

# **The Development of Transition Metal Catalyzed C-N bond Formation Using Nitroarenes**

BY

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THESIS

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## **Contributions of Authors**

Chapter II represents a published manuscript for which I was the second author. The first author was Michael Shevlin. I assisted in the optimization of reaction conditions and testing the scope. I also contributed to a couple of mechanistic experiments. Chapter III represents a published manuscript for which I was the first author. The second author Haoran Zhu assisted me mainly in the contamination studies and he also contributed to the scope studies. Chapter IV represents an unpublished manuscript for which I was the first author.

Chapter V represents my synthesis of potential small molecule therapeutics in the collaboration with College of Pharmacy, UIC. I am one of the three main synthetic researchers in this work. The other two contributors were Dr. Naijing Su and Dr. Wrickban Mazumdar. The collaboration project has published two patents so far.

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## LIST OF ABBREVIATIONS

Ac acetyl

Alk alkyl

aq aqueous

Ar aryl

atm atmosphere

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

d doublet

dba dibenzylidene acetone

DABCO 1,4-diazabicyclo[2.2.2]octane

DCM dichloromethane

DCE 1,2-dichloroethane

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

dppe 1,2-bis(diphenylphosphino)ethane

dppp 1,3-bis(diphenylphosphino)propane

## LIST OF ABBREVIATIONS (continued)

EDG electron-donating group

EE ethoxyethyl

EI electron impact ionization (in mass spectrometry)

Et ethyl

equiv. molar equivalent

EWG electron withdrawing group

G group, Gibbs free energy

g gram

GC gas chromatography

h, hrs hour(s)

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)

## **LIST OF ABBREVIATIONS (continued)**

mp melting point

$\mu$  micro

[M] metal

M molar

MS mass spectrometry

MS molecular sieves

Me methyl

Mes Mesityl

mg milligram

min minute

mL milliliter

mm millimeter

mmol millimole

mol mole

MOM methoxymethyl

## LIST OF ABBREVIATIONS (continued)

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)



## LIST OF ABBREVIATIONS (continued)

rt room temperature

s singlet (NMR)

SEM 2-(trimethylsilyl)ethoxymethyl

SFC supercritical fluid chromatography

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

cc mentholate

X-Ray X-radiation

## SUMMARY

C-N bond formation has been of great significance due to its presence in natural products and bioactive molecules with wide applications. The Driver group has developed an interest in directly utilizing nitroarenes as the nitrogen source to access valuable nitrogen containing scaffolds such as N-heterocycles and diarylamines.

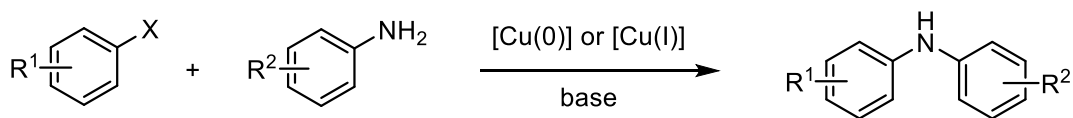
In the introduction of my thesis, I will briefly review some of the research in the field of C-N bond construction that led to the main hypothesis of my research. Then I will spend three chapters summarizing my contributions to new method development over the course of my PhD program. In the first chapter, an iron catalyzed reductive methods that synthesizes N-heterocycles from nitroarenes was explored. The second chapter describes a follow-up investigation in the reductive C-N formation methods, in which, instead of using CO as the stoichiometric deoxygenating reagent to reduce nitroarenes, CO<sub>2</sub> was utilized as a progenitor to produce CO in situ. In the third chapter, an intermolecular C-N cross-coupling reaction was discussed.

In the last part, syntheses of a series of NAMPT inhibitor analogs were described. The C-N formation methods developed by the Driver group allowed us to easily derivatize the tail group of the inhibitors to improve the ligand efficiency and water solubility.

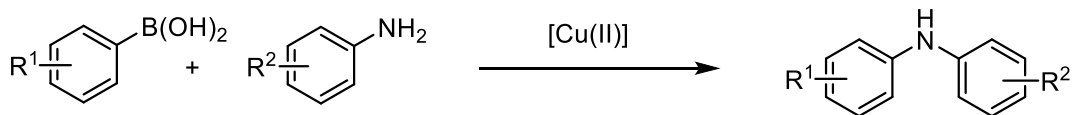
## Chapter I. Introduction

The construction of C-N bonds is of great significance in organic chemistry due to the ubiquitous presence and applications of nitrogen-containing compounds in natural products, pharmaceutical molecules, and multifunctional materials.<sup>1</sup> Over the decades, enormous success has been achieved on using amines as a nucleophilic nitrogen source. More than a century ago, Ullmann and Goldberg built C-N bond between amine nucleophiles and aryl (pseudo)halides in the presence of stoichiometric loading of a copper salt.<sup>2,3</sup> Since then, a lot of efforts have been focused on transition-metal catalyzed C-N bond formation that gave rise to various prominent reactions such as Chan-Lam Coupling, a copper catalyzed coupling between an amine and a boronic acid, or Buchwald-Hartwig aminations using palladium catalysts (**Scheme 1.1**).<sup>4,5</sup>

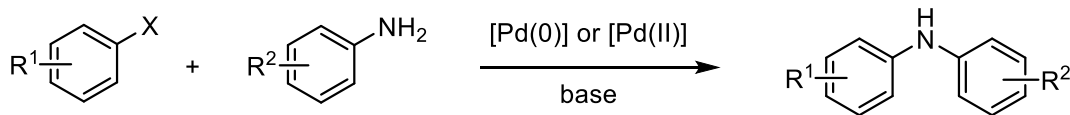
- Ullmann-Goldberg coupling



- Chan-Evans-Lam coupling

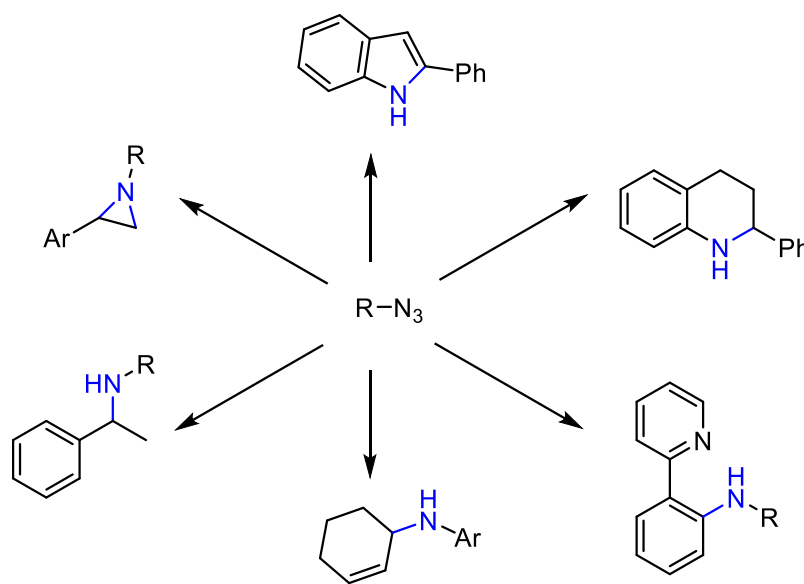


- Buchwald-Hartwig coupling



**Scheme 1.1** Cross coupling reactions to construct C-N bond from amines

With nucleophilic nitrogen source highly developed in the C-N formation, researchers have also been exploring the use of other potential nitrogen sources. Organic azides for example, have also emerged rapidly to become prevalent sources of nitrogen in C-N formation, especially via its nitrene chemistry, varying from cycloaddition, insertion to rearrangement (**Scheme 1.2**).<sup>6</sup> Since the early practice of thermo and photochemical reactions of organic azides to synthesize N-heterocycles, substantial progress has been made in utilizing azides as the nitrogen-atom precursor.<sup>7-10</sup> Not only has significant advances been made in the intramolecular C-N bond formation, but the intermolecular C-H bond amination from azides have also become a growing research area in organic chemistry.<sup>11</sup>

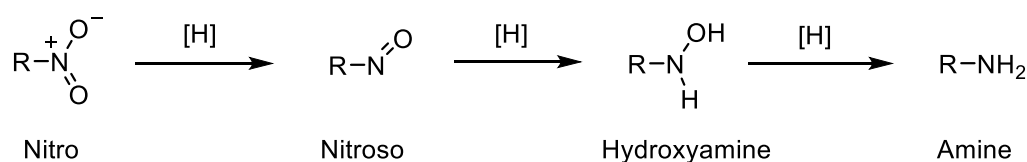


**Scheme 1.2** Applications of organic azides as nitrogen source in C-N bond formation

Contrary to amines and azides, nitro compounds in the past were less commonly recognized as a direct source of nitrogen.<sup>12-13</sup> Despite its stable, inexpensive, and readily available features, it was widely considered as the precursor of primary amines. It was still the amine compounds that served as the direct building block in the synthesis of nitrogen

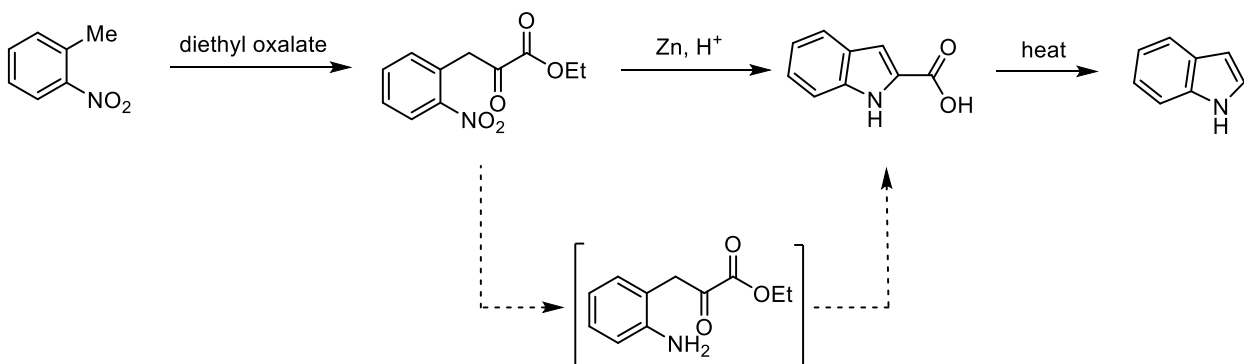
containing molecules and thus various efforts were developed to reduce nitro compounds to amines.<sup>14</sup> However, compared to amination from amine compounds, using the corresponding nitro compounds directly could save at least one synthetic step.<sup>15,16</sup> More importantly, having access to electrophilic nitrogen sources and reductive reaction environment can provide alternative functionalization handles when nucleophilic nitrogen sources or oxidative reagents are not favored under some circumstances. Nowadays, more and more effort has been made to employ nitroarene as direct aminating reagents.

In general, reduction of nitro compounds could follow the path through a nitroso intermediate and a hydroxyamine intermediate before getting fully reduced to aniline (**Scheme 1.3**).<sup>17</sup> While reactions like the Reissert indole synthesis or the Leimgruber-Batcho indole synthesis achieved tandem reduction of nitro to amine followed by C-N formation (**Scheme 1.4**), the Bartoli indole synthesis provides a different inspiration.<sup>20</sup> In the proposed mechanism (**Scheme 1.5**), the addition of the Grignard reagent first occurs to form the O-allylated adduct **1.2**, which spontaneously decomposes into nitrosoarene **1.3**.<sup>18,19</sup> A second equivalent of the Grignard reagent comes in to form the adduct **1.4**. After a 3,3 sigmatropic rearrangement, the resulting intermediate **1.5** then cyclizes to form the N-heterocycle **1.6**, which then tautomerizes to form indoline **1.7**. Finally, reaction work up eliminates a molecule of water to form the indole product **1.8**.

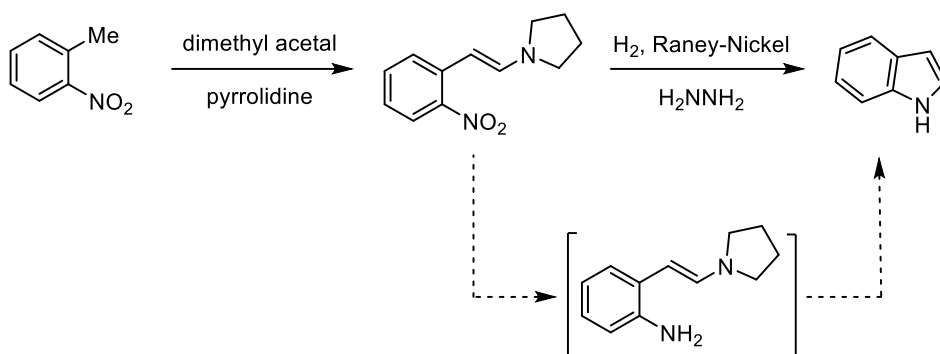


**Scheme 1.3** Reduction of nitro compounds

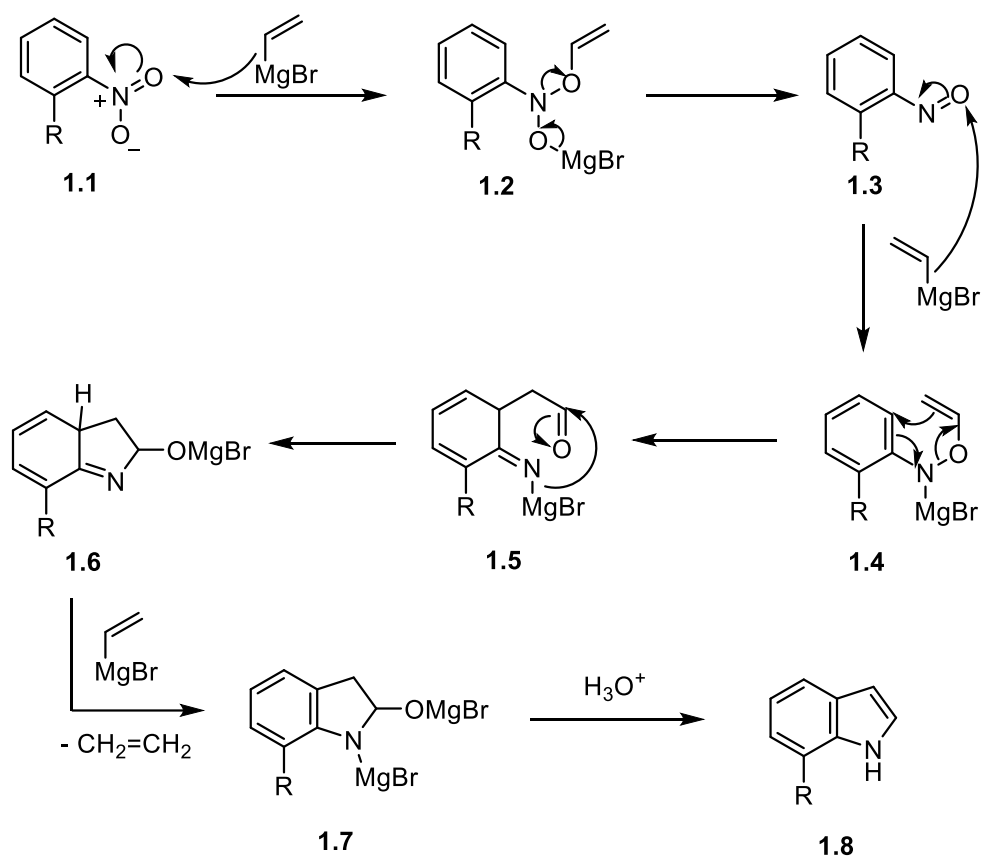
- Reissert indole synthesis



- Leimgruber–Batcho indole synthesis



**Scheme 1.4** Indole synthesis from nitro compounds via aniline intermediate

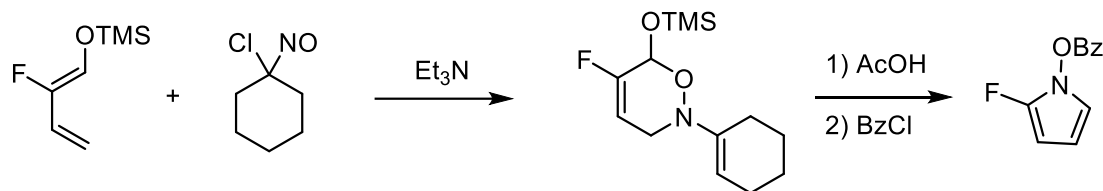


**Scheme 1.5** Bartoli indole synthesis via nitrosoarene intermediate during C-N formation

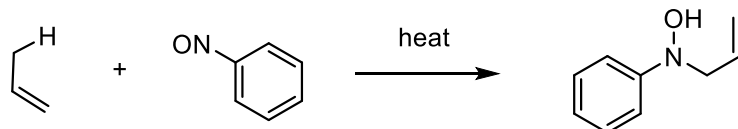
The Driver group has been interested in accessing such nitrosoarene intermediates or other electrophilic nitrogen species from nitroarenes because of their highly reactive nature in C-N bond formation, including hetero Diels-Alder reaction, Ene reaction, Cope reaction, O-nitroso or N-nitroso aldol reaction and electrocyclization (**Scheme 1.6**).<sup>21,22</sup> The investigation began with the synthesis of useful N-heterocycles such as indoles and carbazoles via intramolecular C-H amination. Apart from the Grignard reagent previously mentioned, traditionally, to achieve such transformation using nitroarenes, excessive amount of reductant like zinc dust, phosphites or phosphines are required.<sup>23</sup> Alternatively, under high carbon monoxide pressure, the reductive cyclization can also be achieved with transition metals.<sup>24</sup> These strategies have not been able to emerge further because of either

the generation of a large amount of undesired waste from the reductant, or the requirement of a harsh reaction conditions like high CO pressure.

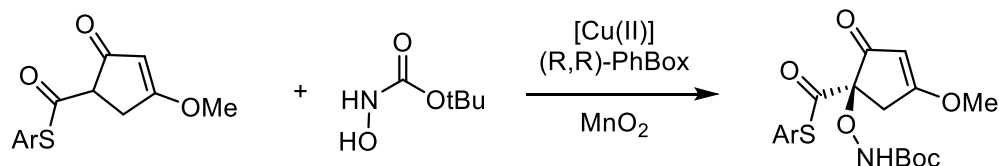
Hetero Diels-Alder reaction:



Ene-reaction



Aldol reaction

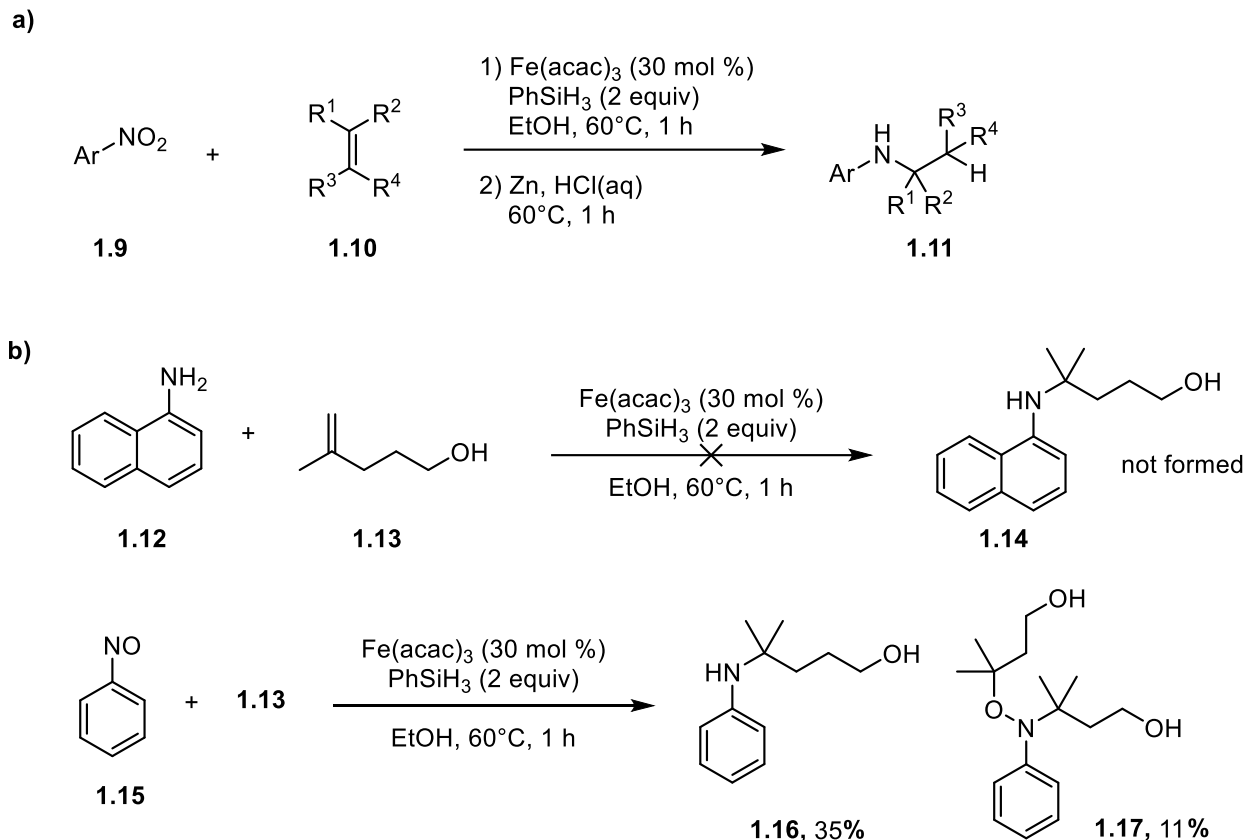


**Scheme 1.6** Examples of nitroso species reactivity

In recent years, alternative of CO gas and other potential reducing agents have been investigated, organophosphorus catalysis has been explored and first-row transition metal catalysts have also been extensively studied.<sup>15,25,26</sup> In 2015, Baran and co-workers published a Fe-catalyzed hydroamination of olefins using nitroarenes as the nitrogen source (**Scheme 1.7a**). Phenyl silane was used as the reductant, but the reaction still required a Zn/HCl(aq.) reductive workup and the Fe catalyst loading was relatively high.<sup>27</sup> After subjecting possible intermediates under the standard reaction conditions, only

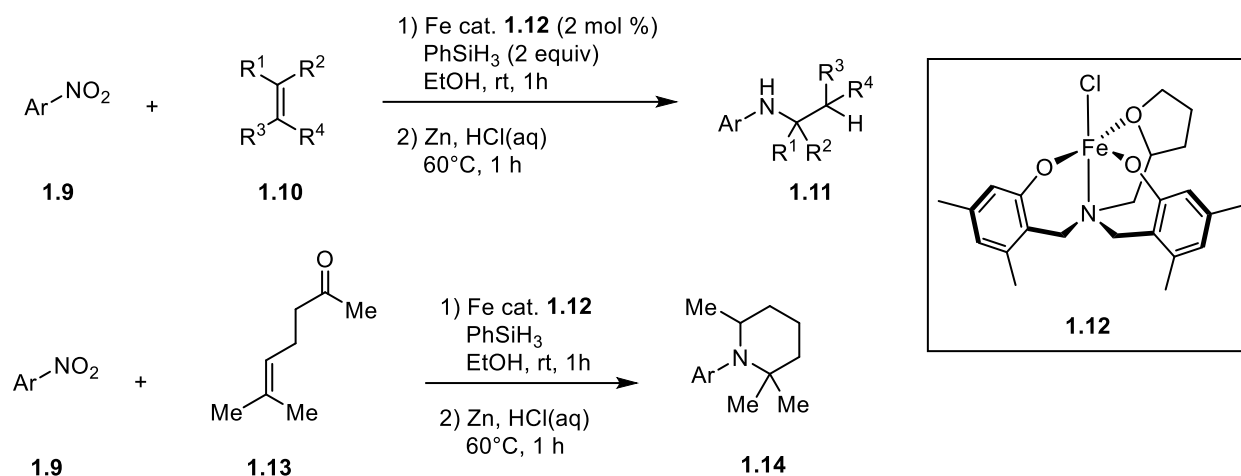


nitrosobenzene was able to generate a decent amount of desired product, suggesting that nitrosoarene was also the intermediate in this synthetic route (**Scheme 1.7b**).



**Scheme 1.7** Fe-catalyzed reductive hydroamination of olefins with nitroarenes

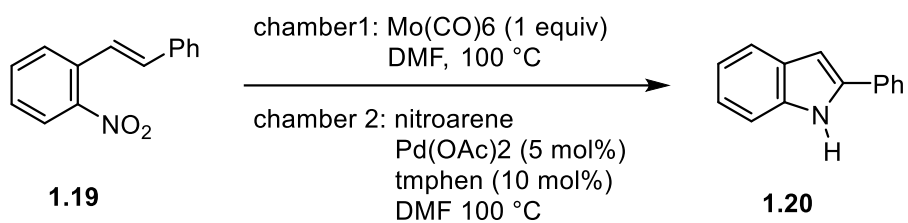
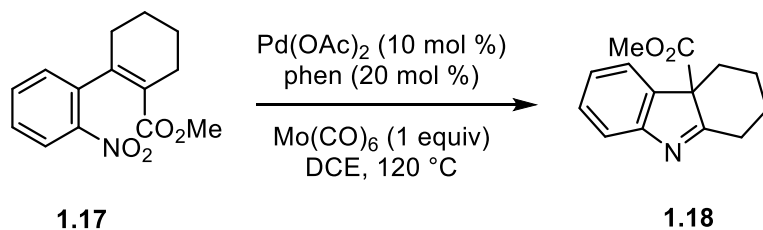
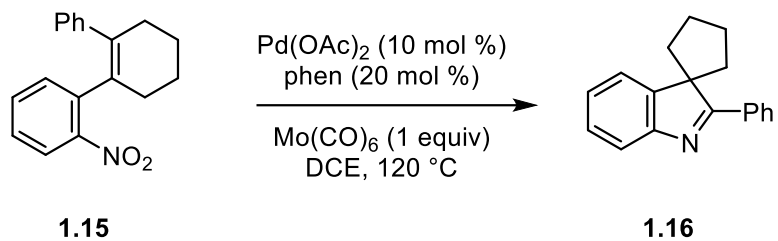
In 2016, using triethoxysilane as a reducing agent, Thomas and co-workers developed a Fe(III) catalyzed hydroamination of alkenes with nitroarenes that could be performed at much lower catalyst loading and room temperature although the yields can still be improved (**Scheme 1.8**).<sup>28</sup> By the time I started my career, the Driver group was putting a lot of interest in developing methods for accessing the nitrosoarene intermediates from nitroarenes using first-row transition metal catalyst. The first chapter of my research work will discuss my contribution to this project.



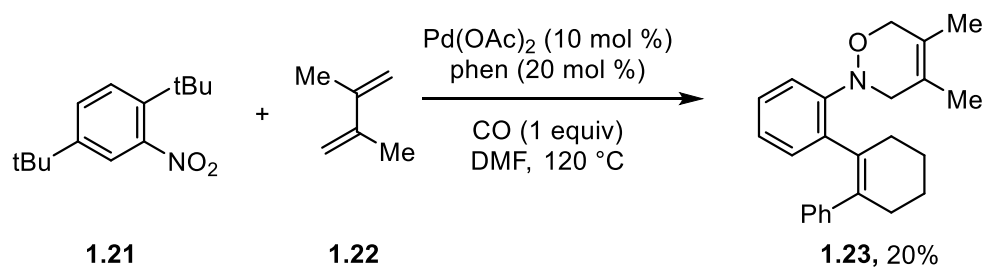
**Scheme 1.8** Amine-bis(phenolate)-Fe(III) catalyzed reductive hydroamination

The second challenge I faced was about the CO reductant. In 2015, the Driver group developed a synthesis of 3H-indoles using  $\text{Mo(CO)}_6$  to release CO gas in situ (**Scheme 1.9a**), in which the mechanism studies also showed strong support for the presence of a nitrosoarene intermediate by the observation of an intercepted intermediate **1.19** (**Scheme 1.9b**).<sup>29</sup> Based on this reaction system, the Driver group later achieved an intermolecular aryl C-H aminocarbonylation using Pd catalyst and  $\text{Mo(CO)}_6$  as the terminal reductant (**Scheme 1.9c**).<sup>30</sup> More recently in 2019, the Driver group was also able to expand the CO reduction system to construct  $\text{sp}^3\text{-C-NHAr}$  bonds intramolecularly using an enolizable nucleophile (**Scheme 1.9d**).<sup>31</sup> To obviate the drawback by using pressured CO atmosphere while maintaining the unique reactivity, I started to seek for a CO progenitor such that CO can be released in situ throughout the course of the reaction. In the second chapter, details in this project will be further discussed.

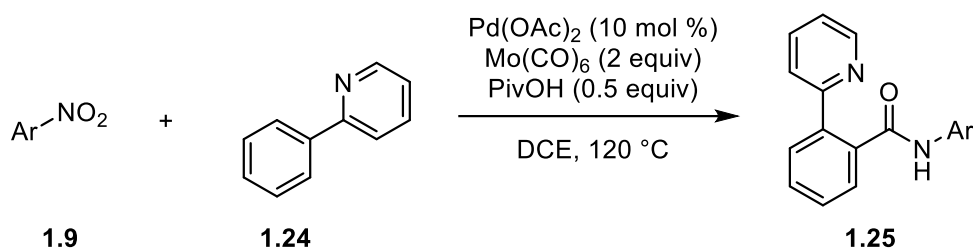
a)



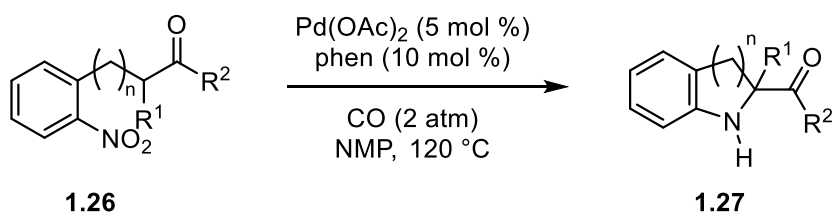
b)



c)



d)



**Scheme 1.9** Recent works of the Driver group on reductive C-N bond formation from nitro compounds

Intermolecular C-N bond formation using nitroarene as the nitrogen source has been an important research topic but has been surprisingly underdeveloped for reactions that go through a nitroso intermediate. With the experience and knowledge that I gained from previous works, my next task in method development is focused on achieving intermolecular animation, which will be unfolded in my third chapter.

This introductory chapter briefly outlines the inspirations, key hypothesis, and challenges of my three methodology projects. Overall speaking, more and more efforts have been made to directly use nitro compounds as aminating reagent both in intramolecular and intermolecular reactions. The Driver group has been devoted to accessing nitroso intermediate from nitro compounds to develop novel reactivities and to synthesize useful nitrogen containing molecules. This type of transformation has good potential to become a

substantial complement to the existing C-N bond formation techniques, most of which are based on amines as the nitrogen source.

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## Chapter II.

# Iron-Catalyzed Reductive Cyclization of o-Nitrostyrenes Using Phenylsilane as the Terminal Reductant

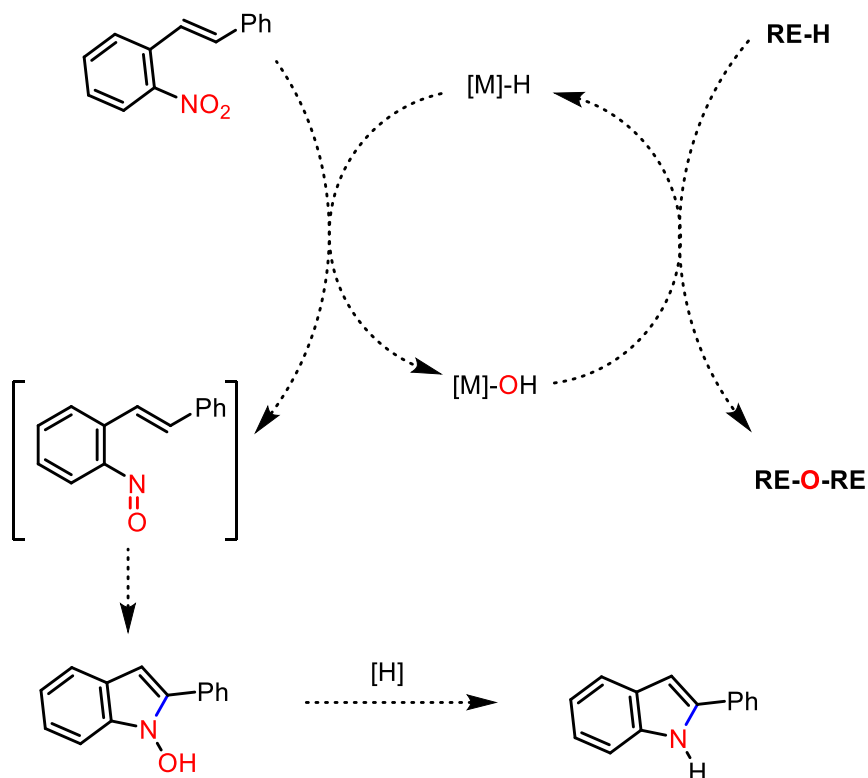
(The structure of this chapter followed the published article and with permission to reprint figures and tables from: Iron-Catalyzed Reductive Cyclization of o-Nitrostyrenes Using Phenylsilane as the Terminal Reductant.

Shevlin, M.; Guan, X.; Driver, T.G. *ACS Catal.* **2017**, 5518-5522)

### 2.1. Introduction.

Nitroarenes are considered as a robust and readily available nitrogen source in the formation of carbon-nitrogen bonds with their versatility in accessing a variety of reactive intermediates.<sup>1</sup> *ortho*-Nitrostyrenes have been widely explored as a scaffold for the synthesis of indoles, the parent substance of a large number of natural- and synthetic molecules with significant biological activity.<sup>2</sup> Generally it is required that stoichiometric amounts of reductants, such as phosphite,<sup>3</sup> Grignard reagent,<sup>4</sup> iron,<sup>5</sup> zinc,<sup>5a,b</sup> titanium(III),<sup>6</sup> diborane reagent,<sup>7</sup> or the combination of a palladium catalyst and carbon monoxide<sup>8</sup> are used to conduct this type of reductive cyclization, raising concerns of restricting its application in making highly functionalized, complex molecules with harsh reaction conditions, namely high temperatures and pressures, strongly acidic-, basic or toxic

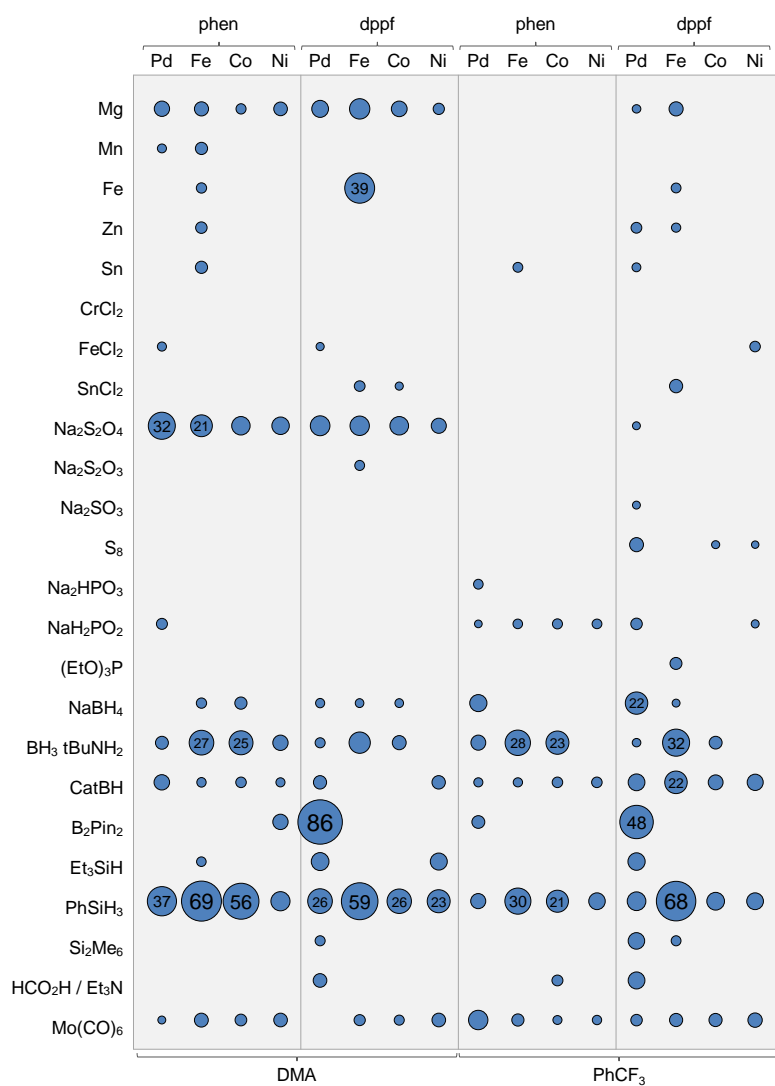
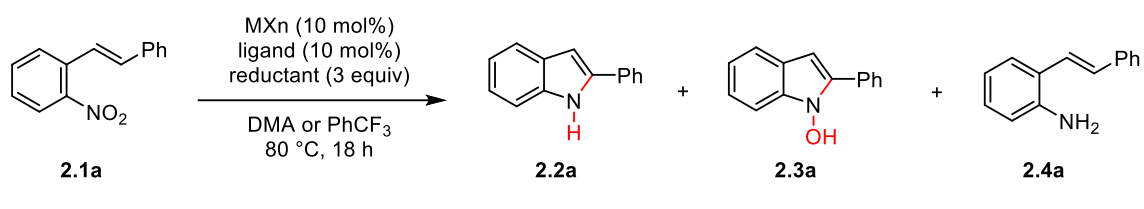
reagents. In pursuit of a solution to the mentioned limitations, we focused on identifying efficient conditions for oxygen-atom transfer catalysis. In our hypothesis, the combination of an oxophilic first-row transition metal with a low-valent or hydridic p-block compounds as oxygen-atom acceptors could achieve the desired conversion under mild conditions (**Scheme 2.1**).<sup>9</sup> Less expensive, more abundant and having more accessible oxidation states, the advantage of first-row transition metals compared to the precious metals are highly valued by researchers.<sup>10</sup> Recent works showed the capability of these catalysts performing a profusion reductive transformations,<sup>11</sup> among which stood out to us was an olefin hydroamination with nitroarenes using Fe(II) catalyst reported by Baran and co-workers.<sup>12</sup> We saw a room for improvement for the latter reaction as it not only demands a high-loading of iron catalyst, but the *N*-hydroxylamine intermediate has to undergo a second reduction step to form the desired deoxygenated product, at the cost of an excess amount of a zinc reductant. One of the big challenges for this exploration would be to efficiently determine the optimal conditions from the wide range of combinations of catalyst and reducing agent. This has led us to examine automated microscale high-throughput experimentation to identify the lead conditions.<sup>13,14</sup>



**Scheme 2.1** Finding mild reductive conditions to convert *o*-nitrostyrenes into indoles.

In our effort towards finding a transition metal catalyst and a mild deoxygenating reagent, Dr. Michael Shevlin (Merck) screened the chosen model, forming 2-phenylindole **2a** from *ortho*-nitrostilbene **2.1a** (**Figure 2.1**). After setting the reaction temperature of 80 °C to be the intended mild condition, the efficiency of a series of reducing agents covering low-valent metal compounds and main group reducing agents, were tested in combination with FeCl<sub>2</sub>, CoCl<sub>2</sub> and NiCl<sub>2</sub> in the presence of either 1,10-phenanthroline (phen) or 1,1'-bis(diphenylphosphino)ferrocene (dppf) as their ligands. Each combination was also examined with the analogous Pd-catalyst as the control experiment. To our delight, the desired 2-phenylindole **2.2a** was observed under a good number of conditions but in many cases, we also observed byproduct *N*-hydroxyindole **2.3a** and aniline **2.4a**.<sup>15,16</sup> The

reductive cyclization proceeded in the highest yield for Pd(OAc)<sub>2</sub> and B<sub>2</sub>pin<sub>2</sub> and among the first-row transition metals we studied, Fe- and Co- were found to be more effective using dithionite-, borane- or silane reductant. A promising yield of 69% of **2.2a** was obtained when 10 mol % of FeCl<sub>2</sub> and phen were used together with PhSiH<sub>3</sub>.



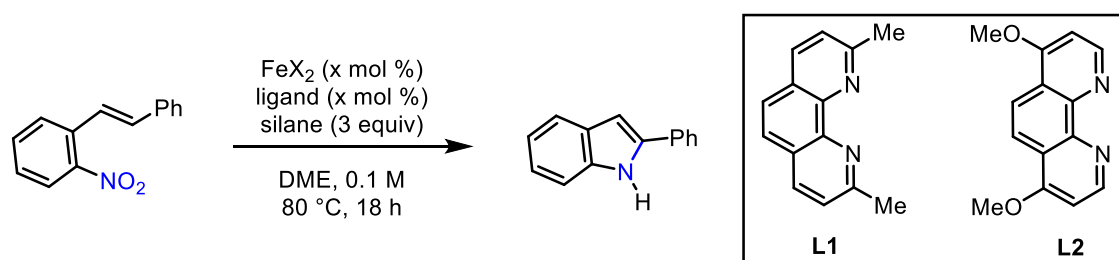
**Figure 2.1.** Initial high-throughput experimentation survey. Conditions: 10  $\mu\text{mol}$  of **2.1a**, 10 mol % of  $\text{Pd}(\text{OAc})_2$ ,  $\text{FeCl}_2$ ,  $\text{CoCl}_2$  or  $\text{NiCl}_2$ , 10 mol % of phen or dppf, 3 equiv of reducing agent, DMA or  $\text{PhCF}_3$ , 80  $^\circ\text{C}$ , 18 h. Size of circles indicate yield of **2.2a** as determined using quantitative HPLC analysis.

Based on the initial screening outcomes, a subsequent investigation of reaction parameters was performed using high-throughput experimentation (**Table 2.1**).<sup>17</sup> Among the solvent examined, DME was also found to be potent with the yield of **2.2a** only second to the yield of the lead hit using DMA (entry 1).<sup>17</sup> DME was preferred because it could provide us an easier work-up and purification of the reaction mixture. The diminished yield after changing solvent was redeemed when the counterion of the catalyst was changed to acetate (entry 2). We believed that the counterion benefited the reaction by increasing the solubility of the catalyst.

Without a supporting ligand for  $\text{Fe}(\text{OAc})_2$ , the yield would drop significantly, and if the reaction was performed without any iron, no indole was formed in the presence of  $\text{PhSiH}_3$  (entries 3 and 4). Extensive screening on ligand identity (entries 5 – 9) revealed that the use of other conventional bidentate ligands such as dppe or dtbpy did not result in a higher yield, whereas TMEDA led to poorer yield of **2.2a**. Next, I examined the effect of different substituents on phenanthroline ligands (entries 8 and 9). It was discovered with great delight that the reaction proceeded in higher yields with sterically encumbered 2,9-dimethyl-1,10-phenanthroline, and was most effective when the electron rich 4,7-dimethoxy-1,10-phenanthroline was used as the ligand. Moreover, I sought to lower the catalyst and ligand (entries 10 – 12). Remarkably, using as little as 0.5 mol % of  $\text{Fe}(\text{OAc})_2$

and 4,7-(MeO)<sub>2</sub>phen resulted in 87 % yield of **2.2a** (entry 12). Further studies showed that no other silanes achieved the same reaction efficiency as PhSiH<sub>3</sub> despite that these silanes have their own merits that caught our interest, for example the environmentally friendly polymethylhydrosiloxane (entries 13 – 16).

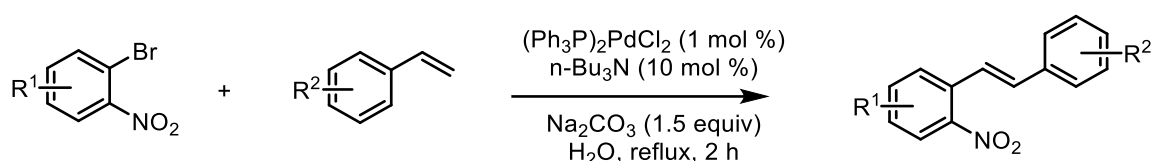
**Table 2.1. Optimization of the reductive cyclization.**



entry	FeX <sub>n</sub>	ligand	mol %	silane	indole, % <sup>a</sup>
1	FeCl <sub>2</sub>	phen	10	PhSiH <sub>3</sub>	57
2	Fe(OAc) <sub>2</sub>	phen	10	PhSiH <sub>3</sub>	75
3	Fe(OAc) <sub>2</sub>	---	10	PhSiH <sub>3</sub>	46
4	---	---	---	PhSiH <sub>3</sub>	0
5	Fe(OAc) <sub>2</sub>	dppe	10	PhSiH <sub>3</sub>	73
6	Fe(OAc) <sub>2</sub>	dtbpy	10	PhSiH <sub>3</sub>	72
7	Fe(OAc) <sub>2</sub>	TMEDA	10	PhSiH <sub>3</sub>	52
8	Fe(OAc) <sub>2</sub>	L1	10	PhSiH <sub>3</sub>	81
9	Fe(OAc) <sub>2</sub>	L2	10	PhSiH <sub>3</sub>	99
10	Fe(OAc) <sub>2</sub>	phen	2	PhSiH <sub>3</sub>	83
11	Fe(OAc) <sub>2</sub>	phen	1	PhSiH <sub>3</sub>	94
12	Fe(OAc) <sub>2</sub>	L2	0.5	PhSiH <sub>3</sub>	87 <sup>b</sup>
13	Fe(OAc) <sub>2</sub>	phen	1	Ph <sub>2</sub> SiH <sub>2</sub>	44
14	Fe(OAc) <sub>2</sub>	phen	1	Et <sub>3</sub> SiH	1
15	Fe(OAc) <sub>2</sub>	phen	1	PHMS	32
16	Fe(OAc) <sub>2</sub>	phen	1	(EtO) <sub>3</sub> SiH	76

<sup>a</sup> Yield determined by quantitative HPLC analysis. <sup>b</sup> Isolated yield.

Using these optimal conditions, I started to look at the scope of the reaction. The substrates to explore the scope can be easily prepared in excellent yield by an aqueous phase Heck reaction between readily available *o*-nitrobromobenzenes and styrenes (**Scheme 2.2**).

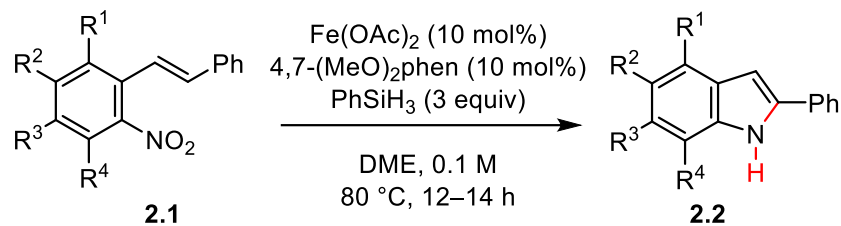


**Scheme 2.2** Heck reaction to prepare 2-nitrostilbenes

The result of the scope investigation was shown in **Table 2.2**. First, I studied the scope with respect to the substituent on the nitroarene. The electronic properties of the groups at the 3-position or 4-position did not have a large effect on the yield of indoles **2.2a** – **2.2j** (entries 1 – 10). In addition, a more sterically hindered environment was studied by having an *ortho*-substituent next to the nitro group or next to the alkenyl substituent, resulting in a very good yield of indole **2.2k** and slightly diminished yield of indole **2.2l** (entries 11 and 12).



**Table 2.2. Scope of the Fe-catalyzed reductive cyclization on nitroarenes.**

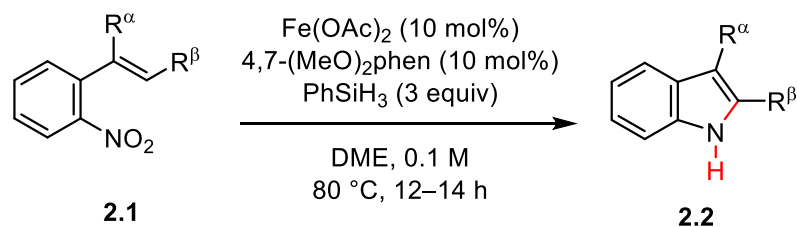


entry	#	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	yield, % <sup>a</sup>
1	<b>a</b>	H	H	H	H	96
2	<b>b</b>	H	H	F <sub>3</sub> C	H	90
3	<b>c</b>	H	H	MeO <sub>2</sub> C	H	98
4	<b>d</b>	H	H	Cl	H	96
5	<b>e</b>	H	H	F	H	88
6	<b>f</b>	H	H	Me	H	86
7	<b>g</b>	H	H	MeO	H	97
8	<b>h</b>	H	F <sub>3</sub> C	H	H	82
9	<b>i</b>	H	Me	H	H	96
10	<b>j</b>	H	MeO	H	H	80
11	<b>k</b>	H	H	-CH=CH-CH=CH-		98
12	<b>l</b>	Me	H	H	H	78

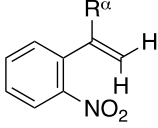
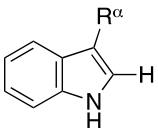
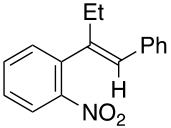
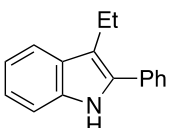
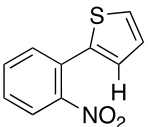
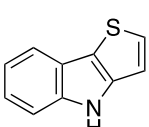
<sup>a</sup> Isolated after silica gel chromatography.

On the other hand, different substituents of the *ortho*-alkene were also investigated (**Table 2.3**). Both  $\beta$ -aryl substituted and  $\beta$ -alkyl substituted nitrostyrene **2.1** proved to be good substrates for this transformation (entries 1 – 5). Substrates bearing  $\alpha$ -phenyl or  $\alpha$ -methyl groups were also tolerated under the optimal conditions (entries 6 and 7). However, in the attempt of using *ortho*-heteroaryl substituted nitroarenes to trigger the reductive cyclization reaction, no desired *N*-heterocycle was observed but reduction to aniline occurred instead (entry 9).

**Table 2.3. Effect of *o*-alkenyl identity on *N*-heterocycle formation.**



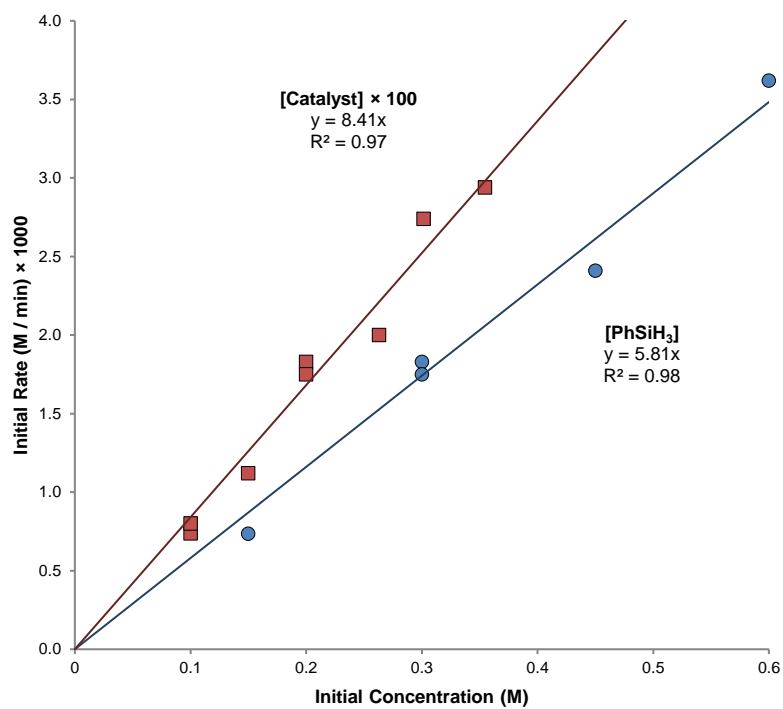
entry	#	nitroarene	<i>N</i> -heterocycle	yield, % <sup>a</sup>
1	<b>m</b>			R = CF <sub>3</sub> , 98
2	<b>n</b>			R = Cl, 88
3	<b>o</b>			R = Me, 83
4	<b>p</b>			R = OMe, 92
5	<b>q</b>			98

6	<b>r</b>			$R^{\alpha} = \text{Ph}$ , 97
7	<b>s</b>			$R^{\alpha} = \text{Me}$ , 71
8	<b>t</b>			90
9	<b>u</b>			n.r. <sup>b</sup>

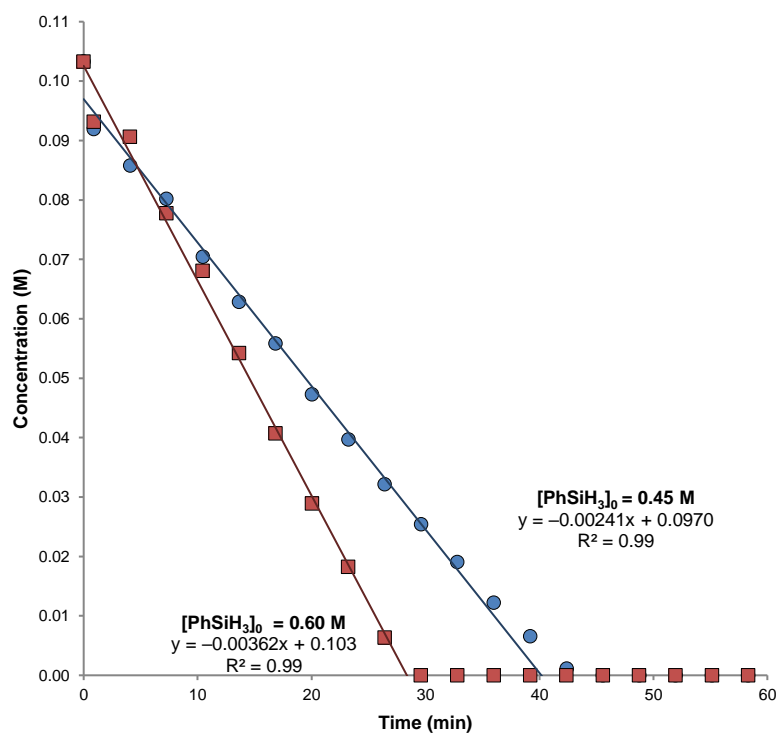
<sup>a</sup> Isolated after silica gel chromatography. <sup>b</sup> Quantitative conversion to the aniline observed.

To gain an insight of the mechanism of the Fe-catalyzed reductive cyclization, we performed a series of experiments to quantitatively measure the effect of changing the concentration of the reagents on the rate of the reaction. Using the methods of initial rates, we determined that the catalyst and phenylsilane reductant were following the first order behavior (**Figure 2.2a**). It was notable that when a large excess of the silane was submitted to the reaction, the reaction progress under detailed kinetic profiling demonstrated a linear consumption of nitrostyrene **2.1a** with time and thus suggesting a zero-order dependence of the rate on the concentration of the substrate (**Figure 2.2b**). From the data we hypothesized that the reaction featured fast nitro reduction and subsequent nitrosoarene cyclization, with the turnover limiting step being the reaction between the catalyst and the silane to regenerate the active catalytic intermediate.

**a**



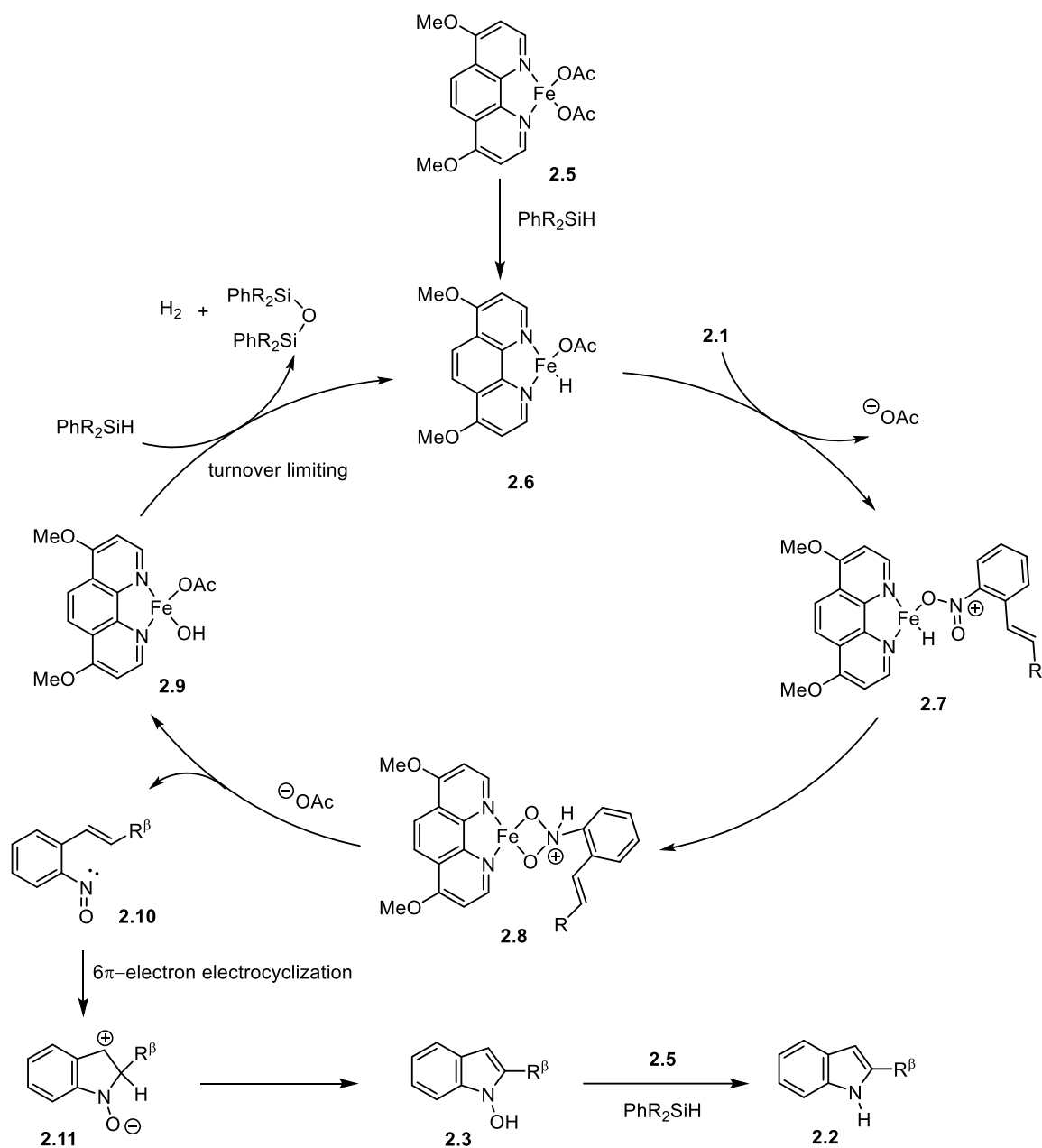
**b**



**Figure 2.2.** (a) Initial rate studies for the reaction of nitrostyrene **2.1a** with PhSiH<sub>3</sub>. (b) Kinetic profiles for the reaction of nitrostyrene **2.1a** in the presence of a large excess of PhSiH<sub>3</sub>.

While multiple plausible mechanisms could be proposed for this transformation, we anticipated the presence of an iron hydride catalytic intermediate in the catalytic cycle for the reductive cyclization reaction (**Scheme 2.3**). Reaction between silane reducing agent and [4,7-(MeO)<sub>2</sub>phen]Fe(OAc)<sub>2</sub> **2.5** produces the reactive iron hydride **2.6**. Our data suggested an absence of an induction period, which by contrast, was observed in the (boxmi)Fe( $\kappa^2$ -OAc)-catalyzed reduction of ketones using (EtO)<sub>2</sub>MeSiH.<sup>11e,f</sup> We envisioned that it is due to the coordinately less saturated nature of **2.5**, its  $\sigma$ -bond metathesis with the silane can occur more readily, while (boxmi)Fe( $\kappa^2$ -OAc) requires a slow reduction by the silane to convert the acetate to ethoxide in order to produce the active catalyst.<sup>11f</sup> Consequently, coordination of nitrostyrene **2.1** with iron hydride **2.6** produces a coordinated complex **2.7**.<sup>18</sup> Then the nitro group is reduced by the iron hydride to generate complex **2.8** ( $\kappa^1$ - or  $\kappa^2$ -coordinated).<sup>19,20</sup> This is followed by complex **2.8** fragmenting into iron hydroxide **2.9** and nitrosostyrene **2.10**,<sup>21</sup> ensuring a subsequent rate-limiting reduction of **2.9** with silane to regenerate the active iron hydride and extrudes siloxane and H<sub>2</sub>. On the other hand, electrocyclization of nitrosostyrene **2.10** occurs and *N*-hydroxyindole **2.3** is produced by proton elimination.<sup>22</sup> Finally, *N*-hydroxyindole **2.3** gets further reduced to form indole **2.2**.

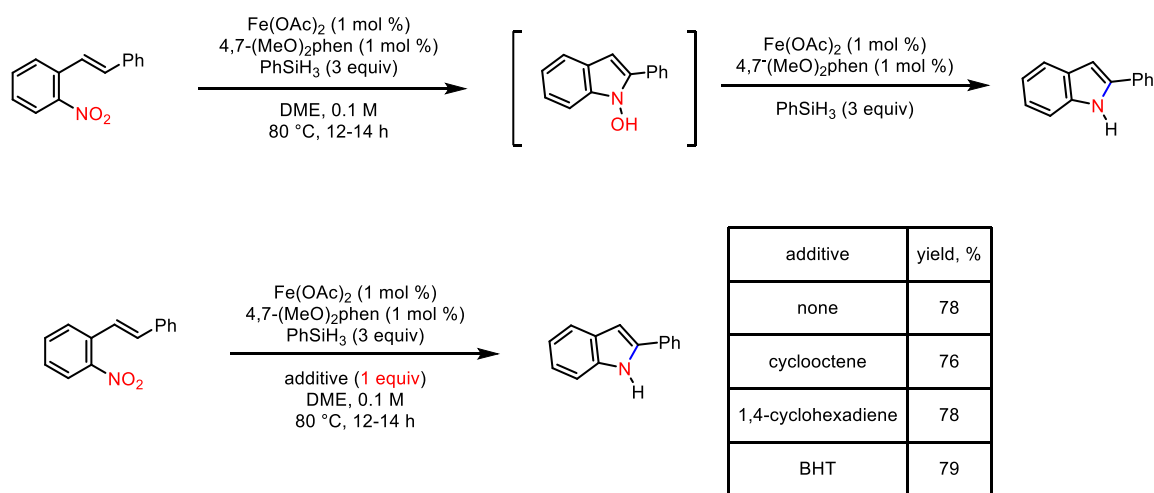
To test our proposed catalytic cycle, several experiments were performed. The first thing we were curious to know was the identity of the gas by-product during the vigorous effervescence observed in larger scale reactions. Utilizing <sup>1</sup>H NMR spectroscopy we identified that the gas generated in the reaction was indeed H<sub>2</sub>.



**Scheme 2.3.** Potential mechanism for the Fe-catalyzed reductive cyclization of *o*-nitrostyrenes to synthesize indoles.

In addition, we confirmed the identity of an intermediate to be *N*-hydroxyindole **2.3a** by independent synthesis (**Scheme 2.4**). This intermediate can be observed under HPLC

monitoring of the reaction. When **2.3a** was exposed to 1 mol % of  $\text{Fe}(\text{OAc})_2$  and 4,7-(MeO) $_2$ phen, it led to partial reduction (49%) to indole **2.2a** while a complete conversion occurred only when both the iron catalyst and phenylsilane reductant were used in the reaction. In comparison to previous outcomes, if metal catalyst was removed from the reaction and only phenylsilane was in presence, no reduction of **2.3a** was observed. To examine if radical intermediates were involved, we designed several control experiments by subjecting different additives to the reaction mixture. We observed that the addition of cyclooctene, 1,4-cyclohexadiene, or BHT, to the reaction mixture showed consistent outcome compared to the blank control. Hence, we believe that either free radical reactive intermediates are not formed in the reductive cyclization or they fail to escape the coordination sphere of the catalyst thus not be observed in our experiments.



**Scheme 2.4.** Control experiments on Fe-catalyzed reductive cyclization

In conclusion, we have discovered the optimal reaction conditions using an earth abundant iron phenanthroline catalyst in combination with phenylsilane to synthesize indoles from *ortho*-nitrostyrenes. The outstanding efficiency we experienced in the screening of the conditions validated high-throughput experimentation to be a very powerful tool in reaction discovery and optimization. Our investigations support the hypothesis that in this reductive cyclization transformation, nitrostyrene is likely to be reduced by an iron hydride intermediate and generate a reactive nitroso intermediate, which undergoes further cyclization to form the *N*-hydroxyindole intermediate before it finally gets reduced by phenylsilane catalyzed by Fe-catalyst to generate *N*-heterocycle product. We inspected the scope and limitations of the method and conducted kinetic experiments, implying that the turnover-limiting step is regeneration of the iron hydride with phenylsilane.

## Experimental

(This part was taken from supporting information of my published paper: Shevlin, M.; Guan, X.; Driver, T.G. *ACS Catal.* **2017**, 5518-5522.)

**General.** <sup>1</sup>H NMR and <sup>13</sup>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

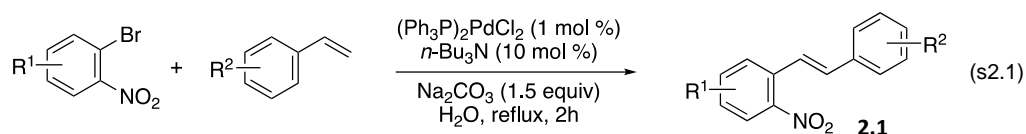


from internal tetramethylsilane on the  $\delta$  scale, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz) and integration. High-resolution mass spectra were obtained by peak matching. Melting points are reported uncorrected. Infrared 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. HPLC analysis was conducted on an Agilent 1100 instrument equipped with a binary pump and diode array detector. Liquid chromatography was performed using forced flow (flash chromatography) of the indicated solvent system on 60Å (40 – 60  $\mu$ m) mesh silica gel (SiO<sub>2</sub>). Medium pressure liquid chromatography (MPLC) was performed to force flow the indicated solvent system down columns that had been packed with 60Å (40 – 60  $\mu$ m) mesh silica gel (SiO<sub>2</sub>). 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<sub>2</sub>O, and CH<sub>2</sub>Cl<sub>2</sub> were dried by filtration through alumina according to the procedure of Grubbs.<sup>1</sup> Metal salts were stored in a nitrogen atmosphere dry box.

## **I. Synthesis of 2-substituted Nitrostilbenes.**

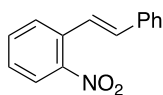
### **A. General Procedure.**

The requisite (*E*)-1-nitro-2-styrylbenzenes were prepared from substituted 1-bromo-2-nitrobenzene and styrene using a Heck reaction as reported by Bumagin, Beletskaya and co-workers (eq s1).{Bumagin, 1995 #8188}



To a solution of 1-bromo-2-nitrobenzene (1.0 equiv),  $\text{PdCl}_2(\text{PPh}_3)_2$  (1 mol%),  $n\text{-Bu}_3\text{N}$  (10 mol%) and  $\text{Na}_2\text{CO}_3$  (1.5 equiv) in  $\text{H}_2\text{O}$  was added styrene (1.5 equiv). The resultant mixture was then purged with  $\text{N}_2$  and heated to reflux. After 2 h, the mixture was cooled to room temperature and quenched with a 1 M aq soln of  $\text{HCl}$ . The resulting mixture was then extracted with  $3 \times 10$  mL of MTBE and washed with 10 mL of water and 10 mL of brine. The resulting organic phase was dried over  $\text{Na}_2\text{SO}_4$ , and the mixture was filtered through a pad of Celite. The filtrate was concentrated *in vacuo*. Purification via MPLC (0:100 – 15:85 EtOAc:hexanes) afforded the product.

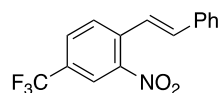
## B. Characterization Data.



**2.1a**

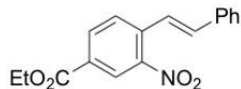
**2-Nitrostilbene (2.1a).** The general procedure was followed using 0.249 g of 2-iodo-1-nitrobenzene (1.00 mmol), 0.156 g of styrene (1.50 mmol), 0.007 g of  $\text{PdCl}_2(\text{PPh}_3)_2$  (0.01 mmol), 0.019 g of  $n\text{-Bu}_3\text{N}$  (0.10 mmol), 0.159 g of  $\text{Na}_2\text{CO}_3$  (1.50 mmol) in 2.0 mL of water. Purification via MPLC (0:100 – 15:85 EtOAc:hexanes) afforded **2.1a** as a yellow solid (0.169 g, 75%). The spectral data of **2.1a** matched that reported by Driver and co-workers:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  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);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz):  $\delta$  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  $\text{cm}^{-1}$ .



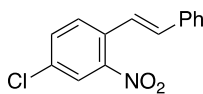
**2.1b**

**2-Nitro-4-trifluoromethylstilbene (2.1b).** The general procedure was followed using 0.317 g of 3-iodo-2-nitro-4-(trifluoromethyl)benzene (1.00 mmol), 0.156 g of styrene (1.50 mmol), 0.007 g of  $\text{PdCl}_2(\text{PPh}_3)_2$  (0.01 mmol), 0.019 g of  $n\text{-Bu}_3\text{N}$  (0.10 mmol), 0.159 g of  $\text{Na}_2\text{CO}_3$  (1.50 mmol) in 2.0 mL of water. Purification via MPLC (0:100 – 15:85 EtOAc:hexanes) afforded **2.1b** as a yellow solid (0.240 g, 82%). The spectral data of **2.1b** matched that reported by Driver and co-workers:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  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);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  140.6 (C), 135.6 (C), 131.6 (C), 129.2 (CH), 128.5 (CH), 125.4 (CH), 124.1 (q,  $J_{\text{CF}} = 268.8$  Hz, C), 120.9 (CH), 117.0 (CH), 111.0 (C), 108.4 (CH), 100.1 (CH), only peaks visible;  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ , 282 MHz)  $\delta$  –60.1, IR (thin film): 3444, 1456, 1342, 1155, 1105, 829, 766, 690  $\text{cm}^{-1}$ .



**2.1c**

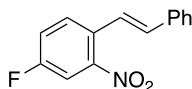
**Ethyl (E)-3-nitro-4-styrylbenzoate (2.1c).** The general procedure was followed using 0.321 g of methyl 4-iodo-3-nitrobenzoate (1.00 mmol), 0.156 g of styrene (1.50 mmol), 0.007 g of  $\text{PdCl}_2(\text{PPh}_3)_2$  (0.01 mmol), 0.019 g of *n*-Bu<sub>3</sub>N (0.10 mmol), 0.159 g of Na<sub>2</sub>CO<sub>3</sub> (1.50 mmol) in 2.0 mL of water. Purification via MPLC (0:100 – 15:85 EtOAc:hexanes) afforded **2.1c** as a yellow solid (0.256 g, 86%). The spectral data of **2.1c** matched that reported by Driver and co-workers: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$  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); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz)  $\delta$  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<sub>2</sub>), 14.3 (CH<sub>3</sub>); IR (thin film): 1720, 1613, 1558, 1529, 1349, 1291, 1263, 1113 cm<sup>-1</sup>.



**2.1d**

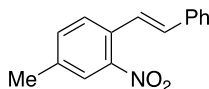
**4-Chloro-2-nitrostilbene (1d).** The general procedure was followed using 0.283 g of 4-chloro-1-iodo-2-nitrobenzene (1.00 mmol), 0.156 g of styrene (1.50 mmol), 0.007 g of  $\text{PdCl}_2(\text{PPh}_3)_2$  (0.01 mmol), 0.019 g of *n*-Bu<sub>3</sub>N (0.10 mmol), 0.159 g of Na<sub>2</sub>CO<sub>3</sub> (1.50 mmol) in 2.0 mL of water. Purification via MPLC (0:100 – 15:85 EtOAc:hexanes) afforded **2.1d** as a yellow solid (0.179 g, 69%). The spectral data of **2.1d** matched that reported by Driver and co-workers: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$  7.94 (d, *J* = 2.0 Hz, 1H), 7.69 (d, *J* = 8.4 Hz, 1H), 7.55 – 7.52 (m, 4H), 7.39 (t, *J* = 7.4 Hz, 2H), 7.35 (d, *J* = 7.1 Hz, 1H), 7.07 (d, *J* = 16.1 Hz, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz)  $\delta$  148.0 (C), 136.2 (C), 134.5 (CH), 133.5

(C), 133.2 (CH), 131.5 (C), 129.2 (CH), 128.9 (CH), 127.2 (CH), 124.8 (CH), 122.3 (CH), only peaks visible; IR (thin film): 1626, 1524, 1446, 1344, 1254, 1150, 1110, 960, 890, 818, 763, 694, 532  $\text{cm}^{-1}$ .



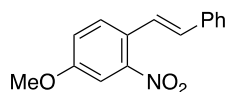
### 2.1e

**4-Fluoro-2-nitrostilbene (2.1e).** The general procedure was followed using 0.267 g of 4-fluoro-1-iodo-2-nitrobenzene (1.00 mmol), 0.156 g of styrene (1.50 mmol), 0.007 g of  $\text{PdCl}_2(\text{PPh}_3)_2$  (0.01 mmol), 0.019 g of *n*- $\text{Bu}_3\text{N}$  (0.10 mmol), 0.159 g of  $\text{Na}_2\text{CO}_3$  (1.50 mmol) in 2.0 mL of water. Purification via MPLC (0:100 – 15:85 EtOAc:hexanes) afforded **2.1e** as a yellow solid (0.222 g, 91%). The spectral data of **2.1e** matched that reported by Driver and co-workers:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  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);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  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);  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ , 282 MHz)  $\delta$  -119.9, IR (thin film): 3434, 1499, 1446, 1356, 1254, 1142, 813, 757  $\text{cm}^{-1}$ .



### 2.1f

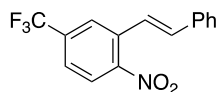
**4-Methyl-2-nitrostilbene (2.1f).** The general procedure was followed using 0.263 g of 4-iodo-3-nitrotoluene (1.00 mmol), 0.156 g of styrene (1.50 mmol), 0.007 g of  $\text{PdCl}_2(\text{PPh}_3)_2$  (0.01 mmol), 0.019 g of *n*-Bu<sub>3</sub>N (0.10 mmol), 0.159 g of  $\text{Na}_2\text{CO}_3$  (1.50 mmol) in 2.0 mL of water. Purification via MPLC (0:100 – 15:85 EtOAc:hexanes) afforded **2.1f** as a yellow solid (0.201 g, 84%). The spectral data of **2.1f** matched that reported by Driver and co-workers:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  7.76 (s, 1H), 7.65 (d,  $J$  = 8.0 Hz, 1H), 7.58 – 7.52 (m, 3H), 7.41 – 7.36 (m, 3H), 7.31 (t,  $J$  = 7.3 Hz, 1H), 7.05 (d,  $J$  = 16.1 Hz, 1H), 2.44 (s, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  147.9 (C), 138.6 (C), 136.7 (C), 134.0 (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<sub>3</sub>); IR (thin film): 1558, 1520, 1449, 1343, 1260, 958  $\text{cm}^{-1}$ .



**2.1g**

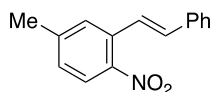
**4-Methoxy-2-nitrostilbene (2.1g).** The general procedure was followed using 0.279 g of 4-iodo-3-nitroanisole (1.00 mmol), 0.156 g of styrene (1.50 mmol), 0.007 g of  $\text{PdCl}_2(\text{PPh}_3)_2$  (0.01 mmol), 0.019 g of *n*-Bu<sub>3</sub>N (0.10 mmol), 0.159 g of  $\text{Na}_2\text{CO}_3$  (1.50 mmol) in 2.0 mL of water. Purification via MPLC (0:100 – 15:85 EtOAc:hexanes) afforded **2.1g** as a yellow solid (0.199 g, 78%). The spectral data of **2.1g** matched that reported by Driver and co-workers:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  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);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  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<sub>3</sub>); IR (thin film): 3387, 2922, 2852, 1622, 1598, 1452, 1259, 1203, 1159, 1116, 1019 cm<sup>-1</sup>.



### 2.1h

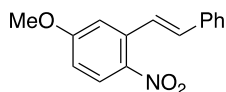
**2-Nitro-5-trifluoromethylstilbene (2.1h).** The general procedure was followed using 0.270 g of 3-bromo-4-nitrobenzotrifluoride (1.00 mmol), 0.156 g of styrene (1.50 mmol), 0.007 g of PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (0.01 mmol), 0.019 g of *n*-Bu<sub>3</sub>N (0.10 mmol), 0.159 g of Na<sub>2</sub>CO<sub>3</sub> (1.50 mmol) in 2.0 mL of water. Purification via MPLC (0:100 – 15:85 EtOAc:hexanes) afforded **2.1h** as a yellow solid (0.164 g, 56%). The spectral data of **2.1h** matched that reported by Driver and co-workers: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 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); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 149.7 (C), 135.9 (C), 135.7 (CH), 134.6 (q, *J*<sub>CF</sub> = 33.5 Hz, C), 133.6 (C), 129.2 (CH), 128.9 (CH), 128.1 (q, *J*<sub>CF</sub> = 135 Hz, CH), 127.3 (CH), 125.3 (q, *J*<sub>CF</sub> = 8.9 Hz, CH), 124.6 (CH), 123.1 (q, *J*<sub>CF</sub> = 270.9, C), 121.7 (CH); <sup>19</sup>F NMR (CDCl<sub>3</sub>, 282 MHz) δ –62.8; IR (thin film): 1617, 1589, 1524, 1497, 1323, 1256, 1173 cm<sup>-1</sup>



### 1i

**5-Methyl-2-nitrostilbene (1i).** The general procedure was followed using 0.263 g of 3-iodo-4-nitroanisole (1.00 mmol), 0.156 g of styrene (1.50 mmol), 0.007 g of PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>

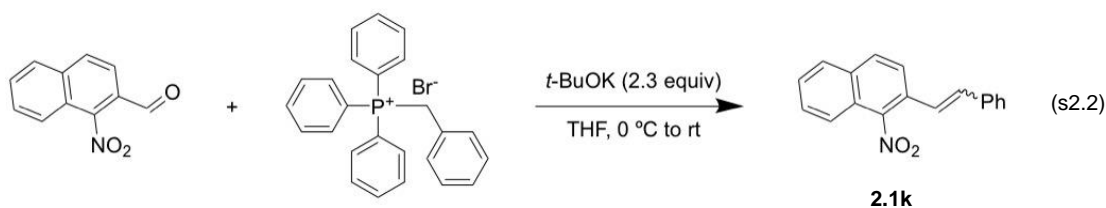
(0.01 mmol), 0.019 g of *n*-Bu<sub>3</sub>N (0.10 mmol), 0.159 g of Na<sub>2</sub>CO<sub>3</sub> (1.50 mmol) in 2.0 mL of water. Purification via MPLC (0:100 – 15:85 EtOAc:hexanes) afforded **1i** as a yellow solid (0.218 g, 91%). The spectral data of **1i** matched that reported by Driver and co-workers: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 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); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 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<sub>3</sub>), only peaks visible; IR (thin film): 1605, 1580, 1510, 1447, 1337, 961 cm<sup>-1</sup>.



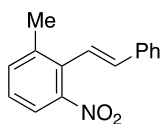
### 2.1j

**5-Methoxy-2-nitrostilbene (2.1j).** The general procedure was followed using 0.279 g of 3-iodo-4-nitroanisole (1.00 mmol), 0.156 g of styrene (1.50 mmol), 0.007 g of PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (0.01 mmol), 0.019 g of *n*-Bu<sub>3</sub>N (0.10 mmol), 0.159 g of Na<sub>2</sub>CO<sub>3</sub> (1.50 mmol) in 2.0 mL of water. Purification via MPLC (0:100 – 15:85 EtOAc:hexanes) afforded **2.1j** as a yellow solid (0.191 g, 75%). The spectral data of **2.1j** matched that reported by Driver and co-workers: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 8.03 (d, *J* = 9.5 Hz, 1H), 7.71 (d, *J* = 16.0 Hz, 1H), 7.53 (d, *J* = 7.4 Hz, 2H), 7.37 (t, *J* = 7.4 Hz, 2H), 7.31 (t, *J* = 7.3 Hz, 1H), 7.11 (d, *J* = 2.7 Hz, 1H), 7.00 (d, *J* = 16.1 Hz, 1H), 6.82 (dd, *J* = 9.1, 2.7 Hz, 1H), 3.89 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 163.3 (C), 141.0 (C), 136.6 (C), 136.2 (C), 133.6 (CH), 128.8 (CH), 128.6 (CH), 127.6 (CH), 127.2 (CH), 124.8 (CH), 113.2 (CH), 113.0 (CH), 56.0 (CH<sub>3</sub>); IR (thin film): 1600, 1579, 1506, 1476, 1335, 1290, 1235 cm<sup>-1</sup>.



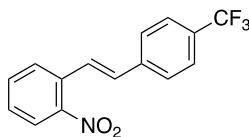


**(*E*)-1-Nitro-2-styrylnaphthalene (2.1k).** To 0.282 g of benzyltriphenylphosphonium bromide (0.65 mmol) in 5 mL of THF was added 0.129 g of *t*-BuOK (1.15 mmol) and stirred at 0 °C for 30 min. 0.100 g of 1-nitro-2-naphthaldehyde (0.50 mmol) was then added and the reaction mixture was warmed to room temperature. After 14 h. the mixture was diluted with 10 mL of water and 10 mL of CH<sub>2</sub>Cl<sub>2</sub>. The phases were separated and the resulting aqueous phase was extracted with an additional 2 × 10 mL of CH<sub>2</sub>Cl<sub>2</sub>. The combined organic phases were washed with 1 × 10 mL of distilled water and 1 × 10 mL of brine. The resulting organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, and the heterogeneous mixture was filtered. The filtrate was concentrated in vacuo. Purification via MPLC (0:100 – 20:80 EtOAc:hexanes) afforded **2.1k**, as a yellow solid (0.048 g, 34%). The spectral data of **2.1k** matched that reported by Peters and co-workers: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 7.94 (d, *J* = 8.7 Hz, 1H), 7.88 (d, *J* = 8.1 Hz, 1H), 7.85 (d, *J* = 8.8 Hz, 1H), 7.73 (d, *J* = 8.4 Hz, 1H), 7.64 – 7.61 (m, 1H), 7.56 (dd, *J* = 12.8, 7.7 Hz, 3H), 7.40 (t, *J* = 7.4 Hz, 2H), 7.35 – 7.31 (m, 2H), 7.17 (d, *J* = 16.1 Hz, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 136.2 (C), 134.7 (CH), 132.9 (C), 130.6 (C), 128.9 (CH), 128.9 (CH), 128.0 (CH), 127.3 (CH), 127.2 (CH), 126.6 (C), 124.8 (C), 122.4 (CH), 121.8 (CH), 120.8 (CH); IR (thin film): 1713, 1632, 1598, 1517, 1448, 1360, 1261 cm<sup>-1</sup>.



## 2.11

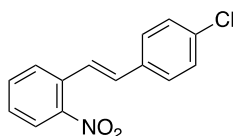
**(E)-1-Methyl-3-nitro-2-styrylbenzene (2.11).** The general procedure was followed using 0.263 g of 2-iodo-3-nitrotoluene (1.00 mmol), 0.156 g of styrene (1.50 mmol), 0.007 g of  $\text{PdCl}_2(\text{PPh}_3)_2$  (0.01 mmol), 0.019 g of *n*- $\text{Bu}_3\text{N}$  (0.10 mmol), 0.159 g of  $\text{Na}_2\text{CO}_3$  (1.50 mmol) in 2.0 mL of water. Purification via MPLC (0:100 – 15:85 EtOAc:hexanes) afforded **2.11** as a yellow solid (0.242 g, 75%). Nitrostyrene **2.11** was previously reported by Shafiee and co-workers:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  7.66 (d,  $J$  = 8.1 Hz, 1H), 7.50 (d,  $J$  = 7.5 Hz, 2H), 7.45 (d,  $J$  = 7.6 Hz, 1H), 7.38 (t,  $J$  = 7.4 Hz, 2H), 7.33 – 7.28 (m, 2H), 7.20 (d,  $J$  = 16.6 Hz, 1H), 6.59 (d,  $J$  = 16.6 Hz, 1H), 2.45 (s, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  150.1 (C), 139.0 (C), 136.6 (C), 135.0 (CH), 134.1 (CH), 132.0 (C), 128.8 (CH), 128.3 (CH), 127.3 (CH), 126.7 (CH), 122.6 (CH), 121.5 (CH), 20.9 ( $\text{CH}_3$ ); IR (thin film): 1520, 1495, 1449, 1349, 1287  $\text{cm}^{-1}$ .



## 2.1m

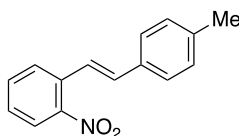
**(E)-1-Nitro-2-(4-(trifluoromethyl)styryl)benzene (2.1m).** The general procedure was followed using 0.249 g of 1-iodo-2-nitrobenzene (1.00 mmol), 0.258 g of 4-(trifluoromethyl)styrene (1.50 mmol), 0.007 g of  $\text{PdCl}_2(\text{PPh}_3)_2$  (0.01 mmol), 0.019 g of *n*- $\text{Bu}_3\text{N}$  (0.10 mmol), 0.159 g of  $\text{Na}_2\text{CO}_3$  (1.50 mmol) in 2.0 mL of water. Purification via MPLC (0:100 – 15:85 EtOAc:hexanes) afforded **2.1m** as a yellow solid (0.202 g, 69%). The spectral data of **2.1m** matched that reported by Driver and co-workers:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  7.98 (d,  $J$  = 8.1 Hz, 1H), 7.74 (d,  $J$  = 7.8 Hz, 1H), 7.67 (d,  $J$  = 16.1

Hz, 1H), 7.61 (d,  $J = 10.7$  Hz, 5H), 7.45 – 7.42 (m, 1H), 7.06 (d,  $J = 16.1$  Hz, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  148.0 (C), 139.9 (C), 133.3 (CH), 132.4 (C), 132.0 (CH), 130.2 (q,  $J_{\text{CF}} = 32.8$  Hz, C), 128.6 (CH), 128.3 (CH), 127.2 (CH), 126.3 (CH), 125.7 (CH), 124.8 (CH); 124.0 (q,  $J_{\text{CF}} = 270.9$  Hz, C);  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ , 282 MHz)  $\delta$  –62.2; IR (thin film): 1615, 1528, 1344, 1325, 1107, 1068, 821  $\text{cm}^{-1}$ .



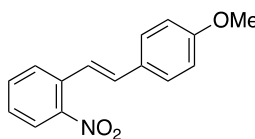
### 2.1n

**(E)-1-(4-Chlorostyryl)-2-nitrobenzene (2.1n).** The general procedure was followed using 0.249 g of 1-iodo-2-nitrobenzene (1.00 mmol), 0.208 g of 4-chlorostyrene (1.50 mmol), 0.007 g of  $\text{PdCl}_2(\text{PPh}_3)_2$  (0.01 mmol), 0.019 g of  $n\text{-Bu}_3\text{N}$  (0.10 mmol), 0.159 g of  $\text{Na}_2\text{CO}_3$  (1.50 mmol) in 2.0 mL of water. Purification via MPLC (0:100 – 15:85 EtOAc:hexanes) afforded **2.1n** as a yellow solid (0.216 g, 83%). The spectral data of **2.1n** matched that reported by Driver and co-workers:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  7.96 (d,  $J = 8.1$  Hz, 1H), 7.72 (d,  $J = 7.8$  Hz, 1H), 7.59 (t,  $J = 7.9$  Hz, 1H), 7.55 (d,  $J = 16.2$  Hz, 1H), 7.44 (d,  $J = 8.4$  Hz, 2H), 7.40 (t,  $J = 7.7$  Hz, 1H), 7.33 (d,  $J = 8.4$  Hz, 2H), 7.01 (d,  $J = 16.1$  Hz, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  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), 128.2 (CH), 124.8 (CH), 124.2 (CH); IR (thin film): 1520, 1492, 1342, 1093, 961, 811  $\text{cm}^{-1}$ .



## 2.1o

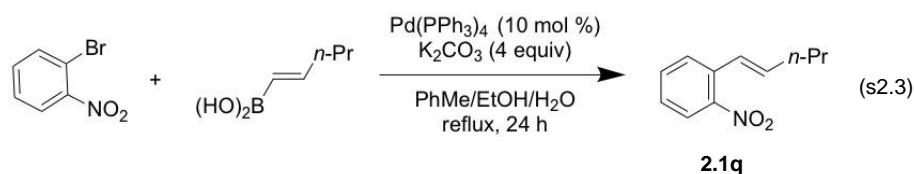
**(E)-1-(4-Methylstyryl)-2-nitrobenzene (2.1o).** The general procedure was followed using 0.249 g of 1-iodo-2-nitrobenzene (1.00 mmol), 0.177 g of 4-methylstyrene (1.50 mmol), 0.007 g of  $\text{PdCl}_2(\text{PPh}_3)_2$  (0.01 mmol), 0.019 g of *n*-Bu<sub>3</sub>N (0.10 mmol), 0.159 g of Na<sub>2</sub>CO<sub>3</sub> (1.50 mmol) in 2.0 mL of water. Purification via MPLC (0:100 – 15:85 EtOAc:hexanes) afforded **2.1o** as a yellow solid (0.182 g, 76%). The spectral data of **2.1o** matched that reported by Driver and co-workers: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$  7.94 (dd, *J* = 8.2, 1.0 Hz, 1H), 7.76 (d, *J* = 7.7 Hz, 1H), 7.60 – 7.54 (m, 2H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.39 – 7.36 (m, 1H), 7.20 (d, *J* = 7.9 Hz, 2H), 7.07 (d, *J* = 16.1 Hz, 1H), 2.38 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz)  $\delta$  148.0 (C), 138.7 (C), 133.9 (CH), 133.8 (C), 133.2 (C), 133.0 (CH), 129.6 (CH), 128.0 (CH), 127.7 (CH), 127.1 (CH), 124.8 (CH), 122.4 (CH), 21.4 (CH<sub>3</sub>); IR (thin film): 1603, 1571, 1515, 1341, 1298, 1261 cm<sup>-1</sup>.



## 2.1p

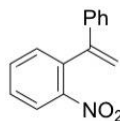
**(E)-1-(4-Methoxystyryl)-2-nitrobenzene (2.1p).** The general procedure was followed using 0.249 g of 1-iodo-2-nitrobenzene (1.00 mmol), 0.201 g of 4-vinylanisole (1.50 mmol), 0.007 g of  $\text{PdCl}_2(\text{PPh}_3)_2$  (0.01 mmol), 0.019 g of *n*-Bu<sub>3</sub>N (0.10 mmol), 0.159 g of Na<sub>2</sub>CO<sub>3</sub> (1.50 mmol) in 2.0 mL of water. Purification via MPLC (0:100 – 15:85 EtOAc:hexanes) afforded **2.1p** as a yellow solid (0.230 g, 90%). The spectral data of **2.1p** matched that reported by Driver and co-workers: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$  7.93 (dd, *J* = 8.2, 0.7 Hz, 1H), 7.74 (d, *J* = 7.8 Hz, 1H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.49 – 7.45 (m, 3H), 7.37 – 7.34

(m, 1H), 7.05 (d,  $J = 16.1$  Hz, 1H), 6.91 (d,  $J = 8.7$  Hz, 2H), 3.81 (s, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  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 ( $\text{CH}_3$ ); IR (thin film): 1599, 1569, 1509, 1464, 1340, 1248, 1173  $\text{cm}^{-1}$ .



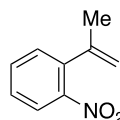
**(E)-1-nitro-2-(pent-1-en-1-yl)benzene (2.1q).** To a solution of 0.160 g of 1-penten-1-ylboronic acid (1.40 mmol), 0.115 g of  $\text{Pd}(\text{PPh}_3)_4$  (0.100 mmol) and 0.553 g of  $\text{K}_2\text{CO}_3$  (4.00 mmol) in 6 mL of toluene, 2.4 mL of EtOH and 1.2 mL of water was added 0.202 g of 1-bromo-2-nitrobenzene (1.00 mmol). The resultant mixture was then purged with  $\text{N}_2$  and refluxed. After 24 h, the mixture was cooled to room temperature and diluted with 30 mL of water and 30 mL of  $\text{CH}_2\text{Cl}_2$ . The phases were separated and the resulting aqueous phase was extracted with an additional  $2 \times 30$  mL of  $\text{CH}_2\text{Cl}_2$ . The combined organic phases were washed with  $1 \times 20$  mL of distilled water and  $1 \times 20$  mL of brine. The resulting organic phase was dried over  $\text{Na}_2\text{SO}_4$ , and the heterogeneous mixture was filtered. The filtrate was concentrated in vacuo. Purification via MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **2.1q** as a brown liquid (0.178 g, 93%). The spectral data of **2.1q** matched that reported by Driver and co-workers:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  7.83 (dd,  $J = 8.2, 0.9$  Hz, 1H), 7.56 (d,  $J = 7.2$  Hz, 1H), 7.51 – 7.48 (m, 1H), 7.32 – 7.29 (m, 1H), 6.81 (d,  $J = 15.7$  Hz, 1H), 6.22 (dt,  $J = 15.6, 7.0$  Hz, 1H), 2.22 (qd,  $J = 7.2, 1.0$  Hz, 2H), 1.51 (sextet,  $J = 7.4$  Hz, 2H), 0.96 (t,  $J = 7.4$  Hz, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  147.7 (C), 136.7

(CH), 133.4 (C), 132.8 (CH), 128.4 (CH), 127.3 (CH), 125.0 (CH), 124.3 (CH), 35.2 (CH<sub>2</sub>), 22.2 (CH<sub>2</sub>), 13.7 (CH<sub>3</sub>); IR (thin film): 1605, 1572, 1519, 1343, 962, 856 cm<sup>-1</sup>.



### 2.1r

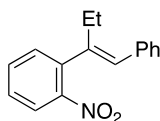
**1-Nitro-2-(1-phenylvinyl)benzene (2.1r).** The procedure for **2.1q** was followed using 0.202 g of 1-bromo-2-nitrobenzene (1.00 mmol), 0.207 g of (1-phenylvinyl)boronic acid (1.40 mmol), 0.115 g of Pd(PPh<sub>3</sub>)<sub>4</sub> (0.100 mmol) and 0.553 g of K<sub>2</sub>CO<sub>3</sub> (4.00 mmol) in 6 mL of toluene, 2.4 mL of EtOH and 1.2 mL of water. Purification via MPLC (0:100 – 15:85 EtOAc:hexanes) afforded **2.1r** as a brown solid (0.155 g, 69%). The spectral data of **2.1r** matched that reported by Driver and co-workers: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 7.94 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.63 (td, *J* = 7.5, 1.3 Hz, 1H), 7.51 (td, *J* = 7.8, 1.2 Hz, 1H), 7.46 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.30 – 7.23 (m, 5H), 5.75 (s, 1H), 5.32 (s, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 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<sub>2</sub>); IR (thin film): 2921, 2851, 1605, 1571, 1522, 1494, 1346, 1026 cm<sup>-1</sup>.



### 2.1s

**1-Nitro-2-(prop-1-en-2-yl)benzene (2.1s).** The procedure for **2.1q** was followed using 0.202 g of 1-bromo-2-nitrobenzene (1.00 mmol), 0.235 g of isopropenylboronic acid

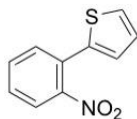
pinacol ester (1.40 mmol), 0.115 g of Pd(PPh<sub>3</sub>)<sub>4</sub> (0.100 mmol) and 0.553 g of K<sub>2</sub>CO<sub>3</sub> (4.00 mmol) in 6 mL of toluene, 2.4 mL of EtOH and 1.2 mL of water. Purification via MPLC (0:100 – 15:85 EtOAc:hexanes) afforded **2.1s** as a brown liquid (0.150 g, 92%). The spectral data of **2.1s** matched that reported by Driver and co-workers: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 7.85 (dd, *J* = 8.1, 1.0 Hz, 1H), 7.54 (td, *J* = 7.5, 1.2 Hz, 1H), 7.40 (td, *J* = 7.8, 1.1 Hz, 1H), 7.33 (dd, *J* = 7.6, 1.3 Hz, 1H), 5.18 – 5.16 (m, 1H), 4.94 – 4.93 (m, 1H), 2.09 – 2.08 (m, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 148.3 (C), 142.8 (C), 139.0 (C), 132.7 (CH), 130.6 (CH), 127.9 (CH), 124.0 (CH), 115.4 (CH<sub>2</sub>), 23.3 (CH<sub>3</sub>); IR (thin film): 1608, 1570, 1523, 1482, 1349, 1309, 904 cm<sup>-1</sup>.



**2.1t**

**(E)-1-nitro-2-(1-phenylbut-1-en-2-yl)benzene (2.1t).** The procedure for **2.1q** 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<sub>3</sub>)<sub>4</sub> (0.100 mmol) and 0.553 g of K<sub>2</sub>CO<sub>3</sub> (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 **2.1t** as a brown liquid (0.242 g, 96%). The spectral data of **2.1t** matched that reported by Driver and co-workers: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 7.94 (d, *J* = 7.7 Hz, 1H), 7.62 – 7.59 (m, 1H), 7.47 – 7.36 (m, 6H), 7.30 (t, *J* = 7.0 Hz, 1H), 6.43 (s, 1H), 2.70 (q, *J* = 7.6 Hz, 2H), 1.03 (t, *J* = 7.6 Hz, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 149.0 (C), 141.8 (C), 138.9 (C), 137.2 (C), 132.5 (CH), 131.4 (CH), 129.2 (CH), 128.9 (CH), 128.4 (CH), 127.9 (CH), 127.1 (CH),

124.3 (CH), 25.2 (CH<sub>2</sub>), 13.0 (CH<sub>3</sub>); IR (thin film): 1606, 1572, 1523, 1495, 1346, 1073 cm<sup>-1</sup>.



**2.1u**

**2-(2-Nitrophenyl)thiophene (2.1u).**{ Yabe, 2010 #8192} The procedure for **2.1q** was followed using 0.202 g of 1-bromo-2-nitrobenzene (1.00 mmol), 0.179 g of 2-thienylboronic acid (1.40 mmol), 0.115 g of Pd(PPh<sub>3</sub>)<sub>4</sub> (0.100 mmol) and 0.553 g of K<sub>2</sub>CO<sub>3</sub> (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 **2.1u** as a brown solid (0.158 g, 77%). The spectral data of **2.1u** matched that reported by Sajika and co-workers:{ Yabe, 2010 #8192} <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 7.74 (d, *J* = 8.0 Hz, 1H), 7.59 – 7.55 (m, 2H), 7.46 (t, *J* = 7.2 Hz, 1H), 7.42 – 7.41 (m, 1H), 7.10 – 7.07 (m, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 149.5 (C), 137.2 (C), 132.3 (CH), 131.9 (CH), 128.6 (CH), 128.4 (C), 127.8 (CH), 127.2 (CH), 127.1 (CH), 123.9 (CH); IR (thin film): 1711, 1606, 1570, 1525, 1477, 1427, 1359, 1267, 1221, 1090, 1040 cm<sup>-1</sup>.

## II. High-Throughput Optimization of Metal-Catalyzed Reductive Cyclization.

### A. General Microscale Screening Procedure.

Microscale reactions were carried out in 8 × 30 mm glass vial inserts in aluminum 96-well microtiter plates. Solutions of metal precursor (Pd in THF and Fe, Co, and Ni in MeOH)



and ligand in THF were subjected to magnetic tumble stirring for 30 min followed by removal of the volatiles using a vacuum centrifuge. Solutions of the substrate and reducing agents in the reaction solvent were introduced, and the plate was sealed and heated to the appropriate temperature with magnetic tumble stirring for 18 h. The reaction mixture was analyzed using reverse phase HPLC with authentic reference material, and the yield of the reaction was calculated using biphenyl as the internal standard. HPLC conditions for reaction screening and optimization were 50 × 4.5 mm SB-CN column, 1.8 μm particle size, 1.5 mL / min, 20-95% MeCN / 0.1% H<sub>3</sub>PO<sub>4</sub> in 3 minutes, hold at 95% for 1 min, post run at 20% for 1 min, 35 °C, 210 nm with the following retention times: **2.1a**: 2.703 min, **2.2a**: 2.593 min, **2.3a**: 2.490 min, **2.4a**: 1.733 min, biphenyl internal standard: 2.529 min.

## Screening and Optimization Results.

Screening of reaction conditions was conducted using the general microscale screening procedure on 10  $\mu$ mol (2.3 mg) scale with substrate **2.1a** using 10 mol % of Pd(OAc)<sub>2</sub>, FeCl<sub>2</sub>, CoCl<sub>2</sub>, or NiCl<sub>2</sub>, 10 mol % of phen or dppe, 3 equiv  $\times$  24 reductants, DMA or PhCF<sub>3</sub>, 0.1 M, 80  $^{\circ}$ C, 18 h.

**Table S2.1.** Initial survey of reaction conditions.

Yield of 2a		Zn	Sn	Fe	Mg	Mn	HOCH/EtN	SnCl <sub>2</sub>	CrCl <sub>3</sub>	FeCl <sub>2</sub>	Na <sub>2</sub> S <sub>2</sub> O <sub>4</sub>	Na <sub>2</sub> S <sub>2</sub> O <sub>5</sub>	Na <sub>2</sub> SO <sub>3</sub>	Na <sub>2</sub> HPO <sub>4</sub>	NaH <sub>2</sub> PO <sub>4</sub>	(EtO) <sub>3</sub> P	S <sub>8</sub>	Et <sub>3</sub> SH	PhSH <sub>3</sub>	NaBH <sub>4</sub>	BH <sub>3</sub> ·tBuNH <sub>2</sub>	catBH	B <sub>2</sub> Pin <sub>2</sub>	(TMS) <sub>2</sub>	Mo(CO) <sub>6</sub>	
Pd(OAc) <sub>2</sub>	phen	0.0	0.0	0.0	10.2	3.5	0.0	0.0	0.0	3.7	31.6	0.0	0.0	0.0	5.1	0.0	0.0	36.6	0.0	7.3	10.4	0.0	0.0	0.0	2.7	DMA
FeO <sub>2</sub>		5.8	6.5	4.5	8.8	6.6	0.0	0.0	0.0	0.0	20.8	0.0	0.0	0.0	0.0	0.0	4.0	69.2	4.5	26.6	3.8	0.0	0.0	8.5		
CoO <sub>2</sub>		0.0	0.0	0.0	4.5	6.0	0.0	0.0	0.0	0.0	14.7	0.0	0.0	0.0	0.0	0.0	0.0	55.7	6.5	24.9	4.8	0.0	0.0	6.0		
NiCl <sub>2</sub>		0.0	0.0	0.0	8.1	0.0	0.0	0.0	0.0	0.0	13.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	15.9	0.0	10.1	3.6	10.1	0.0	8.1	
Pd(OAc) <sub>2</sub>	dppe	0.0	0.0	0.0	12.4	0.0	8.1	0.0	0.0	2.9	17.0	0.0	0.0	0.0	0.0	0.0	0.0	13.7	26.5	3.7	4.5	7.5	85.6	4.4	0.0	
FeO <sub>2</sub>		0.0	0.0	39.2	17.9	0.0	0.0	4.9	0.0	0.0	16.2	4.3	0.0	0.0	0.0	0.0	0.0	0.0	58.7	3.3	19.8	0.0	0.0	5.3		
CoO <sub>2</sub>		0.0	0.0	0.0	10.7	0.0	0.0	2.9	0.0	0.0	14.9	0.0	0.0	0.0	0.0	0.0	0.0	0.0	26.0	3.2	8.5	0.0	0.0	4.5		
NiCl <sub>2</sub>		0.0	0.0	0.0	5.4	0.0	0.0	0.0	0.0	0.0	9.9	0.0	0.0	0.0	0.0	0.0	0.0	12.5	23.0	0.0	7.8	0.0	0.0	8.2		
Pd(OAc) <sub>2</sub>	phen	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	4.1	2.5	0.0	0.0	9.8	12.7	9.7	3.5	7.1	0.0	16.3	PhCF <sub>3</sub>	
FeO <sub>2</sub>		0.0	4.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	4.0	0.0	0.0	0.0	29.6	0.0	27.9	3.7	0.0	6.4		
CoO <sub>2</sub>		0.0	0.0	0.0	0.0	0.0	5.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	4.3	0.0	0.0	0.0	21.2	0.0	23.2	4.7	0.0	3.5		
NiCl <sub>2</sub>		0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	4.0	0.0	0.0	0.0	12.0	0.0	0.0	4.9	0.0	3.8		
Pd(OAc) <sub>2</sub>	dppe	5.0	3.4	0.0	3.1	0.0	12.3	0.0	0.0	0.0	2.7	0.0	2.7	0.0	5.7	0.0	8.6	13.2	15.4	21.9	3.1	12.4	48.3	11.9	5.7	
FeO <sub>2</sub>		3.7	0.0	4.2	8.8	0.0	0.0	7.7	0.0	0.0	0.0	0.0	0.0	0.0	6.2	0.0	0.0	0.0	67.7	2.6	32.1	22.1	0.0	4.3	7.7	
CoO <sub>2</sub>		0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	2.8	0.0	13.5	0.0	7.0	9.4	0.0	0.0	7.5	
NiCl <sub>2</sub>		0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	4.8	0.0	0.0	0.0	0.0	2.8	0.0	2.4	0.0	12.2	0.0	0.0	11.2	0.0	0.0	8.9	
Conversion to 2a		Zn	Sn	Fe	Mg	Mn	HOCH/EtN	SnCl <sub>2</sub>	CrCl <sub>3</sub>	FeCl <sub>2</sub>	Na <sub>2</sub> S <sub>2</sub> O <sub>4</sub>	Na <sub>2</sub> S <sub>2</sub> O <sub>5</sub>	Na <sub>2</sub> SO <sub>3</sub>	Na <sub>2</sub> HPO <sub>4</sub>	NaH <sub>2</sub> PO <sub>4</sub>	(EtO) <sub>3</sub> P	S <sub>8</sub>	Et <sub>3</sub> SH	PhSH <sub>3</sub>	NaBH <sub>4</sub>	BH <sub>3</sub> ·tBuNH <sub>2</sub>	catBH	B <sub>2</sub> Pin <sub>2</sub>	(TMS) <sub>2</sub>	Mo(CO) <sub>6</sub>	
Pd(OAc) <sub>2</sub>	phen	0.0	0.0	0.0	100.0	5.6	0.0	0.0	0.0	5.1	72.5	0.0	0.0	0.0	8.3	0.0	0.0	0.0	75.0	0.0	100.0	20.3	0.0	0.0	3.9	DMA
FeO <sub>2</sub>		8.0	9.8	7.4	100.0	12.4	0.0	0.0	0.0	0.0	84.2	0.0	0.0	0.0	0.0	0.0	0.0	10.4	84.0	25.5	37.9	5.8	0.0	0.0	12.5	
CoO <sub>2</sub>		0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	42.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	100.0	100.0	100.0	8.2	0.0	0.0	9.2	
NiCl <sub>2</sub>		0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	33.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	46.2	0.0	28.3	5.3	14.6	0.0	12.5	
Pd(OAc) <sub>2</sub>	dppe	0.0	0.0	0.0	38.6	0.0	22.5	0.0	0.0	3.6	35.2	0.0	0.0	0.0	0.0	0.0	0.0	29.1	53.5	20.8	14.3	13.0	94.2	9.6	0.0	
FeO <sub>2</sub>		0.0	0.0	51.2	45.6	0.0	0.0	6.4	0.0	0.0	34.9	6.2	0.0	0.0	0.0	0.0	0.0	0.0	68.2	18.9	25.1	0.0	0.0	0.0	8.0	
CoO <sub>2</sub>		0.0	0.0	0.0	100.0	0.0	0.0	3.6	0.0	0.0	39.7	0.0	0.0	0.0	0.0	0.0	0.0	0.0	83.9	17.4	33.5	0.0	0.0	0.0	6.4	
NiCl <sub>2</sub>		0.0	0.0	0.0	19.7	0.0	0.0	0.0	0.0	0.0	18.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	33.5	65.6	0.0	0.0	12.9	0.0	14.7	
Pd(OAc) <sub>2</sub>	phen	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	6.8	4.5	0.0	0.0	0.0	33.7	37.4	100.0	12.8	12.4	0.0	23.1	PhCF <sub>3</sub>
FeO <sub>2</sub>		0.0	6.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	6.5	0.0	0.0	0.0	84.6	0.0	56.7	16.7	0.0	0.0	9.9	
CoO <sub>2</sub>		0.0	0.0	0.0	0.0	0.0	6.7	0.0	0.0	0.0	0.0	0.0	0.0	0.0	7.7	0.0	0.0	0.0	100.0	0.0	100.0	16.1	0.0	0.0	5.4	
NiCl <sub>2</sub>		0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	7.0	0.0	0.0	0.0	43.9	0.0	0.0	13.4	0.0	0.0	5.8	
Pd(OAc) <sub>2</sub>	dppe	8.5	5.3	0.0	4.9	0.0	29.6	0.0	0.0	0.0	4.2	0.0	4.3	0.0	11.2	0.0	11.2	40.5	29.1	86.8	11.4	25.0	67.7	20.6	8.4	
FeCl <sub>2</sub>		5.3	0.0	5.8	9.5	0.0	0.0	12.1	0.0	0.0	0.0	0.0	0.0	0.0	8.4	0.0	8.4	0.0	92.3	3.7	51.6	38.7	0.0	4.6	12.4	
CoO <sub>2</sub>		0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	3.4	0.0	100.0	0.0	65.5	27.3	0.0	0.0	12.0	
NiCl <sub>2</sub>		0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	4.3	0.0	0.0	0.0	0.0	4.0	0.0	3.4	0.0	53.8	0.0	0.0	20.0	0.0	0.0	13.8	

Conversion to 4a		Zn	Sn	Fe	Mg	Mn	HCO <sub>2</sub> H / EtN	SrCl <sub>2</sub>	CrCl <sub>3</sub>	FeCl <sub>3</sub>	Na <sub>2</sub> S <sub>2</sub> O <sub>4</sub>	Na <sub>2</sub> S <sub>2</sub> O <sub>5</sub>	Na <sub>2</sub> SO <sub>3</sub>	Na <sub>2</sub> HPO <sub>4</sub>	NaH <sub>2</sub> PO <sub>4</sub>	(EO) <sub>2</sub> P	S <sub>8</sub>	Et <sub>3</sub> SH	PhSH <sub>3</sub>	NaBH <sub>4</sub>	BH <sub>3</sub> ·tBuNH <sub>2</sub>	CalBH	B <sub>2</sub> P <sub>2</sub>	(TMS) <sub>2</sub>	Me(CO) <sub>2</sub>	
Pd(OAc) <sub>2</sub>	phen	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	27.5	0.0	0.0	0.0	30.3	0.0	0.0	87.0	25.0	100.0	0.0	16.8	0.0	0.0	11.7	DMA
FeCl <sub>2</sub>		0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	9.8	74.5	9.5	0.0	0.0	0.0	20.3	
CoCl <sub>2</sub>		0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	57.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	21.8	
NiCl <sub>2</sub>		0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	31.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	53.8	100.0	71.7	0.0	0.0	0.0	22.7	
Pd(OAc) <sub>2</sub>	dppe	14.2	0.0	0.0	61.4	0.0	77.5	0.0	34.8	0.0	34.1	0.0	0.0	8.5	30.9	0.0	0.0	42.5	46.5	79.2	85.7	0.0	0.0	0.0	13.8	DMA
FeCl <sub>2</sub>		0.0	0.0	14.0	43.0	0.0	5.7	53.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	8.3	53.4	10.5	0.0	0.0	0.0	19.9	
CoCl <sub>2</sub>		0.0	0.0	0.0	0.0	0.0	0.0	50.0	0.0	23.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	16.1	50.5	51.8	0.0	0.0	16.8	
NiCl <sub>2</sub>		0.0	0.0	0.0	80.3	0.0	21.8	0.0	48.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	20.7	34.4	100.0	0.0	0.0	0.0	0.0	29.7	
Pd(OAc) <sub>2</sub>	phen	0.0	0.0	0.0	0.0	0.0	72.5	0.0	0.0	0.0	0.0	0.0	0.0	15.2	36.6	0.0	0.0	44.6	66.3	36.7	0.0	0.0	27.4	0.0	PhCF <sub>3</sub>	
FeCl <sub>2</sub>		0.0	0.0	0.0	0.0	0.0	7.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	16.1	0.0	0.0	0.0	15.4	0.0	43.3	0.0	0.0	0.0		
CoCl <sub>2</sub>		0.0	0.0	0.0	0.0	0.0	26.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	11.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0		
NiCl <sub>2</sub>		0.0	0.0	0.0	0.0	0.0	7.7	0.0	0.0	0.0	0.0	0.0	0.0	0.0	11.7	0.0	0.0	0.0	18.6	0.0	100.0	0.0	0.0	0.0		
Pd(OAc) <sub>2</sub>	dppe	0.0	0.0	0.0	0.0	0.0	59.9	0.0	0.0	0.0	0.0	0.0	0.0	15.6	34.5	0.0	0.0	14.2	70.9	0.0	88.6	0.0	21.9	0.0	7.3	
FeCl <sub>2</sub>		0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	7.7	0.0	38.2	0.0	0.0	12.9		
CoCl <sub>2</sub>		0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	34.5	0.0	0.0	0.0		
NiCl <sub>2</sub>		0.0	0.0	0.0	0.0	0.0	0.0	4.7	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0		
Conversion to 3a		Zn	Sn	Fe	Mg	Mn	HCO <sub>2</sub> H / EtN	SrCl <sub>2</sub>	CrCl <sub>3</sub>	FeCl <sub>3</sub>	Na <sub>2</sub> S <sub>2</sub> O <sub>4</sub>	Na <sub>2</sub> S <sub>2</sub> O <sub>5</sub>	Na <sub>2</sub> SO <sub>3</sub>	Na <sub>2</sub> HPO <sub>4</sub>	NaH <sub>2</sub> PO <sub>4</sub>	(EO) <sub>2</sub> P	S <sub>8</sub>	Et <sub>3</sub> SH	PhSH <sub>3</sub>	NaBH <sub>4</sub>	BH <sub>3</sub> ·tBuNH <sub>2</sub>	CalBH	B <sub>2</sub> P <sub>2</sub>	(TMS) <sub>2</sub>	Me(CO) <sub>2</sub>	
Pd(OAc) <sub>2</sub>	phen	0.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	61.4	0.0	0.0	0.0	0.0	0.0	0.0	9.6	0.0	0.0	0.0	DMA
FeCl <sub>2</sub>		0.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	6.2	0.0	52.6	0.0	0.0	0.0	0.0	
CoCl <sub>2</sub>		0.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	7.9	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
NiCl <sub>2</sub>		0.0	0.0	0.0	0.0	0.0	26.9	100.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	23.9	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
Pd(OAc) <sub>2</sub>	dppe	0.0	0.0	0.0	0.0	0.0	0.0	100.0	23.5	16.2	20.2	0.0	0.0	0.0	69.1	0.0	0.0	0.0	0.0	0.0	36.3	0.0	0.0	0.0	0.0	DMA
FeCl <sub>2</sub>		8.4	0.0	6.7	0.0	7.3	0.0	83.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	17.8	0.0	57.0	0.0	0.0	0.0	0.0	
CoCl <sub>2</sub>		0.0	0.0	0.0	0.0	0.0	0.0	90.4	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
NiCl <sub>2</sub>		0.0	0.0	0.0	0.0	0.0	7.5	100.0	0.0	0.0	0.0	0.0	0.0	0.0	34.4	0.0	0.0	45.8	0.0	0.0	100.0	11.6	0.0	0.0	0.0	
Pd(OAc) <sub>2</sub>	phen	0.0	0.0	0.0	0.0	0.0	0.0	27.4	0.0	0.0	0.0	0.0	0.0	0.0	18.6	0.0	0.0	14.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	PhCF <sub>3</sub>
FeCl <sub>2</sub>		0.0	0.0	0.0	0.0	0.0	0.0	9.9	0.0	0.0	0.0	0.0	0.0	0.0	13.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
CoCl <sub>2</sub>		0.0	0.0	0.0	0.0	0.0	0.0	9.2	0.0	0.0	0.0	0.0	0.0	0.0	7.9	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
NiCl <sub>2</sub>		0.0	0.0	0.0	0.0	0.0	10.2	5.5	0.0	0.0	0.0	0.0	0.0	0.0	16.2	0.0	0.0	0.0	37.5	0.0	0.0	0.0	0.0	0.0	0.0	
Pd(OAc) <sub>2</sub>	dppe	0.0	0.0	0.0	0.0	0.0	0.0	7.3	0.0	0.0	0.0	0.0	0.0	0.0	16.0	0.0	0.0	33.7	0.0	0.0	14.6	0.0	0.0	0.0	0.0	PhCF <sub>3</sub>
FeCl <sub>2</sub>		0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
CoCl <sub>2</sub>		0.0	0.0	0.0	0.0	0.0	0.0	38.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
NiCl <sub>2</sub>		0.0	0.0	0.0	0.0	0.0	0.0	4.7	21.2	0.0	0.0	0.0	0.0	0.0	7.5	0.0	0.0	0.0	46.2	0.0	9.5	0.0	0.0	0.0	0.0	

Screening of metal precursors and ligand classes was conducted using the general microscale screening procedure on 10  $\mu\text{mol}$  (2.3 mg) scale with substrate **2.1a** using 10 mol % of  $\text{FeCl}_2$ ,  $\text{CoCl}_2$ ,  $\text{Fe}(\text{OAc})_2$ , or  $\text{Co}(\text{OAc})_2$ , 10 mol %  $\times$  12 ligands, 3 equiv of  $\text{PhSiH}_3$ , DMA or DME, 0.1 M, 60 or 80  $^\circ\text{C}$ , 18 h.

Table S2.2. Screen of metal precursors and ligands.

Yield of product 2a	phen	dppe	IPr	dtbpf	dtbpy	8-HQ	salen	salox	DM-DACH	TMEDA	none	no catalyst		
FeCl <sub>2</sub>	73.2	65.1	47.5	79.0	65.9	58.0	74.0	67.5	65.6	29.4	72.2	14.0	DMA	80 °C
CoCl <sub>2</sub>	57.9	38.5	29.4	62.6	50.4	15.6	19.3	22.5	28.7	19.6	20.8	14.3		
Fe(OAc) <sub>2</sub>	60.2	40.2	21.2	58.6	86.5	45.7	23.4	44.0	59.9	64.4	60.1	13.6		
Co(OAc) <sub>2</sub>	7.3	16.2	12.8	26.8	7.7	33.2	23.3	25.0	22.0	32.6	31.1	13.5		
FeCl <sub>2</sub>	56.5	75.6	52.6	46.2	46.4	22.5	8.8	60.8	40.5	43.8	47.5	-0.2	DME	80 °C
CoCl <sub>2</sub>	16.3	11.2	7.9	36.7	24.4	0.3	20.5	13.3	12.0	10.0	11.8	-0.2		
Fe(OAc) <sub>2</sub>	75.3	72.7	18.4	38.2	71.5	47.8	17.8	27.9	46.9	52.1	46.4	-0.2		
Co(OAc) <sub>2</sub>	6.6	10.4	12.2	12.8	6.4	13.0	30.2	13.4	15.2	19.8	12.2	0.3		
FeCl <sub>2</sub>	9.1	41.6	43.8	51.3	4.1	4.9	8.9	34.3	6.1	9.7	28.8	3.7	DMA	60 °C
CoCl <sub>2</sub>	52.5	2.3	21.2	33.7	36.1	2.2	20.9	7.1	44.0	14.6	7.7	2.8		
Fe(OAc) <sub>2</sub>	42.8	32.2	23.3	47.7	80.2	47.0	23.9	34.5	47.4	60.2	45.0	4.4		
Co(OAc) <sub>2</sub>	7.3	15.3	13.2	26.8	7.9	20.2	17.3	22.7	19.0	24.9	25.7	4.1		
FeCl <sub>2</sub>	0.3	51.9	44.4	41.9	7.4	0.3	-0.2	11.0	0.7	42.0	1.6	-0.2	DME	60 °C
CoCl <sub>2</sub>	16.6	6.8	5.7	16.9	24.9	0.2	7.1	-0.2	10.0	7.6	7.9	-0.2		
Fe(OAc) <sub>2</sub>	77.5	49.3	7.4	25.4	60.9	41.7	10.2	20.9	54.9	52.2	24.1	-0.2		
Co(OAc) <sub>2</sub>	7.1	9.7	8.0	12.2	7.3	12.0	21.0	8.8	14.1	21.1	13.3	-0.2		
Conversion to product 2a	phen	dppe	IPr	dtbpf	dtbpy	8-HQ	salen	salox	DM-DACH	TMEDA	none	no catalyst		
FeCl <sub>2</sub>	83.7	72.1	77.2	94.7	76.6	70.1	84.1	84.2	79.8	49.9	87.2	19.4	DMA	80 °C
CoCl <sub>2</sub>	100.0	91.2	76.7	92.0	98.9	50.7	85.6	45.8	93.9	79.3	38.8	19.7		
Fe(OAc) <sub>2</sub>	85.0	55.8	41.9	75.4	95.1	80.7	44.2	66.9	91.2	85.5	74.5	19.0		
Co(OAc) <sub>2</sub>	77.5	54.3	64.4	79.6	68.7	82.3	56.7	84.7	81.5	84.2	70.4	19.0		
FeCl <sub>2</sub>	92.4	81.5	91.3	70.5	93.1	42.1	14.4	70.6	96.5	92.8	91.8	0.0	DME	80 °C
CoCl <sub>2</sub>	63.6	83.4	35.1	91.6	96.5	0.7	49.9	40.5	79.4	84.7	30.7	0.0		
Fe(OAc) <sub>2</sub>	96.7	86.4	31.8	59.6	94.4	92.9	68.7	83.0	92.2	81.9	85.1	0.0		
Co(OAc) <sub>2</sub>	100.0	59.9	64.6	57.7	91.9	52.7	79.6	65.7	66.8	78.5	42.8	0.6		
FeCl <sub>2</sub>	13.7	67.6	70.1	63.5	6.2	7.0	13.1	45.6	10.4	16.5	37.9	5.2	DMA	60 °C
CoCl <sub>2</sub>	92.7	4.4	59.4	62.5	93.0	3.7	71.8	12.7	91.8	66.9	12.3	4.0		
Fe(OAc) <sub>2</sub>	68.5	48.0	40.7	64.6	91.9	76.7	40.8	57.4	89.2	82.3	63.4	6.1		
Co(OAc) <sub>2</sub>	69.9	52.3	57.3	78.2	85.4	79.2	41.5	83.5	71.7	70.5	67.6	5.6		
FeCl <sub>2</sub>	0.6	75.0	84.2	70.6	7.9	0.7	0.0	21.8	1.2	86.1	2.8	0.0	DME	60 °C
CoCl <sub>2</sub>	100.0	75.6	58.0	38.6	87.4	0.5	33.8	0.0	59.7	51.2	38.5	0.0		
Fe(OAc) <sub>2</sub>	93.9	63.2	14.2	42.4	87.1	89.2	37.3	69.4	85.7	75.4	41.9	0.0		
Co(OAc) <sub>2</sub>	93.3	50.9	38.1	63.4	86.2	55.0	57.2	78.4	63.1	72.4	62.4	0.0		
Conversion to aniline 4a	phen	dppe	IPr	dtbpf	dtbpy	8-HQ	salen	salox	DM-DACH	TMEDA	none	no catalyst		
FeCl <sub>2</sub>	6.4	0.0	21.6	4.9	5.2	7.4	8.4	5.4	4.0	4.7	8.2	5.5	DMA	80 °C
CoCl <sub>2</sub>	0.0	8.8	23.3	7.3	0.0	8.8	11.8	4.2	6.1	3.7	6.6	5.7		
Fe(OAc) <sub>2</sub>	12.6	36.5	58.1	23.8	4.3	17.9	54.8	31.8	6.9	12.4	24.2	5.8		
Co(OAc) <sub>2</sub>	22.5	36.8	35.6	20.4	31.3	2.7	39.0	15.3	18.5	13.5	10.8	5.8		
FeCl <sub>2</sub>	7.6	12.8	8.7	29.5	5.4	24.3	5.7	15.3	3.5	7.2	4.7	1.2	DME	80 °C
CoCl <sub>2</sub>	3.6	6.2	3.6	0.0	0.0	0.8	3.9	2.4	16.9	10.8	1.7	1.2		
Fe(OAc) <sub>2</sub>	3.3	12.2	68.2	40.4	5.6	6.3	31.3	17.0	7.8	8.9	14.9	1.2		
Co(OAc) <sub>2</sub>	0.0	20.9	32.0	21.9	0.0	6.4	20.4	4.8	31.0	21.5	7.3	1.3		
FeCl <sub>2</sub>	5.5	19.6	28.6	4.8	3.0	3.5	8.7	5.7	4.4	5.1	4.7	1.2	DMA	60 °C
CoCl <sub>2</sub>	6.7	18.8	33.0	16.5	6.0	1.6	13.7	4.0	8.2	4.9	3.9	1.1		
Fe(OAc) <sub>2</sub>	31.5	52.0	59.3	35.4	8.1	23.3	59.2	42.6	10.8	16.4	36.6	1.5		
Co(OAc) <sub>2</sub>	30.1	46.0	40.0	21.8	14.6	8.6	58.5	16.5	28.3	24.6	17.2	1.4		
FeCl <sub>2</sub>	0.0	23.9	14.8	29.4	3.7	2.4	3.4	4.1	1.4	8.4	0.0	0.6	DME	60 °C
CoCl <sub>2</sub>	0.0	13.7	12.5	3.2	5.3	0.8	11.2	0.0	25.8	12.1	3.4	0.0		
Fe(OAc) <sub>2</sub>	5.6	24.1	85.8	29.1	12.9	9.6	62.7	30.6	14.3	17.3	16.6	0.0		
Co(OAc) <sub>2</sub>	6.7	26.8	57.8	27.9	6.2	6.8	42.8	5.7	36.9	20.6	9.3	0.7		
Conversion to HO-Indole 3a	phen	dppe	IPr	dtbpf	dtbpy	8-HQ	salen	salox	DM-DACH	TMEDA	none	no catalyst		
FeCl <sub>2</sub>	10.0	21.2	0.0	0.0	5.6	21.2	7.5	7.7	12.8	0.0	4.6	7.7	DMA	80 °C
CoCl <sub>2</sub>	0.0	0.0	0.0	0.0	0.0	0.0	2.6	50.0	0.0	17.0	52.8	8.1		
Fe(OAc) <sub>2</sub>	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	7.4		
Co(OAc) <sub>2</sub>	0.0	1.7	0.0	0.0	0.0	15.0	4.3	0.0	0.0	2.3	18.7	7.5		
FeCl <sub>2</sub>	0.0	0.0	0.0	0.0	1.6	8.0	3.7	0.0	0.0	0.0	3.5	6.3	DME	80 °C
CoCl <sub>2</sub>	0.0	8.1	57.2	8.4	0.0	6.8	46.2	56.1	0.0	0.0	65.1	6.3		
Fe(OAc) <sub>2</sub>	0.0	0.0	0.0	0.0	0.0	0.8	0.0	0.0	0.0	9.2	0.0	5.8		
Co(OAc) <sub>2</sub>	0.0	19.3	0.0	20.4	0.0	40.9	0.0	29.5	0.0	0.0	49.9	6.2		
FeCl <sub>2</sub>	11.7	3.0	1.2	14.0	2.1	9.3	9.2	31.7	0.0	33.9	34.3	1.4	DMA	60 °C
CoCl <sub>2</sub>	0.0	0.0	6.5	21.0	0.0	0.0	0.0	0.0	0.0	0.0	16.4	1.3		
Fe(OAc) <sub>2</sub>	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	2.1		
Co(OAc) <sub>2</sub>	0.0	1.7	2.6	0.0	0.0	0.0	0.0	0.0	0.0	0.0	11.1	1.7		
FeCl <sub>2</sub>	3.4	0.0	0.0	0.0	0.0	2.5	1.6	4.9	1.7	2.5	3.3	1.9	DME	60 °C
CoCl <sub>2</sub>	0.0	7.5	20.5	58.1	0.0	4.3	39.3	0.9	0.0	0.0	49.4	1.6		
Fe(OAc) <sub>2</sub>	0.4	11.3	0.0	13.2	0.0	1.2	0.0	0.0	0.0	7.3	15.7	1.6		
Co(OAc) <sub>2</sub>	0.0	22.2	0.0	8.7	0.0	27.7	0.0	0.0	0.0	0.0	19.0	2.0		

Screening of solvents was conducted using the general microscale screening procedure on 10  $\mu\text{mol}$  (2.3 mg) scale with substrate **2.1a** using 2 or 10 mol % of  $\text{FeCl}_2$  / no ligand,  $\text{FeCl}_2$  / dcpf,  $\text{Fe}(\text{OAc})_2$  / dtbpy or  $\text{Fe}(\text{OAc})_2$  / phen, 3 equiv of silane, 12 solvents, 0.1 M, 80  $^\circ\text{C}$ , 18h.

**Table S2.3.** Solvent screening under different iron catalyst combinations.

Yield of product 2a	DMA	NMP	MeCN	PC	DME	Me-THF	CPME	Pyr	PhMe	PhCF <sub>3</sub>	PhCl	iPrOH			
PhSiH <sub>3</sub>	70.2	13.6	35.1	42.8	36.5	37.2	20.7	3.6	13.4	16.4	15.4	8.3	10%	FeCl <sub>2</sub>	no ligand
	24.3	9.0	26.6	5.1	1.9	27.0	18.4	4.3	13.7	21.0	15.8	6.6	2%		
	76.5	85.4	41.8	16.9	7.3	17.2	26.7	18.3	8.6	16.2	20.8	7.7	10%	FeCl <sub>2</sub>	dcpf
	42.7	13.6	12.4	35.6	1.1	2.3	3.0	6.7	8.7	4.2	3.9	5.6	2%		
	82.4	67.9	60.0	25.3	78.4	67.6	62.2	85.4	66.9	47.7	66.9	26.9	10%	Fe(OAc) <sub>2</sub>	dtbpy
	86.2	87.3	88.3	74.9	73.9	72.9	63.5	36.8	67.9	63.2	53.7	28.4	2%		
	49.4	46.1	49.8	35.3	77.2	72.6	77.0	53.6	84.3	68.0	62.0	27.7	10%	Fe(OAc) <sub>2</sub>	phen
	79.3	81.4	81.5	84.6	83.0	75.5	70.6	45.1	60.1	76.8	58.9	36.8	2%		
Ph <sub>2</sub> SiH <sub>2</sub>	35.9	9.6	12.9	59.7	32.2	31.8	20.2	0.9	20.0	30.4	21.5	8.2	10%	FeCl <sub>2</sub>	no ligand
	7.3	4.6	5.2	32.0	17.7	11.8	21.0	0.6	16.5	23.4	18.1	6.5	2%		
	34.2	43.8	30.8	47.7	16.4	17.0	7.7	3.9	11.0	14.9	10.2	2.6	10%	FeCl <sub>2</sub>	dcpf
	13.4	11.2	19.1	12.9	6.1	39.4	2.4	-0.1	2.1	11.6	5.7	16.7	2%		
	91.2	85.6	91.8	67.4	80.0	73.5	48.5	80.2	65.0	63.9	73.5	35.6	10%	Fe(OAc) <sub>2</sub>	dtbpy
	36.6	32.1	51.1	27.8	50.8	39.4	33.7	10.8	31.5	49.1	35.3	25.8	2%		
	91.1	84.6	87.4	77.8	74.4	70.6	58.7	81.0	84.2	78.4	70.5	43.6	10%	Fe(OAc) <sub>2</sub>	phen
	60.0	57.8	69.7	35.1	83.2	80.0	78.5	52.5	52.5	52.3	44.7	42.9	2%		
Me <sub>2</sub> PhSiH	8.9	6.1	20.6	29.7	16.3	14.9	-0.1	-0.1	21.3	15.7	16.4	2.2	10%	FeCl <sub>2</sub>	no ligand
	7.3	4.0	10.3	27.1	10.1	18.0	17.0	-0.1	-0.1	18.5	21.5	2.6	2%		
	-0.1	-0.1	17.9	-0.1	-0.1	-0.1	-0.1	-0.1	-0.1	-0.1	-0.1	6.0	10%	FeCl <sub>2</sub>	dcpf
	-0.1	-0.1	16.2	14.1	-0.1	-0.1	-0.1	-0.1	-0.1	-0.1	-0.1	-0.1	2%		
	51.4	57.5	26.1	47.3	20.0	27.0	17.7	48.7	25.1	41.4	31.7	23.0	10%	Fe(OAc) <sub>2</sub>	dtbpy
	35.3	53.2	14.4	27.7	-0.1	20.5	-0.1	-0.1	-0.1	-0.1	20.8	13.9	2%		
	55.9	66.2	50.4	43.2	25.6	22.2	-0.1	67.0	-0.1	15.3	14.3	17.8	10%	Fe(OAc) <sub>2</sub>	phen
	62.2	70.4	15.1	45.8	19.7	-0.1	-0.1	47.6	-0.1	-0.1	4.5	22.7	2%		
(Me <sub>2</sub> SiH) <sub>2</sub> O	12.9	14.9	11.2	24.7	5.5	16.1	0.7	1.0	3.6	16.1	16.3	7.7	10%	FeCl <sub>2</sub>	no ligand
	17.3	11.4	13.8	24.1	3.8	12.4	2.2	1.6	1.8	28.4	30.9	7.6	2%		
	20.9	15.4	9.1	16.9	1.9	2.4	2.1	0.2	1.1	9.6	4.7	7.9	10%	FeCl <sub>2</sub>	dcpf
	3.4	2.3	8.3	18.4	1.4	1.7	4.1	0.1	0.9	7.4	3.5	5.6	2%		
	69.7	79.9	33.9	37.1	46.5	40.1	37.4	72.8	42.9	59.9	61.0	48.8	10%	Fe(OAc) <sub>2</sub>	dtbpy
	54.2	74.0	37.3	72.2	12.4	11.9	6.9	4.9	7.9	13.1	14.4	11.3	2%		
	61.8	57.1	43.3	49.2	85.4	78.6	78.2	51.2	53.5	78.5	77.2	43.1	10%	Fe(OAc) <sub>2</sub>	phen
	76.0	70.0	66.4	70.0	41.2	18.9	22.1	73.8	11.8	21.2	6.7	37.0	2%		
Conversion to aniline 4a	DMA	NMP	MeCN	PC	DME	Me-THF	CPME	Pyr	PhMe	PhCF <sub>3</sub>	PhCl	iPrOH			
PhSiH <sub>3</sub>	8.8	1.8	1.7	3.5	3.7	4.2	8.3	4.0	13.8	33.3	31.2	40.4	10%	FeCl <sub>2</sub>	no ligand
	6.0	2.0	8.6	2.9	1.9	11.3	26.9	2.5	33.5	34.5	30.6	12.3	2%		
	3.8	3.3	2.7	1.2	4.2	6.0	1.5	1.8	2.2	1.4	1.1	4.0	10%	FeCl <sub>2</sub>	dcpf
	4.1	1.6	3.3	1.1	4.1	7.7	3.3	1.9	1.9	3.9	2.7	4.8	2%		
	6.5	5.6	7.0	3.3	5.5	6.1	5.9	1.7	7.0	6.8	10.0	1.6	10%	Fe(OAc) <sub>2</sub>	dtbpy
	3.2	2.7	1.7	2.3	3.9	3.0	4.4	1.5	3.9	4.3	4.5	0.0	2%		
	20.4	18.5	15.2	2.5	3.6	3.7	3.7	2.3	3.3	4.4	4.7	7.7	10%	Fe(OAc) <sub>2</sub>	phen
	6.8	3.9	6.9	0.7	4.5	3.6	5.6	1.5	5.9	5.2	4.9	5.4	2%		
Ph <sub>2</sub> SiH <sub>2</sub>	15.9	3.9	8.8	14.2	8.9	13.9	25.5	1.2	32.0	30.8	33.7	27.2	10%	FeCl <sub>2</sub>	no ligand
	6.3	3.7	7.6	17.9	34.7	18.0	32.6	0.7	38.5	32.8	29.3	73.5	2%		
	1.6	0.8	4.4	5.2	2.2	3.8	0.6	2.1	1.8	1.9	0.8	2.4	10%	FeCl <sub>2</sub>	dcpf
	1.7	1.6	5.0	5.9	2.3	10.2	5.8	2.3	1.9	5.1	0.7	5.6	2%		
	4.7	3.6	6.5	0.5	11.7	9.2	16.3	2.6	17.5	15.8	13.6	12.2	10%	Fe(OAc) <sub>2</sub>	dtbpy
	10.9	4.1	9.2	9.8	16.4	11.6	17.6	3.7	22.0	14.6	17.3	2.8	2%		
	2.9	2.2	3.9	0.7	12.9	13.4	5.1	4.3	3.2	9.9	8.0	2.2	10%	Fe(OAc) <sub>2</sub>	phen
	6.7	4.6	8.3	10.9	8.9	5.7	7.1	3.7	10.4	13.1	12.2	2.4	2%		
Me <sub>2</sub> PhSiH	12.0	27.0	48.4	36.1	20.2	40.8	18.2	44.5	32.4	32.7	22.6	57.7	10%	FeCl <sub>2</sub>	no ligand
	5.2	13.0	66.6	30.7	6.3	9.0	7.4	36.9	3.6	36.0	24.2	3.2	2%		
	6.3	5.8	5.9	4.5	0.0	0.0	0.0	0.0	0.0	1.0	0.0	43.5	10%	FeCl <sub>2</sub>	dcpf
	2.4	2.1	9.2	21.8	0.0	0.6	0.0	0.0	0.0	1.8	0.0	16.6	2%		
	15.4	20.2	24.0	0.0	3.2	2.4	2.8	33.5	2.8	16.7	7.5	0.0	10%	Fe(OAc) <sub>2</sub>	dtbpy
	14.3	5.8	3.4	2.9	2.7	1.7	1.4	79.2	1.1	5.0	3.8	0.0	2%		
	17.8	16.5	21.6	12.2	4.8	5.7	3.1	25.7	9.8	22.1	8.5	53.8	10%	Fe(OAc) <sub>2</sub>	phen
	5.2	4.5	8.2	9.7	2.7	3.0	1.9	15.0	2.6	8.8	6.2	24.9	2%		
(Me <sub>2</sub> SiH) <sub>2</sub> O	6.9	22.7	75.4	47.8	4.9	61.2	3.6	23.8	1.1	43.5	17.2	0.0	10%	FeCl <sub>2</sub>	no ligand
	0.0	5.9	73.3	51.7	2.7	9.5	4.6	16.9	1.2	21.7	28.2	0.0	2%		
	3.7	4.3	6.1	1.7	0.6	1.1	0.7	0.0	0.0	3.7	0.8	55.6	10%	FeCl <sub>2</sub>	dcpf
	4.0	3.9	9.1	26.0	1.3	1.5	2.2	0.0	0.0	3.8	0.8	29.0	2%		
	13.8	10.2	44.0	19.3	3.5	3.6	3.0	15.3	5.4	6.3	5.1	1.1	10%	Fe(OAc) <sub>2</sub>	dtbpy
	3.5	10.3	9.1	8.2	1.6	1.3	1.2	62.8	1.0	2.1	2.6	6.1	2%		
	21.6	24.9	30.3	27.5	1.4	3.0	2.1	16.9	1.5	3.5	1.0	15.6	10%	Fe(OAc) <sub>2</sub>	phen
	11.5	14.2	13.8	10.1	1.4	1.4	0.7	15.1	0.7	1.0	0.6	20.9	2%		

Conversion to product 2a	DMA	NMP	MeCN	PC	DME	Me-THF	CPME	Pyr	PhMe	PhCF <sub>3</sub>	PhCl	iPrOH			
PhSiH <sub>3</sub>	87.8	18.9	88.9	96.5	96.3	95.1	90.6	6.0	86.2	65.5	68.8	49.5	10%	FeCl <sub>2</sub>	no ligand
	36.6	12.2	55.8	9.4	3.4	79.9	65.5	7.1	61.0	65.5	68.4	9.1	2%		
	94.9	96.7	57.8	24.9	10.6	25.4	40.4	23.6	11.9	22.5	29.4	12.5	10%	FeCl <sub>2</sub>	dcpf
	52.2	19.5	18.4	98.9	1.7	3.8	4.6	9.9	12.3	6.1	5.9	9.8	2%		
	93.5	94.4	92.5	95.0	94.5	93.9	94.1	98.3	93.0	93.2	90.0	98.4	10%	Fe(OAc) <sub>2</sub>	dtbpy
	95.7	97.3	98.3	97.2	96.1	97.0	95.6	45.9	96.1	95.7	95.5	87.8	2%		
	77.8	81.5	84.8	97.5	96.4	96.3	96.3	97.1	96.7	95.6	95.3	41.5	10%	Fe(OAc) <sub>2</sub>	phen
	92.4	96.1	93.1	98.9	95.5	96.4	94.4	59.0	94.1	86.7	93.4	57.5	2%		
Ph <sub>2</sub> SiH <sub>2</sub>	59.7	15.1	24.4	85.8	77.9	76.6	72.9	1.7	68.0	65.6	60.7	48.0	10%	FeCl <sub>2</sub>	no ligand
	13.3	7.8	10.4	73.7	65.3	34.7	63.6	1.2	61.5	67.2	64.5	15.4	2%		
	53.0	60.7	43.0	63.7	23.0	27.8	12.2	5.7	14.7	20.5	15.3	4.7	10%	FeCl <sub>2</sub>	dcpf
	19.6	16.7	28.0	20.6	10.0	49.0	3.9	0.0	3.4	17.3	9.0	20.6	2%		
	95.3	96.4	93.5	99.1	88.3	90.8	83.7	96.9	82.5	84.2	86.4	85.9	10%	Fe(OAc) <sub>2</sub>	dtbpy
	54.7	51.8	78.7	53.4	78.8	85.4	82.4	24.4	78.0	85.4	82.7	72.2	2%		
	96.0	95.3	95.8	99.3	87.1	86.6	94.9	95.7	96.8	90.1	92.0	67.5	10%	Fe(OAc) <sub>2</sub>	phen
	76.2	79.3	87.2	68.0	91.1	94.3	92.5	82.9	87.9	86.5	87.8	76.5	2%		
Me <sub>2</sub> PhSiH	29.1	19.7	45.2	62.4	21.2	24.9	0.0	0.0	46.7	37.1	40.7	7.9	10%	FeCl <sub>2</sub>	no ligand
	18.9	9.7	24.9	68.8	13.1	23.8	21.4	0.0	0.0	45.1	53.4	13.2	2%		
	0.0	0.0	22.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	13.9	10%	FeCl <sub>2</sub>	dcpf
	0.0	0.0	21.9	18.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	2%		
	58.8	72.9	32.3	100.0	27.4	30.9	20.1	60.5	26.8	32.3	38.3	61.1	10%	Fe(OAc) <sub>2</sub>	dtbpy
	49.6	94.2	19.8	32.0	0.0	26.3	0.0	0.0	0.0	0.0	26.4	43.1	2%		
	79.9	83.5	78.4	87.8	28.5	26.1	0.0	74.3	0.0	23.4	18.7	35.8	10%	Fe(OAc) <sub>2</sub>	phen
	67.6	84.5	18.1	56.9	22.1	0.0	0.0	53.7	0.0	0.0	7.6	41.9	2%		
(Me <sub>2</sub> SiH) <sub>2</sub> O	62.1	73.2	24.6	52.2	5.9	38.8	1.3	5.0	4.0	56.5	26.5	93.8	10%	FeCl <sub>2</sub>	no ligand
	85.3	70.4	26.7	47.2	5.8	19.9	3.8	6.7	2.9	75.2	71.8	86.8	2%		
	30.5	26.8	13.9	24.7	3.0	4.2	3.4	0.4	1.7	13.7	7.2	20.2	10%	FeCl <sub>2</sub>	dcpf
	5.4	3.9	12.9	37.8	2.3	2.8	7.4	0.4	1.5	10.9	5.6	12.6	2%		
	86.2	89.8	56.0	70.9	61.0	54.4	51.1	84.7	94.6	93.7	94.9	98.9	10%	Fe(OAc) <sub>2</sub>	dtbpy
	96.5	89.7	70.4	91.1	17.7	18.0	10.2	18.3	11.2	20.1	23.5	16.5	2%		
	77.9	74.4	66.7	72.0	98.1	97.0	95.8	74.0	78.0	94.2	98.0	73.1	10%	Fe(OAc) <sub>2</sub>	phen
	88.1	85.0	85.8	89.9	71.0	13.6	34.2	84.9	19.8	14.6	10.5	77.8	2%		
Conversion to HO-Indole 3a	DMA	NMP	MeCN	PC	DME	Me-THF	CPME	Pyr	PhMe	PhCF <sub>3</sub>	PhCl	iPrOH			
PhSiH <sub>3</sub>	3.4	20.6	0.0	0.0	0.0	0.0	0.0	6.3	0.0	0.0	0.0	10.1	10%	FeCl <sub>2</sub>	no ligand
	34.0	15.5	7.2	0.0	3.8	7.5	7.7	12.7	0.0	0.0	0.0	0.0	2%		
	0.4	0.0	3.3	0.0	2.2	4.2	5.5	1.4	0.0	0.0	0.0	1.3	10%	FeCl <sub>2</sub>	dcpf
	4.9	1.7	1.9	0.0	4.8	10.9	2.9	0.0	0.0	0.0	0.0	3.9	2%		
	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	10%	Fe(OAc) <sub>2</sub>	dtbpy
	0.0	0.0	0.0	0.0	0.0	0.0	0.0	52.6	0.0	0.0	0.0	0.0	2%		
	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.6	0.0	0.0	0.0	0.0	10%	Fe(OAc) <sub>2</sub>	phen
	0.0	0.0	0.0	0.0	0.0	0.0	0.0	39.0	0.0	1.0	0.0	0.0	2%		
Ph <sub>2</sub> SiH <sub>2</sub>	24.4	5.8	0.0	0.0	13.2	9.5	0.0	0.0	0.0	0.0	5.5	24.8	10%	FeCl <sub>2</sub>	no ligand
	12.7	8.8	0.0	1.1	0.0	32.9	3.8	0.0	0.0	0.0	6.2	11.1	2%		
	0.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	10%	FeCl <sub>2</sub>	dcpf
	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	2%		
	0.0	0.0	0.0	0.4	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	10%	Fe(OAc) <sub>2</sub>	dtbpy
	31.3	4.1	0.0	0.0	0.0	1.6	0.0	0.0	0.0	0.0	0.0	0.0	2%		
	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	10%	Fe(OAc) <sub>2</sub>	phen
	6.4	4.6	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	2%		
Me <sub>2</sub> PhSiH	56.1	50.7	0.0	0.0	5.7	0.5	3.7	29.4	0.0	0.0	0.0	0.0	10%	FeCl <sub>2</sub>	no ligand
	74.9	76.8	0.0	0.0	4.9	4.6	5.5	9.7	0.6	1.3	2.6	23.7	2%		
	2.1	2.3	3.1	1.5	0.7	1.5	1.5	0.0	0.0	0.6	0.0	2.5	10%	FeCl <sub>2</sub>	dcpf
	2.7	4.8	0.3	17.7	0.6	2.6	1.1	0.0	0.0	1.5	0.0	8.7	2%		
	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	10%	Fe(OAc) <sub>2</sub>	dtbpy
	0.3	0.0	0.0	0.0	2.9	3.7	0.5	0.0	0.0	0.0	4.0	0.0	2%		
	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	10%	Fe(OAc) <sub>2</sub>	phen
	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	33.5	0.0	2%		
(Me <sub>2</sub> SiH) <sub>2</sub> O	2.7	1.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	10%	FeCl <sub>2</sub>	no ligand
	12.3	18.1	0.0	0.0	0.8	0.0	0.0	0.0	0.0	0.0	0.0	3.9	2%		
	2.6	0.0	1.3	0.0	0.0	0.0	0.0	0.0	0.0	0.5	0.0	0.0	10%	FeCl <sub>2</sub>	dcpf
	5.3	3.6	1.3	11.8	0.0	1.6	0.0	0.0	0.0	1.5	0.0	0.0	2%		
	0.0	0.0	0.0	0.4	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	10%	Fe(OAc) <sub>2</sub>	dtbpy
	0.0	0.0	0.0	0.0	0.5	1.0	0.0	0.0	0.0	0.0	0.0	0.0	2%		
	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	10%	Fe(OAc) <sub>2</sub>	phen
	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	2.4	0.0	2%		



Screening of silanes was conducted using the general microscale screening procedure on 10 or 20  $\mu$ mol (2.3 or 4.6 mg) scale with substrate **2.1a** using 0.5 or 1 mol % Fe(OAc)<sub>2</sub> / neocuproine, 5 or 9 equiv.  $\times$  12 silanes (calculated as Si-H), DME, 0.1 or 0.2 M, 80 °C, 18h.

**Table S2.4.** Screening of silanes.

Yield of product 2a	PhSiH <sub>3</sub>	Ph <sub>2</sub> SiH <sub>2</sub>	Ph <sub>3</sub> SiH	Ph <sub>2</sub> MeSiH	PhMe <sub>2</sub> SiH	Et <sub>3</sub> SiH	iPr <sub>3</sub> SiH	(TMS) <sub>3</sub> SiH	(EO) <sub>3</sub> SiH	(EO) <sub>2</sub> MeSiH	(Me <sub>2</sub> SiH) <sub>2</sub> O	PMHS		
1.0%	93.5	43.9	0.2	1.7	-0.2	1.4	-0.2	4.2	75.5	53.4	4.4	32.1	9 eq Si-H	0.1 M
0.5%	85.1	10.1	-0.2	0.5	-0.2	0.5	-0.2	3.1	77.7	38.3	3.0	13.8	5 eq Si-H	
1.0%	55.4	11.8	0.3	1.0	-0.2	1.0	-0.2	3.4	52.5	57.0	10.7	20.3	9 eq Si-H	0.2 M
0.5%	34.7	4.4	-0.2	0.5	-0.2	0.7	-0.2	2.0	35.6	34.5	2.7	47.8	5 eq Si-H	
1.0%	78.9	62.2	0.2	1.2	-0.1	2.2	-0.2	5.9	86.1	38.2	18.1	15.1	9 eq Si-H	0.1 M
0.5%	74.4	10.4	0.3	0.7	4.8	0.9	0.4	2.3	71.9	33.5	12.6	13.0	5 eq Si-H	0.2 M
1.0%	65.9	12.5	0.3	1.4	-0.1	1.7	-0.2	3.1	72.0	35.1	19.9	54.0	9 eq Si-H	0.1 M
0.5%	35.2	7.1	-0.2	1.0	-0.2	0.8	-0.2	1.9	32.2	26.5	12.2	14.5	5 eq Si-H	
Conversion to product 2a	PhSiH <sub>3</sub>	Ph <sub>2</sub> SiH <sub>2</sub>	Ph <sub>3</sub> SiH	Ph <sub>2</sub> MeSiH	PhMe <sub>2</sub> SiH	Et <sub>3</sub> SiH	iPr <sub>3</sub> SiH	(TMS) <sub>3</sub> SiH	(EO) <sub>3</sub> SiH	(EO) <sub>2</sub> MeSiH	(Me <sub>2</sub> SiH) <sub>2</sub> O	PMHS		
1.0%	95.2	37.7	0.5	6.2	0.0	2.3	0.0	6.0	97.1	83.4	7.7	87.4	9 eq Si-H	0.1 M
0.5%	91.0	19.1	0.0	1.7	0.0	0.8	0.0	4.6	95.5	75.3	4.8	36.7	5 eq Si-H	
1.0%	82.5	29.7	0.7	2.5	0.0	1.5	0.0	4.9	75.1	85.5	21.8	62.3	9 eq Si-H	0.2 M
0.5%	71.8	8.2	0.0	1.5	0.0	1.1	0.0	3.0	83.1	69.8	4.1	54.8	5 eq Si-H	
1.0%	93.1	78.3	0.6	5.1	0.0	3.4	0.0	9.0	94.2	66.7	35.2	60.3	9 eq Si-H	0.1 M
0.5%	85.5	23.9	0.7	3.3	10.3	1.4	0.7	3.7	91.9	61.5	26.1	23.7	5 eq Si-H	0.2 M
1.0%	91.8	35.4	0.6	4.0	0.0	2.7	0.0	4.8	89.9	60.0	33.1	75.6	9 eq Si-H	0.1 M
0.5%	72.2	15.1	0.0	3.0	0.0	1.3	0.0	3.4	38.1	52.4	21.8	28.0	5 eq Si-H	
Conversion to aniline 4a	PhSiH <sub>3</sub>	Ph <sub>2</sub> SiH <sub>2</sub>	Ph <sub>3</sub> SiH	Ph <sub>2</sub> MeSiH	PhMe <sub>2</sub> SiH	Et <sub>3</sub> SiH	iPr <sub>3</sub> SiH	(TMS) <sub>3</sub> SiH	(EO) <sub>3</sub> SiH	(EO) <sub>2</sub> MeSiH	(Me <sub>2</sub> SiH) <sub>2</sub> O	PMHS		
1.0%	1.7	1.6	0.0	2.3	2.0	0.0	0.0	9.0	1.2	5.6	1.7	2.5	9 eq Si-H	0.1 M
0.5%	1.8	5.1	0.0	0.0	0.0	0.0	0.0	8.8	0.0	4.4	1.6	1.4	5 eq Si-H	
1.0%	1.9	8.1	0.0	0.9	5.3	0.0	0.0	7.1	0.9	4.3	0.9	0.0	9 eq Si-H	0.2 M
0.5%	2.7	5.9	0.0	0.8	1.4	0.0	0.0	6.7	2.0	2.2	0.9	0.0	5 eq Si-H	
1.0%	1.1	2.5	0.0	0.7	10.2	0.0	0.0	10.9	2.6	9.8	11.9	0.0	9 eq Si-H	0.1 M
0.5%	1.3	8.6	1.7	0.7	35.2	1.1	0.0	9.6	1.1	11.0	13.2	1.0	5 eq Si-H	0.2 M
1.0%	1.9	10.2	0.0	1.4	18.3	0.9	0.0	8.9	2.1	3.4	2.6	0.0	9 eq Si-H	0.1 M
0.5%	2.9	9.7	0.0	1.0	3.7	0.7	0.0	7.8	2.8	3.7	2.5	0.9	5 eq Si-H	
Conversion to HO-indole 3a	PhSiH <sub>3</sub>	Ph <sub>2</sub> SiH <sub>2</sub>	Ph <sub>3</sub> SiH	Ph <sub>2</sub> MeSiH	PhMe <sub>2</sub> SiH	Et <sub>3</sub> SiH	iPr <sub>3</sub> SiH	(TMS) <sub>3</sub> SiH	(EO) <sub>3</sub> SiH	(EO) <sub>2</sub> MeSiH	(Me <sub>2</sub> SiH) <sub>2</sub> O	PMHS		
1.0%	0.5	0.7	1.6	6.5	3.9	0.0	0.0	33.0	0.0	0.0	24.1	7.9	9 eq Si-H	0.1 M
0.5%	0.6	3.7	3.9	1.9	1.1	0.0	0.0	38.9	0.0	13.3	14.3	7.1	5 eq Si-H	
1.0%	12.2	6.8	0.7	1.2	1.2	0.7	0.0	21.1	0.0	0.0	33.8	11.9	9 eq Si-H	0.2 M
0.5%	15.9	5.0	2.6	1.2	3.1	0.0	0.0	27.1	9.5	12.8	6.5	14.1	5 eq Si-H	
1.0%	1.3	0.0	0.0	0.0	19.3	0.0	0.0	38.8	0.0	0.0	16.9	13.6	9 eq Si-H	0.1 M
0.5%	2.5	8.6	4.3	0.0	27.4	1.0	0.9	32.1	3.1	5.9	16.7	3.8	5 eq Si-H	0.2 M
1.0%	3.5	4.6	0.0	0.0	22.4	0.0	0.0	35.0	0.0	4.7	10.3	11.6	9 eq Si-H	0.1 M
0.5%	10.2	2.9	0.0	0.0	2.5	0.8	0.0	25.0	0.0	10.8	14.2	5.2	5 eq Si-H	

Screening of  $sp^2$  bidentate N-N ligands was conducted using the general microscale screening procedure on 10  $\mu$ mol (2.3 mg) scale with substrate **2.1a** using 10 mol % of  $Fe(OAc)_2$ , 10 mol %  $\times$  24 ligands, 3 equiv of  $PhSiH_3$ , DME, 0.1M, 80  $^\circ$ C, 18 h.

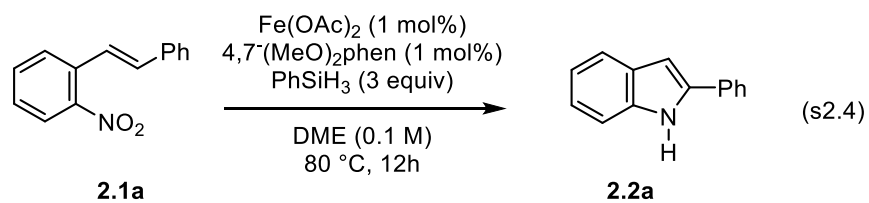
**Table S2.5.** Screen of  $sp^2$  bidentate *N-N* ligands.

Ligand	Conversion to product 2.2a	Conversion to aniline 2.4a	Conversion to HO- indole 2.3a	Yield of product 2.2a
phen	91.4	1.1	0.0	76.6
neocuproine	96.7	1.0	0.0	80.6
3,4,7,8-Me-phen	92.5	3.5	0.0	67.6
4,7-MeO-phen	94.8	0.9	0.0	100.1
bipy	96.8	0.9	0.0	75.4
2,2'-biquinoline	94.1	2.2	0.0	70.8
dtbpy	90.9	2.9	3.9	67.5
4,4'-MeO-bipy	92.4	0.8	0.0	73.7
dpk	93.8	3.1	0.0	69.6
NacNac	85.2	3.5	0.0	45.1
2,6-MePh-NacNac	85.9	2.8	0.0	45.1
2-picolinamidine	97.1	1.6	0.0	80.6
2,2'-bis(2-oxazoline)	97.7	1.4	0.0	81.9

Me <sub>2</sub> -PyMOX	89.8	1.8	0.0	68.3
QuiMOX	91.5	1.9	0.0	74.5
Me <sub>2</sub> -QuiMOX	86.6	1.7	0.0	70.9
2-(2-pyridyl)imidazole	80.9	2.5	0.0	61.1
2-(2-pyridyl)benzimidazole	92.9	3.9	0.0	73.0
N-Ph-2-picolinimine	93.7	2.6	0.0	63.0
myosmine	91.9	2.6	0.0	68.8
DIP-H <sub>2</sub> -DI	81.5	2.7	0.0	49.7
DIP-Me <sub>2</sub> -DI	81.2	3.3	0.0	47.2
dimethylglyoxime	89.7	1.7	0.0	61.4
2-picolinamidoxime	94.0	1.6	0.0	80.1

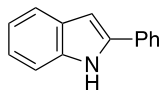
### III. Fe-Catalyzed Reductive Cyclization.

#### A. Optimized Conditions.



To a 10 mL Schlenk tube under nitrogen was added (*E*)-1-nitro-2-styrylbenzene (0.1 mmol), iron(II) acetate (0.001 mmol), 4,7-dimethoxy-1,10-phenanthroline (0.001 mmol) and 1 mL of 1,2-dimethoxyethane. Then phenylsilane (0.3 mmol) was added to the Schlenk tube. The Schlenk tube was sealed, and the reaction mixture was stirred at 80 °C for 12 h. Then the reaction mixture was cooled to room temperature and extracted with 3 × 10 mL EtOAc followed by washing with 10 mL of H<sub>2</sub>O and 10 mL of brine. The combined organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and filtered. The filtrate was concentrated *in vacuo*, and the crude mixture was purified by MPLC (3:97 – 20:80 EtOAc:hexane) to afford the product.

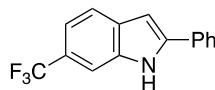
## B. Characterization Data.



**2.2a**

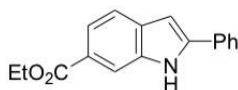
**2-Phenylindole (2.2a).** The optimized method was followed using 0.0225 g of nitrostilbene **2.1a** (0.100 mmol), 0.00017 g of Fe(OAc)<sub>2</sub> (0.001 mmol), 0.00024 g of 4,7-dimethoxy-1,10-phenanthroline (0.001 mmol), 0.0324 g of PhSiH<sub>3</sub> (0.300 mmol) and 1.0 mL of DME. Purification via MPLC (3:97 – 20:80 EtOAc:hexanes) afforded **2.2a** as a yellow solid (0.0711 g, 96%). The spectral data of **2.2a** matched that reported by Driver and co-workers: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 8.33 (br s, 1H), 7.68 (t, *J* = 6.5 Hz, 2H), 7.47 (t, *J* = 7.8 Hz, 2H), 7.42 (d, *J* = 8.1 Hz, 1H), 7.35 (t, *J* = 7.4 Hz 1H), 7.23 (t, *J* = 7.0 Hz, 2H), 7.16 (t, *J* = 7.0 Hz, 1H), 6.86 (d, *J* = 1.3 Hz, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 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), 100.0 (CH); IR (thin film): 3446, 1457, 1403, 1352, 798, 763, 741, 688 cm<sup>-1</sup>.



### 2.2b

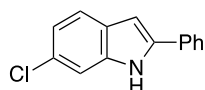
**2-Phenyl-6-(trifluoromethyl)-1H-indole (2.2b).** The optimized method was followed using 0.0262 g of nitrostilbene **2.1b** (0.100 mmol), 0.00017 g of Fe(OAc)<sub>2</sub> (0.001 mmol), 0.00024 g of 4,7-dimethoxy-1,10-phenanthroline (0.001 mmol), 0.0324 g of PhSiH<sub>3</sub> (0.300 mmol) and 1.0 mL of DME. Purification via MPLC (3:97 – 20:80 EtOAc:hexanes) afforded **2.2b** as a yellow solid (0.0235 g, 90%). The spectral data of **2.2b** matched that reported by Driver and co-workers: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 8.56 (br s, 1H), 7.71 – 7.69 (m, 4H), 7.48 (t, *J* = 7.7 Hz, 2H), 7.38 (dd, *J* = 7.7, 14.6 Hz, 2H), 6.88 (d, *J* = 1.5 Hz, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 140.6 (C), 135.6 (C), 131.6 (C), 131.6 (C), 129.2 (CH), 128.5 (CH), 125.4 (CH), 124.1 (q, *J*<sub>CF</sub> = 268.8 Hz, C), 120.9 (CH), 117.0 (q, *J*<sub>CF</sub> = 3.8 Hz CH), 108.4 (C), 108.4 (CH), 100.1 (CH), only peaks visible; <sup>19</sup>F NMR (CDCl<sub>3</sub>, 282 MHz) δ –60.1, IR (thin film): 3444, 1456, 1342, 1155, 1105, 829, 766, 690 cm<sup>-1</sup>.



### 2.2c

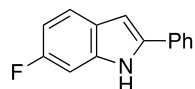
**Ethyl 2-phenyl-1H-indole-6-carboxylate (2.2c).** The optimized method was followed using 0.0251 g of nitrostilbene **2.1c** (0.100 mmol), 0.00017 g of Fe(OAc)<sub>2</sub> (0.001 mmol), 0.00024 g of 4,7-dimethoxy-1,10-phenanthroline (0.001 mmol), 0.0324 g of PhSiH<sub>3</sub> (0.300 mmol) and 1.0 mL

of DME. Purification via MPLC (3:97 – 30:70 EtOAc:hexanes) afforded **2.2c** as a yellow solid (0.0261 g, 98%). The spectral data of **2.2c** matched that reported by Driver and co-workers:  $^1\text{H}$  NMR (DMSO- $d_6$ , 500 MHz)  $\delta$  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);  $^{13}\text{C}$  NMR (DMSO- $d_6$ , 125 MHz)  $\delta$  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<sub>2</sub>), 14.8 (CH<sub>3</sub>); IR (thin film): 3353, 2922, 2853, 1691, 1619, 1452, 1367, 1319, 1283, 1260, 1217  $\text{cm}^{-1}$ .



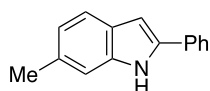
**2.2d**

**6-Chloro-2-phenyl-1H-indole (2.2d).** The optimized method was followed using 0.0228 g of nitrostilbene **2.1d** (0.100 mmol), 0.00017 g of Fe(OAc)<sub>2</sub> (0.001 mmol), 0.00024 g of 4,7-dimethoxy-1,10-phenanthroline (0.001 mmol), 0.0324 g of PhSiH<sub>3</sub> (0.300 mmol) and 1.0 mL of DME. Purification via MPLC (3:97 – 20:80 EtOAc:hexanes) afforded **2.2d** as a yellow solid (0.0219 g, 96%). The spectral data of **2.2d** matched that reported by Driver and co-workers:  $^1\text{H}$  NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$  8.31 (br s, 1H), 7.64 (d,  $J$  = 7.9 Hz, 2H), 7.53 (d,  $J$  = 8.4 Hz, 1H), 7.45 (t,  $J$  = 7.7 Hz, 2H), 7.39 (s, 1H), 7.35 (t,  $J$  = 7.4 Hz, 1H), 7.09 (d,  $J$  = 8.4 Hz, 1H), 6.79 (s, 1H);  $^{13}\text{C}$  NMR (CDCl<sub>3</sub>, 125 MHz)  $\delta$  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, 1537, 1485, 1451, 1346, 1230, 1065  $\text{cm}^{-1}$ .



## 2.2e

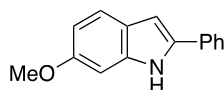
**6-Fluoro-2-phenyl-1H-indole (2.2e).** The optimized method was followed using 0.0211 g of nitrostilbene **2.1e** (0.100 mmol), 0.00017 g of Fe(OAc)<sub>2</sub> (0.001 mmol), 0.00024 g of 4,7-dimethoxy-1,10-phenanthroline (0.001 mmol), 0.0324 g of PhSiH<sub>3</sub> (0.300 mmol) and 1.0 mL of DME. Purification via MPLC (3:97 – 20:80 EtOAc:hexanes) afforded **2.2e** as a yellow solid (0.0186 g, 88%). The spectral data of **2.2e** matched that reported by Driver and co-workers: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 8.33 (br s, 1H), 7.63 (d, *J* = 7.5 Hz, 2H), 7.54 (dd, *J* = 5.4, 8.6 Hz, 1H), 7.45 (t, *J* = 7.7 Hz, 2H), 7.33 (t, *J* = 7.4 Hz, 1H), 7.09 (dd, *J* = 1.8, 9.5 Hz, 1H), 6.92 – 6.88 (m, 1H), 6.80 (d, *J* = 1.9 Hz, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 160.1 (C, d, *J* = 242.4 Hz), 138.4 (C), 136.8 (C, d, *J* = 12.4 Hz), 132.2 (C), 129.1 (CH), 127.8 (CH), 125.8 (C), 125.0 (CH), 121.4 (CH, d, *J* = 10.0 Hz), 109.1 (CH, d, *J* = 24.4 Hz), 99.9 (CH), 97.3 (CH, d, *J* = 26.2 Hz); <sup>19</sup>F NMR (CDCl<sub>3</sub>, 282 MHz) δ –119.9; IR (thin film): 3433, 1497, 1446, 1356, 1255, 1142, 813, 757 cm<sup>–1</sup>.



## 2.2f

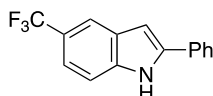
**6-Methyl-2-phenyl-1H-indole (2.2f).** The optimized method was followed using 0.0207 g of nitrostilbene **2.1f** (0.100 mmol), 0.00017 g of Fe(OAc)<sub>2</sub> (0.001 mmol), 0.00024 g of 4,7-dimethoxy-1,10-phenanthroline (0.001 mmol), 0.0324 g of PhSiH<sub>3</sub> (0.300 mmol) and 1.0 mL of DME. Purification via MPLC (3:97 – 20:80 EtOAc:hexanes) afforded **2.2f** as a yellow solid (0.0178 g, 86%). The spectral data of **2.2f** matched that reported by Driver and co-workers: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 8.20 (br s, 1H), 7.65 (d, 2H, *J* = 7.3 Hz), 7.53 (d, 1H, *J* = 8.0 Hz), 7.44 (t, 2H, *J* = 7.8 Hz), 7.32 (t, 1H, *J* = 7.4 Hz), 7.20 (s, 1H), 6.98 (d, 1H, *J* = 8.0 Hz), 6.80 (d, 1H, *J* = 1.3 Hz), 2.49 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 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<sub>3</sub>); IR (thin film): 3429, 1454, 1350, 1232, 814, 760, 740, 686 cm<sup>-1</sup>.



### 2.2g

**6-Methoxy-2-phenyl-1H-indole (2.2g).** The optimized method was followed using 0.0223 g of nitrostilbene **2.1g** (0.100 mmol), 0.00017 g of Fe(OAc)<sub>2</sub> (0.001 mmol), 0.00024 g of 4,7-dimethoxy-1,10-phenanthroline (0.001 mmol), 0.0324 g of PhSiH<sub>3</sub> (0.300 mmol) and 1.0 mL of DME. Purification via MPLC (3:97 – 20:80 EtOAc:hexanes) afforded **2.2e** as a yellow solid (0.0217 g, 97%). The spectral data of **2.2g** matched that reported by Driver and co-workers: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 8.24 (br s, 1H), 7.62 (d, *J* = 7.6 Hz, 2H), 7.50 (d, *J* = 8.6 Hz, 1H), 7.43 (t, *J* = 7.7 Hz, 2H), 7.30 (t, *J* = 7.4 Hz, 1H), 6.90 (s, 1H), 6.81 (dd, *J* = 1.9, 8.6 Hz, 1H), 6.77 (s, 1H), 3.87 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 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<sub>3</sub>); IR (thin film): 3388, 2924, 2853, 1621, 1598, 1452, 1258, 1203, 1157, 1117, 1019 cm<sup>-1</sup>.

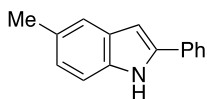


### 2.2h

**2-Phenyl-5-(trifluoromethyl)-1H-indole (2.2h).** The optimized method was followed using 0.0261 g of nitrostilbene **2.1h** (0.100 mmol), 0.00017 g of Fe(OAc)<sub>2</sub> (0.001 mmol), 0.00024 g of 4,7-dimethoxy-1,10-phenanthroline (0.001 mmol), 0.0324 g of PhSiH<sub>3</sub> (0.300 mmol) and 1.0 mL of DME. Purification via MPLC (3:97 – 20:80 EtOAc:hexanes) afforded **2.2h** as a yellow solid

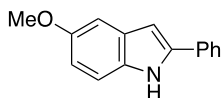


(0.0214 g, 82%). The spectral data of **2.2h** matched that reported by Driver and co-workers:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  8.50 (br s, 1H), 7.93 (s, 1H), 7.68 (d,  $J = 7.5$  Hz, 2H), 7.49 – 7.42 (m, 4H), 7.38 (t,  $J = 7.3$  Hz, 1H), 6.90 (d,  $J = 1.6$  Hz, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  139.7 (C), 138.1 (C), 131.7 (C), 129.2 (CH), 128.6 (C), 128.3 (CH), 125.3 (CH), 124.2 (q,  $J_{\text{CF}} = 266.3$  Hz, C), 122.8 (q,  $J_{\text{CF}} = 30.3$  Hz, C), 119.0 (CH), 118.3 (CH), 111.1 (CH), 100.6 (CH);  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ , 282 MHz)  $\delta$  –60.1; IR (thin film): 3432, 1496, 1449, 1355, 1338, 1130, 1102  $\text{cm}^{-1}$ .



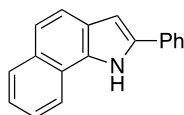
**2.2i**

**5-Methyl-2-phenyl-1H-indole (2.2i).** The optimized method was followed using 0.0207 g of nitrostilbene **1i** (0.100 mmol), 0.00017 g of  $\text{Fe}(\text{OAc})_2$  (0.001 mmol), 0.00024 g of 4,7-dimethoxy-1,10-phenanthroline (0.001 mmol), 0.0324 g of  $\text{PhSiH}_3$  (0.300 mmol) and 1.0 mL of DME. Purification via MPLC (3:97 – 20:80 EtOAc:hexanes) afforded **2.2i** as a yellow solid (0.0199 g, 96%). The spectral data of **2.2i** matched that reported by Driver and co-workers:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  8.24 (br s, 1H), 7.66 (d,  $J = 7.5$  Hz, 2H), 7.46 – 7.43 (m, 3H), 7.33 – 7.29 (m, 2H), 7.02 (d,  $J = 8.0$  Hz, 1H), 6.76 (s, 1H), 2.45 (s, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  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 ( $\text{CH}_3$ ); IR (thin film): 3405, 2918, 2852, 1457, 1317, 1299, 1203, 1072  $\text{cm}^{-1}$ .



**2.2j**

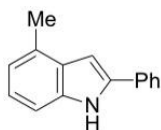
**5-Methoxy-2-phenyl-1H-indole (2.2j).** The optimized method was followed using 0.0223 g of nitrostilbene **2.1j** (0.100 mmol), 0.00017 g of Fe(OAc)<sub>2</sub> (0.001 mmol), 0.00024 g of 4,7-dimethoxy-1,10-phenanthroline (0.001 mmol), 0.0324 g of PhSiH<sub>3</sub> (0.300 mmol) and 1.0 mL of DME. Purification via MPLC (3:97 – 20:80 EtOAc:hexanes) afforded **2.2j** as a yellow solid (0.0179 g, 80%). The spectral data of **2.2j** matched that reported by Driver and co-workers: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 8.24 (br s, 1H), 7.66 – 7.64 (m, 2H), 7.44 (t, *J* = 7.7 Hz, 2H), 7.32 (t, *J* = 7.4 Hz, 1H), 7.29 (d, *J* = 8.7 Hz, 1H), 7.10 (d, *J* = 2.3 Hz, 1H), 6.87 (dd, *J* = 8.7, 2.4 Hz, 1H), 6.77 (d, *J* = 1.4 Hz, 1H), 3.88 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 154.5 (C), 138.6 (C), 132.5 (C), 132.0 (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<sub>3</sub>); IR (thin film): 3426, 2999, 2919, 2842, 1619, 1539, 1476, 1456, 1215, 1150, 1028 cm<sup>-1</sup>.



**2.2k**

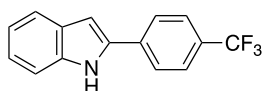
**2-Phenyl-1H-benzo[g]indole (2.2k).**{Fang, 2008 #1736} The optimized method was followed using 0.0243 g of nitrostilbene **2.1k** (0.100 mmol), 0.00017 g of Fe(OAc)<sub>2</sub> (0.001 mmol), 0.00024 g of 4,7-dimethoxy-1,10-phenanthroline (0.001 mmol), 0.0324 g of PhSiH<sub>3</sub> (0.300 mmol) and 1.0 mL of DME. Purification via MPLC (3:97 – 20:80 EtOAc:hexanes) afforded **2.2k** as a yellow solid (0.0238 g, 98%). The spectral data of **2.2k** matched that reported by Fang and Lautens:{Fang, 2008 #1736} <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 9.04 (br s, 1H), 8.08 (d, *J* = 8.2 Hz, 1H), 7.94 (d, *J* = 8.1 Hz, 1H), 7.75 – 7.72 (m, 3H), 7.58 – 7.53 (m, 2H), 7.50 – 7.43 (m, 3H), 7.34 (t, *J* = 7.4 Hz, 1H), 6.97 (d, *J* = 2.2 Hz, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 136.3 (C), 132.5 (C), 131.4 (C),

130.6 (C), 129.1 (CH), 129.1 (CH), 127.5 (CH), 125.6 (CH), 125.3 (C), 125.0 (CH), 124.0 (CH), 121.6 (C), 121.2 (CH), 120.7 (CH), 119.4 (CH), 101.7 (CH); IR (thin film): 3370, 3051, 2924, 1702, 1629, 1605, 1527, 1487, 1451, 1362, 1315, 1261, 1126, 1134, 1090, 1029  $\text{cm}^{-1}$ .



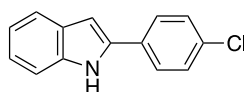
### 2.2l

**4-Methyl-2-phenyl-1H-indole (2.2l).** The optimized method was followed using 0.0207 g of nitrostilbene **2.1l** (0.100 mmol), 0.00017 g of  $\text{Fe}(\text{OAc})_2$  (0.001 mmol), 0.00024 g of 4,7-dimethoxy-1,10-phenanthroline (0.001 mmol), 0.0324 g of  $\text{PhSiH}_3$  (0.300 mmol) and 1.0 mL of DME. Purification via MPLC (3:97 – 20:80 EtOAc:hexanes) afforded **2.2l** as a tan solid (0.0162 g, 78%). The spectral data of **2.2l** matched that reported by Buchwald and co-workers:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  8.33 (s, 1H), 7.68 (d,  $J = 7.7$  Hz, 2H), 7.46 (t,  $J = 7.5$  Hz, 2H), 7.34 (t,  $J = 7.3$  Hz, 1H), 7.26 (d,  $J = 7.2$  Hz, 1H), 7.13 (t,  $J = 7.6$  Hz, 1H), 6.95 (d,  $J = 7.0$  Hz, 1H), 6.87 (s, 1H), 2.61 (s, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  137.3 (C), 136.6 (C), 132.5 (C), 130.3 (C), 129.2 (C), 129.0 (CH), 127.6 (CH), 125.1 (CH), 122.5 (CH), 120.4 (CH), 108.5 (CH), 98.6 (CH), 18.8 (CH<sub>3</sub>); IR (thin film): 3420, 3054, 2920, 2855, 1603, 1486, 1450, 1402, 1354, 1336, 1295, 1074, 755, 690  $\text{cm}^{-1}$ .



### 2.2m

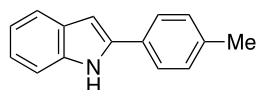
**2-(4-(Trifluoromethyl)phenyl)-1H-indole (2.2m).** The optimized method was followed using 0.0261 g of nitrostilbene **2.1m** (0.100 mmol), 0.00017 g of Fe(OAc)<sub>2</sub> (0.001 mmol), 0.00024 g of 4,7-dimethoxy-1,10-phenanthroline (0.001 mmol), 0.0324 g of PhSiH<sub>3</sub> (0.300 mmol) and 1.0 mL of DME. Purification via MPLC (3:97 – 20:80 EtOAc:hexanes) afforded **2.2m** as a yellow solid (0.0256 g, 98%). The spectral data of **2.2m** matched that reported by Driver and co-workers: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 8.39 (br s, 1H), 7.76 (d, *J* = 8.2 Hz, 2H), 7.70 (d, *J* = 8.2 Hz, 2H), 7.66 (d, *J* = 7.8 Hz, 1H), 7.43 (d, *J* = 8.1 Hz, 1H), 7.24 (d, *J* = 7.4 Hz, 1H), 7.15 (t, *J* = 7.4 Hz, 1H), 6.93 (s, 1H); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>, 125 MHz) δ 138.0 (C), 136.7 (C), 128.9 (C), 127.9 (C), 126.3 (q, *J*<sub>CF</sub> = 3.5 Hz, C), 125.8 (CH), 124.8 (q, *J*<sub>CF</sub> = 270.0 Hz, C), 122.9 (CH), 121.0 (CH), 120.2 (CH), 112.0 (CH), 101.2 (CH); only peaks visible, <sup>19</sup>F NMR (CDCl<sub>3</sub>, 282 MHz) δ -62.6, IR (thin film): 3425, 2927, 2853, 1612, 1426, 1325, 1168, 1111, 1073, 1011 cm<sup>-1</sup>.



**2.2n**

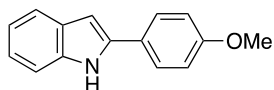
**2-(4-Chlorophenyl)-1H-indole (2.2n).** The optimized method was followed using 0.0228 g of nitrostilbene **2.1n** (0.100 mmol), 0.00017 g of Fe(OAc)<sub>2</sub> (0.001 mmol), 0.00024 g of 4,7-dimethoxy-1,10-phenanthroline (0.001 mmol), 0.0324 g of PhSiH<sub>3</sub> (0.300 mmol) and 1.0 mL of DME. Purification via MPLC (3:97 – 20:80 EtOAc:hexanes) afforded **2.2n** as a yellow solid (0.0200 g, 88%). The spectral data of **2.2n** matched that reported by Driver and co-workers: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 8.28 (br s, 1H), 7.64 (d, *J* = 7.9 Hz, 1H), 7.58 (d, *J* = 8.6 Hz, 2H), 7.42 – 7.39 (m, 3H), 7.23 – 7.20 (m, 1H), 7.16 – 7.13 (m, 1H), 6.81 (dd, *J* = 2.1, 0.8 Hz, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 136.9 (C), 136.7 (C), 133.5 (C), 130.9 (C), 129.2 (CH), 129.2 (C), 126.3

(CH), 122.7 (CH), 120.8 (CH), 120.5 (CH), 111.0 (CH), 100.5 (CH); IR (thin film): 3432, 2923, 2852, 1728, 1481, 1453, 1425, 1348, 1299, 1260, 1095  $\text{cm}^{-1}$ .



### 2.2o

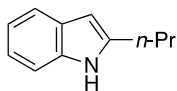
**2-(*p*-Tolyl)-1H-indole (2.2o).**{Fang, 2008 #1736} The optimized method was followed using 0.0207 g of nitrostilbene **2.1o** (0.100 mmol), 0.00017 g of  $\text{Fe}(\text{OAc})_2$  (0.001 mmol), 0.00024 g of 4,7-dimethoxy-1,10-phenanthroline (0.001 mmol), 0.0324 g of  $\text{PhSiH}_3$  (0.300 mmol) and 1.0 mL of DME. Purification via MPLC (3:97 – 20:80 EtOAc:hexanes) afforded **2.2o** as a yellow solid (0.0172 g, 83%). The spectral data of **2.2o** matched that reported Fang and Lautens:{Fang, 2008 #1736}  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  8.30 (br s, 1H), 7.63 (d,  $J = 7.8$  Hz, 1H), 7.57 (d,  $J = 8.1$  Hz, 2H), 7.39 (d,  $J = 8.0$  Hz, 1H), 7.26 (d,  $J = 8.0$  Hz, 3H), 7.20 – 7.17 (m, 1H), 7.14 – 7.11 (m, 1H), 6.79 (d,  $J = 1.5$  Hz, 1H), 2.40 (s, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  138.1 (C), 137.7 (C), 136.7 (C), 129.7 (CH), 129.6 (C), 129.4 (C), 125.1 (CH), 122.1 (CH), 120.5 (CH), 120.2 (CH), 110.8 (CH), 99.4 (CH), 21.3 ( $\text{CH}_3$ ); IR (thin film): 3439, 3003, 2915, 1712, 1502, 1423, 1361, 1299, 1220, 1092  $\text{cm}^{-1}$ .



### 2.2p

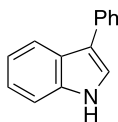
**2-(4-Methoxyphenyl)-1H-indole (2.2p).** The optimized method was followed using 0.0223 g of nitrostilbene **2.1p** (0.100 mmol), 0.00017 g of  $\text{Fe}(\text{OAc})_2$  (0.001 mmol), 0.00024 g of 4,7-dimethoxy-1,10-phenanthroline (0.001 mmol), 0.0324 g of  $\text{PhSiH}_3$  (0.300 mmol) and 1.0 mL of

DME. Purification via MPLC (3:97 – 20:80 EtOAc:hexanes) afforded **2.2p** as a yellow solid (0.0205 g, 92%). The spectral data of **2.2p** matched that reported by Driver and co-workers:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  8.26 (br s, 1H), 7.61 – 7.59 (m, 3H), 7.39 (d,  $J = 8.0$  Hz, 1H), 7.17 (t,  $J = 7.6$  Hz, 1H), 7.11 (t,  $J = 7.4$  Hz, 1H), 6.99 (d,  $J = 8.8$  Hz, 2H), 6.72 (dd,  $J = 2.1, 0.8$  Hz, 1H), 3.86 (s, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  159.4 (C), 138.0 (C), 136.7 (C), 129.4 (C), 126.5 (CH), 125.2 (C), 121.9 (CH), 120.4 (CH), 120.2 (CH), 114.5 (CH), 110.7 (CH), 98.9 (CH), 55.4 ( $\text{CH}_3$ ); IR (thin film): 3427, 1606, 1500, 1452, 1430, 1286, 1248, 1179, 1113, 1048, 1024  $\text{cm}^{-1}$ .



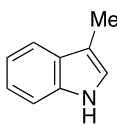
**2.2q**

**2-Propyl-1H-indole (2q).** The optimized method was followed using 0.0159 g of nitrostilbene **2.1q** (0.100 mmol), 0.00017 g of  $\text{Fe}(\text{OAc})_2$  (0.001 mmol), 0.00024 g of 4,7-dimethoxy-1,10-phenanthroline (0.001 mmol), 0.0324 g of  $\text{PhSiH}_3$  (0.300 mmol) and 1.0 mL of DME. Purification via MPLC (3:97 – 20:80 EtOAc:hexanes) afforded **2.2q** as a yellow solid (0.0156 g, 98%). The spectral data of **2.2q** matched that reported by Driver and co-workers:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  7.85 (br s, 1H), 7.54 (d,  $J = 7.7$  Hz, 1H), 7.30 (dd,  $J = 8.0, 0.8$  Hz, 1H), 7.12 (td,  $J = 7.5, 1.2$  Hz, 1H), 7.07 (td,  $J = 7.4, 0.9$  Hz, 1H), 6.25 (dd,  $J = 2.0, 0.9$  Hz, 1H), 2.74 (t,  $J = 7.5$  Hz, 2H), 1.76 (sextet,  $J = 7.5$  Hz, 2H), 1.02 (t,  $J = 7.4$  Hz, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  139.8 (C), 135.8 (C), 128.9 (C), 120.9 (CH), 119.8 (CH), 110.3 (CH), 99.6 (CH), 30.4 ( $\text{CH}_2$ ), 22.5 ( $\text{CH}_2$ ), 13.9 ( $\text{CH}_3$ ), only peaks visible; IR (thin film): 3404, 1457, 1415, 1289, 781, 750  $\text{cm}^{-1}$ .



## 2.2r

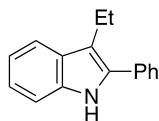
**3-Phenyl-1H-indole (2.2r).** The optimized method was followed using 0.0193 g of nitrostilbene **2.1r** (0.100 mmol), 0.00017 g of Fe(OAc)<sub>2</sub> (0.001 mmol), 0.00024 g of 4,7-dimethoxy-1,10-phenanthroline (0.001 mmol), 0.0324 g of PhSiH<sub>3</sub> (0.300 mmol) and 1.0 mL of DME. Purification via MPLC (3:97 – 20:80 EtOAc:hexanes) afforded **2.2r** as a yellow solid (0.0187 g, 97%). The spectral data of **2.2r** matched that reported by Driver and co-workers: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 8.23 (s, 1H), 7.96 (d, *J* = 7.9 Hz, 1H), 7.69 (d, *J* = 7.3 Hz, 2H), 7.47 – 7.43 (m, 3H), 7.38 (d, *J* = 2.3 Hz, 1H), 7.31 – 7.25 (m, 2H), 7.21 (t, *J* = 7.1 Hz, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 136.7 (C), 135.6 (C), 128.8 (CH), 127.5 (CH), 126.0 (CH), 125.8 (C), 122.4 (CH), 121.7 (CH), 120.3 (CH), 119.8 (CH), 118.4 (C), 111.4 (CH); IR (thin film): 3412, 3053, 1601, 1544, 1486, 1456, 1414, 1335, 1263, 1239, 1113, 1098 cm<sup>-1</sup>.



## 2.2s

**3-Methyl-1H-indole (2r).** The optimized method was followed using 0.0131 g of nitrostilbene **2.1s** (0.100 mmol), 0.00017 g of Fe(OAc)<sub>2</sub> (0.001 mmol), 0.00024 g of 4,7-dimethoxy-1,10-phenanthroline (0.001 mmol), 0.0324 g of PhSiH<sub>3</sub> (0.300 mmol) and 1.0 mL of DME. Purification via MPLC (3:97 – 20:80 EtOAc:hexanes) afforded **2.2s** as a yellow solid (0.0093 g, 71%). The spectral data of **2.2s** matched that reported by Driver and co-workers: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 7.86 (br s, 1H), 7.61 (d, *J* = 7.8 Hz, 1H), 7.36 (d, *J* = 8.1 Hz, 1H), 7.22 (t, *J* = 7.2 Hz, 1H), 7.15 (t, *J* = 7.4 Hz, 1H), 6.97 (s, 1H), 2.37 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 136.3 (C), 128.3 (C),

121.9 (CH), 121.6 (CH), 119.1 (CH), 118.9 (CH), 111.7 (C), 111.0 (CH), 9.7 (CH<sub>3</sub>); IR (thin film): 3416, 1453, 1419, 1333, 1264, 1246, 1086, 1009, 733 cm<sup>-1</sup>.



### 2.2t

**3-Ethyl-2-phenyl-1H-indole (2.2t).** The optimized method was followed using 0.0221 g of nitrostilbene **2.1t** (0.100 mmol), 0.00017 g of Fe(OAc)<sub>2</sub> (0.001 mmol), 0.00024 g of 4,7-dimethoxy-1,10-phenanthroline (0.001 mmol), 0.0324 g of PhSiH<sub>3</sub> (0.300 mmol) and 1.0 mL of DME. Purification via MPLC (3:97 – 20:80 EtOAc:hexanes) afforded **2.2t** as a yellow solid (0.0199 g, 90%). The spectral data of **2.2t** matched that reported by Driver and co-workers: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 8.00 (br s, 1H), 7.69 (d, *J* = 7.9 Hz, 1H), 7.58 (dd, *J* = 8.2, 1.2 Hz, 2H), 7.49 (t, *J* = 7.8 Hz, 2H), 7.40 – 7.38 (m, 2H), 7.25 – 7.22 (m, 1H), 7.19 – 7.16 (m, 1H), 2.95 (q, *J* = 7.6 Hz, 2H), 1.38 (t, *J* = 7.6 Hz, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 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<sub>2</sub>), 15.6 (CH<sub>3</sub>); IR (thin film): 3411, 1603, 1525, 1486, 1457, 1448, 1370, 1340, 1306, 1228, 759 cm<sup>-1</sup>.

## IV. Mechanistic Experiments

### A. Kinetics Experiments

Kinetics experiments were conducted in a glovebox in 25 mm test tubes equipped with septa and magnetic stirbars on 1 mmol scale. Reactions were conducted on an Amigochem reaction platform



equipped with an Integrity 10 parallel reaction block and a refluxing and inerting manifold thermostatted at 10 °C. Reaction tubes were charged with the appropriate volume of stock mixtures of (4,7-MeO-phen)Fe(OAc)<sub>2</sub> as a uniform thin slurry in DME and **2.1a** as a volumetric solution in DME and any remaining DME required to reach the appropriate reaction concentration (calculated to account for the volume of silane added next). The reactions were individually heated to 80 °C for 10 min to stabilize the reaction temperature, then injected with the appropriate volume of neat PhSiH<sub>3</sub>, and sampled periodically every 3 – 5 min into HPLC vials containing MeCN at r.t.

**Table S2.6.** Kinetics experiments.

Experiment	[SM] <sub>0</sub>	[PhSiH <sub>3</sub> ] <sub>0</sub>	[cat] <sub>0</sub>	-[SM] rate <sub>0</sub>	[Prod] rate <sub>0</sub>
1	0.1	0.3	0.002	1.83E-03	1.60E-03
2	0.05	0.3	0.002	1.76E-03	1.52E-03
3	0.1	0.3	0.001	7.37E-04	5.58E-04
4	0.1	0.45	0.002	2.41E-03	2.15E-03
5	0.1	0.6	0.002	3.62E-03	3.16E-03
6	0.1	0.15	0.002	7.36E-04	7.94E-04
7	0.1	0.3	0.002	1.75E-03	1.52E-03
8	0.1	0.3	0.0015	1.12E-03	1.19E-03
9	0.1	0.3	0.0005	1.14E-03	7.97E-04

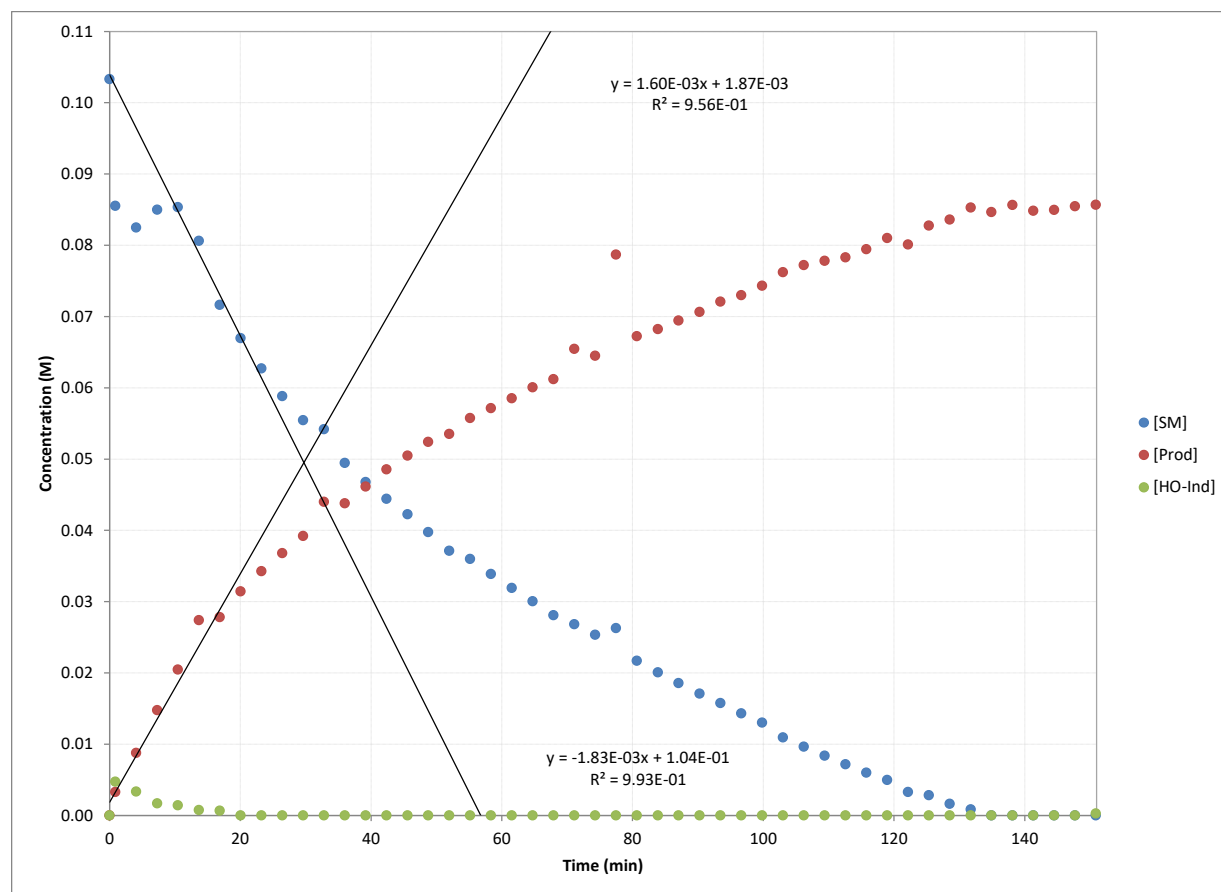
10	0.1	0.3	0.0005	1.30E-03	8.79E-04
11	0.1	0.3	0.00025	1.32E-03	9.08E-04
12	0.1	0.3	0.001	8.00E-04	5.72E-04
13	0.1	0.3	0.00075	1.20E-03	7.95E-04
14 <sup>a</sup>	0.1	0.3	0.001	9.87E-04	7.52E-04
15 <sup>b</sup>	0.1	0.3	0.001	1.15E-03	9.73E-05
16 <sup>c</sup>	0.05	0.3	0.001	1.00E-03	9.48E-04
17	0.1	0.3	0.0026	2.00E-03	1.73E-03
18	0.1	0.3	0.0030	2.74E-03	2.11E-03
19	0.1	0.3	0.0035	2.94E-03	2.43E-03
20	0.1	0.3	0.0040	2.62E-03	2.18E-03
21	0.1	0.3	0.0046	2.57E-03	2.14E-03

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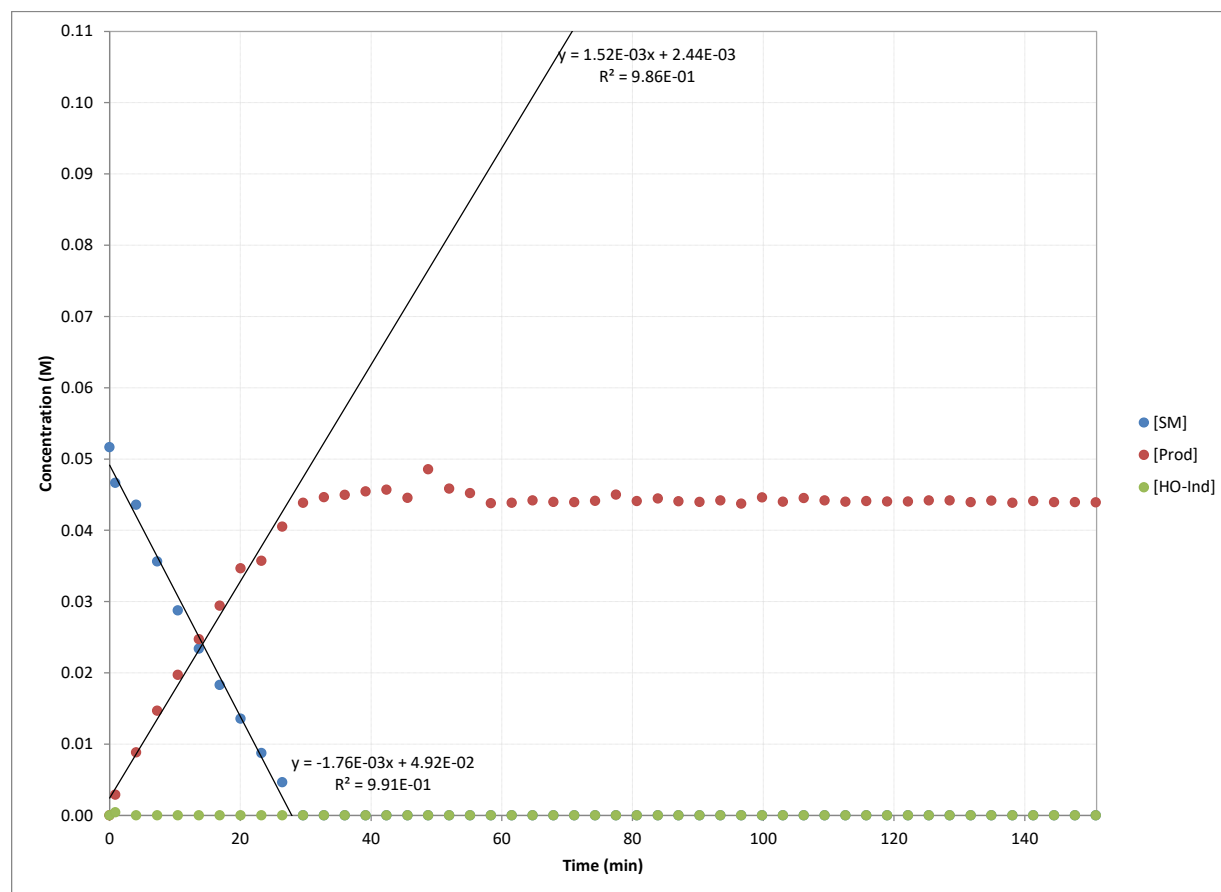
<sup>a</sup>Reaction conducted with added [**2.2a**]<sub>0</sub> = 0.1 M. <sup>b</sup>Reaction conducted instead with (neo)Fe(OAc)<sub>2</sub> catalyst.

<sup>c</sup>Reaction conducted with added [**2.2a**]<sub>0</sub> = 0.05 M.

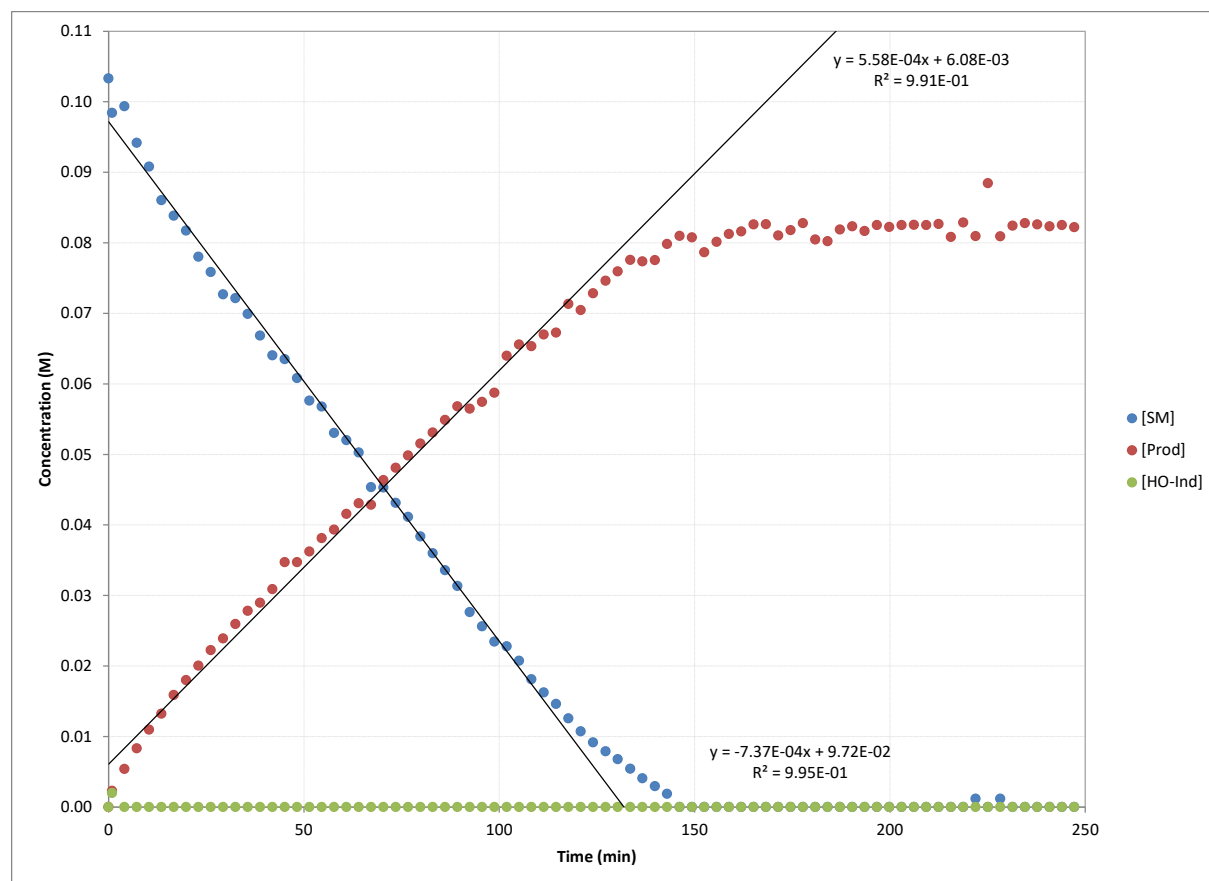
**Figure S2.1.** Kinetics experiment 1.



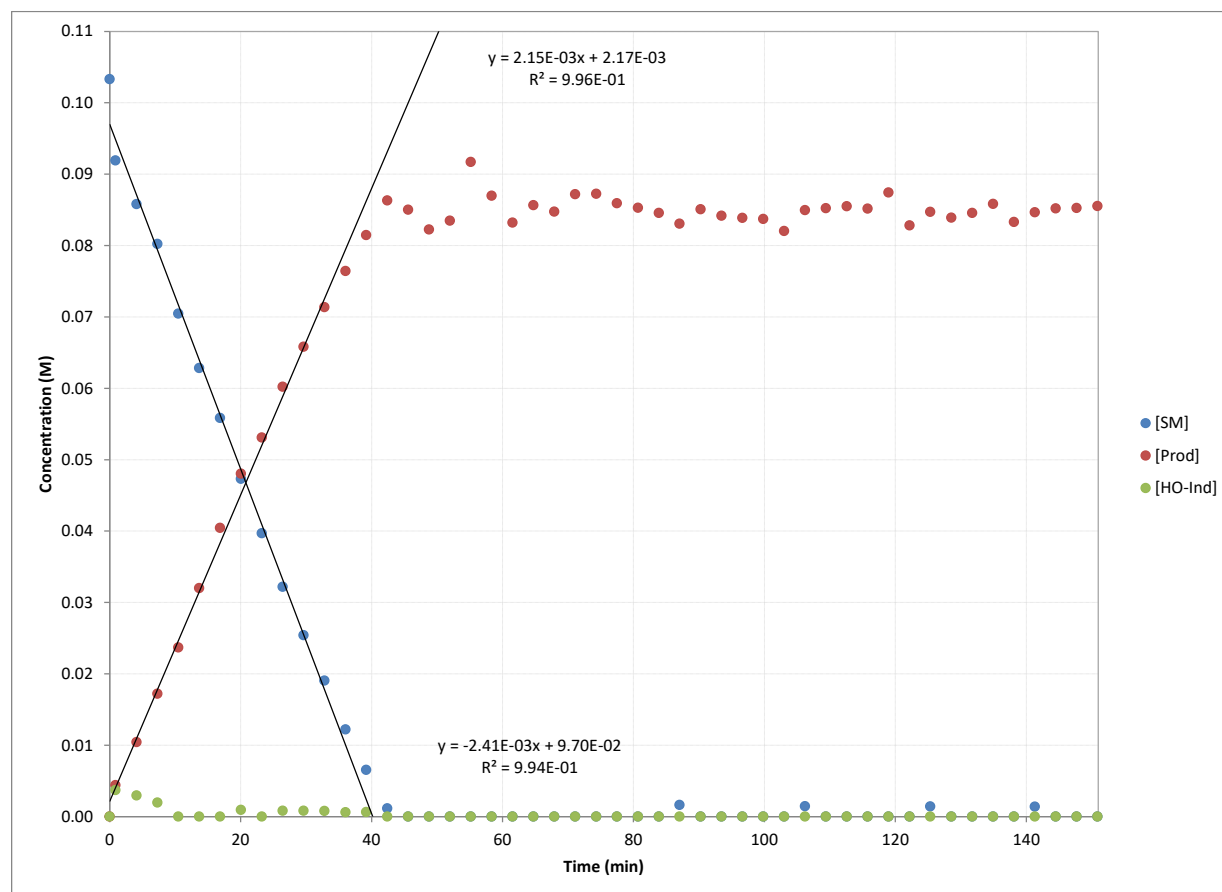
**Figure S2.2.** Kinetics experiment 2.



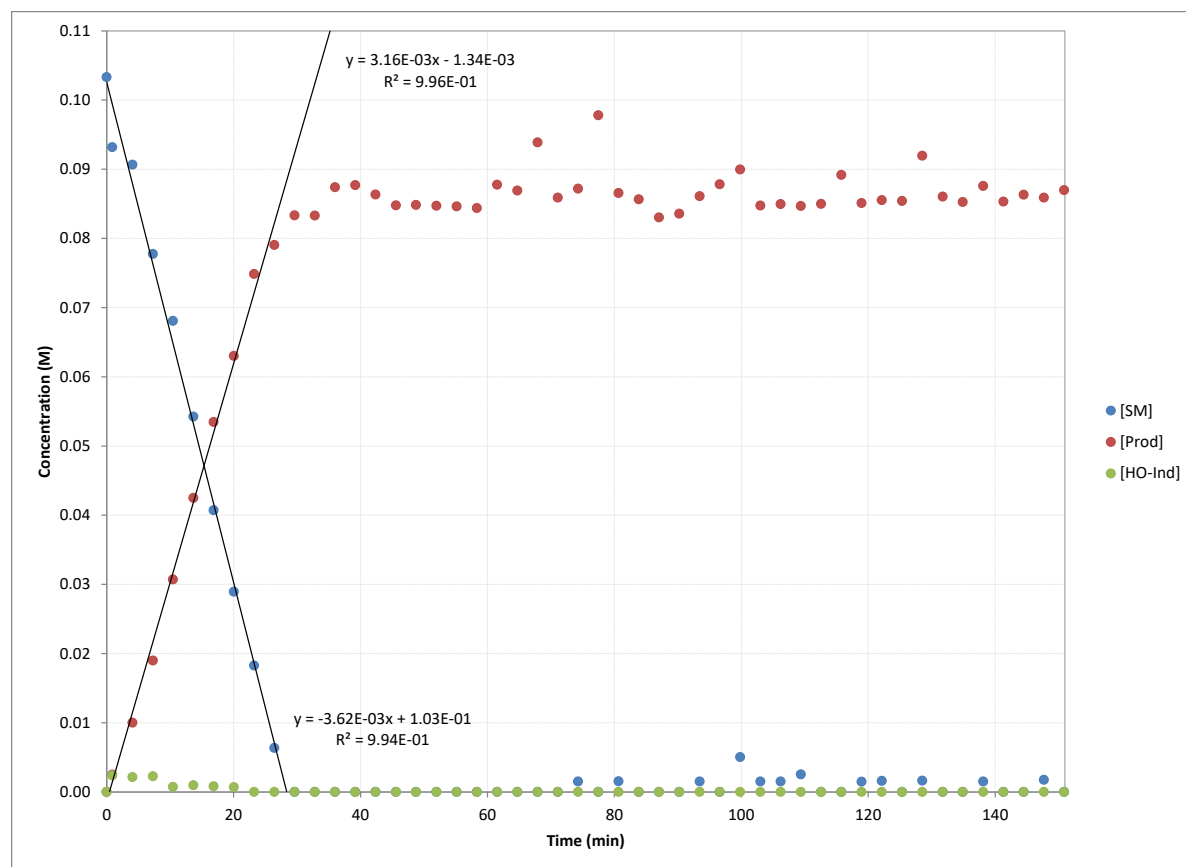
**Figure S2.3.** Kinetics experiment 3.



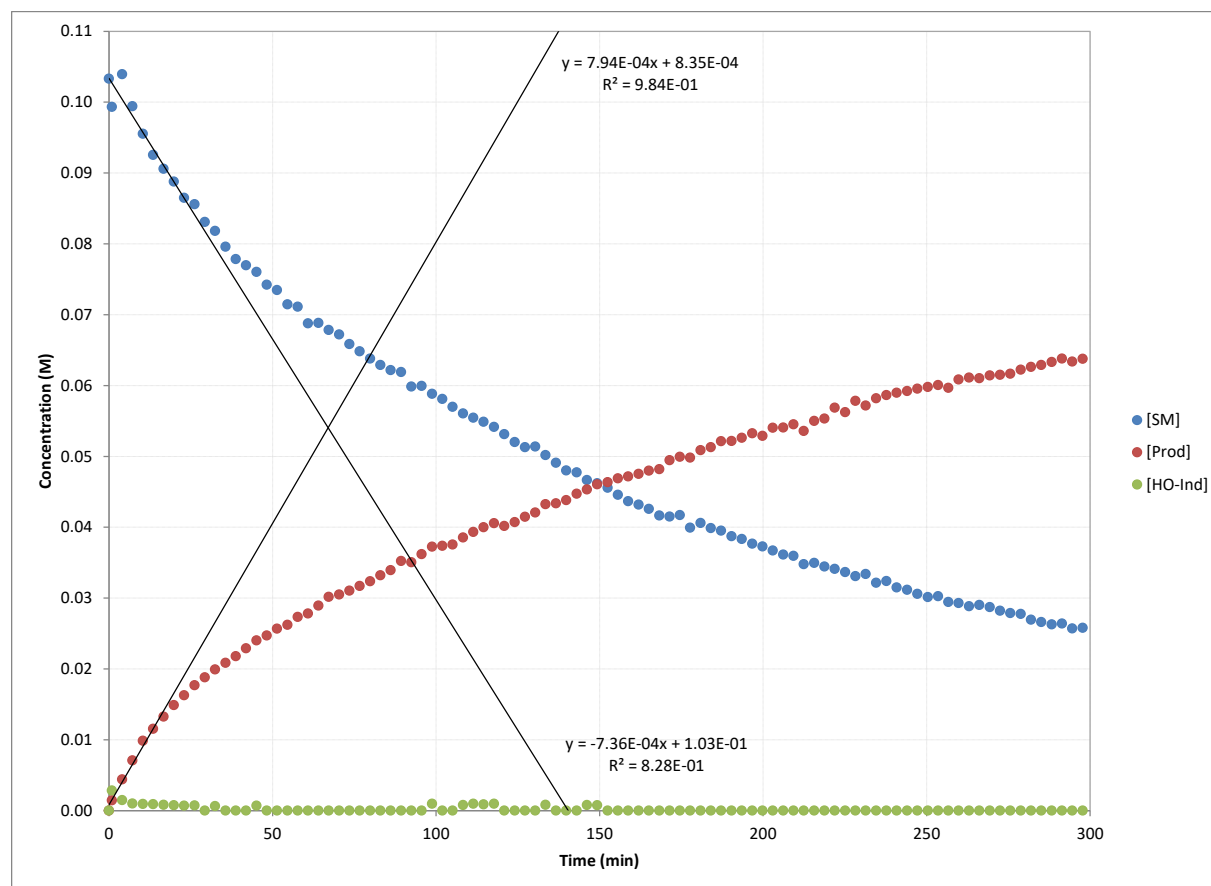
**Figure S2.4.** Kinetics experiment 4.



**Figure S2.5.** Kinetics experiment 5.

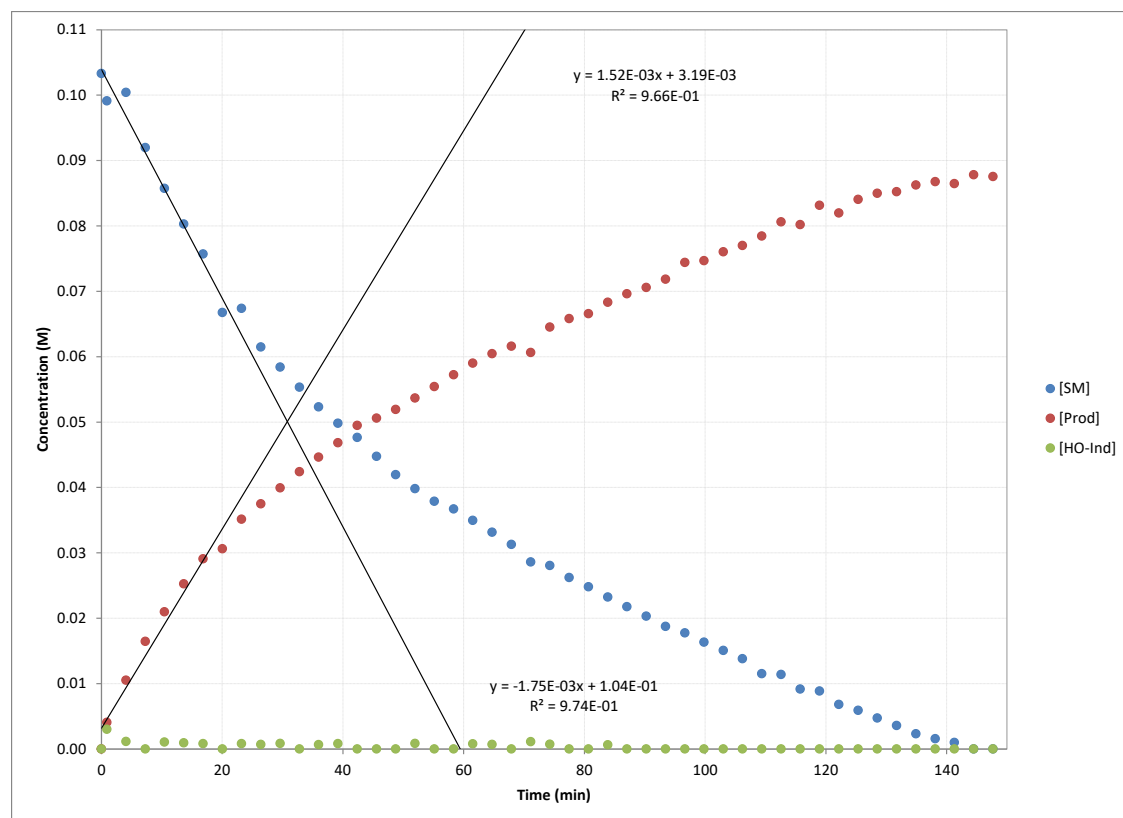


**Figure S2.6.** Kinetics experiment 6.

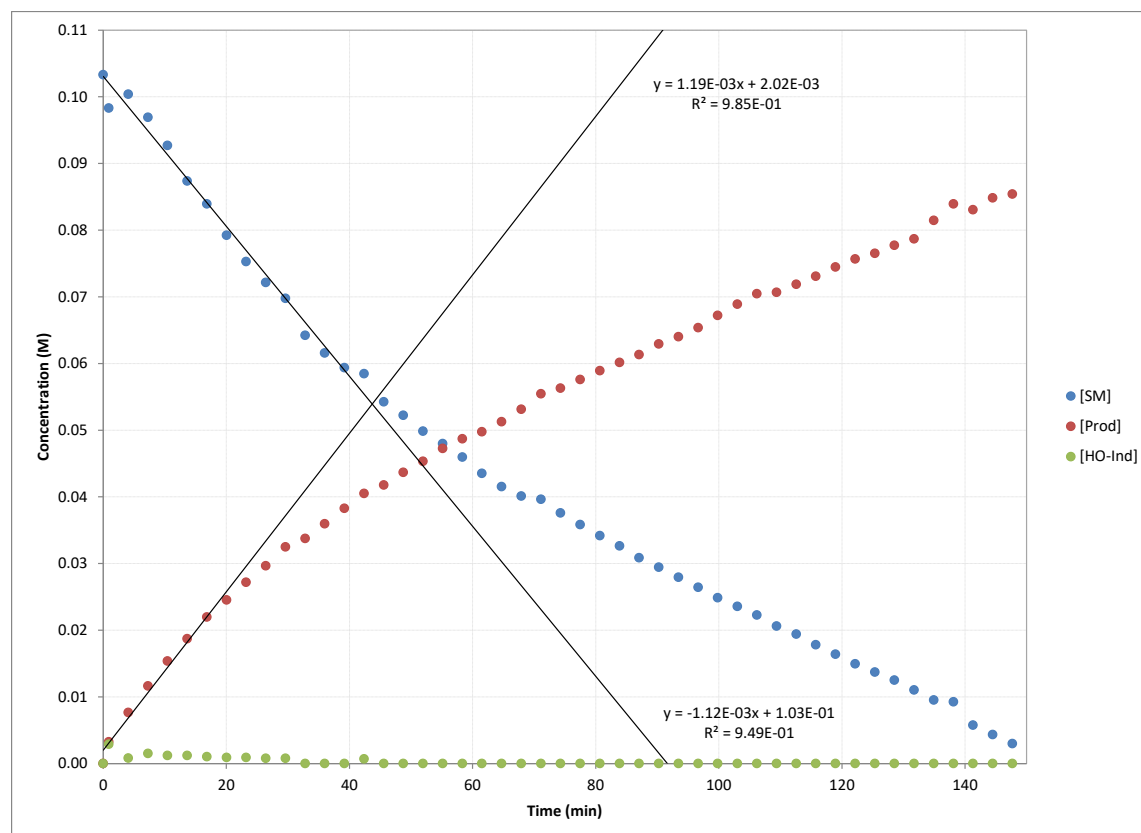




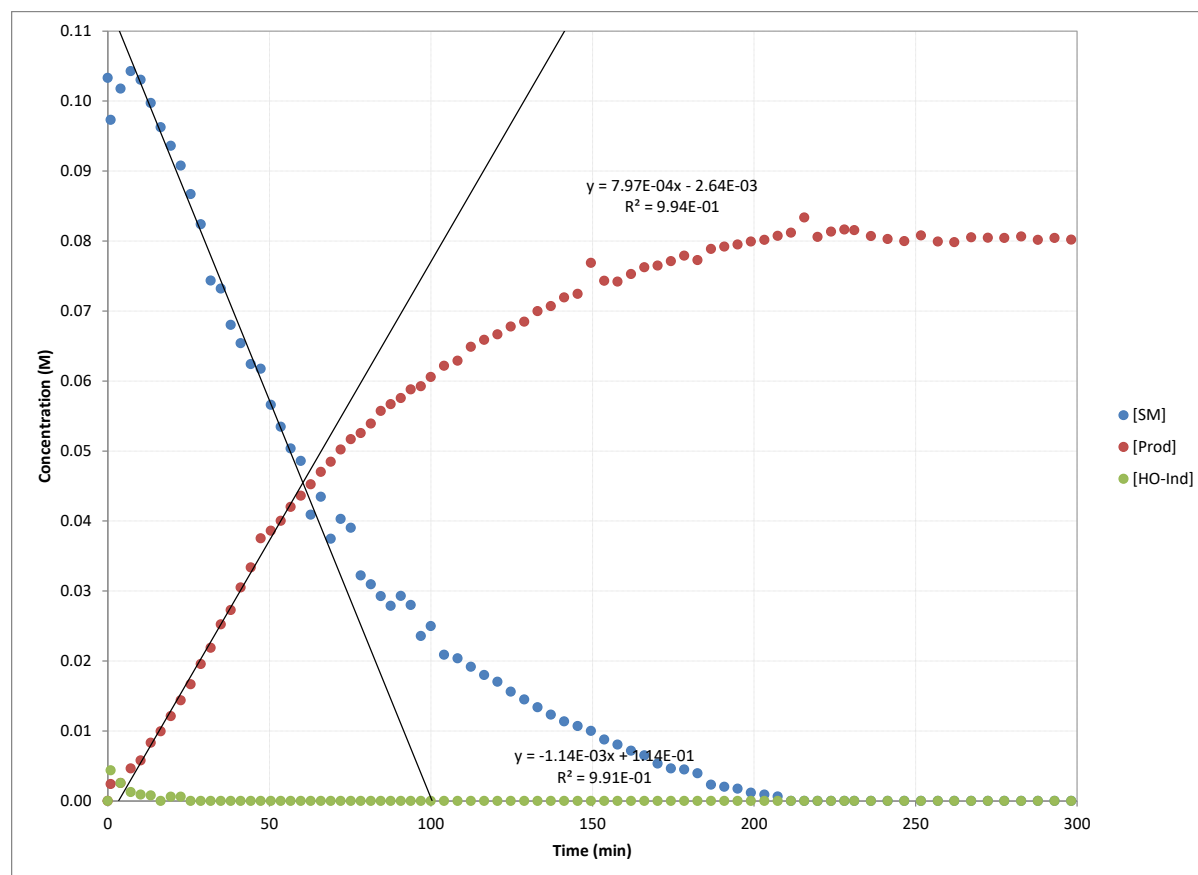
**Figure S2.7.** Kinetics experiment 7.



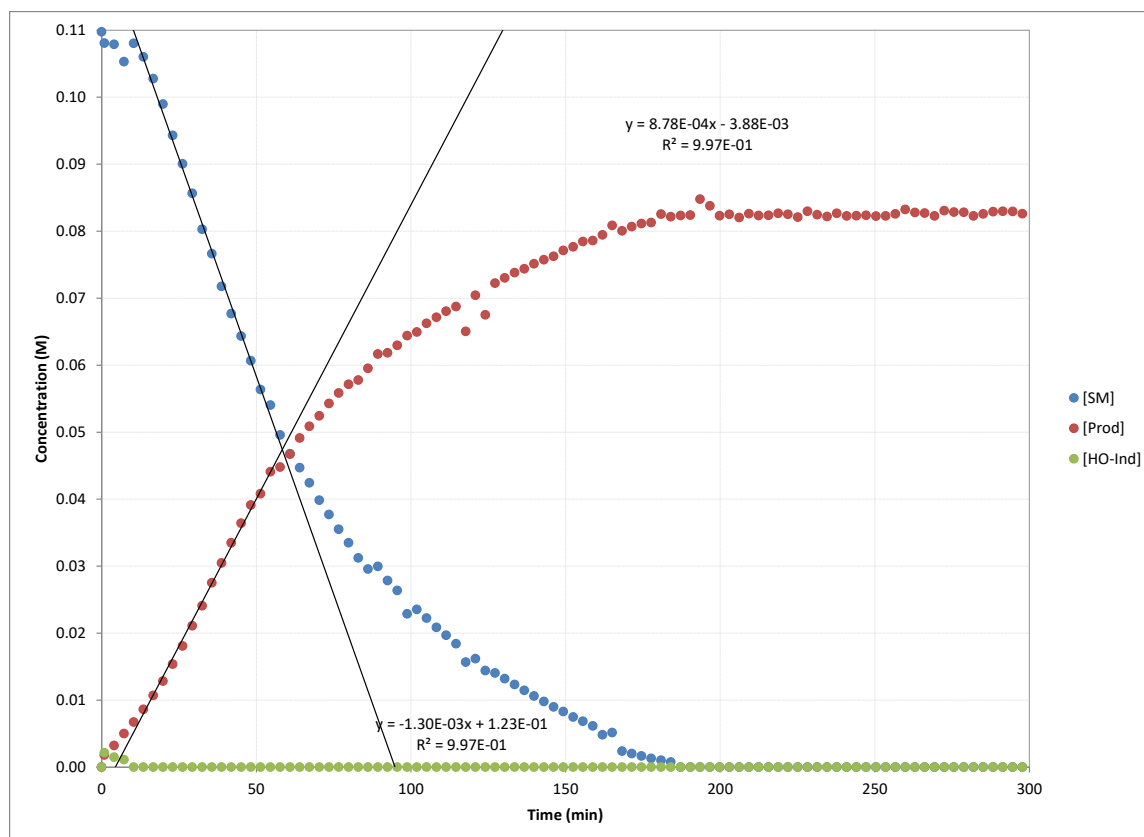
**Figure S2.8.** Kinetics experiment 8.



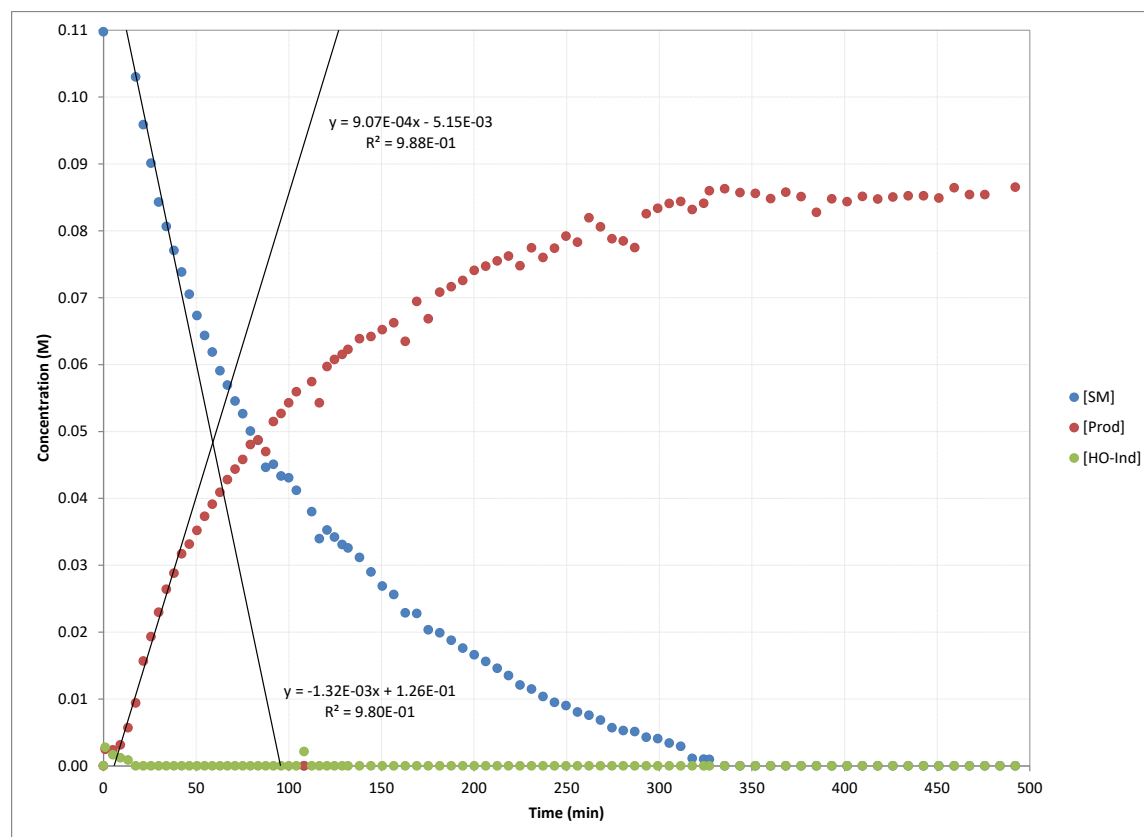
**Figure S2.9.** Kinetics experiment 9.



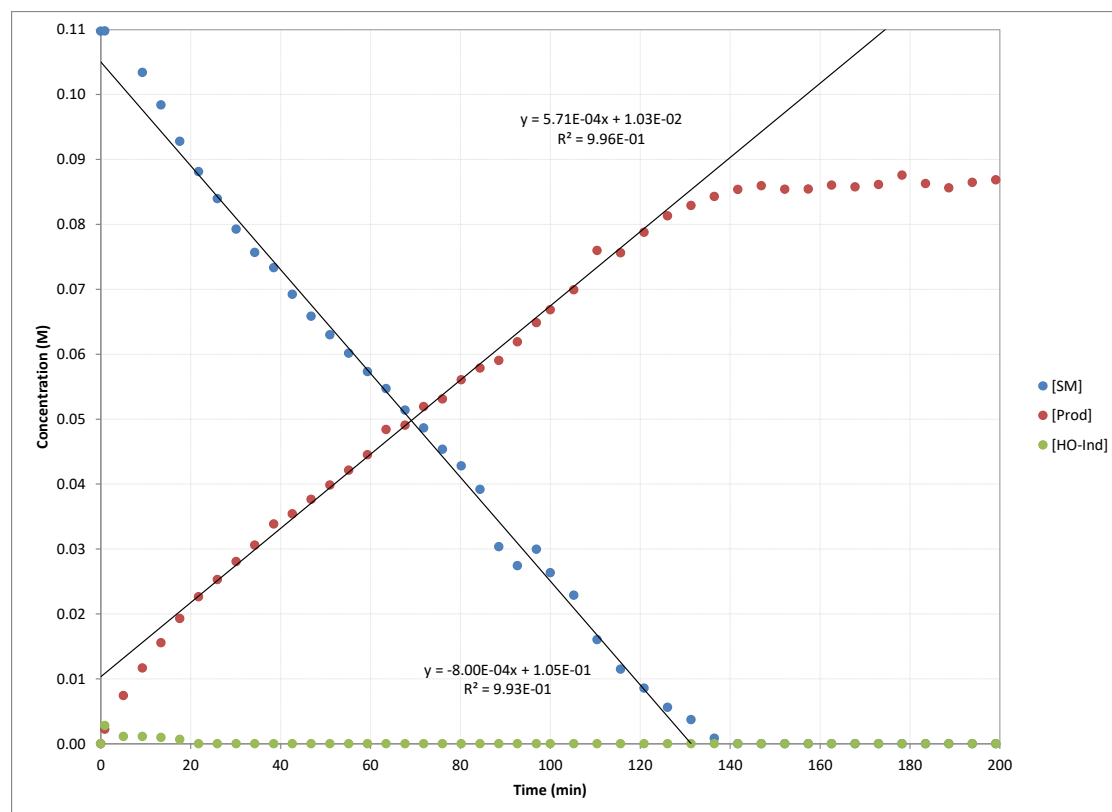
**Figure S2.10.** Kinetics experiment 10.



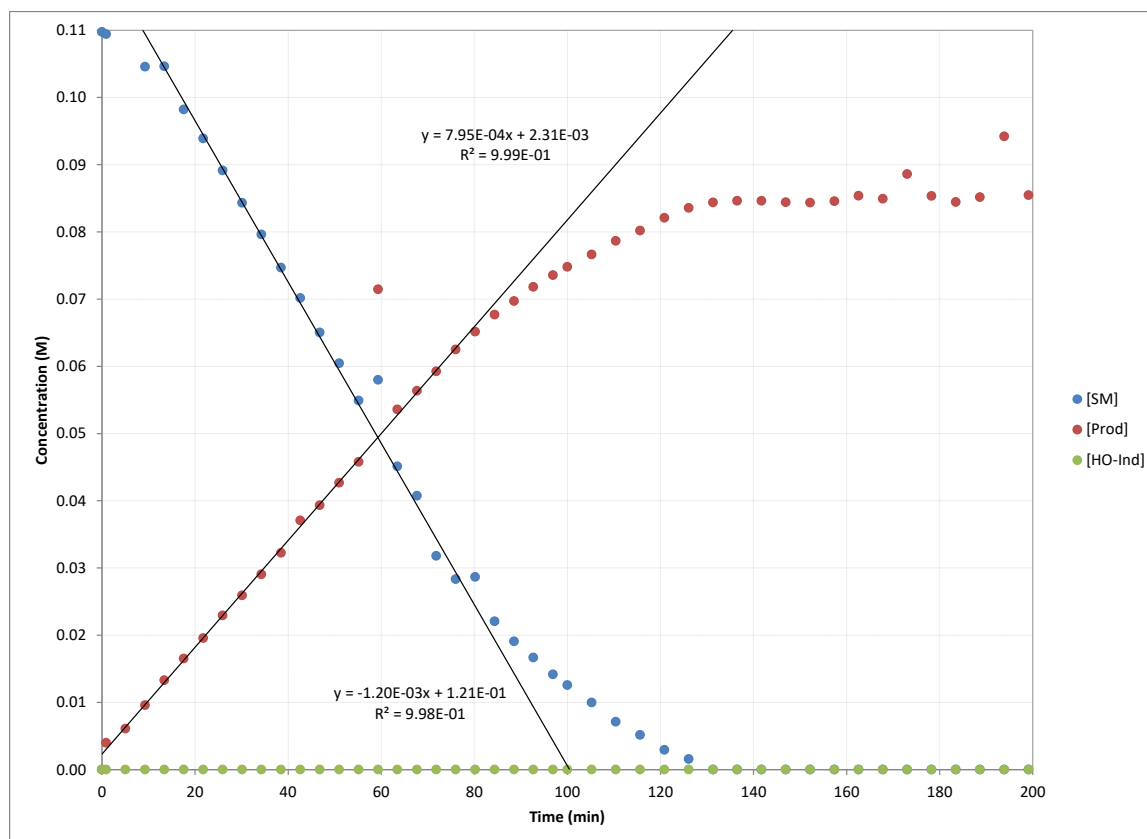
**Figure S2.11.** Kinetics experiment 11.



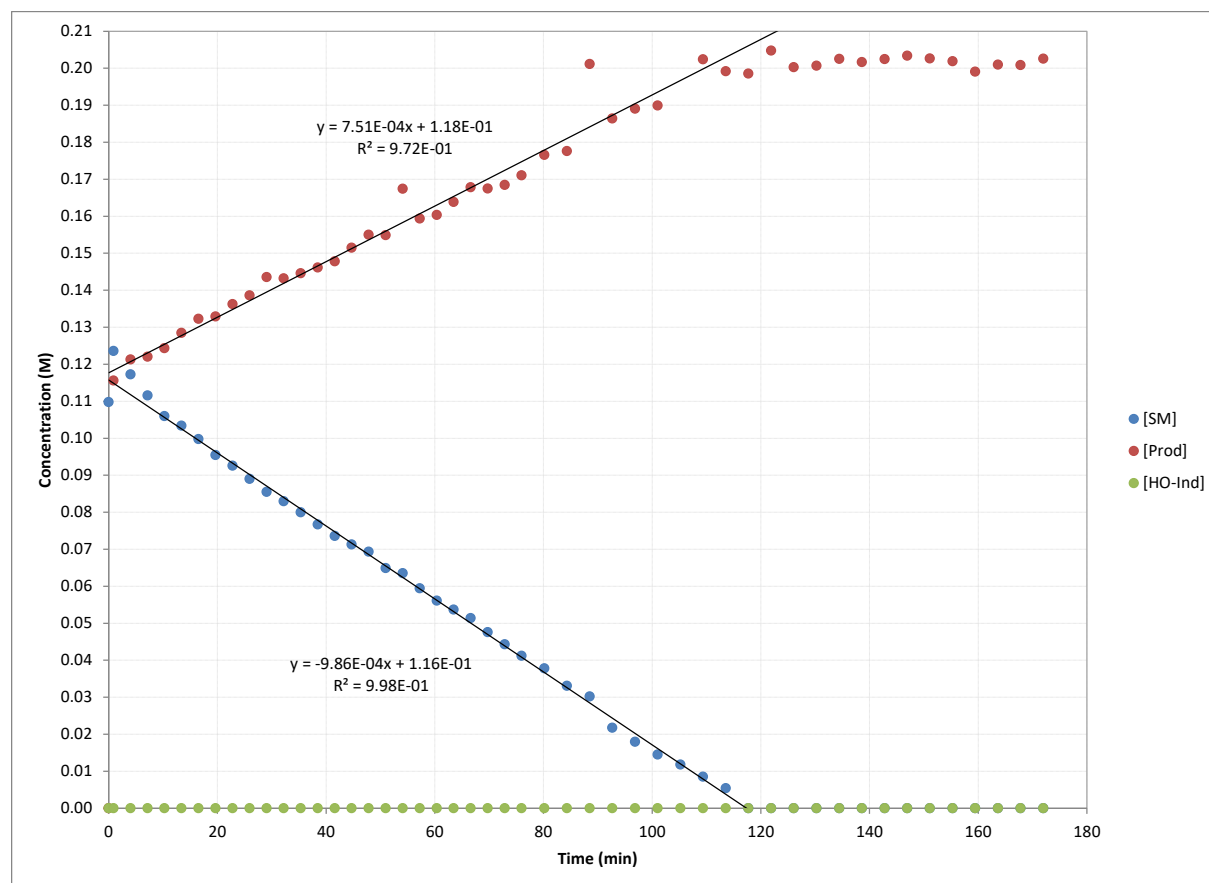
**Figure S2.12.** Kinetics experiment 12.



**Figure S2.13.** Kinetics experiment 13.

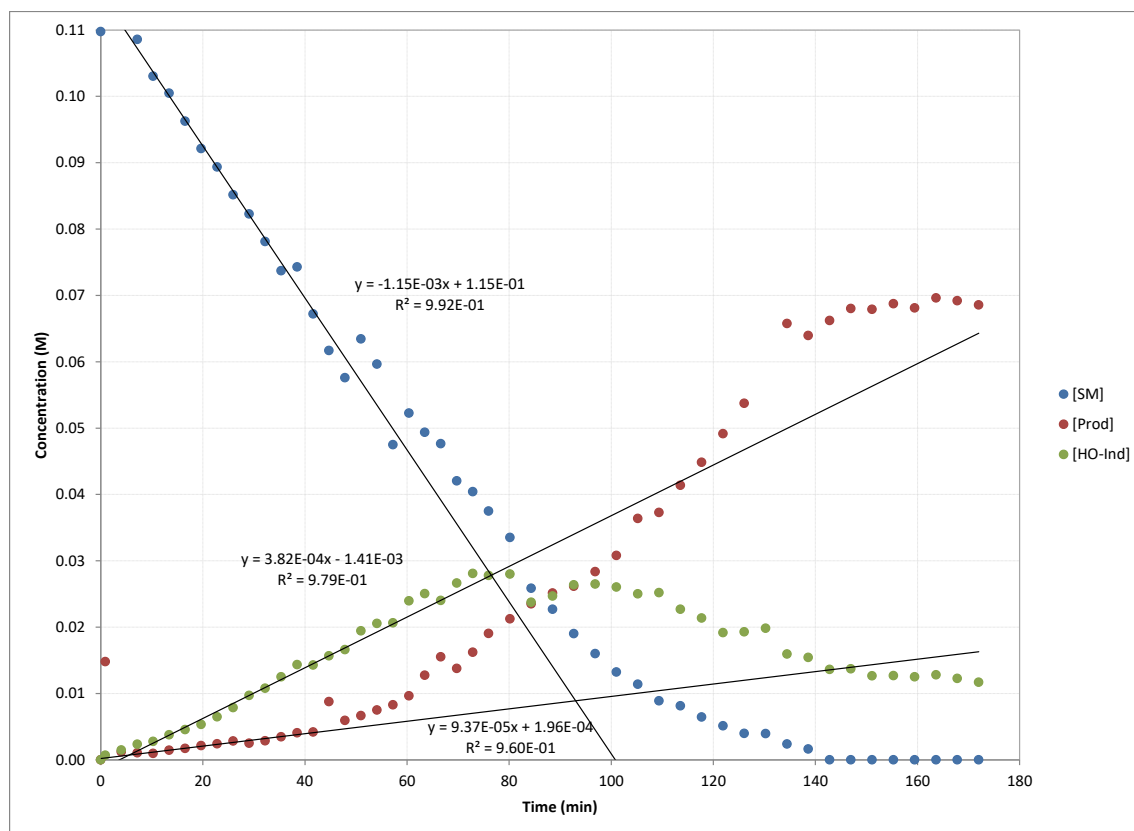


**Figure S2.14.** Kinetics experiment 14.

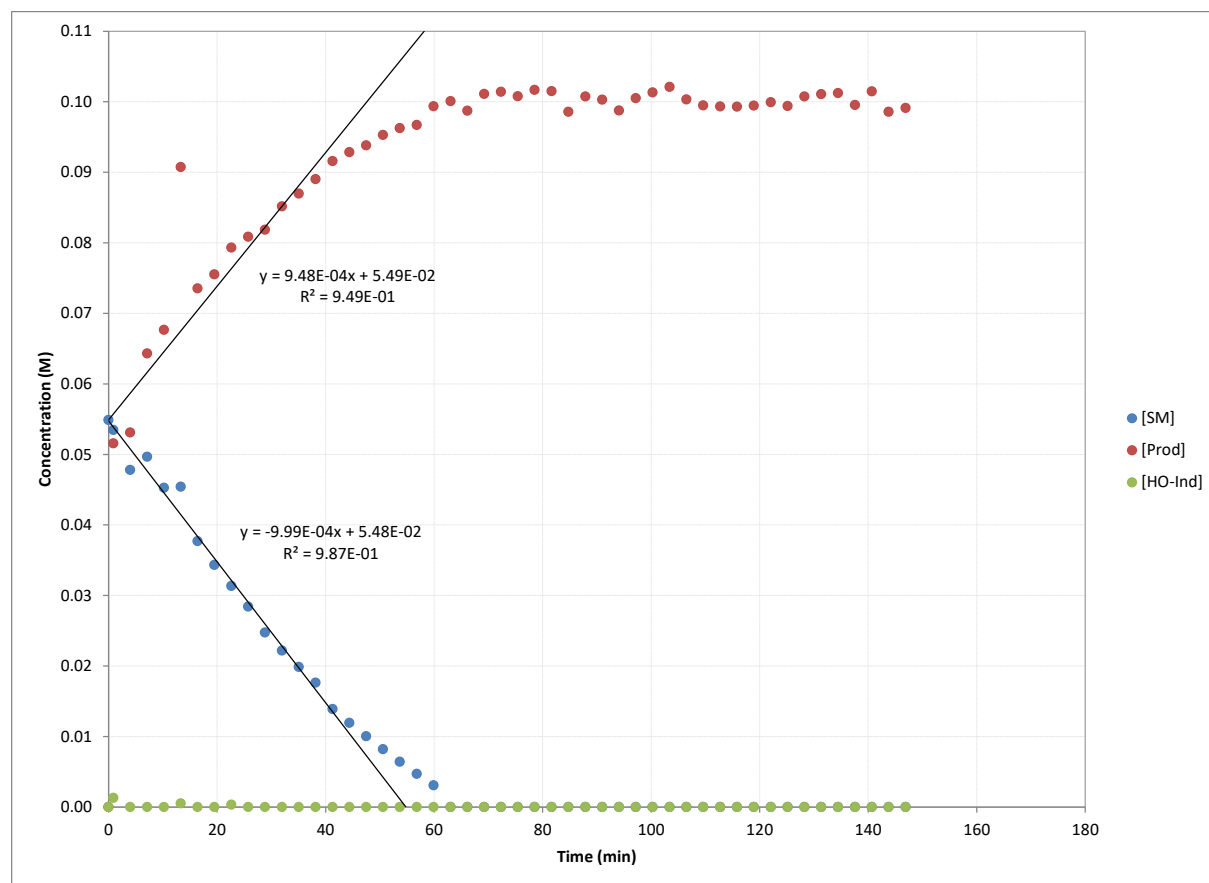




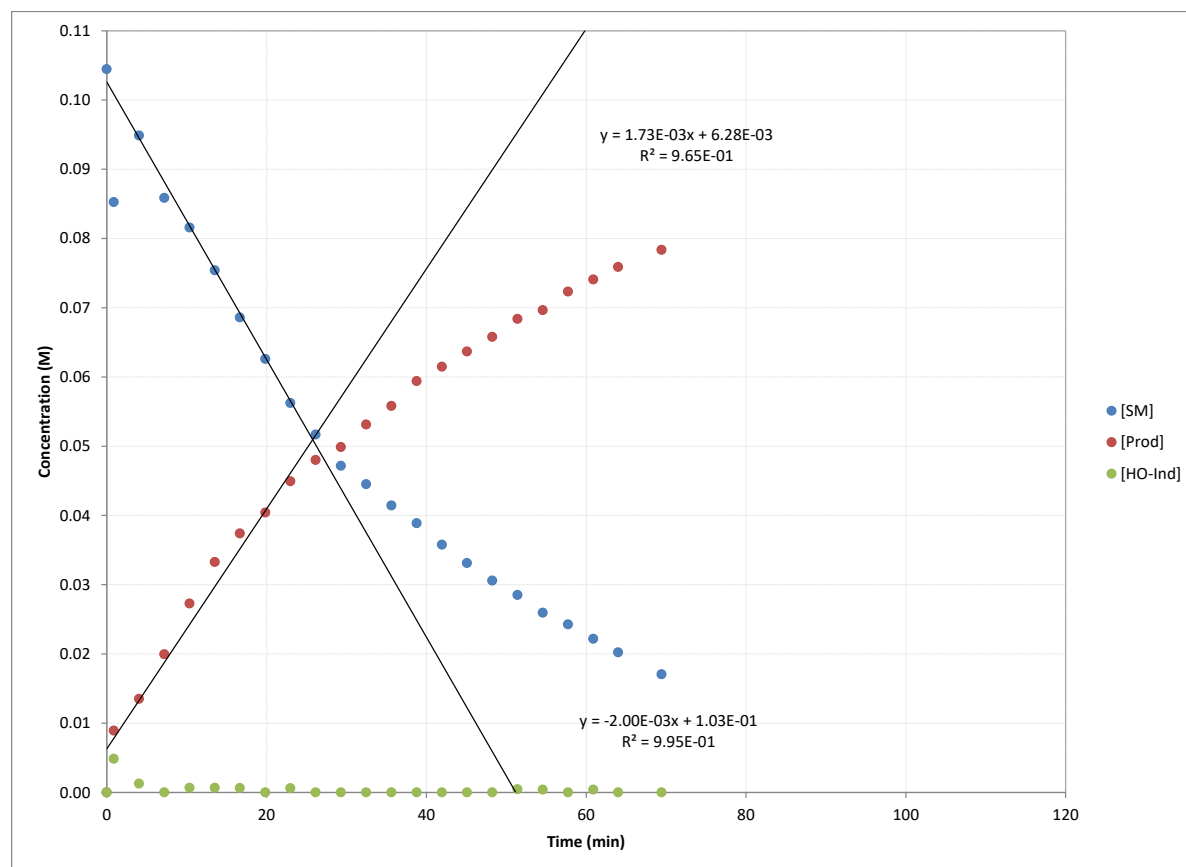
**Figure S2.15.** Kinetics experiment 15.



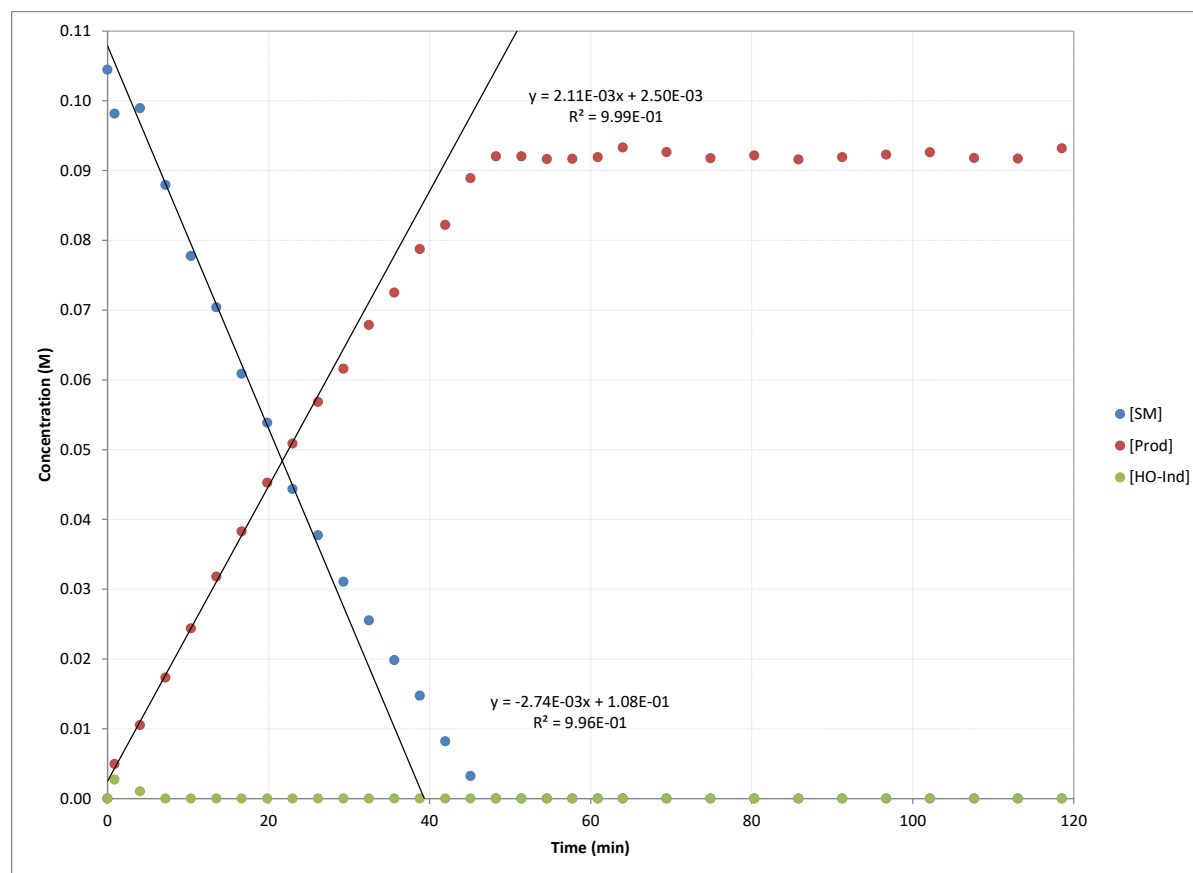
**Figure S2.16.** Kinetics experiment 16.



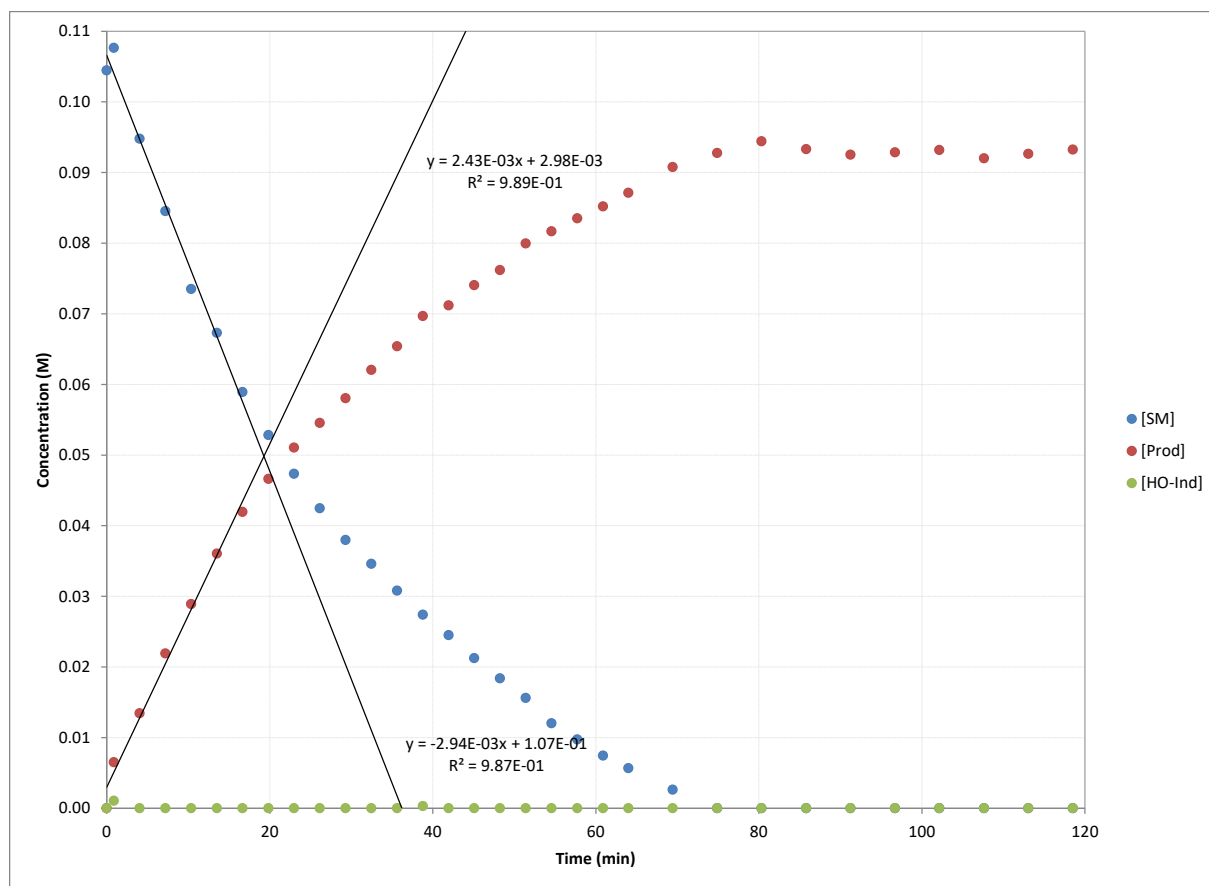
**Figure S2.17.** Kinetics experiment 17.



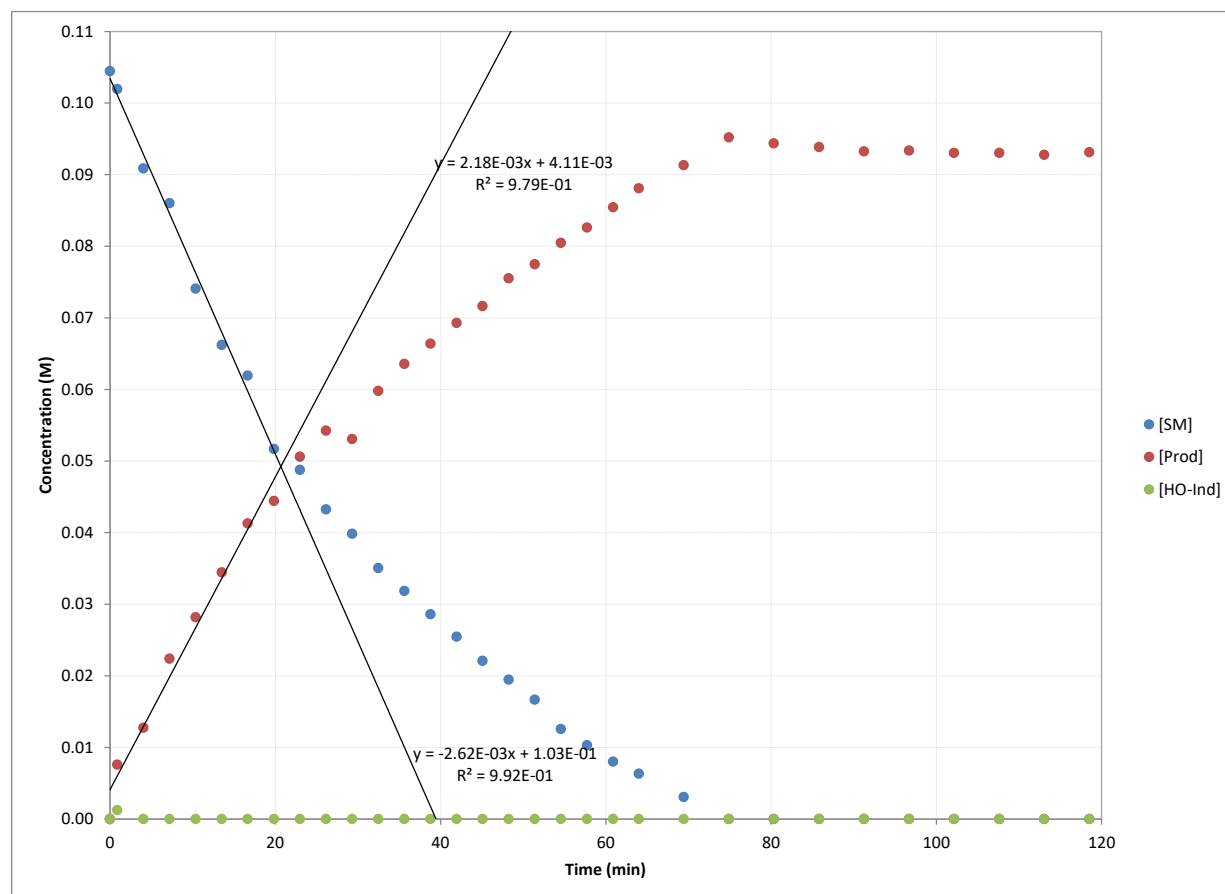
**Figure S2.18.** Kinetics experiment 18.



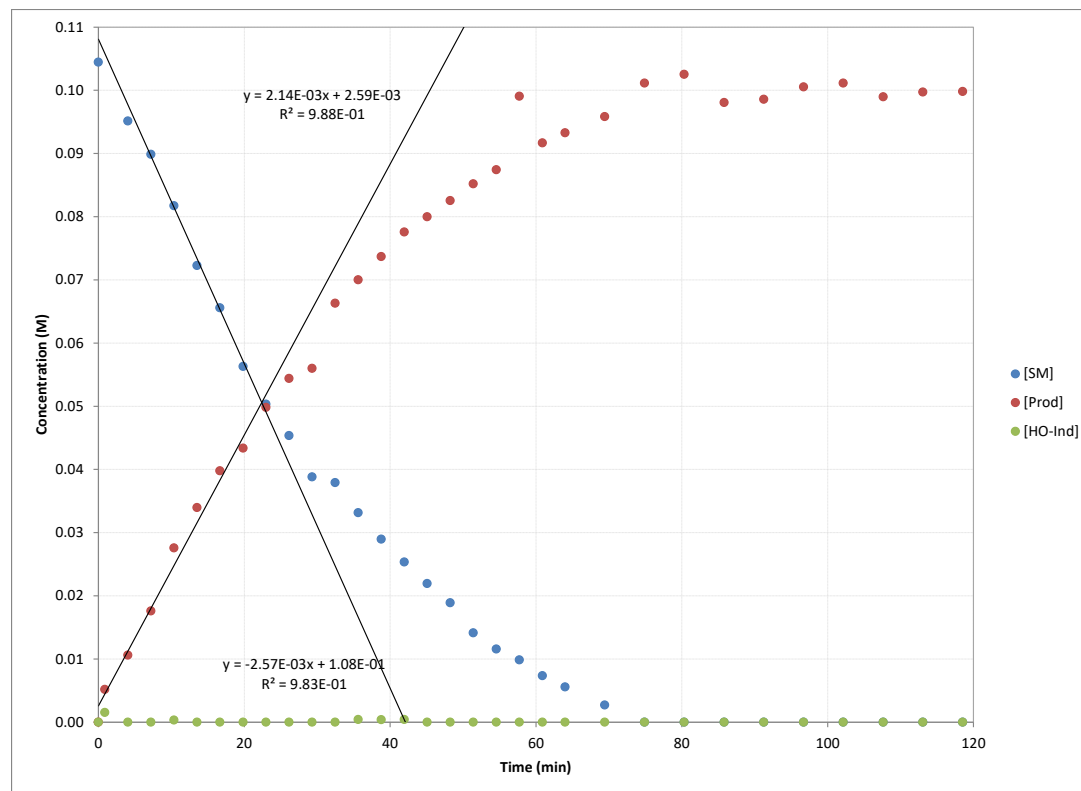
**Figure S2.19.** Kinetics experiment 19.



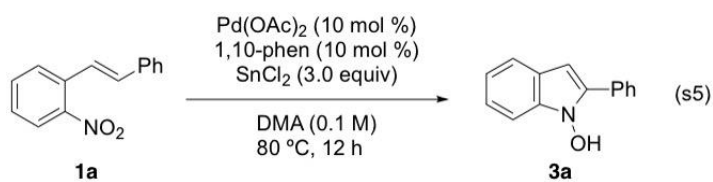
**Figure S2.20.** Kinetics experiment 20.



**Figure S2.21.** Kinetics experiment 21.

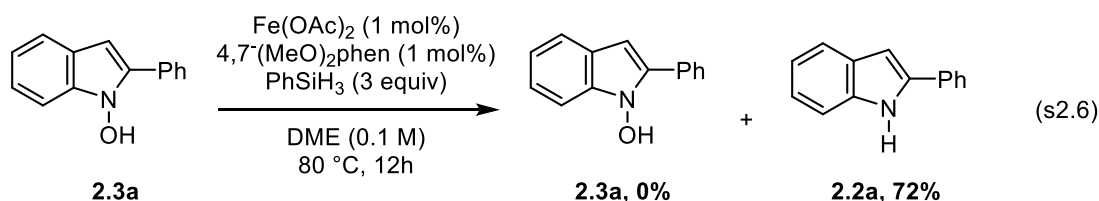


## B. Synthesis and reduction of the *N*-hydroxyindole intermediate



**2-Phenyl-1H-indol-1-ol (2.3a).** To a 50 mL Schlenk tube under nitrogen was added 0.2250 g of (*E*)-1-nitro-2-styrylbenzene (1 mmol), 0.0224 g of palladium(II) acetate (0.1mmol), 0.0180 g of 1,10-phenanthroline (0.1 mmol) and 10 mL of *N,N*-dimethylacetamide. Then 0.5688 g of tin(II) chloride (3 mmol) was added to the Schlenk tube. The Schlenk tube was sealed, and the reaction

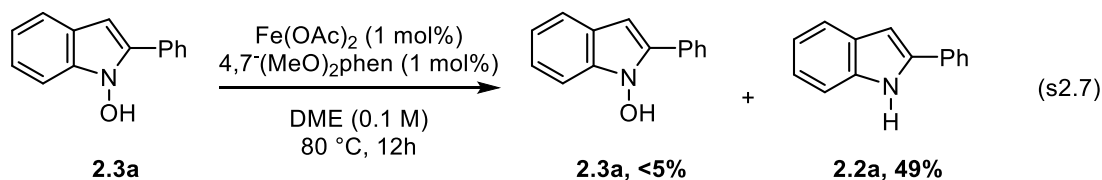
mixture was stirred at 80 °C for 12 h. Then the reaction mixture was cooled to room temperature and filtered through a pad of celite; then extracted with 3 × 10 mL EtOAc followed by washing with 3 × 10 mL of H<sub>2</sub>O and 3 × 10 mL of brine. The combined organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and filtered. The filtrate was concentrated *in vacuo*, and the crude mixture was purified by MPLC (5:95 – 25:75 EtOAc:hexane) to afford the product as a tan solid (0.1078 g, 52%). 2-Phenyl-N-hydroxyindole **2.3a** was previously reported by Yoon and co-workers: <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 500 MHz) δ 11.16 (s, 1H), 7.87 (d, *J* = 7.4 Hz, 2H), 7.54 (d, *J* = 7.9 Hz, 1H), 7.47 (t, *J* = 7.7 Hz, 2H), 7.44 (d, *J* = 8.2 Hz, 1H), 7.36 (t, *J* = 7.4 Hz, 1H), 7.18 (t, *J* = 7.3 Hz, 1H), 7.04 (t, *J* = 7.2 Hz, 1H), 6.62 (s, 1H); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>, 125 MHz) δ 137.0 (C), 135.5 (C), 130.9 (C), 128.6 (CH), 127.7 (CH), 123.0 (C), 121.8 (CH), 120.3 (CH), 119.8 (CH), 108.9 (CH), 96.2 (CH), only peaks visible; IR (thin film): 3382, 3050, 2448, 1705, 1601, 1537, 1489, 1447, 1374, 1336, 1279, 1149 cm<sup>-1</sup>.



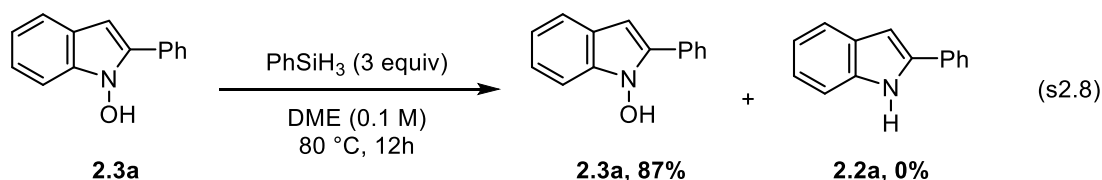
To a 10 mL Schlenk tube under nitrogen was added 0.0146 g of **2.3a** (0.07 mmol), 0.00012 g of Fe(OAc)<sub>2</sub> (0.001 mmol), 0.00017 g of 4,7-dimethoxy-1,10-phenanthroline (0.0007 mmol) and 0.7 mL of DME. Then 0.0227 g of PhSiH<sub>3</sub> (0.21 mmol) was added to the Schlenk tube. The Schlenk tube was sealed, and the reaction mixture was stirred at 80 °C for 12 h. Then the reaction mixture was cooled to room temperature and extracted with 3 × 10 mL EtOAc followed by washing with 10 mL of H<sub>2</sub>O and 10 mL of brine. The combined organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and filtered. The filtrate was concentrated *in vacuo*. Analysis of the resulting residue using <sup>1</sup>H NMR



spectroscopy in DMSO-*d*<sub>6</sub> with 0.1 mmol of CH<sub>2</sub>Br<sub>2</sub> as the internal standard revealed 0.050 mmol of indole **2.2a**.



To a 10 mL Schlenk tube under nitrogen was added 0.0146 g of **2.3a** (0.07 mmol), 0.00012 g of Fe(OAc)<sub>2</sub> (0.001 mmol), 0.00017 g of 4,7-dimethoxy-1,10-phenanthroline (0.0007 mmol) and 0.7 mL of DME. The Schlenk tube was sealed, and the reaction mixture was stirred at 80 °C for 12 h. Then the reaction mixture was cooled to room temperature and extracted with 3 × 10 mL EtOAc followed by washing with 10 mL of H<sub>2</sub>O and 10 mL of brine. The combined organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and filtered. The filtrate was concentrated *in vacuo*. Analysis of the resulting residue using <sup>1</sup>H NMR spectroscopy in DMSO-*d*<sub>6</sub> with 0.1 mmol of CH<sub>2</sub>Br<sub>2</sub> as the internal standard revealed 0.035 mmol of indole **2.2a**.



To a 10 mL Schlenk tube under nitrogen was added 0.0146 g of **2.3a** (0.07 mmol) and 0.7 mL of DME. Then 0.0227 g of PhSiH<sub>3</sub> (0.21 mmol) was added to the Schlenk tube. The Schlenk tube was sealed, and the reaction mixture was stirred at 80 °C for 12 h. Then the reaction mixture was cooled to room temperature and extracted with 3 × 10 mL EtOAc followed by washing with 10 mL of H<sub>2</sub>O and 10 mL of brine. The combined organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and filtered.

The filtrate was concentrated *in vacuo*. Analysis of the resulting residue using  $^1\text{H}$  NMR spectroscopy in  $\text{DMSO}-d_6$  with 0.1 mmol of  $\text{CH}_2\text{Br}_2$  as the internal standard revealed 0.061 mmol of **2.3a**. No formation of **2.2a** was observed.

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## Chapter III.

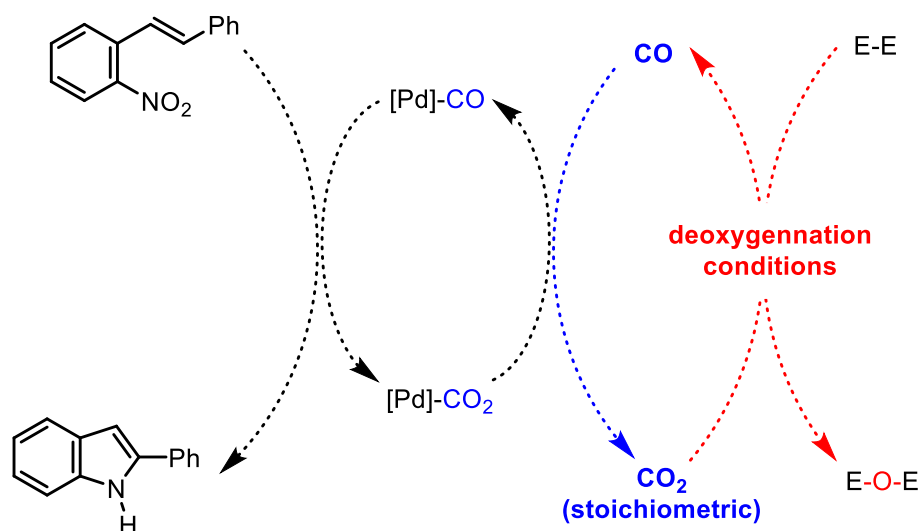
# Pd-Catalyzed Reductive Cyclization of Nitroarenes Using CO<sub>2</sub> as the CO Progenitor

(The structure of this chapter followed the published article: Development of a Pd-Catalyzed Reductive Cyclization of Nitroarenes that Uses CO<sub>2</sub> as the CO Progenitor.

Guan, X.; Zhu, H.; Zhao, Y.; Driver, T.G. *Eur. J. Org. Chem.* **2020**, 57-60.)

### 3.1. Introduction

The development of chemical fixation of CO<sub>2</sub> has received a lot of attention because of the role it plays in the greenhouse effect.<sup>1</sup> While transition metal catalyzed reactions using CO<sub>2</sub> as a C1 source has seen significant progress,<sup>2</sup> converting CO<sub>2</sub> into CO as a building block in carbonylation reactions has received less attention.<sup>3</sup> In addition to being a C1 source for these reactions, another role that carbon monoxide commonly served is a terminal reductant in reductive cyclization reactions of nitroarenes in the syntheses of indoles, carbazoles and other *N*-heterocycles,<sup>4</sup> which are the ubiquitous motif of various bioactive compounds, pharmaceuticals and materials.<sup>5</sup>



**Scheme 3.1.** Towards the Development of a Pd-Catalyzed Reductive Cyclization Reaction to Access *N*-Heterocycles that uses CO<sub>2</sub> as the source of CO.

After looking into the reaction, we found it an interesting idea to adopt CO<sub>2</sub> as the source of CO, considering that the reductive cyclization reaction of nitrostyrenes can produce two molecules of CO<sub>2</sub> as the by product (**Scheme 3.1**). To begin with, I investigated some recently developed reactions that convert CO<sub>2</sub> to CO using homogeneous transition metal catalysts,<sup>6</sup> carbene catalysts<sup>7</sup> or fluoride<sup>8</sup> to see if one of these technologies would create a suitable CO pressure to trigger the reductive cyclization of nitroarenes. In this chapter, I report the development of a method using a combination of disilane and fluoride to deoxygenate CO<sub>2</sub> into CO gas, which is then utilized in situ for a Pd-catalyzed reductive cyclization of nitroarenes to produce indoles, carbazoles or benzimidazoles.



### 3.2. Results and Discussion

To better control the the outcome of the process, a multi-chambered glass reactor was used so that the deoxygenation reaction was separated from the reductive cyclization of the nitrostyrene. A two chambered reactor was investigated first. It was made by fusing two schlenk tubes and only gas and volatile species would be able to communicate between the two chambers. In this system, one chamber was used to hold a palladium catalyzed reductive cyclization of 2-nitrostyrenes to form indole product but without providing any CO atmosphere. The second chamber, deoxygenating conditions were placed and dry ice would be introduced before the system was sealed. This reactor also enabled us to test the deoxygenating coniditons under different temperature from the reductive cyclization reaction.

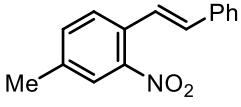
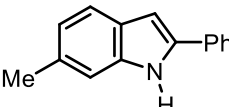
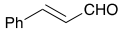
However, early attempts I made in two-chamber system was not satisfactory.<sup>9</sup> Adding dry-ice to the reductive cyclization chamber led to poor conversion of the reaction. Despite some experiments were showing yields of indole higher than 50% when dry ice was added to the deoxygenation chamber, these results could not be consistently reproduced. Although we hypothesized that the inconsistent quality of dry ice with its carbonic acid composition may be the cause of the reproducibility issues, it was hard to re-examine different qualities of dry ice with the lack of flexibility in the way we introduced CO<sub>2</sub> to our reaction system. Further, it was also discovered that the two-chamber system made it very challenging to systematically study other different sources of CO<sub>2</sub> (*vide infra*) under the optimal conditions we determined. This convinced us to abandon the two chamber system and to examine a three-chamber system that separated the formation of CO<sub>2</sub> from both deoxygenating and reductive cyclization reaction. Therefore, a three-chamber aparatus was designed to carry the reaction to find the optimal condition. In chamber 1, CO<sub>2</sub> was generated by thawing a frozen aqueous solution of H<sub>2</sub>SO<sub>4</sub> and K<sub>2</sub>CO<sub>3</sub>. This not only

ensured that CO<sub>2</sub> in this reaction underwent minimum manipulation with better consistency in its purity and quantity, which is beneficial to the reproducibility of the reaction, but also helped to identify a condition that tolerated water vapor. Chamber 2 was where CO<sub>2</sub> was converted to CO, and in order to probe the effectiveness of the CO<sub>2</sub> deoxygenation, I selected a well established CO consuming condition in Chamber 3, where 5 mol % of [Pd(OAc)<sub>2</sub>] together with 10 mol % of tetramethylphenanthroline catalyzed the reductive cyclization of nitrostilbene **3.1a** into indole **3.2a**.<sup>4k, 10, 11</sup>

Based on the set-up mentioned previously, deoxygenation conditions in chamber 2 were screened (Table 3.1). First, several conditions reported to deoxygenate CO<sub>2</sub> including the use of *N*-heterocyclic carbene catalyst and cinnamaldehyde as the reductant,<sup>7</sup> or in situ generation of a carbodiphosphorane and zinc bromide<sup>6d</sup> or reduction by B<sub>2</sub>pin<sub>2</sub> with copper NHC catalyst were examined.<sup>6a</sup> Unfortunately, none of these conditions showed reactivity in the three-chamber system (entries 1 – 3). While trace reduction of nitrostilbene to aniline was observed when a fluoride catalyst with B<sub>2</sub>(OH)<sub>4</sub> was employed under 100 °C (entry 4), indole **3.2a** was obtained when (Ph<sub>2</sub>MeSi)<sub>2</sub> was used as the terminal reductant with 4 mol % of KF catalyst (entry 5).<sup>8</sup> This result stimulated me to explore further the fluoride catalyzed deoxygenation conditions using disilanes as the terminal reductant. In order to enhance the yield of the initial hit, different fluorides, silanes and solvents were examined. While switching from KF to HF·pyridine, Et<sub>3</sub>N·3HF or *n*-Bu<sub>4</sub>NF resulted in complete shutdown of the reaction (entries 6 – 8), delightfully nearly quantitative yield of **3.2a** was observed when 20 mol % of CsF was used (entry 9). Changing the loading of CsF, whether increasing or decreasing, only lead to deteriorated yields of indole (entries 10 and 11). Next, I scrutinized a number of silanes and found that only (Me<sub>3</sub>Si)<sub>3</sub>SiH was almost

as effective as (Ph<sub>2</sub>MeSi)<sub>2</sub> (entry 12) while other silanes failed to show any desired reactivity (entries 13–16). Finally, solvents in which CsF has moderate to good solubility in were screened. While no reduction in chamber 3 was observed with DMSO and alcohol as the solvent (entry 16 and 17), the reaction proceeded to give 63% of 2-phenylindole in  $\gamma$ -valerolactone when chamber 2 was heated to 100 °C (entry 18). —“In parallel, I attempted to optimize the process using B<sub>2</sub>(OH)<sub>4</sub> as the reductant. Despite its potential merits to enable a greener process, its use resulted in a complicated reaction set up and poor reproducibility. As a result, I focused on the optimization of the disilane-fluoride combination.<sup>9</sup> Therefore, it can be summarized that the optimal condition for chamber 2 involved the usage of 20 mol % CsF and 2 equivalents of (Ph<sub>2</sub>MeSi)<sub>2</sub> in DMF at room temperature, indicated by the most efficient reductive cyclization reaction performed in chamber 3.

**Table 3.1.** Optimization of deoxygenation of CO<sub>2</sub> for Pd-catalysed reductive cyclization for indole synthesis.

<div style="display: flex; align-items: center; justify-content: space-around;"> <div style="text-align: center;">  <p><b>3.1c</b></p> </div> <div style="text-align: center;"> <p><b>chamber 1:</b> H<sub>2</sub>SO<sub>4</sub> (8 equiv), K<sub>2</sub>CO<sub>3</sub> (4 equiv)</p> <p><b>chamber 2:</b> conditions</p> <p><b>chamber 3:</b> nitroarene <b>3.1c</b> Pd(OAc)<sub>2</sub> (5 mol%) tmphen (10 mol%) DMF 100 °C</p> </div> <div style="text-align: center;">  <p><b>3.2c</b></p> </div> </div>					
Entry <sup>a</sup>	catalyst (mol %)	reductant (2 equiv)	solvent	T (°C)	%, Yield <b>2a</b>
1	IMesCl, K <sub>2</sub> CO <sub>3</sub>		DMF	100	n.r.
2	ZnBr <sub>2</sub> , CH <sub>2</sub> I <sub>2</sub>	Et <sub>3</sub> P	PhMe	100	n.r.

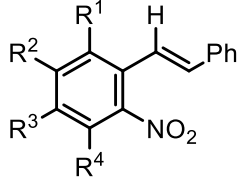
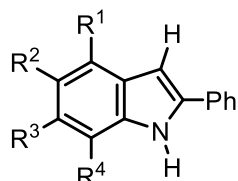
3	(IPr)CuOt-Bu (1)	B <sub>2</sub> pin <sub>2</sub>	THF	100	n.r.
4	CsF (10)	B <sub>2</sub> (OH) <sub>4</sub>	DMF	100	0 <sup>b</sup>
5	KF (10)	(Ph <sub>2</sub> MeSi) <sub>2</sub>	DMF	25	18
6	HF·py (20)	(Ph <sub>2</sub> MeSi) <sub>2</sub>	DMF	25	n.r.
7	Et <sub>3</sub> N·3HF (20)	(Ph <sub>2</sub> MeSi) <sub>2</sub>	DMF	25	n.r.
8	( <i>n</i> -Bu) <sub>4</sub> NF (20)	(Ph <sub>2</sub> MeSi) <sub>2</sub>	DMF	25	n.r.
9	CsF (20)	(Ph <sub>2</sub> MeSi) <sub>2</sub>	DMF	25	94
10	CsF (40)	(Ph <sub>2</sub> MeSi) <sub>2</sub>	DMF	25	61
11	CsF (10)	(Ph <sub>2</sub> MeSi) <sub>2</sub>	DMF	25	10
12	CsF (20)	(Me <sub>3</sub> Si) <sub>3</sub> SiH	DMF	25	90
13	CsF (20)	(Me <sub>3</sub> Si) <sub>2</sub>	DMF	25	n.r.
14	CsF (20)	Et <sub>3</sub> SiH	DMF	25	n.r.
15	CsF (20)	Ph <sub>3</sub> SiH	DMF	25	n.r.
16	CsF (20)	(Ph <sub>2</sub> MeSi) <sub>2</sub>	DMSO	25	n.r.
17	CsF (20)	(Ph <sub>2</sub> MeSi) <sub>2</sub>	EtOH	25	n.r.
18	CsF (20)	(Ph <sub>2</sub> MeSi) <sub>2</sub>	γ-valero- lactone	100	63 <sup>c</sup>

---

<sup>a</sup> Conditions: **chamber 1**: 1 M H<sub>2</sub>SO<sub>4</sub> (8 equiv), K<sub>2</sub>CO<sub>3</sub> (4 equiv) in 0.8 mL of H<sub>2</sub>O; **chamber 3**: Pd(OAc)<sub>2</sub> (5 mol %), tmphen (10 mol %), 0.1 M DMF, 14 h. <sup>b</sup> trace aniline observed. <sup>c</sup> poor conversion seen at lower temperatures. tmphen = 3,4,7,8-tetramethyl-1,10-phenanthroline.

Under the optimized reaction conditions, I next examined the scope and limitation of this method together with my colleague Haoran Zhu (**Table 3.2**). Overall, no obvious trend could be established with regard to the electronic nature of the nitroarene transforming into indole **3.2** (entries 1 – 12). Substrates bearing strong electron-withdrawing CF<sub>3</sub> ( $\sigma_m = + 0.43$ ,  $\sigma_p = + 0.54$ ) substituents resulted in relatively moderate yields, but at the same time, ester group ( $\sigma_m = + 0.36$ ,  $\sigma_p = + 0.45$ ) lead to a very good yield of indole **2**. Electron-donating methoxy group ( $\sigma_m = + 0.12$ ,  $\sigma_p = - 0.27$ ) by contrast, gave an excellent yield of the product. Increasing the catalyst loading under a higher CO pressure allowed the reaction to overcome a more sterically hindered environment around the *ortho*-styryl substituent or the nitro group, to successfully produce indoles **3.2m** and **3.2n** (entries 13 and 14). While good functional group tolerance was also observed for different R<sup>6</sup>-substituents (entries 15 – 19), trifluoromethyl group again appeared to be more challenging, requiring the use of higher catalyst loading to construct indole **3.2q** (entry 17). Gratifyingly not only different 2-aryl indoles such as **3.2o** – **3.2q** could be smoothly produced, but also 2-alkyl or even 2-carboxyl substituents were readily constructed. To our delight, the reductive cyclization was not limited to the formation of 2-substituted indoles: 3-phenyl indole **3.2t** was formed in 86% and 2,3-disubstituted indole **3.2u** was accessed in 81% yield (entries 20 and 21).

**Table 3.2.** Scope and limitations of the three-chamber Pd-catalyzed reductive indole formation.

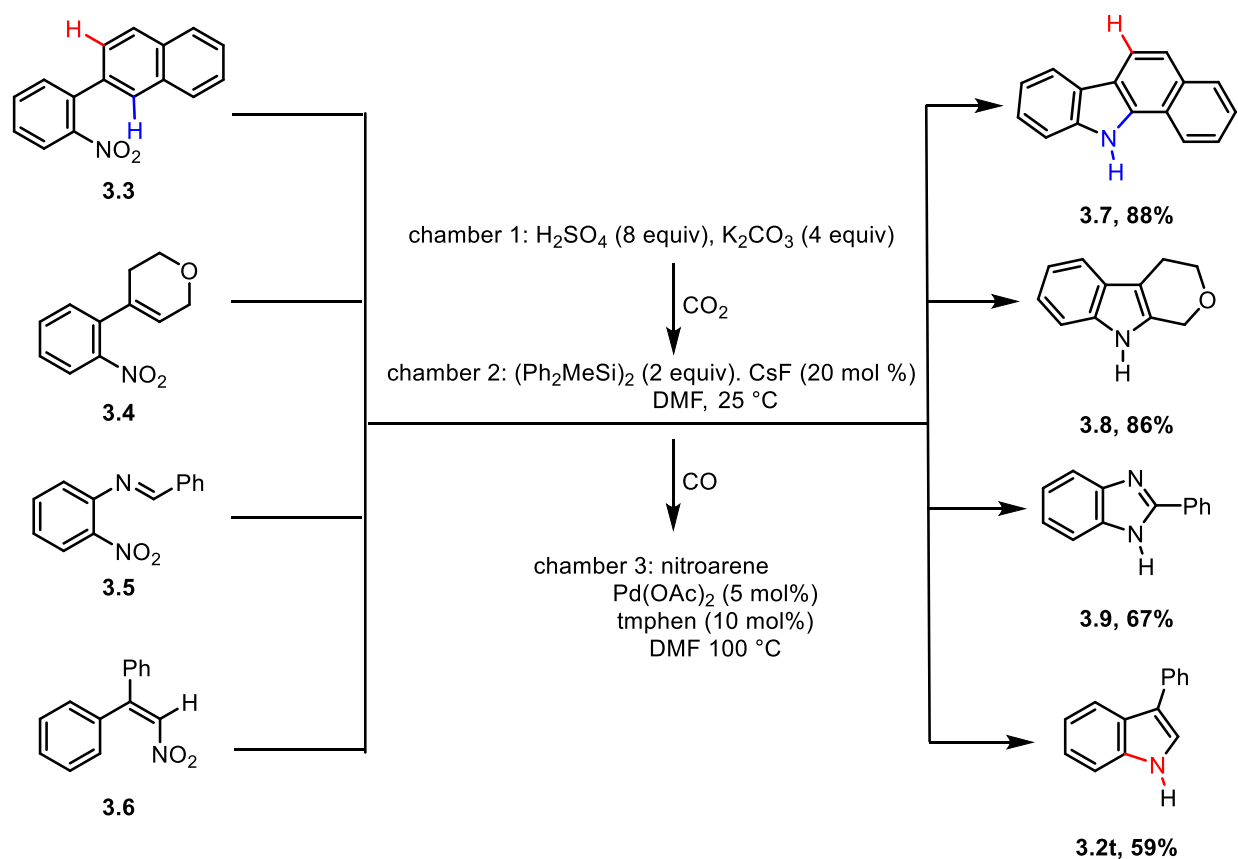
<div style="display: flex; align-items: center; justify-content: space-around;"> <div style="text-align: center;">  <p><b>3.1</b></p> </div> <div style="text-align: center;"> <p>chamber 1: H<sub>2</sub>SO<sub>4</sub> (8 equiv), K<sub>2</sub>CO<sub>3</sub> (4 equiv)              chamber 2: (Ph<sub>2</sub>MeSi)<sub>2</sub> (2 equiv). CsF (20 mol %)              DMF, 25 °C</p> <hr style="width: 100%;"/> <p>chamber 3: nitroarene              Pd(OAc)<sub>2</sub> (5 mol%)              tmphen (10 mol%)              DMF 100 °C</p> </div> <div style="text-align: center;">  <p><b>3.2</b></p> </div> </div>								
Entry <sup>[a]</sup>	#	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	R <sup>5</sup>	R <sup>6</sup>	%, yield
1	<b>a</b>	H	H	H	H	H	Ph	91
2	<b>b</b>	H	OMe	H	H	H	Ph	97
3	<b>c</b>	H	Me	H	H	H	Ph	94
4	<b>d</b>	H	F	H	H	H	Ph	98
5	<b>e</b>	H	Cl	H	H	H	Ph	69
6	<b>f</b>	H	CO <sub>2</sub> Me	H	H	H	Ph	90
7	<b>g</b>	H	CF <sub>3</sub>	H	H	H	Ph	57
8	<b>h</b>	H	–OCH <sub>2</sub> O–	H	H	H	Ph	76
9	<b>i</b>	H	H	OMe	H	H	Ph	83
10	<b>j</b>	H	H	Me	H	H	Ph	78
11	<b>k</b>	H	H	F	H	H	Ph	69
12	<b>l</b>	H	H	CF <sub>3</sub>	H	H	Ph	72
13 <sup>[b]</sup>	<b>m</b>	H	H	H	Me	H	Ph	68

14 <sup>[b,c]</sup>	<b>n</b>	Me	H	H	H	H	Ph	72
15	<b>o</b>	H	H	H	H	H	4-MeOC <sub>6</sub> H <sub>4</sub>	92
16	<b>p</b>	H	H	H	H	H	4-FC <sub>6</sub> H <sub>4</sub>	61
17 <sup>[b]</sup>	<b>q</b>	H	H	H	H	H	4-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	70 <sup>[d]</sup>
18	<b>r</b>	H	H	H	H	H	<i>n</i> -Pr	79
19	<b>s</b>	H	H	H	H	H	CO <sub>2</sub> Me	88
20	<b>t</b>	H	H	H	H	Ph	H	86
21	<b>u</b>	H	H	H	H	Et	Ph	81

[a] Conditions: **chamber 1**: 1 M H<sub>2</sub>SO<sub>4</sub> (8 equiv), K<sub>2</sub>CO<sub>3</sub> (4 equiv) in 0.8 mL of H<sub>2</sub>O; **chamber 2**: CsF (20 mol %), (Ph<sub>2</sub>MeSi)<sub>2</sub> (2 equiv), DMF, 25 °C; **chamber 3**: [Pd(OAc)<sub>2</sub>] (5 mol %), phen (10 mol %), 0.1 M, 14 h. [b] 10 mol % of [Pd(OAc)<sub>2</sub>] and 20 mol % of tmphen used. [c] 8 equiv of K<sub>2</sub>CO<sub>3</sub>, 10 equiv of H<sub>2</sub>SO<sub>4</sub>, 4 equiv of (Ph<sub>2</sub>MeSi)<sub>2</sub> and 40 mol % of CsF used. [d] 6% of the *N*-OH indole obtained.

After establishing the generality of this reductive cyclization method for effectively making indoles with various electronic- and steric nature, we switched our focus to the construction of more complex *N*-heterocycles (**Scheme 3.2**). We demonstrated that carbazoles such as **3.7** could be accessed by site-selective reductive cyclization of nitrobiarenes **3.3** using double the amount of K<sub>2</sub>CO<sub>3</sub> and disilane compared to the optimal condition. Utilizing the same modified process tetrahydropyrano[3,4-*b*]indole **3.8a** was obtained in decent yield and even benzimidazoles **3.9a** could be accessed in slightly attenuated yield. In addition, we established that this process was not

limited to ortho-substituted nitroarenes like **3.6**, but nitroalkenes were competent substrates if twice as much  $\text{K}_2\text{CO}_3$  and disilane were used. From the results above we can conclude that a higher pressure of CO is critical in these transformations because the C–N bond formation needs to go through a disruption of aromaticity.

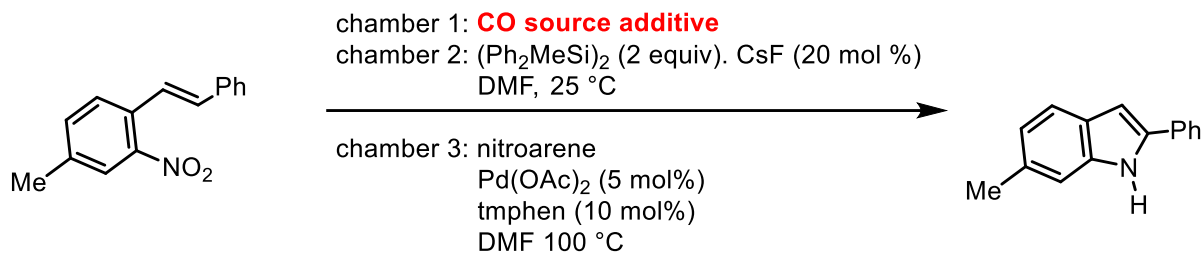


**Scheme 3.2.** Construction of carbazoles, indoles or benzimidazoles through Pd-catalyzed reductive cyclization of nitroarenes or nitroalkenes.

Using a three-chamber system enabled us to examine systematically different sources of  $\text{CO}_2$  (**Scheme 3.3**). We were particularly interested to determine whether flue gas might serve as the source of  $\text{CO}_2$ . Cryogenic distillation of industrial flue gas is an effective method to capture  $\text{CO}_2$



as dry ice.<sup>12</sup> By doing so, we could develop a general idea of the robustness of our system in potential industrial applications which have an increasing need to minimize the emission of CO<sub>2</sub> into the atmosphere. To test if our process was still viable, dry ice was first examined in the three-chamber apparatus and fortunately the conversion of nitrostilbene **3.1c** to indole **3.2c** was found to be equally efficient with 86% yield. Then we wondered, now that the carbon-capture product from flue gas was feasible, would the reaction still proceed smoothly if flue gas was used directly as the CO<sub>2</sub> source. While the exact composition of flue gas varies depending on its origin, its common contaminants include H<sub>2</sub>O, SO<sub>2</sub>, NO and H<sub>2</sub>S, which are produced during pre- and post-combustion processes.<sup>13, 14</sup> The established optimal conditions, bearing an aqueous solution of K<sub>2</sub>CO<sub>3</sub> and H<sub>2</sub>SO<sub>4</sub> in chamber 2, already demonstrated that the reductive cyclization reaction was impervious to water vapor (*vide supra*). To systematically study the effect of small quantities of H<sub>2</sub>S, SO<sub>2</sub> or NO in the reaction atmosphere, we decided to independently introduce each of this component to CO<sub>2</sub> at the approximate level of their actual composition in flue gas by subjecting a number of salts in chamber 1. Among all these experiments we performed, only the presence of SO<sub>2</sub> resulted in a slight drop of the yield while in other cases, indole **3.2c** could still be formed effectively. These results effectively demonstrate that flue gas could serve as the CO<sub>2</sub>-source in the reductive cyclization to produce *N*-heterocycles.



CO source (equiv)	additive (equiv)	gas	% yield
dry ice (6)	---	---	86
K <sub>2</sub> CO <sub>3</sub> (4) + H <sub>2</sub> SO <sub>4</sub> (8)	K <sub>2</sub> S (0.04)	H <sub>2</sub> S	90
K <sub>2</sub> CO <sub>3</sub> (4) + H <sub>2</sub> SO <sub>4</sub> (8)	NaHSO <sub>3</sub> (0.032)	SO <sub>2</sub>	75
K <sub>2</sub> CO <sub>3</sub> (4) + H <sub>2</sub> SO <sub>4</sub> (8)	Cu (0.002) + HNO <sub>3</sub> (0.008)	NO	86

**Scheme 3.3.** Investigation of the effect of the origin and composition of CO<sub>2</sub> on the reductive cyclization reaction.

### 3.3. Conclusions

A three-chamber process using (or employing) CO<sub>2</sub> as the source of the superstoichiometric CO was developed and its efficacy was successfully demonstrated by reductive cyclization of nitroarenes and nitroalkenes into N-heterocycles using CO as the reductant. The deoxygenation conditions were screened and the combination of disilane and fluoride catalyst enabled the CO formation to occur smoothly at room temperature, which created a suitable CO pressure for palladium-catalyzed reductive amination reaction in a separate chamber. Irrespective of the steric- or electronic nature of the nitroarene substrate, this process provides access to a broad range of N-heterocycles, including indoles, carbazoles and benzimidazoles. While the method was developed upon in situ generation of CO<sub>2</sub>, it also tolerates the use of dry ice and the reaction efficiency was not significantly affected even if the atmosphere is contaminated with H<sub>2</sub>S, SO<sub>2</sub>, NO or H<sub>2</sub>O.

Future investigation can be made to explore reactions using CO<sub>2</sub> as the source of CO building block, and conditions using B<sub>2</sub>(OH)<sub>4</sub> as the reductant can also be further studied to develop greener and more atom economical process.

### 3.4. Experimental

(This part was taken from supporting information of my published paper: Guan, X.; Zhu, H.; Zhao, Y.; Driver, T.G. *Eur. J. Org. Chem.* **2020**, 57-60.)

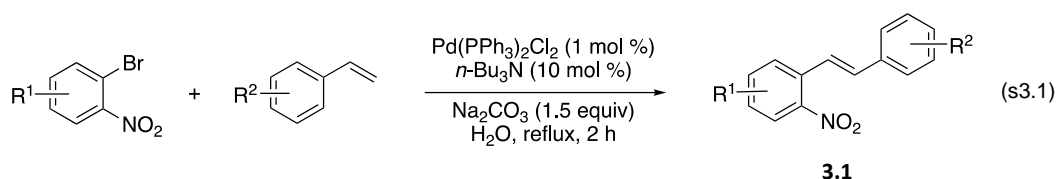
**General.** <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were recorded at ambient temperature using 500 MHz or 300 MHz spectrometers. The data are reported as follows: chemical shift in ppm from internal tetramethylsilane on the δ scale, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, 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. HPLC analysis was conducted on an Agilent 1100 instrument equipped with a binary

pump and diode array detector. Liquid chromatography was performed using forced flow (flash chromatography) of the indicated solvent system on 60Å (40 – 60 µm) mesh silica gel (SiO<sub>2</sub>). 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<sub>2</sub>). 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<sub>2</sub>O, and CH<sub>2</sub>Cl<sub>2</sub> were dried by filtration through alumina according to the procedure of Grubbs.<sup>{Pangborn, 1996 #4481}</sup> Metal salts were stored in a nitrogen atmosphere dry box.

## I. Synthesis of 2-Substituted Nitrostilbenes.

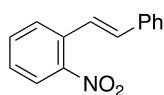
### A. General Procedure.

The requisite (*E*)-1-nitro-2-styrylbenzenes were prepared from substituted 1-bromo-2-nitrobenzene and styrene using a Heck reaction following the procedure reported by Bumagin, Beletskaya and co-workers. Yields were not optimized.



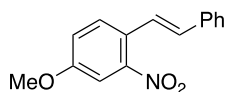
To a solution of 1-bromo-2-nitrobenzene (1.0 equiv), PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (1 mol %), *n*-Bu<sub>3</sub>N (10 mol %) and Na<sub>2</sub>CO<sub>3</sub> (1.5 equiv) in H<sub>2</sub>O was added styrene (1.5 equiv). The resultant mixture was then purged with N<sub>2</sub> and heated to reflux. After 2 h, the mixture was cooled to room temperature and quenched with 3 mL of a 1 M aq soln of HCl. The resulting mixture was then extracted with 3 × 10 mL of ethyl acetate and washed with 10 mL of water and 10 mL of brine. The resulting organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, and the mixture was filtered through a pad of Celite. The filtrate was concentrated *in vacuo*. Purification by MPLC (0:100 – 15:85 EtOAc:hexanes) afforded the product.

### B. Characterization Data



**3.1a**

**2-Nitrostilbene 3.1a.** The general procedure was followed using 0.249 g of 2-iodo-1-nitrobenzene (1.00 mmol), 0.156 g of styrene (1.50 mmol), 0.007 g of  $\text{PdCl}_2(\text{PPh}_3)_2$  (0.01 mmol), 0.019 g of *n*- $\text{Bu}_3\text{N}$  (0.10 mmol), 0.159 g of  $\text{Na}_2\text{CO}_3$  (1.50 mmol) in 2.0 mL of water. Purification by MPLC (0:100 – 15:85 EtOAc:hexanes) afforded **3.1a** as a yellow solid (0.180 g, 80%). The spectral data of **3.1a** matched that reported by Driver and co-workers:<sup>1</sup>  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  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);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz):  $\delta$  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), 126.4 (C), 124.8 (CH), 123.5 (CH); IR (thin film): 1611, 1574, 1520, 1496, 1347, 968, 774  $\text{cm}^{-1}$ .

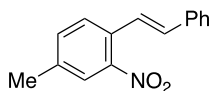


**3.1b**

**4-Methoxy-2-nitrostilbene 3.1b.** The general procedure was followed using 0.558 g of 4-iodo-3-nitroanisole (2.00 mmol), 0.312 g of styrene (3.00 mmol), 0.014 g of  $\text{PdCl}_2(\text{PPh}_3)_2$  (0.02 mmol), 0.038 g of *n*- $\text{Bu}_3\text{N}$  (0.20 mmol), 0.318 g of  $\text{Na}_2\text{CO}_3$  (3.00 mmol) in 4.0 mL of water as a yellow solid. (0.230 g, 90%). The spectral data of **3.1b** matched that reported by Driver and co-workers:<sup>1</sup>  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  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);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  156.8 (C), 137.7 (C), 136.8 (C), 132.6 (C),

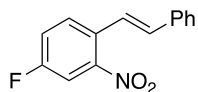
<sup>1</sup>. F. Zhou, D.-S. Wang and T. G. Driver, *Adv. Synth. Catal.*, 2015, **357**, 3463.

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<sub>3</sub>); IR (thin film): 3387, 2922, 2852, 1622, 1598, 1452, 1259, 1203, 1159, 1116, 1019 cm<sup>-1</sup>.



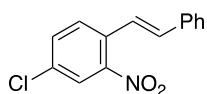
### 3.1c

**4-Methyl-2-nitrostilbene 3.1c.** The general procedure was followed using 0.526 g of 4-iodo-3-nitrotoluene (2.00 mmol), 0.312 g of styrene (3.00 mmol), 0.014 g of PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (0.02 mmol), 0.038 g of *n*-Bu<sub>3</sub>N (0.20 mmol), 0.318 g of Na<sub>2</sub>CO<sub>3</sub> (3.00 mmol) in 4.0 mL of water. Purification by MPLC (0:100 – 10:90 EtOAc:hexanes) afforded **3.1c** as a yellow solid (0.436 g, 91%). The spectral data of **3.1c** matched that reported by Driver and co-workers:<sup>1</sup> <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 7.77 (s, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.59 – 7.53 (m, 3H), 7.42 – 7.36 (m, 3H), 7.32 (t, *J* = 7.3 Hz, 1H), 7.06 (d, *J* = 16.1 Hz, 1H), 2.45 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 147.8 (C), 138.6 (C), 136.7 (C), 134.0 (CH), 133.1 (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<sub>3</sub>); IR (thin film): 1557, 1521, 1450, 1343, 1260, 958, 768, 655 cm<sup>-1</sup>.



### 3.1d

**4-Fluoro-2-nitrostilbene 3.1d.** The general procedure was followed using 0.267 g of 4-fluoro-1-iodo-2-nitrobenzene (1.00 mmol), 0.156 g of styrene (1.50 mmol), 0.007 g of PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (0.01 mmol), 0.019 g of *n*-Bu<sub>3</sub>N (0.10 mmol), 0.159 g of Na<sub>2</sub>CO<sub>3</sub> (1.50 mmol) in 2.0 mL of water. Purification by MPLC (0:100 – 15:85 EtOAc:hexanes) afforded **3.1d** as a yellow solid (0.222 g, 91%). The spectral data of **3.1d** matched that reported by Driver and co-workers:<sup>1</sup> <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$  7.75 – 7.70 (m, 1H), 7.69 (dd, *J* = 8.3, 2.6 Hz, 1H), 7.59 – 7.49 (m, 3H), 7.42 – 7.35 (m, 2H), 7.32 (dd, *J* = 12.7, 5.1 Hz, 2H), 7.01 (d, *J* = 16.1 Hz, 1H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz)  $\delta$  161.1 (C, d, *J* = 250.0 Hz), 148.0 (C, d, *J* = 8.8 Hz), 136.3 (C), 134.0 (CH), 129.9 (CH, d, *J* = 8.8 Hz), 129.5 (C, d, *J* = 3.8 Hz), 128.9 (CH), 128.7 (CH), 127.1 (CH), 122.6 (CH), 120.8 (CH, d, *J* = 21.2 Hz), 112.2 (CH, d, *J* = 26.2 Hz); <sup>19</sup>F NMR (CDCl<sub>3</sub>, 282 MHz)  $\delta$  –119.9, IR (thin film): 3003, 1710, 1534, 1499, 1357, 1291, 1220, 1091 cm<sup>-1</sup>.

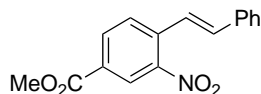


**3.1e**

**4-Chloro-2-nitrostilbene 3.1e.** The general procedure was followed using 0.283 g of 4-chloro-1-iodo-2-nitrobenzene (1.00 mmol), 0.156 g of styrene (1.50 mmol), 0.007 g of PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (0.01 mmol), 0.019 g of *n*-Bu<sub>3</sub>N (0.10 mmol), 0.159 g of Na<sub>2</sub>CO<sub>3</sub> (1.50 mmol) in 2.0 mL of water. Purification by MPLC (0:100 – 10:90 EtOAc:hexanes) afforded **3.1e** as a yellow solid (0.166 g, 64%). The spectral data of **3.1e** matched that reported by Driver and co-workers:<sup>1</sup> <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$  7.94 (d, *J* = 2.0 Hz, 1H), 7.69 (d, *J* = 8.4 Hz, 1H), 7.55 – 7.52 (m, 4H), 7.39 (t, *J* = 7.4 Hz, 2H), 7.35 (d, *J* = 7.1 Hz, 1H), 7.07 (d, *J* = 16.1 Hz, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz)  $\delta$  148.0 (C), 136.2 (C), 134.5 (CH), 133.5 (C), 133.2 (CH), 131.5 (C), 129.2 (CH), 128.9 (CH), 127.2

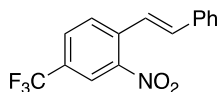


(CH), 124.8 (CH), 122.3 (CH), only peaks visible; IR (thin film): 1628, 1527, 1447, 1346, 1257, 1151, 1112, 960, 893, 818, 766, 698, 535  $\text{cm}^{-1}$ .



### 3.1f

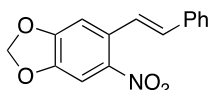
**Methyl (E)-3-nitro-4-styrylbenzoate 3.1f.** The general procedure was followed using 0.307 g of methyl 4-iodo-3-nitrobenzoate (1.00 mmol), 0.156 g of styrene (1.50 mmol), 0.007 g of  $\text{PdCl}_2(\text{PPh}_3)_2$  (0.01 mmol), 0.019 g of *n*- $\text{Bu}_3\text{N}$  (0.10 mmol), 0.159 g of  $\text{Na}_2\text{CO}_3$  (1.50 mmol) in 2.0 mL of water. Purification by MPLC (0:100 – 15:85 EtOAc:hexanes) afforded **3.1f** as a yellow solid (0.226 g, 80%). Nitrostillbene **3.1f** was previously reported by Delpiccolo and co-workers:<sup>2</sup>  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  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), 7.42 – 7.39 (m, 2H), 7.36 – 7.33 (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);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  165.0 (C), 147.9 (C), 136.9 (C), 135.9 (CH), 133.4 (CH), 129.8 (C), 129.2 (CH), 128.9 (CH), 128.1 (CH), 127.4 (CH), 126.6 (C), 126.1 (CH), 122.4 (CH), 52.7 ( $\text{CH}_3$ ); IR (thin film): 1727, 1620, 1546, 1513, 1347, 1288, 1263, 1113, 1011, 768, 682  $\text{cm}^{-1}$ .



<sup>2</sup>. C. I. Traficante, C. Fagundez, G. L. Serra, E. G. Mata and C. M. L. Delpiccolo, *ACS Comb. Sci.*, 2016, **18**, 225.

### 3.1g

**2-Nitro-4-trifluoromethylstilbene 3.1g.** The general procedure was followed using 0.270 g of 3-bromo-4-nitrobenzotrifluoride (1.00 mmol), 0.156 g of styrene (1.50 mmol), 0.007 g of  $\text{PdCl}_2(\text{PPh}_3)_2$  (0.01 mmol), 0.019 g of *n*- $\text{Bu}_3\text{N}$  (0.10 mmol), 0.159 g of  $\text{Na}_2\text{CO}_3$  (1.50 mmol) in 2.0 mL of water. Purification by MPLC (0:100 – 15:85 EtOAc:hexanes) afforded **3.1g** as a yellow solid. The spectral data of **3.1g** matched that reported by Driver and co-workers:<sup>1</sup>  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  8.24 (s, 1H), 7.92 (d,  $J = 8.2$  Hz, 1H), 7.84 (d,  $J = 8.1$  Hz, 1H), 7.62 (d,  $J = 16.1$  Hz, 1H), 7.56 (d,  $J = 7.4$  Hz, 2H), 7.41 (q,  $J = 7.4$  Hz, 2H), 7.36 (t,  $J = 7.2$  Hz, 1H), 7.19 (d,  $J = 16.1$  Hz, 1H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  147.6 (C), 136.4 (C), 136.3 (CH), 135.8 (C), 130.2 (q,  $J_{\text{CF}} = 33.8$  Hz, C), 129.4 (CH), 129.3 (CH), 128.9 (CH), 127.4 (CH), 124.0 (CH), 122.9 (q,  $J_{\text{CF}} = 37.5$  Hz, C), 122.0 (CH);  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ , 282 MHz)  $\delta$  –63.3, IR (thin film): 1727, 1623, 1566, 1534, 1490, 1352, 1324, 1123, 962, 936, 855, 768, 689, 525  $\text{cm}^{-1}$ .

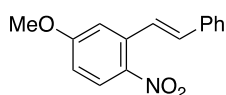


### 3.1h

**(E)-5-Nitro-6-styrylbenzo[d][1,3]dioxole 3.1h.** The general procedure was followed using 0.246 g of 5-bromo-6-nitrobenzo[d][1,3]dioxole (1.00 mmol), 0.156 g of styrene (1.50 mmol), 0.007 g of  $\text{PdCl}_2(\text{PPh}_3)_2$  (0.01 mmol), 0.019 g of *n*- $\text{Bu}_3\text{N}$  (0.10 mmol), 0.159 g of  $\text{Na}_2\text{CO}_3$  (1.50 mmol) in 2.0 mL of water. Purification by MPLC (0:100 – 15:85 EtOAc:hexanes) afforded **3.1h** as a yellow solid. The spectral data of **3.1h** matched that reported by Peters and co-workers:<sup>3</sup>  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ,

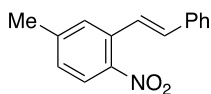
<sup>3</sup>. P. Du, J. L. Brosmer and D. G. Peters, *Org. Lett.*, 2011, **13**, 4072.

500 MHz)  $\delta$  7.67 (t,  $J$  = 12.6 Hz, 1H), 7.53 (d,  $J$  = 6.0 Hz, 3H), 7.38 (t,  $J$  = 7.5 Hz, 2H), 7.31 (t,  $J$  = 7.3 Hz, 1H), 7.13 (s, 1H), 6.96 (d,  $J$  = 16.1 Hz, 1H), 6.12 (s, 2H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  152.0 (C), 147.3 (C), 142.1 (C), 136.6 (C), 132.9 (CH), 130.5 (C), 128.8 (CH), 128.5 (CH), 127.0 (CH), 124.4 (CH), 106.7 (CH), 105.5 (CH), 103.0 (CH). IR (thin film): 2910, 1609, 1504, 1324, 1179, 1035, 960, 876, 762, 692  $\text{cm}^{-1}$ .



### 3.1i

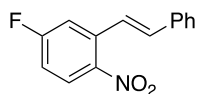
**5-Methoxy-2-nitrostilbene 3.1i.** The general procedure was followed using 0.279 g of 3-iodo-4-nitroanisole (1.00 mmol), 0.156 g of styrene (1.50 mmol), 0.007 g of  $\text{PdCl}_2(\text{PPh}_3)_2$  (0.01 mmol), 0.019 g of  $n\text{-Bu}_3\text{N}$  (0.10 mmol), 0.159 g of  $\text{Na}_2\text{CO}_3$  (1.50 mmol) in 2.0 mL of water. Purification by MPLC (0:100 – 15:85 EtOAc:hexanes) afforded **3.1i** as a yellow solid (0.229 g, 90%). The spectral data of **3.1i** matched that reported by Driver and co-workers:<sup>1</sup>  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  8.03 (d,  $J$  = 9.5 Hz, 1H), 7.71 (d,  $J$  = 16.0 Hz, 1H), 7.53 (d,  $J$  = 7.4 Hz, 2H), 7.37 (t,  $J$  = 7.4 Hz, 2H), 7.31 (t,  $J$  = 7.3 Hz, 1H), 7.11 (d,  $J$  = 2.7 Hz, 1H), 7.00 (d,  $J$  = 16.1 Hz, 1H), 6.82 (dd,  $J$  = 9.1, 2.7 Hz, 1H), 3.89 (s, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  163.3 (C), 141.0 (C), 136.6 (C), 136.2 (C), 133.6 (CH), 128.8 (CH), 128.6 (CH), 127.6 (CH), 127.2 (CH), 124.8 (CH), 113.2 (CH), 113.0 (CH), 56.0 ( $\text{CH}_3$ ); IR (thin film): 1601, 1577, 1504, 1476, 1335, 1290, 1235, 958, 876, 764, 691  $\text{cm}^{-1}$ .



### 3.1j

**5-Methyl-2-nitrostilbene 3.1j.** The general procedure was followed using 0.263 g of 3-iodo-4-nitroanisole (2.00 mmol), 0.312 g of styrene (3.00 mmol), 0.014 g of  $\text{PdCl}_2(\text{PPh}_3)_2$  (0.02 mmol), 0.038 g of *n*- $\text{Bu}_3\text{N}$  (0.10 mmol), 0.318 g of  $\text{Na}_2\text{CO}_3$  (3.00 mmol) in 4.0 mL of water. Purification by MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **3.1j** as a yellow solid (0.422 g, 88%). The spectral data of **3.1j** matched that reported by Driver and co-workers:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  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);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  145.8 (C), 144.2 (C), 136.6 (C), 133.5 (CH), 133.3 (C), 128.8 (CH), 128.7 (CH), 128.5 (CH), 128.2 (C), 127.1 (CH), 125.1 (CH), 124.1 (CH), 21.6

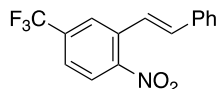
(CH<sub>3</sub>), only peaks visible; IR (thin film): 3004, 1710, 1580, 1520, 1419, 1359, 902  $\text{cm}^{-1}$ .



### 3.1k

**5-Fluoro-2-nitrostilbene 3.1k.** The general procedure was followed using 0.267 g of 5-fluoro-1-iodo-2-nitrobenzene (1.00 mmol), 0.156 g of styrene (1.50 mmol), 0.007 g of  $\text{PdCl}_2(\text{PPh}_3)_2$  (0.01 mmol), 0.019 g of *n*- $\text{Bu}_3\text{N}$  (0.10 mmol), 0.159 g of  $\text{Na}_2\text{CO}_3$  (1.50 mmol) in 2.0 mL of water. Purification by MPLC (0:100 – 15:85 EtOAc:hexanes) afforded **3.1k** as a yellow solid. The

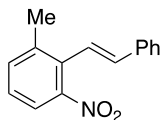
spectral data of **3.1k** matched that reported by Gooßen and co-workers:<sup>4</sup> <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz): δ 8.06 (dd, *J* = 9.0, 5.2 Hz, 1H), 7.64 (d, *J* = 16.1 Hz, 1H), 7.55 (d, *J* = 7.4 Hz, 2H), 7.45 – 7.31 (m, 4H), 7.12 – 7.03 (m, 2H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 165.9 (C), 163.8 (C), 136.6 (C, d, *J* = 8.8 Hz), 136.1 (C), 135.1 (CH), 129.0 (CH), 128.9 (CH), 127.8 (CH, d, *J* = 10.0 Hz), 127.3 (CH), 122.9 (CH), 115.0 (CH, d, *J* = 22.5 Hz), 114.6 (CH, d, *J* = 23.8 Hz). <sup>19</sup>F NMR (CDCl<sub>3</sub>, 282 MHz): δ –104.4. IR (thin film): 1710, 1581, 1527, 1359, 1220, 1092, 902 cm<sup>–1</sup>.



### 3.11

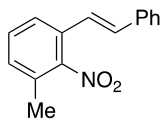
**2-Nitro-5-trifluoromethylstilbene 3.11.** The general procedure was followed using 0.540 g of 2-bromo-1-nitro- 4-(trifluoromethyl)benzene (2.00 mmol), 0.312 g of styrene (3.00 mmol), 0.014 g of PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (0.02 mmol), 0.038 g of *n*-Bu<sub>3</sub>N (0.10 mmol), 0.318 g of Na<sub>2</sub>CO<sub>3</sub> (3.00 mmol) in 4.0 mL of water. Purification by MPLC (0:100 – 10:90 EtOAc:hexanes) afforded **3.11** as a yellow solid (0.274 g, 47%). The spectral data of **3.11** matched that reported by Driver and co-workers:<sup>1</sup> <sup>1</sup>H NMR (CDCl<sub>3</sub>, 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); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 149.7 (C), 135.9 (C), 135.7 (CH), 134.6 (q, *J*<sub>CF</sub> = 33.5 Hz, C), 133.6 (C), 129.2 (CH), 128.9 (CH), 128.1 (q, *J*<sub>CF</sub> = 135 Hz, CH), 127.3 (CH), 125.3 (q, *J*<sub>CF</sub> = 8.9 Hz, CH), 124.6 (CH), 123.1 (q, *J*<sub>CF</sub> = 270.9, C), 121.7 (CH); IR (thin film): 1622, 1589, 1528, 1490, 1327, 1255, 1173, 963, 902, 831, 765, 689, 533 cm<sup>–1</sup>

<sup>4</sup> L. J. Gooßen, B. Zimmermann and T. Knauber, *Beilstein J. Org. Chem.*, 2010, **6**, 43.



### 3.1m

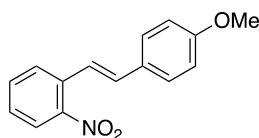
**(E)-1-Methyl-3-nitro-2-styrylbenzene 3.1m.** The general procedure was followed using 0.263 g of 2-iodo-3-nitrotoluene (1.00 mmol), 0.156 g of styrene (1.50 mmol), 0.007 g of  $\text{PdCl}_2(\text{PPh}_3)_2$  (0.01 mmol), 0.019 g of *n*- $\text{Bu}_3\text{N}$  (0.10 mmol), 0.159 g of  $\text{Na}_2\text{CO}_3$  (1.50 mmol) in 2.0 mL of water. Purification by MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **3.1m** as a yellow oil (0.242 g, 75%). Nitrostyrene **3.1m** was previously reported by Driver and co-workers:<sup>5</sup>  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  7.70 (dd,  $J = 34.9, 8.1$  Hz, 1H), 7.51 (d,  $J = 7.4$  Hz, 2H), 7.45 (t,  $J = 8.5$  Hz, 1H), 7.38 (dd,  $J = 20.0, 12.4$  Hz, 2H), 7.31 (dt,  $J = 12.5, 7.6$  Hz, 2H), 7.22 (d,  $J = 16.6$  Hz, 1H), 6.60 (d,  $J = 16.6$  Hz, 1H), 2.46 (s, 3H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  150.1 (C), 139.0 (C), 136.6 (C), 135.0 (CH), 134.2 (CH), 131.9 (C), 128.8 (CH), 128.4 (CH), 127.4 (CH), 126.8 (CH), 122.6 (CH), 121.6 (CH), 20.9 ( $\text{CH}_3$ ). IR (thin film): 3011, 1520, 1495, 1449, 1349, 1287  $\text{cm}^{-1}$ .



### 3.1n

<sup>5</sup>. M. Shevlin, X. Guan and T. G. Driver, *ACS Catal.*, 2017, 5518.

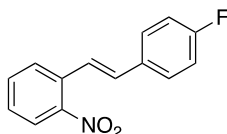
**(E)-1-Methyl-2-nitro-3-styrylbenzene 3.1n.** The general procedure was followed using 0.216 g of 3-iodo-2-nitrotoluene (1.00 mmol), 0.156 g of styrene (1.50 mmol), 0.007 g of  $\text{PdCl}_2(\text{PPh}_3)_2$  (0.01 mmol), 0.019 g of *n*-Bu<sub>3</sub>N (0.10 mmol), 0.159 g of Na<sub>2</sub>CO<sub>3</sub> (1.50 mmol) in 2.0 mL of water. Purification by MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **3.1n** as a yellow oil (0.104 g, 46 %). The spectral data of **3.1n** matched that reported by Gooßen and co-workers:<sup>4</sup> <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$  7.65 (d, *J* = 8.1 Hz, 1H), 7.49 (d, *J* = 7.5 Hz, 2H), 7.45 (d, *J* = 7.6 Hz, 1H), 7.37 (t, *J* = 7.5 Hz, 2H), 7.33 – 7.27 (m, 2H), 7.19 (d, *J* = 16.6 Hz, 1H), 6.58 (d, *J* = 16.6 Hz, 1H), 2.45 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz)  $\delta$  150.1 (C), 139.0 (C), 136.6 (C), 135.0 (CH), 134.1 (CH), 132.0 (C), 128.8 (CH), 128.3 (CH), 127.3 (CH), 126.7 (CH), 122.6 (CH), 121.5 (CH), 20.9 (CH<sub>3</sub>); IR (thin film): 1520, 1495, 1449, 1349, 1287, 1033, 877 cm<sup>-1</sup>



**3.1o**

**(E)-1-(4-Methoxystyryl)-2-nitrobenzene 3.1o.** The general procedure was followed using 0.249 g of 1-iodo-2-nitrobenzene (1.00 mmol), 0.201 g of 4-vinylanisole (1.50 mmol), 0.007 g of  $\text{PdCl}_2(\text{PPh}_3)_2$  (0.01 mmol), 0.019 g of *n*-Bu<sub>3</sub>N (0.10 mmol), 0.159 g of Na<sub>2</sub>CO<sub>3</sub> (1.50 mmol) in 2.0 mL of water. Purification by MPLC (0:100 – 15:85 EtOAc:hexanes) afforded **3.1o** as a yellow solid (0.250 g, 98%). The spectral data of **3.1o** matched that reported by Driver and co-workers:<sup>1</sup> <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$  7.93 (d, *J* = 7.9 Hz, 1H), 7.74 (d, *J* = 7.8 Hz, 1H), 7.57 (t, *J* = 7.5 Hz, 1H), 7.49 – 7.45 (m, 3H), 7.35 (t, *J* = 7.5 Hz, 1H), 7.05 (d, *J* = 16.1 Hz, 1H), 6.91 (d, *J* = 8.7 Hz, 2H), 3.83 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz)  $\delta$  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<sub>3</sub>); IR (thin film): 1596, 1570, 1511, 1465, 1336, 1245, 1174, 966, 797 cm<sup>-1</sup>.

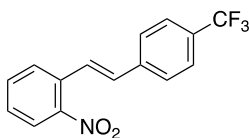


### 3.1p

**(E)-1-(4-Fluorostyryl)-2-nitrobenzene 3.1p.** The general procedure was followed using 0.249 g of 2-iodo-1-nitrobenzene (1.00 mmol), 0.183 g of 1-fluoro-4-vinylbenzene (1.50 mmol), 0.007 g of PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (0.01 mmol), 0.019 g of *n*-Bu<sub>3</sub>N (0.10 mmol), 0.159 g of Na<sub>2</sub>CO<sub>3</sub> (1.50 mmol) in 2.0 mL of water. Purification by MPLC (0:100 – 15:85 EtOAc:hexanes) afforded **3.1p** as a yellow solid. Nitrostillbene **3.1p** was previously reported by Gutmann, Roberge, Kappe and co-workers:<sup>6</sup> <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 7.97 (d, *J* = 8.1 Hz, 1H), 7.75 (d, *J* = 7.8 Hz, 1H), 7.61 (t, *J* = 7.5 Hz, 1H), 7.55 – 7.48 (m, 3H), 7.41 (t, *J* = 7.3 Hz, 1H), 7.07 (dd, *J* = 21.2, 12.4 Hz, 3H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 152.0 (C), 147.3 (C), 136.6 (CH), 132.9 (C), 130.50 (CH), 128.7 (CH, d, *J* = 40.0 Hz), 127.0 (CH), 124.4 (CH), 106.7 (CH), 105.5 (CH), 103.0 (CH), only peaks visible. <sup>19</sup>F NMR (CDCl<sub>3</sub>, 282 MHz): δ –113.0. IR (thin film): 2360, 1709, 1508, 1421, 1358, 1221, 1093, 819, 740 cm<sup>-1</sup>.

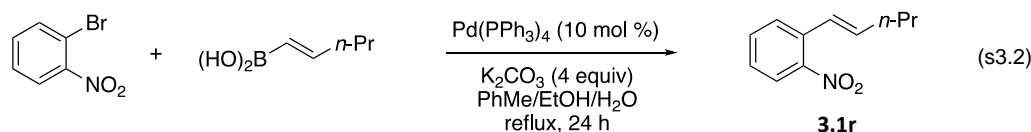
<sup>6</sup> G. Glotz, B. Gutmann, P. Hanselmann, A. Kulesza, D. Roberge and C. O. Kappe, *RCS Adv.*, 2017, **7**, 10469.





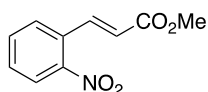
### 3.1q

**(E)-1-Nitro-2-(4-(trifluoromethyl)styryl)benzene 3.1q.** The general procedure was followed using 0.249 g of 1-iodo-2-nitrobenzene (1.00 mmol), 0.258 g of 4-(trifluoromethyl)styrene (1.50 mmol), 0.007 g of  $\text{PdCl}_2(\text{PPh}_3)_2$  (0.01 mmol), 0.019 g of *n*- $\text{Bu}_3\text{N}$  (0.10 mmol), 0.159 g of  $\text{Na}_2\text{CO}_3$  (1.50 mmol) in 2.0 mL of water. Purification by MPLC (0:100 – 15:85 EtOAc:hexanes) afforded **3.1q** as a yellow solid (0.199 g, 68%). The spectral data of **3.1q** matched that reported by Driver and co-workers:<sup>1</sup>  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  7.98 (d,  $J$  = 8.1 Hz, 1H), 7.74 (d,  $J$  = 7.8 Hz, 1H), 7.67 (d,  $J$  = 16.1 Hz, 1H), 7.61 (d,  $J$  = 10.7 Hz, 5H), 7.45 – 7.42 (m, 1H), 7.06 (d,  $J$  = 16.1 Hz, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  148.0 (C), 139.9 (C), 133.3 (CH), 132.4 (C), 132.0 (CH), 130.2 (q,  $J_{\text{CF}}$  = 32.8 Hz, C), 128.6 (CH), 128.3 (CH), 127.2 (CH), 126.3 (CH), 125.7 (CH), 124.8 (CH); 124.0 (q,  $J_{\text{CF}}$  = 270.9 Hz, C);  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ , 282 MHz)  $\delta$  –62.2; IR (thin film): 1615, 1531, 1347, 1326, 1099, 1064, 833  $\text{cm}^{-1}$ .



**(E)-1-Nitro-2-(pent-1-en-1-yl)benzene 3.1r.** To a solution of 0.125 g of 1-penten-1-ylboronic acid (1.10 mmol), 0.115 g of  $\text{Pd}(\text{PPh}_3)_4$  (0.100 mmol) and 0.553 g of  $\text{K}_2\text{CO}_3$  (4.00 mmol) in 6 mL of toluene, 2.0 mL of EtOH and 1.0 mL of water was added 0.202 g of 1-bromo-2-nitrobenzene (1.00 mmol). The resultant mixture was then purged with  $\text{N}_2$  and refluxed. After 24 h, the mixture

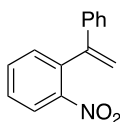
was cooled to room temperature and diluted with 30 mL of water and 30 mL of CH<sub>2</sub>Cl<sub>2</sub>. The phases were separated, and the resulting aqueous phase was extracted with an additional 2 × 30 mL of CH<sub>2</sub>Cl<sub>2</sub>. The combined organic phases were washed with 1 × 20 mL of distilled water and 1 × 20 mL of brine. The resulting organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, and the heterogeneous mixture was filtered. The filtrate was concentrated in vacuo. Purification by MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **3.1r** as a brown liquid (0.178 g, 93%). The spectral data of **3.1r** matched that reported by Driver and co-workers:<sup>1</sup> <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 7.83 (dd, *J* = 8.2, 0.9 Hz, 1H), 7.56 (d, *J* = 7.2 Hz, 1H), 7.51 – 7.48 (m, 1H), 7.32 – 7.29 (m, 1H), 6.81 (d, *J* = 15.7 Hz, 1H), 6.22 (dt, *J* = 15.6, 7.0 Hz, 1H), 2.22 (qd, *J* = 7.2, 1.0 Hz, 2H), 1.51 (sextet, *J* = 7.4 Hz, 2H), 0.96 (t, *J* = 7.4 Hz, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 147.7 (C), 136.7 (CH), 133.4 (C), 132.8 (CH), 128.4 (CH), 127.3 (CH), 125.0 (CH), 124.3 (CH), 35.2 (CH<sub>2</sub>), 22.2 (CH<sub>2</sub>), 13.7 (CH<sub>3</sub>); IR (thin film): 1605, 1570, 1521, 1343, 966, 857 cm<sup>-1</sup>.



**3.1s**

**Methyl 2-nitrocinnamate 3.1s.** To a 25 mL round-bottom flask equipped with magnetic stir bar, reflux condenser, and nitrogen inlet was added 0.193 g of trans-2-nitro-cinnamic acid (1.00 mmol), DMSO (0.2 M substrate concentration), and 1.800 g of dimethyl carbonate (20.00 mmol). To the resulting solution was added 0.055 g of potassium carbonate (0.40 mmol) in one portion. The reaction mixture was magnetically stirred and heated to 90 °C for 16 h. After cooling to room temperature, the reaction was diluted with ethyl acetate (15 mL), washed with water (2 × 10 mL) and brine (1 × 10 mL), and dried with magnesium sulfate. Pure methyl ester **3.1s** was obtained

upon removal of solvent as a pale yellow amorphous solid (0.201 g, 97%). The spectral data of **3.1s** matched that reported by Bergdahl and co-workers:<sup>7</sup> <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 8.08 (d, *J* = 15.8 Hz, 1H), 8.01 (d, *J* = 8.2 Hz, 1H), 7.62 (t, *J* = 8.4 Hz, 2H), 7.53 (t, *J* = 7.5 Hz, 1H), 6.35 (d, *J* = 15.8 Hz, 1H), 3.80 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 166.2 (C), 148.3 (C), 140.1 (CH), 133.6 (CH), 130.5 (C), 130.4 (CH), 129.1 (CH), 124.9 (CH), 122.9 (CH), 52.0 (CH<sub>3</sub>); IR (thin film): 3088, 3049, 2950, 1692, 1606, 1567, 1520, 1437, 1401, 1340, 1273, 1250, 1034, 986, 872 cm<sup>-1</sup>.

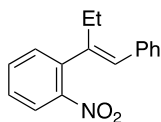


### 3.1t

**(E)-1-Nitro-2-(1-phenylbut-1-en-2-yl)benzene 3.1t.** The procedure for **3.1r** was followed using 0.101 g of 1-bromo-2-nitrobenzene (0.50 mmol), 0.161 g of 1-phenylvinylboronic acid pinacol ester (0.70 mmol), 0.057 g of Pd(PPh<sub>3</sub>)<sub>4</sub> (0.050 mmol) and 0.277 g of K<sub>2</sub>CO<sub>3</sub> (2.00 mmol) in 3 mL of toluene, 1.2 mL of EtOH and 0.6 mL of water. Purification by MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **3.1t** as a yellow oil (0.80 g, 71%). The spectral data of **3.1t** matched that reported by Driver and co-workers:<sup>1</sup> <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 7.94 (dd, *J* = 8.1, 0.9 Hz, 1H), 7.63 (td, *J* = 7.5, 1.2 Hz, 1H), 7.51 (td, *J* = 8.0, 1.4 Hz, 1H), 7.46 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.28 (t, *J* = 5.7 Hz, 3H), 7.25 – 7.23 (m, 2H), 5.75 (s, 1H), 5.32 (s, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 148.9 (C), 146.5 (C), 139.1 (C), 137.0 (C), 132.8 (C), 132.5 (CH), 128.7 (CH), 128.4 (CH),

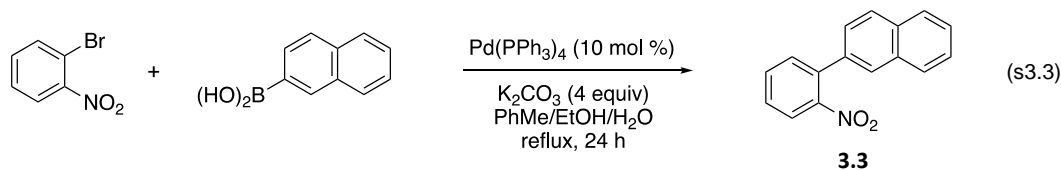
<sup>7</sup> J. Dambacher, W. Zhao, A. El-Batta, R. Anness, C. Jiang and M. Bergdahl, *Tetrahedron Lett.*, 2005, **46**, 4473.

128.2 (CH), 126.5 (CH), 124.4 (CH), 115.5 (CH). IR (thin film): 3416, 3056, 1604, 1544, 1486, 1453, 1415, 1340, 1268, 1241, 1108, 1098  $\text{cm}^{-1}$ .

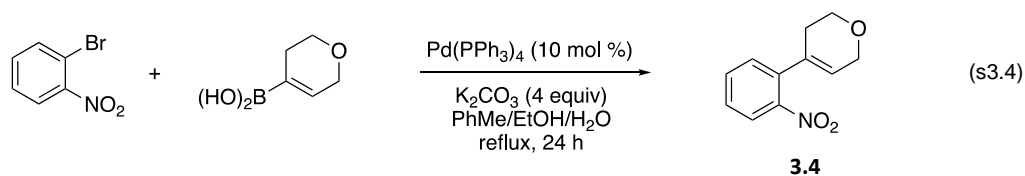


### 3.1u

**(E)-1-nitro-2-(1-phenylbut-1-en-2-yl)benzene 3.1u.**{Zhou, 2015 #7436} The procedure for **3.1r** was followed using 0.101 g of 1-bromo-2-nitrobenzene (0.50 mmol), 0.123 g of (Z)-(1-phenylbut-1-en-2-yl)boronic acid (0.70 mmol), 0.057 g of  $\text{Pd}(\text{PPh}_3)_4$  (0.050 mmol) and 0.277 g of  $\text{K}_2\text{CO}_3$  (2.00 mmol) in 3 mL of toluene, 1.2 mL of EtOH and 0.6 mL of water. Purification by MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **3.1u** as a brown liquid (0.125 g, 99%). The spectral data of **3.1u** matched that reported by Driver and co-workers:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  7.95 (d,  $J$  = 7.7 Hz, 1H), 7.63 – 7.60 (m, 1H), 7.48 – 7.36 (m, 6H), 7.30 (t,  $J$  = 7.0 Hz, 1H), 6.44 (s, 1H), 2.71 (q,  $J$  = 7.6 Hz, 2H), 1.04 (t,  $J$  = 7.6 Hz, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  149.1 (C), 141.8 (C), 138.9 (C), 137.3 (C), 132.4 (CH), 131.4 (CH), 129.1 (CH), 128.9 (CH), 128.3 (CH), 127.9 (CH), 127.1 (CH), 124.2 (CH), 25.2 ( $\text{CH}_2$ ), 13.0 ( $\text{CH}_3$ ); IR (thin film): 1606, 1570, 1523, 1492, 1344, 1073, 873  $\text{cm}^{-1}$ .

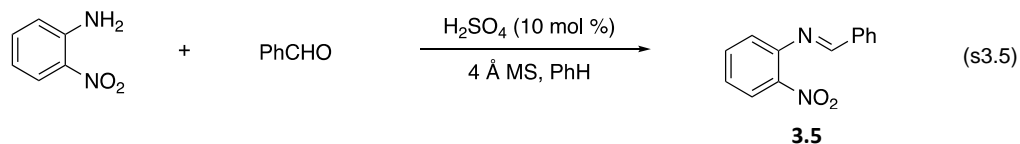


**2-(2-Nitrophenyl)naphthalene 3.3.** To a solution of 0.241 g of naphthalen-2-ylboronic acid (1.40 mmol), 0.115 g of Pd(PPh<sub>3</sub>)<sub>4</sub> (0.100 mmol) and 0.553 g of K<sub>2</sub>CO<sub>3</sub> (4.00 mmol) in 6 mL of toluene, 2.4 mL of EtOH and 1.2 mL of water was added 0.202 g of 1-bromo-2-nitrobenzene (1.00 mmol). The resultant mixture was then purged with N<sub>2</sub> and refluxed. After 24 h, the mixture was cooled to room temperature and diluted with 30 mL of water and 30 mL of CH<sub>2</sub>Cl<sub>2</sub>. The phases were separated, and the resulting aqueous phase was extracted with an additional 2 × 30 mL of CH<sub>2</sub>Cl<sub>2</sub>. 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<sub>2</sub>SO<sub>4</sub>, and the heterogeneous mixture was filtered. The filtrate was concentrated in vacuo. Purification by MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **3.3** as a brown solid (0.178 g, 93%). The spectral data of **3.3** matched that reported by Gooßen and co-workers.<sup>4</sup> <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 7.90 (ddd, *J* = 13.3, 10.5, 5.9 Hz, 4H), 7.83 (s, 1H), 7.65 (t, *J* = 7.4 Hz, 1H), 7.57 – 7.48 (m, 4H), 7.43 (dd, *J* = 8.4, 1.3 Hz, 1H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 149.4, 136.5, 135.0, 133.3 (CH), 132.9 (CH), 132.5 (CH), 132.3 (CH), 128.4 (CH), 128.3 (CH), 128.2 (CH), 127.8 (CH), 127.0 (CH), 126.6 (CH), 125.8 (CH), 124.3 (CH), only peaks visible; IR (thin film): 1710, 1422, 1358, 1220, 1092, 787 cm<sup>-1</sup>.



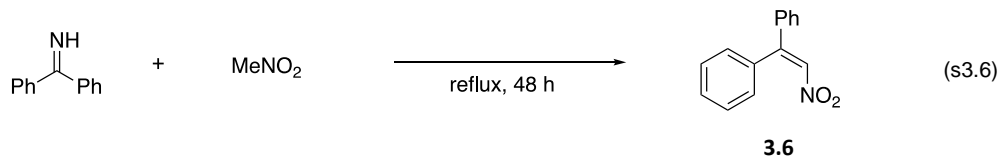
**4-(2-Nitrophenyl)-3,6-dihydro-2H-pyran 3.4.** To a solution of 0.294 g of 3,6-dihydro-2H-pyran-4-boronic acid pinacol ester (1.40 mmol), 0.115 g of Pd(PPh<sub>3</sub>)<sub>4</sub> (0.100 mmol) and 0.553 g of K<sub>2</sub>CO<sub>3</sub> (4.00 mmol) in 6 mL of toluene, 2.4 mL of EtOH and 1.2 mL of water was added 0.202 g

of 1-bromo-2-nitrobenzene (1.00 mmol). The resultant mixture was then purged with N<sub>2</sub> and refluxed. After 24 h, the mixture was cooled to room temperature and diluted with 30 mL of water and 30 mL of CH<sub>2</sub>Cl<sub>2</sub>. The phases were separated, and the resulting aqueous phase was extracted with an additional 2 × 30 mL of CH<sub>2</sub>Cl<sub>2</sub>. 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<sub>2</sub>SO<sub>4</sub>, and the heterogeneous mixture was filtered. The filtrate was concentrated in vacuo. Purification by MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **3.4** as a yellow liquid (0.194 g, 95 %). The spectral data of **3.4a** matched that reported by Driver and co-workers:<sup>1</sup> <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 7.75 (d, *J* = 8.1 Hz, 1H), 7.47 (dd, *J* = 11.0, 4.1 Hz, 1H), 7.40 – 7.28 (m, 1H), 7.22 (d, *J* = 7.6 Hz, 1H), 5.55 (s, 1H), 4.13 (dd, *J* = 5.0, 2.4 Hz, 2H), 3.79 (t, *J* = 5.3 Hz, 2H), 2.22 (dd, *J* = 4.3, 2.4 Hz, 2H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 148.2 (C), 137.3 (C), 133.7 (C), 132.9 (CH), 130.7 (CH), 128.1 (CH), 124.8 (CH), 124.1 (CH), 65.3 (CH<sub>2</sub>), 64.1 (CH<sub>2</sub>), 29.0 (CH<sub>2</sub>); IR (thin film): 1571, 1523, 1383, 1347, 1128, 853 cm<sup>-1</sup>.



**(E)-N-(2-Nitrophenyl)-1-phenylmethanimine 3.5.** A round-bottom flask with a reflux condenser was charged with 20 mL of dry benzene and 0.83 g of 2-nitroaniline (6.0 mmol), 0.53 g of benzaldehyde (5.0 mmol), 5 g of the freshly baked molecular sieves. 0.04 mL of 12 M sulfuric acid was added at 0 °C and the reaction was then heated 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<sub>3</sub>N) afforded **3.5** as a yellow solid (0.531 g, 68%). The spectral data of **3.5** matched that reported by Crenncia and co-workers:<sup>8</sup> <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 8.94 (s, 1H), 8.31 (dd, *J* = 7.8, 1.0 Hz, 1H), 8.07 (dd, *J* = 8.2, 0.8 Hz, 1H), 7.74 (t, *J* = 7.6 Hz, 1H), 7.68 – 7.56 (m, 1H), 7.48 – 7.34 (m, 2H), 7.33 – 7.22 (m, 3H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) 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<sup>-1</sup>.



**(2-Nitroethene-1,1-diyl)dibenzene 3.6.** Benzophenone imine (0.91 g, 5.00 mmol) and nitromethane (2.44 g, 40.0 mmol) were placed in a 10 mL flask and the mixture was refluxed for 2 d. After cooling to room temperature, the reaction mixture was evaporated and purified by a silica gel column chromatography (0:100 – 1:40 EtOAc:hexanes) afforded **3.6** as a yellow solid (0.87 g, 3.87 mmol, 78%). The spectral data of **3.6** matched that reported by Hsieh and Dong:<sup>9</sup> <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 7.49 – 7.41 (m, 5H), 7.39 (t, *J* = 7.6 Hz, 2H), 7.29 (d, *J* = 7.5 Hz, 2H), 7.25 – 7.20 (m, 2H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 150.5 (C), 137.1 (C), 135.6 (C), 134.4 (CH), 130.9 (CH), 129.4 (CH), 128.9 (CH), 128.9 (CH), 128.8 (CH), 128.5 (CH). IR (thin film): 3109, 3061, 1618, 1593, 1573, 1506, 1485, 1440, 1390, 1346, 1330, 1240, 1186, 1155, 1072, 1030, 993, 767 cm<sup>-1</sup>.

<sup>8</sup>. E. C. Crencia, M. Kosaka, T. Muramatsu, M. Kobayashi, T. Iizuka, T. Horaguchi, *J. Heterocycl. Chem.* 2009, **46**, 1309.

<sup>9</sup>. T. H. H. Hsieh and V. M. Dong, *Tetrahedron*, 2009, **65**, 3062.

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

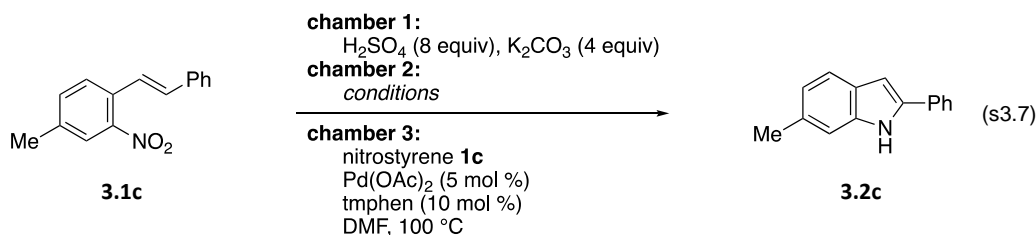
### A. Screening of Deoxygenation Conditions

To a 30 mL 3-chamber reactor, K<sub>2</sub>CO<sub>3</sub> (4 equiv) in water and a 1 M aq soln of H<sub>2</sub>SO<sub>4</sub> (8 equiv) were added and frozen sequentially in chamber 1, reductant (0.2 equiv), catalyst and solvent were added to chamber 2, 0.10 mmol of nitrostyrene, palladium acetate (5 mol %), tetramethylphenanthroline (10 mol %) and 1 mL of DMF was added to chamber 3. The 3-chamber reactor was sealed from outer environment while allowing gas exchange among each other. Then the frozen reaction mixture in chamber 1 was allowed to thaw and stir until effervescence of CO<sub>2</sub> was no longer observed. Chamber 3 was heated at 100 °C while chamber 1 and 2 were stirring at room temperature (Figure S3.1). After 14 h, the reaction mixture was cooled to room temperature and filtered through a pad of silica gel. The filtrate was concentrated *in vacuo*, and the residue was analyzed using <sup>1</sup>H NMR spectroscopy using CH<sub>2</sub>Br<sub>2</sub> as the internal standard.

**Figure S3.1.** 30 mL three-chamber reactor.

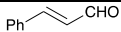


**Table S3.1.** Optimization of deoxygenation of CO<sub>2</sub> for Pd-catalyzed reductive cyclization into indoles.



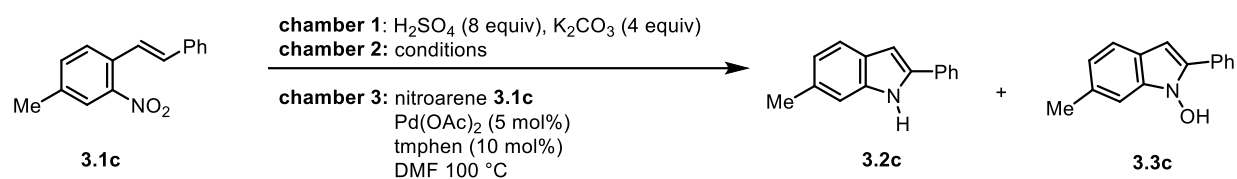
Entry <sup>a</sup>	catalyst (mol %)	reductant (2 equiv)	solvent	T (°C)	%, Yield <b>3.2a</b>
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1	IMesCl, K <sub>2</sub> CO <sub>3</sub>		DMF	100	n.r.
2	ZnBr <sub>2</sub> , CH <sub>2</sub> I <sub>2</sub>	Et <sub>3</sub> P	PhMe	100	n.r.
3	(IPr)CuOt-Bu (1)	B <sub>2</sub> pin <sub>2</sub>	THF	100	n.r.
4	CsF (10)	B <sub>2</sub> (OH) <sub>4</sub>	DMF	100	0 <sup>b</sup>
5	CsF (20)	B <sub>2</sub> (OH) <sub>4</sub>	DMC	80	79 <sup>c</sup>
6	KF (10)	(Ph <sub>2</sub> MeSi) <sub>2</sub>	DMF	25	18
7	HF·py (20)	(Ph <sub>2</sub> MeSi) <sub>2</sub>	DMF	25	n.r.
8	Et <sub>3</sub> N·3HF (20)	(Ph <sub>2</sub> MeSi) <sub>2</sub>	DMF	25	n.r.
9	( <i>n</i> -Bu) <sub>4</sub> NF (20)	(Ph <sub>2</sub> MeSi) <sub>2</sub>	DMF	25	n.r.
10	CsF (20)	(Ph <sub>2</sub> MeSi) <sub>2</sub>	DMF	25	94
11	CsF (40)	(Ph <sub>2</sub> MeSi) <sub>2</sub>	DMF	25	61
12	CsF (10)	(Ph <sub>2</sub> MeSi) <sub>2</sub>	DMF	25	10
13	CsF (20)	(Me <sub>3</sub> Si) <sub>3</sub> SiH	DMF	25	90
14	CsF (20)	(Me <sub>3</sub> Si) <sub>2</sub>	DMF	25	n.r.
15	CsF (20)	Et <sub>3</sub> SiH	DMF	25	n.r.
16	CsF (20)	Ph <sub>3</sub> SiH	DMF	25	n.r.
17	CsF (20)	(Ph <sub>2</sub> MeSi) <sub>2</sub>	DMSO	25	n.r.
18	CsF (20)	(Ph <sub>2</sub> MeSi) <sub>2</sub>	EtOH	25	n.r.

<sup>a</sup> Conditions: **chamber 1**: 1 M H<sub>2</sub>SO<sub>4</sub> (8 equiv), K<sub>2</sub>CO<sub>3</sub> (4 equiv) in 0.8 mL of H<sub>2</sub>O; **chamber 3**: Pd(OAc)<sub>2</sub> (5 mol %), tmphen (10 mol %), 0.1 M DMF, 14 h. <sup>b</sup> trace aniline observed. <sup>c</sup> K<sub>2</sub>CO<sub>3</sub> (4 equiv) was added <sup>d</sup> poor conversion seen at lower temperatures. tmphen = 3,4,7,8-tetramethyl-1,10-phenanthroline.

**Table S3.2.** Exploration of deoxygenation of CO<sub>2</sub> for Pd-catalyzed reductive cyclization using B<sub>2</sub>(OH)<sub>4</sub> as the reductant.



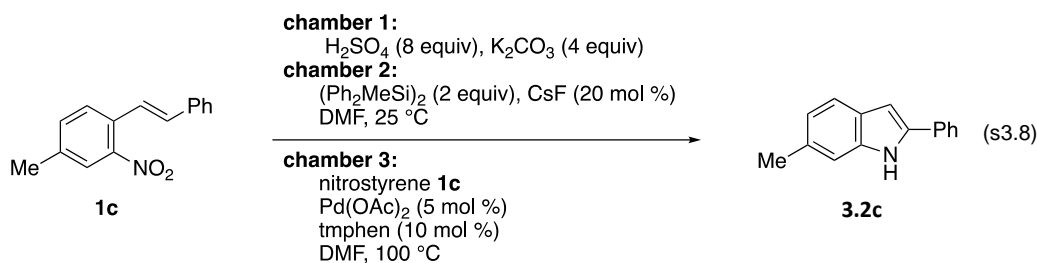
Entry <sup>a</sup>	catalyst (mol %)	reductant (equiv)	solvent	T (°C)	Product (%, Yield)
1	CsF (20)	B <sub>2</sub> (OH) <sub>4</sub> (4)	DMF	100	<b>3.3a</b> (trace)
2	CsF (20)	B <sub>2</sub> (OH) <sub>4</sub> (4)	<i>n</i> -BuOH	100	<b>3.3c</b> (71)
3	—	B <sub>2</sub> (OH) <sub>4</sub> (4)	<i>n</i> -BuOH	100	n.r.
4	CsF (30)	B <sub>2</sub> (OH) <sub>4</sub> (6)	<i>n</i> -BuOH	100	<b>3.2c</b> (41) + <b>3.3c</b> (35)
5	CsF (40)	B <sub>2</sub> (OH) <sub>4</sub> (8)	<i>n</i> -BuOH	100	<b>3.2c</b> (51) + <b>3.3c</b> (36)
6	CsF (20)	B <sub>2</sub> (OH) <sub>4</sub> (8)	<i>n</i> -BuOH	100	<b>3.1c</b> (60) + <b>3.3c</b> (35)
7	CsF (50)	B <sub>2</sub> (OH) <sub>4</sub> (10)	<i>n</i> -BuOH	100	<b>3.2c</b> (40) + <b>3.3c</b> (40)

8	CsF (40)	B <sub>2</sub> (OH) <sub>4</sub> (8)	Ethylene glycol	100	<b>3.1c</b> (90) + <b>3.3c</b> (trace)
9	CsF (40)	B <sub>2</sub> (OH) <sub>4</sub> (8)	1-octanol	100	<b>3.1c</b> (88) + <b>3.3c</b> (trace)
10	CsF (20)	B <sub>2</sub> (OH) <sub>4</sub> (4)	DMC	60	<b>3.1c</b> (85) + <b>3.2c</b> (trace)
11 <sup>b</sup>	CsF (20)	B <sub>2</sub> (OH) <sub>4</sub> (4)	DMC	60	<b>3.2c</b> (15)
12 <sup>b</sup>	CsF (20)	B <sub>2</sub> (OH) <sub>4</sub> (4)	DMC	80	<b>3.2c</b> (79) <sup>d</sup>
13 <sup>b</sup>	CsF (20)	B <sub>2</sub> (OH) <sub>4</sub> (4)	DMC	100	<b>3.2c</b> (37) <sup>d</sup>
14 <sup>b, c</sup>	CsF (20)	B <sub>2</sub> (OH) <sub>4</sub> (4)	DMC	80	<b>3.2c</b> (45) <sup>d</sup>
15 <sup>b, c</sup>	CsF (10)	B <sub>2</sub> (OH) <sub>4</sub> (4)	DMC	80	n.r.
16 <sup>b, c</sup>	CsF (30)	B <sub>2</sub> (OH) <sub>4</sub> (4)	DMC	80	<b>3.3c</b> (58) <sup>d</sup>
17 <sup>b, c</sup>	CsF (40)	B <sub>2</sub> (OH) <sub>4</sub> (4)	DMC	80	<b>3.3c</b> (60) <sup>d</sup>

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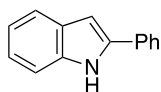
<sup>a</sup> Conditions: **chamber 1**: 1 M H<sub>2</sub>SO<sub>4</sub> (8 equiv), K<sub>2</sub>CO<sub>3</sub> (4 equiv) in 0.8 mL of H<sub>2</sub>O; **chamber 3**: Pd(OAc)<sub>2</sub> (5 mol %), tmphen (10 mol %), 0.1 M DMF, 14 h. <sup>b</sup> K<sub>2</sub>CO<sub>3</sub> (4 equiv) was added to chamber 2. <sup>c</sup> chamber 1 was kept empty without CO<sub>2</sub> formation. <sup>d</sup> Reproducibility of the reaction was not satisfying.

## B. Optimized Conditions



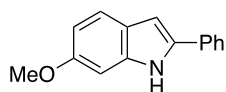
To a 30 mL 3-chamber reactor,  $\text{K}_2\text{CO}_3$  (4 equiv) in water and a 1 M aq soln of  $\text{H}_2\text{SO}_4$  (8 equiv) was added and frozen sequentially in chamber 1, CsF (0.02 equiv), disilane (0.2 equiv) and 0.8 mL of DMF were added to chamber 2, 0.10 mmol of nitrostyrene, palladium acetate (5 mol %), tetramethylphenanthroline (10 mol %) and 1 mL of DMF were added to chamber 3. The 3-chamber reactor was sealed from outer environment while allowing gas exchange among each other. Then the frozen reaction mixture in chamber 1 was allowed to thaw and stir until effervescence of  $\text{CO}_2$  was no longer observed. Chamber 3 was heated at 100 °C while chamber 1 and 2 were stirring at room temperature (Figure S1). After 14 h, the reaction mixture was cooled to room temperature and filtered through a pad of silica gel. The filtrate was concentrated *in vacuo*, and the residue was purified using MPLC to afford the *N*-heterocycle.

### C. Characterization Data



**3.2a**

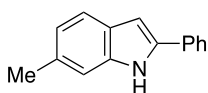
**2-Phenylindole 3.2a.** The optimized method was followed by adding 0.0552 g of K<sub>2</sub>CO<sub>3</sub>, 0.80 mL of H<sub>2</sub>O and 0.80 mL of a 1M aq soln of H<sub>2</sub>SO<sub>4</sub> in chamber 1, 0.0789 g of (Ph<sub>2</sub>MeSi)<sub>2</sub> (0.200 mmol), 0.0035 g of CsF (0.023 mmol) and 1.0 mL of DMF in chamber 2, 0.0225 g of nitrostilbene **3.1a** (0.100 mmol), 0.0011 g of Pd(OAc)<sub>2</sub> (0.005 mmol), 0.0023 g of 3,4,7,8-tetramethyl-1,10-phenanthroline (0.010 mmol) and 1 mL of DMF in chamber 3. Purification by MPLC (3:97 – 20:80 EtOAc:hexanes) afforded **3.2a** as a yellow solid (0.0176 g, 91%). The spectral data of **3.2a** matched that reported by Driver and co-workers:<sup>1</sup> <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 8.33 (br s, 1H), 7.68 (t, *J* = 6.5 Hz, 2H), 7.47 (t, *J* = 7.8 Hz, 2H), 7.42 (d, *J* = 8.1 Hz, 1H), 7.35 (t, *J* = 7.4 Hz 1H), 7.23 (t, *J* = 7.0 Hz, 2H), 7.16 (t, *J* = 7.0 Hz, 1H), 6.86 (d, *J* = 1.3 Hz, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 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), 100.0 (CH); IR (thin film): 3446, 1458, 1407, 1350, 798, 763, 743, 690 cm<sup>-1</sup>.



**3.2b**

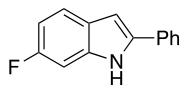
**6-Methoxy-2-phenyl-1H-indole 3.2b.** The optimized method was followed by adding 0.0552 g of K<sub>2</sub>CO<sub>3</sub>, 0.80 mL of H<sub>2</sub>O and 0.80 mL of a 1M aq soln of H<sub>2</sub>SO<sub>4</sub> in chamber 1, 0.0789 g of (Ph<sub>2</sub>MeSi)<sub>2</sub> (0.200 mmol), 0.0035 g of CsF (0.023 mmol) and 1.0 mL of DMF in chamber 2, 0.0223 g of nitrostilbene **3.1b** (0.100 mmol), 0.0011 g of Pd(OAc)<sub>2</sub> (0.005 mmol), 0.0023 g of 3,4,7,8-tetramethyl-1,10-phenanthroline (0.010 mmol) and 1 mL of DMF in chamber 3. Purification by MPLC (3:97 – 20:80 EtOAc:hexanes) afforded **3.2b** as a yellow solid (0.0217 g, 97%). The spectral data of **3.2b** matched that reported by Driver and co-workers:<sup>1</sup> <sup>1</sup>H NMR (CDCl<sub>3</sub>,

500 MHz)  $\delta$  8.24 (br s, 1H), 7.62 (d,  $J$  = 7.6 Hz, 2H), 7.50 (d,  $J$  = 8.6 Hz, 1H), 7.43 (t,  $J$  = 7.7 Hz, 2H), 7.30 (t,  $J$  = 7.4 Hz, 1H), 6.90 (s, 1H), 6.81 (dd,  $J$  = 1.9, 8.6 Hz, 1H), 6.77 (s, 1H), 3.87 (s, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  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 ( $\text{CH}_3$ ); IR (thin film): 3387, 2924, 2852, 1622, 1598, 1454, 1260, 1202, 1155, 1117, 1019, 797  $\text{cm}^{-1}$ .



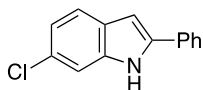
**3.2c**

**6-Methyl-2-phenyl-1H-indole 3.2c.** The optimized method was followed by adding 0.0552 g of  $\text{K}_2\text{CO}_3$ , 0.80 mL of  $\text{H}_2\text{O}$  and 0.80 mL of a 1M aq soln of  $\text{H}_2\text{SO}_4$  in chamber 1, 0.0789 g of  $(\text{Ph}_2\text{MeSi})_2$  (0.200 mmol), 0.0035 g of CsF (0.023 mmol) and 1.0 mL of DMF in chamber 2, 0.0207 g of nitrostilbene **3.1c** (0.100 mmol), 0.0011 g of  $\text{Pd}(\text{OAc})_2$  (0.005 mmol), 0.0023 g of 3,4,7,8-tetramethyl-1,10-phenanthroline (0.010 mmol) and 1 mL of DMF in chamber 3. Purification by MPLC (3:97 – 10:90 EtOAc:hexanes) afforded **3.2c** as a yellow solid (0.0195 g, 94%). The spectral data of **3.2c** matched that reported by Driver and co-workers:<sup>1</sup>  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  8.20 (br s, 1H), 7.65 (d,  $J$  = 7.3 Hz, 2H), 7.53 (d,  $J$  = 8.0 Hz, 1H), 7.44 (t,  $J$  = 7.8 Hz, 2H), 7.32 (t,  $J$  = 7.4 Hz, 1H), 7.20 (s, 1H), 6.98 (d,  $J$  = 8.0 Hz, 1H), 6.80 (d,  $J$  = 1.3 Hz, 1H), 2.49 (s, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  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 ( $\text{CH}_3$ ); IR (thin film): 3432, 1456, 1351, 1233, 816, 759, 738  $\text{cm}^{-1}$ .



### 3.2d

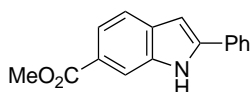
**6-Fluoro-2-phenyl-1H-indole 3.2d.** The general procedure was followed by adding 0.056 g  $\text{K}_2\text{CO}_3$  (0.40 mmol) and 0.8 mL of a 1M aq soln of  $\text{H}_2\text{SO}_4$  (20.0 mmol) to chamber 1, 0.078 g of 1,2-dimethyl-1,1,2,2-tetraphenyldisilane (0.20 mmol), 0.003 g CsF (0.02 mmol) and 0.8 mL of DMF to chamber 2, 0.0239 g of 6-fluoro-2-nitrostilbene (0.10 mmol), 0.0023 g of  $\text{Pd}(\text{OAc})_2$  (0.01 mmol), 0.0046 g of 3,4,7,8-tetramethyl-1,10-phenanthroline (0.02 mmol) and 1 mL of DMF to chamber 3, Purification by MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **3.2d** as a yellow solid (0.0207 g, 98%). The spectral data of **3.2d** matched that reported by Driver and co-workers:<sup>5</sup>  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  8.32 (s, 1H), 7.62 (t,  $J = 9.9$  Hz, 2H), 7.53 (dt,  $J = 18.2, 9.1$  Hz, 1H), 7.48 – 7.41 (m, 2H), 7.33 (t,  $J = 7.4$  Hz, 1H), 7.12 – 7.04 (m, 1H), 6.94 – 6.85 (m, 1H), 6.80 (s, 1H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  160.0 (C, d,  $J_{\text{CF}} = 357.5$  Hz), 137.2 (C) 136.7 (C, d,  $J_{\text{CF}} = 40.0$  Hz), 132.1 (C), 129.1 (CH), 127.8 (CH), 125.8 (C), 125.0 (CH), 121.4 (CH, d,  $J_{\text{CF}} = 10.0$  Hz), 109.0 (CH, d,  $J_{\text{CF}} = 25.0$  Hz), 99.9 (CH), 97.3 (CH, d,  $J_{\text{CF}} = 25.0$  Hz). IR (thin film): 3434, 1499, 1446, 1356, 1254, 1142, 813, 757  $\text{cm}^{-1}$ .



### 3.2e

**6-Chloro-2-phenyl-1H-indole 3.2e.** The optimized method was followed by adding 0.0552 g of  $\text{K}_2\text{CO}_3$ , 0.80 mL of  $\text{H}_2\text{O}$  and 0.80 mL of a 1 M aq soln of  $\text{H}_2\text{SO}_4$  in chamber 1, 0.0789 g of

(Ph<sub>2</sub>MeSi)<sub>2</sub> (0.200 mmol), 0.0035 g of CsF (0.023 mmol) and 1.0 mL of DMF in chamber 2, 0.0228 g of nitrostilbene **3.1e** (0.100 mmol), 0.0011 g of Pd(OAc)<sub>2</sub> (0.005 mmol), 0.0023 g of 3,4,7,8-tetramethyl-1,10-phenanthroline (0.010 mmol) and 1 mL of DMF in chamber 3. Purification by MPLC (3:97 – 15:85 EtOAc:hexanes) afforded **3.2e** as a yellow solid (0.0157 g, 69%). The spectral data of **3.2e** matched that reported by Driver and co-workers:<sup>1</sup> <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 8.31 (br s, 1H), 7.64 (d, *J* = 7.9 Hz, 2H), 7.53 (d, *J* = 8.4 Hz, 1H), 7.45 (t, *J* = 7.7 Hz, 2H), 7.39 (s, 1H), 7.35 (t, *J* = 7.4 Hz, 1H), 7.09 (d, *J* = 8.4 Hz, 1H), 6.79 (s, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 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<sup>-1</sup>.

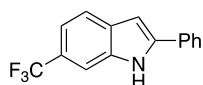


### 3.2f

**Methyl 2-phenyl-1H-indole-6-carboxylate 3.2f.** The optimized method was followed by adding 0.0552 g of K<sub>2</sub>CO<sub>3</sub>, 0.80 mL of H<sub>2</sub>O and 0.80 mL of a 1M aq soln of H<sub>2</sub>SO<sub>4</sub> in chamber 1, 0.0789 g of (Ph<sub>2</sub>MeSi)<sub>2</sub> (0.200 mmol), 0.0035 g of CsF (0.023 mmol) and 1.0 mL of DMF in chamber 2, 0.0283 g of nitrostilbene **3.1f** (0.100 mmol), 0.0011 g of Pd(OAc)<sub>2</sub> (0.005 mmol), 0.0023 g of 3,4,7,8-tetramethyl-1,10-phenanthroline (0.010 mmol) and 1 mL of DMF in chamber 3. Purification by MPLC (3:97 – 30:70 EtOAc:hexanes) afforded **3.2f** as a yellow solid (0.0226 g, 90 %). The spectral data of **3.2f** matched that reported by Driver and co-workers:<sup>5</sup> <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 8.66 (s, 1H), 8.19 (s, 1H), 7.82 (dd, *J* = 8.3, 1.1 Hz, 1H), 7.71 (d, *J* = 7.4 Hz, 2H), 7.64 (d, *J* = 8.3 Hz, 1H), 7.48 (t, *J* = 7.7 Hz, 2H), 7.38 (t, *J* = 7.4 Hz, 1H), 6.87 (s, 1H), 3.95 (s,

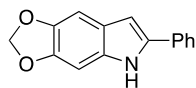


3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  168.1 (C), 141.3 (C), 136.11 (C), 133.0 (C), 131.7 (C), 129.2 (CH), 128.5 (CH), 125.5 (CH), 123.8 (C), 121.4 (CH), 120.1 (CH), 113.3 (CH), 100.3 (CH), 52.0 (CH<sub>3</sub>). IR (thin film): 3361, 29240, 2829, 1687, 1615, 1436, 1380, 1319, 1275, 1217, 1080, 794  $\text{cm}^{-1}$ .



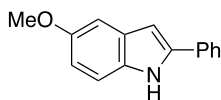
### 3.2g

**2-Phenyl-6-(trifluoromethyl)-1H-indole 3.2g.** The general procedure was followed by adding 0.056 g  $\text{K}_2\text{CO}_3$  (0.40 mmol) and 0.80 mL of a 1 M aq soln of  $\text{H}_2\text{SO}_4$  (20.0 mmol) to chamber 1, 0.078 g of 1,2-dimethyl-1,1,2,2-tetraphenyldisilane (0.20 mmol), 0.003 g of CsF (0.02 mmol) and 0.8 mL of DMF to chamber 2, 0.0293 g of 2-Nitro-4-trifluoromethylstilbene (0.10 mmol), 0.0023 g of  $\text{Pd}(\text{OAc})_2$  (0.01 mmol), 0.0046 g of 3,4,7,8-tetramethyl-1,10-phenanthroline (0.02 mmol) and 1 mL of DMF to chamber 3, Purification by MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **3.2g** as a yellow solid (0.0141 g, 57%). The spectral data of **3.2g** matched that reported by Driver and co-workers:<sup>1</sup>  $^1\text{H}$  NMR (500 MHz;  $\text{CDCl}_3$ )  $\delta$  8.53 (s, 1H), 7.69 (t,  $J$  = 6.9 Hz, 4H), 7.48 (t,  $J$  = 7.6 Hz, 2H), 7.38 (dd,  $J$  = 13.9, 7.6 Hz, 2H), 6.88 (s, 1H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  140.6 (C), 135.6 (C), 131.6 (d,  $J$  = 5.0 Hz, C), 129.2 (CH), 128.5 (CH), 125.4 (CH), 124.1 (q,  $J_{\text{CF}}$  = 268.8 Hz, C), 120.9 (CH), 117.0 (CH), 108.4 (CH), 100.1 (CH), only peaks visible;  $^{19}\text{F}$  NMR( $\text{CDCl}_3$ , 282 MHz)  $\delta$  -60.1, IR (thin film): 3444, 1456, 1342, 1155, 1105, 829, 766, 690  $\text{cm}^{-1}$ .



### 3.2h

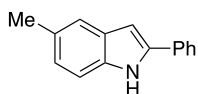
**6-Phenyl-5H-[1,3]dioxolo[4,5-*f*]indole 3.2h.** The general procedure was followed by adding 0.056 g K<sub>2</sub>CO<sub>3</sub> (0.40 mmol) and 0.80 mL of a 1 M aq soln of H<sub>2</sub>SO<sub>4</sub> (20.0 mmol) to chamber 1, 0.078 g of 1,2-dimethyl-1,1,2,2-tetraphenyldisilane (0.20 mmol), 0.003 g of CsF (0.02 mmol) and 0.8 mL of DMF to chamber 2, 0.0269 g of (E)-5-nitro-6-styrylbenzo[d][1,3]dioxole **3.1h** (0.10 mmol), 0.0023 g of Pd(OAc)<sub>2</sub> (0.01 mmol), 0.0046 g of 3,4,7,8-tetramethyl-1,10-phenanthroline (0.02 mmol) and 1 mL of DMF to chamber 3, Purification by MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **3.2h** as a yellow solid (0.0181 g, 76%): The spectral data of **3.2h** matched that reported by Yu and co-workers:<sup>10</sup> <sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>) δ 8.20 (s, 1H), 7.59 (d, *J* = 7.4 Hz, 2H), 7.41 (t, *J* = 7.7 Hz, 2H), 7.28 (t, *J* = 6.5 Hz, 1H), 7.00 (s, 1H), 6.86 (s, 1H), 6.71 (d, *J* = 1.4 Hz, 1H), 5.94 (s, 2H). <sup>13</sup>C NMR (CDCl<sub>3</sub> 125 MHz) δ 145.2 (C), 143.3 (C), 136.7 (C), 132.5 (C), 131.8 (C), 129.0 (CH), 127.2 (CH), 124.5 (CH), 123.2 (C), 100.6 (CH), 100.3 (CH), 99.1 (CH), 91.9 (CH<sub>2</sub>); IR (thin film): 1467, 1451, 1341, 1209, 1157, 1041, 943, 853, 755 cm<sup>-1</sup>.



### 3.2i

<sup>10</sup>. Q. Wang, H. Chai and Z. Yu, *Organometallics*, 2018, **37**, 584.

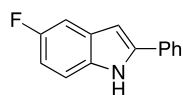
**5-Methoxy-2-phenyl-1*H*-indole 3.2i.** The optimized method was followed using 0.0552 g of  $\text{K}_2\text{CO}_3$ , 0.80 mL of  $\text{H}_2\text{O}$  and 0.80 mL of a 1 M aq soln of  $\text{H}_2\text{SO}_4$  in chamber 1, 0.0789 g of  $(\text{Ph}_2\text{MeSi})_2$  (0.200 mmol), 0.0035 g of CsF (0.023 mmol) and 1.0 mL of DMF in chamber 2, 0.0223 g of nitrostilbene **3.1i** (0.100 mmol), ), 0.0011 g of  $\text{Pd}(\text{OAc})_2$  (0.005 mmol), 0.0023 g of 3,4,7,8-tetramethyl-1,10-phenanthroline (0.010 mmol) and 1 mL of DMF in chamber 3. Purification by MPLC (3:97 – 20:80 EtOAc:hexanes) afforded **3.2i** as a yellow solid (0.0186 g, 83%). The spectral data of **3.2i** matched that reported by Driver and co-workers:<sup>1</sup>  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  8.24 (br s, 1H), 7.66 – 7.64 (m, 2H), 7.44 (t,  $J$  = 7.7 Hz, 2H), 7.32 (t,  $J$  = 7.4 Hz, 1H), 7.29 (d,  $J$  = 8.7 Hz, 1H), 7.10 (d,  $J$  = 2.3 Hz, 1H), 6.87 (dd,  $J$  = 8.7, 2.4 Hz, 1H), 6.77 (d,  $J$  = 1.4 Hz, 1H), 3.88 (s, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  154.5 (C), 138.6 (C), 132.5 (C), 132.0 (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 ( $\text{CH}_3$ ); IR (thin film): 3426, 2999, 2919, 2842, 1619, 1539, 1476, 1456, 1215, 1150, 1028  $\text{cm}^{-1}$ .



**3.2j**

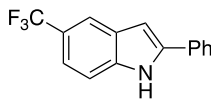
**5-Methyl-2-phenyl-1*H*-indole 3.2j.** The general procedure was followed by adding 0.056 g  $\text{K}_2\text{CO}_3$  (0.40 mmol) and 0.80 mL of a 1 M aq soln of  $\text{H}_2\text{SO}_4$  (20.0 mmol) to chamber 1, 0.078 g of 1,2-dimethyl-1,1,2,2-tetraphenyldisilane (0.20 mmol), 0.003 g of CsF (0.02 mmol) and 0.8 mL of DMF to chamber 2, 0.0239 g of 5-methyl-2-nitrostilbene **3.1j** (0.10 mmol), 0.0023 g of  $\text{Pd}(\text{OAc})_2$  (0.01 mmol), 0.0046 g of 3,4,7,8-tetramethyl-1,10-phenanthroline (0.02 mmol) and 1 mL of DMF to chamber 3, Purification by MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **3.2j** as a yellow solid

(0.0161g, 78%). The spectral data of **3.2j** matched that reported by Driver and co-workers:<sup>1</sup> <sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>) δ 8.24 (ddt, *J* = 2.2, 1.2, 0.6 Hz, 1H), 7.67 – 7.65 (m, 2H), 7.45 – 7.42 (m, 3H), 7.31 (dt, *J* = 11.4, 5.7 Hz, 2H), 7.03-7.02 (m, 1H), 6.76 (s, 1H), 2.46 (s, 3H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 138.0 (C), 135.2 (C), 132.5 (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<sub>3</sub>). IR (thin film): 3405, 2918, 2852, 1457, 1317, 1299, 1203, 1072 cm<sup>-1</sup>.



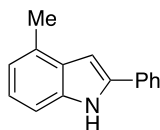
### 3.2k

**5-Fluoro-2-phenyl-1H-indole 3.2k.** The general procedure was followed by adding 0.056 g K<sub>2</sub>CO<sub>3</sub> (0.40 mmol) and 0.80 mL of a 1 M aq soln of H<sub>2</sub>SO<sub>4</sub> (20.0 mmol) to chamber 1, 0.078 g of 1,2-dimethyl-1,1,2,2-tetraphenyldisilane (0.20 mmol), 0.003 g of CsF (0.02 mmol) and 0.8 mL of DMF to chamber 2, 0.0239 g of 5-fluoro-2-nitrostilbene **3.1k** (0.10 mmol), 0.0023 g of Pd(OAc)<sub>2</sub> (0.01 mmol), 0.0046 g of 3,4,7,8-tetramethyl-1,10-phenanthroline (0.02 mmol) and 1 mL of DMF to chamber 3, Purification by MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **3.2k** as a yellow solid (0.0145 g, 69%). The spectral data of **3.2k** matched that reported by Driver and co-workers:<sup>5</sup> <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 8.25 (s, 1H), 7.66 (d, *J* = 7.6 Hz, 2H), 7.47 – 7.40 (m, 3H), 7.31 (dd, *J* = 17.5, 7.9 Hz, 2H), 7.02 (t, *J* = 11.4 Hz, 1H), 6.76 (s, 1H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 159.2 (C), 157.3 (C), 139.7 (C), 133.3 (C), 132.1 (C), 129.1 (CH), 128.1 (CH), 125.2 (CH), 111.5 (d, *J* = 5.0 Hz, CH), 110.7 (d, *J* = 5.0 Hz, CH), 105.4 (d, *J* = 5.0 Hz, CH), 100.1 (d, *J* = 5.0 Hz, CH); <sup>19</sup>F NMR(CDCl<sub>3</sub>, 282 MHz) δ –124.1; IR (thin film): 3480, 2985, 1465, 1285, 770 cm<sup>-1</sup>.



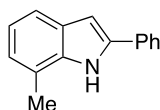
### 3.2l

**2-Phenyl-5-trifluoromethyl-1H-indole 3.2l.** The general procedure was followed by adding 0.056 g  $\text{K}_2\text{CO}_3$  (0.40 mmol) and 0.80 mL of a 1 M aq soln of  $\text{H}_2\text{SO}_4$  (20.0 mmol) to chamber 1, 0.078 g of 1,2-dimethyl-1,1,2,2-tetraphenyldisilane (0.20 mmol), 0.003 g of CsF (0.02 mmol) and 0.8 mL of DMF to chamber 2, 0.0293 g of 5-trifluoromethyl-2-nitrostilbene **3.1l** (0.10 mmol), 0.0023 g of  $\text{Pd}(\text{OAc})_2$  (0.01 mmol), 0.0046 g of 3,4,7,8-tetramethyl-1,10-phenanthroline (0.02 mmol) and 1 mL of DMF to chamber 3, Purification by MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **3.2l** as a white solid (0.0188 g, 72%). The spectral data of **3.2l** matched that reported by Driver and co-workers:<sup>1</sup>  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  8.55 (s, 1H), 7.92 (s, 1H), 7.68 (d,  $J = 7.5$  Hz, 2H), 7.49 – 7.40 (m, 4H), 7.38 (t,  $J = 7.4$  Hz, 1H), 6.89 (s, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  139.7 (C), 138.1 (C), 131.7 (C), 129.2 (CH), 128.6 (C), 128.3 (CH), 125.3 (CH), 125.3 (q,  $J_{\text{CF}} = 266.3$  Hz, C), 122.8 (q,  $J_{\text{CF}} = 30.3$  Hz, C), 119.0 (CH), 118.3 (CH), 111.1 (CH), 100.6 (CH); IR (thin film): 3437, 1492, 1448, 1357, 1341, 1127, 1100  $\text{cm}^{-1}$ .



### 3.2m

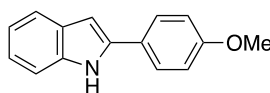
**4-Methyl-2-phenyl-1*H*-indole 3.2m.** The general procedure was followed by adding 0.056 g  $\text{K}_2\text{CO}_3$  (0.40 mmol) and 0.80 mL of a 1 M aq soln of  $\text{H}_2\text{SO}_4$  (20.0 mmol) to chamber 1, 0.078 g of 1,2-dimethyl-1,1,2,2-tetraphenyldisilane (0.20 mmol), 0.003 g of CsF (0.02 mmol) and 0.8 mL of DMF to chamber 2, 0.0239 g of (*E*)-1-methyl-3-nitro-2-styrylbenzene **3.1m** (0.10 mmol), 0.0023 g of  $\text{Pd}(\text{OAc})_2$  (0.01 mmol), 0.0046 g of 3,4,7,8-tetramethyl-1,10-phenanthroline (0.02 mmol) and 1 mL of DMF to chamber 3, Purification by MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **3.2m** as a yellow solid (0.0141 g, 68%). The spectral data of **3.2m** matched that reported by Driver and co-workers:<sup>5</sup>  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  8.34 (s, 1H), 7.68 (d,  $J = 7.5$  Hz, 2H), 7.45 (t,  $J = 7.6$  Hz, 2H), 7.32 (dd,  $J = 16.9, 9.7$  Hz, 1H), 7.26 (s, 1H), 7.12 (t,  $J = 7.6$  Hz, 1H), 6.94 (d,  $J = 7.0$  Hz, 1H), 6.86 (s, 1H), 2.60 (s, 3H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  137.3 (C), 136.5 (C), 132.5 (C), 130.3 (C), 129.2 (C), 129.0 (CH), 127.6 (CH), 125.1 (CH), 122.5 (CH), 120.4 (CH), 108.5 (CH), 98.6 (CH), 18.8 ( $\text{CH}_3$ ). IR (thin film): 3420, 3054, 2920, 2855, 1603, 1486, 1402, 1354, 1295, 1074, 755, 690  $\text{cm}^{-1}$ .



**3.2n**

**7-Methyl-2-phenyl-1*H*-indole 3.2n.** The general procedure was followed by adding 0.056 g  $\text{K}_2\text{CO}_3$  (0.40 mmol) and 0.80 mL of a 1 M aq soln of  $\text{H}_2\text{SO}_4$  (20.0 mmol) to chamber 1, 0.078 g of 1,2-dimethyl-1,1,2,2-tetraphenyldisilane (0.20 mmol), 0.003 g of CsF (0.02 mmol) and 0.8 mL of DMF to chamber 2, 0.0239 g of (*E*)-1-methyl-3-nitro-2-styrylbenzene **3.1n** (0.10 mmol), 0.0023 g of  $\text{Pd}(\text{OAc})_2$  (0.01 mmol), 0.0046 g of 3,4,7,8-tetramethyl-1,10-phenanthroline (0.02 mmol) and

1 mL of DMF to chamber 3, Purification by MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **3.2n** as a yellow solid (0.0150 g, 72%). The spectral data of **3.2n** matched that reported by Fang and Lautens:<sup>11</sup> <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 8.34 (s, 1H), 7.68 (d, *J* = 7.5 Hz, 2H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.32 (dd, *J* = 16.9, 9.7 Hz, 1H), 7.26 (s, 1H), 7.12 (t, *J* = 7.6 Hz, 1H), 6.94 (d, *J* = 7.0 Hz, 1H), 6.86 (s, 1H), 2.60 (s, 3H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 137.3 (C), 136.5 (C), 132.5 (C), 130.2 (C), 129.0 (CH), 128.7 (C), 127.6 (CH), 125.1 (CH), 122.5 (CH), 120.4 (CH), 108.5 (CH), 98.6 (CH), 18.8 (CH<sub>3</sub>). IR (thin film): 3462, 1621, 1478, 1446, 1371, 1331, 1301, 797 cm<sup>-1</sup>.

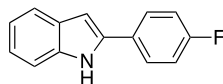


**3.2o**

**2-(4-Methoxyphenyl)-1H-indole 3.2o.** The optimized method was followed using 0.0552 g of K<sub>2</sub>CO<sub>3</sub>, 0.80 mL of H<sub>2</sub>O and 0.80 mL of a 1 M aq soln of H<sub>2</sub>SO<sub>4</sub> in chamber 1, 0.0789 g of (Ph<sub>2</sub>MeSi)<sub>2</sub> (0.200 mmol), 0.0035 g of CsF (0.023 mmol) and 1.0 mL of DMF in chamber 2, 0.0223 g of nitrostilbene **3.1o** (0.100 mmol), ), 0.0011 g of Pd(OAc)<sub>2</sub> (0.005 mmol), 0.0023 g of 3,4,7,8-tetramethyl-1,10-phenanthroline (0.010 mmol) and 1 mL of DMF in chamber 3. Purification by MPLC (3:97 – 20:80 EtOAc:hexanes) afforded **3.2o** as a yellow solid (0.0209 g, 92%). The spectral data of **3.2o** matched that reported by Driver and co-workers:<sup>1</sup> <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 8.26 (br s, 1H), 7.61 – 7.59 (m, 3H), 7.39 (d, *J* = 8.0 Hz, 1H), 7.17 (t, *J* = 7.6 Hz, 1H), 7.11 (t, *J* = 7.4 Hz, 1H), 6.99 (d, *J* = 8.8 Hz, 2H), 6.72 (dd, *J* = 2.1, 0.8 Hz, 1H), 3.86 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 159.4 (C), 138.0 (C), 136.7 (C), 129.4 (C), 126.5 (CH), 125.2 (C),

<sup>11</sup>. Y.-Q. Fang and M. Lautens, *J. Org. Chem.*, 2008, **73**, 538.

121.9 (CH), 120.4 (CH), 120.2 (CH), 114.5 (CH), 110.7 (CH), 98.9 (CH), 55.4 (CH<sub>3</sub>); IR (thin film): 3427, 1606, 1500, 1452, 1430, 1286, 1248, 1179, 1113, 1048, 1024 cm<sup>-1</sup>.

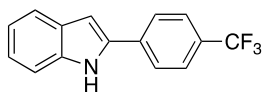


**3.2p**

**2-(4-Fluorophenyl)-1H-indole 3.2p.** The general procedure was followed by adding 0.056 g K<sub>2</sub>CO<sub>3</sub> (0.40 mmol) and 0.80 mL of a 1 M aq soln of H<sub>2</sub>SO<sub>4</sub> (20.0 mmol) to chamber 1, 0.078 g of 1,2-dimethyl-1,1,2,2-tetraphenyldisilane (0.20 mmol), 0.003g CsF (0.02 mmol) and 0.8 mL of DMF to chamber 2, 0.0243 g of (*E*)-1-(4-fluorostyryl)-2-nitrobenzene **3.1p** (0.10 mmol), 0.0023 g of Pd(OAc)<sub>2</sub> (0.01 mmol), 0.0046 g of 3,4,7,8-tetramethyl-1,10-phenanthroline (0.02 mmol) and 1 mL of DMF to chamber 3, Purification by MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **3.2p** as a yellow solid (0.0129 g, 61%). The spectral data of **3.2p** matched that reported by Ackermann and co-workers:<sup>12</sup> <sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>) δ 8.25 (dd, *J* = 1.0, 0.6 Hz, 1H), 7.63 (dt, *J* = 6.8, 3.5 Hz, 3H), 7.41 – 7.39 (m, 1H), 7.22 – 7.19 (m, 1H), 7.16 – 7.12 (m, 3H), 6.76 (d, *J* = 1.3 Hz, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 162.4 (d, *J* = 245.0 Hz, C), 137.1 (C), 136.9 (C), 129.3 (C), 128.7 (d, *J* = 2.5 Hz, C), 126.9 (d, *J* = 15.0 Hz, CH), 122.5 (CH), 120.7 (CH), 120.4 (CH), 116.1 (d, *J* = 21.3 Hz, CH), 110.9 (CH), 100.0 (CH); <sup>19</sup>F NMR (CDCl<sub>3</sub>, 282 MHz) δ –113.8; IR (thin film): 3413, 1606, 1545, 1498, 1484, 1428, 1346, 1298, 1233, 1160, 1100, 1011 cm<sup>-1</sup>.

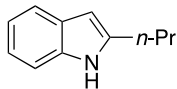
<sup>12</sup>. H. Long, K. Xu, S. Chen, J. Lin, D. Wu, B. Wu, X. Tian and L. Ackermann, *Org. Lett.*, 2019, **21**, 3053.





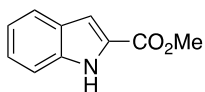
### 3.2q

**2-(4-Trifluoromethylphenyl)-1H-indole 3.2q.** The general procedure was followed by adding 0.056 g K<sub>2</sub>CO<sub>3</sub> (0.40 mmol) and 0.80 mL of a 1 M aq soln of H<sub>2</sub>SO<sub>4</sub> (20.0 mmol) to chamber 1, 0.078 g of 1,2-dimethyl-1,1,2,2-tetraphenyldisilane (0.20 mmol), 0.003g CsF (0.02 mmol) and 0.8 mL of DMF to chamber 2, 0.0261 g of (*E*)-1-(4-(trifluoromethyl)styryl)-2-nitrobenzene **3.1q** (0.10 mmol), 0.0023 g of Pd(OAc)<sub>2</sub> (0.01 mmol), 0.0046 g of 3,4,7,8-tetramethyl-1,10-phenanthroline (0.02 mmol) and 1 mL of DMF to chamber 3, Purification by MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **3.2q** as a pale yellow solid (0.0183 g, 70%). The spectral data of **3.2q** matched that reported by Driver and co-workers:<sup>5</sup> <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 8.39 (br s, 1H), 7.76 (d, *J* = 8.2 Hz, 2H), 7.70 (d, *J* = 8.2 Hz, 2H), 7.66 (d, *J* = 7.8 Hz, 1H), 7.43 (d, *J* = 8.1 Hz, 1H), 7.24 (d, *J* = 7.4 Hz, 1H), 7.15 (t, *J* = 7.4 Hz, 1H), 6.93 (s, 1H); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>, 125 MHz) δ 138.0 (C), 136.7 (C), 128.9 (C), 127.9 (C), 126.3 (q, *J*<sub>CF</sub> = 3.5 Hz, C), 125.8 (CH), 124.8 (q, *J*<sub>CF</sub> = 270.0 Hz, C), 122.9 (CH), 121.0 (CH), 120.2 (CH), 112.0 (CH), 101.2 (CH), only peaks visible; <sup>19</sup>F NMR (CDCl<sub>3</sub>, 282 MHz) δ –62.6; IR (thin film): 3422, 2928, 2850, 1617, 1433, 1326, 1165, 1107, 1073, 1014 cm<sup>–1</sup>.



### 3.2r

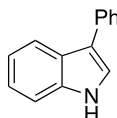
**2-*n*-Propyl-1*H*-indole 3.2r.** The general procedure was followed by adding 0.056 g K<sub>2</sub>CO<sub>3</sub> (0.40 mmol) and 0.80 mL of a 1 M aq soln of H<sub>2</sub>SO<sub>4</sub> (20.0 mmol) to chamber 1, 0.078 g of 1,2-dimethyl-1,1,2,2-tetraphenyldisilane (0.20 mmol), 0.003 g CsF (0.02 mmol) and 0.8 mL of DMF to chamber 2, 0.0261 g of (*E*)-1-propylvinyl-2-nitrobenzene **3.1r** (0.10 mmol), 0.0023 g of Pd(OAc)<sub>2</sub> (0.01 mmol), 0.0046 g of 3,4,7,8-tetramethyl-1,10-phenanthroline (0.02 mmol) and 1 mL of DMF to chamber 3, Purification by MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **3.2r** as a brown oil (0.0125 g, 79%). The spectral data of **3.2r** matched that reported by Driver and co-workers:<sup>5</sup> <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 7.85 (br s, 1H), 7.54 (d, *J* = 7.7 Hz, 1H), 7.29 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.12 (td, *J* = 7.5, 1.2 Hz, 1H), 7.08 (td, *J* = 7.4, 0.9 Hz, 1H), 6.25 (dd, *J* = 2.0, 0.9 Hz, 1H), 2.74 (t, *J* = 7.5 Hz, 2H), 1.76 (sextet, *J* = 7.5 Hz, 2H), 1.02 (t, *J* = 7.4 Hz, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 139.8 (C), 135.8 (C), 128.9 (C), 120.9 (CH), 119.8 (CH), 110.3 (CH), 99.6 (CH), 30.4 (CH<sub>2</sub>), 22.5 (CH<sub>2</sub>), 13.9 (CH<sub>3</sub>), only peaks visible; IR (thin film): 3401, 1461, 1417, 1288, 1033, 781, 752 cm<sup>-1</sup>.



**3.2s**

**Methyl-1*H*-indole-2-carboxylate 3.2s.** The general procedure was followed by adding 0.056 g K<sub>2</sub>CO<sub>3</sub> (0.40 mmol) and 0.80 mL of a 1 M aq soln of H<sub>2</sub>SO<sub>4</sub> (20.0 mmol) to chamber 1, 0.078 g of 1,2-dimethyl-1,1,2,2-tetraphenyldisilane (0.20 mmol), 0.003 g CsF (0.02 mmol) and 0.8 mL of DMF to chamber 2, 0.0207 g of methyl (*E*)-3-(2-nitrophenyl)acrylate **3.1s** (0.10 mmol), 0.0023 g of Pd(OAc)<sub>2</sub> (0.01 mmol), 0.0046 g of 3,4,7,8-tetramethyl-1,10-phenanthroline (0.02 mmol) and 1 mL of DMF to chamber 3, Purification by MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **3.2s**

as a yellow oil (0.0154 g, 88%). The spectral data of **3.2s** matched that reported by Driver and co-workers:<sup>13</sup> <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 8.97 (s, 1H), 7.70 (d, *J* = 8.1 Hz, 1H), 7.43 (d, *J* = 8.3 Hz, 1H), 7.33 (t, *J* = 7.6 Hz, 1H), 7.23 (d, *J* = 1.0 Hz, 1H), 7.16 (t, *J* = 7.5 Hz, 1H), 3.96 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 162.5 (C), 136.9 (C), 127.5 (C), 127.1 (C), 125.5 (CH), 122.7 (CH), 120.9 (CH), 111.9 (CH), 108.8 (CH), 52.0 (CH<sub>3</sub>); IR (thin film): 3401, 1461, 1417, 1288, 1033, 781, 752 cm<sup>-1</sup>.

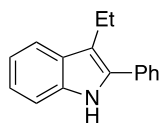


**3.2t**

**3-Phenyl-1H-indole 3.2t.** The general procedure was followed by adding 0.056 g K<sub>2</sub>CO<sub>3</sub> (0.40 mmol) and 0.80 mL of a 1 M aq soln of H<sub>2</sub>SO<sub>4</sub> (20.0 mmol) to chamber 1, 0.078 g of 1,2-dimethyl-1,1,2,2-tetraphenyldisilane (0.20 mmol), 0.003 g CsF (0.02 mmol) and 0.8 mL of DMF to chamber 2, 0.0193 g of 1-(1-phenylvinyl)-2-nitrobenzene **3.1t** (0.10 mmol), 0.0023 g of Pd(OAc)<sub>2</sub> (0.01 mmol), 0.0046 g of 3,4,7,8-tetramethyl-1,10-phenanthroline (0.02 mmol) and 1 mL of DMF to chamber 3, Purification by MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **3.2t** as a brown oil (0.0166 g, 86%). The spectral data of **3.2t** matched that reported by Driver and co-workers:<sup>5</sup> <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 8.23 (s, 1H), 7.96 (d, *J* = 7.9 Hz, 1H), 7.69 (d, *J* = 7.3 Hz, 2H), 7.47 – 7.43 (m, 3H), 7.38 (d, *J* = 2.3 Hz, 1H), 7.31 – 7.25 (m, 2H), 7.21 (t, *J* = 7.1 Hz, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 136.7 (C), 135.6 (C), 128.8 (CH), 127.5 (CH), 126.0 (CH), 125.8 (C), 122.4

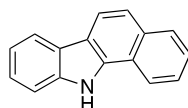
<sup>13</sup>. B. J. Stokes, H. Dong, B. E. Leslie, A. L. Pumphrey and T. G. Driver, *J. Am. Chem. Soc.*, 2007, **129**, 7500.

(CH), 121.7 (CH), 120.3 (CH), 119.8 (CH), 118.4 (C), 111.4 (CH); IR (thin film): 3414, 3052, 1601, 1544, 1486, 1455, 1414, 1330, 1259, 1235, 1110, 1086  $\text{cm}^{-1}$ .



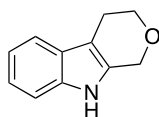
**3.2u**

**3-Ethyl-2-phenyl-1H-indole 3.2u.** The general procedure was followed by adding 0.056 g  $\text{K}_2\text{CO}_3$  (0.40 mmol) and 0.80 mL of a 1 M aq soln of  $\text{H}_2\text{SO}_4$  (20.0 mmol) to chamber 1, 0.078 g of 1,2-dimethyl-1,1,2,2-tetraphenyldisilane (0.20 mmol), 0.003 g  $\text{CsF}$  (0.02 mmol) and 0.8 mL of DMF to chamber 2, 0.0253 g of (E)-1-nitro-2-(1-phenylbut-1-en-2-yl)benzene **3.1u** (0.10 mmol), 0.0023 g of  $\text{Pd}(\text{OAc})_2$  (0.01 mmol), 0.0046 g of 3,4,7,8-tetramethyl-1,10-phenanthroline (0.02 mmol) and 1 mL of DMF to chamber 3, Purification by MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **3.2u** as a brown oil (0.0179 g, 81%). The spectral data of **3.2u** matched that reported by Driver and co-workers:<sup>5</sup>  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  8.00 (br s, 1H), 7.69 (d,  $J$  = 7.9 Hz, 1H), 7.58 (dd,  $J$  = 8.2, 1.2 Hz, 2H), 7.49 (t,  $J$  = 7.8 Hz, 2H), 7.40 – 7.38 (m, 2H), 7.25 – 7.22 (m, 1H), 7.19 – 7.16 (m, 1H), 2.95 (q,  $J$  = 7.6 Hz, 2H), 1.38 (t,  $J$  = 7.6 Hz, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  136.0 (C), 133.7 (C), 133.4 (C), 129.1 (C), 128.9 (CH), 127.9 (CH), 127.5 (CH), 122.2 (CH), 119.5 (CH), 119.2 (CH), 115.5 (C), 110.8 (CH), 17.8 ( $\text{CH}_2$ ), 15.6 ( $\text{CH}_3$ ); IR (thin film): 3411, 1606, 1522, 1484, 1455, 1452, 1373, 1336, 1311, 1227, 759  $\text{cm}^{-1}$ .



### 3.7

**11H-Benzo[*a*]carbazole 3.7.** The general procedure was followed by adding 0.112 g K<sub>2</sub>CO<sub>3</sub> (0.80 mmol) and 2.00 mL of a 1 M aq soln of H<sub>2</sub>SO<sub>4</sub> (20.0 mmol) to chamber 1, 0.156 g of 1,2-dimethyl-1,1,2,2-tetraphenyldisilane (0.40 mmol), 0.006 g of CsF (0.04 mmol) and 1.2 mL of DMF to chamber 2, 0.0249 g of 2-(2-nitrophenyl)naphthalene **3.4** (0.10 mmol), 0.0023 g of Pd(OAc)<sub>2</sub> (0.01 mmol), 0.0046 g of 3,4,7,8-tetramethyl-1,10-phenanthroline (0.02 mmol) and 1 mL of DMF to chamber 3, Purification by MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **3.7** as a yellow solid (0.0219 g, 88%). The spectral data of **3.7** matched that reported by Shirakawa and co-workers:<sup>14</sup> <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$  8.76 (s, 1H), 8.20 – 8.08 (m, 3H), 8.03 (d, *J* = 8.0 Hz, 1H), 7.68 (d, *J* = 8.5 Hz, 1H), 7.60 (t, *J* = 7.8 Hz, 2H), 7.55 (t, *J* = 7.1 Hz, 1H), 7.45 (t, *J* = 7.6 Hz, 1H), 7.32 (t, *J* = 7.4 Hz, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz)  $\delta$  138.5 (C), 134.9 (C), 132.5 (C), 129.1 (CH), 125.6 (CH), 125.3 (CH), 124.9 (CH), 124.2 (C), 121.1 (C), 120.5 (CH), 120.2 (CH), 120.0 (CH), 119.9 (CH), 119.4 (C), 118.5 (C); IR (thin film): 3409, 1478, 1402, 845, 483 cm<sup>-1</sup>.

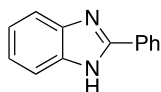


### 3.8

**1,3,4,9-Tetrahydropyrano[3,4-*b*]indole 3.8.** The general procedure was followed by adding 0.056 g K<sub>2</sub>CO<sub>3</sub> (0.40 mmol) and 0.80 mL of a 1 M aq soln of H<sub>2</sub>SO<sub>4</sub> (20.0 mmol) to chamber 1, 0.078 g of 1,2-dimethyl-1,1,2,2-tetraphenyldisilane (0.20 mmol), 0.003g CsF (0.02 mmol) and 0.8

<sup>14</sup>. T. Tsuchimoto, H. Matsubayashi, M. Kaneko, Y. Nagase, T. Miyamura and E. Shirakawa, *J. Am. Chem. Soc.*, 2008, **130**, 15823.

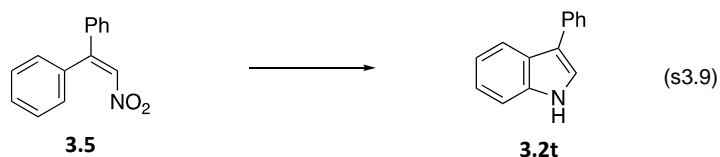
mL of DMF to chamber 2, 0.0205 g of 4-(2-nitrophenyl)-3,6-dihydro-2H-pyran **3.4** (0.10 mmol), 0.0023 g of Pd(OAc)<sub>2</sub> (0.01 mmol), 0.0046 g of 3,4,7,8-tetramethyl-1,10-phenanthroline (0.02 mmol) and 1 mL of DMF to chamber 3, Purification by MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **3.8** as a brown oil (0.0149 g, 86%). The spectral data of **3.8** matched that reported by Driver and co-workers:<sup>5</sup> <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 7.72 (s, 1H), 7.51 (d, *J* = 7.7 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.17 (t, *J* = 7.4 Hz, 1H), 7.12 (t, *J* = 7.4 Hz, 1H), 4.83 (s, 2H), 4.05 (t, *J* = 5.5 Hz, 2H), 2.86 (t, *J* = 5.4 Hz, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 135.9 (C), 131.5 (C), 127.2 (C), 121.8 (CH), 119.6 (CH), 118.0 (CH), 110.9 (CH), 107.7 (C), 65.8 (CH<sub>2</sub>), 63.7 (CH<sub>2</sub>), 22.2 (CH<sub>2</sub>); IR (thin film): 3396, 1466, 1451, 1442, 1234, 1088, 1065, 740 cm<sup>-1</sup>.



### 3.9

**2-Phenyl-1H-benzo[d]imidazole 3.9.** The general procedure was followed by adding 0.056 g K<sub>2</sub>CO<sub>3</sub> (0.40 mmol) and 0.80 mL of a 1 M aq soln of H<sub>2</sub>SO<sub>4</sub> (20.0 mmol) to chamber 1, 0.078 g of 1,2-dimethyl-1,1,2,2-tetraphenyldisilane (0.20 mmol), 0.003g CsF (0.02 mmol) and 0.8 mL of DMF to chamber 2, 0.0226 g of (E)-N-(2-nitrophenyl)-1-phenylmethanimine **3.5** (0.10 mmol), 0.0023 g of Pd(OAc)<sub>2</sub> (0.01 mmol), 0.0046 g of 3,4,7,8-tetramethyl-1,10-phenanthroline (0.02 mmol) and 1 mL of DMF to chamber 3, Purification by MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **3.9** as a yellow solid (0.0130 g, 67%). The spectral data of **3.9** matched that reported by Driver and co-workers:<sup>5</sup> <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 500 MHz) δ 8.18 (d, *J* = 7.4 Hz, 2H), 7.60 (s, 2H), 7.54 (t, *J* = 7.3 Hz, 2H), 7.47 (t, *J* = 7.1 Hz, 1H), 7.19 (dd, *J* = 5.6, 2.8 Hz, 2H), only peaks visible; <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>, 125 MHz) δ 151.7 (C), 144.3 (C), 135.5 (C), 130.6 (C), 130.3 (CH), 129.4

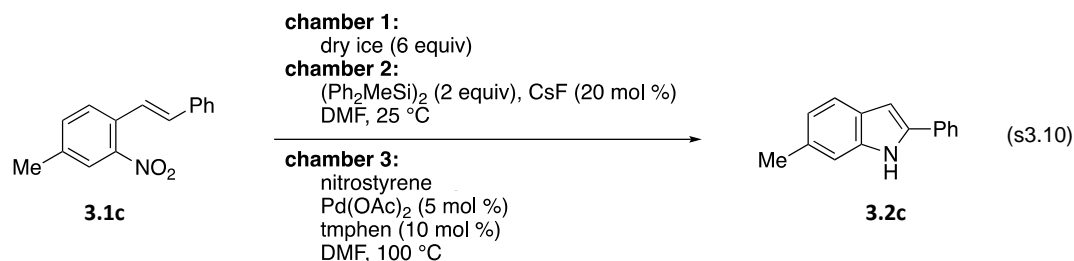
(CH), 126.9 (CH), 123.0 (CH), 122.1 (CH), 119.3 (CH), 111.8 (CH); IR (thin film): 3402, 1471, 1452, 1448, 1229, 1084, 1065, 751 cm<sup>-1</sup>.



**3-Phenyl-1H-indole 3.2t.** The general procedure was followed by adding 0.112 g K<sub>2</sub>CO<sub>3</sub> (0.80 mmol) and 2.00 mL of a 1 M aq soln of H<sub>2</sub>SO<sub>4</sub> (20.0 mmol) to chamber 1, 0.156 g of 1,2-dimethyl-1,1,2,2-tetraphenyldisilane (0.40 mmol), 0.006 g of CsF (0.04 mmol) and 1.2 mL of DMF to chamber 2, 0.0225 g of (2-Nitroethene-1,1-diyl)dibenzene **3.5** (0.10 mmol), 0.0023 g of Pd(OAc)<sub>2</sub> (0.01 mmol), 0.0046 g of 3,4,7,8-tetramethyl-1,10-phenanthroline (0.02 mmol) and 1 mL of DMF to chamber 3, Purification by MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **3.2t** as a yellow solid (0.0112 g, 59%). The spectral data matched that reported by Hsieh and Dong:<sup>9</sup> <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) <sup>1</sup>H NMR (501 MHz, CDCl<sub>3</sub>) δ 8.21 (s, 1H), 7.97 (d, *J* = 7.9 Hz, 1H), 7.77 – 7.64 (m, 2H), 7.45 (dt, *J* = 20.1, 9.5 Hz, 3H), 7.37 (d, *J* = 2.3 Hz, 1H), 7.34 – 7.18 (m, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 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), 119.8 (CH), 118.4 (C), 111.4 (CH). IR (thin film): 3415, 3393, 3056, 3035, 2925, 1597, 1538, 1486, 1416, 1338, 1259, 1237, 1186, 1014, 954, 907 cm<sup>-1</sup>.

### III. Examination of dry ice as the CO<sub>2</sub> source and effect of flue gas contaminants on the reductive cyclization reaction.

## A. Dry Ice.

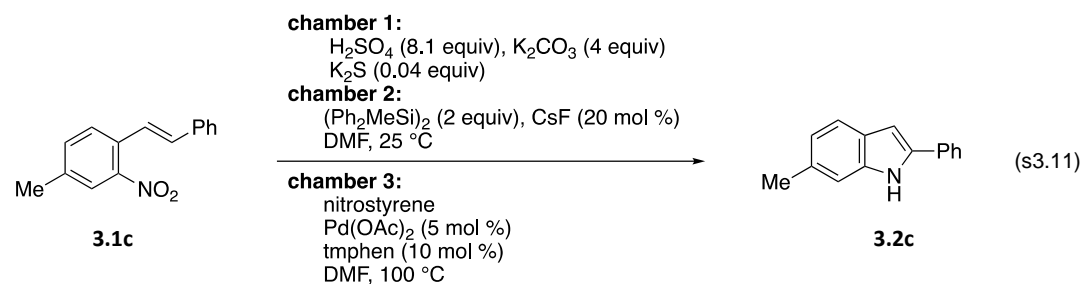


To a 30 mL 3-chamber reactor, 0.0264 g of dry ice (0.6 mmol) was added to chamber 1 and sealed. 0.0035 g of CsF (0.023 mmol), disilane (0.200 mmol) and 0.8 mL of DMF was added to chamber 2, 0.0239 g of nitrostilbene **3.1c** (0.100 mmol), 0.0011 g of  $\text{Pd}(\text{OAc})_2$  (0.005 mmol), 0.0023 g of 3,4,7,8-tetramethyl-1,10-phenanthroline (0.010 mmol) and 1 mL of DMF in chamber 3. The 3-chamber reactor was sealed from the outer environment while allowing gas exchange among each of the chambers. Chamber 3 was heated at 100 °C while chamber 2 was stirred at room temperature. After 14 h, the reaction mixture was cooled to room temperature and filtered through a pad of silica gel. The filtrate was concentrated *in vacuo*. Analysis of the resulting residue using  $^1\text{H}$  NMR spectroscopy with  $\text{CH}_2\text{Br}_2$  as the internal standard revealed 86% formation of indole **3.2c**.

## B. Simulated Flue Gas.

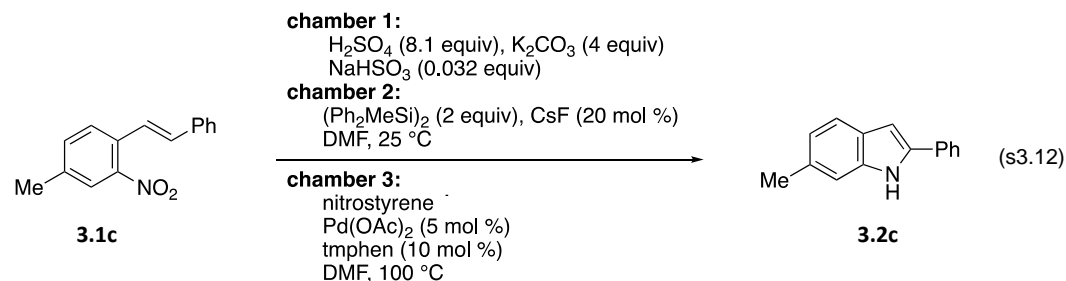
### 1. $\text{H}_2\text{S}$ contaminant





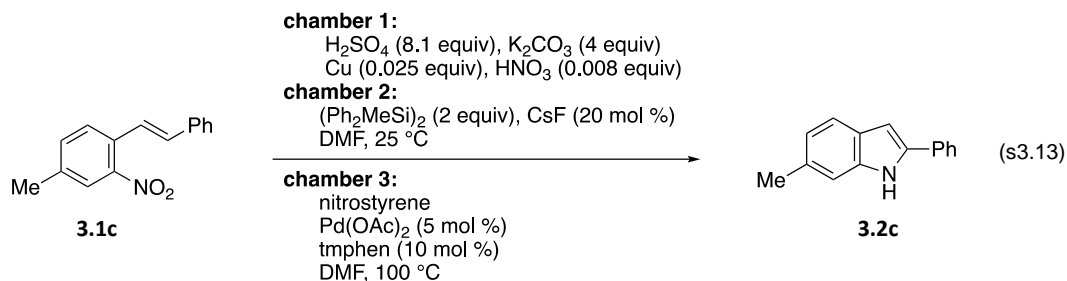
To a 30 mL 3-chamber reactor, 0.0552 g of  $\text{K}_2\text{CO}_3$  (0.4 mmol) and 0.00044 g of  $\text{K}_2\text{S}$  (0.004 mmol) in 0.8 mL of water, 0.81 mL of a 1M aq soln of  $\text{H}_2\text{SO}_4$  (0.8 mmol), was added and frozen sequentially in chamber 1. 0.0035 g of CsF (0.023 mmol), disilane (0.200 mmol) and 0.8 mL of DMF was added to chamber 2, 0.0239 g of nitrostilbene **3.1c** (0.100 mmol), 0.0011 g of  $\text{Pd}(\text{OAc})_2$  (0.005 mmol), 0.0023 g of 3,4,7,8-tetramethyl-1,10-phenanthroline (0.010 mmol) and 1 mL of DMF in chamber 3. The 3-chamber reactor was sealed from outer environment while allowing gas exchange among each other. Then the frozen reaction mixture in chamber 1 was allowed to thaw and stir until effervescence was no longer observed. Chamber 3 was heated at 100 °C while chamber 1 and 2 were stirring at room temperature (Figure S1). After 14 h, the reaction mixture was cooled to room temperature and filtered through a pad of silica gel. The filtrate was concentrated *in vacuo*. Analysis of the resulting residue using  $^1\text{H}$  NMR spectroscopy with  $\text{CH}_2\text{Br}_2$  as the internal standard revealed 90% formation of the indole **3.2c**.

## 2. $\text{SO}_2$ contaminant



To a 30 mL 3-chamber reactor, 0.0552 g of  $\text{K}_2\text{CO}_3$  (0.4 mmol) and 0.00033 g of  $\text{NaHSO}_3$  (0.0032 mmol) in 0.8 mL of water, 0.81 mL of a 1M aq soln of  $\text{H}_2\text{SO}_4$  (0.8 mmol), was added and frozen sequentially in chamber 1. 0.0035 g of  $\text{CsF}$  (0.023 mmol), disilane (0.200 mmol) and 0.8 mL of DMF was added to chamber 2, 0.0239 g of nitrostilbene **3.1c** (0.100 mmol), 0.0011 g of  $\text{Pd}(\text{OAc})_2$  (0.005 mmol), 0.0023 g of 3,4,7,8-tetramethyl-1,10-phenanthroline (0.010 mmol) and 1 mL of DMF in chamber 3. The 3-chamber reactor was sealed from outer environment while allowing gas exchange among each other. Then the frozen reaction mixture in chamber 1 was allowed to thaw and stir until effervescence was no longer observed. Chamber 3 was heated at 100 °C while chamber 1 and 2 were stirring at room temperature (Figure S1). After 14 h, the reaction mixture was cooled to room temperature and filtered through a pad of silica gel. The filtrate was concentrated *in vacuo*. Analysis of the resulting residue using  $^1\text{H}$  NMR spectroscopy with  $\text{CH}_2\text{Br}_2$  as the internal standard revealed 75% formation of the indole **3.2c**.

### 3. NO contaminant



To a 30 mL 3-chamber reactor, under a nitrogen atmosphere, 0.0552 g of  $\text{K}_2\text{CO}_3$  (0.4 mmol) in 0.8 mL of water, 0.80 mL of a 1M aq soln of  $\text{H}_2\text{SO}_4$  (0.8 mmol), 1 mg  $\text{Cu}$  powder (0.0025 mmol) and 0.08 mL of 0.01 M aq soln of  $\text{HNO}_3$  (0.0008 mmol) was added and frozen sequentially in chamber 1, 0.0035 g of  $\text{CsF}$  (0.023 mmol), disilane (0.200 mmol) and 0.8 mL of DMF was added

to chamber 2, 0.0239 g of nitrostilbene **3.1c** (0.100 mmol), 0.0011 g of Pd(OAc)<sub>2</sub> (0.005 mmol), 0.0023 g of 3,4,7,8-tetramethyl-1,10-phenanthroline (0.010 mmol) and 1 mL of DMF in chamber 3. The 3-chamber reactor was sealed from outer environment while allowing gas exchange among each other. Then the frozen reaction mixture in chamber 1 was allowed to thaw and stir until effervescence was no longer observed. Chamber 3 was heated at 100 °C while chamber 1 and 2 were stirring at room temperature (Figure S3.1). After 14 h, the reaction mixture was cooled to room temperature and filtered through a pad of silica gel. The filtrate was concentrated *in vacuo*. Purification by MPLC (3:97 – 10:90 EtOAc:hexanes) afforded **3.2c** as a yellow solid (0.0178 g, 86%).

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9. See Supporting Information for more details.

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11. For other Pd-catalyzed reductive cyclization conditions investigated, please see the Supporting Information.

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13. In addition to CO<sub>2</sub>, the benchmark parameters of gaseous composition of flue gas was reported Long and co-workers in ref 12b to be 1.1% H<sub>2</sub>S and 0.2% H<sub>2</sub>O precombustion and 500 ppm NO<sub>x</sub>, <800 ppm SO<sub>x</sub> and 5–7% H<sub>2</sub>O postcombustion.

14. For other leading references on the composition of flue gas, see: a) J. Wilcox, R. Haghpanah, E. C. Rupp, J. He, K. Lee, *Ann. Rev. Chem. Biomol. Eng.* **2014**, *5*, 479; b) L. K. G. Bhatta, S. Subramanyam, M. D. Chengala, S. Olivera, K. Venkatesh, *J. Cleaner Prod.* **2015**, *103*, 171.

## Chapter IV.

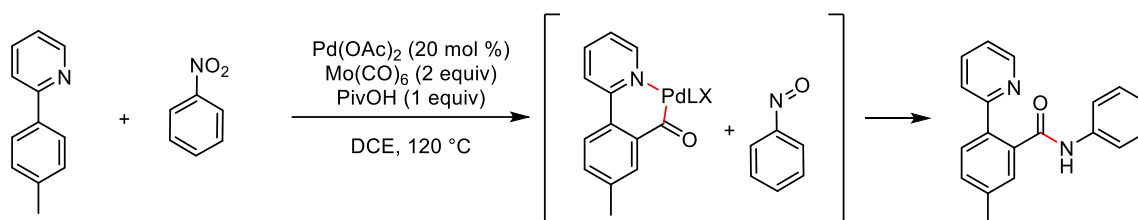
# Cu-Catalyzed Cross-Coupling of Nitroarenes with Aryl Boronic Acids to Construct Diarylamines

### 4.1 Introduction

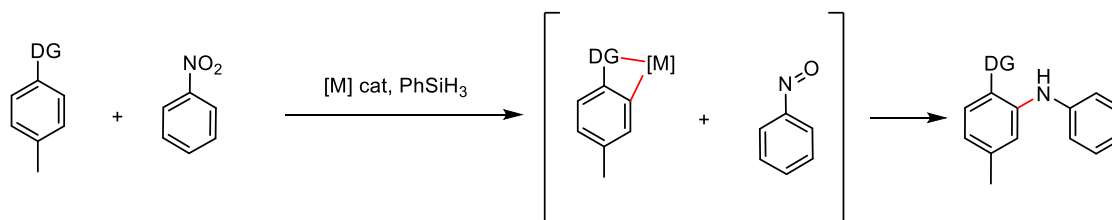
In the previous chapters, I discussed about my investigations into the intramolecular C-N bond construction to produce useful N-heterocycles. Then I asked myself if the experience we acquired from working with reductive cyclization, especially ones using silane reductant, could open an alternative solution to the intermolecular C-H amination using nitroarenes.<sup>1</sup> Initially I was trying to pursue the idea of directed C-H amination based on my colleague Dr. Fei Zhou's work on directed C-H bond aminocarbonylation reaction (**Scheme 4.1a**).<sup>1b</sup> Accessing the nitrosoarene intermediate using the condition we developed to make 1-H indoles seemed to be a perfect replacement for the Mo(CO)<sub>6</sub> reductant to avoid carbonyl insertion (**Scheme 4.1b**). However, after screening for a variety of metal catalysts and ligands, or trying different directing groups, no C-N bond formation was observed and only reductions of nitroarenes all the way to aniline occurred, which made me wonder if the silane reduction system was not compatible with the directing group type of C-H activation system that I tried so far. Therefore, I started to look at another way of C-N bond construction, the cross-coupling reactions. I was curious if we could develop a cross-coupling reaction where nitroarenes serve as the nitrogen component (**Scheme 4.1c**). In this chapter, my investigation into the intermolecular C-N bond formation using nitroarenes via a

cross-coupling type reaction will be discussed. To begin with, I chose *N,N*-diaryl amines as the synthetic target with their well reported biological and material activities of the family along with an increasing need for C-N bond construction strategies using nitrogen sources other than amines.<sup>2</sup>

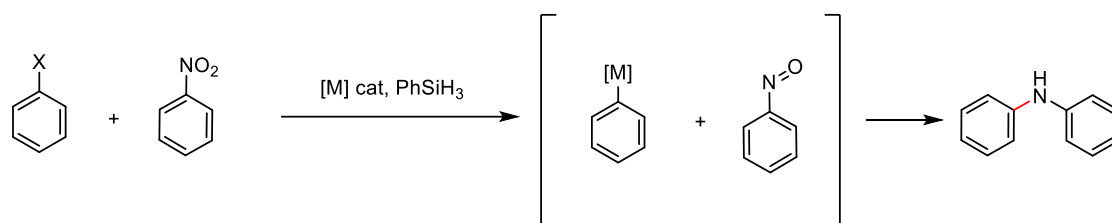
a) 2017 Zhou — Pd catalyzed aminocarbonylation



b) Early attempt: directed C-H amination



c) New hypothesis: C-N cross-coupling



**Scheme 4.1** Strategy development for intermolecular C-N bond formation

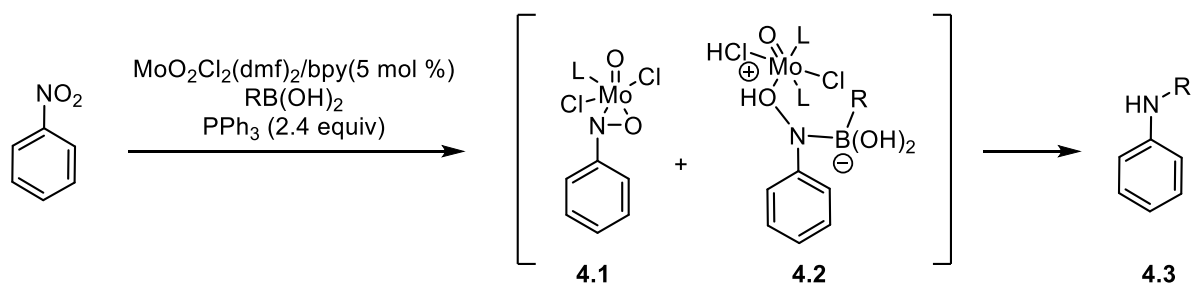
Although transition metal-catalyzed cross-coupling reactions are very well developed in the synthesis of *N,N*-diaryl amines, there exist only a small number of examples using nitroarenes as the cross-coupling partner. In 2002, Sapountzis and Knochel reported a syntheses of diarylamines



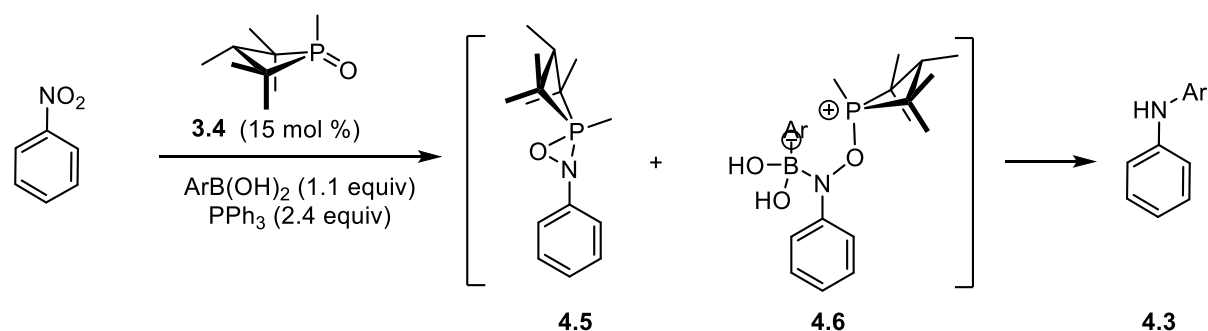
by reacting arylmagnesium compounds with nitroarenes.<sup>3</sup> Later, Niggemann and co-workers successfully synthesized a series of secondary aryl amines using alkyl or aryl zinc reagents and B<sub>2</sub>Pin<sub>2</sub>. They believed that the reaction underwent a nitrenoid intermediate during the C-N formation.<sup>4</sup> On the other hand, when Baran and co-workers reported an iron catalyzed olefin hydroamination reaction with nitroarenes, they hypothesized that the corresponding C-N bond was formed by the addition of alkyl radicals derived from the olefins to a nitrosoarene intermediate.<sup>5</sup> These reports encouraged researchers to investigate further into the C-N bond formation methods using nitroarenes.<sup>6</sup>

Recently, Suazéz-Pantiga, Sanz and co-workers reported a Mo-catalyzed reductive coupling between nitroarenes and boronic acids with the usage of triphenylphosphine as the stoichiometric reductant (**Scheme 4.2a**).<sup>7c</sup> In this method, 5 mol % of MoO<sub>2</sub>Cl<sub>2</sub>(dmf)<sub>2</sub> and bipyridine was used and the authors hypothesized a metallocycle intermediate formed between Mo and nitrosoarene. In 2018, an organophosphorous-catalyzed reductive coupling of nitroarenes and aryl boronic acids using phenyl silane as the terminal reductant was reported by Radosevitch and co-workers.<sup>7a,b</sup> They designed a phosphacyclobutane catalyst that was able to carry out efficient P(III)/P(V)=O cycling with phenylsilane while using the commercial cyclic or acyclic phosphine reagents like triphenylphosphine or 5-Phenyl-5h-benzo[b]phosphindole showed little to no reactivity (**Scheme 4.2b**). With the consistency in the idea of the nitrosoarene being the key intermediate in the C-N formation mechanism, these works inspired me that such transformation may also be achieved by using first row non-noble metal catalysts such as Fe, Co, Ni and Cu using the reduction system in my previous works.

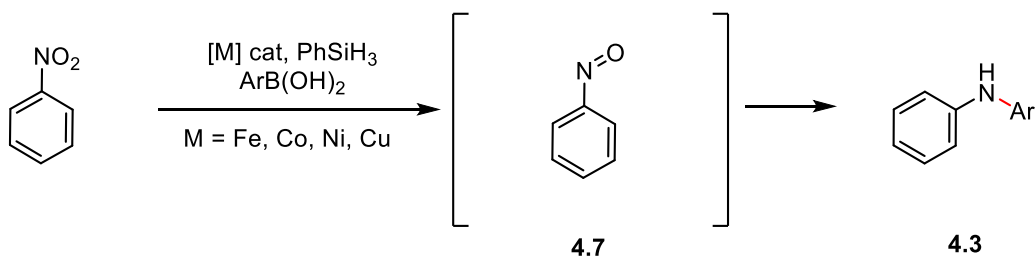
a) 2019 Sanz — Mo catalyzed reductive C-N cross-coupling



b) 2018 Radosevitch — Phosphetane/Phosphetane oxide-catalyzed reductive C-N cross-coupling



c) Target reaction — Non-noble metal catalyzed reductive C-N cross-coupling



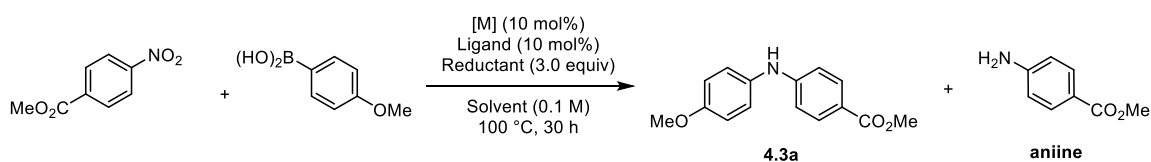
**Scheme 4.2** Previous works for intermolecular C-N bond formation

## 4.1 Early Investigations

To test my idea, a mixture of methyl 4-nitrobenzoate and 4-methoxyphenylboronic acid were exposed to phenylsilane and a number of common first row transition metal catalysts and ligands

(Table 4.1 entry 1–16). To my delight, a small amount of desired *N,N*-diaryl amines was observed when Cu(II) catalyst and phosphine ligands were used. However, with the previous works mentioned earlier using phosphines either as stoichiometric reductant or an organocatalyst with a redox cycling, the actual role of copper catalyst and phosphine ligands of my initial hit remained uncertain at this time. To evaluate the novelty of the reaction and decide whether it was worth further pursuit (table 4.1 entry 17–19), the reaction was first repeated under conditions with stoichiometric phosphine and no phenylsilane and no reaction occurred. Increasing the amount of copper catalyst to 2 equivalents did not resume the reaction. Next, phosphine ligand was made absent in the reaction and only trace amount of aniline by-product was observed, and no cross-coupling product was produced at all. Given its distinguishable catalytic behavior and the ubiquitous applications of the corresponding *N,N*-diaryl amines, this reductive C-N cross-coupling reaction of nitroarenes with aryl boronic acids represents a worth pursuit to me.

**Table 4.1.** Early screening and control experiments on reductive intermolecular C-N formation



Entry <sup>a</sup>	catalyst (10 mol %)	ligand (10 mol %)	Reductant (3 equiv)	%, Yield <b>4.3a</b> (aniline)
1	Ni(acac) <sub>2</sub>	DPPB	B <sub>2</sub> Pin <sub>2</sub>	0 (trace)
2	Ni(acac) <sub>2</sub>	1,10-phen	B <sub>2</sub> Pin <sub>2</sub>	n.r.

3	Ni(acac) <sub>2</sub>	DPPB	PhSiH <sub>3</sub>	n.r.
4	Ni(acac) <sub>2</sub>	1,10-phen	PhSiH <sub>3</sub>	n.r.
5	Fe(OAc) <sub>2</sub>	DPPB	B <sub>2</sub> Pin <sub>2</sub>	0 (39)
6	Fe(OAc) <sub>2</sub>	1,10-phen	B <sub>2</sub> Pin <sub>2</sub>	0 (50)
7	Fe(OAc) <sub>2</sub>	DPPB	PhSiH <sub>3</sub>	0 <sup>b</sup>
8	Fe(OAc) <sub>2</sub>	1,10-phen	PhSiH <sub>3</sub>	0 (90)
9	CoCl <sub>2</sub>	DPPB	B <sub>2</sub> Pin <sub>2</sub>	n.r.
10	CoCl <sub>2</sub>	1,10-phen	B <sub>2</sub> Pin <sub>2</sub>	n.r.
11	CoCl <sub>2</sub>	DPPB	PhSiH <sub>3</sub>	n.r.
12	CoCl <sub>2</sub>	1,10-phen	PhSiH <sub>3</sub>	n.r.
13	Cu(OAc) <sub>2</sub>	DPPB	B <sub>2</sub> Pin <sub>2</sub>	0 (trace)
14	Cu(OAc) <sub>2</sub>	1,10-phen	B <sub>2</sub> Pin <sub>2</sub>	n.r.
15	Cu(OAc) <sub>2</sub>	DPPB	PhSiH <sub>3</sub>	39 (42)
16	Cu(OAc) <sub>2</sub>	1,10-phen	PhSiH <sub>3</sub>	0 (90)
17	Cu(OAc) <sub>2</sub>	DPPB (2 equiv)	none	n.r
18	Cu(OAc) <sub>2</sub> (2 equiv)	DPPB (2 equiv)	none	n.r
19	Cu(OAc) <sub>2</sub>	none	PhSiH <sub>3</sub>	0 (trace)

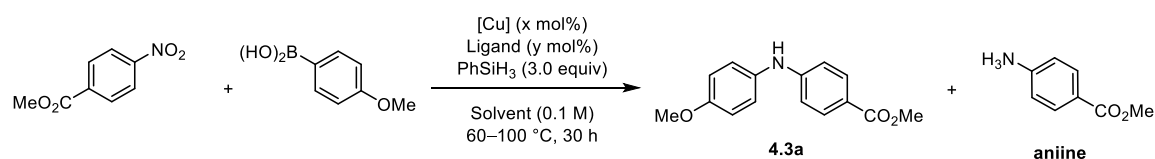
<sup>a</sup> Conditions: 0.1 mmol of methyl 4-nitrobenzoate, 0.1 mmol of 4-methoxyphenylboronic acid, 0.1 M PhMe, 100 °C, 14 h. <sup>b</sup> decomposition and a messy reaction outcome.

## 4.2 Results and discussions

The initial condition I discovered showed crucial competition between cross-coupling product and a fully reduced aniline. To improve the product selectivity, further development of the optimal conditions was performed (**Table 4.2**). It was found that increasing the ratio of DPPB ligand to copper from 1:1 to 2:1 reduced the amount of aniline to a great extent and when 1.5 equivalents of arylboronic acid was used, about 65% of the diarylamine product was formed. Based on this modified catalyst ratio, a variety of solvents were surveyed, and apart from xylene, only MeCN showed comparable results to the original toluene. For the ease of preparing stock solutions of the Cu(OAc)<sub>2</sub> /DPPB, MeCN was used instead of toluene for its better solubility despite the yield was slightly lower. Decreasing the catalyst loading down to 5 mol % Cu(OAc)<sub>2</sub> did not attenuate the ratio between diarylamine product and aniline while further decreasing the Cu(OAc)<sub>2</sub> loading to 2 mol % only caused a slight decrease in the product ratio. Next, different counterion on copper was investigated and except for Cu(TFA)<sub>2</sub> and Cu(Tfacac)<sub>2</sub>, all other copper(II) salts showed poorer reaction efficiency or product ratio. Different additives were subjected to the reaction mixture including acids, bases, and silver salts, yet none showed an improvement of the reaction outcome. To our delight, when carrying the reaction at 60 °C, the ratio of diarylamine to aniline improved to about 2:1. Further lowering the temperature resulted in an overly slow reaction with a large amount of unreacted nitroarenes. Under the optimized reaction temperature, we then

investigated the effect of co-solvent. The best combination was found to be 1:1 mixture of MeCN and toluene, which produced as much as 76% of the desired diarylamine product and only 18% of aniline after 30 hours of reaction. Higher temperature was reinvestigated in order to shorten the reaction time, but the product ratio got worse. Therefore, we moved on our optimization under 60 °C using 1:1 MeCN/tolunene. We performed screening on different commercial silanes but all of them lead to much worse reaction outcome. Changing the identity of phosphine ligands also seemed to have only negative impact on the diaryl amine formation and when we replace phosphine ligands with bipyridine or phenanthroline ligands, vigorous bubbling was observed upon addition of the phenylsilane into the reaction mixture and the nitroarene was almost entirely reduced to aniline. Lastly, the concentration of phenylsilane was examined and the highest ratio of diarylamine to aniline was obtained when using 2.8 equivalents of phenylsilane.

**Table 4.2.** Determination of the optimal conditions



Entry <sup>a</sup>	catalyst (mol %)	ligand (mol %)	Solvent (°C, Temperature)	%, Yield <b>4.3a</b> (aniline)
1	Cu(OAc) <sub>2</sub> (10)	DPPB (10)	PhMe (100)	39 (42) <sup>b</sup>
2	Cu(OAc) <sub>2</sub> (10)	DPPB (20)	PhMe (100)	35 (21) <sup>b</sup>
3	Cu(OAc) <sub>2</sub> (10)	DPPB (20)	PhMe (100)	65 (32)

4	Cu(OAc) <sub>2</sub> (10)	DPPB (20)	Xylene (100)	55 (35)
5	Cu(OAc) <sub>2</sub> (10)	DPPB (20)	MeCN (100)	52 (28)
6	Cu(OAc) <sub>2</sub> (5)	DPPB (10)	MeCN (100)	55 (26)
7	Cu(OAc) <sub>2</sub> (2)	DPPB (4)	MeCN (100)	50 (31)
8	CuCl <sub>2</sub> (5)	DPPB (10)	MeCN (100)	35 (50)
9	Cu(tfacac) <sub>2</sub> (5)	DPPB (10)	MeCN (100)	45 (28)
10	CuSO <sub>4</sub> (5)	DPPB (10)	MeCN (100)	36 (34)
11	Cu(TFA) <sub>2</sub> (5)	DPPB (10)	MeCN (100)	55 (25)
12	Cu(OAc) <sub>2</sub> (5)	DPPB (10)	MeCN (80)	61 (24)
13	Cu(OAc) <sub>2</sub> (5)	DPPB (10)	MeCN (60)	63 (33)
14	Cu(OAc) <sub>2</sub> (5)	DPPB (10)	MeCN (40)	21 (8)
15	Cu(OAc) <sub>2</sub> (5)	DPPB (10)	MeCN/PhMe 9:1 (60)	55 (25)
16	Cu(OAc) <sub>2</sub> (5)	DPPB (10)	MeCN/PhMe 4:1 (60)	70 (20)
17	Cu(OAc) <sub>2</sub> (5)	DPPB (10)	MeCN/PhMe 1:1 (60)	76 (18)
18	Cu(OAc) <sub>2</sub> (5)	DPPB (10)	MeCN/iPrOAc 1:1 (60)	65 (24)
19	Cu(OAc) <sub>2</sub> (5)	DPPB (10)	MeCN/DCE 1:1 (60)	67 (29)
20	Cu(OAc) <sub>2</sub> (5)	DPPB (10)	MeCN/THF 1:1 (60)	63 (18)
21	Cu(OAc) <sub>2</sub> (5)	DPPB (10)	MeCN/DCE 1:1 (60)	67 (29)
22	Cu(OAc) <sub>2</sub> (5)	DPPB (10)	MeCN/PhMe 1:1 (60)	27 (48) <sup>c</sup>

23	Cu(OAc) <sub>2</sub> (5)	DPPP (10)	MeCN/PhMe 1:1 (60)	55 (27).
24	Cu(OAc) <sub>2</sub> (5)	BINAP (10)	MeCN/PhMe 1:1 (60)	33 (37).
25	Cu(OAc) <sub>2</sub> (5)	1,10-phen (10)	MeCN/PhMe 1:1 (60)	0 (90).
26	Cu(OAc) <sub>2</sub> (5)	DPPB (10)	MeCN/PhMe 1:1 (60)	83 (16) <sup>d</sup>
27	Cu(OAc) <sub>2</sub> (5)	DPPB (10)	MeCN/PhMe 1:1 (60)	80 (20) <sup>e</sup>

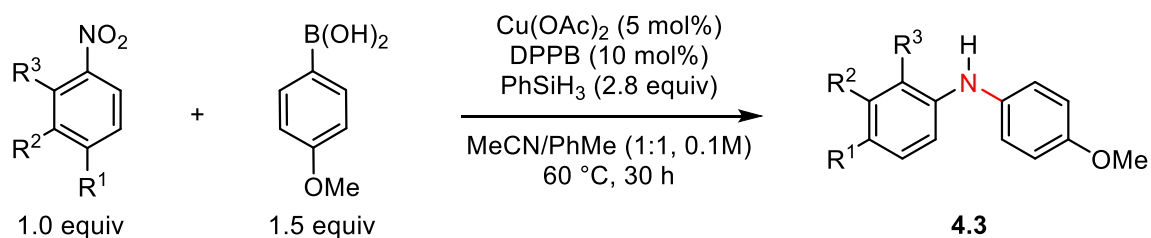
<sup>a</sup> Conditions: 0.10 mmol of methyl 4-nitrobenzoate, 0.15 mmol of 4-methoxyphenylboronic acid, 0.1 M Solvent, 30 h. <sup>b</sup> 0.10 mmol of 4-methoxyphenylboronic acid used. <sup>c</sup> 3 equiv of (MeO)<sub>2</sub>MeSiH used as the reductant. <sup>d</sup> 2.8 equiv of PhSiH<sub>3</sub> used. <sup>e</sup> 2.6 equiv of PhSiH<sub>3</sub> used.

Using the optimal condition, the scope and limitation of this reaction were investigated (**Table 4.3**). First, the effect of changing the substituents on nitroarenes was examined. Overall speaking, for para-substituents on nitroarenes, the reaction worked better with electron-deficient substituents on the nitroarene. No reaction occurred when I performed the reaction using 4-nitroanisole while 4-nitrotoluene and nitrobenzene did react and formed diarylamines with diminished yield. Taking advantage of this electronic behavior of the reaction, a selective cross-coupling can be performed on 1,4-dinitrobenzene to react with only one of the two nitro groups. On the other hand, the electronic nature of the meta-substituents did not share the same trend with the para- ones. Both electron rich and electron deficient reactants gave good yields of the cross-coupling product. Contrary to what we expected, this reaction also had a good ortho-substituent tolerance such as Et-, NC-, Br-, or F<sub>3</sub>C-, but we were even more surprised that electron-donating methoxy group also gave a good yield of the product despite showing no reactivity when it was at para-position.

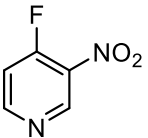


We were also encouraged to see that nitropyridines can react to give desired product in good yields despite their coordinative characteristic.

**Table 4.3** Scope and limitations with regards to the nitroarene.



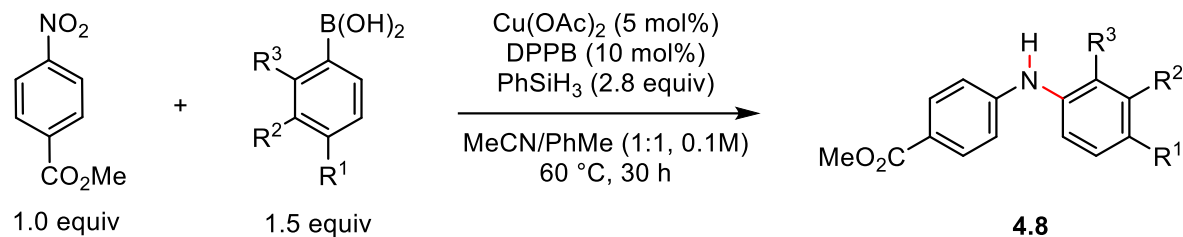
Entry	#	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	%, yield <sup>a</sup> <b>4.3</b>
1	<b>a</b>	MeO <sub>2</sub> C	H	H	83 (81) <sup>b</sup>
2	<b>b</b>	F <sub>3</sub> C	H	H	84
3	<b>c</b>	H	H	H	66
4	<b>d</b>	Cl	H	H	85
5	<b>e</b>	MeO	H	H	n.r.
6	<b>f</b>	N <sub>2</sub> O	H	H	59
7	<b>g</b>	H	F <sub>3</sub> C	H	89
8	<b>h</b>	H	Me	H	73

9	<b>i</b>	H	MeO	H	85
10	<b>j</b>	H	H	NC	83
11	<b>k</b>	H	H	F <sub>3</sub> C	77
12	<b>l</b>	H	H	Br	89
13	<b>m</b>	H	H	Et	82
14	<b>n</b>	Me	H	OMe	72
15	<b>o</b>	-HC=CH-CH=CH-		H	96
16	<b>p</b>				75

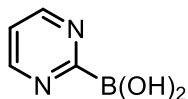
<sup>a</sup> Isolated yield determined after silica gel chromatography. <sup>b</sup> 1 mmol reaction scale.

Next, I investigated the scope of the boronic acids (**Table 4.4**). By looking at a variety of para- and meta-substituents, the effect of changing the electronic nature of the aryl boronic acid was examined. We observed that the yield of the transformation was unaffected by either an electron-donating- or electron-withdrawing group. The only exception was a para- thiomethyl substituent that resulted in a much lower yield compared to other substituents. Unlike nitroarene, arylboronic acids showed a higher sensitivity toward steric environment when we surveyed different substituents on the ortho- position. While 2-methoxyphenyl boronic acid reacted effectively to product 85% of the corresponding diarylamines, the reaction was completely turned off when using 2-ethylphenylboronic acid. Apart from regular phenylboronic acids, the reaction also showed a good tolerance to naphthalene, quinoline and pyridine substituents on boronic acids.

**Table 4.4** Scope and limitations with regards to the boronic acids.



Entry <sup>[a]</sup>	#	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	%, yield <sup>a</sup> <b>4.8</b>
1	<b>a</b>	F <sub>3</sub> C	H	H	90
2	<b>b</b>	F	H	H	97
3	<b>c</b>	Me	H	H	90
4	<b>d</b>	MeS	H	H	64
5	<b>e</b>	H	F	H	88
6	<b>f</b>	H	MeO	H	92
7	<b>g</b>	H	Me	H	88
8	<b>h</b>	H	H	MeO	85
9	<b>i</b>	H	H	Et	n.r.
10	<b>j</b>	H	-HC=CH-CH=CH-		83



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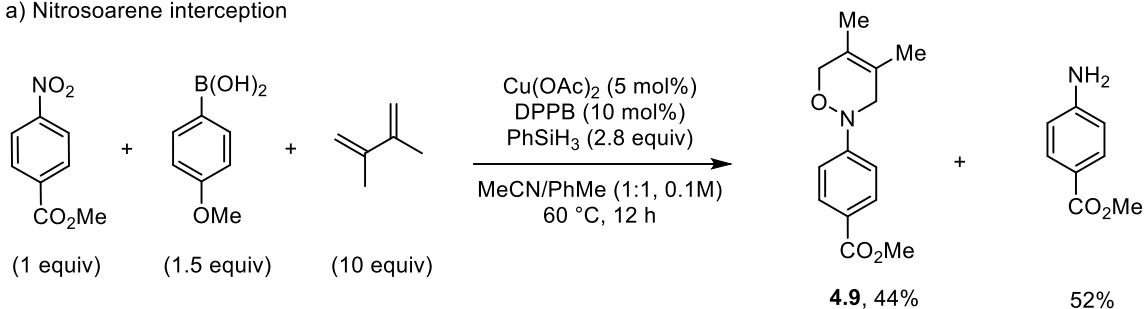
<sup>a</sup> Isolated yield determined after silica gel chromatography.

A series of experiments were performed to provide insight into the mechanism of this cross-coupling reaction. Like before, one major hypothesis we made based on our previous works was that the nitroarene would undergo a nitrosoarene intermediate during reduction and C-N bond formation. Therefore, it would be very supportive if such intermediate can be observed or trapped. After looking into the literature, we found that hetero Diels-Alder reaction between nitrosoarene as the dienophiles and 1,3-dienes could potentially allow us to trap the nitroso species as oxazines.<sup>8</sup> Following the optimized condition using methyl 4-nitrobenzoate and 4-methoxyphenylboronic acid, 10 equivalents of 2,3-dimethylbutadiene was added together (**Scheme 4.3a**). Upon consumption of the nitroarene, formation of oxazine **4.9** was observed, along with that we only found a small amount of aniline. Despite a part of the missing mass balance remained unclear, this result was still very supportive of our hypothesis as the formation of the oxazine and the absence of the diarylamine product were likely the result of interception of the dissociated nitrosoarene species by the diene additive.<sup>9</sup> The next concern we had was whether the C-N bond formation occurred directly on the nitrosoarene intermediate, or the aniline that it got further reduced to, because aniline itself was also a well-known cross-coupling substrate in C-N bond formation. A cross-over control experiment was carried by subjecting both methyl 4-nitrobenzoate and 4-trifluoromethyl aniline into the reaction conditions (**Scheme 4.3b**), in which we only observed diarylamine product of 4-nitrobenzoate. On the other hand, when nitrosoarene was subjected directly to the reaction condition in place of nitroarene, the cross-coupled diarylamine could still

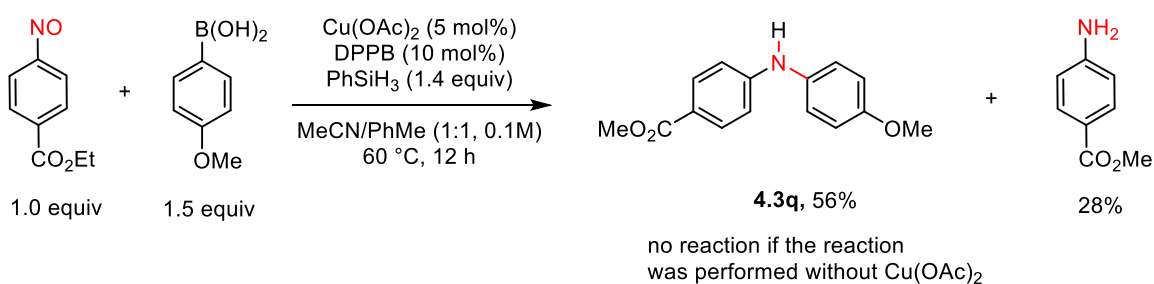
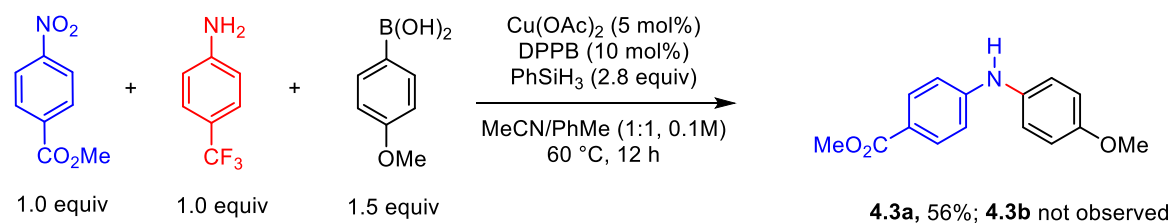
be formed at a moderate yield. It was mentioned in the initial hit that if we removed copper from the condition, the reaction completely stopped. This also held true even when we were using nitrosoarene as the substrate. During the early investigation of the optimal conditions, I also tried several different leaving groups such as halides or boronic esters. Although boronic esters were usually considered less reactive than their corresponding aryl boronic acids, when I performed this reaction, however, the use of aryl boronic esters or trifluoroborate salts always triggered violent bubbling at the beginning of the reaction, which was likely due to decomposition of phenylsilane generating hydrogen gas. And after the consumption of the starting materials, only aniline formation was observed (**Scheme 4.3c**). These results suggested that the hydroxyl group on the boronic acids may play a crucial role in the reaction process. Finally, the latest stage of the reaction may involve a reduction of a N-hydroxylamine intermediate by either copper hydride or phenylsilane. To find out if phenylsilane alone is strong enough to reduce N-hydroxylamine, a N-hydroxy-N-arylaniline was subjected to phenylsilane under reaction solvent and temperature while another group also contained copper catalyst and phosphine ligands (**Scheme 4.3d**). It was found that only when copper presented, was the N-hydroxylamine reduced.

### **Scheme 4.3** Mechanistic Experiments

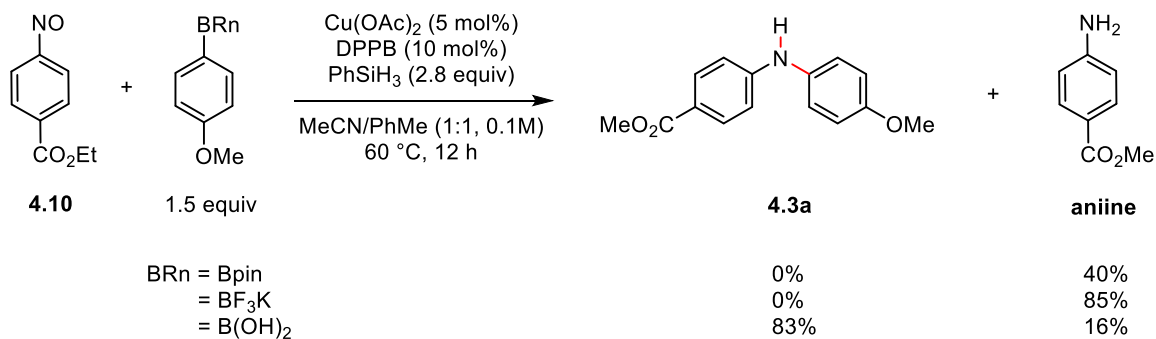
a) Nitrosoarene interception



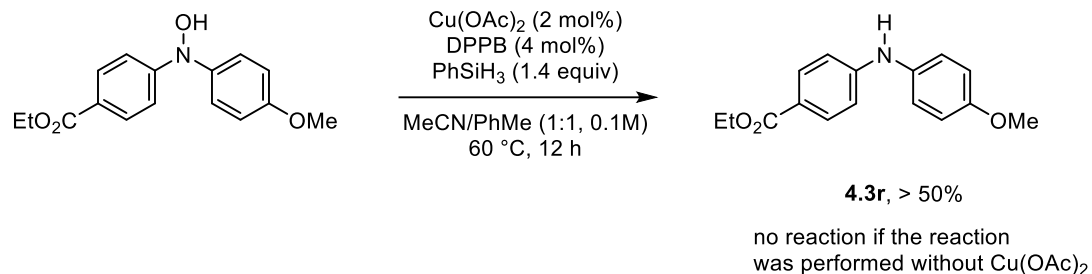
b) Investigating the reactivity of aniline and nitrosoarene intermediate



c) Important role of boronic acid hydroxy substituents

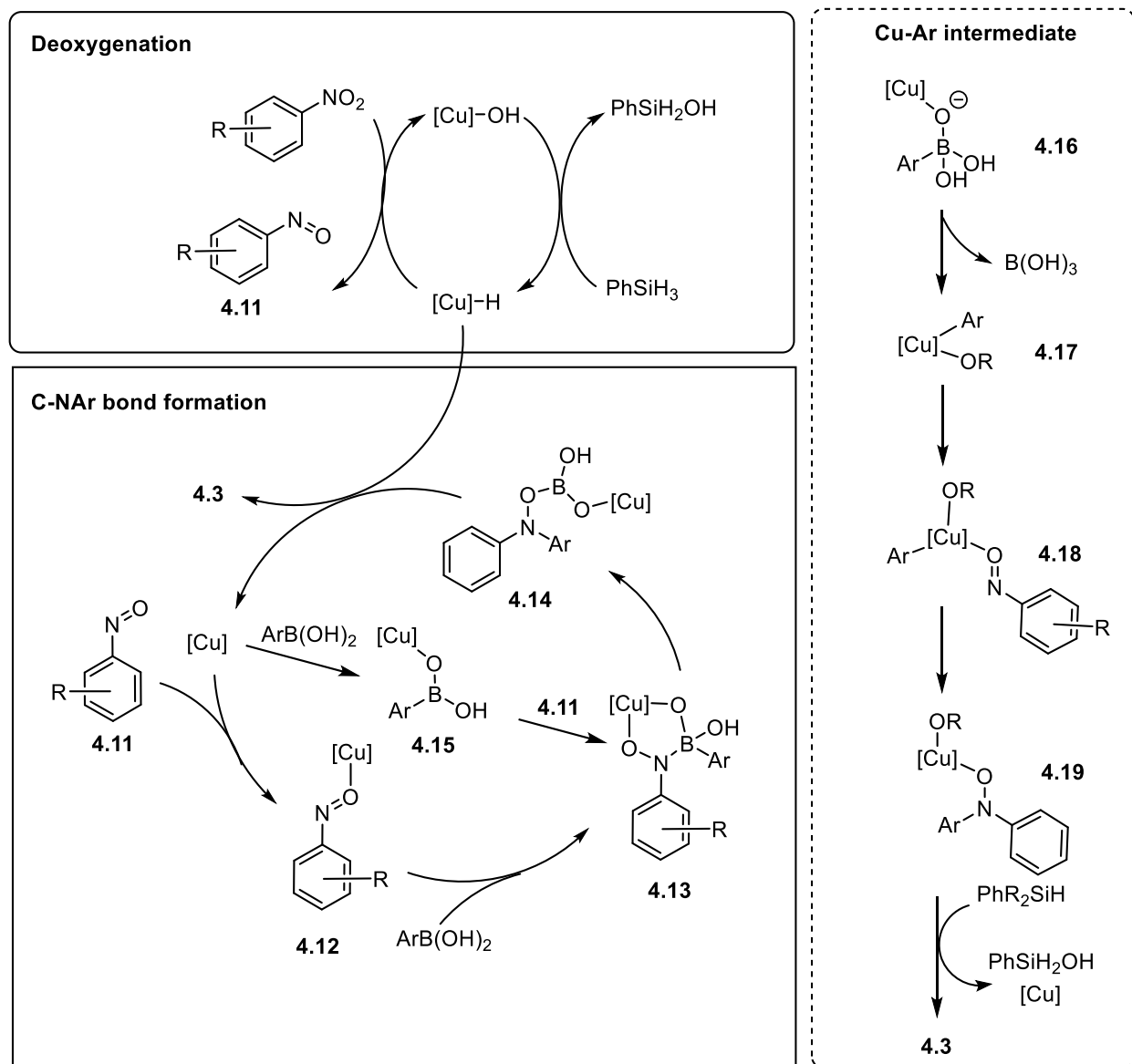


d) N-hydroxy amine reduction



A mechanism was proposed based on all these results (**Scheme 4.4**). Unlike our intramolecular reductive C-N bond formation using Fe catalyst, where Fe only participates in the reduction of the nitroarenes but not directly involved in the C-N bond formation process, this cross-coupling reaction requires the copper catalyst for both the nitro-group deoxygenation and the C-N bond formation. The deoxygenation is done by a copper hydride species, resulting in the formation of the nitrosoarene intermediate, along with which is a copper hydroxide that could be converted back to copper hydride by phenylsilane. Inspired by the previous works, we hypothesized that coordination of the copper complex to the nitrosoarene and the arylboronic acid consecutively forms a metallocycle intermediate **4.13**, which is followed by a 1,2-aryl shift to form the C-N bond and become intermediate **4.14**.<sup>9,10</sup> Finally this N-hydroxylamine intermediate is reduced by copper hydride into diarylamine product and regenerates the copper catalyst.

**Scheme 4.4** Potential Mechanism



Alternatively, one may hypothesize the formation of a  $\text{Ar}[\text{Cu}]$  intermediate **4.18** via transmetallation, similar to the Chan-Evans-Lam reaction. Association and insertion of the nitrosoarene then accomplish the C-N bond formation step, followed by another reduction to form the diarylamine product. The concern would be that this mechanism does not explain the unique reactivity of aryl boronic acids compared to their pinacol esters or trifluoroborate salts. Also, it

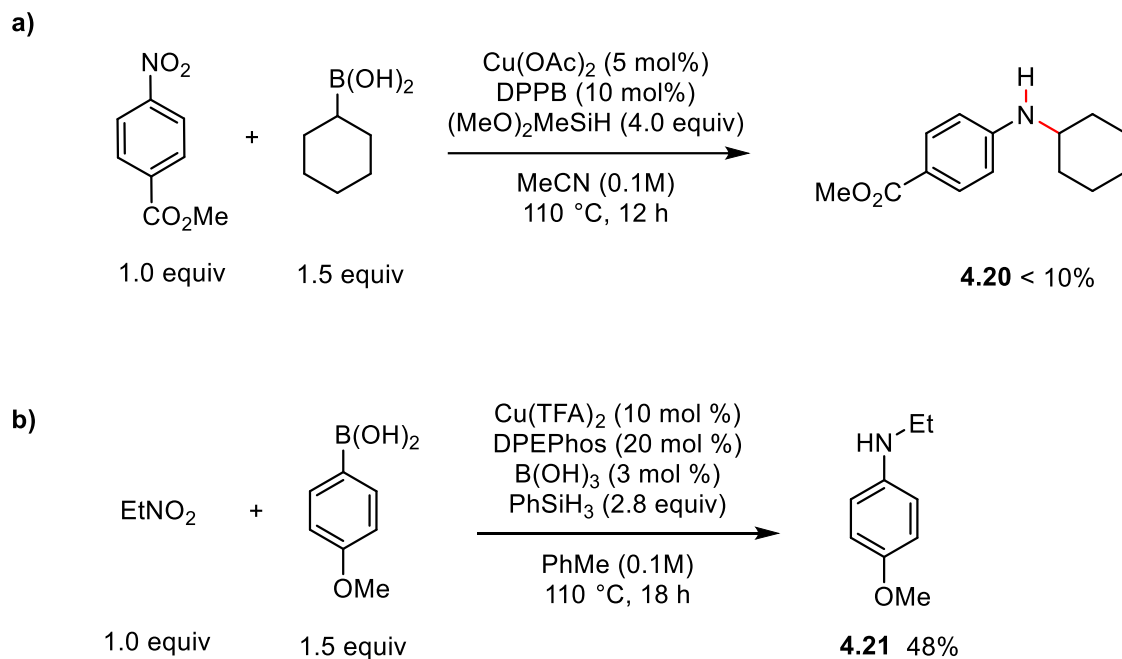


was unlikely to not have seen a competing product from aniline xx if the reaction follows this mechanism.

#### 4.3 Further investigations on alkyl boronic acids and nitroalkanes

With the optimized condition of synthesizing diarylamines, we were also curious if this condition can also be used to construct sp<sup>3</sup> C-N bond, which means we could replace the cross-coupling partner by either alkyl boronic acids or nitroalkanes. Unfortunately, the efficiency of the reaction significantly reduced when using alkyl boronic acids and when nitroalkanes were used instead of introarenes, no reaction occurred under the current condition. Re-optimization of the condition was considered necessary to improve this reaction further.

For reactions of alkylboronic acids, I only screened a few other silane reductants so far and despite trace product formation was observed in a couple cases, the formation of a large amount of aniline by-product can hardly be neglected (**Scheme 4.5a**). Since we hypothesized that the hydroxyl group of the arylboronic acid played a critical role in the performance of the reaction, changing the identity of arylboronic acid to alkyl boronic acid may lead to a significant difference in the reactivity as the pka of the boronic acid group changes from 8-9 to the range of 9-10. Right now, there are not enough experiments to find any trend or form any solid hypothesis. Further investigations need to be done.



**Scheme 4.5** Cross-coupling using alkylboronic acids or nitroalkanes

At the same time, I also screened conditions for reactions of nitroalkanes and arylboronic acids (**Scheme 4.5b**). An initial hit was observed when the catalyst and ligand was modified to  $\text{Cu(TFA)}_2$ , DPEPhos and heating the reaction at  $110\text{ }^\circ\text{C}$  in MeCN. Improvement of yield was achieved by changing the solvent back to toluene. Another increase of yield was made when a catalytic amount of acetic acid or boric acid was added into the mixture. Further optimization needs to be done to improve the reaction efficiency and hopefully the condition can be made milder.

#### 4.4 Conclusion

In conclusion, a mild cross-coupling reaction of nitroarenes and aryl boronic acids using first-row copper catalyst and phenylsilane as the terminal reductant was discovered. This reaction tolerates

a good variety of nitroarenes and arylboronic acids, allowing mild and efficient access of useful *N,N*-diaryl amine products. Based on experimental observations, we believe that this reaction follows a distinguishable mechanism that requires copper catalyst to participate in both reduction and C-N bond construction. Observations also supported our idea that C-N bond formation occurred via nitrosoarene intermediate rather than aniline. The important role of arylboronic acids in this reaction leads to a unique reactivity that allowed nitroarenes to form C-N bond in the presence of anilines, a common competent in the C-N cross-coupling reactions. With further development of conditions for alkyl boronic acids and nitroalkanes, this type of reaction could be used as a handy tool in orthogonal functionalization involving C-N bond formation.

## Experimental

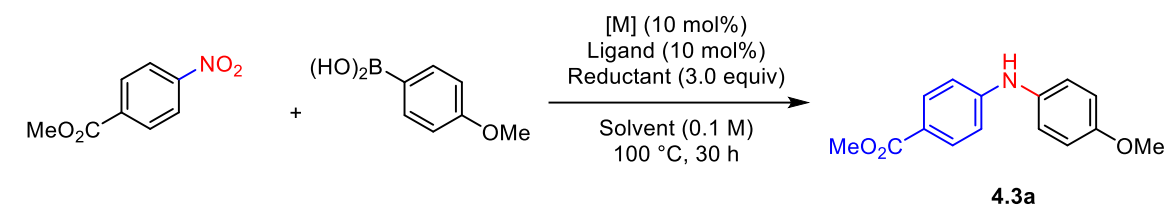
**General.**  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra were recorded at ambient temperature using 500 MHz or 300 MHz spectrometers. The data are reported as follows: chemical shift in ppm from internal tetramethylsilane on the  $\delta$  scale, multiplicity (br = broad, s = singlet, d = doublet, 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. HPLC analysis was conducted on an Agilent 1100 instrument equipped with a binary pump and diode array detector. Liquid chromatography was performed using forced flow (flash chromatography) of the indicated solvent system on 60Å (40 – 60  $\mu\text{m}$ ) mesh silica gel ( $\text{SiO}_2$ ). Medium pressure liquid chromatography (MPLC) was performed to force flow the indicated solvent system down columns that had been packed with 60Å (40 – 60  $\mu\text{m}$ ) mesh silica gel ( $\text{SiO}_2$ ). 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,  $\text{Et}_2\text{O}$ , and  $\text{CH}_2\text{Cl}_2$  were dried by filtration through alumina according to the procedure of Grubbs.<sup>{Pangborn, 1996 #4481}</sup> Metal salts were stored in a nitrogen atmosphere dry box.

## I. Cu-Catalyzed Formation of Diarylamines

### D. Screening of Reductive Cross-coupling Conditions

To a 10 mL Schlenk tube under nitrogen were added methyl 4-nitrobenzoate (1 equiv) and 4-methoxyphenylboronic acid were added. Catalyst and ligands were then added followed by 1 mL of solvent and finally reductants were added before the Schlenk tube was sealed. The reaction mixture was stirred and heated for 14-30 h, before it was cooled to room temperature and filtered through a pad of silica gel. The filtrate was concentrated *in vacuo*, and the residue was analyzed using  $^1\text{H}$  NMR spectroscopy using  $\text{CH}_2\text{Br}_2$  as the internal standard.

**Table S4.1.** Early screening on metal reductant combinations



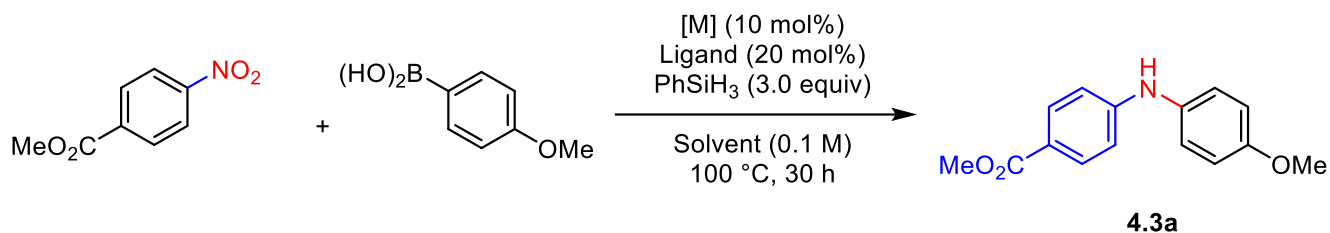
Entry <sup>a</sup>	catalyst (10 mol %)	ligand (10 mol %)	Reductant (3 equiv)	%, Yield <b>4.3a</b> (aniline)
1	Ni(acac) <sub>2</sub>	DPPB	B <sub>2</sub> Pin <sub>2</sub>	0 (trace)
2	Ni(acac) <sub>2</sub>	1,10-phen	B <sub>2</sub> Pin <sub>2</sub>	n.r.
3	Ni(acac) <sub>2</sub>	DPPB	PhSiH <sub>3</sub>	n.r.

4	Ni(acac) <sub>2</sub>	1,10-phen	PhSiH <sub>3</sub>	n.r.
5	Fe(OAc) <sub>2</sub>	DPPB	B <sub>2</sub> Pin <sub>2</sub>	0 (39)
6	Fe(OAc) <sub>2</sub>	1,10-phen	B <sub>2</sub> Pin <sub>2</sub>	0 (50)
7	Fe(OAc) <sub>2</sub>	DPPB	PhSiH <sub>3</sub>	0 <sup>b</sup>
8	Fe(OAc) <sub>2</sub>	1,10-phen	PhSiH <sub>3</sub>	0 (90)
9	CoCl <sub>2</sub>	DPPB	B <sub>2</sub> Pin <sub>2</sub>	n.r.
10	CoCl <sub>2</sub>	1,10-phen	B <sub>2</sub> Pin <sub>2</sub>	n.r.
11	CoCl <sub>2</sub>	DPPB	PhSiH <sub>3</sub>	n.r.
12	CoCl <sub>2</sub>	1,10-phen	PhSiH <sub>3</sub>	n.r.
13	Cu(OAc) <sub>2</sub>	DPPB	B <sub>2</sub> Pin <sub>2</sub>	0 (trace)
14	Cu(OAc) <sub>2</sub>	1,10-phen	B <sub>2</sub> Pin <sub>2</sub>	n.r.
15	Cu(OAc) <sub>2</sub>	DPPB	PhSiH <sub>3</sub>	39 (42)
16	Cu(OAc) <sub>2</sub>	1,10-phen	PhSiH <sub>3</sub>	0 (90)
17	Cu(OAc) <sub>2</sub>	DPPB (2 equiv)	none	n.r
18	Cu(OAc) <sub>2</sub> (2 equiv)	DPPB (2 equiv)	none	n.r
19	Cu(OAc) <sub>2</sub>	none	PhSiH <sub>3</sub>	0 (trace)

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<sup>a</sup> Conditions: 0.1 mmol of methyl 4-nitrobenzoate, 0.1 mmol of 4-methoxyphenylboronic acid, 0.1 M PhMe, 100 °C, 14 h. <sup>b</sup> decomposition and a messy reaction outcome.

**Table S4.2.** Discovery of the initial lead conditions



Entry <sup>a</sup>	catalyst (mol %)	ligand (mol %)	Solvent	%, Yield <b>4.3a</b>
				(%, Yield aniline)
1	Pd(OAc) <sub>2</sub> (10)	Cy <sub>2</sub> PhP (20)	PhMe	0 (86) <sup>b</sup>
2	Fe(OAc) <sub>2</sub> (10)	Cy <sub>2</sub> PhP (20)	PhMe	decomp. <sup>b</sup>
3	Ni(acac) <sub>2</sub> (10)	Cy <sub>2</sub> PhP (20)	PhMe	n.r. <sup>b</sup>
4	Cu(OAc) <sub>2</sub> (10)	Cy <sub>2</sub> PhP (20)	PhMe	21 (40) <sup>b</sup>
5	Cu(OAc) <sub>2</sub> (10)	DPPB (10)	PhMe	39 (42) <sup>b</sup>
6	Cu(OAc) <sub>2</sub> (10)	DPPB (20)	PhMe	35 (21) <sup>b</sup>
7	Cu(OAc) <sub>2</sub> (10)	DPPB (20)	PhMe	65 (32)
8	Cu(OAc) <sub>2</sub> (10)	DPPB (20)	PhMe	33 (42) <sup>c</sup>
9	Cu(OAc) <sub>2</sub> (10)	DPPB (20)	PhMe	42 (54) <sup>d</sup>
10	Cu(OAc) <sub>2</sub> (10)	DPPB (20)	PhMe	45 (69) <sup>e</sup>
11	Cu(OAc) <sub>2</sub> (10)	DPPB (20)	Xylene	55 (35)

12	Cu(OAc) <sub>2</sub> (10)	DPPB (20)	DMF	10 (10)
13	Cu(OAc) <sub>2</sub> (10)	DPPB (20)	DME	23 (74)
14	Cu(OAc) <sub>2</sub> (10)	DPPB (20)	Dioxane	56 (40)
15	Cu(OAc) <sub>2</sub> (10)	DPPB (20)	DCE	52 (42)
16	Cu(OAc) <sub>2</sub> (10)	DPPB (20)	EtOH	n.r.
17	Cu(OAc) <sub>2</sub> (10)	DPPB (20)	MeCN (100)	52 (28)

<sup>a</sup> Conditions: 0.10 mmol of methyl 4-nitrobenzoate, 0.15 mmol of 4-methoxyphenylboronic acid, 0.30 mmol of phenyl silane, 0.1 M Solvent, 100 °C, 30 h. <sup>b</sup> 0.10 mmol of 4-methoxyphenylboronic acid used. <sup>c</sup> 0.20 mmol of 4-methoxyphenylboronic acid used. <sup>d</sup> 0.15 mmol of methyl 4-nitrobenzoate and 0.10 mmol of 4-methoxyphenylboronic acid used. <sup>e</sup> 0.20 mmol of methyl 4-nitrobenzoate and 0.10 mmol of 4-methoxyphenylboronic acid used.

**Table S4.3.** Screening of copper salts, additives, and reaction temperature

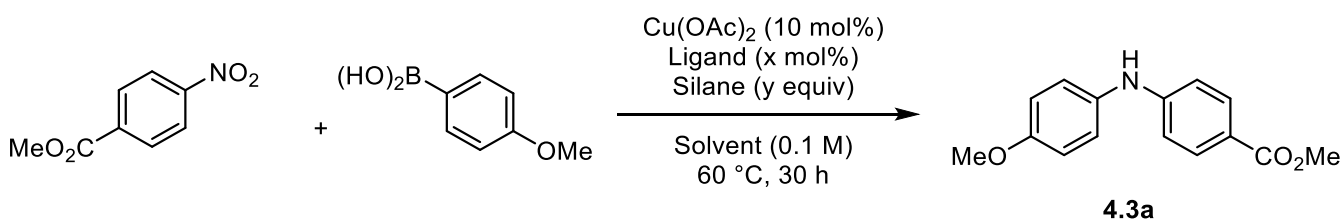
Entry <sup>a</sup>	catalyst (mol %)	Ligand (mol %)	°C, Temperature	Additives	%, Yield <b>4.3a</b>
				(mol %)	(%, Yield aniline)
1	Cu(OAc) <sub>2</sub> (10)	DPPB (20)	100	none	52 (28)



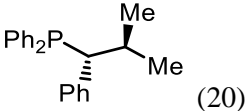
2	Cu(OAc) <sub>2</sub> (10)	DPPB (20)	100	AcOH (10)	46 (33)
3	Cu(OAc) <sub>2</sub> (10)	DPPB (20)	100	K <sub>2</sub> CO <sub>3</sub> (10)	0 (45)
4	Cu(OAc) <sub>2</sub> (10)	DPPB (20)	100	KOtBu (10)	24 (50)
5	Cu(OAc) <sub>2</sub> (10)	DPPB (20)	100	CsF (10)	39 (28)
6	Cu(OAc) <sub>2</sub> (10)	DPPB (20)	100	MgO (10)	44 (32)
7	Cu(OAc) <sub>2</sub> (5)	DPPB (10)	100	none	55 (26)
8	Cu(OAc) <sub>2</sub> (2)	DPPB (4)	100	none	50 (31)
9	Cu(OAc) <sub>2</sub> (1)	DPPB (2)	100	none	31 (47)
10	CuCl <sub>2</sub> (5)	DPPB (10)	100	none	35 (50)
11	CuCl <sub>2</sub> (5)	DPPB (10)	100	AgClO <sub>4</sub> (10)	0 (64)
12	CuCl <sub>2</sub> (5)	DPPB (10)	100	AgSbF <sub>4</sub> (10)	0 (80)
13	Cu(acac) <sub>2</sub> (5)	DPPB (10)	100	none	50 (21)
14	Cu(tfacac) <sub>2</sub> (5)	DPPB (10)	100	none	45 (28)
15	CuSO <sub>4</sub> (5)	DPPB (10)	100	none	36 (34)
16	Cu(TFA) <sub>2</sub> (5)	DPPB (10)	100	none	55 (25)
17	Cu(OAc) <sub>2</sub> (5)	DPPB (10)	80	none	61 (24)
18	Cu(OAc) <sub>2</sub> (5)	DPPB (10)	60	none	63 (33)
19	Cu(OAc) <sub>2</sub> (5)	DPPB (10)	40	none	21 (8)
20	Cu(OAc) <sub>2</sub> (5)	DPPB (10)	r.t.	none	n.r.

<sup>a</sup> Conditions: 0.10 mmol of methyl 4-nitrobenzoate, 0.15 mmol of 4-methoxyphenylboronic acid, 5 mol % of copper salt, 10 mol % of DPPB, 0.30 mmol of phenyl silane, 0.1 M MeCN, 30 h.

**Table S4.4.** Screening of co-solvent, ligands and silanes.



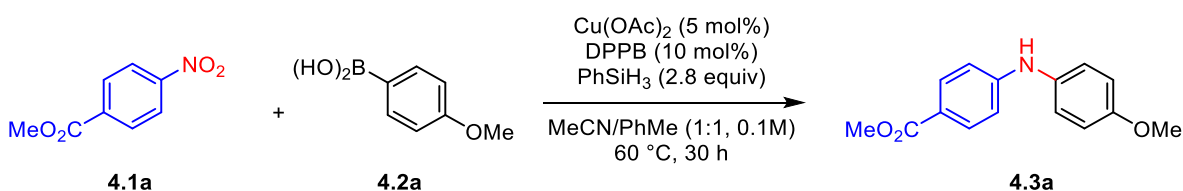
Entry <sup>a</sup>	Ligand (mol %)	Silanes (equiv.)	Solvent (ratio)	%, Yield <b>4.3a</b>
				(%, Yield aniline)
1	DPPB (20)	PhSiH <sub>3</sub> (3.0)	MeCN/PhMe (9:1)	55 (25)
2	DPPB (20)	PhSiH <sub>3</sub> (3.0)	MeCN/PhMe (4:1)	70 (20)
3	DPPB (20)	PhSiH <sub>3</sub> (3.0)	MeCN/PhMe (1:1)	76 (18)
4	DPPB (20)	PhSiH <sub>3</sub> (3.0)	MeCN/Xylene (1:1)	55 (26)
5	DPPB (20)	PhSiH <sub>3</sub> (3.0)	MeCN/PhCF <sub>3</sub> (1:1)	65 (24)
6	DPPB (20)	PhSiH <sub>3</sub> (3.0)	MeCN/iPrOAc (1:1)	61 (25)
7	DPPB (10)	PhSiH <sub>3</sub> (3.0)	MeCN/DCE (1:1)	67 (29)
8	DPPB (10)	PhSiH <sub>3</sub> (3.0)	MeCN/DMF (1:1)	60 (19)
9	DPPB (10)	PhSiH <sub>3</sub> (3.0)	MeCN/PhMe (1:1)	60 (24) <sup>b</sup>

10	DPPB (10)	PhSiH <sub>3</sub> (3.0)	MeCN/PhMe (1:1)	33 (13) <sup>c</sup>
11	DPPP (10)	PhSiH <sub>3</sub> (3.0)	MeCN/PhMe (1:1)	55 (27)
12	Davephos (10)	PhSiH <sub>3</sub> (3.0)	MeCN/PhMe (1:1)	31 (50)
13	DPEPhos (20)	PhSiH <sub>3</sub> (3.0)	MeCN/PhMe (1:1)	31 (26)
14	BINAP (10)	PhSiH <sub>3</sub> (3.0)	MeCN/PhMe (1:1)	33 (37)
15	 (20)	PhSiH <sub>3</sub> (3.0)	MeCN/PhMe (1:1)	46 (22)
16	PPh <sub>3</sub> (20)	PhSiH <sub>3</sub> (3.0)	MeCN/PhMe (1:1)	0 (89)
17	1,10-phen (10)	PhSiH <sub>3</sub> (3.0)	MeCN/PhMe (1:1)	0 (90)
18	DPPB (10)	Me <sub>2</sub> ClSiH (4.0)	MeCN/PhMe (1:1)	n.r.
19	DPPB (10)	iPr <sub>3</sub> SiH (4.0)	MeCN/PhMe (1:1)	n.r.
20	DPPB (10)	(MeO) <sub>2</sub> MeSiH (4.0)	MeCN/PhMe (1:1)	27 (48)
21	DPPB (10)	(MeO) <sub>2</sub> MeSiH (4.0)	MeCN/PhMe (1:1)	0 (93)
22	DPPB (10)	BnMe <sub>2</sub> SiH (4.0)	MeCN/PhMe (1:1)	n.r.
23	DPPB (10)	PHMS (4.0)	MeCN/PhMe (1:1)	n.r.
24	DPPB (10)	PhSiH <sub>3</sub> (3.2)	MeCN/PhMe (1:1)	70 (18)
25	DPPB (10)	PhSiH <sub>3</sub> (3.4)	MeCN/PhMe (1:1)	62 (21)
26	DPPB (10)	PhSiH <sub>3</sub> (3.6)	MeCN/PhMe (1:1)	28 (58)
27	DPPB (10)	PhSiH <sub>3</sub> (2.8)	MeCN/PhMe (1:1)	83 (16)

28	DPPB (10)	PhSiH <sub>3</sub> (2.6)	MeCN/PhMe (1:1)	83 (20)
29	DPPB (10)	PhSiH <sub>3</sub> (2.4)	MeCN/PhMe (1:1)	55 (17)

<sup>a</sup> Conditions: 0.10 mmol of methyl 4-nitrobenzoate, 0.15 mmol of 4-methoxyphenylboronic acid, 5 mol % of Cu(OAc)<sub>2</sub>, 10 mol % phosphine ligand, silane, 0.1 M Solvent, 60 °C, 30 h. <sup>b</sup> 0.2M solvent used. <sup>c</sup> 0.05M solvent used.

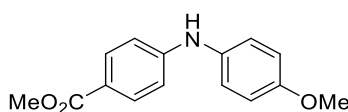
## E. Optimized Conditions



To a 10 mL schlenk tube under nitrogen, 0.10 mmol of nitroarene and 0.15 mmol of arylboronic acid were added. Cu(OAc)<sub>2</sub> (5 mol %) and 1,4-bis(diphenylphosphino)butane (dppb) (10 mol%) in 0.5 mL of MeCN were then added. After added 0.5 mL of toluene, phenyl silane was added into the Schlenk tube in one portion before sealing the reaction system under nitrogen. The reaction mixture was stirred at 60 °C for 30 h. After completion of the reaction, the mixture was cooled to room temperature and filtered through a pad of silica gel. The filtrate was concentrated *in vacuo*, and the residue was purified using MPLC to afford the diarylamines.

## F. Characterization Data

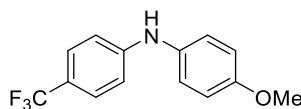
### 1. Scope and limitations with regards to the nitroarene



**4.3a**

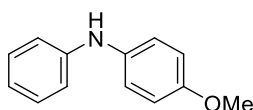
**Methyl 4-((4-methoxyphenyl)amino)benzoate 4.3a.** The optimized method was followed by adding 0.0181 g of methyl 4-nitrobenzoate, 0.0228 mg of 4-methoxyphenylboronic acid and 0.50 mL of MeCN solution of 0.0009 mg Cu(OAc)<sub>2</sub> and 0.0043 1,4-bis(diphenylphosphino)butane (dppb). Then 0.50 mL of toluene was added followed by adding 0.0303 mg of phenylsilane. Purification by MPLC (3:97 – 20:80 EtOAc:hexanes) afforded **4.3a** as a white solid (0.0214 g, 83%). The spectral data of **1a** matched that reported by Organ and co-workers:<sup>15</sup> mp = 83–84 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 7.87 (d, *J* = 8.7 Hz, 2H), 7.13 (d, *J* = 8.9 Hz, 2H), 6.90 (d, *J* = 8.9 Hz, 2H), 6.80 (d, *J* = 8.7 Hz, 2H), 5.92 (s, 1H), 3.86 (s, 3H), 3.81 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 167.1 (C), 156.6 (C), 149.8 (C), 133.3 (C), 131.5 (CH), 124.5 (CH), 120.0 (C), 114.8 (CH), 113.2 (CH), 55.6 (CH<sub>3</sub>), 51.6 (CH<sub>3</sub>); IR (thin film): 3384, 2954, 2801, 1690, 1595, 1520, 1448, 1411, 1346, 1248, 1236, 798, 763, 690 cm<sup>-1</sup>.

<sup>15</sup>. Pompeo, M.; Farmer, J.L.; Froese, R. D. J.; Organ, M.G. *Angew. Chem. Int. Ed.* **2014**, *53*, 3223.



### 4.3b

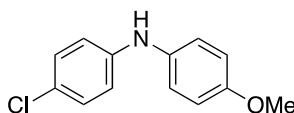
**4-Methoxy-N-(4-(trifluoromethyl)phenyl)aniline 4.3b.** The optimized method was followed by adding 0.0191 g of 4-nitrobenzotrifluoride, 0.0228 mg of 4-methoxyphenylboronic acid and 0.50 mL of MeCN solution of 0.0009 mg  $\text{Cu}(\text{OAc})_2$  and 0.0043 1,4-bis(diphenylphosphino)butane (dppb). Then 0.50 mL of toluene was added followed by adding 0.0303 mg of phenylsilane. Purification by MPLC (3:97 – 20:80 EtOAc:hexanes) afforded **4.3b** as a dark brown solid (0.0224 g, 84%). The spectral data of **4.3b** matched that reported by Nocera and co-workers:<sup>16</sup>  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  7.42 (d,  $J = 8.8$  Hz, 2H), 7.12 (d,  $J = 8.9$  Hz, 2H), 6.91 (d,  $J = 8.9$  Hz, 2H), 6.86 (d,  $J = 8.8$  Hz, 2H), 5.72 (s, 1H), 3.82 (s, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  156.5 (C), 148.6 (C), 133.7 (C), 126.7 (q,  $J_{\text{CF}} = 3.7$  Hz, CH), 124.7 (q,  $J_{\text{CF}} = 270.3$  Hz, C), 124.3 (CH), 120.6 (q,  $J_{\text{CF}} = 32.8$  Hz, C), 114.8 (CH), 113.7 (CH), 55.7 ( $\text{CH}_3$ );  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ , 282 MHz)  $\delta$  -61.2; IR (thin film): 3415, 2936, 2837, 1670, 1563, 1454, 1377, 1150, 797  $\text{cm}^{-1}$ .



### 4.3c

<sup>16</sup>. Sun, R.; Qin, Y.; Nocera, D.G. General Paradigm in Photoredox Nickel-Catalyzed Cross-Coupling Allows for Light-Free Access to Reactivity. *Angew. Chem. Int. Ed.* **2020**, *59*, 9527.

**4-Methoxy-N-phenylaniline 4.3c.** The optimized method was followed by adding 0.0123 g of nitrobenzene, 0.0228 mg of 4-methoxyphenylboronic acid and 0.50 mL of MeCN solution of 0.0009 mg Cu(OAc)<sub>2</sub> and 0.0043 1,4-bis(diphenylphosphino)butane (dppb). Then 0.50 mL of toluene was added followed by adding 0.0303 mg of phenylsilane. Purification by MPLC (3:97 – 20:80 EtOAc:hexanes) afforded **4.3c** as a pale yellow solid (0.0132 g, 66%). The spectral data of **4.3c** matched that reported by Lavigne and Cesar and co-workers:<sup>17</sup> <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 7.24 (t, *J* = 7.5 Hz, 2H), 7.10 (d, *J* = 7.5 Hz, 2H), 6.93 (d, *J* = 8.4 Hz, 2H), 6.91 – 6.83 (m, 3H), 5.51 (s, 1H), 3.83 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 155.2 (C), 145.1 (C), 135.7 (C), 129.2 (CH), 122.2 (CH), 119.5 (CH), 115.6 (CH), 114.5 (CH), 55.6 (CH<sub>3</sub>); IR (thin film): 3387, 3013, 2960, 2841, 1561, 1507, 1498, 1443, 1307, 1252, 1236, 750, 693 cm<sup>-1</sup>.



**4.3d**

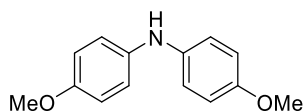
**N-(4-Methoxyphenyl)-4-chloroaniline 4.3d.** The optimized method was followed by adding 0.0158 g of 4-chloro-1-nitrobenzene, 0.0228 g of 4-methoxyphenylboronic acid and 0.50 mL of MeCN solution of 0.0009 g Cu(OAc)<sub>2</sub> and 0.0043 g of 1,4-bis(diphenylphosphino)butane (dppb). Then 0.50 mL of toluene and 0.0303 g of phenylsilane were sequentially added. Purification by MPLC (3:97 – 20:80 EtOAc:hexanes) afforded **4.3d** as a pale yellow foam (0.0199 g, 85%). The spectral data of **4.3d** matched that reported by Fort and co-workers:<sup>18</sup> <sup>1</sup>H NMR (CDCl<sub>3</sub>,

<sup>17</sup>. Zhang, Y.; Cesar V.; Storch, G.; Lugan N.; Lavigne, G. Skeleton Decoration of NHCs by Amino Groups and its Sequential

Booster Effect on the Palladium-Catalyzed Buchwald–Hartwig Amination. *Angew. Chem. Int. Ed.* **2014**, 53, 6482.

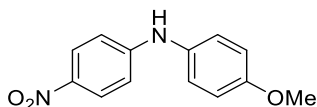
<sup>18</sup>. Desmarests, C.; Schneider, R.; Fort, Y. *J. Org. Chem.* **2002**, 67, 3029.

500 MHz)  $\delta$  7.15 (d,  $J$  = 8.6 Hz, 2H), 7.05 (d,  $J$  = 8.7 Hz, 2H), 6.87 (d,  $J$  = 8.6 Hz, 2H), 6.81 (d,  $J$  = 8.6 Hz, 2H), 5.46 (s, 1H), 3.80 (s, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  155.7 (C), 144.0 (C) 134.5 (C), 129.2 (CH), 122.6 (CH), 116.6 (CH), 114.8 (CH), 113.0 (C), 55.6 ( $\text{CH}_3$ ); IR (thin film): 3379, 3010, 2954, 2838, 1562, 1521, 1499, 1387, 783,  $695\text{ cm}^{-1}$ .



### 4.3e

**N-(4-methoxyphenyl)-4-methoxyaniline 4.3e.** The optimized method was followed by adding 0.0153 g of 4-nitroanisole, 0.0228 mg of 4-methoxyphenylboronic acid and 0.50 mL of MeCN solution of 0.0009 mg  $\text{Cu}(\text{OAc})_2$  and 0.0043 1,4-bis(diphenylphosphino)butane (dppb). Then 0.50 mL of toluene was added followed by adding 0.0303 mg of phenylsilane. The cross-coupling product was not observed and 4-nitroanisole starting material was recovered.

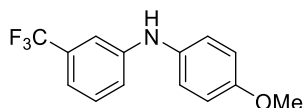


### 4.3f

**N-(4-methoxyphenyl)-4-nitroaniline 4.3f.** The optimized method was followed by adding 0.0168 g of 1,4-dinitrobenzene, 0.0228 mg of 4-methoxyphenylboronic acid and 0.50 mL of MeCN solution of 0.0009 mg  $\text{Cu}(\text{OAc})_2$  and 0.0043 1,4-bis(diphenylphosphino)butane (dppb). Then 0.50 mL of toluene was added followed by adding 0.0303 mg of phenylsilane. Purification



by MPLC (3:97 – 20:80 EtOAc:hexanes) afforded **4.3f** as a brown solid (0.0144 g, 59%). The spectral data of **4.3f** matched that reported by Buchwald and co-workers:<sup>19</sup> <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$  8.09 (d,  $J$  = 9.3 Hz, 2H), 7.16 (d,  $J$  = 8.9 Hz, 2H), 6.94 (d,  $J$  = 9.3 Hz, 2H), 6.77 (d,  $J$  = 9.3 Hz, 2H), 6.10 (s, 1H), 3.84 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz)  $\delta$  157.5 (C), 151.7 (C), 140.4 (C), 132.0 (C), 126.4 (CH), 125.6 (CH), 115.0 (CH), 112.6 (CH), 55.6 (CH<sub>3</sub>); IR (thin film): 3326, 3199, 3124, 2953, 2835, 1592, 1511, 1482, 1444, 1293, 1230, 762, 749, 697 cm<sup>-1</sup>.

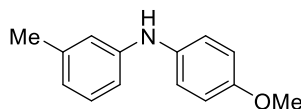


**4.3g**

**N-(4-methoxyphenyl)-3-trifluoromethylaniline 4.3g.** The optimized method was followed by adding 0.0191 g of 3-(trifluoromethyl)nitrobenzene, 0.0228 mg of 4-methoxyphenylboronic acid and 0.50 mL of MeCN solution of 0.0009 mg Cu(OAc)<sub>2</sub> and 0.0043 1,4-bis(diphenylphosphino)butane (dppb). Then 0.50 mL of toluene was added followed by adding 0.0303 mg of phenylsilane. Purification by MPLC (3:97 – 20:80 EtOAc:hexanes) afforded **4.3g** as a white solid (0.0238 g, 89%). The spectral data of **4.3g** matched that reported by Lavigne and Cesar and co-workers:<sup>3</sup> <sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>)  $\delta$  7.29 (t,  $J$  = 7.9 Hz, 1H), 7.13 – 7.05 (m, 3H), 7.03 (d,  $J$  = 7.6 Hz, 1H), 7.00 (d,  $J$  = 7.6 Hz, 1H), 6.90 (d,  $J$  = 8.8 Hz, 2H), 5.62 (s, 1H), 3.82 (s, 3H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz)  $\delta$  156.2 (C), 146.0 (C), 134.3 (C), 131.6 (q,  $J_{CF}$  = 31.7 Hz, C), 129.8 (CH), 124.2 (q,  $J_{CF}$  = 272.5 Hz, C), 123.5 (CH), 117.9 (CH), 115.6 (q,  $J_{CF}$  = 3.8 Hz, C),

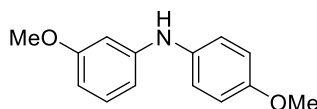
<sup>19</sup>. Wolfe, J.P.; Tomori, H.; Sadighi, J.P.; Yin J.; Buchwald, S.L. Simple, Efficient Catalyst System for the Palladium-Catalyzed Amination of Aryl Chlorides, Bromides, and Triflates. *J. Org. Chem.* **2000**, 65, 1158.

114.9 (CH), 111.3 (q,  $J_{\text{CF}} = 3.8$  Hz, CH), 55.5 (CH<sub>3</sub>);  $^{19}\text{F}$  NMR (CDCl<sub>3</sub>, 282 MHz)  $\delta$  -62.8; IR (thin film): 3421, 2944, 2812, 1673, 1559, 1421, 1375, 1141, 772 cm<sup>-1</sup>.



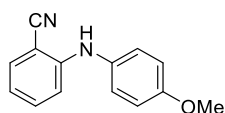
### 4.3h

**N-(4-methoxyphenyl)-3-methylaniline 4.3h.** The optimized method was followed by adding 0.0137 g of 3-nitrotoluene, 0.0228 mg of 4-methoxyphenylboronic acid and 0.50 mL of MeCN solution of 0.0009 mg Cu(OAc)<sub>2</sub> and 0.0043 1,4-bis(diphenylphosphino)butane (dppb). Then 0.50 mL of toluene was added followed by adding 0.0303 mg of phenylsilane. Purification by MPLC (3:97 – 20:80 EtOAc:hexanes) afforded **4.3h** as a yellow oil (0.0156 g, 73%). The spectral data of **4.3h** matched that reported by Fort and co-workers:<sup>4</sup>  $^1\text{H}$  NMR (500 MHz; CDCl<sub>3</sub>)  $\delta$  7.13 – 7.05 (m, 3H), 6.87 (d,  $J = 8.8$  Hz, 2H), 6.73 (d,  $J = 7.7$  Hz, 2H), 6.67 (d,  $J = 6.6$  Hz, 1H), 3.81 (s, 3H), 2.29 (s, 3H).  $^{13}\text{C}$  NMR (CDCl<sub>3</sub> 125 MHz)  $\delta$  155.3 (C), 145.2 (C), 139.2 (C), 129.2 (CH), 124.4 (C), 122.3 (CH), 120.6 (CH), 116.4 (CH), 114.7 (CH), 112.9 (CH), 55.6 (CH<sub>3</sub>), 21.6 (CH<sub>3</sub>); IR (thin film): 3406, 2956, 2817, 1665, 1523, 1436, 1354, 1014, 912, 772 cm<sup>-1</sup>.



### 4.3i

**N-(4-methoxyphenyl)-3-methoxyaniline 2i.** The optimized method was followed by adding 0.0153 g of 4-nitroanisole, 0.0228 mg of 4-methoxyphenylboronic acid and 0.50 mL of MeCN solution of 0.0009 mg Cu(OAc)<sub>2</sub> and 0.0043 1,4-bis(diphenylphosphino)butane (dppb). Then 0.50 mL of toluene was added followed by adding 0.0303 mg of phenylsilane. Purification by MPLC (3:97 – 20:80 EtOAc:hexanes) afforded **4.3i** as a white solid (0.0195 g, 85%). The spectral data of **4.3i** matched that reported by Hartwig and co-workers:<sup>20</sup> <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 7.21 – 7.04 (m, 3H), 6.86 (d, *J* = 8.8 Hz, 2H), 6.58 – 6.42 (m, 2H), 6.40 (d, *J* = 7.8 Hz, 1H), 5.62 (s, 1H), 3.80 (s, 3H), 3.76 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 160.8 (C), 155.5 (C), 146.7 (C), 135.4 (C), 130.1 (CH), 122.8 (CH), 114.7 (CH), 108.4 (CH), 104.8 (CH), 101.4 (CH), 55.6 (CH<sub>3</sub>), 55.2 (CH<sub>3</sub>); IR (thin film): 3380, 2924, 2071, 1634, 1414, 1379, 952 cm<sup>-1</sup>.

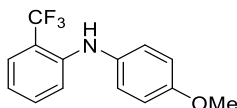


**4.3j**

**2-[(4-Methoxyphenyl)amino]benzonitrile 4.3j** The optimized method was followed by adding 0.0148 g of 2-nitrobenzonitrile, 0.0228 mg of 4-methoxyphenylboronic acid and 0.50 mL of MeCN solution of 0.0009 mg Cu(OAc)<sub>2</sub> and 0.0043 1,4-bis(diphenylphosphino)butane (dppb). Then 0.50 mL of toluene was added followed by adding 0.0303 mg of phenylsilane. Purification by MPLC (3:97 – 20:80 EtOAc:hexanes) afforded **4.3j** as a white solid (0.0186 g, 83%). The

<sup>20</sup>. Shen, Q.; Ogata, T.; Hartwig, J.F. Highly Reactive, General and Long-Lived Catalysts for Palladium-Catalyzed Amination of Heteroaryl and Aryl Chlorides, Bromides, and Iodides: Scope and Structure–Activity Relationships. *J. Am. Chem. Soc.* **2008**, *130*, 6586

spectral data of **2j** matched that reported by Zeng and co-workers:<sup>21</sup> <sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>)  $\delta$  7.46 (d,  $J$  = 7.8 Hz, 1H), 7.30 (t,  $J$  = 7.8 Hz, 1H), 7.15 (d,  $J$  = 8.8 Hz, 2H), 6.91 (dd,  $J$  = 12.8, 9.0 Hz, 3H), 6.76 (t,  $J$  = 7.4 Hz, 1H), 6.19 (s, 1H), 3.83 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz)  $\delta$  159.6 (C), 149.0 (C), 139.7 (C), 134.0 (CH), 132.8 (CH), 125.7 (CH), 118.1 (CH), 116.7 (C), 114.9 (CH), 112.9 (CH), 100.3 (C) 55.6 (CH<sub>3</sub>); IR (thin film): 3392, 2921, 2852, 2241, 1317, 1290, 1203, 966 cm<sup>-1</sup>.

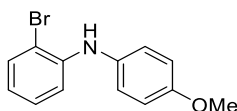


**4.3k**

**N-(4-methoxyphenyl)-2-trifluoromethylaniline 4.3k.** The optimized method was followed by adding 0.0161 g of 2-trifluoromethyl-1-nitrobenzene, 0.0228 mg of 4-methoxyphenylboronic acid and 0.50 mL of MeCN solution of 0.0009 mg Cu(OAc)<sub>2</sub> and 0.0043 1,4-bis(diphenylphosphino)butane (dppb). Then 0.50 mL of toluene was added followed by adding 0.0303 mg of phenylsilane. Purification by MPLC (3:97 – 20:80 EtOAc:hexanes) afforded **4.3k** as a white solid (0.0206 g, 77%). <sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>)  $\delta$  7.50 (d,  $J$  = 7.7 Hz, 1H), 7.29 (d,  $J$  = 7.6 Hz, 1H), 7.11 (d,  $J$  = 8.7 Hz, 2H), 7.00 (d,  $J$  = 8.3 Hz, 1H), 6.90 (d,  $J$  = 8.8 Hz, 2H), 6.82 (t,  $J$  = 7.4 Hz, 1H), 5.94 (s, 1H), 3.82 (s, 3H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz)  $\delta$  155.7 (C), 144.2 (C), 133.9 (C), 132.7 (CH), 126.8 (q,  $J$  = 5.7 Hz, CH), 125.1 (q,  $J$  = 272.8 Hz, C), 125.0 (CH), 120.6 (CH), 118.1 (CH), 115.4 (CH), 114.8 (CH), 106.54 (CH), 55.6 (CH<sub>3</sub>); <sup>19</sup>F NMR (CDCl<sub>3</sub>, 282 MHz)

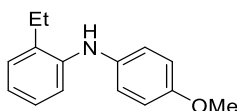
<sup>21</sup>. Rao, B.; Zeng, X. Aminocyanation by the Addition of N–CN Bonds to Arynes: Chemoselective Synthesis of 1,2-Bifunctional Aminobenzonitriles. *Org. Lett.* **2014**, *16*, 314

$\delta$  –61.9 ; IR (thin film): 3410, 2937, 2846, 2253 1322, 1289, 1211, 996, 785  $\text{cm}^{-1}$ . HRMS (ESI)  $m/z$  calculated for  $\text{C}_{14}\text{H}_{12}\text{F}_3\text{NO}$  ( $\text{M}+\text{H}$ ) $^{+}$ : 268.0944, found: 268.0939.



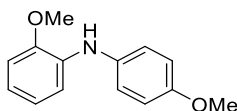
### 4.3I

**N-(4-methoxyphenyl)-2-bromoaniline 4.3I.** The optimized method was followed by adding 0.0202 g of 2-bromo-1-nitrobenzene, 0.0228 mg of 4-methoxyphenylboronic acid and 0.50 mL of MeCN solution of 0.0009 mg  $\text{Cu}(\text{OAc})_2$  and 0.0043 1,4-bis(diphenylphosphino)butane (dppb). Then 0.50 mL of toluene was added followed by adding 0.0303 mg of phenylsilane. Purification by MPLC (3:97 – 20:80 EtOAc:hexanes) afforded **4.3I** as a yellow oil (0.0248 g, 89%). The spectral data of **4.3I** matched that reported by Driver and co-workers:<sup>1</sup>  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  7.48 (d,  $J = 7.9$  Hz, 1H), 7.15 – 7.07 (m, 3H), 6.95 – 6.89 (m, 3H), 6.65 (t,  $J = 7.8$  Hz, 1H), 5.94 (s, 1H), 3.82 (s, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  156.4 (C), 143.3 (C), 134.2 (C), 132.8 (CH), 128.2 (CH), 124.7 (CH), 119.6 (CH), 114.8 (CH), 114.0 (CH), 110.6 (C), 55.6 ( $\text{CH}_3$ ); IR (thin film): 3401, 3061, 2925, 2878, 1603, 1422, 1250, 947  $\text{cm}^{-1}$ .



### 4.3m

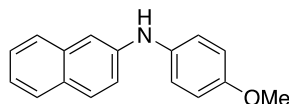
**N-(4-methoxyphenyl)-2-ethylaniline 4.3m.** The optimized method was followed by adding 0.0151 g of 2-ethyl-1-nitrobenzene, 0.0228 g of 4-methoxyphenylboronic acid and 0.50 mL of MeCN solution of 0.0009 g Cu(OAc)<sub>2</sub> and 0.0043 g of 1,4-bis(diphenylphosphino)butane (dppb). Then 0.50 mL of toluene and 0.0303 g of phenylsilane were sequentially added. Purification by MPLC (3:97 – 20:80 EtOAc:hexanes) afforded **4.3m** as a yellow oil (0.0186 g, 82%). The spectral data of **4.3m** matched that reported by Schmidt and co-workers:<sup>9</sup> <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 7.18 (d, *J* = 7.3 Hz, 1H), 7.07 (d, *J* = 7.3 Hz, 1H), 7.03 – 6.96 (m, 3H), 6.89 – 6.83 (m, 3H), 5.27 (s, 1H), 3.80 (s, 3H), 2.61 (q, *J* = 7.3 Hz, 2H), 1.26 (t, *J* = 7.3 Hz, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 155.0 (C), 149.4 (C), 139.1 (C), 131.6 (C), 128.6 (CH), 126.7 (CH), 121.8 (CH), 120.5 (CH), 116.3 (CH), 114.7 (C), 55.6 (CH<sub>3</sub>), 24.2 (CH<sub>2</sub>), 13.5 (CH<sub>3</sub>); IR (thin film): 3422, 3038, 2961, 2928, 2833, 1595, 1500, 1294, 1243, 1033, 824, 747 cm<sup>-1</sup>.



### 4.3n

**N-(4-methoxyphenyl)-2-methoxyaniline 4.3n.** The optimized method was followed by adding 0.0151 g of 2-ethyl-1-nitrobenzene, 0.0228 g of 4-methoxyphenylboronic acid and 0.50 mL of MeCN solution of 0.0009 g Cu(OAc)<sub>2</sub> and 0.0043 g of 1,4-bis(diphenylphosphino)butane (dppb). Then 0.50 mL of toluene and 0.0303 g of phenylsilane were sequentially added. Purification by

MPLC (3:97 – 20:80 EtOAc:hexanes) afforded **4.3n** as a yellow oil (0.0165 g, 72%). The spectral data of **4.3n** matched that reported by Ichitsuka, Koumura, Kobayashi and co-workers:<sup>22</sup> <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$  7.18 – 7.07 (m, 2H), 7.00 (dd,  $J$  = 19.4, 9.4 Hz, 1H), 6.93 – 6.69 (m, 5H), 3.90 (s, 3H), 3.80 (s, 3H), 3.77 (s, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz)  $\delta$  155.2 (C), 147.4 (C), 128.6 (C), 122.7 (CH), 120.9 (CH), 120.4 (C), 118.5 (CH), 114.5 (CH), 112.5 (CH), 110.1 (CH), 55.6 (CH<sub>3</sub>), only signals visible; IR (thin film): 3371, 2932, 1631, 1582, 1418, 1336, 929 cm<sup>-1</sup>.



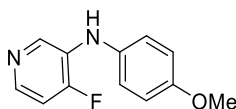
**4.3o**

**N-(3-pyridyl)-4-methoxyaniline 4.3o.** The optimized method was followed by adding 0.0173 g of 2-nitronaphthalene, 0.0228 g of 4-methoxyphenylboronic acid and 0.50 mL of MeCN solution of 0.0009 g Cu(OAc)<sub>2</sub> and 0.0043 g of 1,4-bis(diphenylphosphino)butane (dppb). Then 0.50 mL of toluene and 0.0303 g of phenylsilane were sequentially added. Purification by MPLC (3:97 – 20:80 EtOAc:hexanes) afforded **4.3o** as a yellow oil (0.0266 g, 96%). The spectral data of **4.3o** matched that reported by Deng, Huang and co-workers:<sup>23</sup> <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) 8.00 (d,  $J$  = 8.0 Hz, 1H), 7.84 (d,  $J$  = 7.2 Hz, 1H), 7.53 – 7.42 (m, 3H), 7.32 (t,  $J$  = 7.9 Hz, 1H), 7.10 (d,  $J$  = 7.4 Hz, 1H), 7.06 (d,  $J$  = 8.8 Hz, 2H), 6.88 (d,  $J$  = 8.8 Hz, 2H), 5.86 (s, 1H), 3.81 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz)  $\delta$  153.2 (C), 149.0 (C), 134.2 (C), 128.6 (CH), 126.2 (CH), 126.0 (C), 125.4 (CH), 121.8 (CH), 121.1 (CH), 120.9 (CH), 114.8 (CH), 111.7 (CH), 55.6 (CH<sub>3</sub>), only signals

<sup>22</sup>. Ichitsuka, T.; Takahashi, I.; Koumura, N.; Sato, K.; Kobayashi, S. *Angew. Chem. Int. Ed.* **2020**, 59, 15891.

<sup>23</sup>. Wang, Z.; Li, C.; Huang, H.; Deng, G-J. *J. Org. Chem.* **2020**, 85, 9415

visible; IR (thin film): 3461, 3358, 3037, 2944, 2339, 1673, 1665, 1521, 1466, 1256, 1030, 837, 742 cm<sup>-1</sup>.



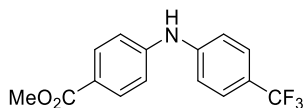
### 4.3p

**4-Fluoro-N-(4-methoxyphenyl)pyridine-3-amine 4.3p.**<sup>24</sup> The optimized method was followed by adding 0.0142 g of 4-fluoro-3-nitropyridine, 0.0228 g of 4-methoxyphenylboronic acid and 0.50 mL of MeCN solution of 0.0009 g Cu(OAc)<sub>2</sub> and 0.0043 g of 1,4-bis(diphenylphosphino)butane (dppb). Then 0.50 mL of toluene and 0.0303 g of phenylsilane were sequentially added. Purification by MPLC (3:97 – 20:80 EtOAc:hexanes) afforded **4.3p** as a white solid (0.0164 g, 75%). The spectral data of **4.3p** matched that reported by Clark and co-workers:<sup>11</sup> mp = 122–126 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 7.81 (t, *J* = 2.4 Hz, 1H), 7.34 (ddd, *J* = 9.8, 6.7, 3.0 Hz, 1H), 7.07 – 6.96 (m, 2H), 6.92 – 6.82 (m, 2H), 6.79 (dd, *J* = 8.8, 3.4 Hz, 1H), 5.41 (s, 1H), 3.80 (s, 3H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 158.7 (C), 155.8 (C), 139.7 (C), 135.2 (C), 134.8 (d, *J* = 14.8 Hz, CH), 128.5 (d, *J* = 7.4 Hz, CH), 121.9 (CH), 115.0 (CH), 109.4 (d, *J* = 39.3 Hz, CH), 55.6 (CH<sub>3</sub>). IR (thin film): 3253, 3177, 3052, 2911, 2865, 1508, 1336, 1259, 1033 cm<sup>-1</sup>.

## 2. Scope and limitations with regards to the boronic acid

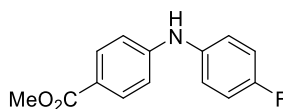
<sup>24</sup>. Wilson, R. J.; Rosenberg, A. J.; Kaminsky, L.; Clark, D. A. *J. Org. Chem.* **2014**, 79, 2203.





#### 4.8a

**Methyl 4-[4-(trifluoromethyl)anilino]benzoate 4.8a.** The optimized method was followed by adding 0.0181 g of methyl 4-nitrobenzoate, 0.0285 g of 4-trifluoromethylphenylboronic acid and 0.50 mL of MeCN solution of 0.0009 g  $\text{Cu}(\text{OAc})_2$  and 0.0043 g of 1,4-bis(diphenylphosphino)butane (dppb). Then 0.50 mL of toluene and 0.0303 g of phenylsilane were sequentially added. Purification by MPLC (3:97 – 20:80 EtOAc:hexanes) afforded **4.8a** as a white foam (0.0266 g, 90%). The spectral data of **4.8a** matched that reported by Winkler, Penning and co-workers:<sup>25</sup>  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  8.02 – 7.93 (m, 2H), 7.55 (d,  $J$  = 8.5 Hz, 2H), 7.19 (d,  $J$  = 8.8 Hz, 2H), 7.14 – 7.02 (m, 2H), 6.22 (s, 1H), 3.90 (s, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  166.7 (C), 146.1 (C), 144.5 (C), 131.5 (CH), 126.8 (q,  $J$  = 3.6 Hz, CH), 124.6 (q,  $J$  = 270.6 Hz, C), 123.9 (C), 123.0 (C), 117.9 (CH), 116.4 (CH), 51.9 ( $\text{CH}_3$ );  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ , 282 MHz)  $\delta$  – 61.8; IR (thin film)  $\text{cm}^{-1}$ ; 3403, 2955, 2844, 1685, 1401, 1314, 1225, 764  $\text{cm}^{-1}$

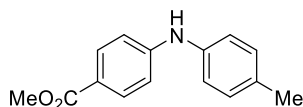


#### 4.8b

**Methyl 4-[4-(4-fluorophenyl)amino]benzoate 4.8b.** The optimized method was followed by adding 0.0181 g of methyl 4-nitrobenzoate, 0.0210 g of 4-fluorophenylboronic acid and 0.50 mL

<sup>25</sup>. Adeniji, A.O.; Twenter, B.M.; Byrns, M.C.; Jin, Y.; Chen, M.; Winkler, J.D.; Penning, T.M. *J. Med. Chem.* **2012**, *55*, 2311.

of MeCN solution of 0.0009 g Cu(OAc)<sub>2</sub> and 0.0043 g of 1,4-bis(diphenylphosphino)butane (dppb). Then 0.50 mL of toluene and 0.0303 g of phenylsilane were sequentially added. Purification by MPLC (3:97 – 20:80 EtOAc:hexanes) afforded **4.8b** as a pale yellow viscous oil (0.0238 g, 97%). The spectral data of **4.8b** matched that reported by Xue and co-workers:<sup>26</sup> <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 7.90 (d, *J* = 8.4 Hz, 2H), 7.16 – 7.13 (m, 2H), 7.04 (t, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 5.91 (s, 1H), 3.87 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 167.3 (C), 159.5 (d, *J*<sub>CF</sub> = 241.3 Hz, C), 149.1 (C), 137.0 (d, *J*<sub>CF</sub> = 2.8 Hz, CH), 131.9 (CH), 123.7 (d, *J*<sub>CF</sub> = 8.1 Hz, CH), 121.1 (C), 116.6 (d, *J*<sub>CF</sub> = 22.5 Hz, CH), 114.2 (CH), 52.1 (CH<sub>3</sub>); <sup>19</sup>F NMR (CDCl<sub>3</sub>, 282 MHz) δ –118.7; IR (thin film): 3401, 1687, 1579, 1461, 1413, 1245, 752 cm<sup>–1</sup>.



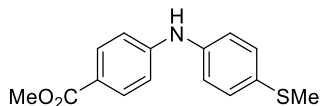
**4.8c**

**Methyl 4-(tolylamino)benzoate 4.8c.** The optimized method was followed by adding 0.0181 g of methyl 4-nitrobenzoate, 0.0204 g of 4-tolylboronic acid and 0.50 mL of MeCN solution of 0.0009 g Cu(OAc)<sub>2</sub> and 0.0043 g of 1,4-bis(diphenylphosphino)butane (dppb). Then 0.50 mL of toluene and 0.0303 g of phenylsilane were sequentially added. Purification by MPLC (3:97 – 20:80 EtOAc:hexanes) afforded **4.8c** as a white solid (0.0217 g, 90%). The spectral data of **4.8c** matched that reported by Ma and co-workers:<sup>27</sup> mp = 105–106 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 7.94 – 7.84 (m, 2H), 7.15 (d, *J* = 8.2 Hz, 2H), 7.11 – 7.02 (m, 2H), 6.96 – 6.86 (m, 2H), 6.01 (s, 1H), 3.87

<sup>26</sup>. Li, G.; Yang, L.; Liu, J.-J.; Zhang, W.; Cao, R.; Wang, C.; Zhang, Z.; Xiao, J.; Xue, D. *Angew. Chem. Int. Ed.* **2021**, *60*, 5230.

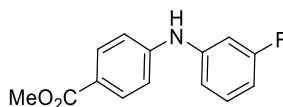
<sup>27</sup>. Zhang, H.; Cai, Q.; Ma, D. *J. Org. Chem.* **2005**, *70*, 5164.

(s, 3H), 2.34 (s, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  167.1 (C), 148.9 (C), 138.1 (C), 133.2 (C), 131.5 (CH), 130.1 (CH), 121.4 (CH), 120.5 (C), 114.0 (CH), 51.7 ( $\text{CH}_3$ ), 20.9 ( $\text{CH}_3$ ); IR (thin film): 3396, 1676, 1553, 1477, 1405, 1062, 771  $\text{cm}^{-1}$ .



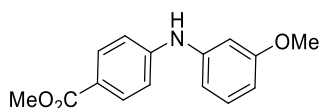
#### 4.8d

**Methyl 4-[(4-methylthiophenyl)amino]benzoate 4.8d.** The optimized method was followed by adding 0.0181 g of methyl 4-nitrobenzoate, 0.0252 g of 4-(Methylthio)phenylboronic acid and 0.50 mL of MeCN solution of 0.0009 g  $\text{Cu}(\text{OAc})_2$  and 0.0043 g of 1,4-bis(diphenylphosphino)butane (dppb). Then 0.50 mL of toluene and 0.0303 g of phenylsilane were sequentially added. Purification by MPLC (3:97 – 20:80 EtOAc:hexanes) afforded **4.8d** as a pale yellow solid (0.0175 g, 64%). The spectral data of **4.8d** matched that reported by Xue and co-workers:<sup>11</sup>  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  7.91 (d,  $J$  = 8.8 Hz, 2H), 7.27 (t,  $J$  = 8.8 Hz, 2H), 7.11 (d,  $J$  = 8.4 Hz, 2H), 6.95 (d,  $J$  = 8.4 Hz, 2H), 5.95 (s, 1H), 3.87 (s, 3H), 2.49 (s, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  167.8 (C), 156.7 (C), 135.9 (C), 134.6 (C), 131.5 (CH), 129.0 (CH), 126.0 (CH), 121.4 (CH), 114.5 (CH), 52.6 ( $\text{CH}_3$ ), 19.9 ( $\text{CH}_3$ ); IR (thin film): 3393, 1681, 1560, 1468, 1399, 1059, 852, 771  $\text{cm}^{-1}$ .



#### 4.8e

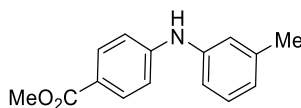
**Methyl 4-(3-Fluorophenylamino)benzoate 4.8e.** The optimized method was followed by adding 0.0181 g of methyl 4-nitrobenzoate, 0.0210 g of 3-fluorophenylboronic acid and 0.50 mL of MeCN solution of 0.0009 g Cu(OAc)<sub>2</sub> and 0.0043 g of 1,4-bis(diphenylphosphino)butane (dppb). Then 0.50 mL of toluene and 0.0303 g of phenylsilane were sequentially added. Purification by MPLC (3:97 – 20:80 EtOAc:hexanes) afforded **4.8e** as a white solid (0.0216 g, 88%). Diaryl amine **4.8e** was previously reported by Griffioen *et al.*:<sup>14</sup> mp = 39–40 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 8.00 – 7.90 (m, 2H), 7.30 – 7.26 (m, 1H), 7.05 – 6.99 (m, 2H), 6.93 – 6.84 (m, 2H), 6.73 (ddd, *J* = 10.1, 7.9, 2.7 Hz, 1H), 6.07 (s, 1H), 3.89 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 166.8 (C), 163.6 (d, *J* = 245.5 Hz, C), 146.9 (C), 142.9 (d, *J* = 9.3 Hz, C), 131.5 (CH), 130.7 (d, *J* = 9.7 Hz, CH), 122.2 (C), 115.6 (CH), 115.0 (CH), 109.3 (d, *J* = 21.3 Hz, CH), 106.4 (d, *J* = 24.5 Hz, CH), 51.8 (CH<sub>3</sub>); IR (thin film): 3364, 3041, 2959, 2841, 1610, 1501, 1232, 837, 764 cm<sup>-1</sup>.



#### 4.8f

**Methyl 4-(3-Methoxyphenylamino)benzoate 4.8f.** The optimized method was followed by adding 0.0181 g of methyl 4-nitrobenzoate, 0.0228 g of 3-methoxyphenylboronic acid and 0.50 mL of MeCN solution of 0.0009 g Cu(OAc)<sub>2</sub> and 0.0043 g of 1,4-bis(diphenylphosphino)butane (dppb). Then 0.50 mL of toluene and 0.0303 g of phenylsilane were sequentially added. Purification by MPLC (3:97 – 20:80 EtOAc:hexanes) afforded **4.8f** as a pale yellow oil (0.0237 g,

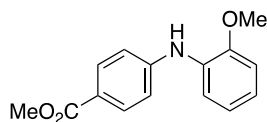
92%). The spectral data of **4.8f** matched that reported by Winkler, Penning and co-workers:<sup>28</sup> <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 7.92 (d, *J* = 8.8 Hz, 2H), 7.24 (t, *J* = 8.1 Hz, 1H), 7.01 (d, *J* = 8.8 Hz, 2H), 6.76 (d, *J* = 7.9 Hz, 1H), 6.73 (t, *J* = 2.2 Hz, 1H), 6.61 (dd, *J* = 8.2, 2.4 Hz, 1H), 6.14 (s, 1H), 3.88 (s, 3H), 3.79 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 167.0 (C), 160.7 (C), 147.9 (C), 142.3 (C), 131.5 (CH), 130.3 (CH), 121.2 (C), 115.0 (CH), 112.6 (CH), 108.3 (CH), 106.0 (CH), 55.3 (CH<sub>3</sub>), 51.8 (CH<sub>3</sub>); IR (thin film): 3361, 2945, 2813, 1689, 1517, 1440, 1409, 1352, 1248, 789, 689 cm<sup>-1</sup>.



**4.8g**

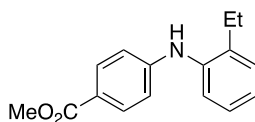
**Methyl 4-(3-Tolylamino)benzoate 4.8g.** The optimized method was followed by adding 0.0181 g of methyl 4-nitrobenzoate, 0.0204 g of 3-methylphenylboronic acid and 0.50 mL of MeCN solution of 0.0009 g Cu(OAc)<sub>2</sub> and 0.0043 g of 1,4-bis(diphenylphosphino)butane (dppb). Then 0.50 mL of toluene and 0.0303 g of phenylsilane were sequentially added. Purification by MPLC (3:97 – 20:80 EtOAc:hexanes) afforded **4.8g** as a yellow oil (0.0212 g, 88%). The spectral data of **4.8g** matched that reported by Winkler, Penning and co-workers:<sup>15</sup> <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 7.91 (d, *J* = 8.8 Hz, 2H), 7.24 – 7.21 (m, 1H), 7.00 – 6.96 (m, 4H), 6.89 (d, *J* = 7.5 Hz, 1H), 6.00 (s, 1H), 3.87 (s, 3H), 2.35 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 167.0 (C), 148.2 (C), 140.8 (C), 139.5 (C), 131.5 (CH), 129.4 (CH), 124.0 (CH), 121.2 (CH), 117.6 (CH), 114.6 (CH), 51.8 (CH<sub>3</sub>), 21.6 (CH<sub>3</sub>), only signals visible; IR (thin film): 3412, 1691, 1565, 1523, 1481, 1416, 1059, 794 cm<sup>-1</sup>.

<sup>28</sup>. Adeniji, A.O.; Twenter, B.M.; Byrns, M.C.; Jin, Y.; Chen, M.; Winkler, J.D.; Penning, T.M. *J. Med. Chem.* **2012**, *55*, 2311.



#### 4.8h

**Methyl 4-((2-methoxyphenyl)amino)benzoate 4.8h.**<sup>16</sup> The optimized method was followed by adding 0.0181 g of methyl 4-nitrobenzoate, 0.0228 g of 2-methoxyphenylboronic acid and 0.50 mL of MeCN solution of 0.0009 g Cu(OAc)<sub>2</sub> and 0.0043 g of 1,4-bis(diphenylphosphino)butane (dppb). Then 0.50 mL of toluene and 0.0303 g of phenylsilane were sequentially added. Purification by MPLC (3:97 – 20:80 EtOAc:hexanes) afforded **4.8h** as a light yellow oil (0.0219 g, 85%). The spectral data of **4.8h** matched that reported by Organ and co-workers:<sup>29</sup> <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ7.96 – 7.90 (m, 2H), 7.40 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.10 – 7.05 (m, 2H), 7.02 – 6.90 (m, 3H), 6.37 (s, 1H), 3.89 (s, 3H), 3.88 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ167.0 (C), 149.5 (C), 147.6 (C), 131.4 (CH), 130.5 (C), 122.2 (CH), 121.2 (C), 120.8 (CH), 117.7 (CH), 115.2 (CH), 110.9 (CH), 55.6 (CH<sub>3</sub>), 51.7 (CH<sub>3</sub>); IR (thin film): cm<sup>-1</sup>. 3324, 2950, 1682, 1447, 1398, 1084, 844 cm<sup>-1</sup>

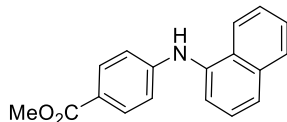


#### 4.8i

**Methyl 4-((2-ethylphenyl)amino)benzoate 4.8i.** The optimized method was followed by adding 0.0181 g of methyl 4-nitrobenzoate, 0.0228 g of 2-ethylphenylboronic acid and 0.50 mL of MeCN

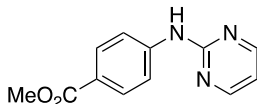
<sup>29</sup>. Pompeo, M.; Farmer, J. L.; Froese, R. D. J.; Organ, M. G. *Angew. Chem. Int. Ed.* **2014**, 53, 3223.

solution of 0.0009 g Cu(OAc)<sub>2</sub> and 0.0043 g of 1,4-bis(diphenylphosphino)butane (dppb). Then 0.50 mL of toluene and 0.0303 g of phenylsilane were sequentially added. The cross-coupling product was not observed.



**4.8j**

**Methyl 4-(naphthalen-1-ylamino)benzoate 4.8j.** The optimized method was followed by adding 0.0181 g of methyl 4-nitrobenzoate, 0.0258 g of 1-naphthylboronic acid and 0.50 mL of MeCN solution of 0.0009 g Cu(OAc)<sub>2</sub> and 0.0043 g of 1,4-bis(diphenylphosphino)butane (dppb). Then 0.50 mL of toluene and 0.0303 g of phenylsilane were sequentially added. Purification by MPLC (3:97 – 20:80 EtOAc:hexanes) afforded **4.8j** as a yellow oil (0.0230 g, 83%). The spectral data of **4.8j** matched that reported by Deng, Huang and co-workers:<sup>17</sup> <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 8.00 – 7.93 (m, 2H), 7.80 (dd, *J* = 10.9, 8.1 Hz, 2H), 7.72 (d, *J* = 8.2 Hz, 1H), 7.58 (d, *J* = 2.4 Hz, 1H), 7.46 (ddd, *J* = 8.3, 6.8, 1.4 Hz, 1H), 7.38 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 1H), 7.30 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.11 – 7.05 (m, 2H), 3.89 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 167.0 (C), 147.9 (C), 138.5 (C), 134.3 (C), 131.6 (CH), 130.1 (C), 129.4 (CH), 127.7 (CH), 126.9 (CH), 126.7 (CH), 124.6 (CH), 121.5 (C), 121.3 (CH), 115.6 (CH), 115.0 (CH), 51.8 (CH<sub>3</sub>); IR (thin film): 3467, 3385, 3042, 2933, 1677, 1623, 1586, 1496, 1464, 1330, 1180, 857, 738 cm<sup>-1</sup>.

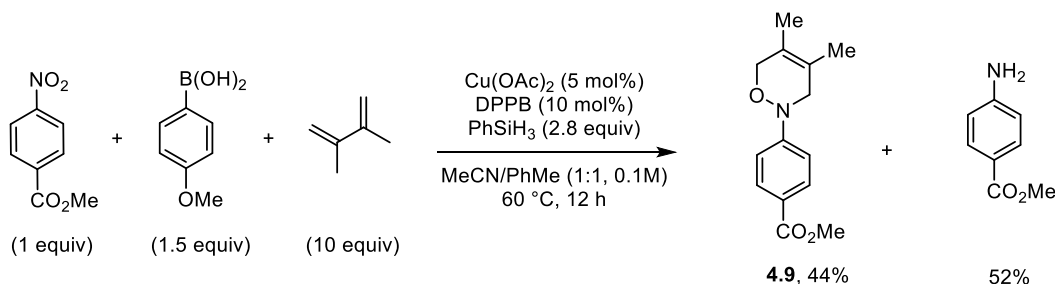


## 4.8k

**Methyl 4-(pyrimidine-2-ylamino)benzoate 4.8k.**<sup>17</sup> The optimized method was followed by adding 0.0362 g of methyl 4-nitrobenzoate, 0.0372 g of pyrimidin-2-yl-boronic acid and 1.00 mL of MeCN solution of 0.0018 g Cu(OAc)<sub>2</sub> and 0.0086 g of 1,4-bis(diphenylphosphino)butane (dppb). Then 1.00 mL of toluene and 0.0606 g of phenylsilane were sequentially added. Purification by MPLC (20:80 – 50:50 EtOAc:hexanes) afforded **4.8k** as a yellow solid (0.0270 g, 59%). The spectral data of **4.8k** matched that reported by Deng, Huang and co-workers:<sup>17</sup> mp = 149–150 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) 8.37 (d, J = 4.8 Hz, 2H), 7.78 (s, 1H), 7.48 (d, J = 8.8 Hz, 2H), 6.90 (d, J = 8.8 Hz, 2H), 6.64 (t, J = 4.8 Hz, 1H), 3.80 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 160.8 (C), 158.1 (CH), 155.8 (CH), 132.4 (C), 122.4 (C), 114.3 (CH), 111.9 (CH), 55.6 (CH<sub>3</sub>); IR (thin film): 3345, 2960, 2830, 1679, 1650, 1525, 1263, 764 cm<sup>-1</sup>.

### III. Mechanistic Experiments

#### a) Nitrosoarene interception

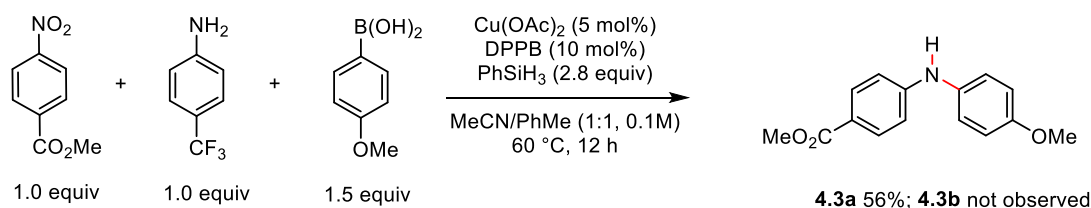


To a 10 mL schlenk tube under nitrogen, 0.0181 g of methyl 4-nitrobenzoate, 0.0228 mg of 4-methoxyphenylboronic acid and 0.50 mL of MeCN solution of 0.0009 mg Cu(OAc)<sub>2</sub> and 0.0043



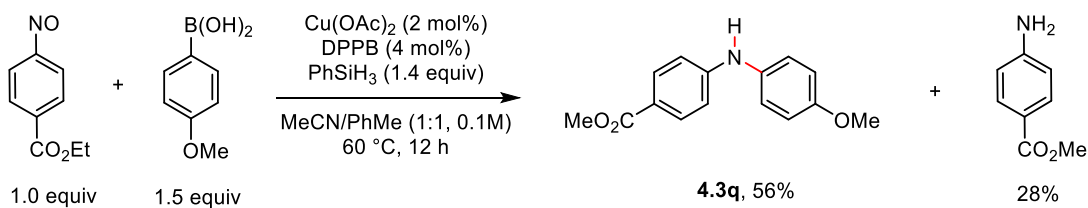
1,4-bis(diphenylphosphino)butane (dppb). Then 0.50 mL of toluene was added followed by adding 0.0303 mg of phenylsilane. After added 0.5 mL of toluene, 0.11 mL of 2,3-dimethyl-1,3-butadiene was added into the Schlenk tube in one portion before sealing the reaction system under nitrogen. The reaction mixture was stirred at 60 °C for 12 h. After completion of the reaction, the mixture was cooled to room temperature and filtered through a pad of silica gel. The filtrate was concentrated *in vacuo*. Analysis of the resulting residue using  $^1\text{H}$  NMR spectroscopy in  $\text{CDCl}_3$  with 0.1 mmol of  $\text{CH}_2\text{Br}_2$  as the internal standard revealed formation of 44% oxazoline.

b) Investigating the reactivity of aniline and nitrosoarene intermediate

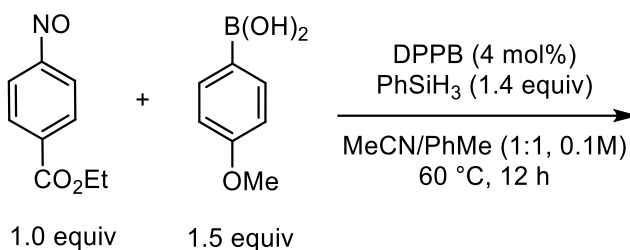


To a 10 mL schlenk tube under nitrogen, 0.0181 g of methyl 4-nitrobenzoate, 0.0228 g of 4-methoxyphenylboronic acid and 0.50 mL of MeCN solution of 0.0009 mg  $\text{Cu}(\text{OAc})_2$  and 0.0043 1,4-bis(diphenylphosphino)butane (dppb). Then 0.50 mL of toluene was added followed by adding 0.0161 g of 4-tridfluoromethyl aniline. After added 0.5 mL of toluene, 0.0303 mg of phenylsilane was added into the Schlenk tube in one portion before sealing the reaction system under nitrogen. The reaction mixture was stirred at 60 °C for 12 h. After completion of the reaction, the mixture was cooled to room temperature and filtered through a pad of silica gel. The filtrate was concentrated *in vacuo*. Analysis of the resulting residue using  $^1\text{H}$  NMR spectroscopy in  $\text{CDCl}_3$

with 0.1 mmol of CH<sub>2</sub>Br<sub>2</sub> as the internal standard revealed formation of 56% of the diarylamine from nitro substrate. Crossover product from aniline was not observed.

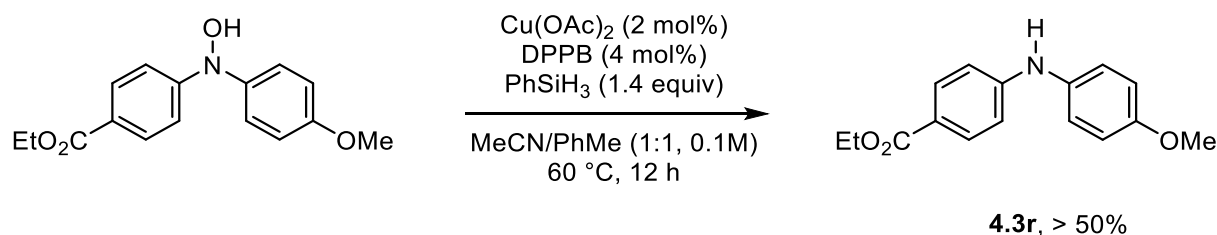


To a 10 mL schlenk tube under nitrogen, 0.0179 g of ethyl 4-nitrosobenzoate, 0.0228 g of 4-methoxyphenylboronic acid and 0.50 mL of MeCN solution of 0.0003 g Cu(OAc)<sub>2</sub> and 0.0016 g 1,4-bis(diphenylphosphino)butane (dppb). Then 0.50 mL of toluene was added. After added 0.5 mL of toluene, 0.0151 mg of phenylsilane was added into the Schlenk tube in one portion before sealing the reaction system under nitrogen. The reaction mixture was stirred at 60 °C for 12 h. After completion of the reaction, the mixture was cooled to room temperature and filtered through a pad of silica gel. The filtrate was concentrated *in vacuo*. Analysis of the resulting residue using <sup>1</sup>H NMR spectroscopy in CDCl<sub>3</sub> with 0.1 mmol of CH<sub>2</sub>Br<sub>2</sub> as the internal standard revealed formation of 56% of the diarylamine and 28% of the over reduction aniline.



To a 10 mL schlenk tube under nitrogen, 0.0179 g of ethyl 4-nitrosobenzoate, 0.0228 g of 4-methoxyphenylboronic acid and 0.0016 g 1,4-bis(diphenylphosphino)butane (dppb). After adding 0.5 mL of toluene and 0.5 mL of MeCN, 0.0151 mg of phenylsilane was added into the Schlenk tube in one portion before sealing the reaction system under nitrogen. The reaction mixture was stirred at 60 °C for 12 h. After completion of the reaction, the mixture was cooled to room temperature and filtered through a pad of silica gel. The filtrate was concentrated *in vacuo*. Analysis of the resulting residue using  $^1\text{H}$  NMR spectroscopy in  $\text{CDCl}_3$  with 0.1 mmol of  $\text{CH}_2\text{Br}_2$  as the internal standard and no reaction occurred.

c) N-hydroxy amine reduction



To a 10 mL schlenk tube under nitrogen, 0.0287 g of ethyl 4-nitrosobenzoate and 0.5 mL MeCN solution of 0.0003 g  $\text{Cu}(\text{OAc})_2$  and 0.0016 g 1,4-bis(diphenylphosphino)butane (dppb) were added. Then 0.50 mL of toluene was added. Finally 0.0151 mg of phenylsilane was added into the Schlenk tube in one portion before sealing the reaction system under nitrogen. The reaction mixture was stirred at 60 °C for 12 h. After completion of the reaction, the mixture was cooled to room temperature and filtered through a pad of silica gel. The filtrate was concentrated *in vacuo*. Analysis of the resulting residue using  $^1\text{H}$  NMR spectroscopy in  $\text{CDCl}_3$  with 0.1 mmol of  $\text{CH}_2\text{Br}_2$  as the internal standard and slightly over 50% of the reduced diarylamine product was formed.

Repeating the reaction without the presence of Cu(OAc)<sub>2</sub> led to no reaction.

## References

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## **Chapter V.**

### **Synthesis of Novel NAMPT Inhibitors for Treatment of Pulmonary Arterial Hypertension (PAH)**

#### **5.1. Introduction.**

Pulmonary arterial hypertension (PAH) is a constellation of diseases involving vascular remodeling resulting in heart failure and death. Despite its rarity, it not only leads to catastrophic implications on individuals, but also causes serious social ramifications.<sup>1, 2</sup> By expert consensus, PAH is diagnosed when a mean pulmonary artery pressure (mPAP) rises above 25 mmHg with the PA occlusion pressure (PAOP) lower than 15 mmHg based on normal or reduced cardiac output and a normal pulmonary capillary wedge pressure.<sup>3, 4</sup> This deadly disease has its median survival being 2.8 years,<sup>6</sup> killing its patients at a productive age, and higher prevalence has been observed for patients with associated conditions such as HIV and scleroderma.<sup>7, 8</sup> However, the cure of this disease remains a big challenge when existing vasodilator-treatments failed to meet their initial expectations<sup>9</sup> because PAH is not a result of vasoconstriction but rather the main pathological process involves the proliferative vascular remodeling.<sup>10, 11</sup>

With the urgent need to develop novel therapies and to understand the various active mechanisms that lead to vascular constriction, cellular proliferation, and a prothrombotic state – an abnormality in the coagulation system that increases the tendency for blood to thrombose - in varying degrees, researchers hypothesized a cancer model for PAH<sup>12</sup> based on the similarities PAH shared with cancers in pathogenic mechanisms. It was discovered that various cellular processes of PAH have analogous features with carcinogenesis including sustained proliferative signaling, evasion of growth suppressors, resistance to cell death, limitless replicative potential, and genome instability. It was also observed that chronic inflammation, pathological angiogenesis, and immune system evasion showed similarities for the pathogenesis of both PAH and cancer.<sup>13-15</sup>

Nicotinamide phosphoribosyl-transferase (NAMPT) represents a pleiotropic molecule serving multiple roles as an enzyme, a cytokine and a growth factor, playing part in regulating cell proliferation, resistance to senescence and apoptosis, as well as inflammatory responses at the pathological level.<sup>17-21</sup> NAMPT functions in two forms: intracellular (iNAMPT) and extracellular (eNAMPT). iNAMPT is known to play an important role in the salvaging pathways of nicotinamide adenine dinucleotide (NAD<sup>+</sup>) synthesis, while eNAMPT acts as an adipokine, one of the bioactive factors secreted by adipose tissue that was discovered to be related with inflammatory diseases. Inspired by recent studies revealing that the decrease in the G6PD expression and activity result in increased oxidative stress and decreased nitric oxide bioactivity, leading to endothelial dysfunction in various pathological conditions, hypothesis was made that iNAMPT, the crucial component of the mammalian nicotinamide adenine dinucleotide (NAD) biosynthesis pathway from nicotinamide, thus playing an important role in regulating G6PD

activity, could be promoting pulmonary vascular remodeling during pulmonary hypertension development.<sup>16, 17</sup> Prof. Roberto Machado demonstrated that expression of NAMPT was increased in the lungs and isolated pulmonary artery endothelial cells from patients with PAH, as well as in three different rodent models of pulmonary hypertension.<sup>22, 23</sup>

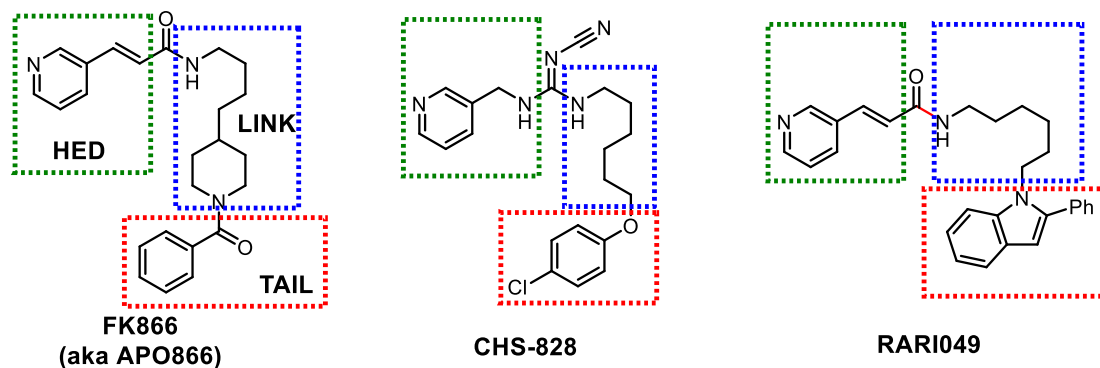
In addition, from in vitro studies, Machado's group also found that NAMPT can significantly promote the proliferation of human pulmonary artery smooth muscle cells (PASMCs) via calcium signaling. In vivo results further showed that NAMPT antagonism with FK866 prevented and reversed the development of PAH in preclinical models.<sup>24</sup> NAMPT inhibitors like FK866 and CHS828 were previously known active in cancer models by inhibiting cell proliferation and accelerating cell death, some of which have been studied in phase I to II human clinical trials for treating cancer.<sup>25-27</sup> In Machado's animal model experiments, MCT-induced PAH symptoms in rats were observed significantly reduced upon the treatment of FK866, indicated by the RVSP (right ventricular systolic pressure), degree of right ventricular hypertrophy (RVH) as well as pulmonary vascular remodeling.<sup>24</sup> Combining these results with the resolved crystal structure of human NAMPT in complex with NMN or FK866,<sup>28</sup> they concluded that FK866 was an effective inhibitor for NAMPT by serving as a NAM mimetic substrate resulting in decreased NAD levels.

However, application of FK866 and other potent small molecule NAMPT inhibitors to therapeutic treatment was plagued by their toxicities, of which retinal toxicity was the most severe problem observed with FK866 in animal models.<sup>29</sup> Holen and co-workers also determined that the most significant dose-limiting toxicity of FK866 is thrombocytopenia, a condition with low



concentration of platelets in the blood.<sup>30</sup> The platelets help with blood clotting and therefore thrombocytopenia can increase the probability of internal bleeding. Therefore, there is a major need for the development of safe, non-toxic small molecule NAMPT inhibitors for practical use in treating pulmonary arterial hypertension (PAH).<sup>31</sup>

By comparing a series of NAMPT inhibitors including FK866 and CHS828, our group first looked into their commonly shared structural motif, which contains a pyridyl HED group, an alkyl LINK 7.0 to 9.0 Å long, and a N-heterocycle TAIL group (**Figure 5.1**). Among the analogs our group previously synthesized, RARI049 was identified to exhibit NAMPT inhibition similar to FK866 and it also reversed PAH process in rodent models.



**Figure 5.1. Common structural motifs of small molecule NAMPT inhibitor candidates.**

Despite its encouraging bioactivity towards NAMPT inhibition in both *in vitro* and *in vivo* studies, RARI049 still showed problems in water solubility, metabolic stability, and toxicity. This

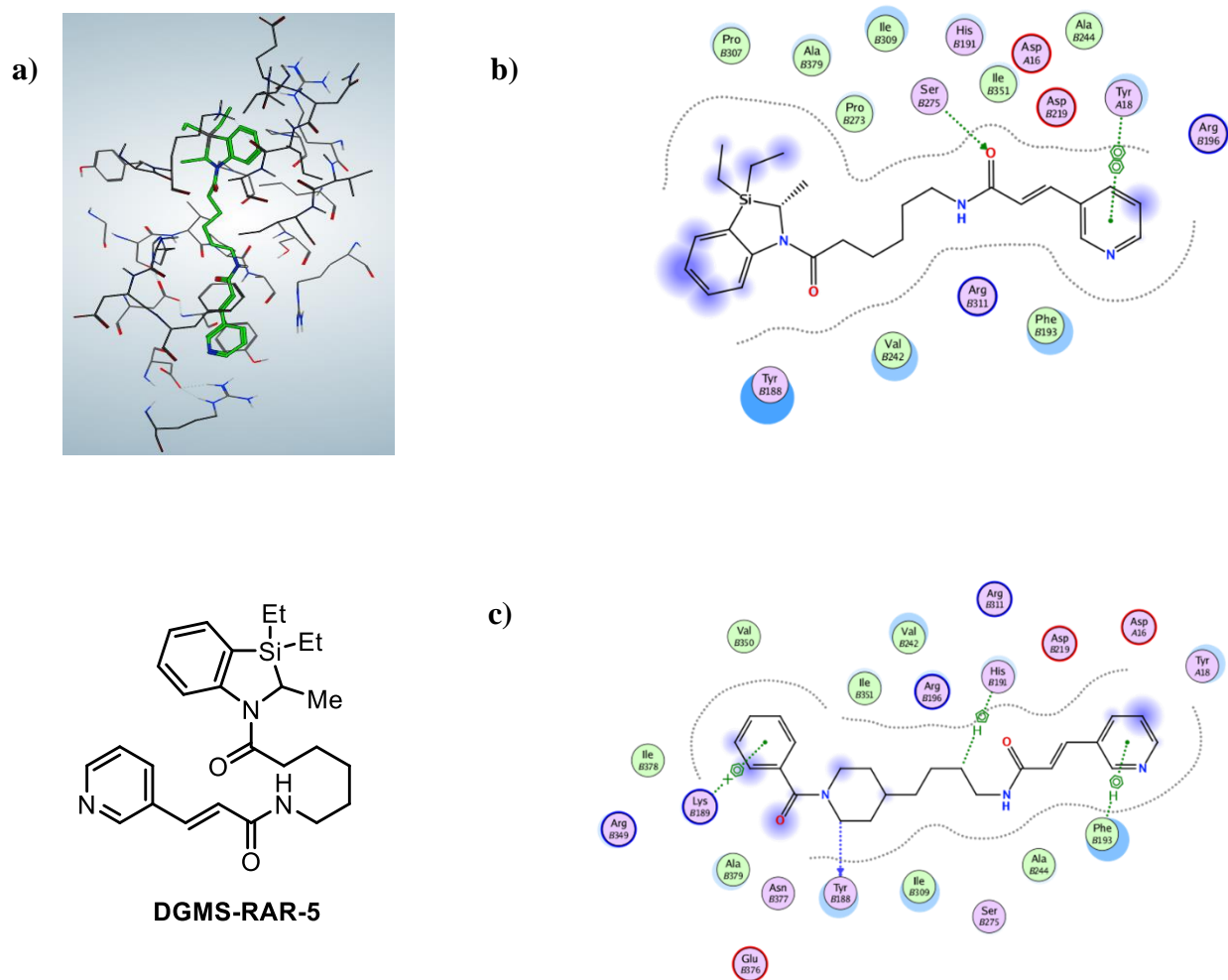
motivated us to design and synthesize more NAMPT inhibitor analogs based on the initial lead RARI049.

## 5.2. Results and Discussion

To gain more insight into the efficacy of the lead compound, Computer Assisted Molecule Design (CAMD) was performed by Prof. Petukhov's Group using Molecular Operating Environment (MOE). First it was found that the 3-pyridyl HED group is critical for the inhibition due to the  $\pi$ - $\pi$  stacking interactions with Tyr18 and Phe193, which also explained the length requirement for the LINK moieties in order for the HED group to reach binding site. Therefore, it was anticipated that modification to the 3-pyridyl or the LINK group may result in drastic change of inhibitor activities. On the other hand, the surface view indicated that the 2-phenyl indole TAIL of the lead compound significantly enhanced the hydrophobic interactions with the binding pocket compared to the less efficient probes in the library.

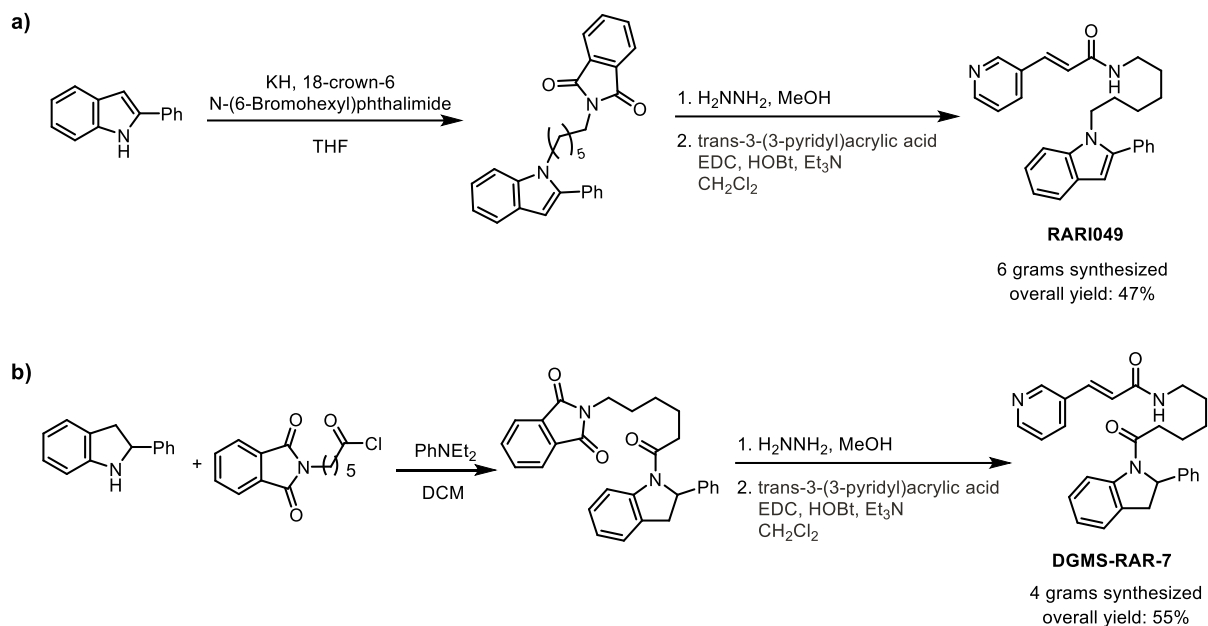
Following the same software settings, I continued the CAMD docking studies on a more focused library of RARI analogs which we had easy access to using the techniques of N-heterocycle construction of our group. The MOE docking scores suggested that the difference in the efficiency of indole derivatized TAIL groups was no more than two order of magnitude, scoring between 8.7 to 10.5, while changing the identity of 3-pyridyl HED, lengthening or shortening the LINK all resulted in scores falling below 7.

Moreover, I discovered that using an indoline HED scaffold attached by the LINK moieties via acylation instead of alkylation lead to noticeable increase of the van der Waals interactions between the probe and the binding pocket, particularly when comparing the silylindoline analog DGMS-RAR-6 with the control FK866 (**Figure 5.2**).

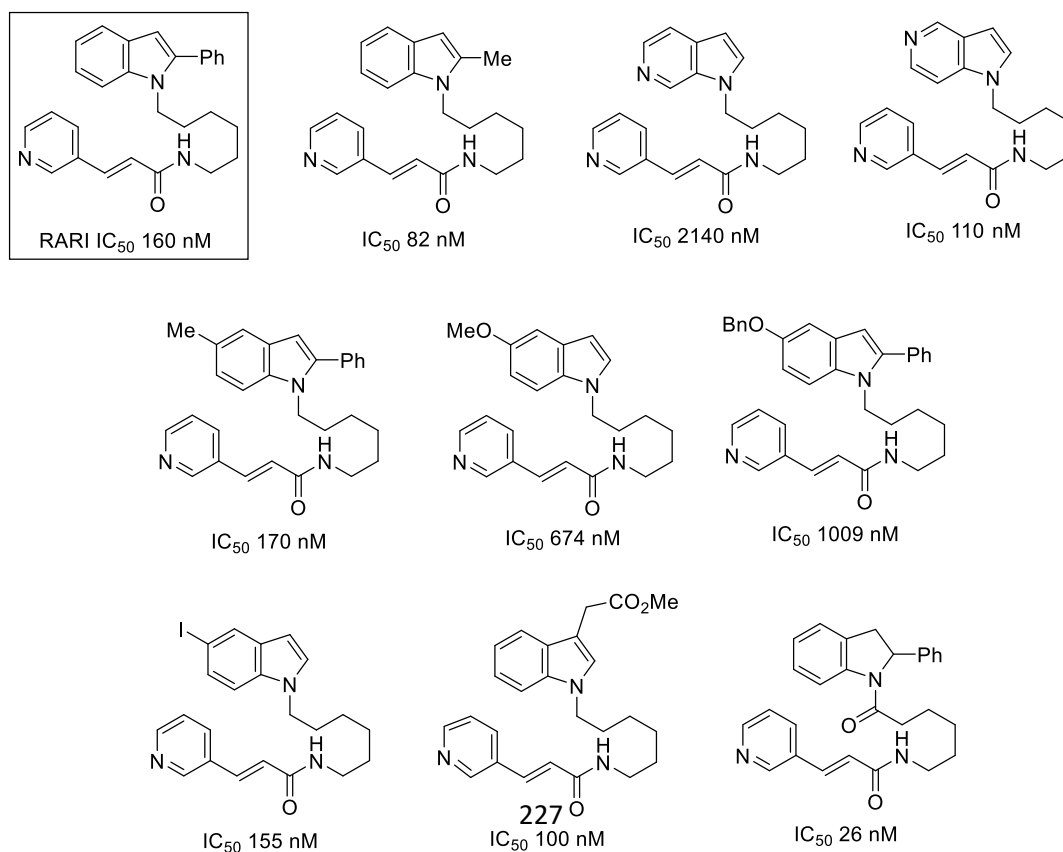


**Figure 5.2. In silico study of RARI analogs.** a) Silylindoline type ligand docked with NAMPT crystal data 2GVJ.pdb. b) Two-dimensional representation of the ligand-receptor interaction map of DGMS-RAR-5. c) Two-dimensional representation of the ligand-receptor interaction map of FK866.

With the docking evaluation of our focused library of ligand candidates, we rationalized that it was more beneficial to synthesize new NAMPT analogs by modifying the N-heterocycle TAIL group of the lead compound. Using my reductive cyclization method introduced in previous chapters, I was able to construct a variety of different indole moieties. Then, N-alkylation of the indole was performed by adding KH and 18-crown-6 into a solution of the indole, followed by addition of N-(6-bromohexyl)phthalimide which introduced the six-carbon LINK chain. Deprotection of the phthalimide 4.2.1. by hydrazine formed the primary amine 4.2.2., which was then coupled with *trans*-3-(3-pyridyl) acrylic acid under EDC/HOBt conditions to produce the final analog (**Scheme 5.1a**). Alternatively for indoline TAILs, acylation was conducted to the indoline using N,N-diethylaniline as the base to produce phthalimide 4.2.4. which then underwent the same deprotection and amine coupling conditions to generate the desired probe (**Scheme 5.1b**). Both routes enabled me to conduct multi-gram synthesis of the analogs without reducing the overall yield of the reactions. Using the standard procedures, I synthesized a series of analogs and their IC<sub>50</sub> values were determined by Prof. Kiira Ratia via High-Throughput Screening (HTS) experiments using CycLex NAMPT Colorimetric Assay Kit (**Scheme 5.1**). Compared to the lead RARI049, it seemed that the TAIL group tolerates a variety of functional groups on the indole except for 5-alkoxy groups or 6-azaindole structure.

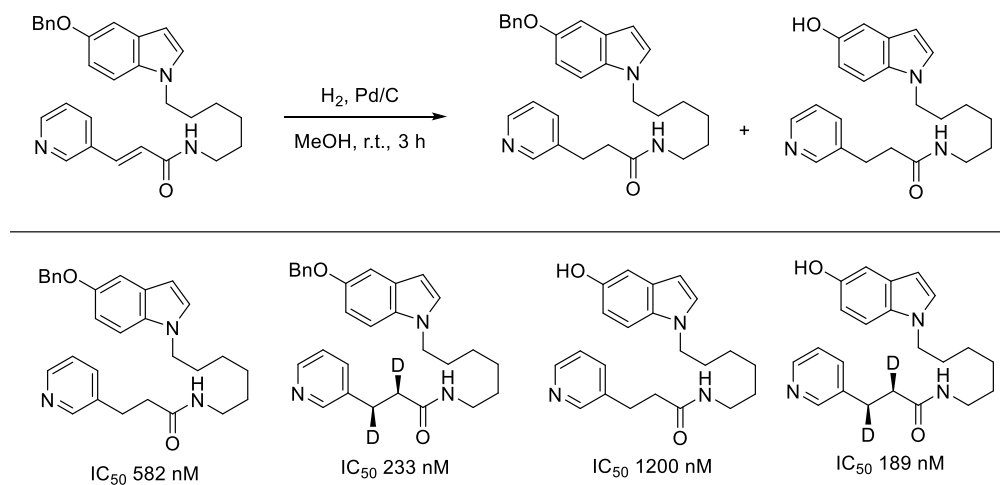


**Scheme 5.1. Synthesis of RARI NAMPT inhibitor overview.** a) Synthesis of RARI analogs with indole TAILs. b) Synthesis of RARI analogs with indoline TAILs.



### Scheme 5.2. Activity of NAMPT inhibitor analogs with indole TAIL moieties.

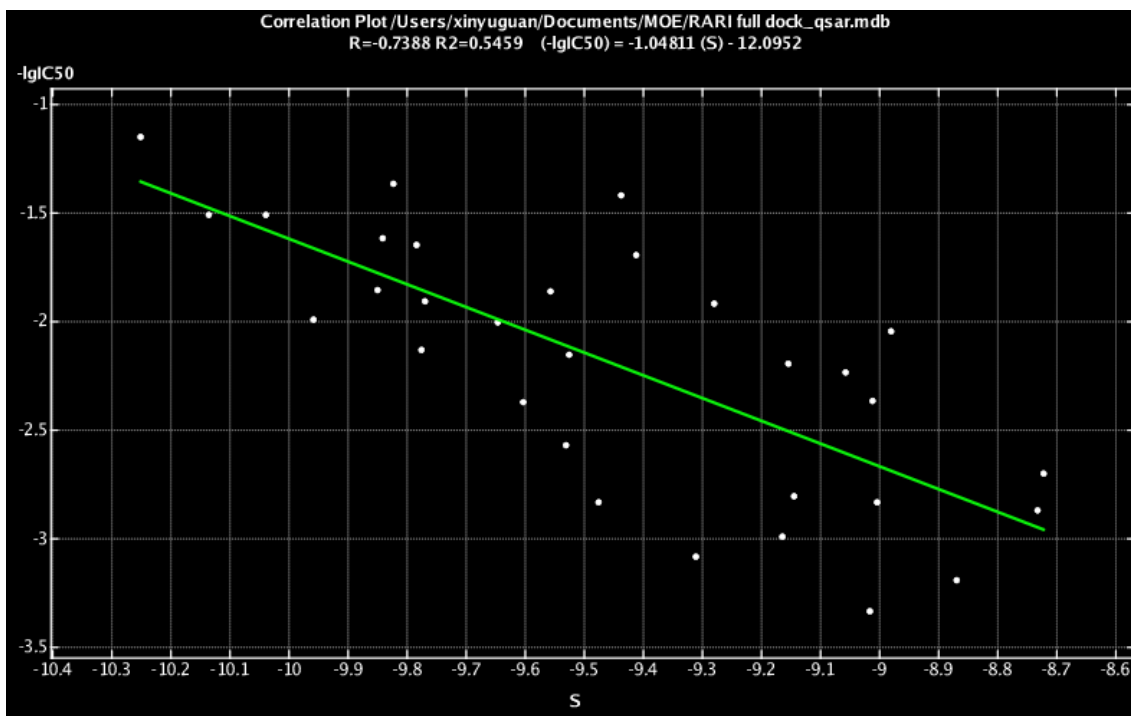
Next, together with my colleagues Naijing Su and Wrickban Mazumdar, we saturated the acrylamide carbon-carbon double bond of the RARI analogs by hydrogenation to gain some insights about the SAR. While my colleagues' data suggested that reducing the double bond by H<sub>2</sub> or D<sub>2</sub> would significantly lower NAMPT inhibition activity of the analogs compared to the unsaturated parent molecule, I saw instead a slightly improved inhibition for the 5-(benzyloxy)indole analog. Hydrogenation conditions also lead to benzyl deprotection and the resulting 5-hydroxyl indole analog did not suffer from a tremendous attenuation of enzyme activity.



### Scheme 5.3. H<sub>2</sub> and D<sub>2</sub> hydrogenated RARI NAMPT inhibitors.

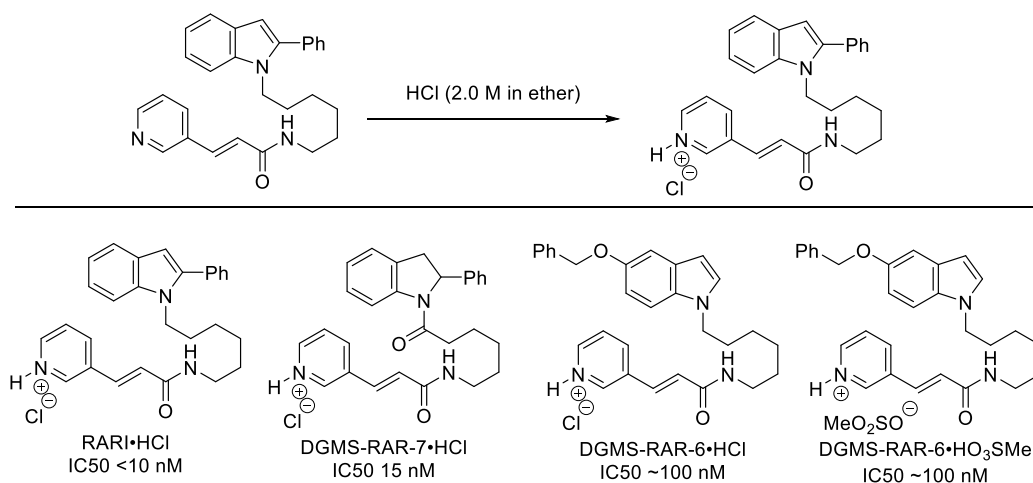
At this point, I was able to look back and evaluate my CAMD studies by comparing the results of docking with the HTS outcomes (**Figure 5.6**). It was not too unexpected that only moderate

correlation was observed for the docking scores and IC<sub>50</sub> values considering that the majority of the candidates in the library turned out to fall into a narrow range of NAMPT activity and thus suffering from larger errors. However, I was still delighted to find that the docking scores were useful in predicting unfavored structural modifications that largely reduce the probe activity, in particular, changing the length of the linker, changing the position of the 3-pyridyl nitrogen, adding more than one hydrogen bond donor or acceptor functional groups on the TAIL motif. This sets us a minimum criteria for our decision in future probe synthesis and thus can accelerate optimization of probe's attributes or lead identification in related subjects.



**Fig 5.3. Evaluation of docking scores.**

With my colleagues' indoline, silylindoline and benzazepine analogs also showing comparable NAMPT inhibition, a common challenge we met for all the analogs were their poor water solubility, leading to inconsistency in some HTS data as well as causing precipitations when subjected to pulmonary artery endothelial and smooth muscle cells (PAECs and PASMCs) cellular assays. Initial attempts to functionalize indole TAIL with hydrogen bond acceptors failed to improve the solubility to a practical level. Therefore, I switched my focus to salt formation, a straightforward and effective way to increase solubility and dissolution rate commonly applied in drug optimizations.<sup>32</sup> By treating the RARI analogs with a stoichiometric amount of HCl in ether, I obtained pyridinium salts of the selected analogs, which not only showed good water solubility, but also exhibited a more crystalline solid form compared to their previous form as viscous oil. To my delight, these salts even showed better IC<sub>50</sub> values than their parent compounds (**Scheme 5.4**). The HRMS result of RARI·HCl showed mass value of one equivalence of HCl molecule associated with the RARI analog. Despite that the exact protonation site was not exactly clear, the requirement for the interaction of pyridine nitrogen would likely require the proton to exchange to other positions.





#### Scheme 5.4. Salt formation of RARI NAMPT inhibitors.

In conclusion, with the help of in-silico docking technique, a more focused library of the novel RARI NAMPT inhibitors was built and over 60 analogs and intermediates were synthesized. Most of our compounds showed great *in vitro* NAMPT inhibition activity and were overall consistent with the docking prediction. Poor water solubility of the refined leads was resolved by salt formation and all these optimized analogs could be made in multi-gram scale with good yields, which allows us to further study their efficacy in animal models and gain information for their toxicity and drug metabolism.

#### 5.3. Experimental.

(This part partially contains data from supporting information of my published patent: Driver, T. G.; Guan, X.; Mazumdar, W.; Su, N.; Ratia, K.; Hickok, J.; Lockett, A. D.; Machado, R. Pub. No.: WO/2019/153007)

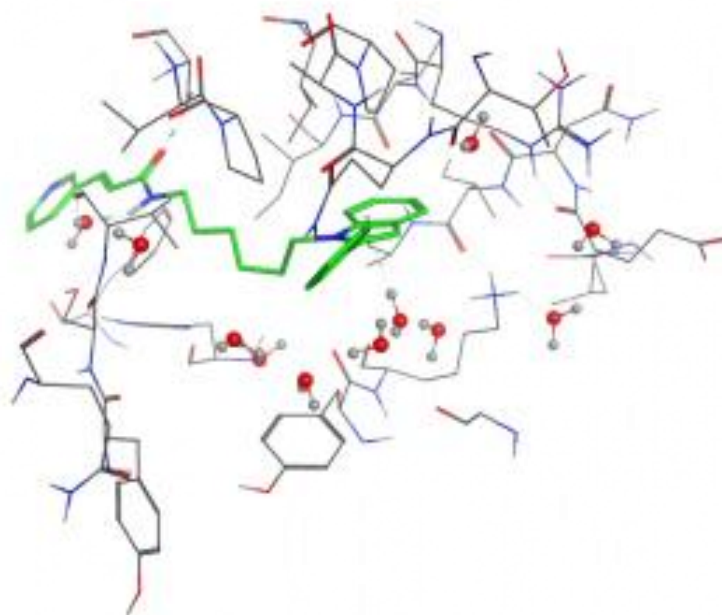
General.  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra were recorded at ambient temperature using 500 MHz or 300 MHz spectrometers. The data are reported as follows: chemical shift in ppm from internal tetramethylsilane on the  $\delta$  scale, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz) and integration. High-resolution mass spectra were obtained by peak matching. Melting points are reported uncorrected. Analytical thin layer chromatography was performed on 0.25 mm silica gel plates with UV254 fluorescent indicator. Liquid chromatography was performed using forced flow (flash chromatography) of the indicated solvent system on 60Å (40 – 60  $\mu\text{m}$ ) mesh silica gel ( $\text{SiO}_2$ ). Medium pressure liquid

chromatography (MPLC) was performed using pumps to force flow the indicated solvent system down columns that had been packed with 60Å (40 – 60 µm) mesh silica gel (SiO<sub>2</sub>). All reactions were carried out under an atmosphere of nitrogen in glassware that was oven-dried. Unless otherwise noted, all reagents were commercially obtained and, where appropriate, purified prior to use. Acetonitrile, methanol, toluene, THF, Et<sub>2</sub>O, and CH<sub>2</sub>Cl<sub>2</sub> were dried by filtration through alumina according to the procedure of Grubbs.<sup>33</sup> Metal salts were stored in a nitrogen atmosphere dry box.

## **I. Docking and scoring of NAMPT inhibitors.**

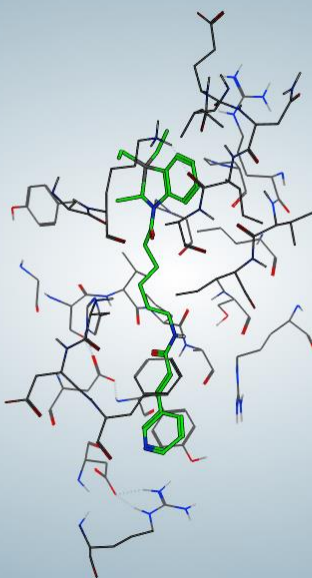
Docking was performed using Molecular Operating Environment (MOE) software and the general settings were obtained from Jesse Gordon-Blake from Prof. Petukhov's Group to dock 2GVJ crystal data. This uses Receptor+Solvent for the Receptor, and Ligand Atoms for both the Ligand and Site. Ligand conformations are generated with the bond rotation method. These are then placed in the site with the Triangle Matcher method and ranked with the London dG scoring function. The Retain option specifies the number of poses (30) to pass to the Refinement, for energy minimization in the pocket, before rescoring with the GBVI/WSA dG scoring function. Over 60 RARI analogs were included in the focused library along with the lead compound RARI049 as well as FK866 as the internal standards.

Entry: 6/10  
mol:

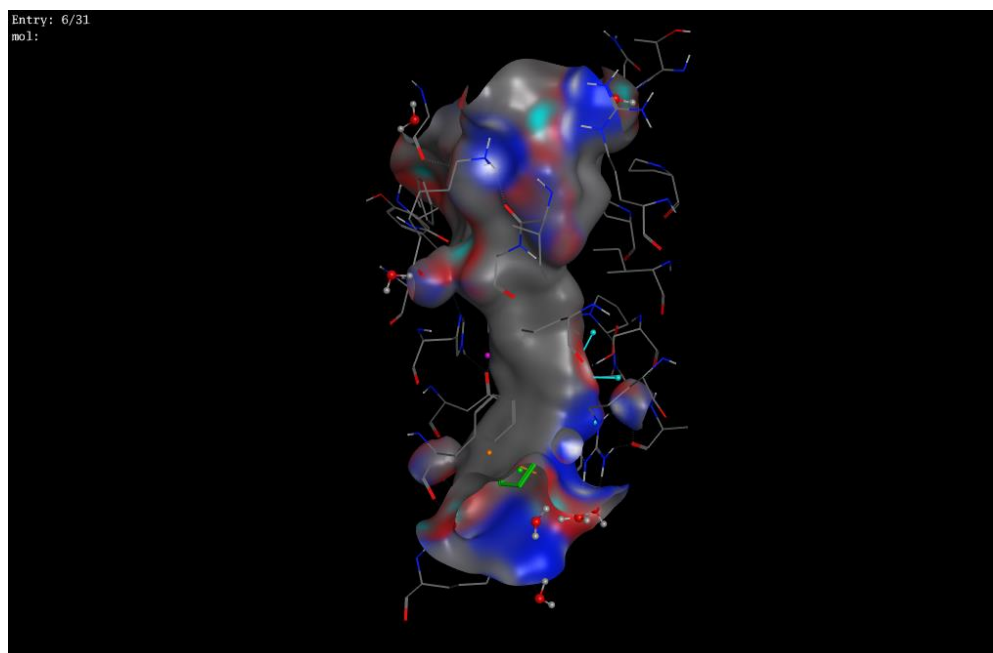


**Fig S5.1.** Docking of RARI049 lead with NAMPT active site.

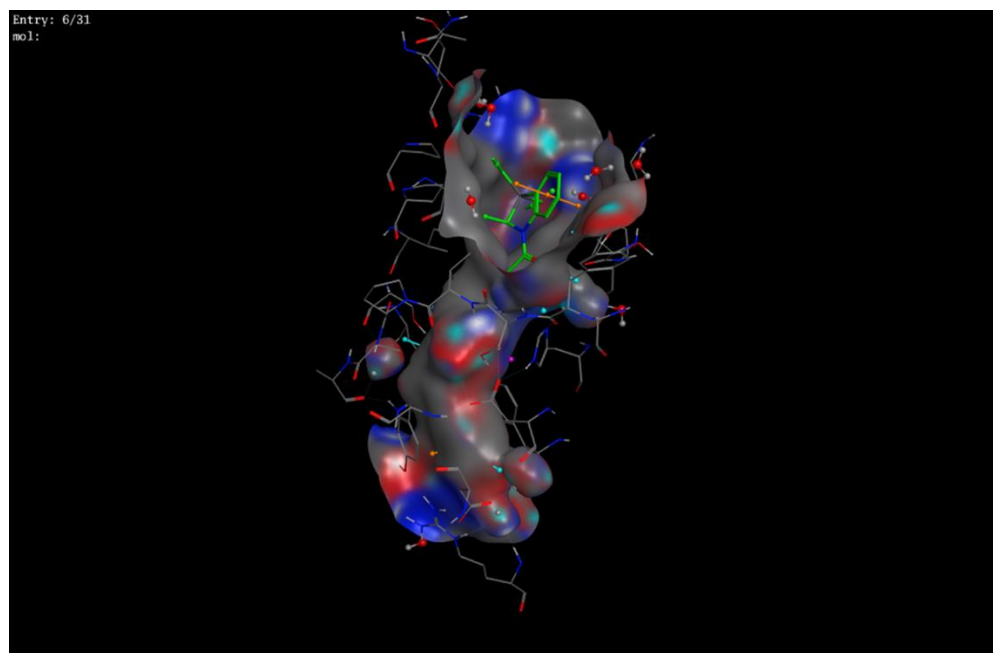
Entry: 6/30  
mol:



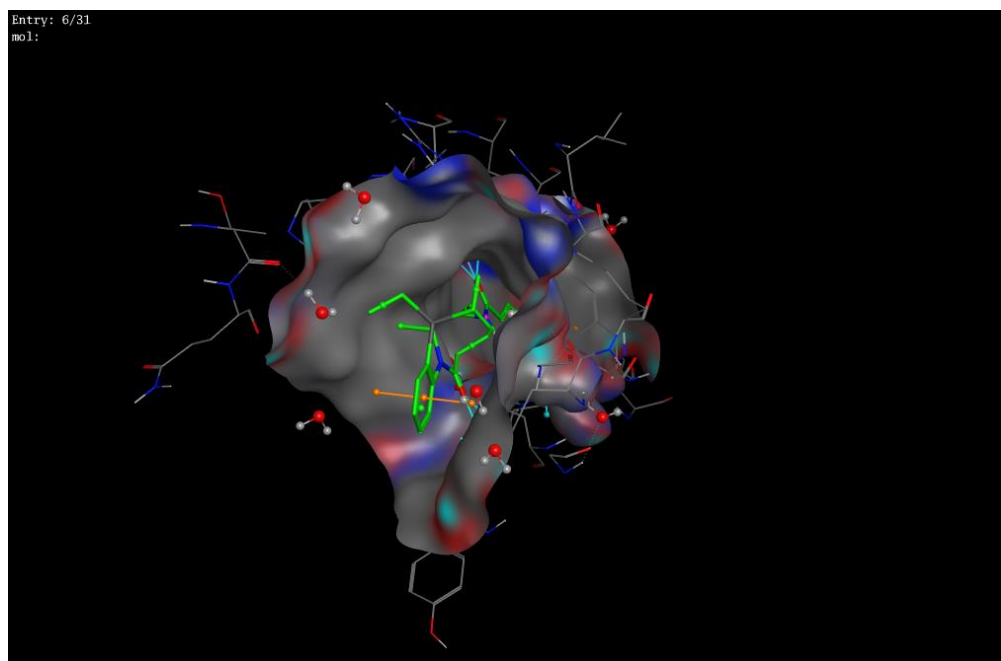
**Fig S5.2.** Docking of DGMS-RAR-6 with NAMPT active site.



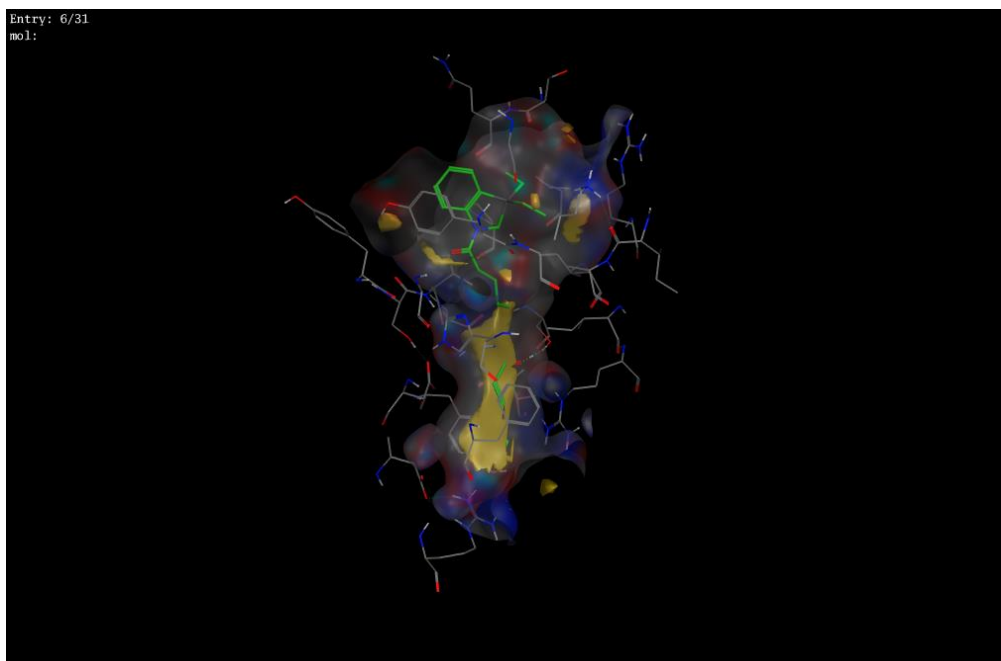
**Fig S5.3.** Surface mapping of DGMS-RAR-6 binding to NAMPT active site.



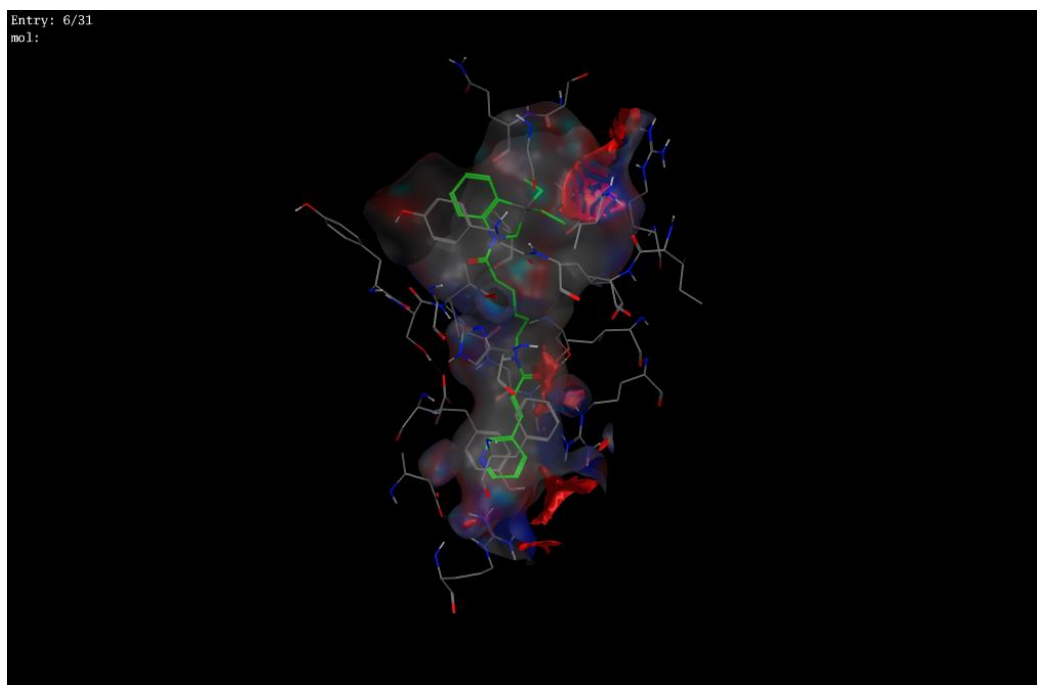
**Fig S5.4.** Surface mapping of DGMS-RAR-6 binding to NAMPT active site.



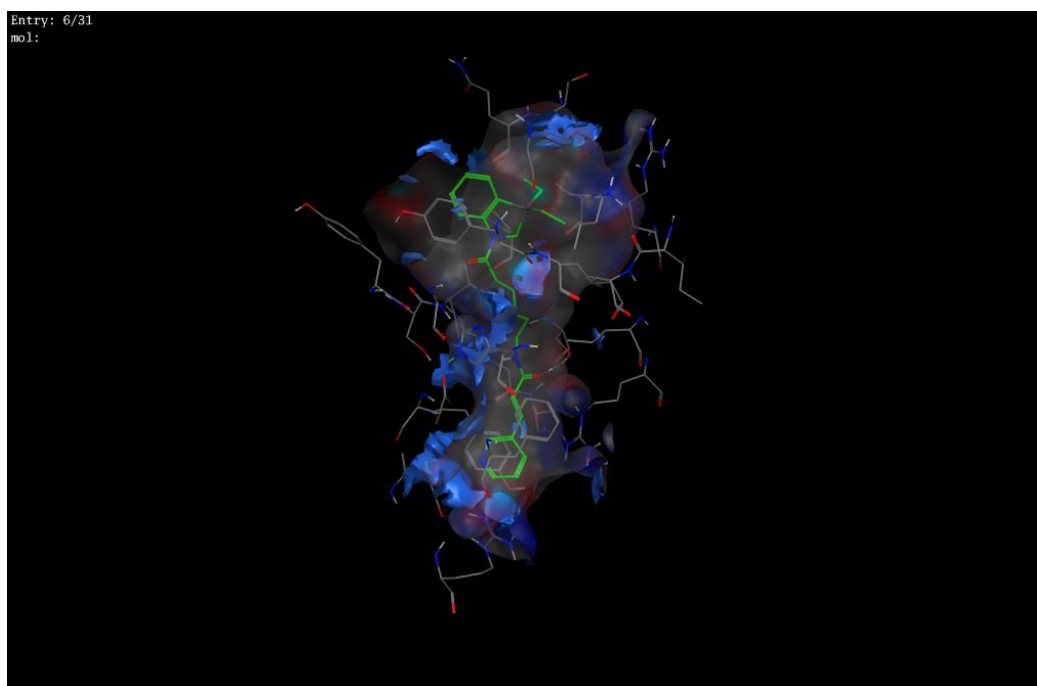
**Fig S5.5.** Surface mapping of DGMS-RAR-6 binding to NAMPT active site.



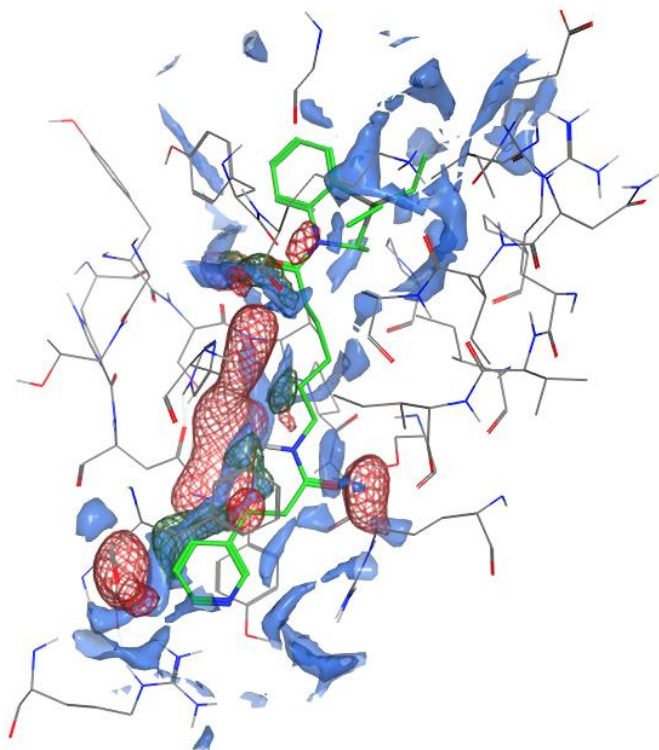
**Fig S5.6.** Hydrophobic surface map of NAMPT active site with DGMS-RAR-6.



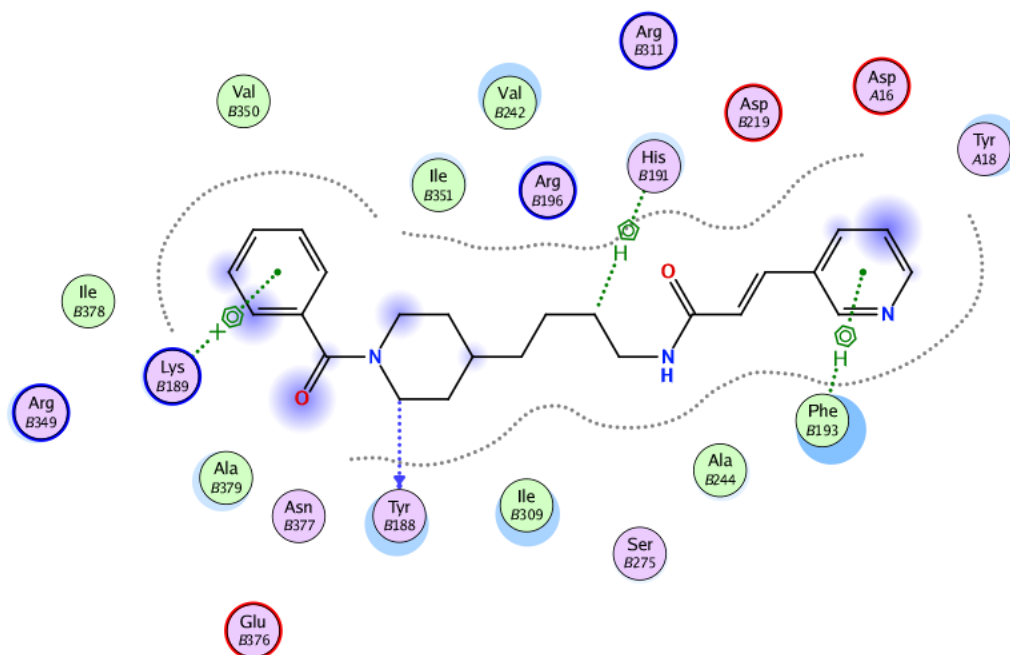
**Fig S5.7.** H-acceptor map of NAMPT active site with DGMS-RAR-6.



**Fig S5.8.** H-donor map of NAMPT active site with DGMS-RAR-6.

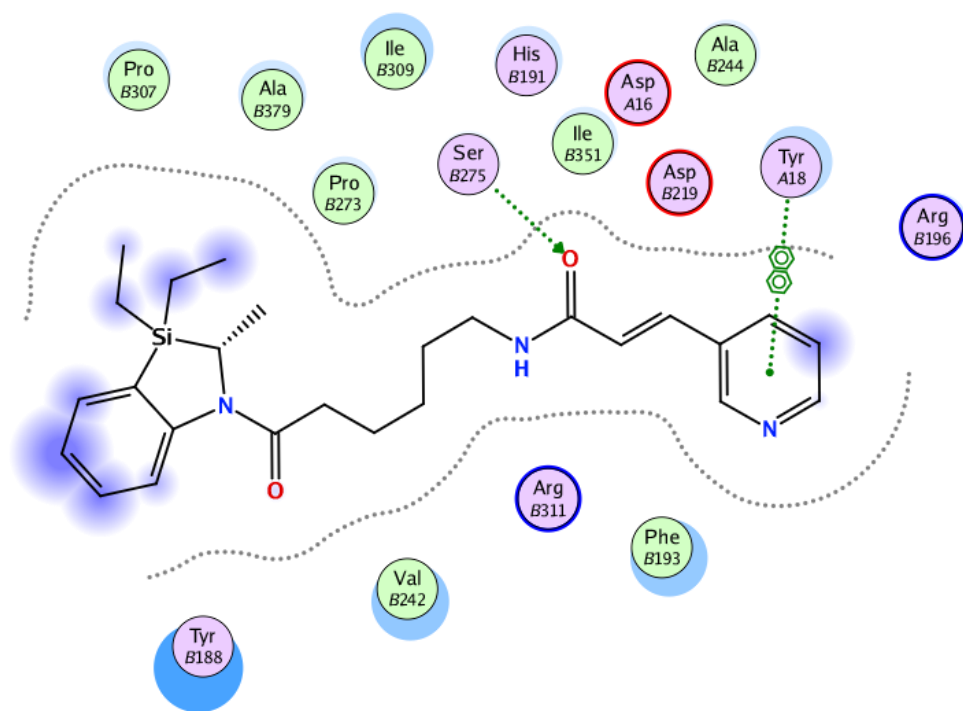


**Fig S5.9.** Solvent analysis of NAMPT active site with DGMS-RAR-6.

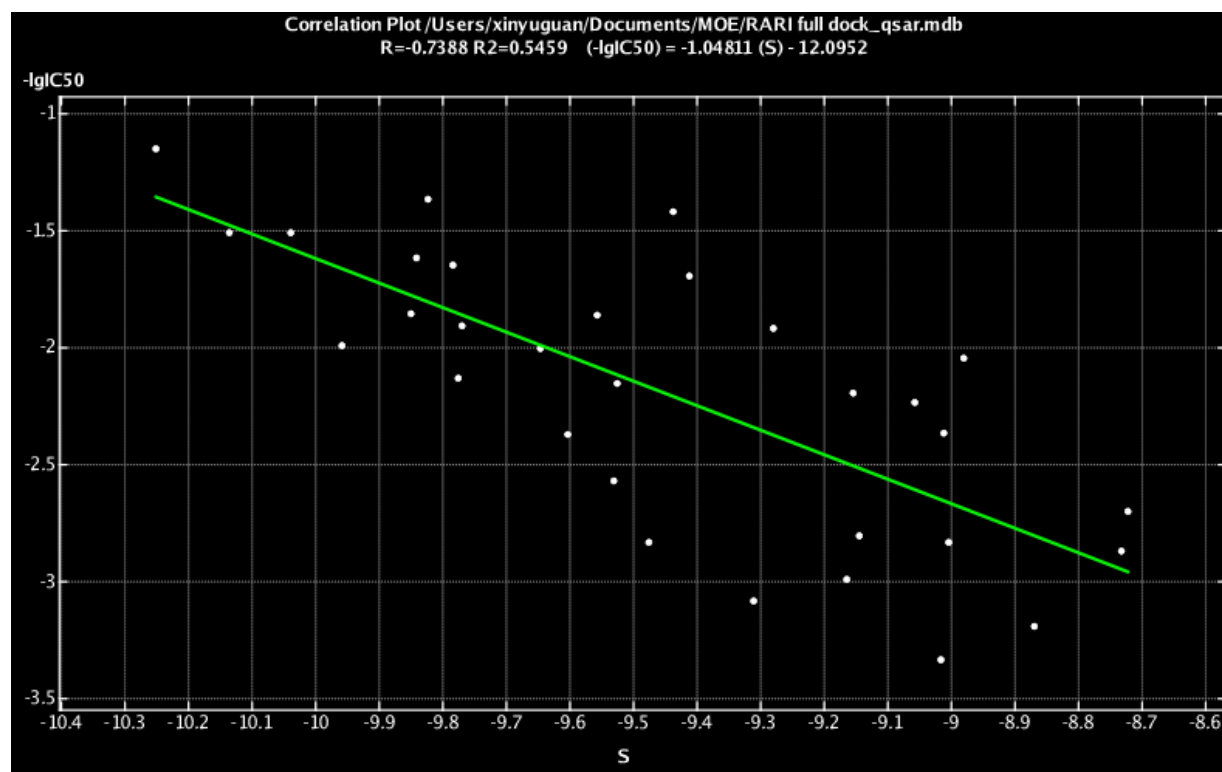


**Fig S5.10.** 2-D interaction map of FK866 and NAMPT docking.





**Fig S5.11.** 2-D interaction map of DGMS-RAR-6 and NAMPT docking.



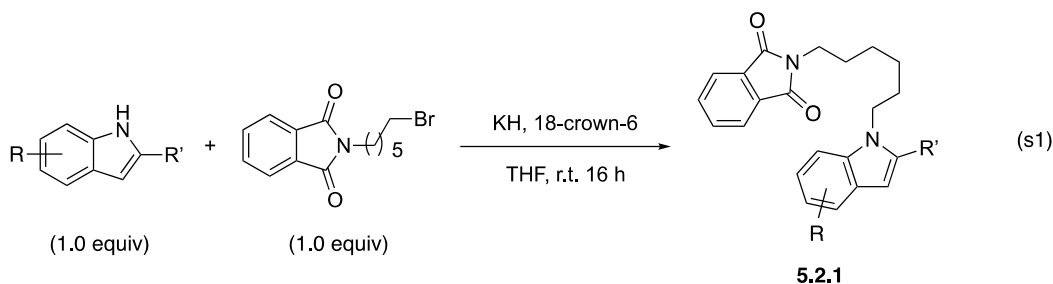
**Fig S5.12.** Correlation between docking scores and  $IC_{50}$  of the RARI analogs

## II. Synthesis of NAMPT inhibitors.

(This part was partially taken from supporting information of our published patent: “Nicotinamide phosphoribosyltransferase inhibitors and methods for use of the same.” Driver, T. G.; Guan, X.; Mazumdar, W.; Su, N.; Ratia, K.; Hickok, J.; Lockett, A. D.; Machado, R. International Patent Application No. PCT/US2019/016684 filed 2-16-2019, published 8-8-2019.)

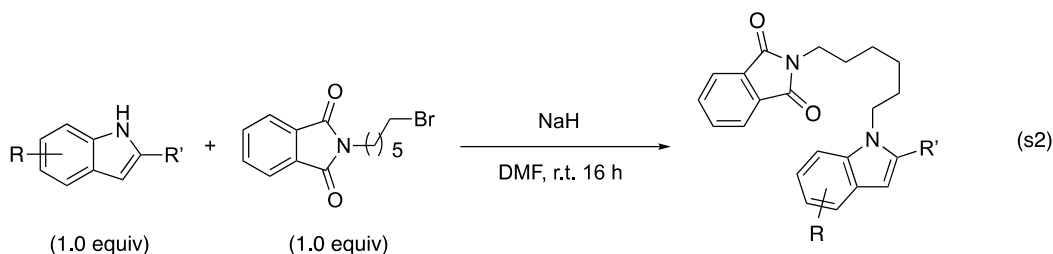
### A. Synthesis of *N*-(6-indolehexyl)-phthalimide. (Route A)

a) General procedure A.



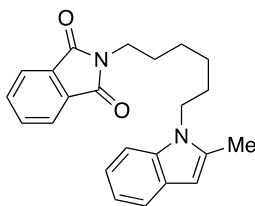
To a stirred 0.5 M solution of 18-crown-6 (1.5 equiv) and KH (1.5 equiv, 30% w/w suspension in mineral oil) in dry THF was added a 0.5 M solution of indole (1.0 equiv) in dry THF dropwise over 10 min under N<sub>2</sub> atmosphere. After stirring at room temperature for 30 min, a 0.5 M solution of *N*-(6-bromohexyl) phthalimide (1.2 equiv) in dry THF was added to the reaction mixture dropwise over 10 min. The reaction mixture was allowed to stir at room temperature overnight. The reactives were then quenched by the addition of 20 mL of water. The resulting mixture was extracted by 3 × 15 mL of EtOAc. The combined organic extracts were washed with 2 × 20 mL of water and 20 mL of brine. The resulting organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and the filtrate was concentrated *in vacuo*. The resulting residue was purified by MPLC to afford the product.

b) General procedure B.



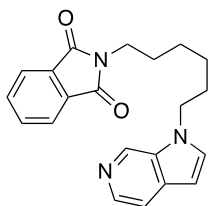
In a three-necked flask, equipped with a magnetic stir bar, was charged with indole (1.0 equiv). Dry DMF (3 mL/1 mmol of indole) was added under Ar atmosphere and the reaction mixture cooled to 0 °C. NaH (2.0 equiv, 60 % w/w in mineral oil) was added in a single portion and the reaction mixture stirred at 0 °C. After 10 minutes, the reaction was warmed to room temperature. After 1 h, the reaction mixture was cooled to 0 °C and *N*-(6-bromohexyl) phthalimide (2.0 equiv) dissolved in 2 mL of dry DMF was added dropwise over 10 min. The reaction mixture was slowly warmed to room temperature and stirred overnight. The reactives were then quenched by addition of 20 mL of water. The resulting mixture was extracted with 3 × 15 mL of EtOAc. The combined organic extracts were washed with 2 × 20 mL of water and 20 mL of brine. The resulting organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and the filtrate was concentrated *in vacuo*. The resulting residue was purified by MPLC to afford the product.

#### B. Characterization data for *N*-(6-indolehexyl)-phthalimides 5.1.



**5.1a**

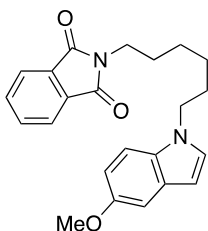
***N*-(6-Indolehexyl)-phthalimide 5.1a.** The general procedure was followed using 131.2 mg of 2-ethylinole (1.0 mmol), 620.4 mg of *N*-(6-bromohexyl) phthalimide (2.0 mmol), 80 mg of 60 % w/w NaH in mineral oil (2.0 mmol) in total 5 mL of DMF. Purification by MPLC chromatography (10:1 hexanes:EtOAc) afforded **5.1a** as a yellow oil ( 54 mg, 15% yield). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.85 – 7.82 (m, 2H), 7.72 – 7.69 (m, 2H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.24 (d, *J* = 8.0 Hz, 1H), 7.11 (dt, *J* = 8.0 Hz, 1.0 Hz, 1H), 7.05 – 7.02 (m, 1H), 6.22 (s, 1H), 4.04 (t, *J* = 7.5 Hz, 2H), 3.67 (t, *J* = 7.0 Hz, 2H), 2.41 (s, 3H), 1.75 (quin, *J* = 7.0 Hz, 2H), 1.67 (quin, *J* = 7.0 Hz, 2H), 1.44 – 1.34 (m, 4H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 168.4 (C), 136.6 (C), 136.3 (C), 133.9 (CH), 132.1 (C), 128.0 (C), 123.2 (CH), 120.3 (CH), 119.6 (CH), 119.1 (CH), 109.0 (CH), 99.9 (CH), 43.1 (CH<sub>2</sub>), 37.8 (CH<sub>2</sub>), 30.1 (CH<sub>2</sub>), 28.5 (CH<sub>2</sub>), 26.6 (CH<sub>2</sub>), 26.6 (CH<sub>2</sub>), 12.8 (CH<sub>3</sub>). ATR-FTIR (thin film): 3054, 2935, 2858, 1771, 1707, 1614, 1550, 1465, 1395, 1357, 1055, 718 cm<sup>-1</sup>. HRMS (ESI) *m/z* calcd for C<sub>23</sub>H<sub>25</sub>N<sub>2</sub>O<sub>2</sub> [M + H]<sup>+</sup>: 361.1916, found: 361.1911.



**5.1b**

***N*-(6-Indolehexyl)-phthalimide 5.1b.** The general procedure was followed using 118.1 mg of 6-azaindole (1.0 mmol), 620.4 mg of *N*-(6-bromohexyl) phthalimide (2.0 mmol), 80 mg of 60 % w/w NaH in mineral oil (2.0 mmol) in total 5 mL of DMF. Purification by MPLC chromatography (5:1 – 1:1 hexanes:EtOAc – 100 % EtOAc) afforded **5.1b** as a yellow oil (70 mg, 20% yield). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.71 (s, 1H), 8.17 (d, *J* = 5.5 Hz, 1H), 7.78 – 7.75 (m, 2H), 7.66 – 7.63

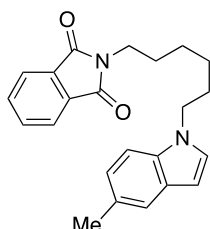
(m, 2H), 7.44 (dd,  $J = 5.5$  Hz, 1.0 Hz, 1H), 7.16 (d,  $J = 3.0$  Hz, 1H), 6.41 (d,  $J = 3.0$  Hz, 1H), 4.13 (t,  $J = 7.5$  Hz, 2H), 3.60 (t,  $J = 7.0$  Hz, 2H), 1.82 (quin,  $J = 3.5$  Hz, 2H), 1.63 – 1.57 (m, 2H), 1.33 – 1.29 (m, 4H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  168.4 (C), 138.4 (CH), 133.9 (CH), 133.2 (C), 133.0 (C), 132.8 (CH), 132.0 (C), 131.3 (CH), 123.1 (CH), 115.3 (CH), 100.5 (CH), 46.6 ( $\text{CH}_2$ ), 37.7 ( $\text{CH}_2$ ), 30.3 ( $\text{CH}_2$ ), 28.4 ( $\text{CH}_2$ ), 26.4 ( $\text{CH}_2$ ), 26.4 ( $\text{CH}_2$ ). ATR-FTIR (thin film): 3044, 2934, 2858, 1771, 1707, 1668, 1395, 1090, 818, 719  $\text{cm}^{-1}$ . HRMS (ESI)  $m/z$  calcd for  $\text{C}_{21}\text{H}_{22}\text{N}_3\text{O}_2$  [ $\text{M} + \text{H}$ ] $^+$  348.1712, found: 348.1708.



### 5.1f

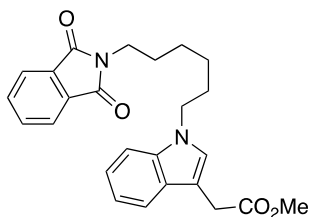
***N*-(6-indolehexyl)-phthalimide 5.1f.** The general procedure was followed using 147 mg of indole (1.00 mmol), 310 mg of *N*-(6-bromohexyl) phthalimide (1.50 mmol), 60.2 mg of 30 % w/w KH in mineral oil (1.50 mmol), 396 mg of 18-crown-6 in a total of 6 mL of THF. Purification by MPLC chromatography (1:10 EtOAc:hexanes) afforded **5.1f** as a yellow oil (280 mg, 74% yield):  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.83 (dd,  $J = 5.5, 3.0$  Hz, 2H), 7.70 (dd,  $J = 5.5, 3.0$  Hz, 2H), 7.20 (d,  $J = 8.5$  Hz, 1H), 7.07 (d,  $J = 2.0$  Hz, 1H), 7.05 (d,  $J = 3.0$  Hz, 1H), 6.85 (dd,  $J = 8.5, 2.0$  Hz, 1H), 6.38 (d,  $J = 2.5$  Hz, 1H), 4.06 (t,  $J = 7.5$  Hz, 2H), 3.84 (s, 3H), 3.66 (t,  $J = 7.5$  Hz, 2H), 1.81 (quintet,  $J = 7.0$  Hz, 2H), 1.65 (quintet,  $J = 7.0$  Hz, 2H), 1.39 – 1.32 (m, 4H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  168.4 (C), 153.9 (C), 133.9 (CH), 132.1 (C), 131.3 (C), 128.9 (C), 128.3 (CH), 123.2

(CH), 111.7 (CH), 110.1 (CH), 102.6 (CH), 100.4 (CH), 55.9 (CH<sub>3</sub>), 46.5 (CH<sub>2</sub>), 37.8 (CH<sub>2</sub>), 30.2 (CH<sub>2</sub>), 28.5 (CH<sub>2</sub>), 26.6 (CH<sub>2</sub>), 26.5 (CH<sub>2</sub>).



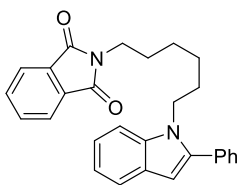
### 5.1g

***N*-(6-Indolehexyl)-phthalimide 5.1g.** The general procedure was followed using 131 mg of indole (1.00 mmol), 310 mg of *N*-(6-bromohexyl) phthalimide (1.50 mmol), 60.2 mg of 30 % w/w KH in mineral oil (1.50 mmol), 396 mg of 18-crown-6 in a total of 6 mL of THF. Purification by MPLC chromatography (1:10 EtOAc:hexane) afforded **5.1g** as a yellow oil (250 mg, 69% yield): <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.84 (dd, *J* = 5.3, 3.1 Hz, 2H), 7.70 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.42 (s, 1H), 7.23 (d, *J* = 8.3 Hz, 1H), 7.04 (dd, *J* = 9.6, 5.7 Hz, 2H), 6.40 (d, *J* = 2.9 Hz, 1H), 4.08 (t, *J* = 7.0 Hz, 2H), 3.68 (t, *J* = 7.2 Hz, 2H), 2.47 (s, 3H), 1.89 – 1.79 (m, 2H), 1.72 – 1.62 (m, 2H), 1.41 – 1.34 (m, 4H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 168.5 (C), 134.4 (C), 133.9 (CH), 132.2 (C), 128.9 (C), 128.3 (C), 127.9 (CH), 123.2 (CH), 123.0 (CH), 120.6 (CH), 109.1 (CH), 100.3 (CH), 46.3 (CH<sub>2</sub>), 37.9 (CH<sub>2</sub>), 30.1 (CH<sub>2</sub>), 28.5 (CH<sub>2</sub>), 26.6 (CH<sub>2</sub>), 26.5 (CH<sub>2</sub>), 21.4 (CH<sub>3</sub>). IR (thin film): 2933, 2858, 1771, 1706, 1436, 1394, 1357, 1333, 1056, 878, 791, 759, 717 cm<sup>-1</sup>; HRMS (ESI) *m/z* calculated for C<sub>23</sub>H<sub>25</sub>N<sub>2</sub>O<sub>2</sub> (M+H)<sup>+</sup>: 361.1916, found: 361.1919.



### 5.1h

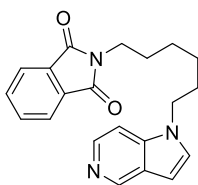
***N*-(6-Indolehexyl)-phthalimide **5.1h**.** The general procedure was followed using 189 mg of indole (1.00 mmol), 310 mg of *N*-(6-bromohexyl) phthalimide (1.5 mmol), 60.2 mg of 30 % w/w KH in mineral oil (1.50 mmol), 396 mg of 18-crown-6 in a total of 6 mL of THF. Purification by MPLC chromatography (1:5 EtOAc:hexanes) afforded **5.1h** as a yellow oil (50 mg, 12% yield):  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.84 – 7.82 (m, 2H), 7.70 – 7.69 (m, 2H), 7.59 (d,  $J$  = 8.0 Hz, 1H), 7.28 (d,  $J$  = 8.5 Hz, 1H), 7.19 (t,  $J$  = 7.5 Hz, 1H), 7.10 (t,  $J$  = 7.5 Hz, 1H), 7.07 (s, 1H), 4.06 (t,  $J$  = 7.0 Hz, 2H), 3.76 (s, 2H), 3.69 (s, 3H), 3.66 (t,  $J$  = 7.0 Hz, 2H), 1.83 – 1.81 (m, 2H), 1.69 – 1.65 (m, 2H), 1.39 – 1.35 (m, 4H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  172.6 (C), 168.4 (C), 136.2 (C), 133.9 (CH), 132.1 (C), 127.8 (C), 126.7 (CH), 123.2 (CH), 121.6 (CH), 119.1 (CH), 119.0 (CH), 109.4 (CH), 106.8 (C), 51.9 ( $\text{CH}_3$ ), 46.2 ( $\text{CH}_2$ ), 37.8 ( $\text{CH}_2$ ), 31.1 ( $\text{CH}_2$ ), 30.1 ( $\text{CH}_2$ ), 28.5 ( $\text{CH}_2$ ), 26.6 ( $\text{CH}_2$ ), 26.5 ( $\text{CH}_2$ ).



### 5.1j



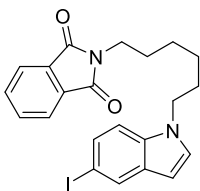
***N*-(6-Indolehexyl)-phthalimide 5.1j.** The general procedure was followed using 386 mg of indole (2.00 mmol), 620 mg of *N*-(6-bromohexyl) phthalimide (3.00 mmol), 120 mg of 30 % w/w KH in mineral oil (3.00 mmol), 792 mg of 18-crown-6 in a total of 12 mL of THF. Purification by MPLC chromatography (1:5 EtOAc:hexanes) afforded **5.1j** as a yellow oil (676 mg, 80% yield):  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.85 – 7.82 (m, 2H), 7.73 – 7.68 (m, 2H), 7.68 – 7.66 (m, 1H), 7.62 (t,  $J$  = 7.8 Hz, 1H), 7.49 – 7.43 (m, 3H), 7.40 – 7.32 (m, 2H), 7.23 – 7.17 (m, 1H), 7.12 (t,  $J$  = 7.5 Hz, 1H), 6.50 (s, 1H), 4.14 – 4.11 (m, 1H), 3.68 (q,  $J$  = 6.9 Hz, 1H), 3.58 (t,  $J$  = 7.3 Hz, 1H), 3.39 (t,  $J$  = 6.8 Hz, 1H), 1.91 – 1.81 (m, 1H), 1.74 – 1.65 (m, 2H), 1.56 – 1.45 (m, 2H), 1.43 – 1.34 (m, 1H), 1.17 (dd,  $J$  = 15.2, 11.7 Hz, 2H). This phthalimide was taken to the next step without any further purification or characterization.



### 5.1k

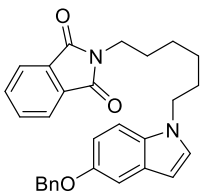
***N*-(6-indolehexyl)-phthalimide 5.1k.** The general procedure was followed using 237 mg of indole (2.00 mmol), 620 mg of *N*-(6-bromohexyl) phthalimide (3.00 mmol), 120 mg of 30 % w/w KH in mineral oil (3.00 mmol), 792 mg of 18-crown-6 in a total of 12 mL of THF. Purification by MPLC chromatography (1:5 EtOAc:hexanes) afforded **5.1k** as a yellow oil (382 mg, 55% yield):  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.13 (dd,  $J$  = 4.6, 1.1 Hz, 1H), 7.69 (dd,  $J$  = 7.8, 1.2 Hz, 1H), 7.60 (dt,  $J$  = 6.8, 3.4 Hz, 2H), 7.50 – 7.40 (m, 2H), 7.03 (d,  $J$  = 3.4 Hz, 1H), 6.84 (dd,  $J$  = 7.8, 4.7 Hz, 1H), 6.24 (d,  $J$  = 3.4 Hz, 1H), 4.09 (t,  $J$  = 7.2 Hz, 2H), 3.53 – 3.33 (m, 2H), 1.70 (dd,  $J$  = 18.1, 11.3 Hz, 2H), 1.56 – 1.38 (m, 2H), 1.20 (s, 4H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  168.1 (C), 147.3 (C), 142.5 (CH),

133.6 (CH), 132.0 (C), 128.5 (CH), 127.8 (CH), 122.9 (CH), 120.4 (C), 115.4 (CH), 99.2 (CH), 44.3 (CH<sub>2</sub>), 37.7 (CH<sub>2</sub>), 30.1 (CH<sub>2</sub>), 28.3 (CH<sub>2</sub>), 26.34 (CH<sub>2</sub>), 26.29 (CH<sub>2</sub>).



### 5.11

***N*-(6-Indolehexyl)-phthalimide 5.11.** The general procedure was followed using 486 mg of indole (2.00 mmol), 620 mg of *N*-(6-bromohexyl) phthalimide (3.00 mmol), 120 mg of 30 % w/w KH in mineral oil (3.00 mmol), 792 mg of 18-crown-6 in a total of 12 mL of THF. Purification by MPLC chromatography (1:5 EtOAc:hexanes) afforded **5.11** as a yellow oil (737 mg, 78% yield): <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.89 (d, *J* = 1.2 Hz, 1H), 7.79 (dd, *J* = 5.3, 3.1 Hz, 2H), 7.66 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.37 (dd, *J* = 8.6, 1.4 Hz, 1H), 7.06 (d, *J* = 8.6 Hz, 1H), 7.00 (d, *J* = 3.1 Hz, 1H), 6.35 (d, *J* = 3.0 Hz, 1H), 4.02 (t, *J* = 7.1 Hz, 2H), 3.63 (t, *J* = 7.2 Hz, 2H), 1.82 – 1.69 (m, 2H), 1.67 – 1.54 (m, 2H), 1.39 – 1.27 (m, 4H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 168.4 (C), 135.0 (C), 133.9 (CH), 132.1 (C), 131.1 (C), 129.7 (CH), 129.6 (CH), 128.6 (CH), 123.2 (CH), 111.4 (CH), 100.4 (CH), 82.7 (C), 46.4 (CH<sub>2</sub>), 37.8 (CH<sub>2</sub>), 30.0 (CH<sub>2</sub>), 28.4 (CH<sub>2</sub>), 26.5 (CH<sub>2</sub>), 26.4 (CH<sub>2</sub>).

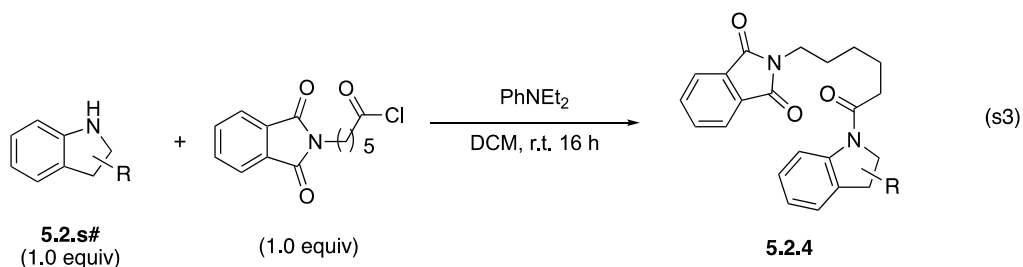


### 5.1m

***N*-(6-Indolehexyl)-phthalimide **5.1m**.** The general procedure was followed using 447 mg of indole (2.00 mmol), 620 mg of *N*-(6-bromohexyl) phthalimide (3.00 mmol), 120 mg of 30 % w/w KH in mineral oil (3.00 mmol), 792 mg of 18-crown-6 in a total of 12 mL of THF. Purification by MPLC chromatography (1:5 EtOAc:hexanes) afforded **5.1m** as a yellow oil (842 mg, 93% yield): <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.73 (dd, *J* = 5.0, 3.0 Hz, 2H), 7.53 (dd, *J* = 5.0, 3.0 Hz, 2H), 7.48 (d, *J* = 7.4 Hz, 2H), 7.36 (t, *J* = 7.4 Hz, 2H), 7.29 (t, *J* = 7.2 Hz, 1H), 7.20 (d, *J* = 8.9 Hz, 2H), 7.03 (d, *J* = 2.6 Hz, 1H), 6.97 (dd, *J* = 8.7, 1.6 Hz, 1H), 6.40 (d, *J* = 2.5 Hz, 1H), 5.07 (s, 2H), 3.95 (t, *J* = 6.8 Hz, 2H), 3.62 (t, *J* = 7.1 Hz, 2H), 1.71 (dd, *J* = 21.2, 15.0 Hz, 2H), 1.66 – 1.50 (m, 2H), 1.28 (d, *J* = 12.8 Hz, 4H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 168.2 (C), 153.2 (C), 138.0 (C), 133.8 (C), 132.1 (CH), 131.6 (C), 129.0 (C), 128.5 (CH), 128.4 (CH), 127.7 (CH), 127.6 (CH), 123.0 (CH), 112.4 (CH), 110.2 (CH), 104.2 (CH), 100.7 (CH), 70.7 (CH<sub>2</sub>), 60.3 (CH<sub>2</sub>), 46.3 (CH<sub>2</sub>), 37.8 (CH<sub>2</sub>), 30.2 (CH<sub>2</sub>), 28.5 (CH<sub>2</sub>), 26.5 (CH<sub>2</sub>). ATR-FTIR (thin film): 2933, 2858, 1770, 1705, 1486, 1395, 1233, 1151, 1056, 717cm<sup>-1</sup>. HRMS (ESI) *m/z* calcd for C<sub>29</sub>H<sub>29</sub>N<sub>2</sub>O<sub>3</sub> [M + H]<sup>+</sup> : 453.2178, found: 453.2175.

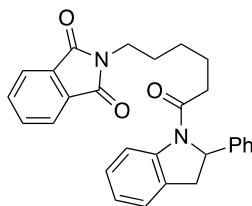
## B. Synthesis of 2-(6-(indolin-1-yl)-6-oxohexyl)phthalimide. (Route B).

a) General procedure.



The synthesis of 2-(6-(indolin-1-yl)-6-oxohexyl)phthalimide **5.4** was performed following the report of Krasnov and co-workers:<sup>36</sup> To a stirred solution of aniline (1.0 equiv) and *N,N*-diethylaniline (1.0 equiv) in 0.2 M dry CH<sub>2</sub>Cl<sub>2</sub> was added a 0.2 M solution of acid chloride (1.0 equiv) in dry CH<sub>2</sub>Cl<sub>2</sub> dropwise over 10 min. After stirring at room temperature for 16 h, a 1.0 N aq soln of HCl was added to the reaction mixture. After 30 min, the reactives were diluted with 20 mL of EtOAc and washed with 2 × 20 mL of water and 20 mL of a 5% aq soln of NaHCO<sub>3</sub>. The resulting organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and the filtrate was concentrated *in vacuo*. The resulting residue was purified by MPLC to afford the product.

b) Characterization data of 2-(6-(indolin-1-yl)-6-oxohexyl)phthalimides **5.4**.



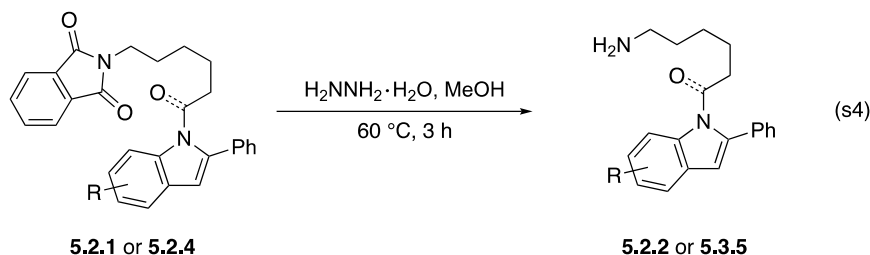
**5.4c**

**2-(6-(Indolin-1-yl)-6-oxohexyl)phthalimide 5.4c.** The general procedure was followed using 195.2 mg of 2-phenylindoline (1.0 mmol), 149.2 mg of *N,N*-diethylaniline (1.0 mmol) and 279.7 mg of acid chloride (1.0 mmol) in a total 4 mL of CH<sub>2</sub>Cl<sub>2</sub>. Purification by MPLC chromatography (5:1 – 2:1 hexanes:EtOAc) afforded **5.4b** as a yellow oil (200 mg, 46% yield): <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.32 (d, *J* = 8.0 Hz, 1H), 7.83 – 7.81 (m, 2H), 7.71 – 7.69 (m, 2H), 7.28 – 7.19 (m, 4H), 7.15 – 7.11 (m, 3H), 7.03 (t, *J* = 7.0 Hz, 1H), 5.41 (d, *J* = 10.0 Hz, 1H), 3.81 – 3.75 (m, 1H), 3.61

(t,  $J = 7.0$  Hz, 2H), 2.96 (d,  $J = 16.0$  Hz, 1H), 2.40 – 2.35 (m, 1H), 2.10 – 2.04 (m, 1H), 1.71 – 1.55 (m, 4H), 1.27 – 1.23 (m, 2H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  171.9 (C), 168.4 (C), 143.5 (C), 143.3 (C), 133.9 (CH), 132.2 (C), 129.1 (CH), 127.7 (CH), 125.0 (CH), 124.8 (CH), 124.0 (CH), 123.1 (CH), 117.0 (CH), 62.7 (CH), 38.9 ( $\text{CH}_2$ ), 37.8 ( $\text{CH}_2$ ), 35.3 ( $\text{CH}_2$ ), 28.3 ( $\text{CH}_2$ ), 26.4 ( $\text{CH}_2$ ), 24.3 ( $\text{CH}_2$ ); only visible signals. ATR-FTIR (thin film): 3030, 2944, 2862, 1771, 1705, 1656, 1393, 1267, 1046, 734  $\text{cm}^{-1}$ . HRMS (ESI)  $m/z$  calcd for  $\text{C}_{28}\text{H}_{27}\text{N}_2\text{O}_3$   $[\text{M} + \text{H}]^+$ : 439.2022, found: 439.2011.

### C. Synthesis of *N*-(6-indolehexyl)-amine and 6-amino-1-(indolin-1-yl)hexan-1-one.

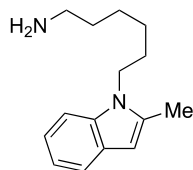
a) General procedure.



To a solution of *N*-(6-indolehexyl)-phthalimide **5.1** (1.0 equiv) *or* 2-(6-(indolin-1-yl)-6-oxohexyl)phthalimide **5.4** (1.0 equiv) in 0.1 M MeOH was added a solution of hydrazine hydrate ( $\text{N}_2\text{H}_4 \cdot \text{H}_2\text{O}$ , 5.0 equiv). The resulting reaction mixture was heated to reflux at 60 °C for 4 h with monitoring the reaction progress by thin layer chromatography (TLC). After complete consumption of the starting materials, the reaction was cooled to room temperature and 20 mL of a 1 N aq soln of NaOH was added. The resulting mixture was then diluted and extracted by 3 × 20 mL of DCM. After additional washes with 2 × 20 mL of a 1 N aq soln of NaOH and 2 × 20 mL of water, the organic phase was dried over  $\text{Na}_2\text{SO}_4$ , filtered and the filtrate was concentrated *in vacuo*.

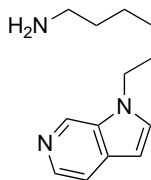
The amine product was used in the subsequent coupling reaction without additional characterization or purification.

b) Characterization data of 2-(6-(indolin-1-yl)-6-oxohexyl)phthalimides **5.2 or 5.5**.



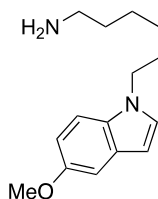
**5.2a**

**N-(6-Indolehexyl)-amine 5.2a.** The general procedure was followed using 36.0 mg of **5.1a** (0.10 mmol), 25.0 mg of hydrazine hydrate (0.5 mmol) in 1.0 mL of MeOH. The crude product **5.2a** was afforded as a yellow gel (23 mg, quant. yield): <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.51 (d, *J* = 8.0 Hz, 1H), 7.27 – 7.25 (m, 1H), 7.15 – 7.11 (m, 1H), 7.05 (t, *J* = 7.5 Hz, 1H), 6.23 (s, 1H), 4.05 (t, *J* = 7.5 Hz, 2H), 2.88 (s, 2H), 2.70 (t, *J* = 7.5 Hz, 2H), 2.42 (s, 3H), 1.75 (quin, *J* = 7.0 Hz, 2H), 1.48 (quin, *J* = 7.0 Hz, 2H), 1.39 – 1.35 (m, 4H). The amine product was used in the subsequent coupling reaction without additional purification or characterization.



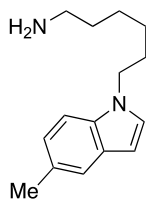
**5.2b**

***N*-(6-Indolehexyl)-amine 5.2b.** The general procedure was followed using 34.7 mg of **5.1b** (0.10 mmol), 25.0 mg of hydrazine hydrate (0.5 mmol) in 1.0 mL of MeOH. The crude product **5.2a** was afforded as a yellow gel (21 mg, quant. yield):  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.74 (s, 1H), 8.19 (d,  $J = 5.5$  Hz, 1H), 7.47 (dd,  $J = 5.5$  Hz, 1.0 Hz, 1H), 7.18 (d,  $J = 3.0$  Hz, 1H), 6.44 (d,  $J = 3.0$  Hz, 1H), 4.16 (t,  $J = 7.0$  Hz, 2H), 2.61 (t,  $J = 7.0$  Hz, 2H), 1.84 (quin,  $J = 7.0$  Hz, 2H), 1.45 – 1.23 (m, 8H). The amine product was used in the subsequent coupling reaction without additional purification or characterization.



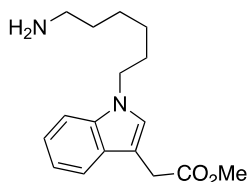
**5.2f**

***N*-(6-Indolehexyl)-amine 5.2f.** The general procedure was followed using 188 mg of **5.1f** (0.50 mmol), 125 mg of hydrazine hydrate (2.50 mmol) in 5 mL of MeOH. Purification by MPLC chromatography (1:5  $\text{Et}_3\text{N}$ :DCM) afforded **5.2f** as a yellow gel (100 mg, 81% yield):  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.21 (d,  $J = 9.0$  Hz, 1H), 7.07 (dd,  $J = 17.0, 2.0$  Hz, 2H), 6.86 (dd,  $J = 9.0, 2.0$  Hz, 1H), 6.39 (d,  $J = 2.5$  Hz, 1H), 4.06 (t,  $J = 7.0$  Hz, 2H), 3.84 (s, 3H), 1.84 – 1.79 (m, 2H), 1.43 – 1.39 (m, 4H), 1.32 – 1.26 (m, 4H). IR (thin film): 3367, 2932, 2857, 1668, 1621, 1488, 1450, 1237, 1150, 1031, 801, 720  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calculated for  $\text{C}_{15}\text{H}_{23}\text{N}_2\text{O}$  ( $\text{M}+\text{H}$ ) $^+$ : 247.1810, found: 247.1801. The amine product was used in the subsequent coupling reaction without additional purification or characterization.



**5.2g**

***N*-(6-Indolehexyl)-amine 5.2g.** The general procedure was followed using 188 mg of **5.1g** (0.500 mmol), 125 mg of hydrazine hydrate (2.50 mmol) in 5 mL of MeOH. Purification by MPLC chromatography (1:5 Et<sub>3</sub>N:DCM) afforded **5.2g** as a yellow gel (110 mg, 96% yield): <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.42 (s, 1H), 7.23 (d, *J* = 8.5 Hz, 1H), 7.05 – 7.02 (m, 2H), 6.39 (d, *J* = 2.5 Hz, 1H), 4.08 (t, *J* = 7.5 Hz, 2H), 2.46 (s, 3H), 1.83 (quintet, *J* = 7.0 Hz, 2H), 1.42 – 1.32 (m, 8H). IR (thin film): 3236, 2930, 2858, 1668, 1489, 1455, 1396, 1333, 1298, 791, 759, 718 cm<sup>-1</sup>; HRMS (ESI) *m/z* calculated for C<sub>15</sub>H<sub>23</sub>N<sub>2</sub> (M+H)<sup>+</sup>: 231.1861, found: 231.1856. The amine product was used in the subsequent coupling reaction without additional purification or characterization.

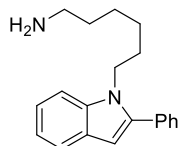


**5.2h**

***N*-(6-Indolehexyl)-amine 5.2h.** The general procedure was followed using 42.0 mg of **5.1h** (0.100 mmol), 25.0 mg of hydrazine hydrate (0.500 mmol) in 1.0 mL of MeOH. The crude product **5.2h** was afforded as a yellow gel (29 mg, 100% yield). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.60 (d, *J* = 8.0 Hz, 1H), 7.30 (d, *J* = 8.5 Hz, 1H), 7.21 (t, *J* = 7.5 Hz, 1H), 7.12 (t, *J* = 7.5 Hz, 1H), 7.08 (s, 1H), 4.06 (t, *J* = 7.0 Hz, 2H), 3.76 (s, 2H), 3.69 (s, 3H), 3.66 (t, *J* = 7.0 Hz, 2H), 1.83 – 1.81 (m, 2H),

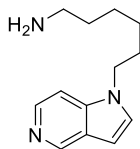


1.40 – 1.33 (m, 8H). The amine product was used in the subsequent coupling reaction without additional purification or characterization.



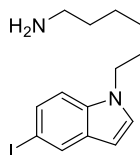
**5.2j**

***N*-(6-Indolehexyl)-amine 5.2j.** The general procedure was followed using 156 mg of **5.1j** (0.37 mmol), 93.0 mg of hydrazine hydrate (1.85 mmol) in 4.0 mL of MeOH. Purification by MPLC chromatography (1:5 MeOH:DCM) afforded **5.2j** as a yellow gel (105 mg, 97 % yield):  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.63 (t,  $J = 9.1$  Hz, 1H), 7.53 – 7.44 (m, 4H), 7.44 – 7.33 (m, 2H), 7.30 – 7.18 (m, 1H), 7.14 (dd,  $J = 9.5, 5.3$  Hz, 1H), 6.53 (d,  $J = 2.9$  Hz, 1H), 4.14 (dd,  $J = 13.7, 6.2$  Hz, 2H), 2.62 (t,  $J = 7.0$  Hz, 2H), 1.73 – 1.62 (m, 2H), 1.44 – 1.27 (m, 2H), 1.22 – 1.07 (m, 4H). The amine product was used in the subsequent coupling reaction without additional purification or characterization.



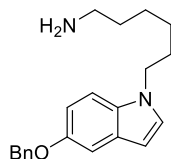
**5.2k**

***N*-(6-Indolehexyl)-amine 5.2k.** The general procedure was followed using 102 mg of **5.1k** (0.370 mmol), 93.0 mg of hydrazine hydrate (1.85 mmol) in 4.0 mL of MeOH. Purification by MPLC chromatography (1:5 MeOH:DCM) afforded **5.2k** as a yellow gel (15.3 mg, 19 % yield):  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.28 (d,  $J = 3.8$  Hz, 1H), 7.85 (d,  $J = 7.7$  Hz, 1H), 7.17 (d,  $J = 2.5$  Hz, 1H), 7.00 (dd,  $J = 7.2, 4.8$  Hz, 1H), 6.40 (d,  $J = 2.7$  Hz, 1H), 4.24 (t,  $J = 6.9$  Hz, 2H), 3.55 (br s, 2H), 2.66 (t,  $J = 6.4$  Hz, 2H), 1.85 – 1.81 (m, 2H), 1.43 (d,  $J = 6.5$  Hz, 2H), 1.31 (s, 4H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  147.4 (C), 142.6 (CH), 128.7 (CH), 127.9 (CH), 120.6 (C), 115.5 (CH), 99.3 (CH), 44.4 ( $\text{CH}_2$ ), 41.4 ( $\text{CH}_2$ ), 32.1 ( $\text{CH}_2$ ), 30.3 ( $\text{CH}_2$ ), 26.6 ( $\text{CH}_2$ ), 26.4 ( $\text{CH}_2$ ). The amine product was used in the subsequent coupling reaction without additional purification or characterization.



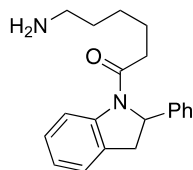
### 5.2l

***N*-(6-Indolehexyl)-amine 5.2l.** The general procedure was followed using 127 mg of **5.1l** (0.370 mmol), 93.0 mg of hydrazine hydrate (1.85 mmol) in 4.0 mL of MeOH. Purification by MPLC chromatography (1:5 MeOH:DCM) afforded **5.2l** as a yellow gel (97 mg, 77 % yield):  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.93 (s, 1H), 7.40 (d,  $J = 8.6$  Hz, 1H), 7.06 (d,  $J = 8.6$  Hz, 1H), 6.99 (d,  $J = 2.6$  Hz, 1H), 6.37 (d,  $J = 2.5$  Hz, 1H), 4.00 (t,  $J = 7.0$  Hz, 2H), 2.62 (s, 2H), 1.75 (dt,  $J = 13.6, 6.9$  Hz, 4H), 1.36 (d,  $J = 6.5$  Hz, 2H), 1.25 (d,  $J = 10.0$  Hz, 4H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  135.1 (C), 131.2 (C), 129.7 (CH), 129.6 (CH), 128.7 (C), 111.5 (CH), 100.3 (CH), 82.7 (C), 46.4 ( $\text{CH}_2$ ), 41.9 ( $\text{CH}_2$ ), 33.4 ( $\text{CH}_2$ ), 30.2 ( $\text{CH}_2$ ), 26.8 ( $\text{CH}_2$ ), 26.5 ( $\text{CH}_2$ ). The amine product was used in the subsequent coupling reaction without additional purification or characterization.



**5.2m**

***N*-(6-Indolehexyl)-amine 5.2m.** The general procedure was followed using 167 mg of **5.1m** (0.37 mmol), 93.0 mg of hydrazine hydrate (1.85 mmol) in 4.0 mL of MeOH. Purification by MPLC chromatography (1:5 MeOH:DCM) afforded **5.2m** as a yellow gel (78 mg, 65 % yield):  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.53 (d,  $J = 7.4$  Hz, 2H), 7.43 (t,  $J = 7.4$  Hz, 2H), 7.37 (d,  $J = 7.2$  Hz, 1H), 7.27 (d,  $J = 11.0$  Hz, 2H), 7.08 (d,  $J = 2.3$  Hz, 1H), 7.04 (d,  $J = 8.7$  Hz, 1H), 6.47 (d,  $J = 1.9$  Hz, 1H), 5.13 (s, 2H), 4.03 (t,  $J = 6.9$  Hz, 2H), 2.65 (t,  $J = 6.5$  Hz, 2H), 1.91 – 1.72 (m, 2H), 1.40 (d,  $J = 6.3$  Hz, 2H), 1.37 – 1.25 (m, 4H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  153.2 (C), 138.0 (C), 131.6 (C), 129.0 (C), 128.6 (C), 128.5 (CH), 127.8 (CH), 127.6 (CH), 112.5 (CH), 110.2 (CH), 104.2 (CH), 100.6 (CH), 70.89 ( $\text{CH}_2$ ), 46.5 ( $\text{CH}_2$ ), 42.2 ( $\text{CH}_2$ ), 33.7 ( $\text{CH}_2$ ), 30.4 ( $\text{CH}_2$ ), 26.9 ( $\text{CH}_2$ ), 26.6 ( $\text{CH}_2$ ). The amine product was used in the subsequent coupling reaction without additional purification or characterization.

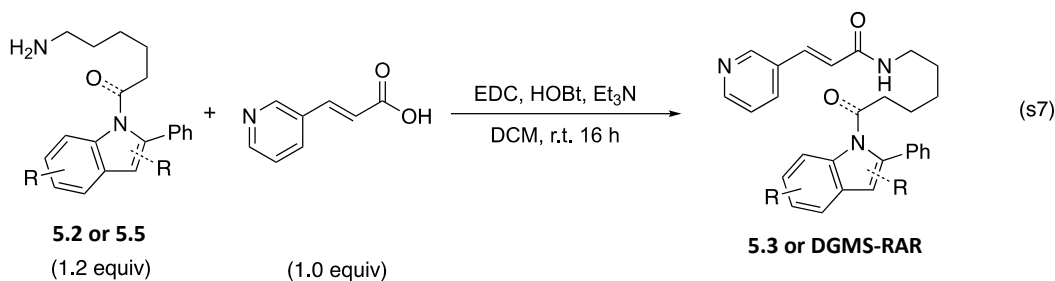


**5.5c**

**6-Amino-1-(indolin-1-yl)hexan-1-one 5.5c.** The general procedure was followed using 43.8 mg of **5.4c** (0.10 mmol), 25.0 mg of hydrazine hydrate (0.5 mmol) in 1.0 mL of MeOH. The crude product **5.5c** was afforded as a yellow gel (30 mg, quant. yield):  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.34 (d,  $J$  = 8.0 Hz, 1H), 7.28 – 7.23 (m, 4H), 7.15 – 7.10 (m, 3H), 7.04 – 7.01 (m, 1H), 5.40 (d,  $J$  = 10.0 Hz, 1H), 3.78 – 3.73 (m, 1H), 2.95 (d,  $J$  = 16.0 Hz, 1H), 2.60 (s, 2H), 2.41 – 2.35 (m, 1H), 2.11 – 2.04 (m, 1H), 1.65 – 1.50 (m, 2H), 1.32 – 1.20 (m, 6H). The amine product was used in the subsequent coupling reaction without additional purification or characterization.

#### D. Synthesis of acrylamide analogues.

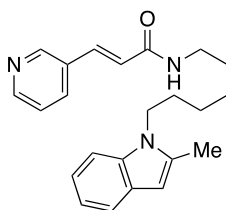
a) General procedure.



To a solution of *trans*-3-(3-pyridyl) acrylic acid (1.0 equiv) in 0.1 M dry  $\text{CH}_2\text{Cl}_2$  was added *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (EDC, 2.0 equiv), 1-hydroxybenzotriazole hydrate (HOBt, 1.5 equiv), and triethylamine (1.5 equiv) sequentially. After stirring at room temperature for 5 min, a solution of amine **5.2** (1.2 equiv) or **5.5** (1.2 equiv) in DCM was added slowly to the reaction mixture. The reaction was allowed to stir at room temperature for overnight. After complete consumption of the starting materials indicated by thin

layer chromatography (TLC), the reactives were quenched by the addition of 10 mL of a saturated NaHCO<sub>3</sub> aqueous solution. The reaction mixture was then washed with 2 × 20 mL water and extracted with 2 × 20 mL of CH<sub>2</sub>Cl<sub>2</sub>. The combined organic phases were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and the filtrate was concentrated *in vacuo*. The crude product was purified by MPLC.

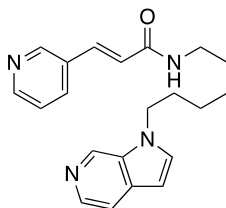
b) Characterization data.



**5.3a**

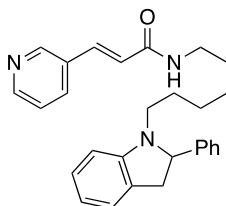
**(*E*)-N-(6-(1*H*-Indol-1-yl)hexyl)-3-(pyridin-3-yl)acrylamide 5.3a.** The general procedure was followed using 46.1 mg of **5.2a** (0.20 mmol), 25.0 mg of *trans*-3-(3-pyridyl) acrylic acid (0.170 mmol), 65.1 mg of EDC•HCl (0.34 mmol), 35.1 mg of HOBt (0.26 mmol), and 26.3 mg of Et<sub>3</sub>N (0.26 mmol) in 4 mL of CH<sub>2</sub>Cl<sub>2</sub>. Purification by MPLC chromatography (2:98 MeOH:CH<sub>2</sub>Cl<sub>2</sub>) afforded **5.3a** as a yellow gel (40 mg, 65%): <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.72 (d, *J* = 2.0 Hz, 1H), 8.55 (d, *J* = 5.0 Hz, 1H), 7.75 (td, *J* = 4.0 Hz, 2.0 Hz, 1H), 7.58 (d, *J* = 15.5 Hz, 1H), 7.52 (d, *J* = 7.5 Hz, 1H), 7.29 – 7.24 (m, 2H), 7.12 (t, *J* = 7.5 Hz, 1H), 7.05 (t, *J* = 7.5 Hz, 1H), 6.41 (d, *J* = 15.5 Hz, 1H), 6.23 (s, 1H), 5.84 (t, *J* = 6.0 Hz, 1H), 4.04 (t, *J* = 7.5 Hz, 2H), 3.33 (quin, *J* = 7.0 Hz, 2H), 2.41 (s, 3H), 1.74 (quin, *J* = 7.5 Hz, 2H), 1.52 (quin, *J* = 7.0 Hz, 2H), 1.40 – 1.30 (m, 4H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 165.1 (C), 150.3 (CH), 149.1 (CH), 137.2 (CH), 136.6 (C), 136.4 (C), 134.4 (CH), 130.7 (C), 128.1 (C), 123.7 (CH), 122.9 (CH), 120.3 (CH), 119.7 (CH), 119.2 (CH), 109.0 (CH), 99.9 (CH), 43.1 (CH<sub>2</sub>), 39.7 (CH<sub>2</sub>), 30.1 (CH<sub>2</sub>), 29.5 (CH<sub>2</sub>), 26.8 (CH<sub>2</sub>),

26.7 (CH<sub>2</sub>), 12.9 (CH<sub>3</sub>). ATR-FTIR (thin film): 3417, 3000, 2915, 1660, 1436, 1385, 1016, 952 701 cm<sup>-1</sup>. HRMS (ESI) m/z calcd for C<sub>23</sub>H<sub>28</sub>N<sub>3</sub>O [M + H]<sup>+</sup>: 362.2232, found: 362.2231.



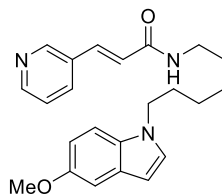
**5.3b**

**(E)-N-(6-(1H-indol-1-yl)hexyl)-3-(pyridin-3-yl)acrylamide 5.3b.** The general procedure was followed using 43.5 mg of **5.2a** (0.2 mmol), 25.0 mg of *trans*-3-(3-pyridyl) acrylic acid (0.17 mmol), 65.1 mg of EDC•HCl (0.34 mmol), 35.1 mg of HOBt (0.26 mmol), and 26.3 mg of Et<sub>3</sub>N (0.26 mmol) in 4 mL of CH<sub>2</sub>Cl<sub>2</sub>. Purification by MPLC chromatography (2:98 MeOH:CH<sub>2</sub>Cl<sub>2</sub>) afforded **5.3b** as a yellow gel (44 mg, 74%): <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.73 (s, 1H), 8.67 (s, 1H), 8.50 (d, *J* = 5.0 Hz, 1H), 8.20 (d, *J* = 5.5 Hz, 1H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.57 (d, *J* = 15.5 Hz, 1H), 7.49 (d, *J* = 5.5 Hz, 1H), 7.25 – 7.22 (m, 1H), 7.19 (d, *J* = 2.5 Hz, 1H), 6.64 (t, *J* = 5.5 Hz, 1H), 6.49 (d, *J* = 15.5 Hz, 1H), 6.46 (d, *J* = 2.5 Hz, 1H), 4.16 (t, *J* = 7.0 Hz, 2H), 3.33 (q, *J* = 7.0 Hz, 2H), 1.82 (quin, *J* = 7.5 Hz, 2H), 1.51 (quin, *J* = 7.0 Hz, 2H), 1.37 – 1.25 (m, 4H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 165.3 (C), 150.2 (CH), 149.1 (CH), 138.2 (CH), 136.9 (CH), 134.3 (CH), 133.3 (C), 133.1 (C), 132.6 (CH), 131.6 (CH), 130.8 (C), 123.7 (CH), 123.1 (CH), 115.5 (CH), 100.6 (CH), 46.7 (CH<sub>2</sub>), 39.6 (CH<sub>2</sub>), 30.3 (CH<sub>2</sub>), 29.5 (CH<sub>2</sub>), 26.5 (CH<sub>2</sub>), 26.5 (CH<sub>2</sub>); ATR-FTIR (thin film): 3418, 3000, 2914, 1651, 1436, 1407, 1313, 1017, 952, 701 cm<sup>-1</sup>. HRMS (ESI) m/z calcd for C<sub>21</sub>H<sub>25</sub>N<sub>4</sub>O [M + H]<sup>+</sup>: 349.2028, found: 349.2020.



### 5.3e (DGMS-RAR-7)

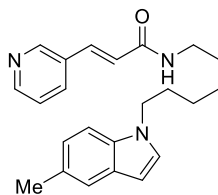
**(E)-N-(6-(1H-Indol-1-yl)hexyl)-3-(pyridin-3-yl)acrylamide 5.3e (DGMS-RAR-7).** The general procedure was followed using 58.9 mg of **5.2e** (0.2 mmol), 25.0 mg of *trans*-3-(3-pyridyl) acrylic acid (0.17 mmol), 65.1 mg of EDC.HCl (0.34 mmol), 35.1 mg of HOBt (0.26 mmol), and 26.3 mg of Et<sub>3</sub>N (0.26 mmol) in 4 mL of DCM. Purification by MPLC chromatography (2% MeOH in DCM) afforded **DGMS-RAR-7** as a yellow gel (38 mg, 52% yield). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.73 (d, *J* = 2.5 Hz, 1H), 8.56 (dd, *J* = 4.5 Hz, 1.5 Hz, 1H), 7.76 (td, *J* = 4.0 Hz, 2.0 Hz, 1H), 7.60 (d, *J* = 16.0 Hz, 1H), 7.41 – 7.39 (m, 2H), 7.34 (t, *J* = 7.5 Hz, 2H), 7.30 – 7.28 (m, 2H), 7.10 (t, *J* = 8.0 Hz, 1H), 7.03 (d, *J* = 7.0 Hz, 1H), 6.66 (t, *J* = 7.5 Hz, 1H), 6.46 (s, 1H), 6.43 (d, *J* = 7.5 Hz, 1H), 5.82 (t, *J* = 6.0 Hz, 1H), 4.62 (t, *J* = 9.5 Hz, 1H), 3.36 – 3.31 (m, 3H), 3.07 (quin, *J* = 7.5 Hz, 1H), 2.95 – 2.86 (m, 2H), 1.52 – 1.42 (m, 4H), 1.30 – 1.20 (m, 4H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 165.1 (C), 152.3 (C), 150.3 (CH), 149.1 (CH), 143.1 (C), 137.3 (CH), 134.4 (CH), 130.7 (C), 128.5 (CH), 128.2 (C), 127.6 (CH), 127.6 (CH), 127.4 (CH), 124.1 (CH), 123.7 (CH), 122.9 (CH), 117.2 (CH), 106.3 (CH), 69.0 (CH), 46.5 (CH<sub>2</sub>), 39.8 (CH<sub>2</sub>), 39.6 (CH<sub>2</sub>), 29.5 (CH<sub>2</sub>), 26.9 (CH<sub>2</sub>), 26.7 (CH<sub>2</sub>), 26.1 (CH<sub>2</sub>); ATR-FTIR (thin film): 3265, 3054, 2992, 2928, 2856, 1667, 1625, 1548, 1023, 767 cm<sup>-1</sup>. HRMS (ESI) *m/z* calcd for C<sub>28</sub>H<sub>30</sub>N<sub>3</sub>O [M + H]<sup>+</sup>: 424.2389, found: 424.2388.



### 5.3f

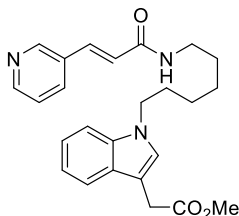
**(E)-N-(6-(1H-Indol-1-yl)hexyl)-3-(pyridin-3-yl)acrylamide 5.3f.** The general procedure was followed using 49.3 mg of **5.2f** (0.200 mmol), 25.0 mg of *trans*-3-(3-pyridyl) acrylic acid (0.170 mmol), 76.7 mg of EDC•HCl (0.400 mmol), 40.5 mg of HOBt (0.300 mmol), and 30.4 mg of Et<sub>3</sub>N (0.300 mmol) 4 mL of DCM. Purification by MPLC chromatography (2% MeOH in DCM) afforded **5.3f** as a yellow gel (63 mg, 100% yield): <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.72 (d, *J* = 1.5 Hz, 1H), 8.55 (dd, *J* = 4.5, 1.0 Hz, 1H), 7.75 (dt, *J* = 7.5, 1.5 Hz, 1H), 7.59 (d, *J* = 16.0 Hz, 1H), 7.28 (dd, *J* = 8.0, 5.0 Hz, 1H), 7.21 (d, *J* = 9.0 Hz, 1H), 7.09 (d, *J* = 2.0 Hz, 1H), 7.05 (d, *J* = 3.0 Hz, 1H), 6.86 (dd, *J* = 9.0, 2.0 Hz, 1H), 6.43 – 6.39 (m, 2H), 5.79 (t, *J* = 5.5 Hz, 1H), 4.07 (t, *J* = 7.0 Hz, 2H), 3.84 (s, 3H), 3.32 (q, *J* = 7.0 Hz, 2H), 1.81 (quintet, *J* = 7.0 Hz, 2H), 1.51 (quintet, *J* = 7.0 Hz, 2H), 1.37 – 1.30 (m, 4H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 165.1 (C), 153.9 (C), 150.4 (CH), 149.2 (CH), 137.3 (CH), 134.4 (CH), 131.3 (C), 130.7 (C), 128.9 (C), 128.4 (CH), 123.7 (CH), 122.8 (CH), 111.8 (CH), 110.1 (CH), 102.6 (CH), 100.4 (CH), 55.9 (CH<sub>3</sub>), 46.5 (CH<sub>2</sub>), 39.6 (CH<sub>2</sub>), 30.1 (CH<sub>2</sub>), 29.5 (CH<sub>2</sub>), 26.7 (CH<sub>2</sub>), 26.6 (CH<sub>2</sub>). IR (thin film): 3444, 2996, 2912, 1662, 1436, 1406, 1310, 1042, 952, 697, 667 cm<sup>-1</sup>; HRMS (ESI) *m/z* calculated for C<sub>23</sub>H<sub>28</sub>N<sub>3</sub>O<sub>2</sub> (M+H)<sup>+</sup>: 380.2338, found: 380.2337.





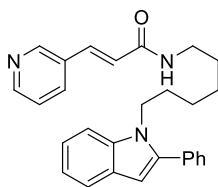
### 5.3g

**(E)-N-(6-(1H-indol-1-yl)hexyl)-3-(pyridin-3-yl)acrylamide 5.3g.** The general procedure was followed using 46.1 mg of **5.2g** (0.200 mmol), 25.0 mg of *trans*-3-(3-pyridyl) acrylic acid (0.170 mmol), 76.7 mg of EDC•HCl (0.400 mmol), 40.5 mg of HOBt (0.300 mmol), and 30.4 mg of Et<sub>3</sub>N (0.300 mmol) in 4 mL of DCM. Purification by MPLC chromatography (2% MeOH in DCM) afforded **5.3g** as a yellow gel (60 mg, 100% yield): <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.73 (s, 1H), 8.56 (d, *J* = 4.0 Hz, 1H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.59 (d, *J* = 20.5 Hz, 1H), 7.41 (s, 1H), 7.29 (dd, *J* = 7.5, 5.0 Hz, 1H), 7.22 (d, *J* = 8.5 Hz, 1H), 7.04 – 7.01 (m, 2H), 6.43 – 6.38 (m, 2H), 5.76 (t, *J* = 5.0 Hz, 1H), 4.08 (t, *J* = 7.0 Hz, 2H), 3.33 (q, *J* = 6.5 Hz, 2H), 2.44 (s, 3H), 1.82 (quintet, *J* = 7.0 Hz, 2H), 1.51 (quintet, *J* = 7.0 Hz, 2H), 1.37 – 1.29 (m, 4H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 165.1 (C), 150.4 (CH), 149.2 (CH), 137.3 (CH), 134.4 (CH), 134.3 (C), 130.7 (C), 128.8 (C), 128.4 (C), 127.9 (CH), 123.7 (CH), 123.0 (CH), 122.8 (CH), 120.6 (CH), 109.1 (CH), 100.3 (CH), 46.4 (CH<sub>2</sub>), 39.7 (CH<sub>2</sub>), 30.1 (CH<sub>2</sub>), 29.5 (CH<sub>2</sub>), 26.7 (CH<sub>2</sub>), 26.6 (CH<sub>2</sub>), 21.4 (CH<sub>3</sub>). HRMS (ESI) *m/z* calculated for C<sub>23</sub>H<sub>28</sub>N<sub>3</sub>O (M+H)<sup>+</sup>: 362.2232, found: 362.2233.



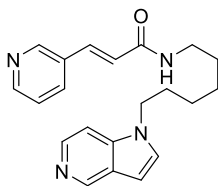
### 5.3h

**(E)-N-(6-(1H-Indol-1-yl)hexyl)-3-(pyridin-3-yl)acrylamide 5.3h.** The general procedure was followed using 28.8 mg of **5.2h** (0.100 mmol), 12.0 mg of *trans*-3-(3-pyridyl) acrylic acid (0.0800 mmol), 30.7 mg of EDC•HCl (0.160 mmol), 16.2 mg of HOBt (0.120 mmol), and 12.1 mg of Et<sub>3</sub>N (0.120 mmol) in 1.6 mL of DCM. Purification by MPLC chromatography (5% MeOH in DCM) afforded **5.3h** as a yellow gel (15 mg, 36% yield): <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.73 (d, *J* = 1.5 Hz, 1H), 8.56 (dd, *J* = 4.5, 1.0 Hz, 1H), 7.76 (td, *J* = 8.0, 1.5 Hz, 1H), 7.60 (d, *J* = 3.5 Hz, 1H), 7.58 (d, *J* = 4.0 Hz, 1H), 7.31 – 7.28 (m, 2H), 7.20 (t, *J* = 8.0 Hz, 1H), 7.10 (t, *J* = 8.0 Hz, 1H), 7.07 (s, 1H), 6.43 (d, *J* = 15.5 Hz, 1H), 5.80 (br s, 1H), 4.08 (t, *J* = 7.0 Hz, 2H), 3.77 (s, 2H), 3.70 (s, 3H), 3.32 (q, *J* = 6.5 Hz, 2H), 1.84 – 1.80 (m, 2H), 1.53 – 1.49 (m, 2H), 1.35 – 1.32 (m, 4H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 172.7 (C), 165.1 (C), 150.3 (CH), 149.2 (CH), 137.3 (CH), 136.2 (C), 134.3 (CH), 130.7 (C), 127.8 (C), 126.7 (CH), 123.7 (CH), 122.9 (CH), 121.7 (CH), 119.2 (CH), 119.0 (CH), 109.5 (CH), 106.8 (C), 52.0 (CH<sub>3</sub>), 46.2 (CH<sub>2</sub>), 39.6 (CH<sub>2</sub>), 31.1 (CH<sub>2</sub>), 30.0 (CH<sub>2</sub>), 29.4 (CH<sub>2</sub>), 26.6 (CH<sub>2</sub>), 26.5 (CH<sub>2</sub>). IR (thin film): 3302, 2929, 2859, 1734, 1663, 1556, 1509, 1426, 1373, 1242, 1046, 805, 730 cm<sup>-1</sup>; HRMS (ESI) *m/z* calculated for C<sub>25</sub>H<sub>30</sub>N<sub>3</sub>O<sub>3</sub> (M+H)<sup>+</sup>: 420.2263, found: 420.2271.



### 5.3j (DGMS-RARI)

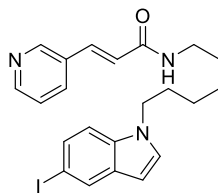
**(E)-N-(6-(1H-indol-1-yl)hexyl)-3-(pyridin-3-yl)acrylamide 5.3j (DGMS-RARI).** The general procedure was followed using 29.2 mg of **5.2j** (0.100 mmol), 12.0 mg of *trans*-3-(3-pyridyl) acrylic acid (0.080 mmol), 30.7 mg of EDC•HCl (0.160 mmol), 16.2 mg of HOBT (0.120 mmol), and 12.1 mg of Et<sub>3</sub>N (0.120 mmol) in 1.6 mL of DCM. Purification by MPLC chromatography (5% MeOH in DCM) afforded **DGMS-RARI** as a yellow gel (39.7 mg, 94% yield): <sup>1</sup>H NMR (501 MHz, CDCl<sub>3</sub>) δ 8.69 (s, 1H), 8.50 (d, *J* = 4.4 Hz, 1H), 7.68 (d, *J* = 7.8 Hz, 1H), 7.63 (d, *J* = 7.8 Hz, 1H), 7.56 (d, *J* = 15.7 Hz, 1H), 7.43 (m, 5H), 7.35 (d, *J* = 8.3 Hz, 1H), 7.21 (t, *J* = 6.4 Hz, 2H), 7.13 (t, *J* = 7.4 Hz, 1H), 6.51 (s, 1H), 6.45 (d, *J* = 15.7 Hz, 1H), 6.35 (d, *J* = 5.0 Hz, 1H), 4.13 (t, *J* = 7.6 Hz, 2H), 3.24 (t, *J* = 6.6 Hz, 2H), 1.64 (t, *J* = 7.1 Hz, 2H), 1.39 (t, *J* = 7.1 Hz, 2H), 1.14 (m, 4H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 165.1 (C), 150.2 (CH), 149.0 (CH), 141.4 (C), 137.4 (C), 137.1 (CH), 134.4 (CH), 133.2 (C), 130.8 (C), 129.4 (CH), 128.6 (CH), 128.2 (C), 128.0 (CH), 123.7 (CH), 123.0 (CH), 121.5 (CH), 120.6 (CH), 119.8 (CH), 110.1 (CH), 102.1 (CH), 43.7 (CH<sub>2</sub>), 39.7 (CH<sub>2</sub>), 29.7 (CH<sub>2</sub>), 29.4 (CH<sub>2</sub>), 26.4 (CH<sub>2</sub>), 26.4 (CH<sub>2</sub>). IR (thin film): 3440, 2997, 2913, 1666, 1436, 1406, 1311, 1018, 952, 698, 667 cm<sup>-1</sup>; HRMS (ESI) *m/z* calculated for C<sub>28</sub>H<sub>30</sub>N<sub>3</sub>O (M+H)<sup>+</sup>: 424.2389, found: 424.2385.



**5.3k**

**(E)-N-(6-(1H-Indol-1-yl)hexyl)-3-(pyridin-3-yl)acrylamide 5.3k.** The general procedure was followed using 21.7 mg of **5.2k** (0.100 mmol), 12.0 mg of *trans*-3-(3-pyridyl) acrylic acid (0.080

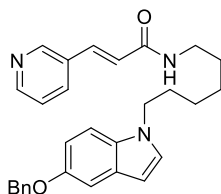
mmol), 30.7 mg of EDC•HCl (0.160 mmol), 16.2 mg of HOBt (0.120 mmol), and 12.1 mg of Et<sub>3</sub>N (0.120 mmol) in 1.6 mL of DCM. Purification by MPLC chromatography (5% MeOH in DCM) afforded **5.3k** as a brown gel (31.1 mg, 89% yield): <sup>1</sup>H NMR (501 MHz, CDCl<sub>3</sub>) δ 8.64 (d, *J* = 1.2 Hz, 1H), 8.50 – 8.43 (m, 1H), 8.25 (dd, *J* = 4.7, 1.3 Hz, 1H), 7.85 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.67 (d, *J* = 7.9 Hz, 1H), 7.55 (d, *J* = 15.7 Hz, 1H), 7.20 (dd, *J* = 7.8, 4.8 Hz, 1H), 7.15 (d, *J* = 3.4 Hz, 1H), 6.99 (dd, *J* = 7.8, 4.7 Hz, 1H), 6.72 (t, *J* = 5.3 Hz, 1H), 6.51 (d, *J* = 15.7 Hz, 1H), 6.40 (d, *J* = 3.4 Hz, 1H), 4.21 (t, *J* = 7.2 Hz, 2H), 3.30 (dd, *J* = 13.0, 6.7 Hz, 2H), 1.84 – 1.73 (m, 2H), 1.53 – 1.44 (m, 2H), 1.31 (m, 4H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 165.3 (C), 150.1 (CH), 149.0 (CH), 147.3 (CH), 142.5 (C), 136.8 (CH), 134.3 (CH), 130.8 (C), 128.8 (CH), 128.0 (CH), 123.7 (CH), 123.3 (CH), 120.6 (C), 115.6 (CH), 99.4 (CH), 44.3 (CH<sub>2</sub>), 39.6 (CH<sub>2</sub>), 30.3 (CH<sub>2</sub>), 29.3 (CH<sub>2</sub>), 26.4 (CH<sub>2</sub>), 26.3 (CH<sub>2</sub>); IR (thin film): 3443, 2995, 2912, 1667, 1436, 1406, 1309, 1260, 1042, 952, 930, 802, 697, 667 cm<sup>-1</sup>; HRMS (ESI) *m/z* calculated for C<sub>21</sub>H<sub>25</sub>N<sub>4</sub>O (M+H)<sup>+</sup>: 349.2028, found: 349.2020.



### 5.3l

**(E)-N-(6-(1H-Indol-1-yl)hexyl)-3-(pyridin-3-yl)acrylamide 5.3l.** The general procedure was followed using 34.7 mg of **5.2l** (0.100 mmol), 12.0 mg of *trans*-3-(3-pyridyl) acrylic acid (0.080 mmol), 30.7 mg of EDC•HCl (0.160 mmol), 16.2 mg of HOBt (0.120 mmol), and 12.1 mg of Et<sub>3</sub>N (0.120 mmol) in 1.6 mL of DCM. Purification by MPLC chromatography (5% MeOH in DCM)

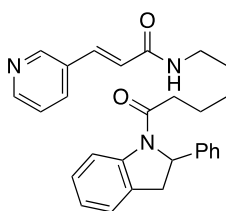
afforded **5.3l** as a brown gel (39.5 mg, 83% yield):  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.68 (s, 1H), 8.49 (d,  $J = 4.2$  Hz, 1H), 7.91 (s, 1H), 7.71 (d,  $J = 7.7$  Hz, 1H), 7.55 (d,  $J = 15.7$  Hz, 1H), 7.39 (d,  $J = 8.6$  Hz, 1H), 7.24 (dd,  $J = 7.7, 5.3$  Hz, 1H), 7.06 (d,  $J = 8.6$  Hz, 1H), 7.00 (d,  $J = 2.5$  Hz, 1H), 6.46 (d,  $J = 15.7$  Hz, 1H), 6.41 – 6.24 (m, 2H), 4.02 (t,  $J = 6.9$  Hz, 2H), 3.30 (dd,  $J = 12.9, 6.5$  Hz, 2H), 1.84 – 1.70 (m, 2H), 1.55 – 1.39 (m, 2H), 1.36 – 1.14 (m, 4H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  165.3 (C), 150.0 (CH), 148.8 (CH), 137.0 (CH), 135.0 (C), 134.6 (CH), 131.1 (C), 130.9 (C), 129.7 (CH), 129.6 (CH), 128.6 (CH), 123.8 (CH), 123.2 (CH), 111.4 (CH), 100.3 (CH), 82.7 (C), 46.4 ( $\text{CH}_2$ ), 39.7 ( $\text{CH}_2$ ), 30.0 ( $\text{CH}_2$ ), 29.4 ( $\text{CH}_2$ ), 26.6 ( $\text{CH}_2$ ), 26.5 ( $\text{CH}_2$ ); IR (thin film): 3398, 2996, 2913, 1660, 1436, 1406, 1315, 1014, 951, 703, 671  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calculated for  $\text{C}_{22}\text{H}_{25}\text{IN}_3\text{O}$  ( $\text{M}+\text{H}$ ) $^+$ : 474.1042, found: 474.1049.



### 5.3m (DGMS-RAR-6)

**(E)-N-(6-(1H-Indol-1-yl)hexyl)-3-(pyridin-3-yl)acrylamide 5.3m (DGMS-RAR-6).** The general procedure was followed using 32.1 mg of **5.2m** (0.100 mmol), 12.0 mg of *trans*-3-(3-pyridyl) acrylic acid (0.080 mmol), 30.7 mg of EDC•HCl (0.160 mmol), 16.2 mg of HOBt (0.120 mmol), and 12.1 mg of  $\text{Et}_3\text{N}$  (0.120 mmol) in 1.6 mL of DCM. Purification by MPLC chromatography (5% MeOH in DCM) afforded **DGMS-RAR-6** as a yellow gel (14.9 mg, 33% yield):  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.71 (d,  $J = 1.1$  Hz, 1H), 8.53 (d,  $J = 3.8$  Hz, 1H), 7.70 (d,  $J = 8.0$  Hz, 1H), 7.58 (d,  $J = 15.7$  Hz, 1H), 7.46 (d,  $J = 7.2$  Hz, 2H), 7.37 (t,  $J = 7.5$  Hz, 2H), 7.31

(d,  $J = 7.3$  Hz, 1H), 7.27 – 7.20 (m, 2H), 7.18 (d,  $J = 2.3$  Hz, 1H), 7.04 (d,  $J = 3.0$  Hz, 1H), 6.95 (dd,  $J = 8.8, 2.4$  Hz, 1H), 6.42 (d,  $J = 15.7$  Hz, 1H), 6.39 (d,  $J = 3.0$  Hz, 1H), 6.07 (t,  $J = 5.5$  Hz, 1H), 5.09 (s, 2H), 4.04 (t,  $J = 7.0$  Hz, 2H), 3.30 (dd,  $J = 13.2, 6.8$  Hz, 2H), 1.95 – 1.65 (m, 2H), 1.53 – 1.44 (m, 2H), 1.34 – 1.27 (m, 4H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  165.2 (C), 153.1 (C), 150.2 (CH), 149.0 (CH), 137.7 (C), 137.1 (CH), 134.4 (CH), 131.5 (C), 130.8 (C), 128.9 (C), 128.5 (CH), 128.4 (CH), 127.8 (CH), 127.6 (CH), 123.7 (CH), 123.1 (CH), 112.5 (CH), 110.1 (CH), 104.2 (CH), 100.5 (CH), 71.0 ( $\text{CH}_2$ ), 46.5 ( $\text{CH}_2$ ), 39.7 ( $\text{CH}_2$ ), 30.2 ( $\text{CH}_2$ ), 29.5 ( $\text{CH}_2$ ), 26.7 ( $\text{CH}_2$ ), 26.6 ( $\text{CH}_2$ ); IR (thin film): 3404, 3002, 2919, 1659, 1436, 1406, 1314, 1015, 951, 702, 671  $\text{cm}^{-1}$ ; HRMS (ESI) see **5.3o H2**.



### 5.3p (DGMS-RAR-7)

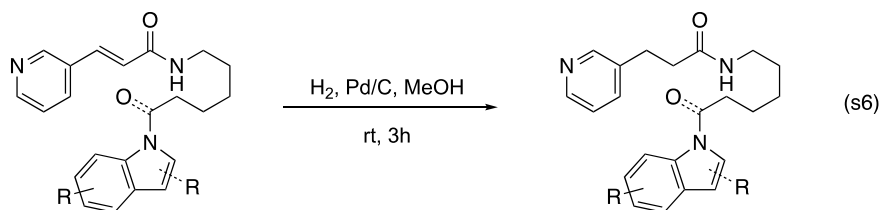
**(E)-N-(6-(1H-indol-1-yl)hexyl)-3-(pyridin-3-yl)acrylamide 5.3p (DGMS-RAR-7).** The general procedure was followed using 61.7 mg of **5.3.5c** (0.2 mmol), 25.0 mg of *trans*-3-(3-pyridyl) acrylic acid (0.17 mmol), 65.1 mg of EDC•HCl (0.34 mmol), 35.1 mg of HOBt (0.26 mmol), and 26.3 mg of  $\text{Et}_3\text{N}$  (0.26 mmol) in 4 mL of DCM. Purification by MPLC chromatography (2% MeOH in DCM) afforded **DGMS-RAR-7** as a yellow gel (45 mg, 60% yield):  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.71 (d,  $J = 2.5$  Hz, 1H), 8.53 (d,  $J = 5.0$  Hz, 1H), 8.35 (d,  $J = 8.0$  Hz, 1H), 7.74 (d,  $J = 8.0$  Hz, 1H), 7.58 (d,  $J = 16.0$  Hz, 1H), 7.29 – 7.22 (m, 4H), 7.14 – 7.11 (m, 3H), 7.04 (t,  $J = 7.5$  Hz, 1H), 6.63 (t,  $J = 5.5$  Hz, 1H), 6.55 (d,  $J = 16.0$  Hz, 1H), 5.40 (d,  $J = 10.0$  Hz, 1H), 3.80 – 3.75 (m, 1H), 3.39 – 3.31 (m, 2H), 2.96 (d,  $J = 16.0$  Hz, 1H), 2.44 – 2.38 (m, 1H), 2.16 – 2.05 (m, 1H), 1.64 –

1.44 (5H), 1.30 – 1.22 (m, 2H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  172.1 (C), 165.2 (C), 150.2 (CH), 149.2 (CH), 143.4 (C), 143.1 (C), 136.7 (CH), 134.2 (CH), 132.0 (C), 130.9 (C), 129.2 (CH), 127.8 (CH), 127.7 (CH), 125.0 (CH), 124.9 (CH), 124.3 (CH), 123.7 (CH), 123.4 (CH), 116.9 (CH), 62.7 (CH), 39.0 ( $\text{CH}_2$ ), 38.9 ( $\text{CH}_2$ ), 35.1 ( $\text{CH}_2$ ), 28.7 ( $\text{CH}_2$ ), 26.1 ( $\text{CH}_2$ ), 23.5 ( $\text{CH}_2$ ); ATR-FTIR (thin film): 3277, 3049, 1727, 1661, 1628, 1402, 1267, 1024, 730  $\text{cm}^{-1}$ . HRMS (ESI)  $m/z$  calcd for  $\text{C}_{28}\text{H}_{30}\text{N}_3\text{O}_2$   $[\text{M} + \text{H}]^+$ : 440.2338, found: 440.2335.

## E. Expanding RARI analogue compound library.

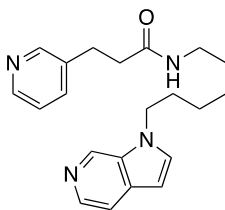
### a) Hydrogenation.

#### 1. General Procedure.



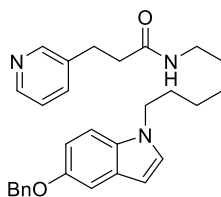
A solution of the RARI analogue (1.0 equiv) and 10 wt % Pd/C (0.20 g/mmol) in MeOH was stirred under 1.0 atm of  $\text{H}_2$  gas. After stirring at room temperature for 3 h, the reaction mixture was filtered through Celite and dried over  $\text{Na}_2\text{SO}_4$ . The filtrate was concentrated in vacuo. Purification via MPLC afforded the product.

#### 2. Characterization data.



### DGMS-RAR-5.3b H2

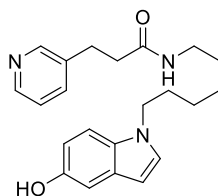
**DGMS-RAR-5.3b H2.** The general procedure was followed using 15.0 mg (0.043 mmol) of **5.3b**, 8.6 mg of Pd/C in 1.0 mL of MeOH under H<sub>2</sub> atmosphere. Purification by MPLC chromatography (2% MeOH in DCM) afforded **DGMS-RAR-5.3b H2** as a yellow gel (12.2 mg, 80% yield): <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.72 (s, 1H), 8.40 – 8.37 (m, 2H), 8.18 (d, *J* = 5.5 Hz, 1H), 7.49 – 7.47 (m, 2H), 7.20 (d, *J* = 3.0 Hz, 1H), 7.15 – 7.12 (m, 1H), 6.46 (d, *J* = 3.5 Hz, 1H), 6.06 (t, *J* = 6.0 Hz, 1H), 4.16 (t, *J* = 7.0 Hz, 2H), 3.15 (q, *J* = 6.5 Hz, 2H), 2.93 (t, *J* = 7.5 Hz, 2H), 2.42 (t, *J* = 7.5 Hz, 2H), 1.81 (quin, *J* = 7.0 Hz, 2H), 1.37 (t, *J* = 7.0 Hz, 2H), 1.28 – 1.23 (m, 4H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 171.4 (C), 149.7 (CH), 147.6 (CH), 138.1 (CH), 136.4 (C), 136.1 (CH), 133.3 (C), 133.1 (C), 132.6 (CH), 131.6 (CH), 123.4 (CH), 115.4 (CH), 100.6 (CH), 46.7 (CH<sub>2</sub>), 39.3 (CH<sub>2</sub>), 37.8 (CH<sub>2</sub>), 30.3 (CH<sub>2</sub>), 29.4 (CH<sub>2</sub>), 28.8 (CH<sub>2</sub>), 26.5 (CH<sub>2</sub>), 26.4 (CH<sub>2</sub>). ATR-FTIR (thin film): 3271, 3043, 2926, 2855, 1645, 1552, 1500, 1320, 1028, 817, 775, 730 cm<sup>-1</sup>. HRMS (ESI) *m/z* calcd for C<sub>21</sub>H<sub>27</sub>N<sub>4</sub>O [M + H]<sup>+</sup>: 351.2185, found: 351.2186.



### DGMS-RAR-6 H2



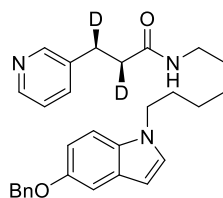
**DGMS-RAR-5.3o H2.** The general procedure was followed using 45.3 mg (0.100 mmol) of **DGMS-RAR-6**, 5.2 mg of Pd/C in 0.6 mL of MeOH under H<sub>2</sub> atmosphere for 1 hour. Purification by MPLC chromatography (2% MeOH in DCM) afforded **DGMS-RAR-6 H2** as a purple gel (27.4 mg, 60% yield): <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.46 – 8.39 (m, 2H), 7.52 (d, *J* = 7.8 Hz, 1H), 7.47 (d, *J* = 7.3 Hz, 2H), 7.38 (t, *J* = 7.5 Hz, 2H), 7.32 (d, *J* = 7.3 Hz, 1H), 7.21 (d, *J* = 8.9 Hz, 1H), 7.16 (d, *J* = 2.4 Hz, 2H), 7.04 (d, *J* = 3.0 Hz, 1H), 6.94 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.38 (d, *J* = 2.9 Hz, 1H), 5.47 (s, 1H), 5.09 (s, 2H), 4.05 (t, *J* = 6.9 Hz, 2H), 3.15 (dd, *J* = 13.1, 6.8 Hz, 2H), 2.95 (t, *J* = 7.5 Hz, 2H), 2.42 (t, *J* = 7.6 Hz, 2H), 1.83 – 1.70 (m, 2H), 1.42 – 1.34 (m, 2H), 1.30 – 1.21 (m, 4H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 171.5 (C), 153.1 (C), 149.3 (CH), 147.2 (CH), 137.7 (C), 136.7 (C), 136.5 (CH), 131.5 (C), 128.9 (C), 128.5 (CH), 128.4 (CH), 127.8 (CH), 127.6 (CH), 123.6 (CH), 112.4 (CH), 110.1 (CH), 104.2 (CH), 100.5 (CH), 71.0 (CH), 46.4 (CH<sub>2</sub>), 39.4 (CH<sub>2</sub>), 37.6 (CH<sub>2</sub>), 30.2 (CH<sub>2</sub>), 29.4 (CH<sub>2</sub>), 28.8 (CH<sub>2</sub>), 26.6 (CH<sub>2</sub>), 26.5 (CH<sub>2</sub>); IR (thin film): 3386, 2256, 1651, 1047, 1023, 993, 824, 762, 630 cm<sup>-1</sup>; HRMS (ESI) *m/z* calculated for C<sub>29</sub>H<sub>34</sub>N<sub>3</sub>O<sub>2</sub> (M+H)<sup>+</sup>: 456.2651, found: 456.2645.



### 5.3t H2

**5.3t H2.** The general procedure was followed using 45.3 mg (0.100 mmol) of **DGMS-RAR-6**, 5.2 mg of Pd/C in 0.6 mL of MeOH under H<sub>2</sub> atmosphere for 4 hours. Purification by MPLC chromatography (2% MeOH in DCM) afforded **5.3t H2** as a purple gel (36.5 mg, 80% yield): <sup>1</sup>H

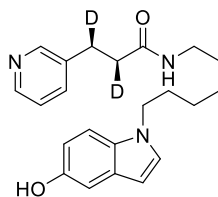
NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  8.47 – 8.31 (m, 2H), 7.51 (d,  $J$  = 7.8 Hz, 1H), 7.16 (dd,  $J$  = 7.7, 4.8 Hz, 1H), 7.12 (d,  $J$  = 8.7 Hz, 1H), 7.04 (d,  $J$  = 2.2 Hz, 1H), 6.98 (d,  $J$  = 3.0 Hz, 1H), 6.80 (dd,  $J$  = 8.7, 2.3 Hz, 1H), 6.29 (d,  $J$  = 2.9 Hz, 1H), 5.65 (t,  $J$  = 5.4 Hz, 1H), 3.98 (s, 2H), 3.09 (dd,  $J$  = 13.1, 6.8 Hz, 2H), 2.92 (t,  $J$  = 7.5 Hz, 2H), 2.39 (t,  $J$  = 7.5 Hz, 2H), 1.77 – 1.64 (m, 2H), 1.31 (dt,  $J$  = 14.4, 7.3 Hz, 2H), 1.23 – 1.05 (m, 4H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  171.5 (C), 150.2 (C), 149.3 (CH), 147.2 (CH), 136.6 (CH), 131.2 (C), 129.2 (C), 128.5 (CH), 123.6 (CH), 111.6 (CH), 110.0 (C), 109.9 (CH), 105.4 (CH), 99.9 (CH), 46.3 (CH<sub>2</sub>), 39.4 (CH<sub>2</sub>), 37.7 (CH<sub>2</sub>), 30.0 (CH<sub>2</sub>), 29.3 (CH<sub>2</sub>), 28.7 (CH<sub>2</sub>), 26.5 (CH<sub>2</sub>), 26.4 (CH<sub>2</sub>); IR (thin film): 3278, 3093, 2930, 2858, 1644, 1555, 1485, 1455, 1373, 1149, 1048, 1027, 948, 846, 800, 714, 630 cm<sup>-1</sup>; HRMS (ESI)  $m/z$  calculated for C<sub>22</sub>H<sub>28</sub>N<sub>3</sub>O<sub>2</sub> (M+H)<sup>+</sup>: 366.2182, found: 366.2172.



### DGMS-RAR-6 D2

**DGMS-RAR-5.3o D2.** The general procedure was followed using 45.3 mg (0.100 mmol) of **DGMS-RAR-6**, 5.2 mg of Pd/C in 0.6 mL of MeOH under D<sub>2</sub> atmosphere for 1 hour. Purification by MPLC chromatography (2% MeOH in DCM) afforded **DGMS-RAR-6 D2** as a purple gel (18.7 mg, 30% yield): <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  8.47 – 8.37 (m, 2H), 7.51 (d,  $J$  = 7.9 Hz, 1H), 7.47 (d,  $J$  = 7.4 Hz, 2H), 7.36 (dd,  $J$  = 21.1, 13.4 Hz, 2H), 7.32 (d,  $J$  = 7.3 Hz, 1H), 7.22 (d,  $J$  = 8.9 Hz, 1H), 7.16 (t,  $J$  = 3.5 Hz, 2H), 7.04 (d,  $J$  = 3.0 Hz, 1H), 6.94 (dd,  $J$  = 8.8, 2.3 Hz, 1H), 6.38 (d,  $J$  = 2.9 Hz, 1H), 5.49 (s, 1H), 5.09 (s, 2H), 4.05 (t,  $J$  = 7.0 Hz, 2H), 3.15 (dd,  $J$  = 13.2, 6.9 Hz, 2H),

2.93 (t,  $J = 7.9$  Hz, 1H), 2.40 (t,  $J = 7.2$  Hz, 1H), 1.78 (dd,  $J = 14.5, 7.1$  Hz, 2H), 1.38 (dd,  $J = 14.2, 7.2$  Hz, 2H), 1.30 – 1.17 (m, 4H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  171.3 (C), 153.1 (C), 149.8 (CH), 147.7 (CH), 137.8 (C), 136.3 (C), 136.1 (CH), 131.5 (C), 128.9 (C), 128.5 (CH), 128.4 (CH), 127.8 (CH), 127.5 (CH), 123.4 (CH), 112.5 (CH), 110.1 (CH), 104.2 (CH), 100.5 (CH), 70.9 ( $\text{CH}_2$ ), 46.5 ( $\text{CH}_2$ ), 39.4 ( $\text{CH}_2$ ), 37.8 – 37.5 (m, CDH), 30.2 ( $\text{CH}_2$ ), 29.4 ( $\text{CH}_2$ ), 28.7 – 28.4 (m, CDH), 26.6 ( $\text{CH}_2$ ), 26.5 ( $\text{CH}_2$ ); IR (thin film): 3404, 3002, 2921, 1652, 1436, 1314, 1015, 952, 702, 670  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calculated for  $\text{C}_{29}\text{H}_{32}\text{D}_2\text{N}_3\text{O}_2$  ( $\text{M}+\text{H}$ ) $^+$ : 458.2777, found: 458.2766.



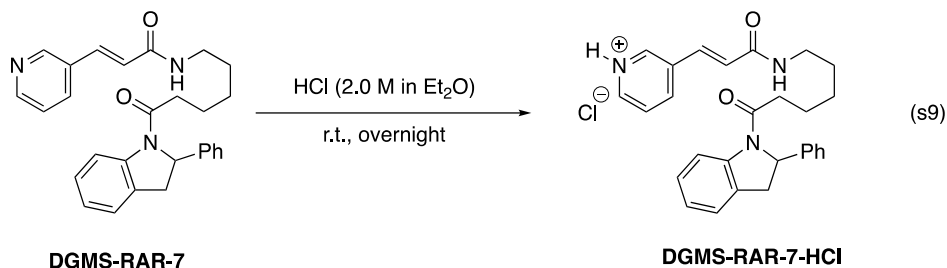
### 5.3t D2

**5.3t D2.** The general procedure was followed using 45.3 mg (0.100 mmol) of **DGMS-RAR-6**, 5.2 mg of Pd/C in 0.6 mL of MeOH under  $\text{D}_2$  atmosphere for 4 hours. Purification by MPLC chromatography (2% MeOH in DCM) afforded **5.3t D2** as a purple gel (35.1 mg, 77% yield):  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.43 (dd,  $J = 14.5, 6.7$  Hz, 2H), 7.55 – 7.46 (m, 1H), 7.20 – 7.11 (m, 2H), 7.02 (dd,  $J = 15.9, 2.6$  Hz, 2H), 6.80 (dd,  $J = 8.7, 2.3$  Hz, 1H), 6.31 (d,  $J = 2.8$  Hz, 1H), 5.44 (s, 1H), 4.02 (t,  $J = 6.9$  Hz, 2H), 3.11 (dd,  $J = 13.1, 6.9$  Hz, 2H), 2.93 (t,  $J = 7.9$  Hz, 1H), 2.38 (d,  $J = 7.0$  Hz, 1H), 1.75 (dd,  $J = 14.5, 7.1$  Hz, 2H), 1.37 – 1.29 (m, 2H), 1.24 – 1.12 (m, 5H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  171.4 (C), 150.0 (C), 149.5 (CH), 147.4 (CH), 136.5 (CH), 136.3 (C), 131.3 (C), 129.2 (C), 128.5 (CH), 123.6 (CH), 111.6 (CH), 110.0 (CH), 105.4 (CH), 100.0 (CH), 46.4 ( $\text{CH}_2$ ), 39.4 ( $\text{CH}_2$ ), 37.7 – 37.3 (m, CDH), 30.0 ( $\text{CH}_2$ ), 29.3 ( $\text{CH}_2$ ), 28.8 – 28.5 (m, CDH), 26.5 ( $\text{CH}_2$ ), 26.4 ( $\text{CH}_2$ ); IR (thin film): 3396, 3000, 2917, 2858, 1653, 1437, 1406, 1314, 1015,

951, 704, 669  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calculated for  $\text{C}_{22}\text{H}_{26}\text{D}_2\text{N}_3\text{O}_2$  ( $\text{M}+\text{H}$ ) $^+$ : 368.2307, found: 368.2294.

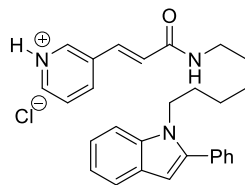
**b) Salt formation.**

1. General procedure.



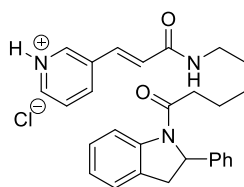
To a solution of RARI analogue **DGMS-RAR-7** was added a 2.0 M  $\text{Et}_2\text{O}$  solution of protic acid (1.0 equiv). The reaction mixture was allowed to stir at room temperature for overnight. The resulting reaction mixture was filtered through Celite and washed by MeOH. The filtrate was then dried over  $\text{Na}_2\text{SO}_4$  and concentrated *in vacuo* to afford the pure product without additional purification.

2. Characterization data.



**DGMS-RARI-HCl**

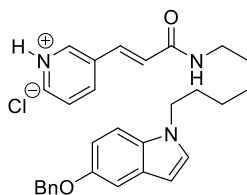
**DGMS-RARI-HCl.** The general procedure was followed using 11.4 mg of **DGMS-RARI** (0.030 mmol) in 3 mL of DCM, and 0.015 mL of 2.0 M of HCl solution in ether (0.030 mmol). After evaporating the solvent, the product **DGMS-RARI-HCl** was afforded as a dark brown gel (12.3 mg, 99% yield).  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO-}d_6$ )  $\delta$  8.81 (s, 1H), 8.76 (d,  $J = 5.3$  Hz, 1H), 8.47 (d,  $J = 7.9$  Hz, 1H), 8.06 – 7.92 (m, 1H), 7.87 (s, 1H), 7.43 (d,  $J = 7.3$  Hz, 3H), 7.39 – 7.27 (m, 4H), 7.10 (d,  $J = 1.8$  Hz, 1H), 6.83 (d,  $J = 8.7$  Hz, 1H), 6.28 (d,  $J = 2.5$  Hz, 1H), 5.72 (s, 1H), 5.06 (s, 2H), 4.06 (t,  $J = 6.7$  Hz, 2H), 3.00 (t,  $J = 7.1$  Hz, 2H), 1.65 (s, 2H), 1.25 (s, 2H), 1.13 (d,  $J = 5.6$  Hz, 4H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{DMSO-}d_6$ ) 164.1 (C), 159.2 (CH), 142.8 (CH), 142.6 (C), 138.4 (C), 135.2 (C), 132.5 (CH), 131.2 (C), 131.2 (CH), 129.4 (CH), 129.2 (CH), 129.0 (CH), 128.7 (CH), 127.9 (C), 127.6 (CH), 124.7 (CH), 123.2 (CH), 119.4 (CH), 113.2 (CH), 110.9 (CH), 39.3 ( $\text{CH}_2$ ), 34.7 ( $\text{CH}_2$ ), 29.4 ( $\text{CH}_2$ ), 29.2 ( $\text{CH}_2$ ), 26.2 ( $\text{CH}_2$ ), 26.0 ( $\text{CH}_2$ ); IR (thin film): 3389, 3000, 2915, 1652, 1436, 1406, 1315, 1013, 951, 704, 671  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calculated for  $\text{C}_{28}\text{H}_{29}\text{N}_3\text{OCl}$  ( $\text{M-H}$ ) $^+$ : 458.1999, found: 458.1991; also parent compound observed  $m/z$  calculated for  $\text{C}_{28}\text{H}_{30}\text{N}_3\text{O}$  ( $\text{M+H}$ ) $^+$ : 424.2389, found: 424.2379.



### **DGMS-RAR-7-HCl**

**DGMS-RAR-7-HCl.** The general procedure was followed using 8.8 mg of **DGMS-RAR-7** (0.020 mmol) in 3 mL of DCM, and 0.010 mL of 2.0 M of HCl solution in ether (0.020 mmol). After evaporating the solvent, the product **DGMS-RAR-7-HCl** was afforded as a pale yellow solid (9.3

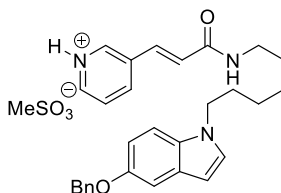
mg, 99% yield).  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO-}d_6$ )  $\delta$  9.02 (s, 1H), 8.79 (d,  $J = 5.2$  Hz, 1H), 8.54 (d,  $J = 7.9$  Hz, 1H), 8.33 (s, 1H), 8.17 (d,  $J = 7.3$  Hz, 1H), 7.96 – 7.90 (m, 1H), 7.52 (d,  $J = 15.9$  Hz, 1H), 7.30 (d,  $J = 6.8$  Hz, 2H), 7.26 – 7.14 (m, 3H), 7.12 (d,  $J = 7.7$  Hz, 2H), 7.00 (t,  $J = 7.4$  Hz, 1H), 6.90 (d,  $J = 15.9$  Hz, 1H), 5.67 (d,  $J = 9.4$  Hz, 1H), 3.79 – 3.60 (m, 1H), 3.08 (d,  $J = 5.1$  Hz, 2H), 2.81 (d,  $J = 16.1$  Hz, 1H), 1.91 (s, 1H), 1.52 – 1.03 (m, 8H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{DMSO-}d_6$ )  $\delta$  171.7 (C), 164.2 (C), 144.2 (C), 143.8 (CH), 143.2 (CH), 141.2 (CH), 134.2 (C), 133.0 (CH), 130.1 (C), 129.5 (CH), 128.0 (CH), 127.9 (CH), 127.7 (CH), 127.0 (CH), 125.6 (CH), 125.2 (CH), 124.2 (CH), 120.4 (C), 116.5 (CH), 62.1 (CH), 39.2 ( $\text{CH}_2$ ), 39.0 ( $\text{CH}_2$ ), 35.0 (CH), 29.3 ( $\text{CH}_2$ ), 26.5 (CH), 24.4 ( $\text{CH}_2$ ). IR (thin film): 3266, 3067, 2928, 2858, 1711, 1665, 1591, 1554, 1462, 1410, 1363, 1262, 1222, 1089, 1023, 805, 785  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calculated for  $\text{C}_{28}\text{H}_{30}\text{N}_3\text{O}_2$  ( $\text{M}+\text{H}^+$ ): 440.2338, found: 440.2332 same as the mass of the parent compound.



### DGMS-RAR-6-HCl

**DGMS-RAR-6-HCl.** The general procedure was followed using 9.1 mg of **DGMS-RAR-6** (0.020 mmol) in 3 mL of DCM, and 0.010 mL of 2.0 M of HCl solution in ether (0.020 mmol). After evaporating the solvent, the product **DGMS-RAR-6-HCl** was afforded as a dark brown gel (9.8 mg, 99% yield).  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO-}d_6$ )  $\delta$  8.56 – 8.51 (m, 2H), 7.93 (d,  $J = 7.3$  Hz, 2H), 7.82 – 7.76 (m, 2H), 7.55 – 7.52 (m, 1H), 7.48 – 7.43 (m, 2H), 7.40 – 7.33 (m, 2H), 7.32 – 7.27 (m, 2H), 7.10 (s, 1H), 6.90 – 6.82 (m, 2H), 6.28 (s, 1H), 5.07 (s, 2H), 4.09 – 4.05 (m, 2H), 2.95 –

2.92 (m, 2H), 2.40 (t,  $J = 7.3$  Hz, 2H), 1.77 – 1.66 (m, 2H), 1.25 – 1.22 (m, 4H);  $^{13}\text{C}$  NMR (125 MHz, DMSO- $d_6$ )  $\delta$  170.9 (C), 153.4 (C), 146.5 (CH), 144.3 (CH), 140.6 (CH), 139.2 (C), 138.1 (C), 133.0 (C), 129.8 (C), 129.6 (CH), 128.1 (CH), 125.2 (CH), 113.0 (CH), 112.1 (CH), 111.8 (CH), 110.9 (CH), 110.0 (CH), 104.2 (CH), 102.2 (CH), 100.4 (CH), 70.2 (CH<sub>2</sub>), 38.8 (CH<sub>2</sub>), 36.4 (CH<sub>2</sub>), 29.4 (CH<sub>2</sub>), 28.4 (CH<sub>2</sub>), 26.4 (CH<sub>2</sub>), 26.2 (CH<sub>2</sub>). IR (thin film): 3394, 2986, 2881, 1652, 1436, 1406, 1315, 1013, 951, 704  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calculated for  $\text{C}_{29}\text{H}_{34}\text{N}_3\text{O}_2$  ( $\text{M}+3\text{H}$ ) $^{+}$ : 456.2651, found: 456.2641 same as the mass of the parent compound.



### DGMS-RAR-6-HO<sub>3</sub>SMe

**DGMS-RAR-6-HO<sub>3</sub>SMe.** The general procedure was followed using 9.1 mg of **DGMS-RAR-6** (0.020 mmol) in 3 mL of DCM, and 0.010 mL of 2.0 M of HCl solution in ether (0.020 mmol). After evaporating the solvent, the product **DGMS-RAR-6-HO<sub>3</sub>SMe** was afforded as a dark brown gel (10.9 mg, 99% yield).  $^1\text{H}$  NMR (500 MHz, DMSO- $d_6$ )  $\delta$  8.80 – 8.76 (m, 2H), 8.47 – 8.45 (m, 2H), 7.99 – 7.97 (m, 2H), 7.84 – 7.82 (m, 2H), 7.48 – 7.23 (m, 6H), 7.10 (s, 1H), 6.83 (d,  $J = 8.6$  Hz, 1H), 6.28 (s, 1H), 5.07 (s, 2H), 4.08 – 4.06 (m, 2H), 2.98 – 2.96 (m, 2H), 2.37 (s, 3H), 1.82 (dd,  $J = 25.0, 11.1$  Hz, 2H), 1.72 – 1.65 (m, 2H), 1.26 – 1.20 (m, 4H);  $^{13}\text{C}$  NMR (125 MHz, DMSO- $d_6$ )  $\delta$  170.7 (C), 153.5 (C), 146.7 (CH), 144.7 (C), 141.9 (CH), 140.1 (CH), 138.3 (C), 133.3 (C), 130.1 (C), 129.6 (CH), 128.8 (CH), 128.0 (CH), 127.2 (CH), 112.1 (CH), 111.8 (CH), 110.9 (CH), 110.0 (CH), 104.2 (CH), 102.2 (CH), 100.4 (CH), 70.2 (CH<sub>2</sub>), 38.8 (CH<sub>2</sub>), 35.7 (CH<sub>2</sub>), 29.4 (CH<sub>2</sub>),

28.2 (CH<sub>2</sub>), 26.4 (CH<sub>2</sub>), 26.2 (CH<sub>2</sub>). IR (thin film): 3394, 2994, 2911, 1652, 1436, 1406, 1310, 1042, 952, 930, 697 cm<sup>-1</sup>; HRMS (ESI) *m/z* calculated for C<sub>29</sub>H<sub>34</sub>N<sub>3</sub>O<sub>2</sub> (M+3H)<sup>+</sup>: 456.2651, found: 456.2647 same as the mass of the parent compound.

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### **Education Background**

2013 – present	<i>Ph.D. Candidate, Organic Chemistry, expected 2021</i> , University of Illinois at Chicago, Chicago, IL, USA
2010 –2013	<i>B. S., Chemistry</i> , the University of Hongkong, Hongkong

### **Research Experience**

2013 – present	<i>Ph. D thesis research</i> , 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. Deoxygenation reaction system to access reactive intermediates 3. NAMPT inhibitor analog synthesis as small molecule therapeutics for pulmonary diseases
2008 –2010	<i>Undergraduate research</i> , Research mentor: W.K. Chan The University of Hongkong Topic: Synthesis of 2,6-bis(2-pyridyl)-4-pyridone derivatives to access low-bandgap polymers.

### **Organization**

2018 –2020	<i>Graduate Student Member</i> , American Chemical Society
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## **Patent and Publications**

"Nicotinamide Phosphoribosyltransferase Inhibitors and Methods for Use of the Same." Driver, T. G.; Guan, X.; Mazumdar, W.; Su. N.; Ratia, K.; Hickok, J.; Lockett, A. D.; Machado, R. Pub. No.: US 2021/0070784 A1.

"Development of a Carbon Neutral Pd-Catalyzed Reductive Cyclization of Nitroarenes." Guan, X.; Zhu, H.; Zhao, Y.; Driver, T. G. *Eur. J. Org. Chem.* **2020**, 57-60.

"Nicotinamide Phosphoribosyltransferase Inhibitors and Methods for Use of the Same." Driver, T. G.; Guan, X.; Mazumdar, W.; Su. N.; Ratia, K.; Hickok, J.; Lockett, A. D.; Machado, R. Pub. No.: WO/2019/153007.

"Iron-Catalyzed Reductive Cyclization of o-Nitrostyrenes Using Phenylsilane as the Terminal Reductant." Shevlin, M.; Guan, X.; Driver, T. G. *ACS Catal.* 2017, 7, 5518-5522.

"Intermolecular Pd-Catalyzed Aryl C–H Bond Aminocarbonylation using Nitroarenes and Mo(CO)<sub>6</sub>." Zhou, F.; Wang, D.-S.; Guan, X.; Driver, T. G. *Angew. Chem. Int. Ed.* 2017, 56, 4530-4534.

"Sequential 1,4-/1,2-Addition of Lithium(trimethylsilyl)diazomethane onto Cyclic Enones to Induce C–C Fragmentation and N–Li Insertion" O'Connor, M.J.; Sun, C.; Guan, X.; Sabbasani, V.R.; Lee, D. *Angew. Chem. Int. Ed.* 2016, 55, 2222.

## **Presentations**

2018	The 56th Annual MIKI Medicinal Chemistry Meeting-in-Miniature. Poster presentation: "Synthesis of NAMPT-targeted Small Molecule Therapeutics for Pulmonary Arterial Hypertension".
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## Appendix

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#### Iron-Catalyzed Reductive Cyclization of o-Nitrostyrenes Using Phenylsilane as the Terminal Reductant

Author: Michael Shevlin, Minyu Guan, Tom G. Driver

Publication: ACS Catalysis

Publisher: American Chemical Society

Date: Aug 1, 2017

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