0.25M), and 0.1 mL of solution of pivalic acid (0.05 mmol) in DCE (0.50 M) were added to the Schlenk tube. The Schlenk tube was sealed, stirred at ambient temperature for 5 to 7 minutes and heated at 120 °C for 14 hours. The entire procedure was performed under air atmosphere. 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 0.080 mmol of **4.3a**.



4.2a 4.0 equiv | **4.13** 0.5 equiv | **4.7a**, < 5%

A 10 mL Schlenk tube was charged with 0.072 g of methyl 4-nitrobenzoate **4.2a** (0.40 mmol), 0.032g of **4.13** (0.05 mmol), 0.052g of molybdenumhexacarbonyl (0.20 mmol). Then 0.5 mL of solution pivalic acid (0.05 mmol) in DCE was added to the Schlenk tube. The Schlenk tube was sealed, stirred at ambient temperature for 5 to 7 minutes and heated at 120 °C for 14 hours. The entire procedure was performed under air atmosphere. 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 0.005 mmol of **4.7a**.



4.1 1 equiv | **4.2a** 4 equiv | **4.13** 0.25 equiv | **4.3a** | **4.7a**

A 10 mL Schlenk tube was charged with 0.072 g of methyl 4-nitrobenzoate **4.2a** (0.40 mmol), 0.016g of **4.13** (0.025 mmol), 0.052g of molybdenumhexacarbonyl (0.20 mmol). Then 0.40 mL of solution of 2-(*p*-tolyl)pyridine **4.1** (0.10 mmol) in DCE, and 0.10 mL of solution pivalic acid (0.05 mmol) in DCE were added to the Schlenk tube. The Schlenk

tube was sealed, stirred at ambient temperature for 5 to 7 minutes and heated at 120 °C for 14 hours. The entire procedure was performed under air atmosphere. 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 the ratio of 0.067 mmol of **4.3a** and 0.030 mmol of **4.7a**. The crude mixture was purified by MPLC (3:97 – 35:65 EtOAc:hexane) to afford the mixture of **4.3a** and **4.7a**.

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Chapter V

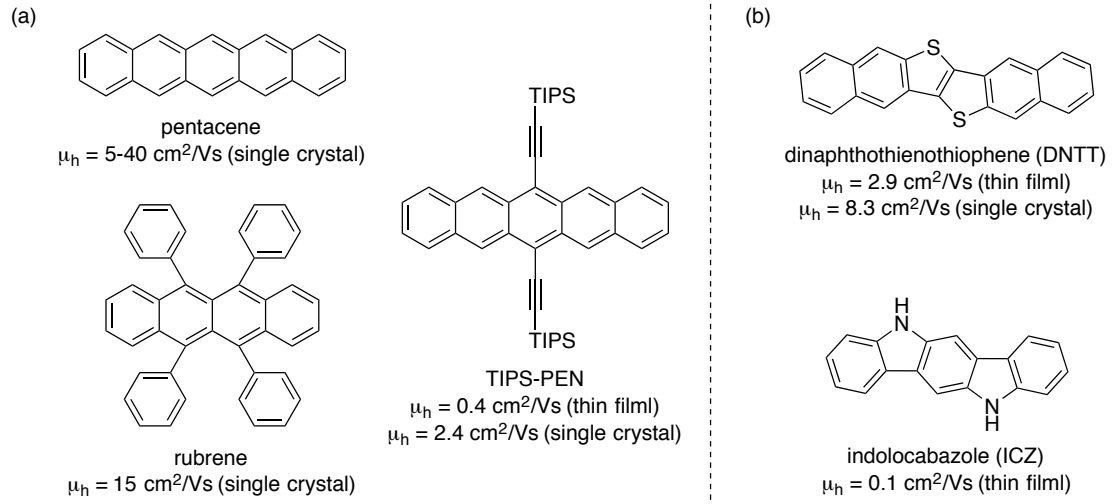
Synthesis and Properties of *N*-heteroheptacenes for Solution-based Organic Field Effect Transistors

The potential of semiconducting polymers and fused-oligomeric aromatic molecules continues to inspire significant research interest because of their easier processibility and tunability.[1,2] Ladder-shape linear polyacenes, such as rubene, pentacene and higher acenes, have been investigated because of their high mobility (Fgure 1a). Impressive performance was achieved using pentacene[3,4] and single crystal rubrene[5]. Their potential, however, is limited by difficult processing because of their low environmental stability and poor solubility in organic solvents.[6] In contrast, field effect transistors based on benzo-fused heteroaromatic small molecules,[7-12] rylenediimides[13] and diketopyrrole (DPP)-based polymers[14-22] have emerged as significant alternatives because of their good to high solubility in organic solvents, which facilitates solution-based processing. Devices constructed with these soluble materials exhibit hole- and electron mobilities surpassing 5 $cm^2 \cdot V^{-1} \cdot s^{-1}$ and as high as 15 $cm^2 \cdot V^{-1} \cdot s^{-1}$. Despite this significant progress, the synthesis of new, easily tunable organic materials continues to be targeted in order to understand the fundamental properties of the material and to construct solution-processed devices that exploit their properties.

Because of their weaknesses, significant strides have been made to develop ladder-based acenes and heteroacenes into solution-processable and air-stable field effect transistors. In acenes, solubilizing substituents were installed to enable the solution-based

process, and improve the stability against oxidation or dermerization (Figure 5.1a). Studies on pentacene derivatives shown the substituents also exerted significant impacts on the packing motif in the solid state.[23-25] Heteroatom replacement to the backbone of these carbon-based acenes improves the stability of the acene by lowering its HOMO as well as improves its solubility by enabling substitution on the heteroatoms. Accordingly, significant attention has been spent on thiophene-[7,11] and pyrrole-based[12,26] heteroacenes to produce promising materials (Scheme 5.1b). Heteroatom substitution in these materials results improved secondary interactions, including hydrogen bonding and interacetion between heteroatoms, to benefit their crystal packing. These materials have been used to construct organic field effect devices that exhibit mobility up to 8.3 cm^2/Vs.

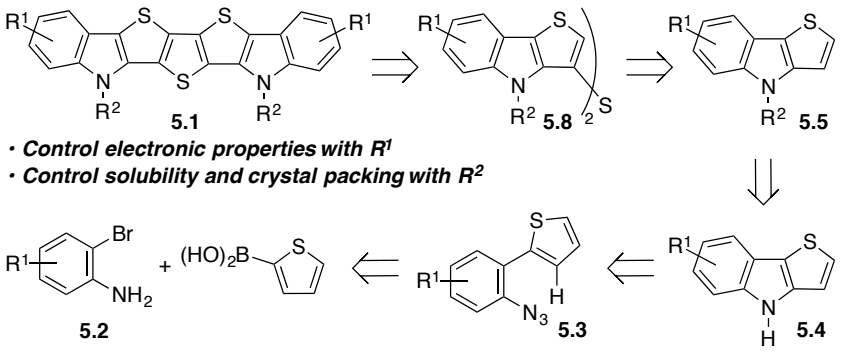
Scheme 5.1 ***Ladder-based acenes and heteroacene electronic materials***



To address these weaknesses, we targeted *N*-heteroheptacenes **5.1** because we anticipated that both their electronic properties and solubility could be controlled by the

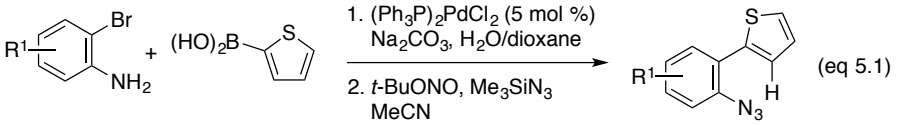
choice (or identity) of the indole R^1-substituent or nitrogen R^2-substituent (Scheme 5.2). We anticipated that these latter heterocycles could be assembled by constructing the central thiophene ring from two molecules of thienoindole **5.5**. *N*-Alkylation or *N*-arylation of **5.4** was envisioned to control the solubility and potentially the crystal packing of the target *N*-heteroacene. A series of thienoindoles **5.4** would be created from *ortho*-substituted aryl azides **5.3** through a Rh_2(II)-catalyzed C–H amination reaction. Our reaction[27-29] would enable varying the electronic nature of the *N*-heteroheptacene **5.1** by varying the identity of the R^1-substituents on the arene. The requisite aryl azides would be constructed from the appropriate 2-bromoanilines **5.2** through a Suzuki–Miyaura cross-coupling reaction followed by an azidation reaction. If successful, this modular route would enable variation of the bulk properties of *N*-heteroacene by substituting both the nitrogen- and the indole portion.

Scheme 5.2 ***Potential synthesis of N-heteroacenes through Rh_2(II)-catalyzed C–H bond amination.***



The synthesis of a focused library of *N*-heteroheptacenes started with the construction of a series of *ortho*-substituted aryl azides **5.3** for Rh_2(II)-catalyzed C–H

bond amination reaction (eq 5.1). These substrates were accessed from cross-coupling commercially available 4- and 5-substituted 2-bromoanilines **5.2** and thiophene boronic acid. Bromoanilines for our study were chosen to contain either electron-donating OMe-, electron-neutral H-, or electron-withdrawing F- or CF_3 R^1-substituents. At the outset of the study, we anticipated that electron-withdrawing groups would be necessary to offset inherent electron-richness of the thienoindole core. After introduction of the *ortho*-thiophene substituent using an unoptimized Suzuki–Miyaura reaction, the azide was installed using conditions reported by Moses and co-workers.[30,31] Submission of the anilines to *tert*-butyl nitrite and trimethylsilyl azide smoothly converted the 2-substituted anilines to the requisite aryl azide **3**.

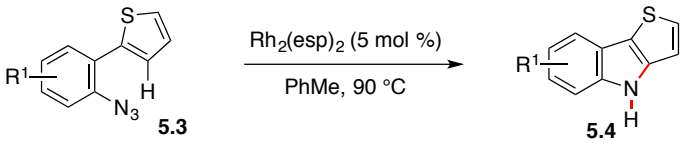


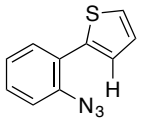
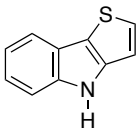
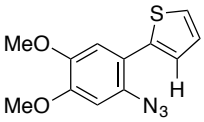
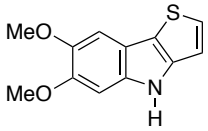
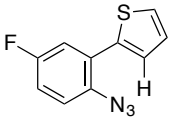
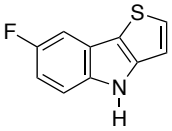
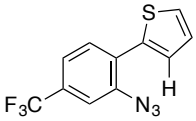
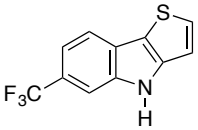
5.2 **5.3**

The thienoindole cores were assembled from aryl azides **5.3** using our Rh_2(II)-catalyzed amination reaction (Table 5.1). After a brief survey of Rh_2(II)-carboxylates, the best catalyst for this transformation was found to be Du Bois's $Rh_2(esp)_2$.[32] Exposure of aryl azide **5.3a** to this catalyst produced thienoindole **5.4a** in nearly quantitative yield. In contrast, thermolysis of **5.3a** produced the thienoindole in only 70% yield. Further, the Rh_2(II)-catalyzed heterocycle formation could be scaled to 5 mmol without reduction of the yield. In a similar fashion, electron-rich aryl azide **5.3b** or electron-deficient aryl azides **5.3c** and **5.3d** were cleanly converted to the analogous substituted thienoindoles **5.4b**–**5.4d** without any complications. We anticipated that the presence of the electron-donating- or electron-withdrawing R^1-substituents on these thienoindole scaffolds would

serve as a focused basis set to modulate the electronic properties of the *N*-heteroheptacene targets.

Table 5.1 ***Rh₂(II)-Catalyzed thienoindole synthesis.***



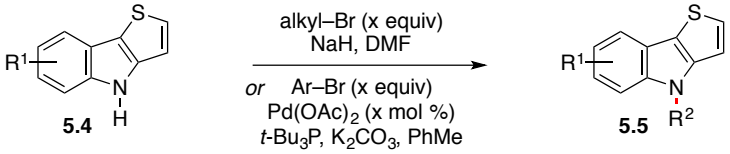
entry	#	aryl azide **5.3**	thienoindole **5.4**	yield, %[a]
1	a			95(70)[b]
2	b			82(66)[b]
3	c			91(68)[b]
4	d			75(59)[b]

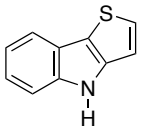
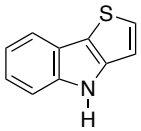
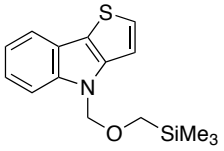
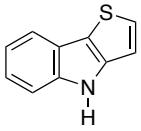
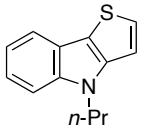
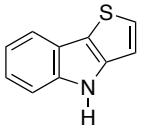
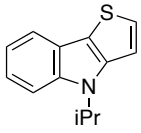
[a] Isolated after silica gel chromatography. [b] Thermolysis conditions: xylenes, 150 °C, 16 h.

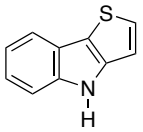
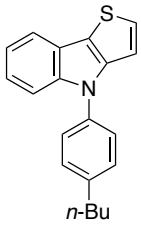
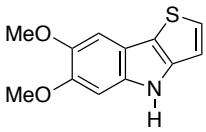
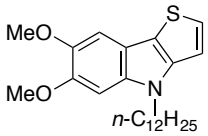
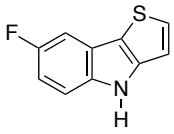
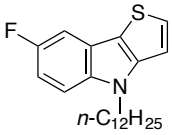
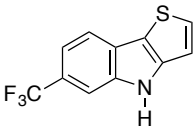
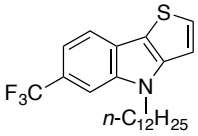
With a series of thienoindoles in hand, the next stage of the synthesis was to add a substituent to the nitrogen in order to attempt to vary the solubility and crystal packing properties of the *N*-heteroacene targets (Table 5.2). To improve the solubility of the *N*-heteroacene, an *n*-dodecyl group was added **(**entry 1**)**. In addition, *N*-alkyl and aryl substituents were appended to determine their effect on the bulk properties of the *N*-heteroacene. A removable SEM group was attached to determine if the identity of the *N*-substituent could be modified at a late stage (entry 2). An *n*-propyl substituent was added

to see if its effect on the solubility of the acene (entry 3). An isopropyl substituent was installed to determine if the additional substitution on the aminomethylene might affect the crystal packing (entry 4). Finally an aryl substituent was added to determine if additional π–π interactions could be introduced between the stacked acenes (entry 5). To an enable comparison to **5.5a**, *n*-dodecyl groups were added to the unsubstituted thienoindoles **5.4f**–**5.4h** (entries 6–8). Together, we anticipated that these *N*-substituents would enable us to begin to develop a structure activity relationship for the *N*-heteroacene target.

Table 5.2 ***N-Alkylation or N-arylation of thienoindole 5.5.***



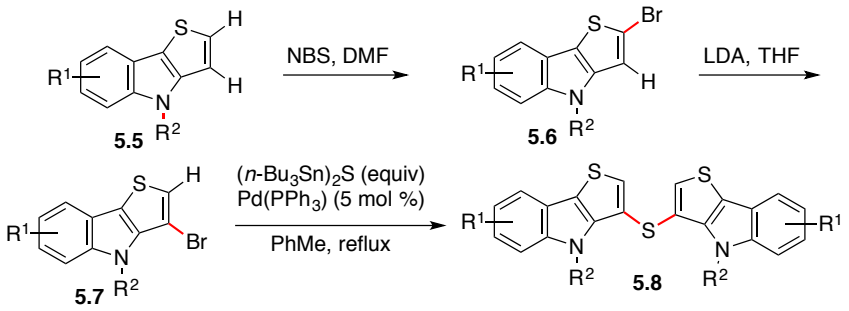
entry	#	thienoindole **5.4**	thienoindole **5.5**	yield, %[a]
1	a			91
2	b			92
3	c			90
4	d			66

entry	#	thienoindole **5.4**	thienoindole **5.5**	yield, %[a]
5	e			64
6	f			85
7	g			92
8	h			84

[a] Isolated after silica gel chromatography.

Next, dimerization of the thienoindoles was accomplished by installing the central thioether bond (Scheme 5.3). Towards this end, C2 bromination of **5.5** was achieved using *N*-bromosuccinimide. Following the report of Kano and co-workers,[33,34] an LDA-mediated "halogen-dance" isomerized **5.6** to the C3-brominated thienoindole **5.7**. The critical central thioether fragment was installed using a Pd-catalyzed Stille reaction using the conditions reported by Kosugi and co-workers.[34,35]

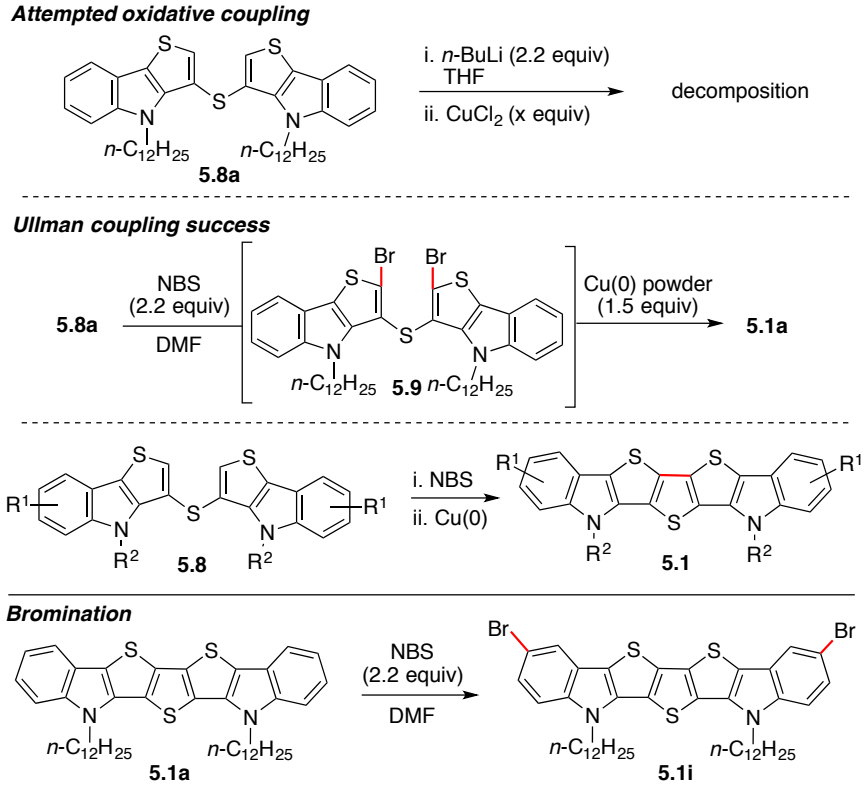
Scheme 5.3 ***Dimerization to form thioether 5.8.***



The final challenge was construction of the C–C bond to assemble the central thiophene ring (Scheme 5.4). The most common way to install this bond is through iterative deprotonation of the α-protons on the thiophene moieties followed by subsequent oxidation using $CuCl_2$.[36,37] Unfortunately, treatment of **5.8a** with these conditions produced only decomposition. Optimization by varying the identity of the base, molarity or copper species did not result in a positive outcome. We attribute this negative outcome to the increased instability of the di-ionized reactive intermediate in comparison to the successful cases in the literature. Recently, Paradies and co-workers have reported that this bond can be formed to produce dithienothiophenes through a Pd-catalyzed dihydro C–H bond coupling reaction.[38] Again, only decomposition was obtained in our system. Successful formation of the central thiophene ring was only realized in our system using an Ullman coupling reaction.[39] The requisite dibromide **5.9** was generated *in situ* through the addition of 2.2 equivalents of *N*-bromosuccinimide in dimethylformamide. After 2 h, 1.5 equivalents of copper powder (+45 μm particle size) was added and the resulting mixture was heated to reflux for 16 hours to produce *N*-heteroheptacene **5.1a**. Any deviation from these conditions had a significant deleterious effect on the reaction outcome. Using these optimized conditions, the central thiophene ring was installed in the other thioethers **5.8b** – **5.8h**. In line with our hypothesis,

bisdodecyl substituted *N*-heteroheptacene **5.1a** was highly soluble in organic solvents. Its solubility in toluene—a common solvent for ink jet printing—was 26 mg/mL (25 °C, 120 mg/mL at 60 °C). This solubility enabled further functionalization: dibromination of **5.1a** with *N*-bromosuccinimide smoothly produced *N*-heteroacene **5.1i** as a single regioisomer. With a focused library of *N*-heteroheptacenes in hand, our attention turned to examining their bulk properties in solution.

Scheme 5.4 ***Ullman coupling to form N-heteroheptacene 5.1.***



Absorption spectra and cyclic voltammetry were performed to study the photophysical and electrochemical properties of the *N*-heteroheptacenes (Table 5.3). Despite their different *N*-substituents, little variation was observed in the properties of

heteroacenes **5.1a** – **5.1d** (entries 1 – 5). All showed similar absorption properties with λ_{max} at 380 nm and a broad peak at approximately 390 nm. Based on the similar appearance of these spectra to related ladder heteroacenes, the peak at 380 nm is tentatively assigned to a π-π* transition and the lower energy peak to a transition that has some charge-transfer character. Consequently, these N-heteroheptacenes all display a similar HOMO-LUMO band gap of approximately 2.90 eV.

In contrast, the identity of the indole R^1-substituent exerted a much larger influence on both the photophysical and electrochemical properties of the *N*-heteroheptacene (entries 1, 5 and 6). In absorption spectra, while the trifluromethyl substituent only slightly changes the absorption peaks of **5.1h**, the dimethoxyl substituents increase the absorption peaks of **5.1f** by 16 and 19 nm. In comparison to **5.1a**, dimethoxy substituted **5.1h** exhibits a higher E_{HOMO} and E_{LUMO}. These higher positions suggest that it is has relatively poor stability towards, which is supported by the empirical observation that it changed from yellow to black under ambient conditions. Replacing the R^1 hydrogen with an electron-withdrawing substituent lowers the E_{HOMO} and E_{LUMO} with the largest drop observed with the bistrifluoromethyl substituted heteroacene **1g**, in which the positions of the HOMO and LUMO are lowered by 0.35 and 0.25 eV. These lowered positions manifest themselves in the observation of only a single oxidation peak in its cyclic voltammogram.

Table 5.3 ***Photophysical and electrochemical data of N-heteroheptacenes 5.1.***

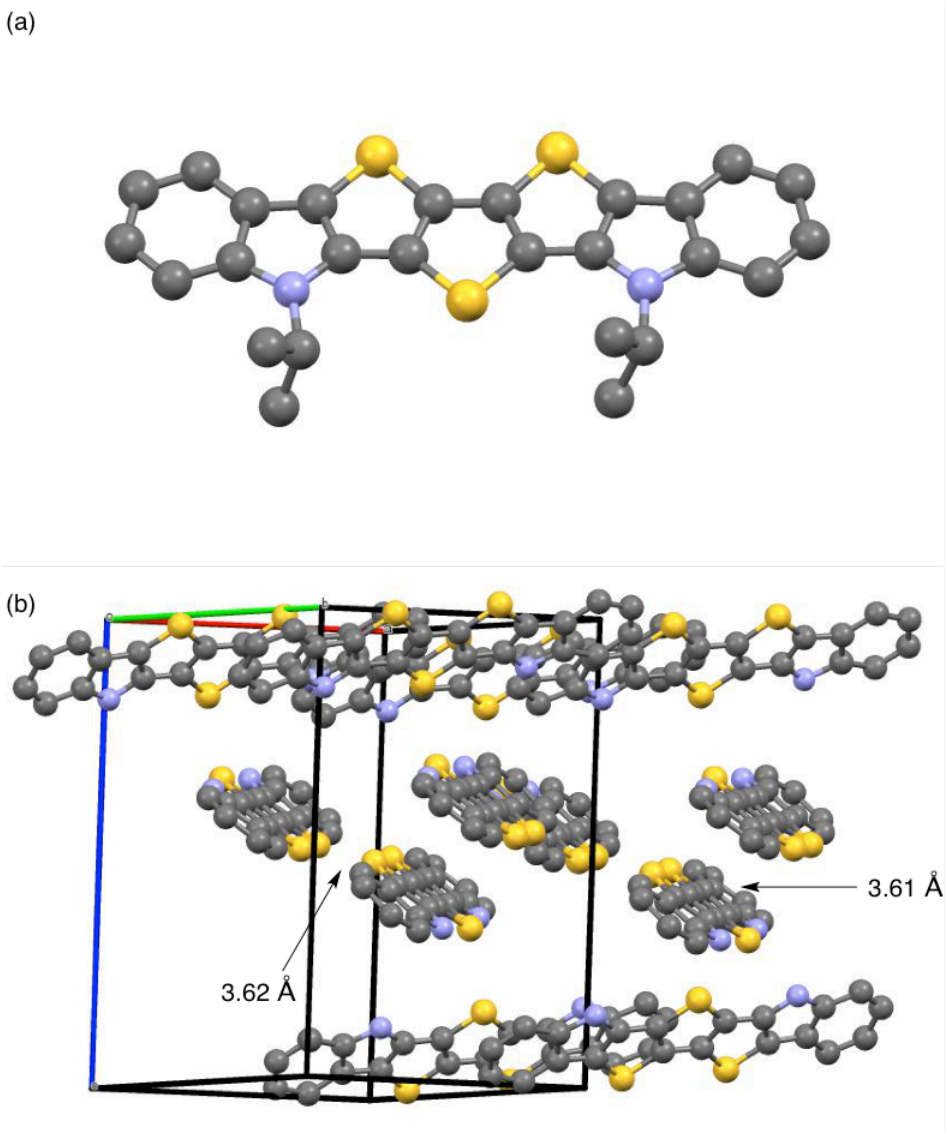
entry	#	λ_{abs} (nm)[a]	E_G (eV)[b]	E_{ox} (V)[c]	E_{ox}^{onset} (V)	E_{HOMO}[d]	E_{LUMO}[e]
1	**5.1a**	377, 397	2.94	0.73, 1.38	0.55	–4.93	–1.99
2	**5.1b**	378, 398	2.93	0.77, 1.37	0.55	–4.93	–2.00

entry	#	λ_{abs} (nm)[a]	E_G (eV)[b]	E_{ox} (V)[c]	E_{ox}^{onset} (V)	E_{HOMO}[d]	E_{LUMO}[e]
3	**5.1c**	381, 402	2.92	0.65, 1.38	0.56	–4.94	–2.02
4	**5.1d**	382, 403	2.95	0.77, 1.37	0.56	–4.94	–1.99
5	**5.1f**	393, 416	2.81	0.51, 0.95	0.20	–4.58	–1.77
6	**5.1h**	384, 407	3.00	1.01	0.86	–5.24	–2.24

[a] Measured in a CH_2Cl_2 solution (1×10^{-6} M). [b] Estimated from the onset of absorption. [c] Potentials vs Ag/AgCl obtained from cyclic voltammetry: 0.1 M *n*-Bu_4NPF_6 in CH_2Cl_2, Pt as the working electrode with a scan rate of 50 $mV \cdot s^{-1}$. The potentials are calibrated with ferrocene as the internal standard. [d] Calculated using the relationship $E_{HOMO} = -(E_{ox}^{onset} + 4.38)$. [e] Derived from E_G and E_{HOMO}.

While the identity of the *N*-substituent did not affect the solution phase electronic nature of the *N*-heteroheptacenes, it did affect their crystal packing. While *N*-heteroacene **5.1a** proved resistant to crystallization, single crystals of **5.1c** and **5.1e** suitable for single-crystal X-ray analysis were obtained by slow evaporation from a mixture of hexanes and dichloromethane at room temperature. Crystal analysis revealed that both *N*-heteroheptacenes **5.1c** and **5.1e** are planar (Figure 5.1). *N*-Isopropyl heteroheptacene **5.1c** packs in an edge-face manner, which leads to a herringbone structure. To minimize the steric effect imposed by the isopropyl substituents, the antiparallel dimer was only formed with the closed C–C distance of 3.61 Å. Within one layer, the S···S interaction of 3.62 Å dominates the distance between the dimers. We attribute edge-face relationship between the layers to the C–H···π interaction of 2.80 Å between a hydrogen atom of the isopropyl group and the backbone of the adjacent molecule.

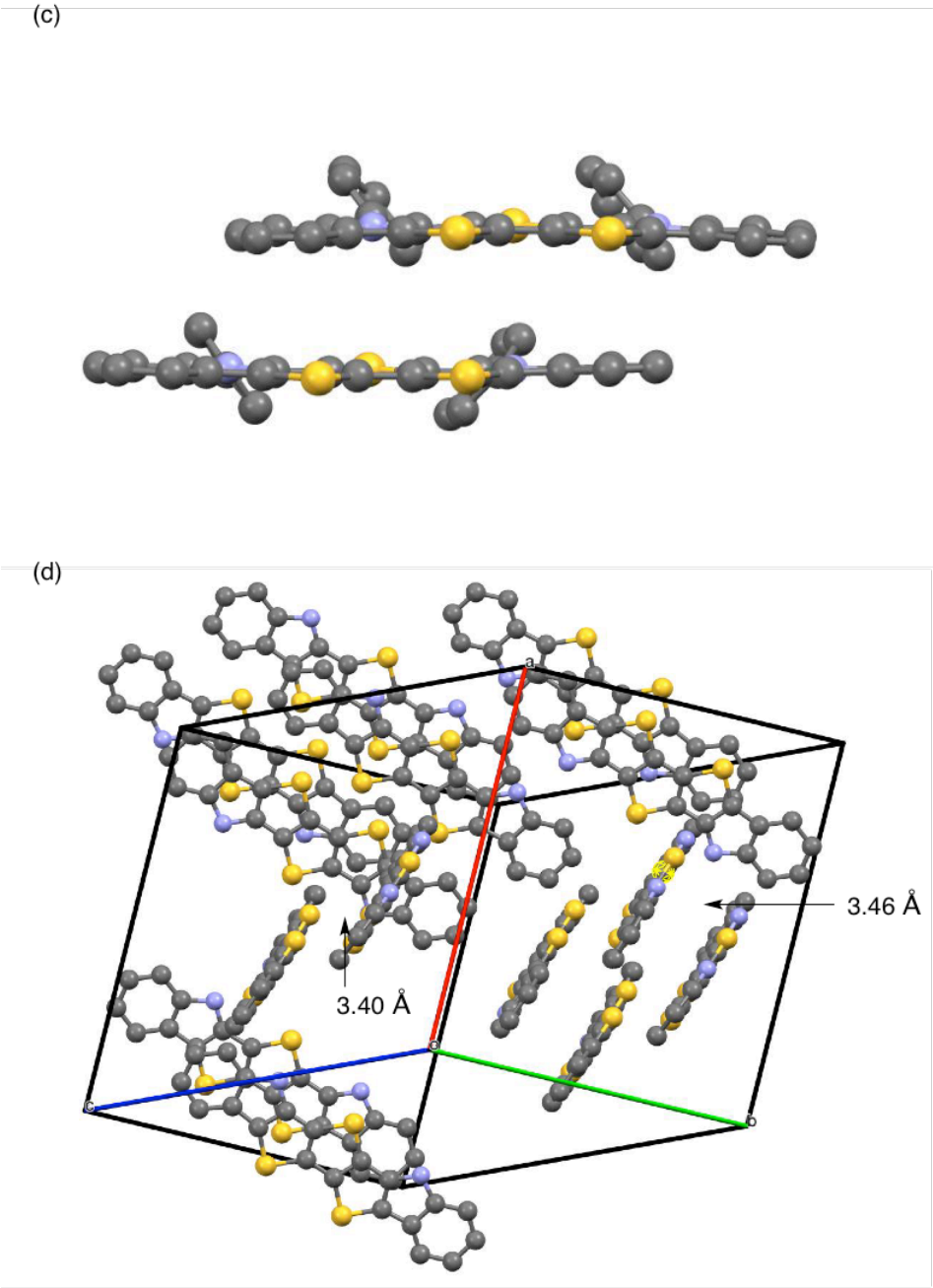
Figure 5.1 ***(a) X-Ray crystal structure of N-heteroheptacene 5.1c. Hydrogen atoms were removed for clarity. (b) Packing motif of N-heteroheptacene 5.1c. Hydrogen atoms and isopropyl groups were removed for clarity.***



In comparison to **5.1c**, *N*-heteroheptacene **5.1e** has a more complicated crystal structure (Figure 5.2). This increased complexity is attributed to the inconsistent torsion angle of the *N*-4-*n*-butylphenyl-substituent within the crystal. In this crystal, two molecules form a parallel dimer to obtain a wide intermolecular π-π stacking that exhibits a closest C–C distance of 3.46 Å. While one molecule shows two parallel aryl groups with a torsion angle of 51.4° and 56.2° with respect to the acene core, the other molecule's aryl groups exhibit a torsion angles 47.1° and 125.9°. This arrangement may

be due to the C–H···π interaction of 3.02 Å between the hydrogen atom (H261) of the aryl group and the π-system of the aryl group in the other molecule. In comparison to **5.1c**, the shorter distance of 3.40 – 3.42 Å between the dimers indicates that S···S interactions are more significant. These interactions lead to a herringbone packing of *N*-heteroheptance **5.1e**.

Figure 5.2 ***(a) X-Ray crystal structure of N-heteroheptacene 5.1e. Hydrogen atoms and n-butyl groups removed for clarity. (b) Packing motif of N-heteroheptacene 5.1e. Hydrogen atoms and n-butylphenyl groups removed for clarity.***



A series of top-gate/bottom-contact thin-film transistors were fabricated using the *N*-heteroacenes **5.1a** – **5.1g**. The semiconductor thin films (ca. 40 – 50 nm) were deposited on untreated Au (S-D contacts)/glass substrates by spin-coating the solutions (ca. 5 – 10 mg·mL^{-1}). After mild film annealing at 110 °C in air for 5 min the Au-gate

electrode was deposited by thermal evaporation. All the device processing and electrical measurements were performed in an ambient atmosphere, except for the Au contact vapor deposition. Among the six *N*-heteroacenes examined, only **5.1a** showed hole-transport mobility of 0.02 $cm^2 \cdot V^{-1} \cdot s^{-1}$ when the thin film was processed with dichlorobenzene as the solvent. Using the single crystal structure of **5.1c** as a model, we attribute the hole-transport properties of **5.1a** to the sterically smaller *N*-dodecyl substituent, which allows for better orbital overlap between the neighboring molecules. The mobility, however, is attenuated from the herringbone crystal packing, whose structure is common among five- or seven-ringed heteroacenes. Other reported thienoindole-based heteroacenes show hole-transport mobility in the absence of *N*-substituents. The success of the *N*-dodecyl substituted **5.1a** in a thin-film field effect transistor encourages future investigation of this *N*-heteroacene scaffold.

In conclusion, we have developed synthesis of a series of soluble *N*-heteroheptacenes with variable substituents on central pyrroles and side phenyl rings. The synthesize enables our study on their crystal structures and properties effected by the substituents. Hole mobility of 0.02 $cm^2\ V^{-1}\ s^{-1}$ was obtained with solution-processed OFET. Future studies to determine the optimal morphology and solution processing method for higher mobility are currently underway.

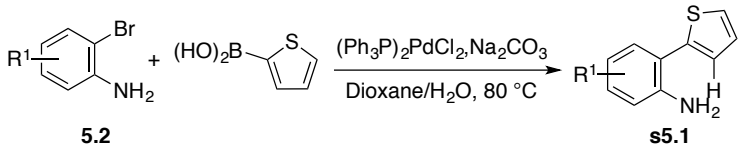
Experiment

A. General.

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

B. Synthesis of 2-(2-azidophenyl)thiophene

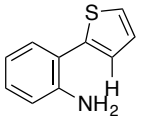
1. General Procedure for 2-(2-aminophenyl)thiophene.



5.2 **s5.1**

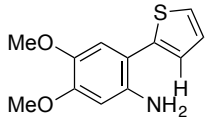
General procedure for synthesizing aniline **S5.1**: Under nitrogen atmosphere, to a 250 mL round bottom flask, a mixture of substituted 2-bromoaniline (1.0 equiv), thiophene-2-boronic acid (1.2 equiv), and $(Ph_3P)_2PdCl_2$ (5 mol %), 1,4-dioxane (0.133 M) was added. The resulting mixture was stirred at room temperature for 1.5 hour. Then 1.0 M Na_2CO_3 aqueous solution (2.5 equiv) was added. The reaction mixture was heated to 80 °C and stirred for 12 hrs. The reaction mixture was quenched with water and extracted with ethyl acetate. The organic phase was dried over Na_2SO_4, filtered, and the filtrate was concentrated *in vacuo*. Purification via MPLC afforded aniline product.

2. Characterization Data.



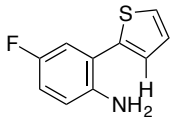
s5.1a

Aniline s5.1a. The general method was followed adding 1.72 g of 2-bromoaniline **5.2a** (10.0 mmol), 1.54 g of thiophene-2-boronic acid (12.0 mmol), 0.350 g of $(Ph_3P)_2PdCl_2$ (0.5 mmol), 75 mL of 1,4-dioxane, and 25 mL of 1.0 M Na_2CO_3 aqueous solution (25.0 mmol). Purification via MPLC (0:100 – 35:65 EtOAc:hexanes) afforded **s5.1a** as a yellow solid (1.66 g, 95%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.37 (dd, J = 5.0, 1.0 Hz, 1H), 7.33 (dd, J = 7.5, 1.0 Hz, 1H), 7.24 (dd, J = 3.5, 1.0 Hz, 1H), 7.20 – 7.14 (m, 2H), 6.83 (td, J = 7.5, 1.0 Hz, 1H), 6.79 (d, J = 8.0 Hz, 1H), 4.01 (br, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 144.1 (C), 141.2 (C), 131.1 (CH), 129.1 (CH), 127.6 (CH), 125.9 (CH), 125.3 (CH), 120.0 (C), 118.6 (CH), 115.9 (CH).



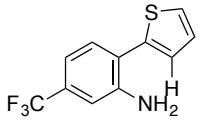
s5.1f

Aniline s5.1f. The general method was followed adding 2.32 g of 2-bromoaniline **5.2f** (10.0 mmol), 1.54 g of thiophene-2-boronic acid (12.0 mmol), 0.350 g of $(Ph_3P)_2PdCl_2$ (0.5 mmol), 75 mL of 1,4-dioxane, and 25 mL of 1.0 M Na_2CO_3 aqueous solution (25.0 mmol). Purification via MPLC (0:100 – 35:65 EtOAc:hexanes) afforded **s5.1f** as a brown solid (1.92 g, 82%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.32 (d, J = 5.0 Hz, 1H), 7.13 (dd, J = 3.5, 1.0 Hz, 1H), 7.10 (dd, J = 5.0, 3.5 Hz, 1H), 6.82 (s, 1H), 6.36 (s, 1H), 3.87 (s, 3H), 3.83 (s, 3H), 3.79 (br, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 150.0 (C), 142.0 (C), 141.3 (C), 138.2 (C), 127.6 (CH), 125.5 (CH), 124.8 (CH), 114.8 (CH), 111.4 (C), 100.7 (CH), 56.7 (CH_3), 55.9 (CH_3).



s5.1g

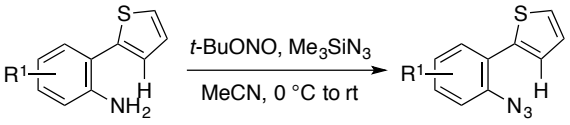
Aniline s5.1g. The general method was followed adding 1.90 g of 2-bromoaniline **5.2g** (10.0 mmol), 1.54 g of thiophene-2-boronic acid (12.0 mmol), 0.350 g of $(Ph_3P)_2PdCl_2$ (0.5 mmol), 75 mL of 1,4-dioxane, and 25 mL of 1.0 M Na_2CO_3 aqueous solution (25.0 mmol). Purification via MPLC (0:100 – 35:65 EtOAc:hexanes) afforded **s5.1g** as a green solid (1.75 g, 91%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.37 (d, J = 5.0 Hz, 1H), 7.22 (d, J = 3.5 Hz, 1H), 7.12 (dd, J = 5.0, 0.5 Hz, 1H), 7.02 (dd, J = 9.5, 3.0 Hz, 1H), 6.87 (td, J = 8.5, 3.0 Hz, 1H), 6.70 (dd, J = 9.0, 5.0 Hz, 1H), 3.87 (br, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 156.1 (d, J = 234.1 Hz, C), 140.2 (C), 140.0 (C), 127.7 (CH), 126.3 (CH), 125.7 (CH), 120.9 (d, J = 7.4 Hz, C), 116.9 (d, J = 29.5 Hz, CH), 116.9 (CH), 115.5 (d, J = 22.0 Hz, CH).



s5.1h

Aniline s5.1h. The general method was followed adding 2.41 g of 2-bromoaniline **5.2h** (10.0 mmol), 1.54 g of thiophene-2-boronic acid (12.0 mmol), 0.350 g of $(Ph_3P)_2PdCl_2$ (0.5 mmol), 75 mL of 1,4-dioxane, and 25 mL of 1.0 M Na_2CO_3 aqueous solution (25.0 mmol). Purification via MPLC (0:100 – 35:65 EtOAc:hexanes) afforded **s5.1h** as a yellow solid (1.82 g, 75%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.41 (dd, *J* = 5.0, 0.5 Hz, 1H), 7.37 (d, *J* = 7.5 Hz, 1H), 7.26 (dd, *J* = 3.5, 1.0 Hz, 1H), 7.16 (dd, *J* = 5.0, 3.5 Hz, 1H), 7.03 (d, *J* = 8.0 Hz, 1H), 7.00 (s, 1H), 4.2 (br, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 144.4 (C), 139.5 (C), 131.4 (CH), 131.0 (q, *J* = 31.4 Hz, C), 127.8 (CH), 126.5 (CH), 126.1 (CH), 124.1 (q, *J* = 269.9 Hz, C) 123.0 (C), 114.9 (q, *J* = 3.6 Hz, CH), 112.2 (q, *J* = 3.6 Hz, CH).

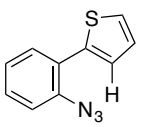
3. General Procedure for 2-(2-azidophenyl)thiophene.



s5.1 **5.3**

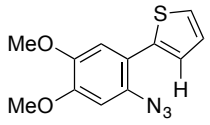
General procedure for synthesizing azide **5.3**: to a 100 mL round bottom flask, aniline **s5.1** (1.0 equiv) in acetonitrile (0.1 M) was added. The solution was cooled to 0 °C and *tert*-butyl nitrite (4.0 equiv) was added slowly. The resulting mixture was stirred at 0 °C for 10 minutes. Then azidotrimethylsilane (3.0 equiv) was added slowly at 0 °C The reaction mixture was warmed to room temperature and stirred for 4 hrs. The resulting solution was concentrated *in vacuo*. Purification via MPLC afforded the azide product.

4. Characterization Data.



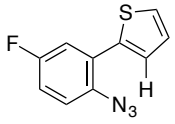
5.3a

Azide 5.3a. The general method was followed adding 0.875 g of aniline **s5.1a** (5.0 mmol), 2.38 mL of *tert*-butyl nitrite (20.0 mmol) and 1.99 mL of azidotrimethylsilane (15.0 mmol). Purification via MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **5.3a** as a brown oil (0.954 g, 95%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.61 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.46 (dd, *J* = 3.5, 1.0 Hz, 1H), 7.39 (dd, *J* = 5.5, 2.0 Hz, 1H), 7.35 (td, *J* = 8.0, 1.5 Hz, 1H), 7.26 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.19 (td, *J* = 7.5, 1.0 Hz, 1H), 7.13 (dd, *J* = 5.0, 3.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 139.1 (C), 136.4 (C), 130.1 (CH), 128.6 (CH), 127.2 (CH), 126.8 (CH), 126.2 (CH), 125.0 (CH), 119.1 (CH), only peaks visible.



5.3f

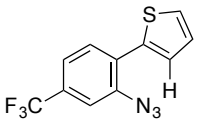
Azide 5.3f. The general method was followed adding 1.17 g of aniline **s5.1f** (5.0 mmol), 2.38 mL of *tert*-butyl nitrite (20.0 mmol) and 1.99 mL of azidotrimethylsilane (15.0 mmol). Purification via MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **5.3f** as a yellow oil (1.07 g, 82%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.33 – 7.32 (m, 2H), 7.08 (dd, *J* = 5.0, 4.0 Hz, 1H), 7.03 (s, 1H), 6.71 (s, 1H), 3.94 (s, 3H), 3.90 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 149.5 (C), 146.5 (C), 139.2 (C), 128.7 (C), 127.1 (CH), 126.1 (CH), 125.5 (CH), 118.5 (C), 112.9 (CH), 102.5 (CH), 56.3 (CH_3), 56.2 (CH_3).



5.3g

Azide 5.3g. The general method was followed adding 0.965 g of aniline **s5.1g** (5.0 mmol), 2.38 mL of *tert*-butyl nitrite (20.0 mmol) and 1.99 mL of azidotrimethylsilane (15.0 mmol). Purification via MPLC (0:100 – 10:90 EtOAc:hexanes) afforded **5.3g** as a

brown oil (0.854 g, 78%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.46 (dd, *J* = 4.0, 1.0 Hz, 1H), 7.40 (dd, *J* = 5.0, 1.0 Hz, 1H), 7.31 (dd, *J* = 9.5, 3.0 Hz, 1H), 7.19 (dd, *J* = 8.5, 4.5 Hz, 1H), 7.11 (dd, *J* = 5.5, 4.0 Hz, 1H), 7.04 (ddd, *J* = 9.0, 7.5, 3.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.7 (d, *J* = 242.4 Hz, C), 137.9 (C), 132.1 (C), 127.3 (CH), 127.0 (CH), 120.5 (CH), 120.4 (CH), 116.4 (d, *J* = 23.9 Hz, CH), 115.3 (d, *J* = 23.9 Hz, CH), only peaks visible.

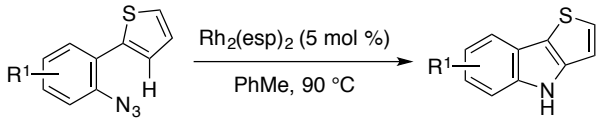


5.3h

Azide 5.3h. The general method was followed adding 1.21 g of aniline **s5.1h** (5.0 mmol), 2.38 mL of *tert*-butyl nitrite (20.0 mmol) and 1.99 mL of azidotrimethylsilane (15.0 mmol). Purification via MPLC (0:100 – 10:90 EtOAc:hexanes) afforded **5.3h** as a brown solid (0.941 g, 70%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.71 (d, *J* = 8.0 Hz, 1H), 7.53 (dd, *J* = 3.5, 1.0 Hz, 1H), 7.45 – 7.44 (m, 2H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.13 (dd, *J* = 5.0, 4.0 Hz, 1H) ; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 137.6 (C), 136.9 (C), 130.5 (q, *J* = 33.1 Hz, C), 130.3 (CH), 129.4 (C), 127.9 (CH), 127.5 (CH), 127.4 (CH), 123.5 (q, *J* = 270.0 Hz, C), 121.7 (CH), 116.1 (q, *J* = 3.6 Hz, CH).

C. Thienoindole synthesis via Rh-catalyzed C–H amination from aryl azide

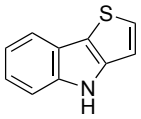
1. General Procedure.



5.3 **5.4**

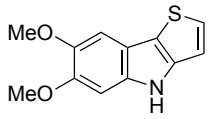
General Procedure: under nitrogen atmosphere, to 10 mL a Schlenk tube, a mixture of aryl azide **5.3** and $Rh_2(esp)_2$ (5 mol%) in toluene (0.1 M) was added. The Schlenk tube was sealed with a Teflon valve. The reaction mixture was heated to 90 °C and stirred for 16 hrs. Then the mixture was cooled to room temperature, diluted with CH_2Cl_2 and concentrated *in vacuo*. Purification of the residue via MPLC (0:100 to 20:80, EtOAc/hexanes) afforded the thienoindole products.

2. Characterization Data.



5.4a

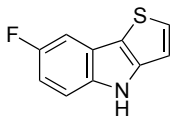
Thienoindole 5.4a. The general method was followed adding 0.020 g of aryl azide **5.3a** (0.10 mmol), 0.0038 g of $Rh_2(esp)_2$ (0.005 mol) and 1 mL of toluene. Purification via MPLC (0:100 – 20:80 EtOAc:hexanes) afforded **5.4a** as a yellow solid (0.016 g, 94%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.15 (br, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.43 (d, J = 8.0 Hz, 1H), 7.37 (d, J = 5.0 Hz, 1H), 7.28 (td, J = 7.5, 1.0 Hz, 1H), 7.20 (td, J = 7.5, 1.0 Hz, 1H), 7.07 (d, J = 5.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 143.1 (C), 141.2 (C), 127.0 (CH), 122.9 (CH), 122.2 (C), 119.8 (CH), 118.9 (CH), 118.1 (C), 111.9 (CH), 111.5 (CH).



5.4f

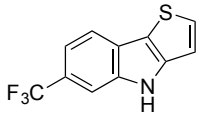
Thienoindole 5.4f. The general method was followed adding 0.026 g of aryl azide **5.3f** (0.10 mmol), 0.0038 g of $Rh_2(esp)_2$ (0.005 mol) and 1 mL of toluene. Purification via MPLC (0:100 – 20:80 EtOAc:hexanes) afforded **5.4f** as a green solid (0.020 g, 86%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.01 (br, 1H), 7.24 (d, J = 5.0 Hz, 1H), 7.20 (s, 1H), 6.99 (d, J

= 5.0 Hz, 1H), 6.87 (s, 1H), 3.96 (s, 3H), 3.90 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 147.2 (C), 144.7 (C), 142.4 (C), 135.6 (C), 124.9 (CH), 117.9 (C), 114.9 (C), 111.7 (CH), 101.1 (CH), 95.7 (CH), 56.4 (CH_3), 56.2 (CH_3).



5.4g

Thienoindole 5.4g. The general method was followed adding 0.022 g of aryl azide **5.3g** (0.10 mmol), 0.0038 g of $Rh_2(esp)_2$ (0.005 mol) and 1 mL of toluene. Purification via MPLC (0:100 – 20:80 EtOAc:hexanes) afforded **5.4g** as a yellow solid (0.017 g, 89%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.14 (br, 1H), 7.42 – 7.39 (m, 2H), 7.34 (dd, *J* = 9.0, 4.5 Hz, 1H), 7.06 (d, *J* = 5.0 Hz, 1H), 7.01 (td, *J* = 9.0, 2.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 157.7 (d, *J* = 233.1 Hz, C), 144.5 (C), 137.6 (C), 127.9 (CH), 122.4 (C), 117.8 (C), 112.4 (d, *J* = 10.1 Hz, CH), 111.5 (CH), 110.8 (d, *J* = 25.6 Hz, CH), 104.3 (d, *J* = 24.0, CH).

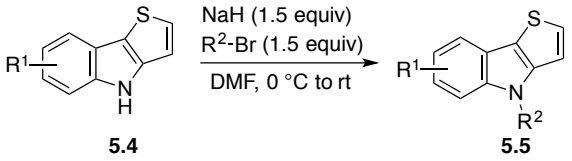


5.4h

Thienoindole 5.4h. The general method was followed adding 0.027 g of aryl azide **5.3h** (0.10 mmol), 0.0038 g of $Rh_2(esp)_2$ (0.005 mol) and 1 mL of toluene. Purification via MPLC (0:100 – 20:80 EtOAc:hexanes) afforded **5.4h** as a orange solid (0.021 g, 87%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.37 (br, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.71 (s, 1H), 7.47 (d, *J* = 5.0 Hz, 1H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.11 (d, *J* = 5.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 144.8 (C), 140.0 (C), 129.2 (CH), 125,0 (q, *J* = 269.7 Hz, C), 124.7 (q, *J* = 31.0 Hz, C), 124.4 (C), 119.0 (CH), 117.8 (C), 116.6 (q, *J* = 3.4 Hz, CH), 111.4 (CH), 109.2 (q, *J* = 5.4 Hz, CH).

D. Thienoindole *N*-alkylation or *N*-arylation.

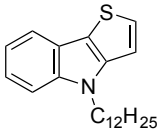
1. General Procudure.



5.4 **5.5**

General procedure for *N*-alkylation: A round bottom flask was flame-dried, evacuated and refill with nitrogen gas. The flask was charged with NaH (60 wt % dispersion in mineral oil, 1.5 equiv). Then a solution of thienoindole (1.0 equiv) in DMF (0.2 M) was added at 0 °C over 30 minutes. The suspension was warmed to room temperature and stirred for 90 minutes. Then alkylbromide (1.5 equiv) was added over 30 minutes. The reaction mixture was stirred at room temperature for 12 hrs. The reaction solution was diluted with water, extracted with EtOAc. The organic phase was washed with water and brine. The resulting solution was dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. Purification via MPLC afforded *N*-substituted thienoindole.

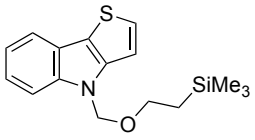
2. Characterization Data.



5.5a

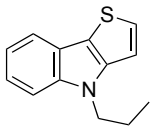
***N*-dodecyl thienoindole 5.5a**. The general method was followed adding 0.519 g of thienoindole **5.4a** (3.0 mmol), 0.180 g of NaH (60 wt % dispersion in mineral oil, 4.5 mmol), 1.12 g of 1-bromododecane (4.5 mmol) and 15 mL of DMF. Purification via MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **5.5a** as a yellow solid (0.931 g, 91%). ^{1}H

NMR ($CDCl_3$, 500 MHz) δ 7.76 (d, *J* = 8.0 Hz, 1H), 7.40 (d, *J* = 8.0 Hz, 1H), 7.37 (d, *J* = 5.0 Hz, 1H), 7.30 (t, *J* = 7.5 Hz, 1H), 7.17 (t, *J* = 7.5 Hz, 1H), 7.08 (d, *J* = 5.0 Hz, 1H), 4.26 (t, *J* = 7.0 Hz, 2H), 1.90 – 1.84 (m, 2H), 1.35 – 1.24 (m, 18H), 0.89 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 145.4 (C), 141.3 (C), 126.6 (CH), 122.3 (CH), 121.8 (C), 119.0 (CH), 118.9 (CH), 115.9 (C), 110.4 (CH), 109.9 (CH), 45.3 (CH_2), 31.9 (CH_2), 29.8 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 27.2 (CH_2), 22.7 (CH_2), 14.1 (CH_3), only peaks visible.



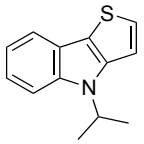
5.5b

***N*-sem thienoindole 5.5b**. The general method was followed adding 0.519 g of thienoindole **5.4a** (3.0 mmol), 0.180 g of NaH (60 wt % dispersion in mineral oil, 4.5 mmol), 0.750 g of 2-(trimethylsilyl)ethoxymethyl chloride (4.5 mmol) and 15 mL of DMF. Purification via MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **5.5b** as a yellow solid (0.836 g, 92%). ^1H NMR ($CDCl_3$, 500 MHz) δ 7.74 (d, *J* = 7.5 Hz, 1H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.39 (d, *J* = 5.0 Hz, 1H), 7.31 (t, *J* = 8.0 Hz, 1H), 7.21 (t, *J* = 7.5 Hz, 1H), 7.16 (d, *J* = 5.0 Hz, 1H), 5.65 (s, 2H), 3.53 (t, *J* = 8.0 Hz, 2H), 0.89 (t, *J* = 8.0 Hz, 2H), -0.09 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 145.3 (C), 141.7 (C), 127.1 (CH), 122.9 (CH), 122.4 (C), 120.1 (CH), 118.9 (CH), 117.5 (C), 110.6 (CH), 110.5 (CH), 74.3 (CH_2), 66.1 (CH_2), 17.8 (CH_2), -1.41 (CH_3).



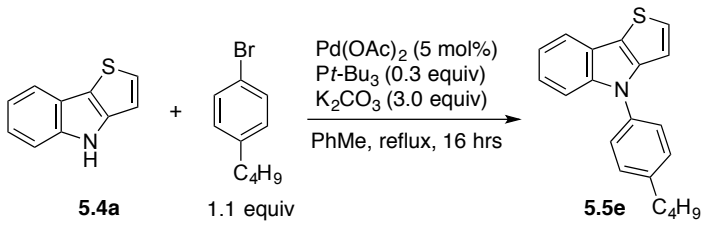
5.5c

***N*-propyl thienoindole 5.5c**. The general method was followed adding 0.519 g of thienoindole **5.4a** (3.0 mmol), 0.180 g of NaH (60 wt % dispersion in mineral oil, 4.5 mmol), 0.553 g of 1-bromopropane (4.5 mmol) and 15 mL of DMF. Purification via MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **5.5c** as a yellow oil (0.580 g, 90%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.78 (d, J = 8.0 Hz, 1H), 7.42 (d, J = 8.0 Hz, 1H), 7.38 (d, J = 5.0 Hz, 1H), 7.31 (t, J = 8.0 Hz, 1H), 7.19 (t, J = 7.5 Hz, 1H), 7.09 (d, J = 5.0 Hz, 1H), 4.25 (t, J = 7.0 Hz, 2H), 1.97 – 1.89 (m, 2H), 0.97 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 145.5 (C), 141.4 (C), 126.7 (CH), 122.3 (CH), 121.8 (C), 119.0 (CH), 118.9 (CH), 115.9 (C), 110.4 (CH), 109.9 (CH), 46.9 (CH_2), 23.2 (CH_2), 11.8 (CH_3).



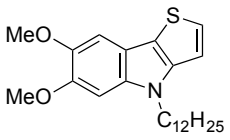
5.5d

N-isopropyl thienoindole **5.5d**. The general method was followed adding 0.519 g of thienoindole **5.4a** (3.0 mmol), 0.180 g of NaH (60 wt % dispersion in mineral oil, 4.5 mmol), 0.553 g of 2-bromopropane (4.5 mmol) and 15 mL of DMF. Purification via MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **5.5d** as a yellow solid (0.425 g, 66%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.75 (d, J = 8.0 Hz, 1H), 7.46 (d, J = 8.5 Hz, 1H), 7.37 (d, J = 5.0 Hz, 1H), 7.29 (t, J = 8.0 Hz, 1H), 7.19 (d, J = 5.0 Hz, 1H), 7.16 (t, J = 7.5 Hz, 1H), 4.92 – 4.83 (m, 1H), 1.66 (s, 3H), 1.64 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 143.0 (C), 140.8 (C), 126.3 (CH), 122.2 (CH), 121.7 (C), 118.9 (CH), 118.8 (CH), 117.2 (C), 112.0 (CH), 110.2 (CH), 47.6 (CH), 21.9 (CH_3).



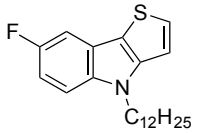
5.4a 1.1 equiv **5.5e**

***N*-4-butylphenyl thienoindole 5.5e**. A round bottom flask was flame-dried, evacuated and refill with nitrogen gas. To this flask, a mixture of 0.346 g of thienoindole **5.4a** (2.0 mmol), 0.023 g of palladium acetate (0.1 mmol), 0.3 mL of tri-*tert*-butylphosphine toluene solution (1.0 M, 0.3 mmol), 0.828 g of potassium carbonate, 0.468 g of 1-bromo-4-butylbenzene and 10 mL of toluene was added. The reaction mixture was heated to 120 °C and stirred for 16 hours. The reaction was cooled to room temperature, diluted with 15 mL of water and extracted with 2 × 15 mL of EtOAc. The combined organic phase was washed with water and brine. The resulting solution was dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. Purification via MPLC (0:100 to 10:90, EtOAc:hexanes) afforded **5.5e** as a yellow solid (0.390 g, 64%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.79 (d, *J* = 8.0 Hz, 1H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.49 (d, *J* = 8.5 Hz, 2H), 7.37 – 7.36 (m, 3H), 7.27 (td, *J* = 8.0, 1.5 Hz, 1H), 7.22 (td, *J* = 8.0, 1.0 Hz, 1H), 7.10 (d, *J* = 5.0 Hz, 1H), 2.72 (t, *J* = 7.5 Hz, 2H), 1.73 – 1.66 (m, 2H), 1.48 – 1.40 (m, 2H), 0.99 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 145.1 (C), 141.7 (C), 141.4 (C), 136.4 (C), 129.7 (CH), 126.7 (CH), 125.0 (CH), 122.9 (CH), 122.3 (C), 120.1 (CH), 118.9 (CH), 117.7 (C), 111.5 (CH), 111.1 (CH), 35.3 (CH_2), 33.7 (CH_2), 22.5 (CH_2), 14.0 (CH_3).



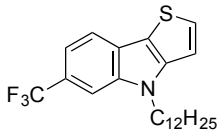
5.5f

***N*-dodecyl thienoindole 5.5f**. The general method was followed adding 0.699 g of thienoindole **5.4b** (3.0 mmol), 0.180 g of NaH (60 wt % dispersion in mineral oil, 4.5 mmol), 1.12 g of 1-bromododecane (4.5 mmol) and 15 mL of DMF. Purification via MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **5.5f** as a green solid (1.02 g, 85%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.24 (d, J = 5.0 Hz, 1H), 7.21 (s, 1H), 7.02 (d, J = 5.0 Hz, 1H), 6.87 (s, 1H), 4.20 (t, J = 7.0 Hz, 2H), 3.99 (s, 3H), 3.97 (s, 3H), 1.88 – 1.82 (m, 2H), 1.32 – 1.24 (m, 18H), 0.89 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 147.1 (C), 144.5 (C), 144.3 (C), 135.8 (C), 124.6 (CH), 115.7 (C), 114.5 (C), 110.5 (CH), 101.4 (CH), 93.9 (CH), 56.5 (CH_3), 56.4 (CH_3), 45.3 (CH_2), 31.9 (CH_2), 29.8 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 27.2 (CH_2), 22.7 (CH_2), 14.1 (CH_3), only peaks visible.



5.5g

***N*-dodecyl thienoindole 5.5g**. The general method was followed adding 0.573 g of thienoindole **5.4c** (3.0 mmol), 0.180 g of NaH (60 wt % dispersion in mineral oil, 4.5 mmol), 1.12 g of 1-bromododecane (4.5 mmol) and 15 mL of DMF. Purification via MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **5.5g** as a white solid (0.991 g, 92%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.45 (dd, J = 9.0, 2.5 Hz, 1H), 7.41 (d, J = 5.0 Hz, 1H), 7.30 (dd, J = 9.0, 4.5 Hz, 1H), 7.08 – 7.04 (m, 2H), 4.22 (t, J = 7.0 Hz, 2H), 1.89 – 1.84 (m, 2H), 1.34 – 1.28 (m, 10H), 0.94 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 157.3 (d, J = 231.7 Hz, C), 146.7 (C), 137.9 (C), 127.6 (CH), 121.8 (d, J = 10.6 Hz, C), 115.5 (d, J = 3.9 Hz, C), 110.5 (CH), 110.4 (CH), 110.2 (d, J = 26.1 Hz, CH), 104.3 (d, J = 23.8 Hz, CH), 45.4 (CH_2), 32.0 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.4 (CH_2), 29.4 (CH_2), 27.2 (CH_2), 22.8 (CH_2), 14.2 (CH_3), only peaks visible.

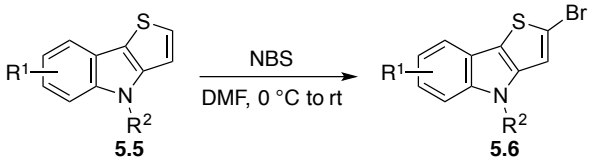


5.5h

***N*-dodecyl thienoindole 5.5h**. The general method was followed adding 0.723 g of thienoindole **5.4d** (3.0 mmol), 0.180 g of NaH (60 wt % dispersion in mineral oil, 4.5 mmol), 1.12 g of 1-bromododecane (4.5 mmol) and 15 mL of DMF. Purification via MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **5.5h** as a white solid (1.03 g, 84%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.81 (d, *J* = 8.5 Hz, 1H), 7.64 (s, 1H), 7.48 (d, *J* = 5.5 Hz, 1H), 7.40 (d, *J* = 8.5 Hz, 1H), 7.10 (d, *J* = 5.5 Hz, 1H), 4.30 (t, *J* = 7.0 Hz, 2H), 1.91 – 1.85 (m, 2H), 1.34 – 1.23 (m, 18H), 0.88 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 147.2 (C), 140.3 (C), 128.8 (CH), 125.3 (q, *J* = 269.9 Hz, C), 124.3 (q, *J* = 62.7 Hz, C), 124.1 (q, *J* = 44.4 Hz, C), 119.1 (CH), 115.8 (C), 115.6 (q, *J* = 2.9 Hz, CH), 110.4 (CH), 107.2 (q, *J* = 3.6 Hz, CH), 45.4 (CH_2), 32.0 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 27.1 (CH_2), 22.8 (CH_2), 14.2 (CH_3), only peaks visible.

E. α-bromination of thienoindole.

1. General Procedure.

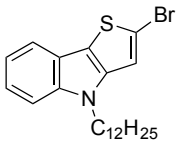


5.5 **5.6**

General procedure: to a 100 mL round bottome flask, thienoindole **5.5** in DMF (0.1 M) was added. The solution was cooled to 0 °C. Then a solution of N-Bromosuccinimide (1.0 equiv) in DMF (0.2 M) was added over 1 hour. Then the reaction

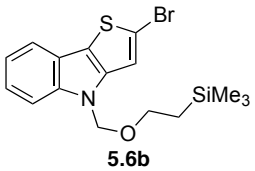
mixture was warmed to room temperature and stirred for 4 hrs. The reaction mixture was diluted with water and extracted with EtOAc. The organic phase was washed with water and brine. The resulting solution was dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. Purification via MPLC afforded the α-bromothienoindole products.

2. Characterization Data.



5.6a

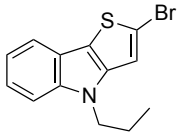
α-bromothienoindole 5.6a. The general method was followed adding 0.682 g of **5.5a** (2.0 mmol), 0.356 g of N-Bromosuccinimide (2.0 mmol) and 30 mL of DMF. Purification via MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **5.6a** as a yellow solid (0.804 g, 95%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.67 (d, J = 8.0 Hz, 1H), 7.38 (d, J = 8.5 Hz, 1H), 7.30 (t, J = 8.0 Hz, 1H), 7.16 (t, J = 8.0 Hz, 1H), 7.12 (s, 1H), 4.20 (t J = 7.0 Hz, 2H), 1.87 – 1.81 (m, 2H), 1.31 – 1.24 (m, 18H), 0.89 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 143.0 (C), 140.1 (C), 122.5 (CH), 121.5 (C), 119.3 (CH), 118.7 (CH), 115.8 (C), 113.9 (CH), 113.2 (C), 110.0 (CH), 45.3 (CH_2), 31.9 (CH_2), 29.8 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 21.1 (CH_2), 22.7 (CH_2), 14.2 (CH_3), only peaks visible.



5.6b

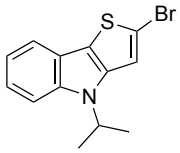
α-bromothienoindole 5.6b. The general method was followed adding 0.606 g of **5.5b** (2.0 mmol), 0.356 g of N-Bromosuccinimide (2.0 mmol) and 30 mL of DMF.

Purification via MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **5.6b** as a yellow solid (0.719 g, 94%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.67 (d, J = 8.0 Hz, 1H), 7.52 (d, J = 8.5 Hz, 1H), 7.32 (td, J = 8.0, 1.0 Hz, 1H), 7.22 – 7.19 (m, 2H), 5.58 (s, 2H), 3.50 (t, J = 8.0 Hz, 2H), 0.89 (t, J = 8.0 Hz, 2H), -0.07 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.0 (C), 140.4 (C), 123.1 (CH), 122.1 (C), 120.4 (CH), 118.8 (CH), 117.4 (C), 114.2 (CH), 113.7 (C), 110.5 (CH); 74.2 (CH_2), 66.2 (CH_2), 17.8 (CH_2), -1.4 (CH_3).



5.6c

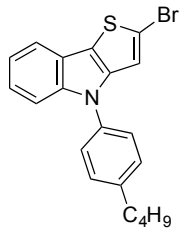
α-bromothienoindole 5.6c. The general method was followed adding 0.430 g of **5.5c** (2.0 mmol), 0.356 g of N-Bromosuccinimide (2.0 mmol) and 30 mL of DMF. Purification via MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **5.6c** as a green solid (0.556 g, 95%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.67 (d, J = 8.0 Hz, 1H), 7.39 (d, J = 6.5 Hz, 1H), 7.30 (td, J = 7.5, 1.0 Hz, 1H), 7.16 (td, J = 7.5, 1.0 Hz, 1H), 7.13 (s, 1H), 4.19 (t, J = 7.0 Hz, 2H), 1.93 – 1.86 (m, 2H), 0.94 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 143.0 (C), 140.1 (C), 122.5 (CH), 121.5 (C), 119.4 (CH), 118.7 (CH), 115.8 (C), 114.0 (CH), 113.3 (C), 110.0 (CH), 46.9 (CH_2), 23.1 (CH_2), 11.7 (CH_3).



5.6d

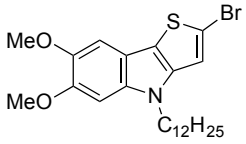
α-bromothienoindole 5.6d. The general method was followed adding 0.430 g of **5.5d** (2.0 mmol), 0.356 g of N-Bromosuccinimide (2.0 mmol) and 30 mL of DMF. Purification via MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **5.6d** as a white solid (0.545 g, 93%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.67 (d, J = 7.5 Hz, 1H), 7.44 (d, J = 8.0

Hz, 1H), 7.30 (td, J = 7.5, 1.0 Hz, 1H), 7.24 (s, 1H), 7.16 (t, J = 8.0 Hz, 1H), 4.87 – 4.79 (m, 1H), 1.63 (s, 3H), 1.61 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 140.5 (C), 139.5 (C), 122.5 (CH), 121.4 (C), 119.2 (CH), 118.7 (CH), 117.1 (C), 115.5 (CH), 112.9 (C), 110.3 (CH), 47.7 (CH), 21.9 (CH_3).



5.6e

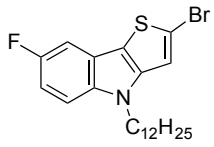
α-bromothienoindole 5.6e. The general method was followed adding 0.610 g of **5.5e** (2.0 mmol), 0.356 g of N-Bromosuccinimide (2.0 mmol) and 30 mL of DMF. Purification via MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **5.6e** as a yellow solid (0.722 g, 94%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.71 (d, J = 8.0 Hz, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.44 – 7.42 (m, 2H), 7.37 – 7.35 (m, 2H), 7.27 (td, J = 7.5, 1.5 Hz, 1H), 7.22 (td, J = 7.5, 1.0 Hz, 1H), 7.13 (s, 1H), 2.71 (t, J = 7.5 Hz, 2H), 1.71 – 1.65 (m, 2H), 1.47 – 1.39 (m, 2H), 0.98 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 142.8 (C), 142.1 (C), 140.2 (C), 135.9 (C), 129.8 (CH), 125.0 (CH), 123.1 (CH), 122.0 (C), 120.5 (CH), 118.7 (CH), 117.5 (C), 115.0 (CH), 113.4 (C), 111.2 (CH).



5.6f

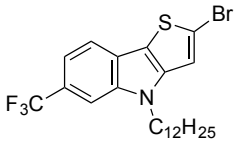
α-bromothienoindole 5.6f. The general method was followed adding 0.802 g of **5.5f** (2.0 mmol), 0.356 g of N-Bromosuccinimide (2.0 mmol) and 30 mL of DMF. Purification via MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **5.6f** as a green solid (0.884 g, 92%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.11 (s, 1H), 7.06 (s, 1H), 6.83 (s, 1H), 4.14 (t, J = 7.0 Hz,

2H), 3.97 (s, 3H), 3.95 (s, 3H), 1.85 – 1.79 (m, 2H), 1.31 – 1.24 (m, 18H), 0.88 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 147.2 (C), 144.6 (C), 142.0 (C), 134.6 (C), 114.2 (C), 114.0 (CH), 111.0 (C), 101.0 (CH), 93.9 (CH), 56.5 (CH_3), 56.4 (CH_3), 45.4 (CH_2), 31.9 (CH_2), 29.8 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 27.1 (CH_2), 22.7 (CH_2), 14.1 (CH_3), only peaks visible.



5.6g

α-bromothienoindole 5.6g. The general method was followed adding 0.719 g of **5.5g** (2.0 mmol), 0.356 g of N-Bromosuccinimide (2.0 mmol) and 30 mL of DMF. Purification via MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **5.6g** as a white solid (0.789 g, 90%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.32 (dd, J = 9.5, 2.5 Hz, 1H), 7.27 (dd, J = 8.5, 4.5 Hz, 1H), 7.09 (s, 1H), 7.03 (td, J = 9.0, 2.5 Hz, 1H), 4.15 (t, J = 7.0 Hz, 2H), 1.84 – 1.78 (m, 2H), 1.30 – 1.24 (m, 18H), 0.90 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 157.4 (d, J = 233.1 Hz, C), 144.2 (C), 136.6 (C), 121.5 (d, J = 11.0 Hz, C), 115.3 (d, J = 5.2 Hz, C), 114.4 (C), 113.9 (CH), 110.6 (d, J = 5.6 Hz, CH), 110.5 (d, J = 10.8 Hz, CH), 104.1 (d, J = 23.9 Hz, CH), 45.5 (CH_2), 32.0 (CH_2), 29.8 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.5 (CH2), 29.4 (CH_2), 29.3 (CH_2), 27.1 (CH_2), 22.7 (CH_2), 14.2 (CH_3), only peaks visible.



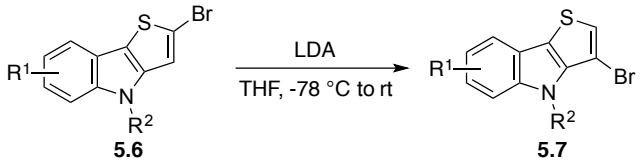
5.6h

α-bromothienoindole 5.6h. The general method was followed adding 0.819 g of **5.5h** (2.0 mmol), 0.356 g of N-Bromosuccinimide (2.0 mmol) and 30 mL of DMF.

Purification via MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **5.6h** as a white solid (0.840 g, 86%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.72 (d, *J* = 8.0 Hz, 1H), 7.63 (s, 1H), 7.40 (d, *J* = 8.5 Hz, 1H), 7.14 (s, 1H), 4.22 (t, *J* = 7.0 Hz, 2H), 1.88 – 1.82 (m, 2H), 1.32 – 1.25 (m, 18H), 0.89 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 144.9 (C), 139.0 (C), 124.5 (C), 124.0 (q, *J* = 81.4 Hz, C), 125.1 (q, *J* = 270.0 Hz, C), 118.9 (CH), 116.1 (q, *J* = 3.4 Hz, CH), 115.8 (q, *J* = 14.6 Hz, C) 113.9 (CH), 107.3 (q, *J* = 4.5 Hz, CH), 45.5 (CH_2), 32.0 (CH_2), 29.8 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.5 (CH2), 29.4 (CH_2), 29.3 (CH_2), 27.1 (CH_2), 22.7 (CH_2), 14.2 (CH_3), only peaks visible.

F. LDA mediated bromine-transferred isomerization

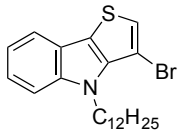
1. General Procedure.



5.6 **5.7**

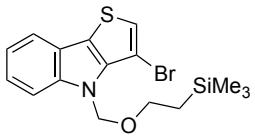
Gereral procedure: A round bottom flask was flame-dried, evacuated and refill with nitrogen gas. To this flask, α-bromidethienoindole **5.6** in THF (0.1 M) was added. Then the solution was cooled to -78 °C and a fresh-made lithium diisopropylamide THF solution (2.0 M, 1.5 equiv) was added. The reaction solution was stirred at -78 °C for 4 hrs. Then the reaction was warmed to room temperature and stirred for 16 hrs. The reaction mixture was diluted with water and extracted with EtOAc. The organic phase was washed with water and brine. The resulting solution was dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. Purification via MPLC afforded the β-bromothienoindole **5.7** products.

2. Characterization Data.



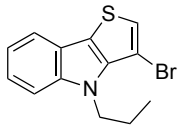
5.7a

β-bromothienoindole 5.7a. The general method was followed adding 0.420 g of **5.6a** (1.0 mmol), 0.75 mL of lithium diisopropylamide THF solution (2.0 M, 1.5 mmol) and 10 mL of THF. Purification via MPLC (0:100 – 20:80 hexanes:pentanes) afforded **5.7a** as a yellow solid (0.281 g, 67%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.72 (d, J = 7.5 Hz, 1H), 7.42 (d, J = 8.5 Hz, 1H), 7.33 (t, J = 8.5 Hz, 1H), 7.25 (s, 1H), 7.19 (t, J = 8.0 Hz, 1H), 4.52 (t, J = 7.5 Hz, 2H), 1.90 – 1.84 (m, 2H), 1.43 – 1.38 (m, 2H), 1.35 – 1.25 (m, 16H), 0.90 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 141.8 (C), 139.7 (C), 123.6 (CH), 123.2 (CH), 121.0 (C), 119.5 (CH), 118.9 (CH), 117.2 (C), 110.2 (CH), 94.0 (C), 32.0 (CH_2), 30.8 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.4 (CH_2), 26.9 (CH_2), 22.7 (CH_2), 14.1 (CH_3), only peaks visible.



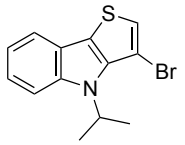
5.7b

β-bromothienoindole 5.7b. The general method was followed adding 0.382 g of **5.6b** (1.0 mmol), 0.75 mL of lithium diisopropylamide THF solution (2.0 M, 1.5 mmol) and 10 mL of THF. Purification via MPLC (0:100 – 50:50 hexanes:pentanes) afforded **5.7b** as a light yellow solid (0.191 g, 50%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.71 (d, J = 8.0 Hz, 1H), 7.59 (d, J = 8.5 Hz, 1H), 7.35 (t, J = 8.0 Hz, 1H), 7.28 (s, 1H), 7.24 (t, J = 8.0 Hz, 1H), 5.94 (s, 2H), 3.61 (t, J = 8.0 Hz, 2H), 0.89 (t, J = 8.0 Hz, 2H), -0.09 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 124.1 (CH), 123.8 (CH), 120.7 (CH), 118.8 (CH), 111.2 (CH).



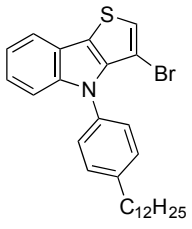
5.7c

β-bromothienoindole 5.7c. The general method was followed adding 0.294 g of **5.6c** (1.0 mmol), 0.75 mL of lithium diisopropylamide THF solution (2.0 M, 1.5 mmol) and 10 mL of THF. Purification via MPLC (0:100 – 3:97 EtOAc:hexanes) afforded **5.7c** as a brown solid (0.141 g, 48%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ; ^{13}C NMR ($CDCl_3$, 125 MHz) δ.



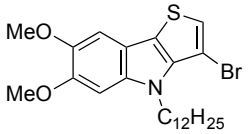
5.7d

β-bromothienoindole 5.7d. The general method was followed adding 0.294 g of **5.6d** (1.0 mmol), 0.75 mL of lithium diisopropylamide THF solution (2.0 M, 1.5 mmol) and 10 mL of THF. Purification via MPLC (0:100 – 3:97 EtOAc:hexanes) afforded **5.7d** as a yellow solid (0.094 g, 32%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.72 (d, J = 8.0 Hz, 1H), 7.64 (d, J = 8.0 Hz, 1H), 7.28 (td, J = 8.0, 1.0 Hz, 1H), 7.26 (s, 1H), 7.17 (t, J = 8.0 Hz, 1H), 5.75 (br, 1H), 1.73 (s, 3H), 1.72 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 140.3 (C), 139.1 (C), 123.8 (CH), 122.9 (CH), 121.8 (C), 119.7 (CH), 119.3 (CH), 119.1 (CH), 113.1 (C), 94.3 (C), 47.3 (CH), 21.7 (CH_3), only peaks visible.



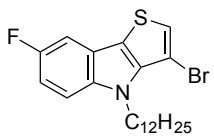
5.7e

β-bromothienoindole 5.7e. The general method was followed adding 0.496 g of **5.6e** (1.0 mmol), 0.75 mL of lithium diisopropylamide THF solution (2.0 M, 1.5 mmol) and 10 mL of THF. Purification via MPLC (0:100 – 50:50 hexanes:pentanes) afforded **5.7e** as a yellow solid (0.238 g, 48%). ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.88 (d, J = 7.5 Hz, 1H), 7.76 (s, 1H), 7.41 (br, 4H), 7.29 – 7.22 (m, 2H), 7.15 (d, J = 8.0 Hz, 1H), 2.70 (t, J = 7.5 Hz, 2H), 1.67 – 1.61 (m, 2H), 1.40 – 1.33 (m, 2H), 0.94 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 143.5 (C), 143.3 (C), 140.4 (C), 133.8 (C), 128.9 (CH), 128.7 (CH), 123.8 (CH), 128.7 (CH), 123.8 (CH), 123.6 (CH), 121.2 (C), 120.4 (CH), 118.7 (CH), 111.4 (C), 94.8 (C), 35.4 (CH_2), 33.6 (CH_2), 22.4 (CH_2), 14.0 (CH_3), only peaks visible.



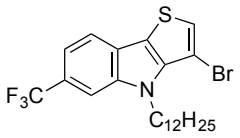
5.7f

β-bromothienoindole 5.7f. The general method was followed adding 0.480 g of **5.6f** (1.0 mmol), 0.75 mL of lithium diisopropylamide THF solution (2.0 M, 1.5 mmol) and 10 mL of THF. Purification via MPLC (0:100 – 30:70 hexanes:pentanes) afforded **5.7f** as a green solid (0.274 g, 57%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.15 (s, 1H), 7.12 (s, 1H), 6.88 (s, 1H), 4.46 (t, J = 7.5 Hz, 2H), 3.99 (s, 3H), 3.96 (s, 3H), 1.88 – 1.82 (m, 2H), 1.41 – 1.24 (m, 18H), 0.88 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 147.8 (C), 144.7 (C), 138.6 (C), 136.4 (C), 121.4 (CH), 113.7 (C), 100.9 (CH), 94.1 (C), 93.8 (CH), 56.4 (CH_3), 56.3 (CH_3), 43.7 (CH_2), 31.9 (CH_2), 30.8 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 26.9 (CH_2), 22.7 (CH_2), 14.1 (CH_3).



5.7g

β-bromothienoindole 5.7g. The general method was followed adding 0.438 g of **5.6g** (1.0 mmol), 0.75 mL of lithium diisopropylamide THF solution (2.0 M, 1.5 mmol) and 10 mL of THF. Purification via MPLC (0:100 – 80:20 hexanes:pentanes) afforded **5.7g** as a white solid (0.197 g, 45%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.37 (dd, *J* = 9.0, 2.5 Hz, 1H), 7.31 (dd, *J* = 9.0, 4.0 Hz, 1H), 7.27 (s, 1H), 7.07 (td, *J* = 9.0, 2.5 Hz, 1H), 4.48 (t, *J* = 7.5 Hz, 2H), 1.88 – 1.82 (m, 2H), 1.39 – 1.26 (m, 18H), 0.90 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 157.4 (d, *J* = 235.1 Hz, C), 140.9 (C), 138.3 (C), 124.5 (CH), 122.0 (d, *J* = 10.2 Hz, C), 116.7 (d, *J* = 5.3 Hz, C), 111.3 (d, *J* = 25.5 Hz, CH), 110.8 (d, *J* = 9.3 Hz, CH), 104.2 (d, *J* = 23.9 Hz, CH), 94.0 (C), 43.8 (CH_2), 32.0 (CH_2), 30.8 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 26.9 (CH_2), 22.7 (CH_2), 14.2 (CH_3), only peaks visible.

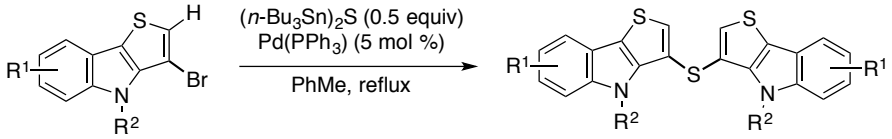


5.7h

β-bromothienoindole 5.7h. The general method was followed adding 0.488 g of **5.6h** (1.0 mmol), 0.75 mL of lithium diisopropylamide THF solution (2.0 M, 1.5 mmol) and 10 mL of THF. Purification via MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **5.7h** as a white solid (0.195 g, 40%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.80 (d, *J* = 8.0 Hz, 1H), 7.67 (s, 1H), 7.42 (d, *J* = 8.5 Hz, 1H), 7.36 (s, 1H), 4.55 (t, *J* = 7.5 Hz, 2H), 1.91 – 1.85 (m, 2H), 1.42 – 1.25 (m, 18H), 0.88 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.0 (C), 141.5 (C), 140.8 (C), 125.8 (CH), 125.5 (q, *J* = 134.3 Hz, C), 124.1 (q, *J* = 263.3 Hz, C), 119.2 (CH), 117.0 (C), 116.2 (q, *J* = 3.5 Hz, CH), 107.5 (q, *J* = 3.4 Hz , CH), 94.0 (C), 43.8 (CH_2), 31.9 (CH_2), 30.8 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 26.8 (CH_2), 22.7 (CH_2), 14.1 (CH_3), only peaks visible.

G. Diaryl sulfide synthesis via Pd-catalyzed Stille coupling reaction.

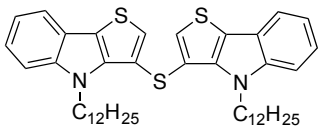
1. General Procedure.



5.7 **5.8**

Gereral procedure: A round bottom flask was flame-dried, evacuated and refilled with nitrogen gas. Under nitrogen atmosphere, to this flask, β-bromothienoindole **5.7** (1.0 equiv) and bis(tri-*n*-butyltin)sulfide (0.5 equiv) in toluene (0.1 M) was added. Then $Pd(PPh_3)_4$ (5 mol %) was added and the reaction mixture was stirred at 120 °C for 24 hrs. The reaction mixture was diluted with water and extracted with EtOAc. The organic phase was washed with water and brine. The resulting solution was dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. Purification via MPLC afforded the diaryl sulfide **5.8** products.

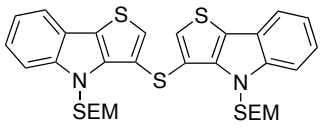
2. Characterization Data.



5.8a

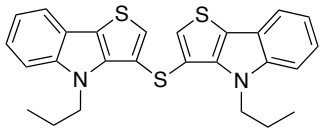
Sulfide 5.8a. The general method was followed adding 0.168 g of **5.7a** (0.40 mmol), 0.072 g of bis(tri-*n*-butyltin)sulfide (0.20 mmol), 0.023 g of $Pd(PPh_3)_4$ (0.02 mmol) and 4 mL of toluene. Purification via MPLC (0:100 – 3:97 EtOAc:hexanes) afforded **5.8a** as a brown solid (0.127 g, 89%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.73 (d, J = 7.5 Hz, 1H), 7.40 (d, J = 7.5 Hz, 1H), 7.32 (t, J = 7.5 Hz, 1H), 7.19 (t, J = 7.5 Hz, 1H), 7.03 (s, 1H), 4.48 (t, J = 7.0 Hz, 2H), 1.80 – 1.77 (m, 2H), 1.26 – 1.12 (m, 18H), 0.88 (t, J = 6.5 Hz, 3H); ^{13}C

NMR ($CDCl_3$, 125 MHz) δ 141.6 (C), 140.8 (C), 127.0 (CH), 123.0 (CH), 121.4 (C), 119.4 (CH), 118.9 (CH), 117.8 (C), 114.3 (C), 110.2 (CH), 44.7 (CH_2), 32.0 (CH_2), 31.0 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 27.1 (CH_2), 22.7 (CH_2), 14.2 (CH_3), only peaks visible.



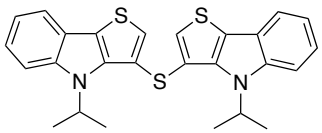
5.8b

Sulfide 5.8b. The general method was followed adding 0.153 g of **5.7b** (0.40 mmol), 0.072 g of bis(tri-*n*-butyltin)sulfide (0.20 mmol), 0.023 g of $Pd(PPh_3)_4$ (0.02 mmol) and 4 mL of toluene. Purification via MPLC (0:100 – 3:97 EtOAc:hexanes) afforded **5.8b** as a red oil (0.079 g, 62%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.72 (d, *J* = 8.0 Hz, 1H), 7.58 (d, *J* = 8.5 Hz, 1H), 7.35 (t, *J* = 8.0 Hz, 1H), 7.24 (t, *J* = 8.0 Hz, 1H), 7.08 (s, 1H), 5.87 (s, 2H), 3.52 (t, *J* = 8.0 Hz, 2H), 0.82 (t, *J* = 8.0 Hz, 2H), -0.12 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 142.2 (C), 141.0 (C), 127.5 (CH), 123.6 (CH), 122.0 (C), 120.5 (CH), 119.5 (C), 118.8 (CH), 114.6 (C), 111.1 (CH), 73.1 (CH_2), 65.7 (CH_2), 17.9 (CH_2), -1.44 (CH_3).



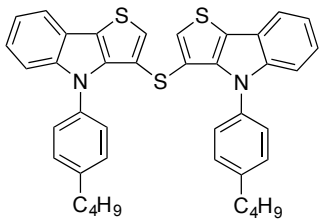
5.8c

Sulfide 5.8c. The general method was followed adding 0.118 g of **5.7c** (0.40 mmol), 0.072 g of bis(tri-*n*-butyltin)sulfide (0.20 mmol), 0.023 g of $Pd(PPh_3)_4$ (0.02 mmol) and 4 mL of toluene. Purification via MPLC (0:100 – 3:97 EtOAc:hexanes) afforded **5.8c** as a brown solid (0.076 g, 83%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ; ^{13}C NMR ($CDCl_3$, 125 MHz) δ.



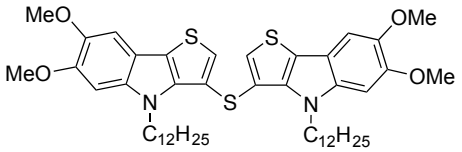
5.8d

Sulfide 5.8d. The general method was followed adding 0.118 g of **5.7d** (0.40 mmol), 0.072 g of bis(tri-*n*-butyltin)sulfide (0.20 mmol), 0.023 g of $Pd(PPh_3)_4$ (0.02 mmol) and 4 mL of toluene. Purification via MPLC (0:100 – 3:97 EtOAc:hexanes) afforded **5.8d** as a green solid (0.045 g, 49%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.74 (d, *J* = 7.5 Hz, 1H), 7.61 (d, *J* 8.5 Hz, 1H), 7.28 (td, *J* = 7.5, 1.0 Hz, 1H), 7.18 (td, *J* = 8.0, 1.0 Hz, 1H), 7.07 (br, 1H), 5.60 (br, 1H), 1.59 (s, 3H), 1.58 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 140.2 (C), 139.9 (C), 127.5 (C), 127.3 (C), 122.6 (CH), 122.3 (C), 119.2 (CH), 113.1 (CH), 113.0 (CH), 48.4 (CH), 21.6 (CH_3), only peaks visible.



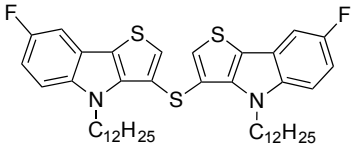
5.8e

Sulfide 5.8e. The general method was followed adding 0.198 g of **5.7e** (0.40 mmol), 0.072 g of bis(tri-*n*-butyltin)sulfide (0.20 mmol), 0.023 g of $Pd(PPh_3)_4$ (0.02 mmol) and 4 mL of toluene. Purification via MPLC (0:100 – 3:97 EtOAc:hexanes) afforded **5.8e** as a brown solid (0.096 g, 75%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.75 – 7.73 (m, 1H), 7.22 – 7.16 (m, 3H), 7.08 (br, 4H), 6.77 (s, 1H), 2.46 (t, *J* = 7.5 Hz, 2H), 1.50 – 1.44 (m, 2H), 1.32 – 1.27 (m, 2H), 0.89 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 143.0 (C), 142.6 (C), 141.2 (C), 134.2 (C), 128.3 (CH), 127.7 (CH), 126.5 (CH), 123.2 (CH), 121.5 (C), 120.1 (CH), 118.6 (CH), 118.5 (C), 115.4 (C), 111.2 (CH), 35.2 (CH_2), 33.3 (CH_2), 22.5 (CH_2), 13.9 (CH_3).



5.8f

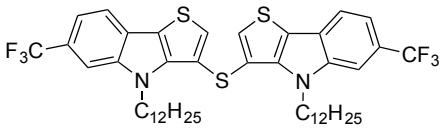
Sulfide 5.8f. The general method was followed adding 0.192 g of **5.7f** (0.40 mmol), 0.072 g of bis(tri-*n*-butyltin)sulfide (0.20 mmol), 0.023 g of $Pd(PPh_3)_4$ (0.02 mmol) and 4 mL of toluene. Purification via MPLC (0:100 – 3:97 EtOAc:hexanes) afforded **5.8f** as a brown oil (0.133 g, 80%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.16 (s, 1H), 6.90 (s, 1H), 6.85 (s, 1H), 4.41 (t, *J* = 7.5 Hz, 2H), 3.98 (s, 3H), 3.96 (s, 3H), 1.80 – 1.74 (m, 2H), 1.28 – 1.14 (m, 18H), 0.87 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 147.6 (C), 144.7 (C), 139.9 (C), 124.9 (CH), 117.7 (C), 114.4 (C), 114.1 (C), 101.1 (CH), 93.9 (CH), 56.5 (CH_3), 56.4 (CH_3), 44.7 (CH_2), 31.9 (CH_2), 31.0 (CH_2), 29.7 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 27.1 (CH_2), 22.7 (CH_2), 14.1 (CH_3), only peaks visible.



5.8g

Sulfide 5.8g. The general method was followed adding 0.175 g of **5.7g** (0.40 mmol), 0.072 g of bis(tri-*n*-butyltin)sulfide (0.20 mmol), 0.023 g of $Pd(PPh_3)_4$ (0.02 mmol) and 4 mL of toluene. Purification via MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **5.8g** as a brown oil (0.112 g, 75%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.38 (dd, *J* = 9.0, 2.5 Hz, 1H), 7.31 (dd, *J* = 9.0, 4.0 Hz, 1H), 7.09 – 7.05 (m, 2H), 4.45 (t, *J* = 7.5 Hz, 2H), 1.78 – 1.72 (m, 2H), 1.30 – 1.09 (m, 18H), 0.89 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 157.4 (d, *J* = 234.1 Hz, C), 142.0 (C), 138.1 (C), 127.9 (d, *J* = 18.9 Hz, CH), 121.4 (d, *J* = 10.2 Hz, C), 117.5 (d, *J* = 4.5 Hz, C), 114.3 (C), 110.8 (CH), 104.4 (d, *J* = 11.9 Hz, CH),

104.2 (d, J = 12.6 Hz, CH), 44.9 (CH_2), 31.9 (CH_2), 31.0 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.4 (CH_2), 27.1 (CH_2), 22.7 (CH_2), 14.2 (CH_3), only peaks visible.



5.8h

Sulfide 5.8h. The general method was followed adding 0.195 g of **5.7h** (0.40 mmol), 0.072 g of bis(tri-*n*-butyltin)sulfide (0.20 mmol), 0.023 g of $Pd(PPh_3)_4$ (0.02 mmol) and 4 mL of toluene. Purification via MPLC (0:100 – 10:90 EtOAc:hexanes) afforded **5.8h** as a white solid (0.093 g, 55%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.81 (d, J = 8.5 Hz, 1H), 7.66 (s, 1H), 7.44 (d, J = 8.5 Hz, 1H), 7.13 (s, 1H), 4.52 (t, J = 7.5 Hz, 2H), 1.82 – 1.76 (m, 2H), 1.30 – 1.10 (m, 18H), 0.88 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 142.5 (C), 140.6 (C), 129.1 (CH), 125.0 (q, J = 269.5 Hz, C), 125.1 (q, J = 31.1 Hz, C), 123.6 (C), 119.2 (CH), 117.9 (C), 116.2 (q, J = 3.1 Hz, CH), 114.2 (C), 107.5 (q, J = 4.3 Hz, CH); 44.9 (CH_2), 31.9 (CH_2), 31.0 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 27.1 (CH_2), 22.7 (CH_2), 14.1 (CH_3), only peaks visible.

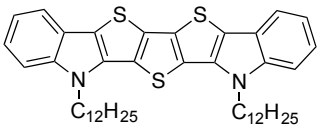
H. *N*-heteroheptacene synthesis via Ullman coupling reaction

1. General Procedure.

General procedure: A round bottom flask was flame-dried, evacuated and refill with nitrogen gas. To this flask, diaryl sulfide **5.7** in DMF (0.01 M) was added. Then the solution was cooled to 0 °C. Then N-Bromosuccinimide (2.2 equiv) in DMF (0.02 M) was added over 1 hour. The reaction mixture was warmed to room temperature and

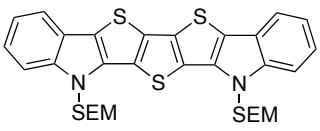
stirred for 2 hours. Then Cu power (1.5 equiv) was added. The resulting suspension was heated to 160 °C and stirred for 16 hrs. The reaction mixture was cooled to room temperature, diluted with water and extracted with EtOAc. The organic phase was washed with water and brine. The resulting solution was dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. Purification via MPLC afforded the diaryl sulfide **5.8** products.

2. Characterization Data.



5.8a

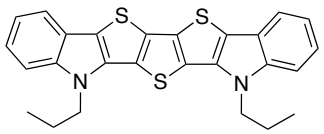
***N*-heteroheptacene 5.8a**. The general method was followed adding 0.072 g of **5.7a** (0.10 mmol), 0.039 g of N-Bromosuccinimide (0.22 mmol), 0.010 g of Cu powder (0.15 mmol) and 15 mL of DMF. Purification via MPLC (0:100 – 10:90 EtOAc:hexanes) afforded **5.8a** as a yellow solid (0.046 g, 65%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.72 (d, J = 7.5 Hz, 1H), 7.40 (d, J = 8.5 Hz, 1H), 7.29 (t, J = 7.0 Hz, 1H), 7.21 (t, J = 7.5 Hz, 1H), 4.34 (t, J = 7.0 Hz, 2H), 1.99 – 1.93 (m, 2H), 1.47 – 1.41 (m, 2H), 1.37 – 1.33 (m, 2H), 1.26 – 1.23 (m, 14H), 0.87 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 142.3 (C), 140.5 (C), 137.0 (C), 133.9 (C), 122.8 (C), 122.6 (C), 122.4 (CH), 119.7 (CH), 118.5 (CH), 110.1 (CH), 45.8 (CH_2), 31.9 (CH_2), 30.7 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.4 (CH_2), 27.2 (CH_2), 22.7 (CH_2), 14.1 (CH_3), only peaks visible.



5.8b

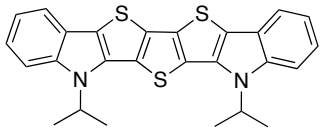
***N*-heteroheptacene 5.8b**. The general method was followed adding 0.064 g of **5.7b** (0.10 mmol), 0.039 g of N-Bromosuccinimide (0.22 mmol), 0.010 g of Cu powder (0.15 mmol)

and 15 mL of DMF. Purification via MPLC (0:100 – 20:80 EtOAc:hexanes) afforded **5.8b** as a green solid (0.029 g, 45%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ; ^{13}C NMR ($CDCl_3$, 125 MHz) δ.



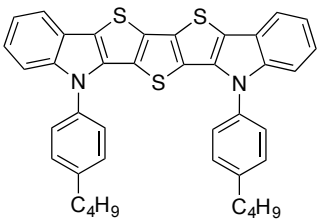
5.8c

***N*-heteroheptacene 5.8c**. The general method was followed adding 0.046 g of **5.7c** (0.10 mmol), 0.039 g of N-Bromosuccinimide (0.22 mmol), 0.010 g of Cu powder (0.15 mmol) and 15 mL of DMF. Purification via MPLC (0:100 – 10:90 EtOAc:hexanes) afforded **5.8c** as a yellow solid (0.025 g, 55%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ; ^{13}C NMR ($CDCl_3$, 125 MHz) δ.



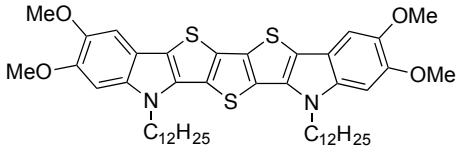
5.8d

***N*-heteroheptacene 5.8d**. The general method was followed adding 0.046 g of **5.7c** (0.10 mmol), 0.039 g of N-Bromosuccinimide (0.22 mmol), 0.010 g of Cu powder (0.15 mmol) and 15 mL of DMF. Purification via MPLC (0:100 – 10:90 EtOAc:hexanes) afforded **5.8d** as a yellow solid (0.018 g, 39%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.74 (d, J = 7.5 Hz, 1H), 7.55 (d, J = 8.5 Hz, 1H), 7.31 (t, J = 7.5 Hz, 1H), 7.22 (t, J = 7.5 Hz, 1H), 5.06 – 4.98 (m, 1H), 1.83 (s, 3H), 1.82 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 139.8 (C), 135.6 (C), 134.1 (C), 123.2 (C), 122.7 (C), 122.3 (CH), 119.6 (CH), 118.6 (CH), 117.8 (C), 110.8 (CH), 48.5 (CH), 23.0 (CH_3).



5.8e

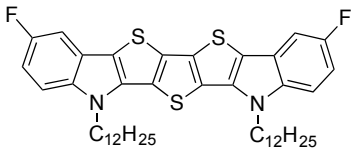
***N*-heteroheptacene 5.8e**. The general method was followed adding 0.064 g of **5.7e** (0.10 mmol), 0.039 g of N-Bromosuccinimide (0.22 mmol), 0.010 g of Cu powder (0.15 mmol) and 15 mL of DMF. Purification via MPLC (0:100 – 10:90 EtOAc:hexanes) afforded **5.8e** as a yellow solid (0.037 g, 58%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.79 – 7.77 (m, 1H), 7.54 – 7.50 (m, 3H), 7.38 (d, *J* = 8.0 Hz, 2H), 7.29 – 7.26 (m, 2H), 2.75 (t, *J* = 7.5 Hz, 2H), 1.76 – 1.70 (m, 2H), 1.51 – 1.45 (m, 2H), 1.03 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 142.4 (C), 140.7 (C), 136.7 (C), 135.1 (C), 133.9 (C), 129.7 (CH), 125.3 (CH), 123.8 (C), 123.2 (C), 123.0 (CH), 120.8 (CH), 118.6 (CH), 118.2 (C), 111.2 (CH), 35.4 (CH_2), 33.7 (CH_2), 22.4 (CH_2), 14.0 (CH_3).



5.8f

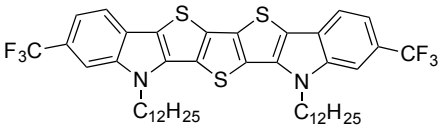
***N*-heteroheptacene 5.8f**. The general method was followed adding 0.083 g of **5.7f** (0.10 mmol), 0.039 g of N-Bromosuccinimide (0.22 mmol), 0.010 g of Cu powder (0.15 mmol) and 15 mL of DMF. Purification via MPLC (0:100 – 10:90 EtOAc:hexanes) afforded **5.8f** as a yellow solid (0.058 g, 70%). ^{1}H NMR (C_6D_6, 500 MHz) δ 7.11 (s, 1H), 6.67 (s, 1H), 3.89 (t, *J* = 7.0 Hz, 2H), 3.63 (s, 3H), 3.53 (s, 3H), 1.78 – 1.72 (m, 2H), 1.30 – 1.19 (m, 18H), 0.90 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (C_6D_6, 125 MHz) δ 148.3 (C), 146.1 (C), 136.2 (C), 135.5. (C), 132.7 (C), 122.8 (C), 116.1 (C), 116.0 (C), 101.8 (CH), 95.0 (CH), 56.1

(CH_3), 56.0 (CH_3), 32.1 (CH_2), 30.7 (CH_2), 29.9 (CH_2), 29.9 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 27.2 (CH_2), 22.9 (CH_2), 14.1 (CH_3), only peaks visible.



5.8g

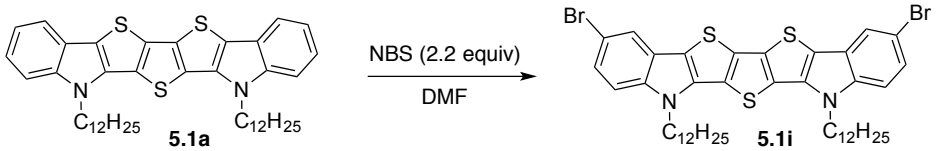
***N*-heteroheptacene 5.8g**. The general method was followed adding 0.075 g of **5.7g** (0.10 mmol), 0.039 g of N-Bromosuccinimide (0.22 mmol), 0.010 g of Cu powder (0.15 mmol) and 15 mL of DMF. Purification via MPLC (0:100 – 30:60 EtOAc:hexanes) afforded **5.8g** as a green solid (0.054 g, 72%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ; ^{13}C NMR ($CDCl_3$, 125 MHz) δ.



5.8h

***N*-heteroheptacene 5.8h**. The general method was followed adding 0.085 g of **5.7h** (0.10 mmol), 0.039 g of N-Bromosuccinimide (0.22 mmol), 0.010 g of Cu powder (0.15 mmol) and 15 mL of DMF. Purification via MPLC (0:100 – 50:50 EtOAc:hexanes) afforded **5.8h** as a green solid (0.061 g, 72%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ; ^{13}C NMR ($CDCl_3$, 125 MHz) δ.

I. Dibromination of *N*-heteroheptacene



5.1a **5.1i**

To a 25 mL round bottom flask, 0.071 g of **5.1a** (0.01 mmol) in 3 mL of DMF was added. Then 0.039 g of N-Bromosuccinimide (0.22 mmol) in 2 mL of DMF was added at room

temperature over 1 hour. The reaction mixture was stirred for 12 hrs. The reaction was diluted with water and extracted with EtOAc. The organic phase was washed with water and brine. The resulting solution was dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. Purification via MPLC (0:100 to 20:80, EtOAc:hexanes) afforded **5.1i** a green solid (0.078 g, 90%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.57 – 7.54 (m, 2H), 7.30 (d, J = 8.5 Hz, 1H), 4.31 (t, J = 7.0 Hz, 2H), 1.97 – 1.92 (m, 2H), 1.46 – 1.40 (m, 2H), 1.37 – 1.33 (m, 2H), 1.25 – 1.22 (m, 14H), 0.85 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ.

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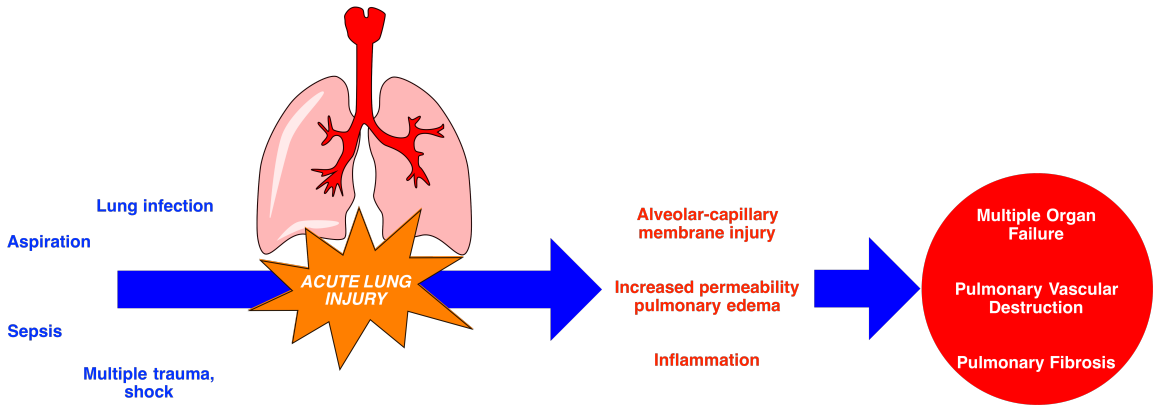
Chapter VI

Synthesis of FTY-720 Phosphonate Analogues for Potential Small Molecule Therapeutics for Acute Lung Injury

Acute lung injury (ALI) is a continuum of clinical and radiographic changes affecting the lungs, characterized by acute onset severe hypoxaemia, that can occur at any age.[1] This characterization originated In 1967 when Ashbaugh and co-workers used the phrase acute respiratory distress syndrome to describe twelve critically ill patients who had refractory hypoxaemis, decreased lung compliance, diffuse pulmony infiltration on chest X-ray (CRX) and required positive end expiratory pressure for ventilation. Acute lung injury (ALI) and the acute respiratory distress syndroma (ARDS) describe clinical syndromes of acute respiratory failure.[2] ALI has a high incidence (200,000- per year in the US) and overall mortality remains high. Patients who survive ALI will have their long-term quality of life attenuated because of high risk of syndromes.[3] Current treatment mainly based on the ventilator and nonventilatory strategies.[4] Both of them could only affect on symptoms, not reverse the lung injury. Several clinical trials, however, have indicated that the current strategies have not been effective in reducing mortality.[5-7] Despite recent advances in our understanding of the mechanisms and pathophysiology of ALI and ARDS, more progress need to be developed to further improve clinical outcomes (Figure 6.1).

Figure 6.1 ***The natural history of ALI/ARDS includes resolution and repair versus persistence and progression.***

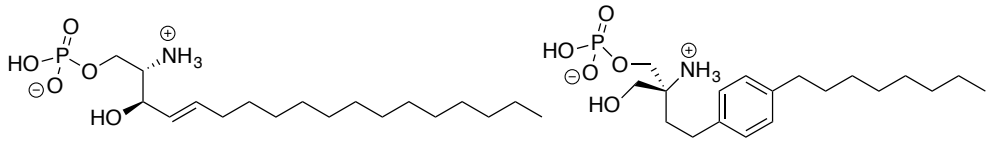


Sustained vascular barriers leak is a marked characteristic of acute inflammatory diseases, such as acute lung injury and acute respiratory distress syndrome.[8] The endothelial cell (EC) layer of the pulmonary vasculature forms a semipermeable barrier between the blood and the interstitium of the lung.[9] The disruption of this barrier causes the movement of fluid and macromolecules into the interstitium and air space of the lung. This process is a key element and a common pathway driving high morbidity and mortality.[10] Novel therapies which could prevent or reverse vascular barrier leak are lacking.[11] Although ventilation with normal tidal volume was used as a supportive care, no specific treatment has been discovered. A number of preclinical treatments failed in clinical Phase 2 or 3.[4]

In recent years, the effect of sphingosin 1-phosphate (S1P) on protecting vascular barrier has drawn people's attention. Sphingosine 1-phosphate (S1P) receptors (S1PRs) belongs to the class A family of G protein-coupled receptors (GPCRs), which are widely expressed on many types of cells. The S1PRs are important mediators of many cellular

processes, including cell differentiation, migration, survival, angiogenesis, calcium homeostasis, inflammation and immunity.[12] Sphingosine 1-phosphate **6.1** is the nature ligand that could bind to S1PRs (Figure 6.2). Five subtypes of S1P receptors have been identified, termed S1P1–S1P5, which all (except for S1P4) bind to S1P with high affinity. FTY720-phosphate **6.2** is structurally analogue to S1P (Figure 6.2). Absorbed FTY720 can be enantiospecific monophosphorylated by sphingosine kinases (SphKs) to form the biologically active FTY720-phosphate, which in turn acts as a mimetic of S1P, targeting S1P-receptor (S1PR) subtypes. This sequestration subsequently modulates the recirculation of lymphocytes between blood and lymphoid tissues.[13]

Figure 6.2 ***Structures of Sphingosine-1-phosphate and FTY720-phosphate***



6.1, Sphingosine-1-phosphate

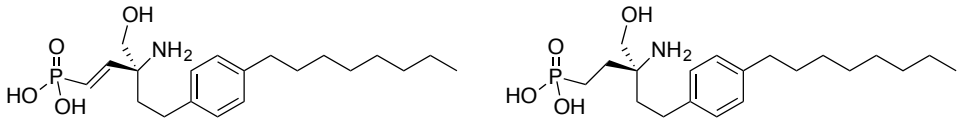
(*S*)-6.2, (*S*)-FTY720-phosphate

Nowadays, disruption of vascular barrier integrity is thought to be a central pathophysiologic mechanism of many inflammatory disease processes. Vascular smooth muscle cells express S1P1, S1P2 and S1P3 receptors. Existing data support a central role for S1P1 and S1P3 receptors in the regulation of the endothelial cell barrier function and permeability. Recent studies by Garcia and co-workers indicated S1P could work as a major barrier-protective agent responsible for the maintenance of vascular barrier integrity *in vitro* and *in vivo*.[14,15] However, as an endogenous bioactive lipid, the

usefulness of S1P for reducing ALI is limited due to its pleiotropic effects.[16] As the structural analogue, FTY720 also showed it could decrease vascular permeability *in vivo*[17,18] and *in vitro*[19]. The multiple physiological responses of FTY720, such as immunosuppressant effects,[11] increased rates of dyspnea and decreased lung function,[20] however, limit its therapeutic utility.

Because of the advantages and limitations of S1P and FTY720, significant interest have arisen in FTY720-phosphate analogues. Among several structural analogues, studies of both (*S*)-FTY720-vinylphosphoate (*S*)-**6.3** and (*S*)-FTY720-phosphoate (*S*)-**6.4** showed both of them could work as a potential vascular barrier protective agent with fewer side effects (Figure 6.3).[21,22] However, the mechanisms of vascular barrier protection by FTY720-phosphonate were unclear. To support the further study on its metabolism, cytotoxicity and pharmacokinetics by Dudek and Natarjan in UIC's School of Medicine, an efficient synthetic route was desired.

Figure 6.3 ***Structures of (S)-FTY720-vinlyphosphonate and (S)-FTY720-phosphonate***

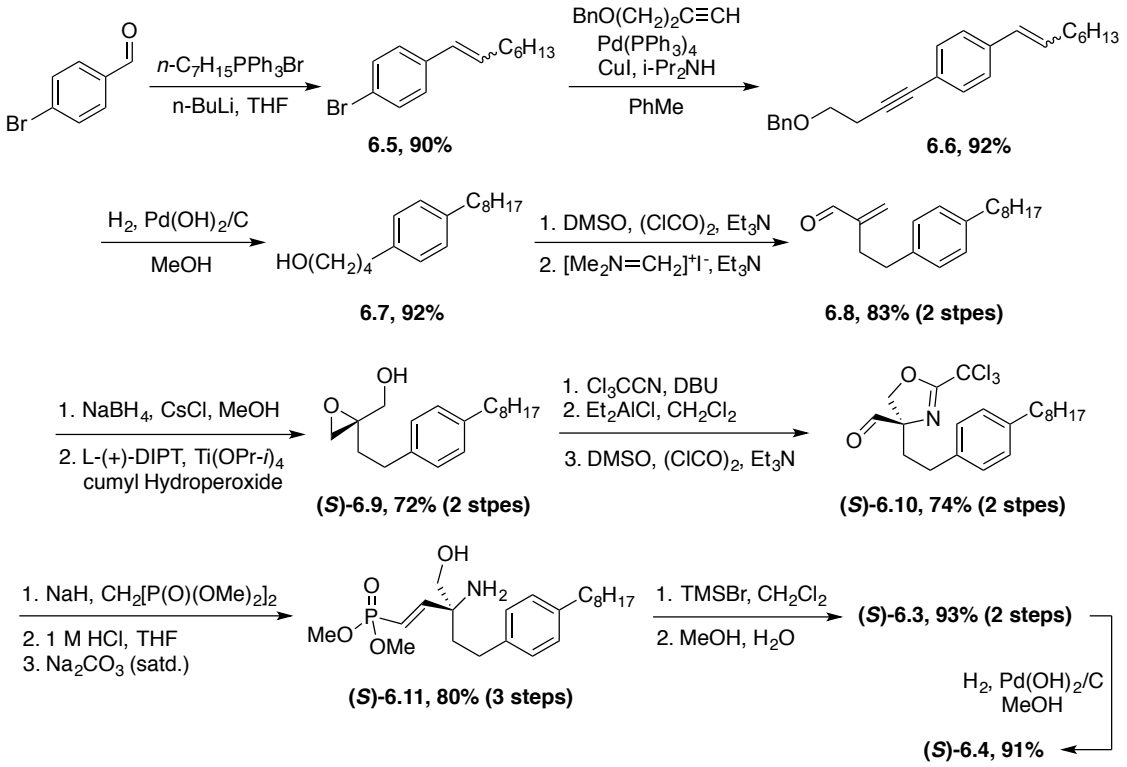


(*S*)-6.3, (*S*)-FTY720-vinylphosphonate **(*S*)-6.4**, (*S*)-FTY720-phosphonate

The synthesis of FTY-720-phosphonate was reported by Bittman and co-workers in 2009 (Figure 6.4).[21] Their synthesis stared with Wittig reaction of 4-bromobenzaldehyde to install the alkyl chain. Sonogashira coupling reaction, followed by hydrogenation with H_2, afforded the alcohol **6.7**. After Swern oxidation provided

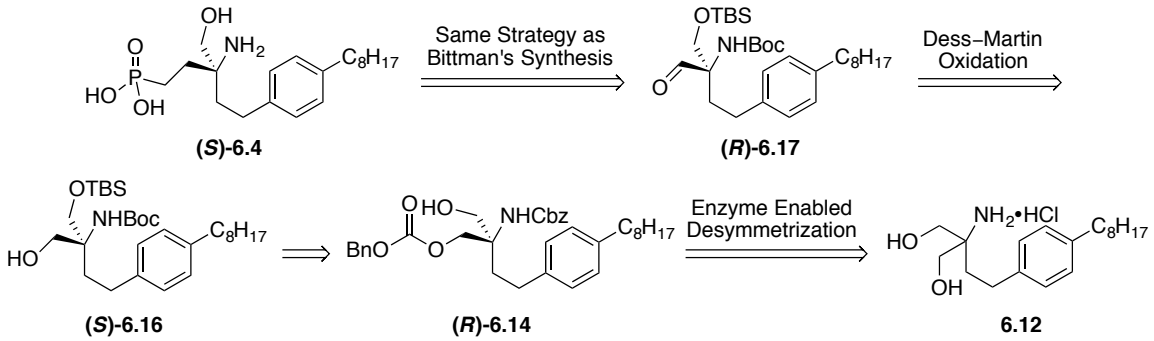
aldehyde intermediate, methylenation was achieved by using a Mannich reagent, Eschenmoser's salt. Next, after reducing aldehyde **6.8** to alcohol intermediate, Sharpless-Katsuki asymmetric epoxidation was chosen to set the chirality. The free alcohol group reacted with trichloroacetonitrile in the presence of DBU. The opening of epoxide occurred with nitrogen substitution to generate the alcohol intermediate. After the Swern oxidation to prepare the aldehyde, Horner–Wadsworth–Emmons reaction with tetramethyl methylenediphosphonate was employed to install the phosphonate methyl ester. Deprotections afforded the FTY-720 vinylphosphonate (*S*)-**6.3** (15 steps, 25% overall yield), followed by hydrogenation to afford FTY-720 phosphonate (*S*)-**6.4** (16 steps, 23% overall yield). No enantiomeric excess data, however, was reported with any synthetic intermediates or final products. Our group has an interest in making potential small molecule therapeutics for pulmonary diseases. Our goal is to come up with a potential treatment for acute lung injury by modulating the activity of the S1P-type 1 receptor. We are taking over the synthesis of FTY-720-phosphonate for Prof. Robert Bittman because of his untimely passing.

Scheme 6.1 ***Previous synthesis of (S)-6.3 and (S)-6.4 by Bittman and co-workers***



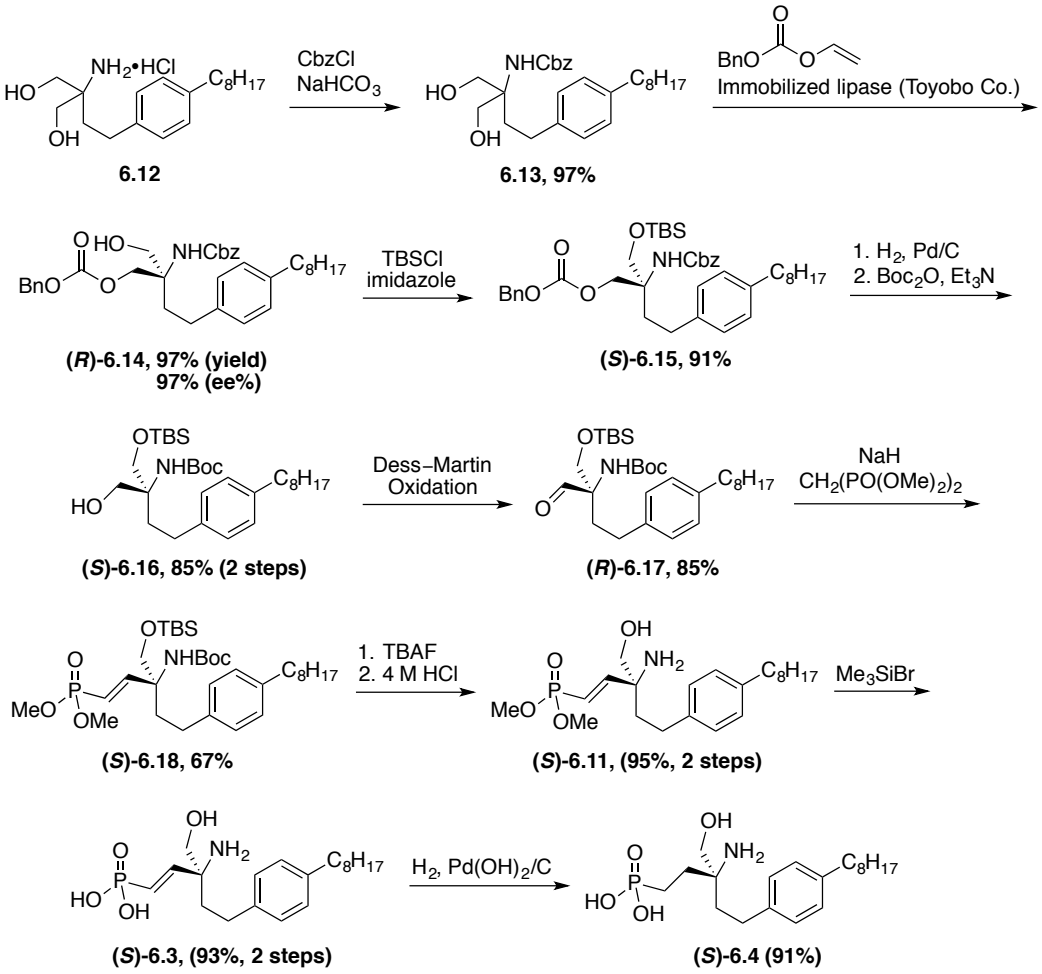
To accomplish this synthesis in time, a shorter synthetic pathway was designed, which started with fingolimod. The same synthetic strategy was followed to convert aldehyde (*R*)-**6.17** to phosphonate (*S*)-**6.4**. Dess–Martin oxidation, instead of Swern oxidation, was chosen to oxidize alcohol (*S*)-**6.16**. A few protection and deprotection steps transformed chiral center to the desired chirality. The key step, enzyme enabled desymmetrization reaction was employed to define the chiral center.

Scheme 6.2 ***Retro synthesis of (S)-6.4***



Our synthesis started with quantitative *N*-benzyloxycarbonation of fingolimod (Scheme 6.3). Then, asymmetric acylation of 2,2-disubstituted propane-1,3-diol **6.13** was carried out using benzyl vinyl carbonate and immobilized lipase to generate (*R*)-**6.14** with 97% yield and 97% enantiomeric excess which was determined by SFC (Chiralcel OD-H, 30% MeOH).[23] After three protecting and deprotecting steps, Horner–Wadsworth–Emmons reaction of aldehyde (*R*)-**6.17** afford ester (*S*)-**6.18** with 67% yield. The *tert*-butyldimethylsilyl- and Boc-carbamate protecting groups were removed with TBAF and HCl to afford the amino alcohol (*S*)-**6.11.** The final steps were carried out using bromotetramethylsilane to remove methyl groups to generate (*S*)-**6.3**, then $Pd(OH)_2$-catalyzed hydrogenation afforded (*S*)-**6.4**.

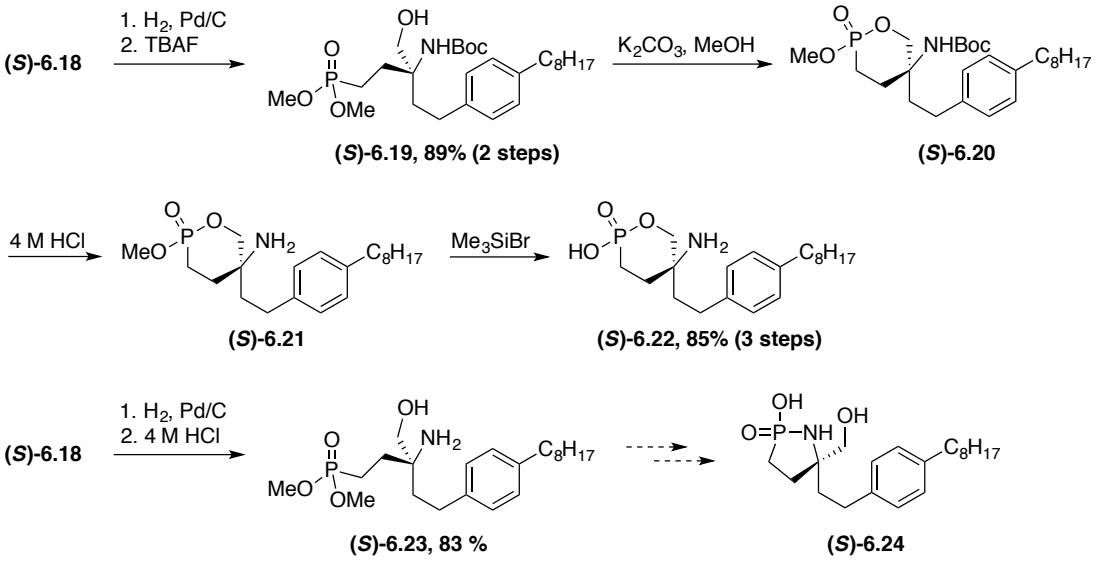
Scheme 6.3 ***Synthesis of (S)-6.3 and (S)-6.4 from fingolimod 6.12.***



At the same time, we anticipated that potential pro-drugs might result if the order of the end-game steps were changed (scheme 6.4). To test our hypothesis, we attempted to synthesize (*S*)-FTY-720-cyclic phosphonate (*S*)-**6.22** and (*S*)-FTY-720-cyclic phophoramidite (*S*)-**6.24**. Hydrogenation followed by silyl deprotection with TBAF afforded the alcohol intermediate (*S*)-**6.19**. Treatment of (*S*)-**6.19** with K_2CO_3 in MeOH generated the cyclic phosphonate. After the removal of methyl and Boc-carbamate group, (*S*)-FTY-720-cyclic phosphonate (*S*)-**6.22** was prepared successfully. To prepare the cyclic phophoramidite (*S*)-**6.24**, the deprotection of amino group would have been achieved selectively with 4 M HCl. However, TBS group was also removed under this

acidic condition. Further attampts to (*S*)-FTY-720-cyclic phophoramidite (*S*)-**6.24** were undergoing.

Scheme 6.4 ***Synthesis of (S)-FTY720-cyclic phosphonate***



In conclusion, (*S*)-FTY720-vinylphosphonate (*S*)-**6.3** (10 steps, 37% overall yield), (*S*)-FTY720-phosphonate (*S*)-**6.4** (11 steps, 33% overall yield) and (*S*)-FTY720-cyclic phosphonate (*S*)-**6.22** (11 steps, 30% overall yield) were prepared with more efficient synthetic route. Enzyme-enabled desymmetrization reaction was applied to define the chiral center. Final product could be prepared in 300 mg-scale using this synthetic route. Further bioactive tests by the Dudek and Natarjan laboratories are ongoing.

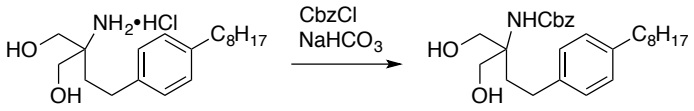
Experimental

A. General.

^{1}H NMR and ^{13}C NMR spectra were recorded at ambient temperature using 500 MHz or 300 MHz spectrometers. The data are reported as follows: chemical shift in ppm from internal tetramethylsilane on the δ scale, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz) and integration. High resolution mass spectra were acquired on a JEOL CGMate II- or Thermo Finnigan brand LTQ FT spectrometer, and were obtained by peak matching. Infared spectroscopy was obtained using a diamond attenuated total reflectance (ATR) accessory. Analytical thin layer chromatography was performed on 0.25 mm extra hard silica gel plates with UV254 fluorescent indicator. Liquid chromatography was performed using forced flow (flash chromatography) of the indicated solvent system on 60Å (40 – 60 μm) mesh silica gel (SiO_2). Medium pressure liquid chromatography (MPLC) was performed to force flow the indicated solvent system down columns that had been packed with 60Å (40 – 60 μm) mesh silica gel (SiO_2). All reactions were carried out under an atmosphere of nitrogen in glassware, which had been oven-dried. Unless otherwise noted, all reagents were commercially obtained and, where appropriate, purified prior to use. Acetonitrile, Methanol, Toluene, THF, Et_2O, and CH_2Cl_2 were dried by filtration through alumina according to the procedure of Grubbs.[24] Metal salts were stored in a nitrogen atmosphere dry box.

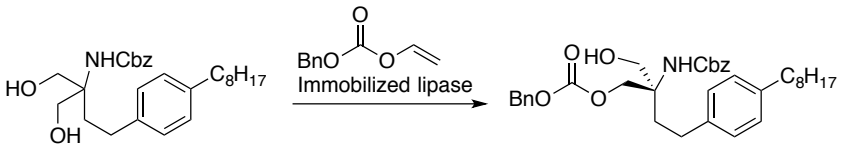
B. Synthesis of (*S*)-FTY720-vinylphosphonate (*S*)-6.3 and (*S*)-FTY720-phosphonate (*S*)-6.4

1. Synthesis of (*S*)-FTY720-Vinylphosphonate (*S*)-6.3 and (*S*)-FTY720-phosphonate (*S*)-6.4



6.12 **6.13**

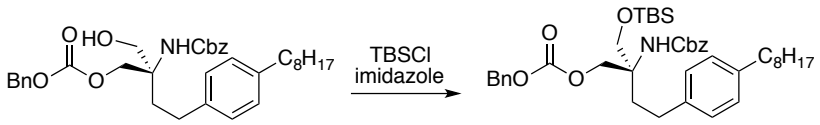
To a 500 mL round bottom flask was added fingolimod hydrochloride (2.00 g, 5.80 mmol), benzyl chloroformate (3.00 mL, 21.0 mmol), $CHCl_3$ (250 mL) and saturated aqueous $NaHCO_3$ (125 mL). After 18 h, the organic layer was separated, washed with 3 × 200 mL of water and 200 mL of brine, and dried with Na_2SO_4. The resulting solution was concentrated *in vacuo*, and crystallized from Et_2O to afford **6.13** (2.48 g, 97%) as a white powder. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.37 – 7.31 (m, 5H), 7.07 (s, 4H), 5.27 (s, 1H), 5.09 (s, 2H), 3.91 (dd, *J* = 11.5, 6.0 Hz, 2H), 3.68 (dd, *J* = 11.5, 6.5 Hz, 2H), 3.24 (br, 2H), 2.59 – 2.53 (m, 4H), 1.92 – 1.88 (m, 2H), 1.54 – 1.61 (m, 2H), 1.33 – 1.26 (m, 10H), 0.88 (t, *J* = 6.5 Hz, 3H).



6.13 **(*R*)-6.14**

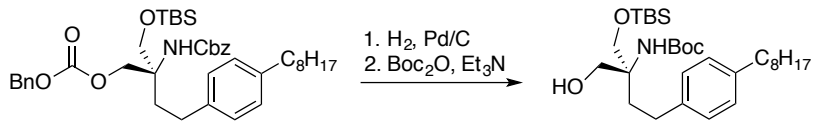
To a 500 mL round bottom flask was added **6.13** (2.20 g, 5.00 mmol), benzyl vinyl carbonate (2.23 g, 12.5 mmol), immobilized lipase (Toyobo, 2.20 g), and THF (40 mL). After 16 h, the reaction mixture was filtered with a pad of Celite. The resulting filtrate was concentrated *in vacuo*, and purified by MPLC (0:100 – 30:70 EtOAc:hexanes) to afford (*R*)-**6.14** (2.78 g, 97%, 97% ee by SFC, Chiralcel OJ-H, 30%

MeOH, the SFC spectrum attached) as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.38 – 7.30 (m, 10H), 7.08 – 7.03 (m, 4H), 5.16 (s, 2H), 5.11 (s, 1H), 5.07 (s, 2H), 4.41 (d, J = 11.0 Hz, 1H), 4.30 (d, J = 11.0 Hz, 1H), 3.79 (dd, J = 12.0, 7.2 Hz, 1H), 3.74 – 3.71 (m, 2H), 2.62 – 2.53 (m, 4H), 2.10 (ddd, J = 14.0, 11.4, 5.2 Hz, 1H), 1.89 (ddd, J = 14.0, 11.8, 5.6Hz, 1H), 1.57 (q, J = 7.2 Hz, 2H), 1.34–1.23 (m, 10H), 0.88 (t, J = 6.8 Hz, 3H).



(*R*)-6.14 (*S*)-6.15

In a 5 mL round bottom flask, (*R*)-**6.14** (0.115 g, 0.200 mmol) was dissolved in 1 mL of DMF. After cooling to 0 °C, imidazole (0.027 g, 0.400 mmol) and *tert*-butyldimethylsilyl chloride (0.036 g, 0.24 mmol) were added. The reaction mixture was warmed to room temperature and stirred for 2 h. Then the reaction mixture was quenched with 5 mL of water and extracted with 2 × 3 mL of CH_2Cl_2. The combined organic phases were washed with 2 × 5 mL of water and 5 mL of brine. The resulting organic solution was dried with Na_2SO_4, filtered, and the filtrate was concentrated *in vacuo*. Purification via MPLC (0:100 – 10:90 EtOAc:hexanes) afforded (*S*)-**6.15** (0.125 g, 91%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.39 – 7.30 (m, 10H), 7.08 – 7.05 (m, 4H), 5.16 (s, 2H), 5.11 – 5.05 (m, 2H), 4.99 (br, 1H), 4.41 – 4.36 (m, 2H), 3.72 (s, 2H), 2.62 – 2.52 (m, 4H), 2.23 – 2.17 (m, 1H), 2.03 – 1.98 (m, 1H), 1.62 – 1.56 (m, 2H), 1.33 – 1.28 (m, 10H), 0.91 – 0.88 (m, 12H), 0.05 (s, 6H).



(*S*)-6.15 (*S*)-6.16

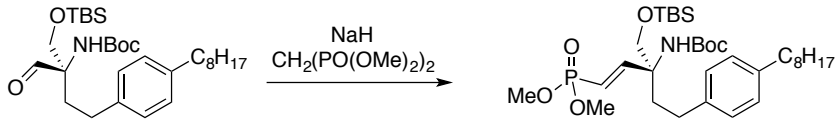
In a 10 mL round bottom flask, (*S*)-**6.15** (0.690 g, 1.00 mmol) was dissolved in 10 mL of MeOH. To the resulting solution was added 10 wt. % Pd/C (0.106 g, 0.10 mmol) and the reaction mixture was stirred under hydrogen atmosphere for 12 h. Then the reaction solution was filtered, and the filtrate was concentrated *in vacuo*. The crude product was directly used in the next step without any further purification.

To a 10 mL round bottom flask, the product from the reaction above was dissolved in 3 mL of THF. To the resulting solution was added di-*tert*-butyl dicarbonate (0.273, 1.25 mmol) and triethylamine (0.300 mL, 2.10 mmol). After 12 h, the reaction mixture was quenched with 5 mL of water and extracted with 2 × 3 mL of CH_2Cl_2. The combined organic phase was washed with 2 × 5 mL of water, 5 mL of brine. The resulting organic solution was dried with Na_2SO_4, filtered, and the filtrate was concentrated *in vacuo*. Purification via MPLC (0:100 – 20:80 EtOAc:hexanes) afforded (*S*)-**6.16** (0.422 g, 85%, 2 steps) as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.10 – 7.06 (m, 4H), 5.30 (s, 1H), 5.14 (br, 1H), 3.88 (d, *J* = 10.0 Hz, 1H), 3.71 (d, *J* = 6.5 Hz, 2H), 3.56 (d, *J* = 9.5 Hz, 1H), 2.63 (td, *J* = 13.0, 4.5 Hz, 1H), 2.55 (t, *J* = 7.5 Hz, 2H), 2.48 (td, *J* = 13.0, 4.5 Hz, 1H), 2.06 – 2.00 (m, 1H), 1.72 (td, *J* = 13.0, 4.5 Hz, 1H), 1.61 – 1.55 (m, 2H), 1.45 (s, 9H), 1.30 – 1.24 (m, 10H), 0.91 (s, 9H), 0.88 (t, *J* = 7.0 Hz, 3H), 0.10 (s, 3H), 0.09 (s, 3H).

(***S***)-**6.16** (***R***)-**6.17**

Under nitrogen atmosphere, (*S*)-**6.16** (0.104 g, 0.200 mmol) was dissolved in 3 mL of CH_2Cl_2 in a 10 mL round bottom flask. The reaction mixture was cooled to 0 °C and Dess–Martin periodinane (0.102 g, 0.24 mmol) was added portion-wise. The reaction

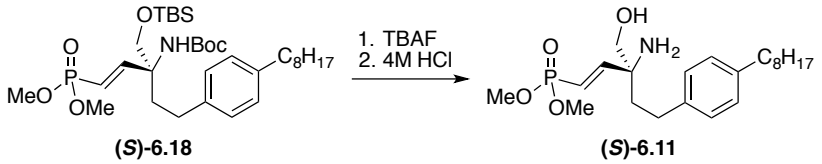
mixture was warmed to room temperature. After 2 h, the resulting mixture was quenched with 5 mL of a saturated aqueous solution of NH_4Cl and extracted 2 × 3 mL of CH_2Cl_2. The combined organic phases were washed with 2 × 5 mL of water and 5 mL of brine. The resulting organic solution was dried with Na_2SO_4, filtered, and the filtrate was concentrated *in vacuo*. Purification via MPLC (0:100 – 10:90 EtOAc:hexanes) afforded (*R*)-**6.17** (0.088 g, 85%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.39 (s, 1H), 7.08 (d, *J* = 8.0 Hz, 2H), 7.05 (d, *J* = 8.0 Hz, 2H), 5.42 (s, 1H), 4.09 (d, *J* = 10.0 Hz, 1H), 3.89 (d, *J* = 10.0 Hz, 1H), 2.58 – 2.54 (m, 3H), 2.36 (br, 2H), 2.02 – 2.00 (m, 1H), 1.60 – 1.57 (m, 2H), 1.47 (s, 9H), 1.31 – 1.27 (m, 10H), 0.90 – 0.87 (m, 12H), 0.05 (s, 3H), 0.04 (s, 3H).



(*R*)-6.17 (*S*)-6.18

Under nitrogen atmosphere, a 10 mL round bottom flask was charged with sodium hydride (0.012 g, 0.3 mmol, 60% by weight in mineral oil). Then the suspension of NaH was cooled to 0 °C. Tetramethyl methylenediphosphonate (0.070 g, 0.3 mmol) in 3 mL of THF was added through syringe injection The resulting mixture was stirred for 10 minutes at 0 °C, and then (*R*)-**6.17** (0.104 g, 0.2 mmol) in 3 mL of THF was added. The reaction mixture was warmed to room temperature. After a the resulting mixture was quenched with 5 mL of NH_4Cl saturated aqueous solution of NH_4Cl and extracted 2 × 5 mL of ethyl acetate. The combined organic phases were washed with 10 mL of a NaOH aqueous solution/MeOH (7:3), 2 × 5 mL of water, and 5 mL of brine. The resulting organic solution was dried with Na_2SO_4, filtered, and the filtrate was concentrated *in vacuo*. Purification via MPLC (0:100 – 50:50 EtOAc:hexanes) afforded

(*S*)-**6.18** (0.084 g, 67%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.09 – 7.05 (m, 4H), 6.77 (dd, *J* = 23.0, 17.5 Hz, 1H), 5.71 (dd, *J* = 18.5, 17.5 Hz, 1H), 4.86 (br, 1H), 3.77 – 3.71 (m, 8H), 2.57 – 2.53 (t, *J* = 8.0 Hz, 4H), 2.14 – 2.08 (m, 1H), 2.02 (br, 1H), 1.61 – 1.55 (m, 2H), 1.43 (s, 9H), 1.30 – 1.26 (m, 10H), 0.89 – 0.86 (m, 12H), 0.6 (s, 3H), 0.5 (s, 3H).



(*S*)-6.18 (*S*)-6.11

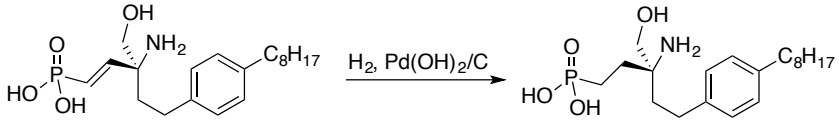
In a 10 mL round bottom flask, (*S*)-**6.18** (0.063 g, 0.1 mmol) was dissolved in 2 mL of THF. Tetrabutylammonium fluoride (0.3 mL, 1.0 M THF solution, 0.3 mmol) was added and the reaction mixture was stirred for 40 minutes at room temperature. The resulting solution was concentrated *in vacuo*. The crude product was used directly for the next step without any further purification.

In a 10 mL round bottom flask, the product from the reaction above was dissolved in 2 mL of 1,4-dioxane. Hydrochloric acid (2 mL, 4.0 M 1,4-dioxane solution) was added and the reaction mixture was stirred for 12 h. The reaction solution concentrated *in vacuo*, and the resulting residue was extracted with 5 mL of Na_2CO_3 and 2 × 5 mL chloroform. The combined organic phases were washed with 2 × 5 mL of water and 5 mL of brine. The resulting organic solution was dried with Na_2SO_4, filtered, and the filtrate was concentrated *in vacuo*. Purification via MPLC (98:0:2 – 78:20:2, $CHCl_3$:MeOH:NH4OH) afforded (*S*)-**6.11** (0.039 g, 95%, 2 steps) as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.08 – 7.04 (m, 4H), 6.84 (dd, *J* = 22.5, 17.0 Hz, 1H), 5.93 (dd, *J* = 20.0, 17.5 Hz, 1H), 3.73 (s, 3H), 3.71 (s, 3H), 3.51 (dd, *J* = 28.0, 9.0, 2H), 3.00

(br, 3H), 2.62 – 2.46 (m, 4H), 1.82 – 1.71 (m, 2H), 1.58 – 1.54 (m, 2H), 1.28 – 1.25 (m, 10H), 0.87 (t, J = 6.5 Hz, 3H).

(*S*)-6.11 (*S*)-6.3

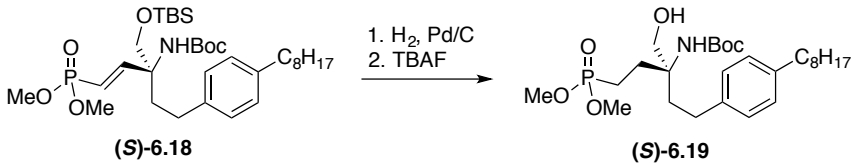
In a 10 mL round bottom flask, (*S*)-**6.11** (0.041 g, 0.10 mmol) was dissolved in 2 mL of CH_2Cl_2. To the resulting solution was added bromotrimethylsilane (0.153 g, 1.0 mmol), and the reaction mixture was stirred at room temperature for 4 h. The resulting solution was concentrated *in vacuo*. The residue was dissolved in 2 mL of 95% EtOH. The solution was stirred at room temperature for 1 h. Removal of the solvent afforded (*S*)-**6.3** (0.035 g, 93%, 2 steps) as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.99 (d, J = 8.0 Hz, 2H), 6.96 (d, J = 8.0 Hz, 2H), 6.50 (dd, J = 23.0, 18.0 Hz, 1H), 6.14 (d, J = 18.0, 17.5 Hz, 1H), 4.69 (br, 6H), 3.69 (br, 2H), 2.56 (td, J = 13.0, 4.5 Hz, 1H), 2.51 – 2.41 (m, 3H), 2.01 (td, J = 14.0, 4.5 Hz, 1H), 1.93 (td, J = 13.5, 4.5 Hz, 1H), 1.46 – 1.43 (m, 2H), 1.18 – 1.15 (m, 10H), 0.76 (t, J = 7.0 Hz, 3H).



(*S*)-6.3 (*S*)-6.4

In a 10 mL round bottom flask, (*S*)-**6.3** (0.038 g, 0.10 mmol) was dissolved in 2 mL of MeOH. To the resulting solution was added 20 wt. % $Pd(OH)_2/C$ (0.014 g, 0.020 mmol) and the reaction mixture was stirred under hydrogen atmosphere for 12 h. Then the reaction solution was filtered. The resulting filtrate was concentrated *in vacuo* to afford (*S*)-**6.4** (0.035 g, 91%) as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.01 (d, J = 7.5 Hz, 2H), 6.97 (d, J = 8.0 Hz, 2H), 4.3 (br, 4H), 3.58 (br, 2H), 2.53 – 2.50 (m, 2H),

2.43 (t, J = 7.5 Hz, 2H), 1.94 (br, 2H), 1.82 – 1.76 (m, 4H), 1.45 (t, J = 4.0 Hz, 2H), 1.18 – 1.14 (m, 10H), 0.76 (t, J = 7.0 Hz, 3H).

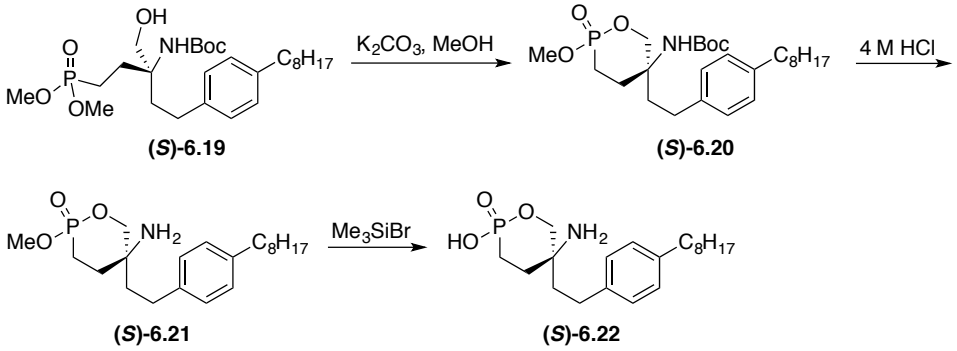


(*S*)-6.18 **(*S*)-6.19**

In a 10 mL round bottom flask, (*S*)-**6.18** (0.062 g, 0.10 mmol) was dissolved in 2 mL of MeOH. To the resulting solution was added 10 wt. % Pd/C (0.011 g, 0.010 mmol), and the reaction mixture was stirred under hydrogen atmosphere for 12 h. Then the reaction solution was filtered and the filtrate was concentrated *in vacuo*. The crude product was directly used in the next step without any further purification.

In a 10 mL round bottom flask, the product from the reaction above was dissolved in 2 mL of THF. To the resulting solution was added tetrabutylammonium fluoride (0.30 mL, 1.0 M THF solution, 0.30 mmol) and the reaction mixture was stirred for 40 minutes at room temperature. The resulting solution was concentrated *in vacuo*. Purification via MPLC (70:30:0 – 50:40:10, hexanes:EA:MeOH) affords (*S*)-**6.19** (0.046 g, 89%) as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.10 – 7.04 (m, 4H), 4.29 – 4.17 (m, 1H), 3.81 (s, 0.6H, minor), 3.79 (s, 0.6H, minor), 3.76 (s, 2.4H, major), 3.74 (s, 2.4H, major), 3.72 – 3.64 (m. 1H), 2.62 – 2.49 (m, 4H), 2.02 – 1.65 (m, 6H), 1.61 – 1.55 (m, 2H), 1.44 (d, J = 11.5 Hz, 9H), 1.30 – 1.28 (m, 10H), 0.87 (t, J = 7.0 Hz, 3H).

2. Synthesis of (*S*)-FTY720-Cyclicphosphonate (*S*)-6.22



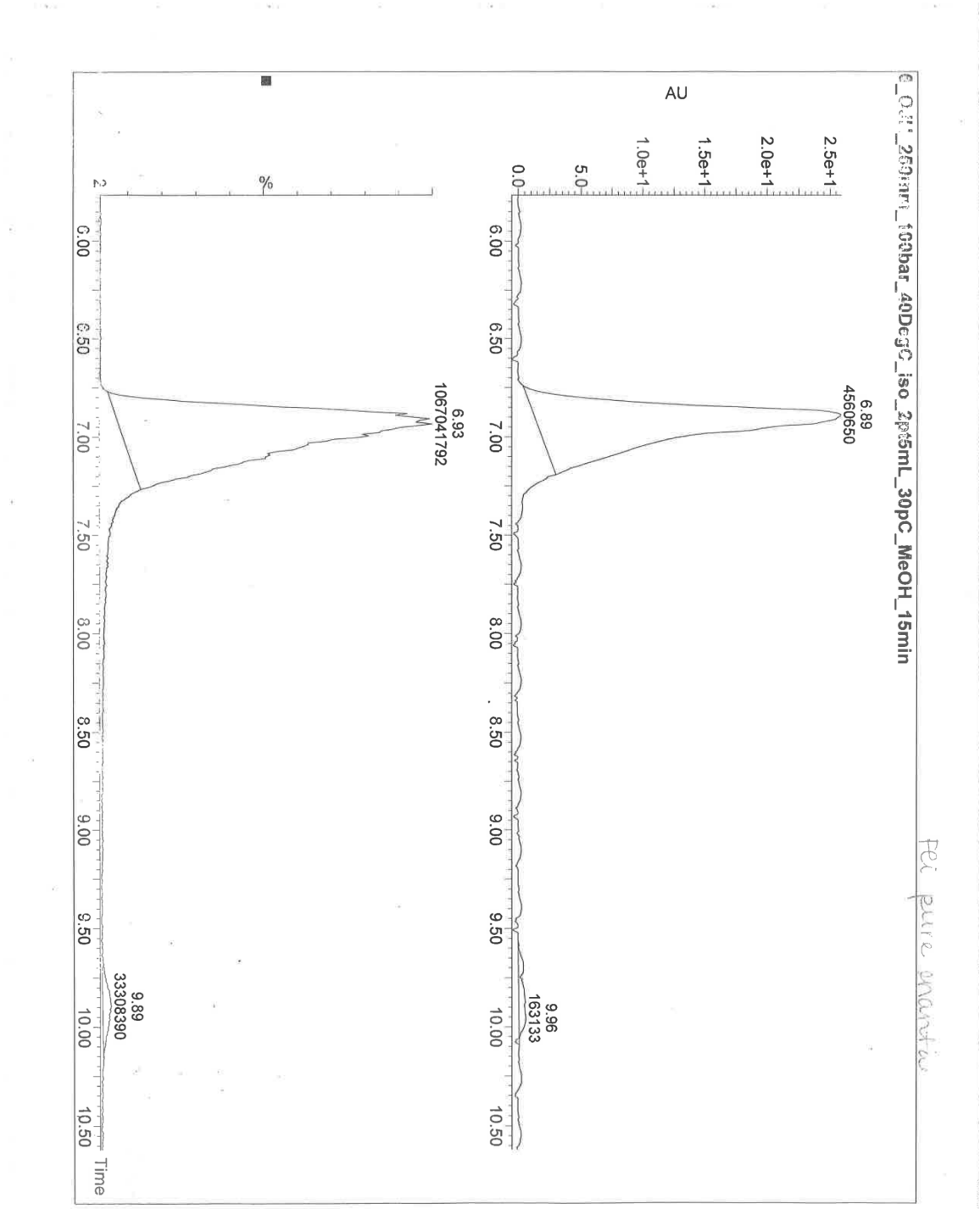
In a 5 mL round bottom flask, (*S*)-**6.19** (0.040 g, 0.078 mmol) was dissolved in 2 mL of MeOH. To the resulting solution was added Na_2CO_3 (0.025 g, 0.023 mmol) and the reaction mixture was stirred. After 12 h, the resulting solution was diluted with 5 mL of a saturated aqueous solution of NH_4Cl and extracted with 2 × 5 mL of chloroform. The combined organic phases were washed with 2 × 5 mL of water, and 5 mL of brine. The resulting solution was dried with Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. Purification via MPLC (100:0 to 50:50, hexanes:EA) affords (*S*)-**6.20** as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.10 – 7.04 (m, 4H), 4.89 (br, 1H), 4.27 – 4.14 (m, 1H), 3.95 (dd, *J* = 12.0, 3.0 Hz, 1H), 3.81 (s, 0.37H, minor), 3.78 (s, 0.37H, minor), 3.77 (s, 1.1H, major), 3.74 (s, 1.1H, major), 2.75 (dd, *J* = 35.5, 10.0 Hz, 1H), 2.62 – 2.51 (m, 3H), 2.44 (td, *J* = 12.0, 4.5 Hz, 1H), 2.32 – 2.17 (m, 1H), 2.02 – 1.84 (m, 2H), 1.78 – 1.68 (m, 2H), 1.58 – 1.56 (m, 2H), 1.46 (s, 9H), 1.29 – 1.25 (m, 10H), 0.87 (t, *J* = 6.5 Hz, 3H).

In a 5 mL round bottom flask, (*S*)-**6.20** was dissolved in 2 mL of 1,4-dioxane. To the resulting solution was added hydrochloridic acid (2 mL, 4.0 M 1,4-dioxane solution) and the reaction mixture was stirred. After 12 h, the reaction solution concentrated *in vacuo* and the residue was extracted with 5 mL of Na_2CO_3 and 2 × 5 mL chloroform. The combined organic phases were washed with 2 × 5 mL of water and 5 mL of brine. The

resulting organic solution was dried with Na_2SO_4, filtered, and the filtrate was concentrated *in vacuo*. Purification via MPLC (70:30:0 – 40:50:10, hexanes:EA:MeOH) afforded (*S*)-**6.21** as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.11 – 7.06 (m, 4H), 4.04 (dd, *J* = 11.0, 4.5 Hz, 1H), 3.93 – 3.87 (m, 1H), 3.77 (s, 1.5H), 3.75 (s, 1.5H), 2.64 (t, *J* = 9.0 Hz, 2H), 2.56 (t, *J* = 8.5 Hz, 2H), 2.08 – 1.86 (m, 4H), 1.65 (dd, *J* = 10.5, 4.0 Hz, 2H), 1.61 – 1.55 (m, 2H), 1.29 – 1.25 (m, 10H), 0.87 (t, *J* = 6.5 Hz, 3H).

In a 5 mL round bottom flask, (*S*)-**6.21** was dissolved in 2 mL of CH_2Cl_2. To the resulting solution was added bromotrimethylsilane (0.120 g, 0.78 mmol) and the reaction mixture was stirred at room temperature. After 4 h, the resulting solution was concentrated *in vacuo*. The residue was dissolved in 2 mL of 95% EtOH. The solution was stirred at room temperature. After 1 h, the reaction mixture was concentrated *in vacuo* to afford (*S*)-**6.22** (0.024 g, 85%, 3 steps) as a white solid. ^{1}H NMR ($CDCl_3$:MeOD (9:1), 500 MHz): δ 6.95 (d, *J* = 7.0 Hz, 2H), 6.92 (d, *J* = 7.0 Hz, 2H), 4.14 – 4.09 (m, 2H), 2.52 (br, 2H), 2.37 – 2.26 (m, 3H), 2.05 – 1.76 (m, 5H), 1.39 (br, 2H), 1.11 – 1.08 (m, 10H), 0.69 (t, *J* = 6.0 Hz, 3H).

C. SFC Spectrum


AU
2.5e+1
2.0e+1
1.5e+1
1.0e+1
5.0
0.0
6.89
4560650
9.96
163133
6.00
6.50
7.00
7.50
8.00
8.50
9.00
9.50
10.00
10.50
%
6.93
1067041792
9.89
3308390
6.00
6.50
7.00
7.50
8.00
8.50
9.00
9.50
10.00
10.50
Time

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2006 –2010 *B. S., Chemistry,* Nanjing University, Nanjing, Jiangsu, P. R. China

Research Experience

2010 – present *Ph. D thesis research,* Research mentor: Prof. Tom Driver, University of Illinois at Chicago
Topic: Method development of C–N bond formation and relative applications on target-oriented synthesis
1. Transition metal catalyzed C-N bond formation
2. Lead-mediated α-Arylation of β-Ketoesters or γ-Lactams
3. High performance N-heteroaromatic organic field-effect transistor synthesis
4. Small molecule therapeutics for pulmonary diseases: Stereo-defined fingolimod phosphonate derivative synthesis

2008 –2010 *Undergraduate research,* Research mentor: Prof. Xudong Jia, Nanjing University
Topic: Preparation and characterization of one new polybenzoxazine precursor

Organization

2016 *Graduate Student Member,* American Chemical Society.

Patent and Publications

- **Polymer Synthesis and Characterization**
  "Preparation Method of A New Polybenzoxazine Precursor"
  Xudong Jia, Liang Heng, Kai Xi, Fei Zhou, Dan Xu, Xuehai Yu. CN 10033398.8 **2009**.

- **Synthetic Method Development**
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Tetrahedron Lett. **2015**, *56*, 3262. (Memorial Symposium-in-Print for Harry Wasserman)
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"Promoting Reductive Tandem Reactions of Nitrostyrenes with $Mo(CO)_6$ and a Palladium Catalyst to Produce 3*H*-Indoles"
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"Pd-Catalyzed formation of N-Heteroarenes from Nitroarenes using $Mo(CO)_6$ as the Source of Carbon Monoxide"
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Fei Zhou, Duosheng Wang and Tom G. Driver.

"Synthesis and Properties of New N-heteroheptacenes for Solution-Based Organic Field Effect Transistors"
Manuscript in preparation
Fei Zhou, Sheng Liu, Bernard Senstario, Donald J. Wink and Tom G. Driver.

"Pd-Catalyzed Aminocarbonylation of Aryl C–H Bond using Nitroarenes"
Manuscript in preparation
Fei Zhou, Duosheng Wang and Tom G. Driver.

"Diborane-Mediated Deoxygenation of *o*-Nitrostyrenes to form Indoles"
Org, Lett. **2016**, accepted.
Kai Yang, Fei Zhou, Zhijie Kuang, Guoliang Gao, Tom G. Driver and Qiuling Song.

Presentation

2015 *Chicago Organic Symposium* (May 2015, University of Illinois at Chicago)

"Promoting Reductive Tandem Reaction of Nitrostyrenes with $Mo(CO)_6$ and a Palladium Catalyst To Produce 3*H*-Indoles "

Navendu Jana, Fei Zhou, and Tom G. Driver

Abstract: The combination of $Mo(CO)_6$ and 10 mol % of palladium acetate catalyzes the transformation of 2-nitroarenes to 3*H*-indoles through a tandem cyclization-[1,2] shift reaction of in situ generated nitrosoarenes. $Mo(CO)_6$ appears to have dual roles in this transformation: generate CO and promote C–N bond formation to increase the yield of the N-heterocycle product.