UNIVERSITY OF CALIFORNIA,
IRVINE

Development of C-C and C-N Bond Forming Reactions Utilizing Palladium Carbene Intermediates

and

Reaction Predictor: Using Machine Learning to Help Identify Unknown Side-Products in Organic Reactions

DISSERTATION

Submitted in partial satisfaction of the requirements
for the degree of

DOCTOR OF PHILOSOPHY

in Chemistry

by

Eugene Gutman

Dissertation Committee:
Professor David L. Van Vranken, Chair
Professor Elizabeth R. Jarvo
Professor Larry E. Overman

2017

DEDICATION

To

My family and friends

In recognition for their unconditional support and love

“Conquering others requires force. Conquering oneself requires strength”

-Laozi

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

ACKNOWLEDGMENTS

I would not be where I am today without the support of my entire family. I'd like to thank my father and mother for working long and tiring hours. My parents have always supported me and I hope to make them proud. Thank you to my grandparents Irene, Alexander, and Mikhail for looking after me when my parents were not able to. The days spent hiking in the woods, learning to play violin, and fishing will stay with me forever. I'd like to apologize to my sister Julia for always running into your room early on Saturday morning when you were trying to sleep, just so I could selfishly play Sonic on Sega Genesis. Thank you to my uncle Sam, aunt Lydia, and cousin Anna for encouraging me to take an interest in science when I was a child. I have to thank my lovely girlfriend Lisa for her support and patience over these last few years. Thank you for always chatting with me on my way home from lab even though it was late on the east coast! One day we might even live in the same state.

Admittingly I was one of those lost souls in high school, not knowing what to make of myself and having no general direction with which to orient my life. That changed my junior year when I took chemistry with Mr. Easterly. The passion with which he delivered his lectures and the interactive labs he designed sparked my interest in chemistry and set me on this journey of which I am still on to this day. Of course I would never have made it past the first few steps without the guidance of my math tutor Svetlana. You presented the concepts in a clear and understandable fashion, never once becoming frustrated with my lack of comprehension. It saddens me that we've lost touch over the years. I consider myself extremely lucky to have taken calculus under the instruction of Dr. John Michael McVoy during the last few years of his life. He was the best teacher I've ever had in my life, RIP.

It was during my junior year of college that I began my career as an experimental chemist under the guidance of Dr. Scott Phillips. I vividly remember rushing into his office to describe some harebrained ideas I had or asking some trivial questions about organic synthesis. Never once did he lose his temper and tell me to get lost, which he had every right to do since he was in the midst of obtaining tenure. Instead he would drop whatever he was doing and hear me out. Thank you Scott for believing in me.

I have to thank the entire faculty and staff here at UCI for creating a uniquely friendly atmosphere in which to conduct research in. Dr. Nowick's spectroscopy class was the most challenging course I've ever taken; it was also the most practically useful. Without the staff of the NMR and mass spec facility (John, Phil, Ben, and Felix) we would all be lost, thank you guys for keeping this whole thing running. Thank you to my committee, Liz and Larry, for the fruitful discussions we've had over the years. Thank you Tenley for always being there to help me out.

Thanks to all my pals outside of the lab, especially the fools I've played hockey with here in sunny southern California. I'd like to thank James for driving me to the hospital when a puck broke my face and for being a great roommate. Thanks to Brian, Kit, the Beardens, Ian, and everyone else I've gotten the pleasure to lace em up with. Thanks to Alex for always being down to grab a beer and commiserate.

I am lucky to have worked with some incredibly intelligent and hard-working lab mates. I'd like to think some of Vanessa and Stan's good habits have rubbed off on me over the years. Thank you guys for teaching me a thing or two in the lab and for being great friends outside of it. I have to thank Chris, Avi, Udara, Thi, Aaron, and all the undergrads that have passed through the labs over the years. Nancy, your contributions to our projects have been immense! You have a great talent for chemistry and I'm sure you will succeed in your own graduate school journey.

Lastly I’d like to thank Dave for accepting me into his group and helping me improve as a scholar and a scientist. Dave is one the best mentors a graduate student could have. His intellectual curiosity and work-ethic is infectious. It would be impossible for me to be where I am today without his mentorship and support. He is also a very kind person and always pays for group meeting food, not to mention, the best professor to grade with!

CURRICULUM VITAE

Eugene Gutman

EDUCATION

2017, July – Bethesda, Md: **Postdoctoral Fellow,** *beginning July 2017*, NIH
Advisor: Dr. Kenner C. Rice

2012 – 2017 – Irvine, CA: **Ph.D. in Organic Chemistry**, *in progress*, University of California, Irvine
Advisor: Professor David L. Van Vranken

2006 – 2010 – State College, PA: **B.Sc. in Chemistry**, Pennsylvania State University
Advisor: Professor Scott T. Phillips

EXPERIENCE

2016 – present: Safety Representative for Van Vranken Laboratory
- Ensured lab was in compliance with all safety regulations

2015 – present: Mentor to Undergraduate Researchers, UC Irvine
- Trained undergraduate researchers in synthetic organic chemistry

2012 – present, Irvine, CA: Graduate and Undergraduate Chemistry Teaching Assistant
- Instruction of upper level organic synthesis laboratory
- Running discussion sections in general and organic chemistry

2011 – 2012, Springhouse, PA: Research Technician, on Assignment at Dow Microbial Control
- Design of novel Ag^{+} based anti-microbial fabric coating formulations
- Creation of new standard operating procedures

2008 – 2010, State College, PA: Undergraduate Research Assistant, Pennsylvania State University
- Synthesis of monomers for polymer based fluoride detection assays

RESEARCH

- Development of new palladium-catalyzed C-C and C-N bond forming reactions
- Design of a mechanism based prediction program used for product matching in synthetic organic chemistry

PUBLICATIONS

1. Arredondo, V.; Hiew, S. C.; **Gutman, E. S.**; Premachandra, I. D. U. A.; Van Vranken, D. L. "Enantioselective Palladium-Catalyzed Carbene Insertion into the N-H Bonds of Aromatic Heterocycles" *Angew. Chem. Int. Ed.* **2017**, *56*, 4156 – 4159.

2. Premachandra, I. D. U. A.; Nguyen, T. A.; Shen, C.; **Gutman, E. S.**; Van Vranken, D. L. "Stereoselectivity in the Aminocarbenylation of Vinyl Iodides involving Palladium Alkylidenes" *Org. Lett.* **2015**, *17*, 5464–5467.

3. **Gutman, E. S.**; Arredondo, V.; Van Vranken, D. L. "Cyclization of η^3-Benzylpalladium Intermediates Derived from Carbene Insertion" *Org. Lett.* **2014**, *16*, 5498-5501.

PRESENTATIONS

"Harnessing the Reactivity of Palladium Carbenes" **Gutman, E. S.** Invited speaker at Arcus Biosciences, October 2016 – Presentation

"Harnessing Palladium-carbenoid reactivity" Premachandra, I. D. U. A.; **Gutman, E. S.**; Arredondo, V.; Van Vranken, D. L. Incoming Graduate Student Recruitment, March 2014-2017 - Poster

REFERENCES

David L. Van Vranken Ph.D
Professor of Chemistry
University of California, Irvine
School of Physical Sciences
1102 Natural Sciences 2,
Irvine, California 92697
(949) 824-5455
david.vv@uci.edu

Tirthankar (Tutul) Ghosh Ph.D
Principal Research Scientist
Agrofresh
400 Arcola Road, P.O. Box 7000, Collegeville, PA 19426
(610) 244-6635
TGhosh@agrofresh.com

Scott T. Phillips Ph.D
Martarano Associate Professor of Chemistry
The Pennsylvania State University
104 Chemistry Research Building, Office: 436,
University Park, PA 16802
(814) 867-2502
sphillips@psu.edu

ABSTRACT OF THE DISSERTATION

Palladium-Catalyzed Carbenylative Insertions

and

Development of Reaction Predictor and its Application towards Identification of Reaction Products and Pathways

By

Eugene S. Gutman

Doctor of Philosophy in Chemistry

University of California, Irvine, 2017

Professor David L Van Vranken, Chair

The research described herein consists of two disparate areas of study. The first and largest portion describes the development of novel palladium-catalyzed C-C and C-N bond forming reactions. The second portion describes the development of the Reaction Predictor system and its application towards identification of reaction products and pathways.

Palladium-carbenes are important intermediates in many modern C-C and C-heteroatom bond forming reactions. Palladium-catalyzed carbenylative coupling reactions are analogous to carbonylative processes with carbon monoxide. Insertion of a *cis* X type ligand into the palladium-carbene can potentially generate a new stereogenic center, making these reactions worthy of study. Carbenylative insertions have been used to generate electrophilic η^3-allylpalladium species which were trapped with nitrogen and carbon nucleophiles. This work describes the cyclization of η^3-benzylpalladium species derived from palladium-catalyzed carbenylative insertion. This optimization and broad substrate scope of this reaction led to the synthesis of 1-arylindanes and 1-aryltetralins in high yields. Additionally, this reaction was used to prepare tetralone **2.30bl**, a synthetic intermediate in the Curran synthesis of (±)-

podophyllotoxin. The carbenylative cyclization also led us to pursue utilizing aliphatic *N*-tosylhydrazones as palladium-carbene precursors in other coupling reactions. It was realized that aliphatic *N*-tosylhydrazones with adjacent hydrogens can effectively participate in three-component palladium-catalyzed carbenylative cross-coupling reactions of vinyl iodides while avoiding β-hydride elimination.

Development of a palladium-catalyzed enantioselective carbene insertion into the N-H bond of aromatic heterocycles to obtain α-(*N*-indolyl)-α-arylesters and α-(*N*-carbazolyl)-α-arylesters, using α-diazo-α-arylacetates as palladium carbene precursors is also described. Aliphatic amines were also competent coupling partners in the reaction, affording biologically active piperdine derivatives in moderate yields. The reaction was applied towards the synthesis of a bioactive carbazole derivative in a concise manner.

In a separate project an inductive machine learning reaction prediction program called Reaction Predicator has been trained and applied towards identification of plausible reaction products in ESI spectra. The reaction predictor training set has been expanded by the addition of new reactions written in our lab. Over 800 transition metal based training reactions have been written. In addition, over 10,000 new complex training reactions have been written and added to the training set. The Reaction Predictor pathway search feature has been customized to match products to unknown *m/z* peaks in ESI spectra. Pathway search was applied towards unknown identification in palladium-catalyzed N-H insertion reactions.

Chapter 1: Accessing η-3 Allylpalladium Intermediates via Carbene Insertion

Introduction

The discovery of palladium-catalyzed cross-coupling reactions has revolutionized the field of synthetic organic chemistry. Previously challenging and in some cases impossible carbon-carbon and carbon-heteroatom bond forming reactions have been rendered trivial by the introduction of palladium catalysis.[1] Palladium catalyzed cross-coupling is the preferred strategy for C-C bond forming reactions among practicing medicinal chemists in industry today.[2] The ease with which palladium shuttles between its two prominent oxidation states, 0 and II, allows the metal to undergo a variety of fundamental reactions such as oxidative addition, reductive elimination, β-hydride elimination, and migratory insertion. Intense effort is currently aimed at discovering and exploiting new modes of palladium reactivity beyond the traditional area of cross-coupling.

One such advance in palladium technology is the generation and interception of palladium carbene intermediates. Generation of palladium carbenes is an important area of research because it couples the versatility of palladium catalysis with the exceptional reactivity of the palladium carbene species. For example, the incorporation of a palladium carbene in an interrupted cross-coupling opens up new strategies for assembly not previously available with traditional cross-coupling partners. This chapter focuses on the formation and trapping of highly reactive palladium species through the intermediacy of palladium carbenes, namely the η^3-allylpalladium and η^3-benzylpalladium units.

Metal Carbenes

A free carbene is one of the most exceptional groups in organic chemistry, challenging traditional notions of valence bond theory. The incomplete valence found on the carbene carbon

defies the octet rule for atoms of the second row of the periodic table. Despite their high level of reactivity, free carbenes are common reactive intermediates. Carbenes which are not stabilized by interaction with a metal will be defined as free carbenes throughout the remainder of this manuscript. Free carbenes are grouped into two distinct classes based on their reactivity, the triplet carbene and the singlet carbene (Figure 1-1).

Figure 1-1: Depiction of Frontier Molecular Orbitals in Singlet and Triplet Carbenes

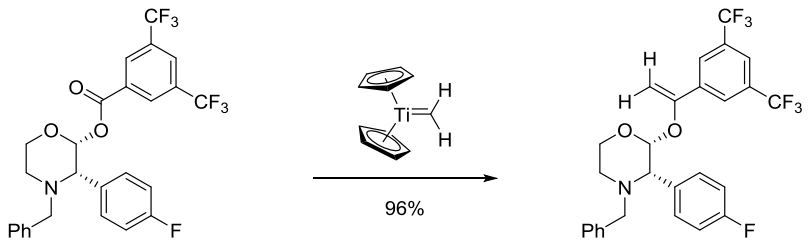
Singlet Carbene *Triplet Carbene*

Singlet carbenes undergo cyclopropanation reactions with olefins in a stereospecific manner indicative of a single concerted transition state. Cyclopropanation reactions believed to involve the intermediacy of triplet carbenes are not stereospecific and result in mixtures of *cis* and *trans* cyclopropanes.[3] Triplet carbenes undergo non-stereospecific stepwise additions to olefins during the course of a cyclopropanation reaction, in this way they behave similarly to radical species.

Carbenes also serve as ligands for transition metal complexes. A formal metal-carbon double bond is typically used to depict the bonding interaction present in metal carbenes. There are two broad classes of metal carbenes, Schrock and Fischer carbenes. Schrock carbenes can be thought of as metal stabilized triplet carbenes.[4] Metal carbenes in this class are nucleophilic on the carbene carbon and react with electrophiles such as aldehydes, ketones, and esters. The olefination of carbonyl groups utilizing Tebbe's reagent or the related Petasis reagent are believed to proceed through a titanium stabilized Schrock carbene intermediate (Figure 1-2).[5] For example, morpholine ester **1.1** was converted to vinyl enol ether **1.2** in one step utilizing an in situ generated Schrock carbene. The mechanism of this transformation is believed to proceed

with coordination of morpholine ester **1.2** to the metal center of the Schrock carbene followed by C-C bond formation between the ester carbon and the methylene carbon of the Schrock carbene.[6]

Figure 1-2: Olefination of ester **1.1** involving a Schrock carbene



1.1 **1.2**

Unlike Schrock carbenes, Fischer carbenes are electrophilic on carbon and are found commonly among low oxidation state transition metals.[6] Fischer carbenes can be viewed as a metal-stabilized singlet carbene. The lone pair of the carbene makes it a strong σ donor ligand for the metal. Backbonding from the electrons in the metal d orbitals stabilize the empty p orbital on the carbene carbon. Heteroatom substituents containing lone pairs on the carbene carbon also serve to stabilize Fischer carbenes (Figure 1-3).[7] *N*-heterocyclic carbenes contain nitrogen substituents on the carbene carbon which can donate directly into the empty p-orbital. The bonding interaction between the nitrogen lonepairs and empty p orbital on the carbene suppress backbonding interactions between the metal and carbene and it is for this reason that *N*-heterocyclic carbenes are typically drawn with a metal-carbon single bond, unlike other Fischer carbene complexes where a metal-carbon double bond is drawn.

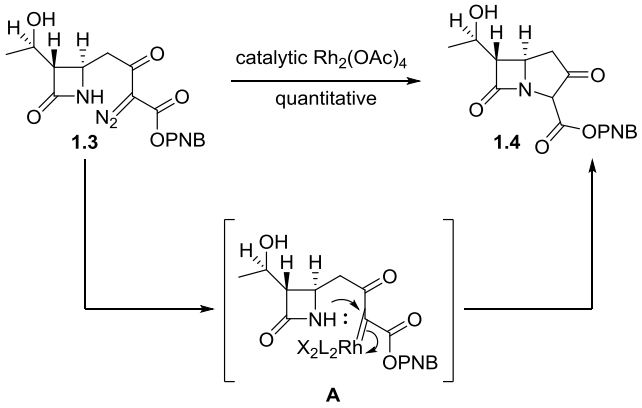
Figure 1-3: Depiction of Bonding Interactions in Fischer and *N*-heterocyclic Carbenes

Fischer Carbene
R or R_1 = H, alkyl, aryl, vinyl, carbonyl, etc...

N-heterocyclic carbene
R = R_1 = N

Fischer carbenes behave similarly to carbonyl compounds in the presence of nucleophiles. Fischer carbenes are attacked by nucleophiles on the carbene carbon, just as carbonyls are attacked by nucleophiles on their carbonyl carbon. Salzmann and co-workers leveraged the unique electrophilicity of Fisher carbenes in their synthesis of the beta-lactam antibiotic (+)-thienamycin (Figure 1-4).[8]

Figure 1-4: Nucleophiles Attack Fischer Carbenes on Carbon

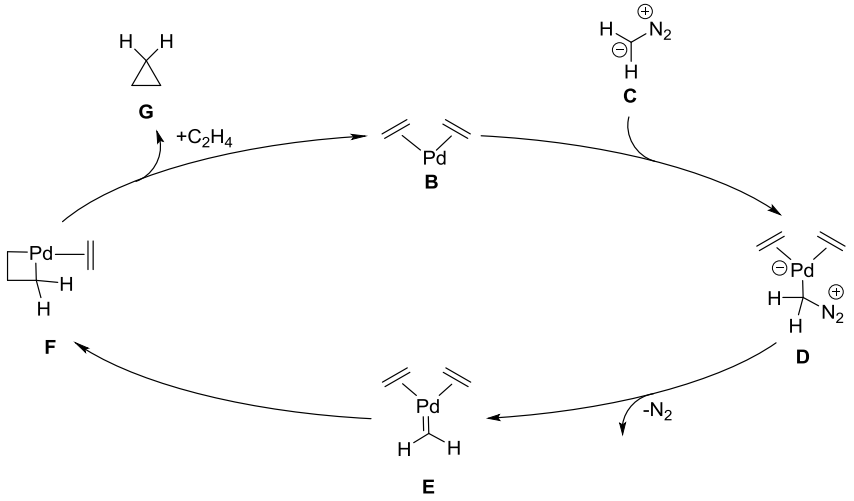


Formation of rhodium(II) carbene species **A** from the diazo azetidinone **1.3** followed by intramolecular cyclization yielded carbapenam product **1.4** in quantitative yield. The following section focuses on a particular subgroup of metal stabilized Fischer carbenes, the palladium(II) carbenes.

Palladium(0) Carbenes: Catalytic Intermediates in the Cyclopropanation of Olefins with Diazo Compounds

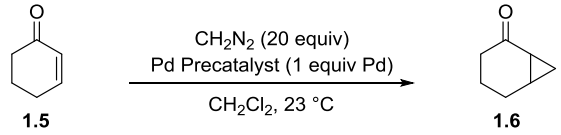
Before beginning a discussion of the structure and reactivity of palladium(II) carbenes, it is important to acknowledge the importance of their reduced counterparts, the palladium(0) carbenes. Palladium(0) carbenes are intermediates in the palladium-catalyzed cyclopropanation of olefins with diazomethane.[9] DFT studies performed by Staub on the cyclopropanation of ethene with diazomethane suggests the participation of palladium(0) carbenes in the reaction mechanism (Figure 1-5). The proposed catalytic cycle begins with the bimolecular reaction of ethene-coordinated palladium(0) species **B** and diazomethane **C** resulting in formation of ylide **D**. Extrusion of nitrogen gas from ylide **D** generates palladium(0) carbene intermediate **E** which is poised to undergo a oxidative cis-rearrangement forming the palladium (II) metallocyclobutane **F**. Such palladacyclobutanes with bidentate tetramethylethylenediamine ligands have been previously isolated and characterized.[10] Reductive elimination of palladacyclobutane **F** and coordination of another equivalent of ethene regenerates palladium(0) species **D** and produces the cyclopropane product **G**.

Figure 1-5: Palladium(0) Catalyzed Cyclopropanation Reaction of Ethene with Diazomethane



These cyclopropanation reactions are catalyzed by palladium(II) pre-catalysts which are reduced in situ yielding the catalytically active palladium(0) species. Illa and co-workers have isolated and characterized palladium(0) nanoparticles ranging from 13 to 40 nm in diameter, formed during the reaction of cyclohexenone with $Pd(OAc)_2$ and diazomethane.[11] The same report found that palladium(0) precatalysts are capable of catalyzing the cyclopropanation reaction, further lending credence to the existence of palladium(0) carbenes as active species in these reactions (Table 1-1, Entries 2 and 4). The olefins in dibenzylideneacetone (dba) compete with cyclohexenone **1.5** for ligation with the active palladium carbene species and cyclopropanation of dba was observed as a side reaction (Entires 2 and 5). Interestingly, when $Pd(PPh_3)_4$ or $Pd(OAc)_2$ spiked with triphenylphosphine was used, no cyclopropane product **1.6** was observed, presumably due to coordinative saturation at the palladium center (Entries 3 and 6).

Table 1-1: Cyclopropanation of Cyclohexenone with Various Palladium Precatalysts



1.5 **1.6**

Entry	Pd Precatalyst	time (min)	% Conversion
1	$Pd(OAc)_2$	5	90
2	$Pd_2(dba)_3$	5	50
3	$Pd(PPh_3)_4$	10	0
4	Pd black powder	5	40
5	$Pd(OAc)_2$ + dba (Pd/dba = 1/3)	5	60
6	$Pd(OAc)_2$ + PPh_3 (Pd/PPh_3 = 1/4)	5	0

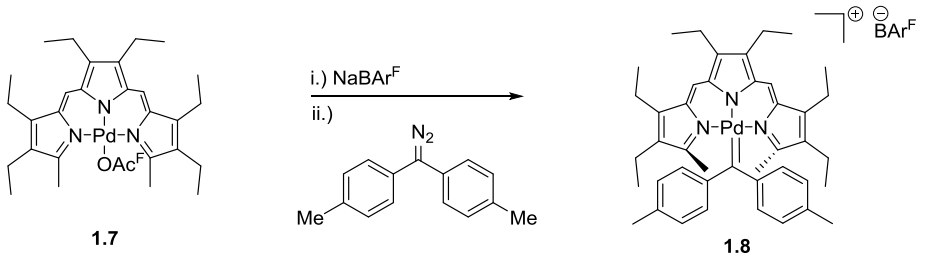
Short reaction times and temperatures typically hovering around zero degrees Celsius are typical for this class of cyclopropanations suggesting an extremely reactive catalyst is involved.[12]

In 1997 Denmark and coworkers reported the cyclopropanation of electron deficient olefins with diazomethane utilizing chiral bis(oxazoline)palladium(II) catalysts.[13] They were able to achieve high yields with these catalysts however only trace levels of asymmetric induction were observed. An in situ generated achiral palladium(0) species is believed to be the reason for the scant asymmetric induction observed in the reaction. Chiral bis(oxazolines) had previously been successfully utilized by Evans and coworkers as ligands for the copper catalyzed asymmetric cyclopropanation of olefins.[14]

Palladium (II) Carbenes: Structure and Reactivity

Treating palladium(II) salts with diazo compounds results in the extrusion of nitrogen gas and the formation of a palladium(II) carbene species, some of which have been isolated and characterized. Bröring and co-workers reported an X-ray crystal structure of a cationic palladium(II) carbene in 2003.[15] Treatment of a palladium(II) tripyrin complex **1.7** with $NaBAr^F$ (BAr^F = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate) followed by di-*p*-tolyldiazomethane resulted in the release of nitrogen gas and formation of carbene complex **1.8** (Figure 1-6). At first glance palladium complex **1.8** appears extremely crowded around the palladium and carbene centers. Backbonding between the palladium and carbene is minimal due to a torsion angle of 47.0° between the planes of the tripyrin-Pd and carbene moieties. Disruption of the backbonding interaction probably accounts for the unusually long Pd-C bond distance (1.978 Å) observed in this molecule.

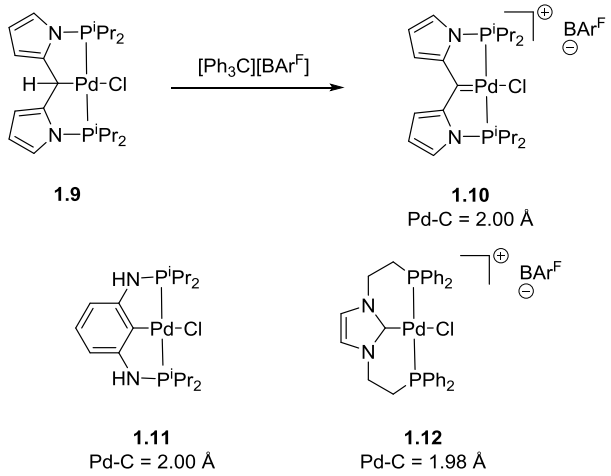
Figure 1-6: First Reported Synthesis and Isolation of a Palladium(II) Carbene



1.7 **1.8**

Unusually long Pd-C bonding distances have been observed in other palladium(II) carbene complexes as well. A bidentate pincer-phosphine palladium complex **1.9** was used by Weng and coworkers as a precursor to palladium(II) carbene **1.10** (Figure 1-7).[16] Abstraction of a hydride from species **1.9** using a stabilized cation, Ph_3C^+, resulted in formation of the cationic palladium carbene complex **1.10**. The Pd-C bond distance of 2.00 Å is the length observed by Bröring and coworkers with their cationic palladium carbene **1.8**. Pd-C bond distances of these lengths are close to the values seen in non-Fischer carbene Pd(II)-C species such as aryl palladium(II) complex **1.11** (2.00 Å) and NHC complex **1.12** (1.98 Å).[17,18] Taken together, these data suggest backbonding is not an important bonding interaction in palladium(II) carbenes and the carbene carbon is rendered more prone towards nucleophilic attack due to its increased cationic character.

Figure 1-7: Synthesis of Palladium(II) Carbene Phosphine Pincer Complex and Selected Pd(II)-C Bond Distances



1.9

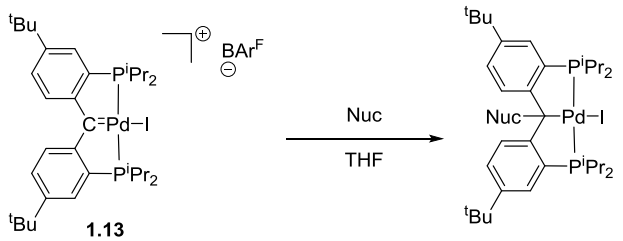
1.10
Pd-C = 2.00 Å

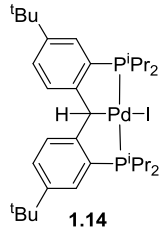
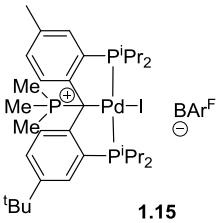
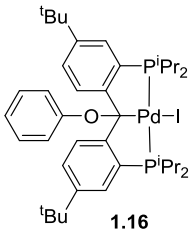
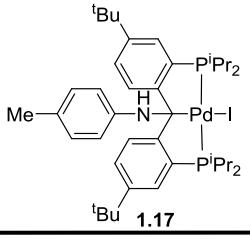
1.11
Pd-C = 2.00 Å

1.12
Pd-C = 1.98 Å

Intermolecular attack of cationic palladium(II) carbenes at the carbene center by charged and uncharged nucleophiles has been reported by Cui and Iluc.[19] Treatment of cationic palladium(II) carbene complex **1.13** with a variety of nucleophiles resulted in successful reactions at low temperatures and short reactions times for most substrates (Figure 1-8). Interestingly, sodium hydride, more known for its basic rather than nucleophilic nature, was capable of serving as a hydride donor to the carbene forming the alkyl palladium(II) complex **1.14**. Longer reaction times were observed with sodium hydride presumably due to its poor solubility in THF. Sodium phenoxides and lithium *p*-methylphenylanalide readily reacted with **1.13** at low temperatures forming products **1.16** and **1.17** in 15 minutes albeit with poor yields. Lithiated alkoxides and phenoxides did not react with carbene **1.13**. Trimethylphosphine reacted with **1.13** at room temperature in 15 minutes affording the phosphonium complex **1.15** in quantitative yield.

Figure 1-8: Nucleophiles Attack Palladium(II) Carbenes



Nucleophile	Product	Temperature, time, yield
Na–H 1.2 equiv	 **1.14**	23 °C, 24 h, n.r
Me Me–P Me 1.1 equiv	 **1.15**	23 °C, 5 min, 100%
ONa 1.1 equiv	 **1.16**	-35 °C, 15 min, 53%
Me–NHLi 1.0 equiv	 **1.17**	-35 °C, 15 min, 49%

The authors did not address whether the rate determining step was bimolecular or unimolecular. A plausible intramolecular pathway could proceed by association of the nucleophile to the metal center forming a penta-coordinate palladium species which could then undergo a intramolecular 1,2-shift generating product (Figure 1-9). Evidence for a multi-step

association/1,2-shift sequence occurring under similar conditions was presented by Hursthouse and co-workers (Figure 1-10). Alkylpalladium(II) complex **1.18** formed the methyl shifted product **1.19** in 60 % yield after treatment with a tridentate pyridine/NHC ligand at -78 °C. Formation of **1.19** is thought to occur through migratory insertion of a methyl group into the NHC carbon in penta-coordinate palladium intermediate **H**.[20] Van Vranken and co-workers were the first to pioneer interception of arylpalladium(II) complexes with carbene moieties and utilize the unique reactivity such intermediates possess.

Figure 1-9: Plausible Pathways for C-Nuc Bond Formation with Palladium(II) Carbenes

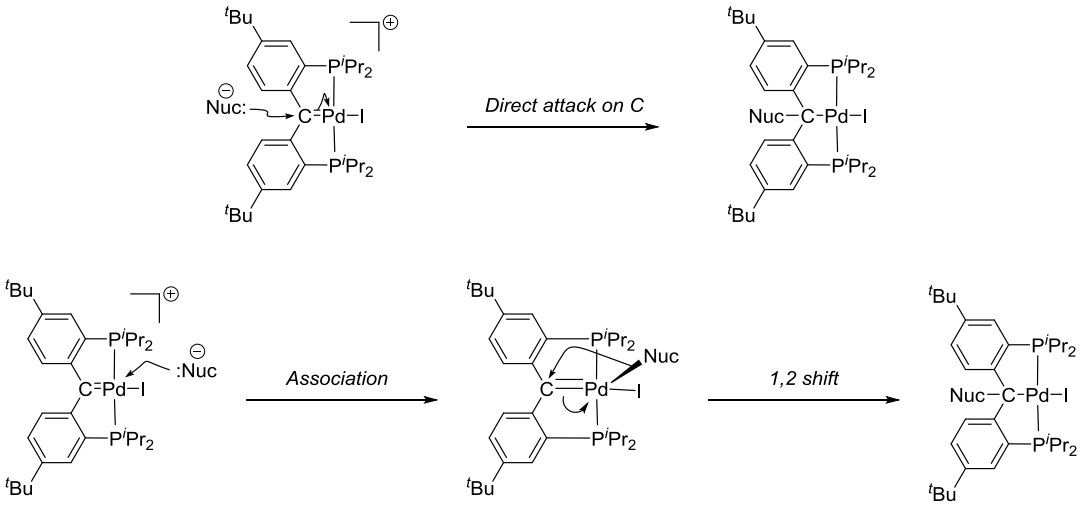
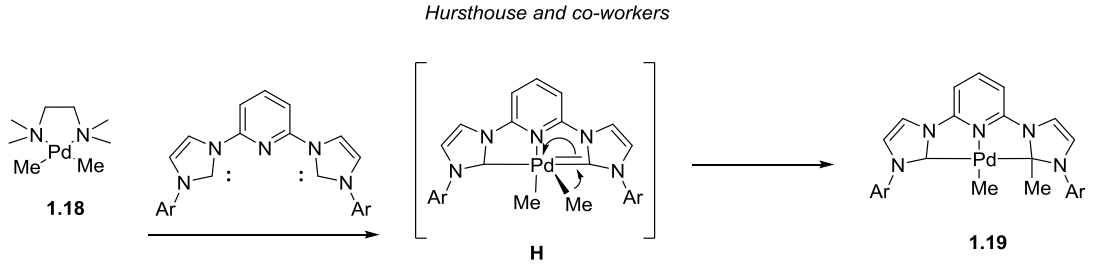


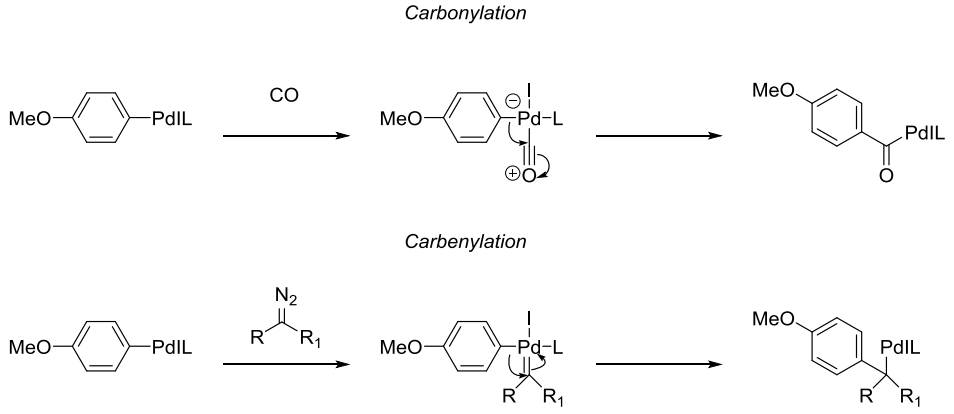
Figure 1-10: Migratory Insertions Observed in Five Coordinate Pd(II) NHC Carbenes



Carbenylative Insertions

Cis-migratory insertion processes are well-precedented in palladium catalysis. Palladium carbonyl complexes readily undergo migratory insertion reactions generating acyl palladium species as intermediates.[21] The acyl palladium intermediates generated in such reactions have been intercepted with boronic acids, copper acetylides, stannanes, and olefins.[22] Mechanistically this carbonylative insertion of a *cis* X type ligand bound to palladium(II) is reminiscent of the migratory insertions Van Vranken and co-workers observed with palladium(II) carbenes (Figure 1-11). Van Vranken coined the term "carbenylative insertion" to describe this process. Unlike carbonylative insertions processes, carbenylative insertions are capable of generating new stereogenic centers between the coupling partners. The possibility of potentially controlling the new stereocenter created by carbenylative insertion processes has spurred intense interest this field.

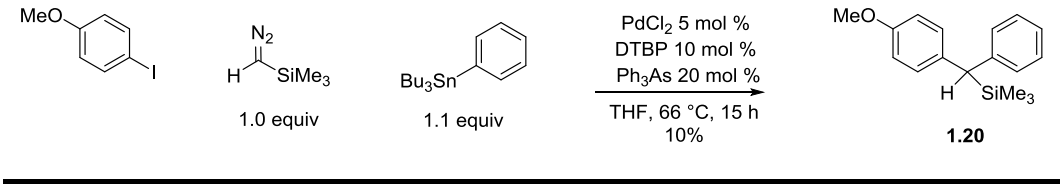
Figure 1-11: Comparison of Palladium-catalyzed Carbonylation and Carbenylation

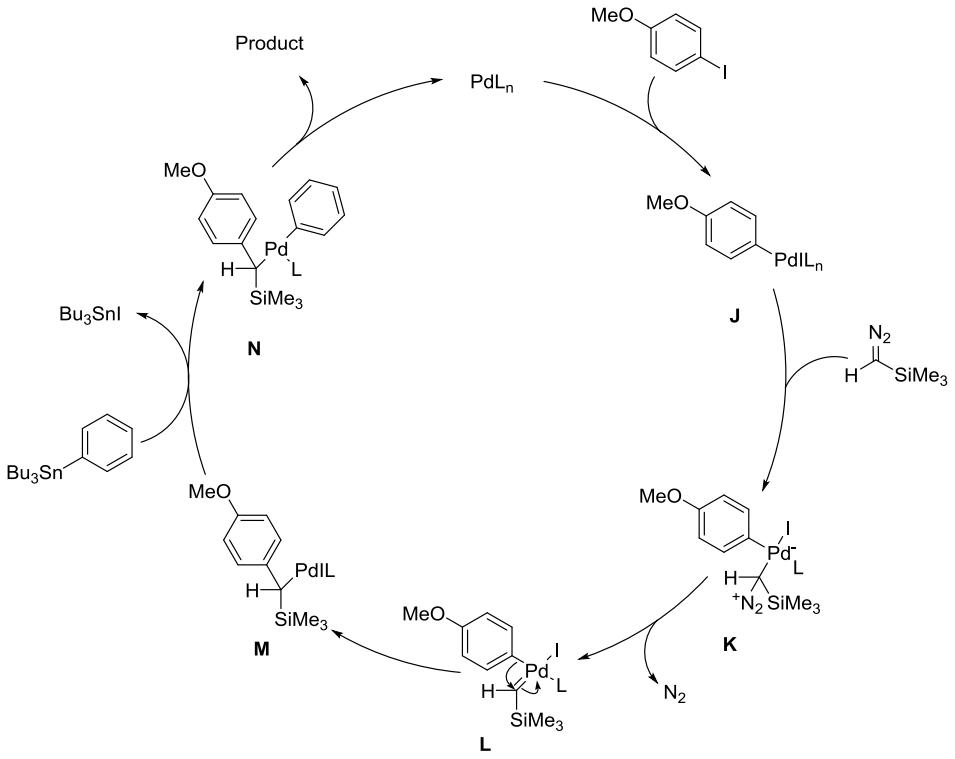


The synthetic utility of the palladium(II) carbene migratory insertion process was realized by Greenman and Carter in the Van Vranken lab in 2001.[23] They were successfully able to interrupt a Stille cross-coupling and form three new C-C bonds while generating a new stereogenic center and forming diarylmethane **1.20** in 10% yield (Figure 1-12). Slow-addition of both arylstannane and trimethylsilyldiazomethane as well as use of the non-nucleophilic triphenylarsine ligand was required. A plausible mechanistic pathway begins by reduction of $PdCl_2$ precatalyst to the active palladium(0) species followed by oxidative addition into *p*-iodoanisole forming arylpalldium(II) intermediate **J**. Reduction of palladium halide salts has previously been observed in cyclopropanation reactions of olefins with diazomethane.[24] Arylpalladium(II) intermediate **J** would normally undergo transmetallation with an arylstannane under standard Stille conditions, however in the presence of a diazo compound, **J** is intercepted before transmetallation can occur resulting in palladium ylide **K**. Extrusion of nitrogen gas results in palladium(II) carbene species **L**. *Cis*-migratory insertion of the *p*-anisole palladium ligand into the carbene carbon results in alkylpalladium(II) intermediate **M**. Transmetallation of **M** with Bu_3SnPh and subsequent reductive elimination from **N** affords diarylmethane product

1.20. This work represents the first example of a palladium-catalyzed carbenylative cross-coupling reaction.

Figure 1-12: Plausible Mechanism of Pd-catalyzed Three Component Coupling of Aryl Iodides, Diazo Compounds, and Arylstannanes

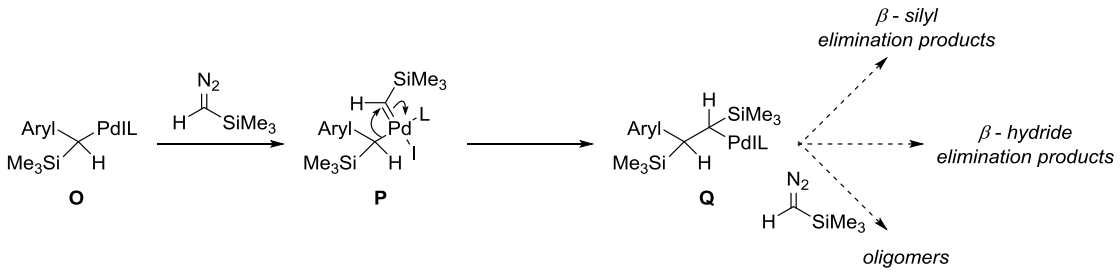




Facile formation of palladium carbenes from palladium(II) complexes and diazo compounds introduces new avenues of reactivity quite unique to palladium-catalyzed carbenylative cross-coupling reactions. For example attack of alkylpalladium(II) intermediates by diazo compounds can potentially outcompete transmetallation with classic cross-coupling partners such as arylstannanes.[25] Greenman and Carter noted that the reason for the poor yields of diarylmethanes in the three-component coupling of of trimethylsilydiazomethane, *p*-

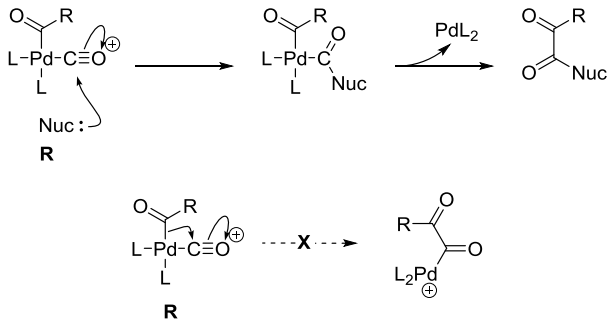
iodoanisole, and Bu_3SnPh was due to the formation of palladium carbenes after the initial migratory insertion event (Figure 1-13). Intermediate **O** could possibly be intercepted by another equivalent of trimethylsilyldiazomethane affording palladium carbene **P** which could then undergo migratory insertion ('overinsertion'), resulting in the homologated species **Q**. β-hydride elimination, β-silyl,[25] or further carbene formation and overinsertion are all possible from intermediate **Q**.[26]

Figure 1-13: Possible Side Reactions Resulting from Overinsertion of Palladium Carbenes



Overinsertion of CO is a process not observed in palladium-catalyzed carbonylative insertion reactions. For example, in 1984 Sen and co-workers demonstrated that the formation of oxalates observed in the palladium-catalyzed copolymerization of alkenes and CO results from nucleophilic attack of intermediate **R** followed by reductive elimination rather than overinsertion (Figure 1-14).[27] Migratory insertion of acylpalladium ligands into carbon monoxide is believed to be thermodynamically unfavorable.[28] Palladium(II) salts are used to synthesize polyketones from CO and ethene monomers in the Shell polyketone process, a synthesis which would be rendered industrially infeasible if CO overinsertion was a facile process.[29]

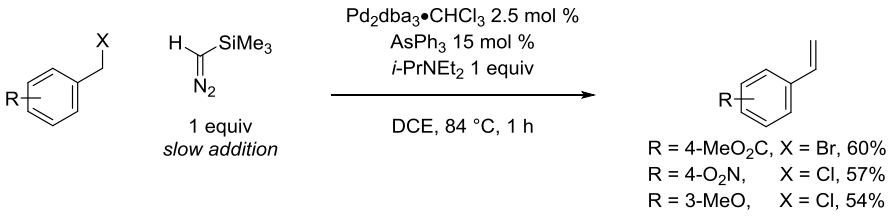
Figure 1-14: Overinsertion of CO is not Favorable



Carbenylative Insertion Followed by β-Hydride Elimination

Van Vranken and co-workers rationalized that homologated alkyl-palladium(II) intermediates such as **Q** (Figure 1-13) could potentially be induced to undergo β-hydride elimination if such a process could be made favorable. They subsequently showed that trimethylsilyldiazomethane can effectively participate in a palladium-catalyzed homologation reaction with benzyl halides affording styrene derivatives in moderate yields (Figure 1-15). Use of non-nucleophilic triphenylarsine ligand provided better catalyst turnover than triphenylphosphine due to SN2 side reactions observed with the latter and benzyl halide starting material.[30] Loss of the silyl group was difficult to overcome under the reaction conditions. Both electron-rich and electron-deficient benzyl halides afforded styrenes in similar yields.

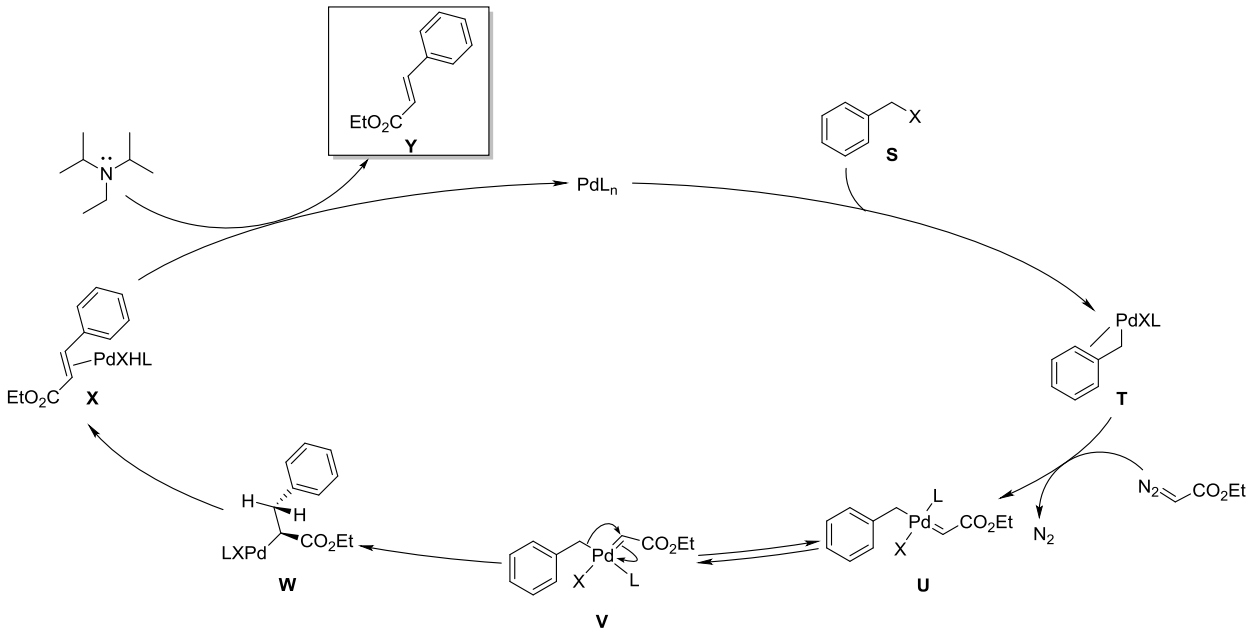
Figure 1-15: Palladium-Catalyzed Homologation of Benzyl Halides with Trimethylsilyldiazomethane



In 2005, Greenman in the Van Vranken lab further elaborated on this class of homologation reactions by altering the carbene precursor from trimethylsilyldiazomethane to α-

diazoesters.[31] The use of α-diazoesters as carbene precursors circumvented the issue of β-silyl elimination inherent with trimethylsilyldiazomethane. Moderate yields of variously substituted cinnamate esters were achieved. A plausible mechanism for the reaction begins with oxidative addition of palladium(0) across the C-X bond of benzyl halide **S** (Figure 1-16). Benzylpalladium(II) intermediate **T** is then intercepted by diazoester, followed by extrusion of nitrogen gas and formation of palladium(II) carbene intermediate **U**. All of the mechanistic steps in the catalytic cycle have been previously demonstrated to occur at low temperatures. The authors note that heating may be required in order isomerize square-planer palladium(II) intermediate **U** to carbene **V** positioning the benzyl ligand *cis* to the carbene. Migratory insertion and β-hydride elimination from alkylpalladium(II) intermediate **W** generates cinammate ligated palladium-hydride **X** which is reduced by amine base regenerating Pd(0).

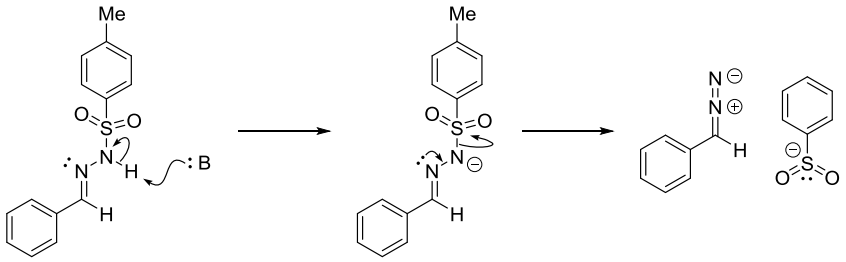
Figure 1-16: Mechanism for Palladium-Catalyzed Carbene Insertion into Benzyl Bromides



The pioneering work performed in our lab has paved the way for further development of palladium-catalyzed carbenylative cross-coupling reactions. Carbenylative cross-couplings have

become a synthetically viable method for the synthesis of highly substituted olefins.[32] In 2001 Aggarwal and co-workers reawakened the synthetic community's interest in *N*-tosylhydrazones.[33] They were able to show that these easily prepared reagents could be effectively utilized as carbene precursors in metal catalyzed cyclopropanation reactions. *N*-tosylhydrazones are acidic enough to be deprotonated by most common bases and readily undergo the Bamford-Stevens reactions (Figure 1-17).[34] Deprotonation of the N-H bond followed by elimination of sulfinite anion generates diazo compounds in situ.

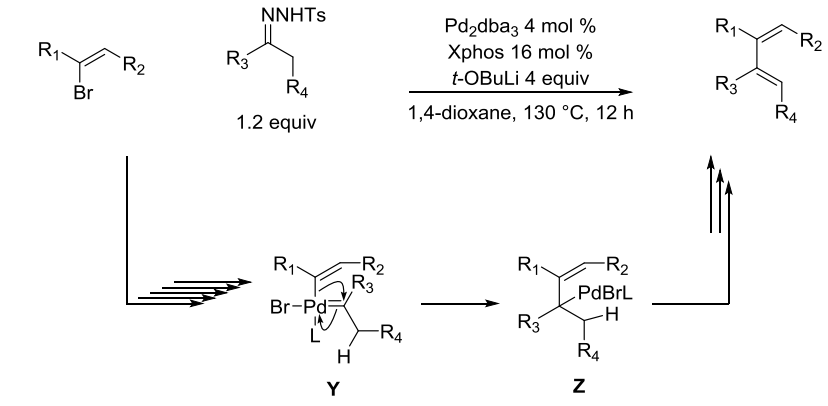
Figure 1-17: Bamford-Stevens Reaction

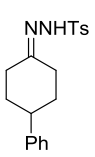
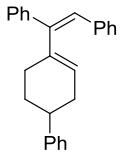
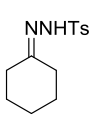
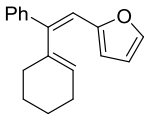
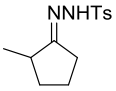
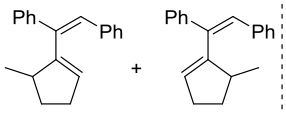
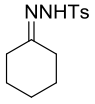
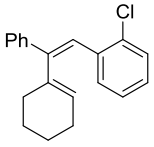
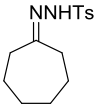
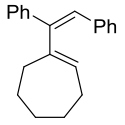
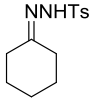
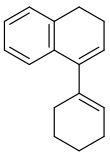


Generation of the diazo compound in situ has expanded the scope of these reactions by obviating the need to synthesize, store, and handle alkyl and aryl diazo compounds. Barluenga and co-workers reported the first use of *N*-tosylhydrazones as diazo precursors in palladium-catalyzed carbenylative cross-couplings.[35] Synthesis of poly-substituted olefins was achieved through the coupling of aryl halides with aliphatic *N*-tosylhydrazones. Valdes, a former co-worker of Barluenga's and co-author on their seminal publication, has carried on research in this area of olefin synthesis. Recently Valdes and co-workers have described an elegant palladium-catalyzed carbenylative cross-coupling process for the synthesis of highly substituted polyenes (Figure 1-18).[36] Mechanistically the transformation resembles the palladium-catalyzed carbenylative cross-coupling of benzyl bromides and trimethylsilyldiazomethane reported by Greenman and Van Vranken in 2005. Oxidative addition of palladium(0) into a vinyl bromide

starting material generates palladium carbene **Y**. Migratory insertion into palladium carbene **Y** followed by reductive elimination of alkylpalladium(II) species **Z** affords highly substituted polyenes in moderate to excellent yields.

Figure 1-18: Carbenylative Cross-Coupling of Alkenyl Bromides and Aliphatic *N*-Tosylhydrazones



hydrazone	product	yield	hydrazone	product	yield
 **1.21a**	 **1.22a**	**94%**	 **1.21d**	 **1.22d**	**87%**
 **1.21b**	 **1.24b**	**48%**	 **1.21e**	 **1.22e**	**67%**
 **1.21c**	 **1.22c**	**50%**	 **1.21f**	 **1.22f**	inseparable isomeric mixture

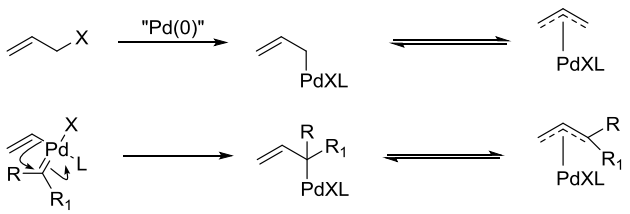
N-tosylhydrazones derived from cyclic ketones were successfully coupled with (*Z*)-(1-bromoethene-1,2-diyl)dibenzene affording substituted dienes (**1.22a-c**). The reaction of unsymmetrical *N*-tosylhydrazone **1.21b** and (*Z*)-(1-bromoethene-1,2-diyl)dibenzene resulted in a

one to one mixture of diene products due to non-selective β-hydride elimination from alkylpalladium intermediate **Z**. The scope of the alkenyl bromide coupling partner was also investigated. The reaction tolerated both electron-rich and electron-deficient alkenyl bromides (**1.22d** and **1.22e**). Curiously, (*E*)-alkenyl bromides were not efficient coupling partners in the reaction. The combination of cyclohexenone *N*-tosylhydrazone **1.21a** and (*E*)-alkenyl bromide resulted in a sluggish reaction yielding an inseparable mixture of isomeric diene coupling products (**1.22f**). *N*-tosyl hydrazones derived from aliphatic aldehydes and both α-bromostyrene and β-bromostyrene were poor substrates for the reaction resulting in low yields of diene product. These results suggest that a stericly crowded environment around the metal center in intermediate **Z** is necessary to promote fast β-hydride elimination.

Generation of η^3-allylpalladium Intermediates through Carbenylative Insertion

Carbenylative insertion offers access to synthetically valuable alkylpalladium(II) intermediates. We have already seen how these intermediates can be intercepted and rendered synthetically valuable, either through transmetallation or β-hydride elimination. In 2007, Sean Devine from the Van Vranken lab discovered that the carbenylative insertion reaction could also be used to access η^3-allylpalladium species (Figure 1-19).[37] η^3-allylpalladium species have typically been accessed through ionization of allylic leaving groups and participate in the Tsuji-Trost reaction.[38] Carbenylative insertion presents a novel method for accessing this mode of reactivity.

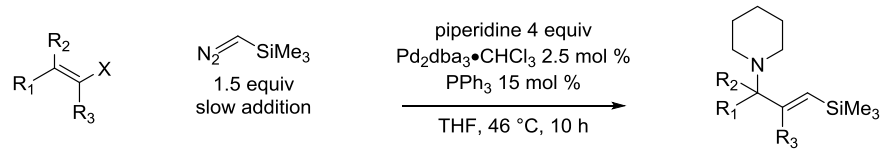
Figure 1-19: Access to η^3-Allylpalladium Intermediates

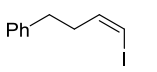
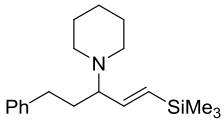
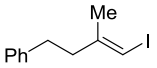
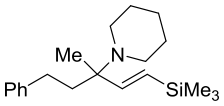
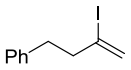
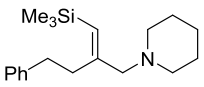
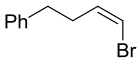
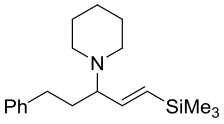


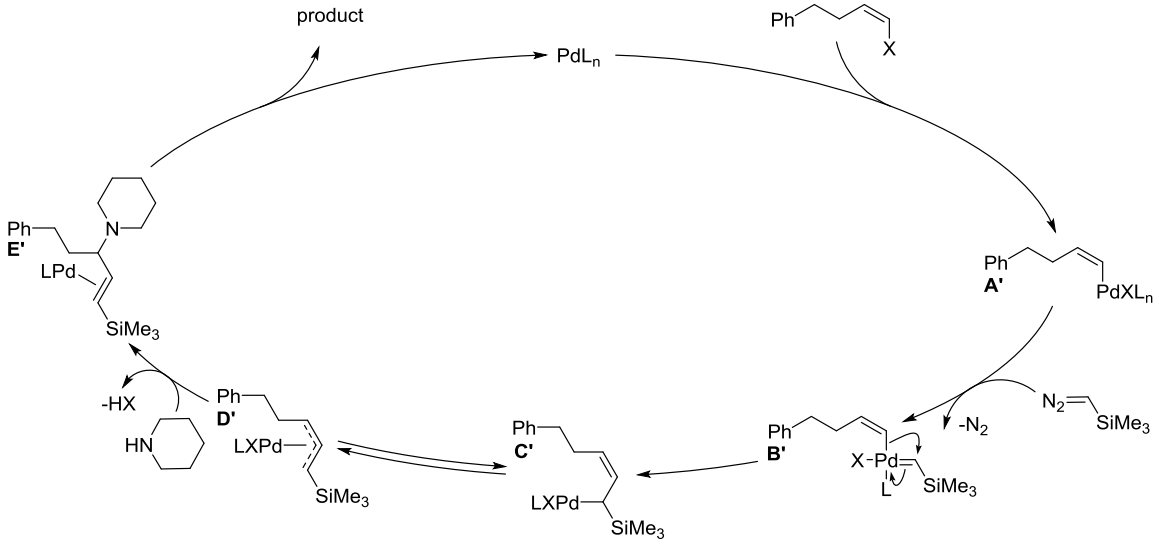
Alkenyl halides participate in three-component carbenylative cross-coupling reactions with trimethylsilyldiazomethane and piperidine (Figure 1-20). The highest yields were observed when the diazo compound was added over 10 hours via syringe pump and piperidine was used as the nucleophile (**1.24a**) in excess. Multiple equivilants of amine are required to neutralize HI generated over the course of the reaction. In all cases the allylamine product was formed with the new C-N bond distal to the TMS bearing carbon. Other cyclic secondary amines were also tolerated under the reaction conditions. For example, morpholine reacted with vinyl iodide **1.23a** in 80% yield while pyrrolidine only gave allylamine product in 27% yield. Addition of 1 equiv each of phenylboronic and K_2CO_3 improved the yields for the coupling of morpholine and pyrrolidine. The advantageous effect of these additives may stem from their ability to reduce PdX_2 species formed during the reaction back to catalytically relevant palladium(0). Methyl substituted vinyl iodide **1.23b** afforded allyl amine product **1.24b** as a single regioisomer in 55% yield. Internal vinyl iodide **1.23c** gave allylamine product **1.24c** in 18% yield as a 3.4:1 mixture of *E/Z* isomers. Alkenyl bromides could also be utilized as coupling partners. When vinyl bromide **1.23d** was submitted to the reaction, allyl amine **1.24a** was isolated in 55% yield. Unfortunately, vinyl triflates were not tolerated.

A plausible mechanism for this transformation begins with oxidative addition of palladium(0) into the C-X bond of the vinyl halide followed by attack of diazo on the electrophilic palladium(II) intermediate **A'**. Extrusion of nitrogen gas affords palladium(II) carbene **B'** which undergoes migratory insertion generating η^1-allylpalladium **C'**. Equilibration of **C'** to **D'**, followed by attack of piperidine generates allyl amine product **1.24a**.

Figure 1-20: Carbenylative Insertion of Alkenyl Halides and Trapping with Piperidine



alkenyl halide		product		yield
	**1.23a**		**1.24a**	**91%**
	**1.23b**		**1.24b**	**55%**
	**1.23c**		**1.24c**	**18%** *E*/*Z* 3.4:1
	**1.23d**		**1.24d**	**55%**



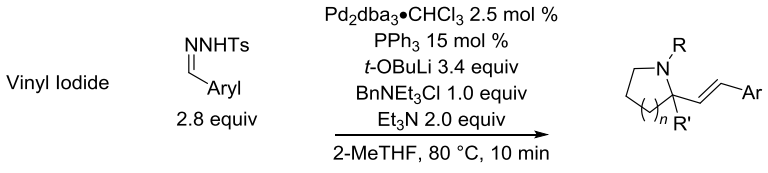
In 2012 Khanna and co-workers in our group expanded the scope of carbenylative aminations by employing *N*-tosylhydrazones as coupling partners.[39] This work utilized mostly (*E*)-vinyl iodides with pendant secondary amines as nucleophiles, a departure from the initial

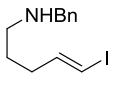
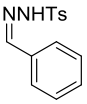
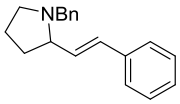
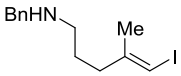
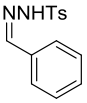
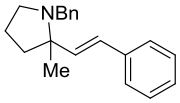
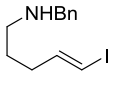
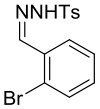
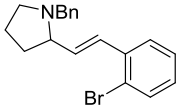
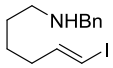
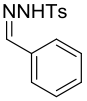
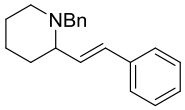
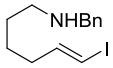
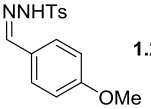
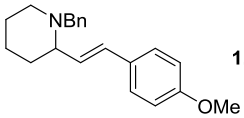
report of carbenylative amination by Devine which used untethered cyclic secondary amines as nucleophiles along with (*Z*)-vinyl halides. Trapping the η^3-allylpalladium species generated after migratory insertion with a tethered secondary amine affords substituted pyrrolidine alkaloids, a motif found in bioactive natural products (Figure 1-21).[40] The use of *N*-tosylhydrazones necessitates the use of strong base such as *t*-BuOLi and higher temperatures compared to carbenylative aminations using diazo compounds reported by Devine. The reaction is also complicated due to the low solubility of *N*-tosylhydrazones salts in ethereal solvents, requiring the addition of one equivalent of benzyltriethylammonium chloride as a phase transfer catalyst and two equivalents of triethylamine. The aryl substituted diazo compounds generated in situ from the Bamford-Stevens reaction of *N*-tosylhydrazones are quite reactive, requiring 2.8 equivalents in order drive the reaction to completion. However, even with the requirement of multiple additives and excess hydrazone, this reaction is remarkable; pyrrolidine products are formed in high yields in only 10 minutes, no syringe pump addition of coupling partner is necessary, and the scope of the diazo coupling partner is expanded to valuable aryl diazo compounds.

Attack of the pendant benzylamine always occurs away from the phenyl substituted carbon of the η^3-allylpalladium species, resulting in pyrrolidines such as **1.27a**, isolated in 95% yield. Internally substituted vinyl iodides are well tolerated. Vinyl iodide **1.25a** was successfully coupled with benzaldehyde *N*-tosylhydrazone **1.26a** in 90% yield. In most cases only the *E* allylamine product was isolated, however *ortho* bromine substituted *N*-tosylhydrazone **1.26b** afforded a 5:1 mixture of *E*/*Z* pyrrolidine isomers in 96% yield. Competitive oxidative addition of palladium(0) into the C-Br of hydrazone **1.26b** or pyrrolidine **1.27c** was not observed.

Piperidine rings could also be synthesized in good yields under the reaction conditions (**1.27d** and **1.27e**).

Figure 1-21: Intramolecular Carbenylative Aminations and Representative Examples

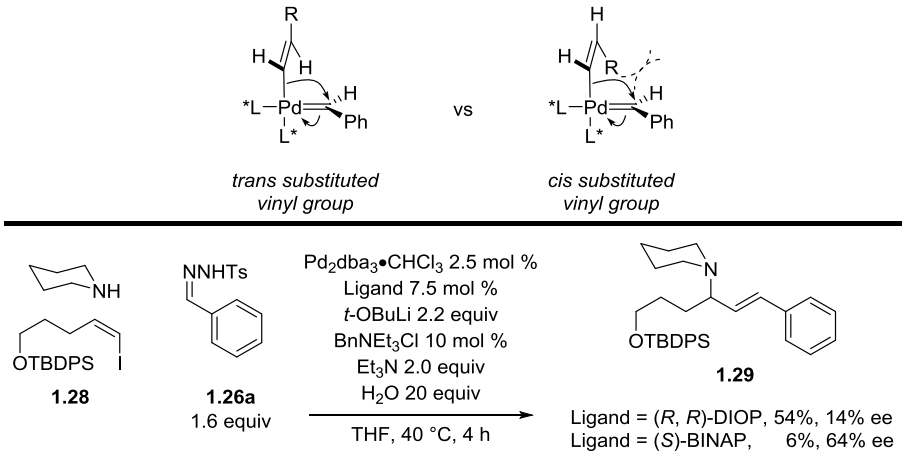


vinyl iodide		*N*-tosylhydrazone		product		yield
	**1.25a**		**1.26a**		**1.27a**	95%
	**1.25b**		**1.26b**		**1.27b**	90%
	**1.25c**		**1.26c**		**1.27c**	96% *E*/*Z* 5:1
	**1.25d**		**1.26d**		**1.27d**	90%
	**1.25e**		**1.26e**		**1.27e**	60%

Khanna and co-workers next examined the possibility of asymmetric induction in carbenylative amination reactions. When triphenylphosphine was replaced with chiral bidentate (*R,R*)-DIOP ligand, pyrrolidine **1.27a** was formed in 86% yield but only 12% ee. (*S*)-BINAP did not perform any better, affording pyrrolidine **1.27a** in 19% yield and 17% *ee*. The migratory insertion of the vinyl group into the palladium carbene is believed to set the absolute stereochemistry in this reaction (Figure 1-22). Vinyl iodides with *cis* substituents such as (*Z*)-vinyl iodide **1.28**, could improve asymmetric induction in the key migratory insertion event by increasing the steric crowding present in the transition state. Vinyl iodide **1.28**, piperidine, and

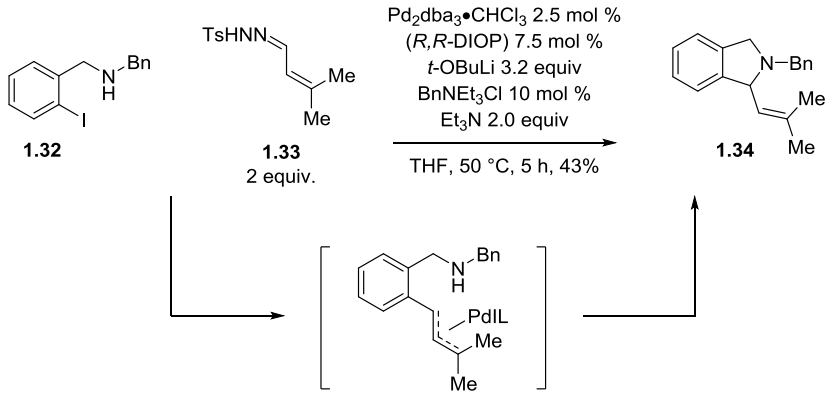
hydrazone **1.26a**, were coupled under slightly modified reaction conditions resulting in piperidine product **1.29**. Reaction with (*R*,*R*)-DIOP resulted in 54% yield but 14% *ee*. (*S*)-BINAP gave low yield of piperidine product but showed 64% *ee* in the product. Two catalyticlly active palladium catalysts, one chiral the other achiral, are probably responsible for the varying levels of enantioselectivity observed in these reactions. The achiral palladium species is evidently more active under the reaction conditions.

Figure 1-22: Asymmetric Induction in Carbenylative Amination



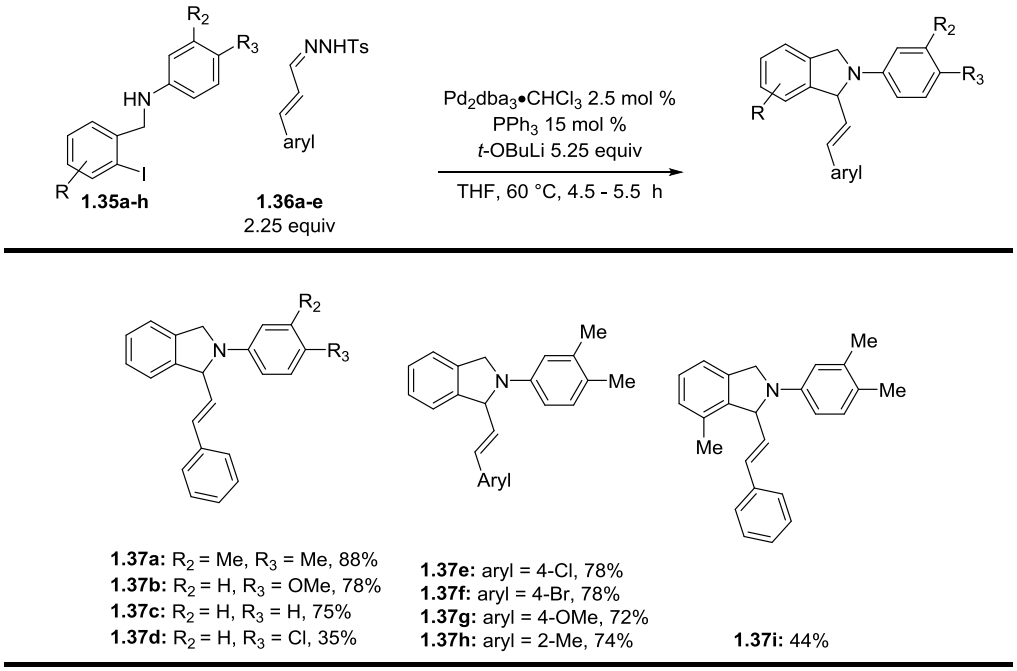
In unpublished work from the Van Vranken group, Chris Agee expanded the scope of carbenylative cyclizations by investigating the cyclization of aryl iodides possessing tethered amine nucleophiles (Figure 1-23).[41] Aryl iodide **1.32** was successfully coupled with *N*-tosylhydrazone **1.33** affording isoindoline **1.34** in 43% yield. Formation of palladium(II) carbene followed by migratory insertion eventually leads to an η^3-allylpalladium which is intercepted with a pendant benzyl amine on the aryl group. Unfortunately allylic isoindolines such as **1.34** proved to be exceedingly sensitive to autoxidation in the presence of ambient oxygen making them difficult to purify and characterize. Homolytic cleavage of the benzylic proton in isoindoline **1.34** generates a captodatively stabilized radical susceptible to further degradation. Aerobic decomposition of related allylic isoindoline ring systems has been reported.[42]

Figure 1-23: Carbenylative Cyclization of 2-Benzylamine Aryliodides



Liang and co-workers reported a very similar isoindoline synthesis in 2013 using *N*-aryl instead of *N*-alkyl amines as nucleophiles and *N*-tosylhydrazones derived from cinnamaldehyde.[43] *N*-arylisoindolines were stable to isolation and a broad substrate scope was exhibited (Figure 1-24). Meta and para substitution on the aniline was well tolerated (Figure 1-25, **1.37a-c**). 4-Cl substituted aniline **1.35d** was a poor substrate for the reaction, presumably due to the decreased nucleophilicity of the nitrogen atom. Substitution on the aryl ring of the *N*-tosylhydrazone did not detrimentally affect the yield (Figure 1-25, **1.37e-h**). 2,5 Di-substituted indane **1.37i** was isolated in 44% yield. Although isoindolines were synthesized in good yields, dearylation of *N*-arylamines is often challenging and requires oxidative deprotection, potentially interfering with further derivatization.[44]

Figure 1-24: Synthesis of *N*-Arylisoindolines



Conclusion

This chapter has presented a general summary on the reactivity of palladium(II) carbenes and their use as catalytic intermediates in various reactions, many of which generate η^3-allylpalladium intermediates. Migratory insertions of ligands bound *cis* to the carbene on the palladium center is the key process which distinguishes these species from other intermediates found in various palladium-catalyzed processes. Recent work involving η^3-benzylpalladium intermediates suggests that they might be accessed through carbene insertion processes.

References

1 Nicolaou, K. C.; Bulger, P.G.; Sarlah, P. G. "Palladium-Catalyzed Cross-Coupling Reactions in Total Synthesis" *Angew. Chem. Int. Ed.* **2005**, *44*, 4442 – 4489.

2 Roughly, S. D.; Jordan, A. M. "The Medicinal Chemist's Toolbox: An Analysis of Reactions Used in the Pursuit of Drug Candidates" *J. Med. Chem.* **2011**, *54*, 345 – 3479.

3 Cyclopropanation reactions believed to involve singlet carbenes as intermediates: Skell, P.S.; Garner, A. Y. "The Stereochemistry of Carbene-Olefin Reactions. Reactions of Dibromocarbene with *cis*- and *trans*-2-Butenes" *J. Am. Chem. Soc.* **1956**, *78*, 3409 – 3411. Skell, P.S.; Garner, A. Y. "Reactions of Bivalent Carbon Compounds. Reactivities in Olefin-Dibromocarbene Reactions " *J. Am. Chem. Soc.* **1956**, *78*, 5430 – 5433. Skell,

P.S.; Woodworth, R. C.; "Structure of Carbene, CH_2" *J. Am. Chem. Soc.* **1956**, *78*, 4496 – 4497.

[4] Meurer, E. C; Santos, L. S.; Pilli, R. A.; Eberlin, M. N. "Probing the Mechanism of the Petasis Olefination Reaction by Atmospheric Pressure Chemical Ionization Mass and Tandem Mass Spectrometry" *Org. Lett*. **2002**, *5*, 1391 – 1394.

[5] Payack, J. F.; Hughes, D. L.; Cai, D.; Cottrell, I. F.; Verhoeven, T. R. "Dimethyltitanocene" *Org. Synth.* **2002**, *79*, 19-23.

[6] Fischer, E, O.; Maasbol, A. "On the Existance of a Tungsten Carbonyl Carbene Complex" *Angew. Chem. Int. Ed.* **1964**, *3*, 580 – 581.

[7] Arduengo, A. J.; Davidson, F.; Dias, H. V. R.; Goerlich, J. R.; Khasnis, D.; Marshall, W. J.; Prakasha, T. K. "An Air Stable Carbene and Mixed Carbene Dimers" *J. Am. Chem. Soc.* **1997**, *119*, 12742 – 12749.

[8] Saltzmann, T. N.; Ratcliffe, R. W.; Christensen, B. G., Bouffard, F. A. "A Stereocontrolled Synthesis of (+)-Thienamycin" *J. Am. Chem. Soc.* **1980**, *102*, 6161 - 6163.

[9] Straub, B. F. "Pd(0) Mechanism of Palladium-Catalyzed Cyclopropanation of Alkenes by CH_2N_2: A DFT Study" *J. Am. Chem. Soc.* **2002**, *124*, 14195 – 14201.

[10] Hoffman, H. M. R.; Otte, A.R.; Wilde, A.; Menzer, S.; Williams, D. J. " Isolation and X-Ray Crystal Structure of a Palladacyclobutane: Insight into the Mechanism of Cyclopropanation" *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 100 – 102.

[11] Illa, O.; Rodriguez-Garcia, C.; Acosta-Silva, C.; Favier, I.; Picurelli, D.; Oliva, A.; Gomez, M.; Branchadell, V.; Ortuno, R. M. "Cyclopropanation of Cyclohexenone by Diazomethane Catalyzed by Palladium Diacetate: Evidence for the Formation of Palladium(0) Nanoparticles" *Organometallics* **2007**, *26*, 3306 – 3314.

[12] Suda, M. "Cyclopropanation of Terminal Olefins Using Diazomethane/Palladium(II) Acetate" *Synthesis* **1981**, 714.

[13] Denmark, S. E.; Stavenger, R. A.; Faucher, A-M.; Edwards, J.P. "Cyclopropanation with Diazomethane and Bis(oxazoline)palladium (II) Complexes" *J. Org. Chem.* **1997**, *62*, 3375 – 3389.

[14] Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. "Bis(oxazolines) as Chiral Ligands in Metal-Catalyzed Asymmetric Reactions. Catalytic, Asymmetric Cyclopropanations of Olefins" *J. Am. Chem. Soc.* **1991**, *113*, 726 – 728.

[15] Bröring, M.; Brandt, C. D.; Stellwag, S. "The First Pd^{II} complex of a non-heteroatom stabilized carbene ligand" *Chem. Commun.* **2003**, 2344 – 2345.

[16] Weng, W.; Chen, C-H.; Foxman, B. M.; Ozerov, O. V. "Palladium complexes of a P_2C= Ligand Containing a Central Carbene Moiety" *Organometallics* **2007**, *26*, 3315 – 3320.

[17] Ozerov, O. V.; Guo, C.; Foxman, B. M. "The Missing Link: PCP Pincer Ligands Containing P-N Bonds and their Pd Complexes" *J. Organomet. Chem.* **2006**, *691*, 4802 – 4806.

[18] Lee, H. M.; Zeng, J Y.; Hu, C-H.; Lee, M-H. "A New Tridentate Pincer Phosphine/*N*-Heterocyclic Carbene Ligand: Palladium Complexes, Their Structures, and Catalytic Activities" *Inorg. Chem.* **2004**, *43*, 6822 – 6829.

[19] Cui, P.; Iluc, V. M. "Redox-Induced Umpolung of Transition Metal Carbenes" *Chem. Sci.* **2015**, *6*, 7343 – 7354.

[20] Danapoulos, A. A.; Tsoureas, N.; Green, J. C.; Hursthouse, M.B. "Migratory Insertion in *N*-Heterocyclic Carbene Complexes of Palladium; An Experimental and DFT Study" *Chem. Commun.* **2003**, 756 – 757.

[21] Wu, X-H.; Neumann, H.; Beller, M. "Palladium-catalyzed Carbonylative Coupling Reactions Between Ar-X and Carbon Nucleophiles" *Chem. Soc. Rev.* **2011**, *40*, 4986 – 5009.

[22] Ishiyama, T.; Kizaki, H.; Hayashi, T.; Suzuki, A.; Miyaura, N. "Palladium-Catalyzed Carbonylative Cross-Coupling Reaction of Arylboronic Acids with Aryl Electrophiles: Synthesis of Biaryl Ketones" *J. Org. Chem.* **1998**, *63*, 4726 – 4731. Kobayashi, T.; Tanaka, M. "Carbonylation of Organic Halides in the Presence of Terminal Acetylenes; Novel Acetylenic Ketone Synthesis" *J. Chem. Soc., Chem. Commun.* **1981**, 333-334. Echavarren, A. M.; Stille, J. K. "Palladium-Catalyzed Carbonylative Coupling of Aryl Triflates with Organostannanes" *J. Am. Chem. Soc.* **1988**, *110*, 1557 – 1565. Schoenberg, A.; Heck, R. F. "Palladium-Catalyzed Formylation of Aryl, Heterocyclic, and Vinylic Halides" *J. Am. Chem. Soc.* **1974**, *96*, 7761 – 7764.

[23] Greenman, K. L.; Carter, D. S. Van Vranken, D.L. "Palladium-catalyzed Insertion Reactions of Trimethylsilyldiazomethane" *Tetrahedron* **2001**, *57*, 5219 – 5225.

[24] Tomilov, Y. V.; Kostitsyn, A. B.; Shulishov, E. V.; Nefedov, O. M. " Palladium(II)-Catalyzed Cyclopropanation of Simple Allyoxy and Allylamino Compounds and of 1-Oxy-1,3-butadienes with Diazomethane" *Synthesis*, **1990**, 246 - 248.

[25] Karabelas, K.; Hallberg, A. "Synthesis of (*E*)-(2-Arylethenyl)silanes by Palladium-Catalyzed Arylation of Vinylsilanes in the Presence of Silver Nitrate" *J. Org. Chem.* **1986**, *51*, 5286 – 5290.

[26] Ihara, E.; Masayasu, F.; Nobuyuki, H.; Itoh, N.; Inoue, K. "First Synthesis of Poly(acylmethylene)s via Palladium-Mediated Polymerization of Diazoketones" *Macromolecules* **2005**, *38*, 2101 – 2108.

[27] Chen, J. T.; Sen, A. "Mechanism of Transition-Metal-Catalyzed Double Carbonylation Reactions. Synthesis and Reactivity of Benzoylformyl Complexes of Palladium(II) and Platinum(II)" *J. Am. Chem. Soc.* **1984**, *106*, 1506 – 1507.

[28] Drent, E.; Budzelaar, P. H. M. "Palladium-Catalyzed Alternating Copolymerization of Alkenes and Carbon Monoxide" *Chem. Rev.* **1996**, *96*, 663 – 681.

[29] Drent, E.; van Broekhoven, J. A. M.; Doyle, M. J. "Efficient Palladium Catalysts for the Copolymerization of Carbon Monoxide with Olefins to Produce Perfectly Alternating Polyketones" *J. Organomet. Chem.* **1991**, *417*, 235 – 251.

[30] Van Vranken, D. L. Department of Chemistry, University of California, Irvine, CA. Personal communication, June 2016.

[31] Greenman, K. L.; Van Vranken, D. L. "Palladium-Catalyzed Carbene Insertion into Benzyl Bromides" *Tetrahedron* **2005**, *61*, 6438 – 6441.

[32] Treguier, B.; Abdallah, H.; Provot, O.; Brion, J.-D. Alami, M. "Expeditious Synthesis of 1,1-diarylethylenes Related to *Iso*combretastatin A-4 (*iso*CA-4) via Palladium-Catalyzed Arylation of *N*-tosylhydrazones with Aryl Triflates" *Tetrahedron Lett.* **2009**, *50*, 6549 – 6552.

[33] Aggarwal, V. K.; de Vicente, J.; Bonnert, R. V. "Catalytic Cyclopropanation of Alkenes Using Diazo Compounds Generated in Situ. A Novel Route to 2-Arylcyclopropylamines" *Org. Lett.* **2001**, *3*, 2785 – 2788.

[34] Bamford, W. R.; Stevens, T. S. "The Decomposition of Toluene-*p*-sulphonylhydrazones by Alkali" *J. Chem. Soc.* **1952**, 4735 – 4740.

[35] Barluenga, J.; Morriel, P.; Valdes, C.; Aznar, F. "*N*-Tosylhydrazones as Reagents for Cross-Coupling Reactions: A Route to Polysubstituted Olefins" *Angew. Chem. Int. Ed.* **2007**, *46*, 5587 – 5590.

[36] Paraja, M.; Barroso, R, Cabal, M. P.; Valdes, C. "Synthesis of Highly Substituted Polyenes by Palladium-Catalyzed Cross–Couplings of Sterically Encumbered Alkenyl Bromides and *N*-Tosylhydrazones" *Adv. Synth. Catal.* **2017**, *359*, 1058 – 1062.

[37] Devine, S. K. J.; Van Vranken, D. L. "Palladium-Catalyzed Carbene Insertion into Vinyl Halides and Trapping with Amines" *Org. Lett.* **2007**, *9*, 2047 – 2049.

[38] Trost, B, M.; Van Vranken, D. L. "Asymmetric Transition Metal-Catalyzed Allylic Alkylations" *Chem. Rev.* **1996**, *96*, 395 – 422.

[39] Khanna, A.; Maung, C.; Johnson, K. R.; Luong, T. T.; Van Vranken, D. L. "Carbenylative Amination with *N*-tosylhydrazones" *Org. Lett.* **2012**, *14*, 3233 – 3235.

[40] Roessler, F.; Ganzinger, D.; Johne, S.; Schopp, E.; Hesse, M. "*Ruspolia hypercrateriformis* M.R.: Isolation and Structure Elucidation of New Pyrrolidine Alkaloids" *Helv. Chim. Acta* **1978**, *61*, 1200 – 1206.

[41] Agee, C. R. Palladium-Catalyzed Carbenylative Cross-Coupling and Carbenylative Amination Utilizing Vinyl Carbenes. Masters Thesis, University of California, Irvine, March 2017.

[42] Rajamaki, S.; Kilburn, J. D. "Lewis Acid Mediated Endo-Cyclisation of Trimethylsilylmethylenecyclopropyl Imines - a Stereoselective Route to Indolizidines" *Chem. Commun*. **2005**, 1637 – 1639.

[43] Zhou, P.-X.; Luo, J.-Y.; Zhao, L.-B.; Ye, Y.-Y.; Liang, Y.-M. "Palladium-Catalyzed Insertion of N-Tosylhydrazones for the Synthesis of Isoindolines" *Chem. Commun.* **2013**, *49*, 3254 – 3256.

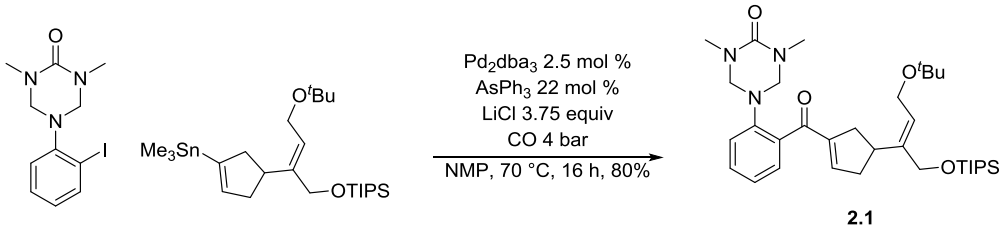
[44] Overman, L. E.; Owen, C. E.; Pawan, M. M. "Catalytic Asymmetric Rearrangement of Allylic N-Aryl Trifluoroacetimidates. A Useful Method for Transforming Prochiral Allylic Alcohols to Chiral Allylic Amines" *Org. Lett.* **2003**, *5*, 1809 – 1812.

Chapter 2: Cyclization of η^3-Benzylpalladium Intermediates Derived from Carbene Insertion

Introduction

The field of palladium catalyzed carbenylative cross-couplings between alkenyl halides and *N*-tosylhydrazones has garnered intense interest in recent years. The mechanistic model for these reactions involves square planar alkylpalladium(II) intermediates where migratory insertion of a *cis* bound alkyl ligand to a substituted carbene ligand, allowing for the incorporation of complex one carbon units between cross-coupling partners. Similar palladium-catalyzed insertion processes of one-carbon units involving isocyanides and carbon monoxide have been extensively demonstrated.[1] For example, palladium-catalyzed carbonylative cross-couplings are an important method for the synthesis of unsymmetrical ketones and esters.[2] Overman and co-workers utilized a carbonylative Stille reaction in order to synthesize ketone **2.1**, an important intermediate in their total synthesis of (–)-strychnine (Figure 2-1).[3]

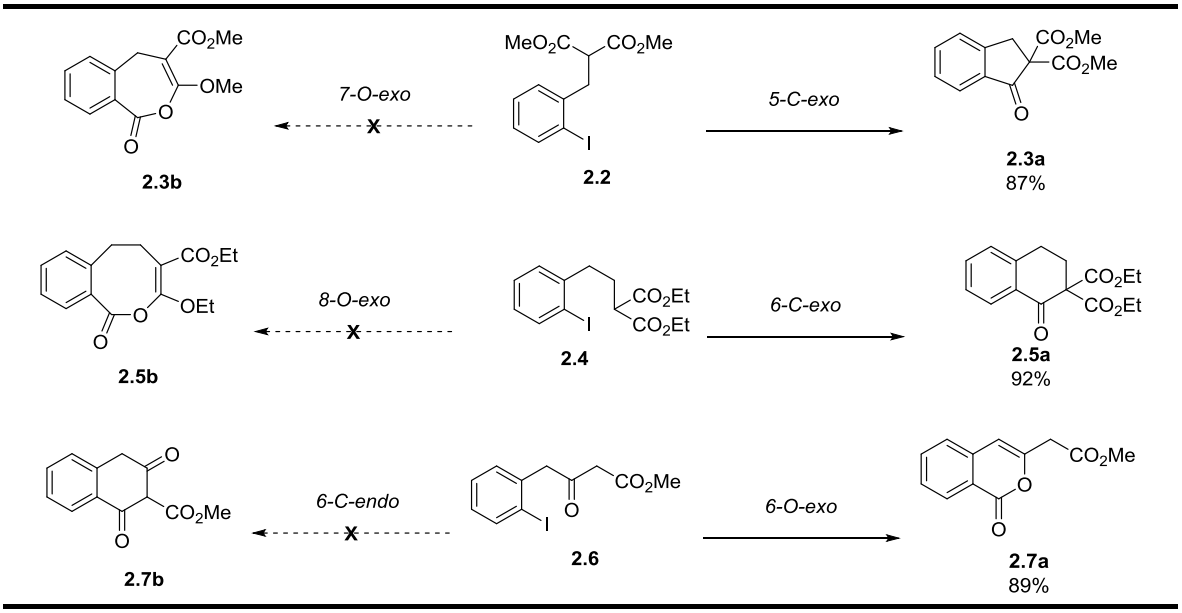
Figure 2-1: Carbonylative Stille Reaction



In 1994 Negeshi and co-workers reported the synthesis of indanones and tetralones via the palladium-catalyzed carbonylative cyclization reaction of *o*-iodobenzylmalonic acid derivatives.[4] Their elegant study revealed the intrinsic regioselectivities in these cyclizations (e.g. exo vs endo and *C* vs *O*) for various ring systems (Figure 2-2). Treatment of aryl iodide **2.2** with catalytic palladium and carbon monoxide in the presence of triethylamine afforded indanone **2.3a** in 87% yield, none of the 7-*O*-exo product **2.3b** was observed. Similarly, aryl iodide **2.4**

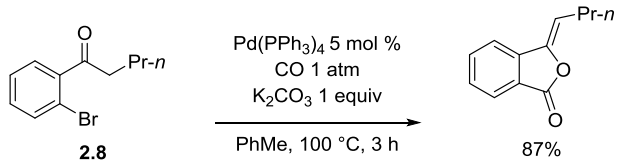
gave tetralone **2.5a** in 92% yield. A palladacycle resulting from oxidative addition and cyclization from **2.4** could in theory reductively eliminate to give indane side products, however no such indanes were isolated.[5] Interestingly, aryl iodide **2.6** strongly preferred 6-*O*-exo over 6-*C*-endo cyclization, affording lactone **2.7a** in 89% yield. A similar observation was made by Shibasaki and co-workers when they exposed aryl bromide **2.8** to similar conditions (Figure 2-3).[6] It appears that 5-exo and 6-exo are preferred over 5-endo and 6-endo cyclization processes in these systems.

Figure 2-2: Cyclization of Acylpalladium Intermediates



Conditions: 5 mol % $Cl_2Pd(PPh_3)_2$, 600 psi CO, 2.0 equiv Et_3N, DMF, 100 °C, 12 - 16 h

Figure 2-3: Synthesis of Lactones from Aryl Bromides and CO



A plausible catalytic cycle for the palladium-catalyzed carbonylative cyclization begins with oxidative addition of palladium(0) across the C-Br bound in **2.2** resulting in

arylpalladium(II) intermediate **A** (Figure 2-4). Coordination of a CO ligand to arylpalladium intermediate **A** followed by migratory insertion furnishes acylpalladium species **C**. Formation of palladacycle intermediate **D** and subsequent reductive elimination affords indanone product and releases palladium(0) back into the catalytic cycle.[7] Formation of a five-membered palladacycle from **A** could potentially compete with CO coordination. Such a process would sequester palladium in a catalytically inactive form. To test if such a process is facile, Negeshi and co-workers heated arylpalladium species **2.9** in MeCN at 100 °C for 6 hours with one equivalent Et_3N in the absence of CO. Formation of palladacycle was not observed and **2.9** was recovered quantitatively at the end of the reaction (Figure 2-5).

Figure 2-4: Plausible Catalytic Cycle for Carbonylative Cyclization

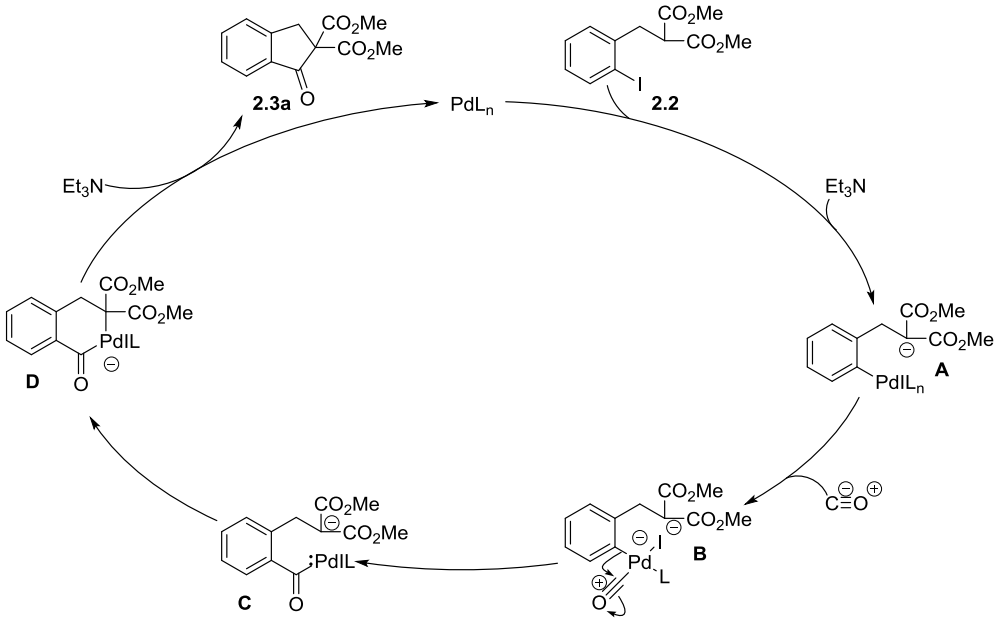
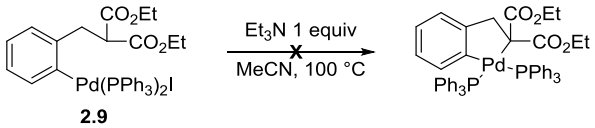


Figure 2-5: Formation of Five-Membered Ring Palladacycles is Not Favored with Malonates

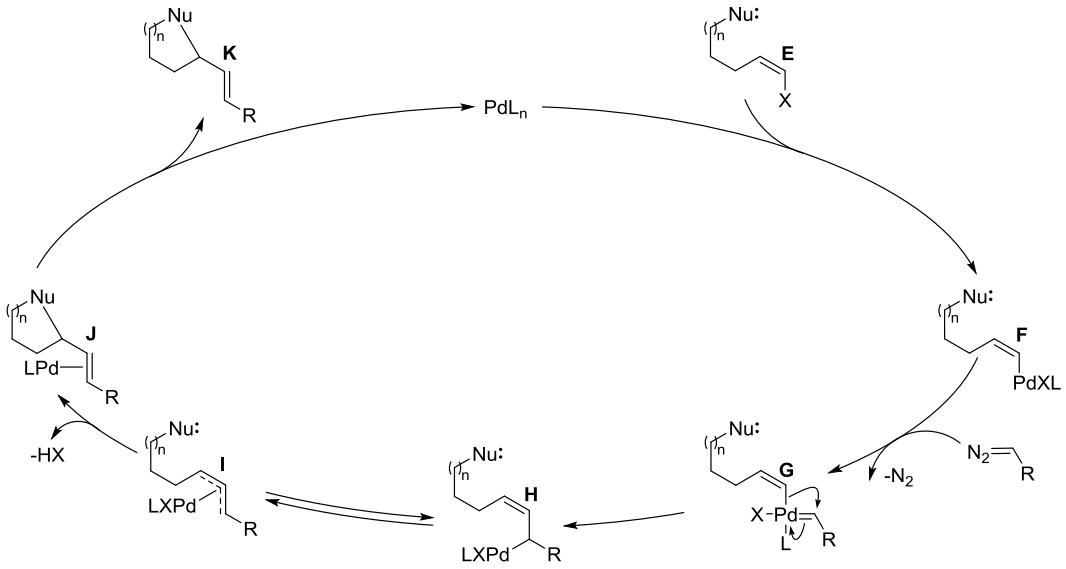


The findings presented by Negeshi on palladium-catalyzed carbonylative cyclizations suggest that an analogous process could be developed using carbenes instead of CO. Such a reaction would afford biologically relevant 1-arylindanes and 1-aryltetralins as products.

Palladium-Catalyzed Carbenylative Cyclizations

The Van Vranken group pioneered palladium-catalyzed carbenylative cyclizations. These cyclization reactions are akin to the carbonylative cyclizations reported by Negeshi and co-workers. A generalized catalytic cycle is presented below (Figure 2-6). Oxidative addition of palladium(0) across the C-X bond of alkenyl halide **E** affords vinylpalladium(II) species **F**. Interception of **F** with diazo and extrusion of nitrogen gas produces palladium(II) carbene **G** which can undergo migratory insertion generating alkylpalladium(II) intermediate **H**. Soft nucleophiles such as phenolates, amines, and malonate anions tend to attack η^3-allylpalladium species **I** at the allyl ligand ultimately leading to cyclized product **K**. Olefins and hard nucleophiles prefer attack on the palladium center in intermediate **H**.

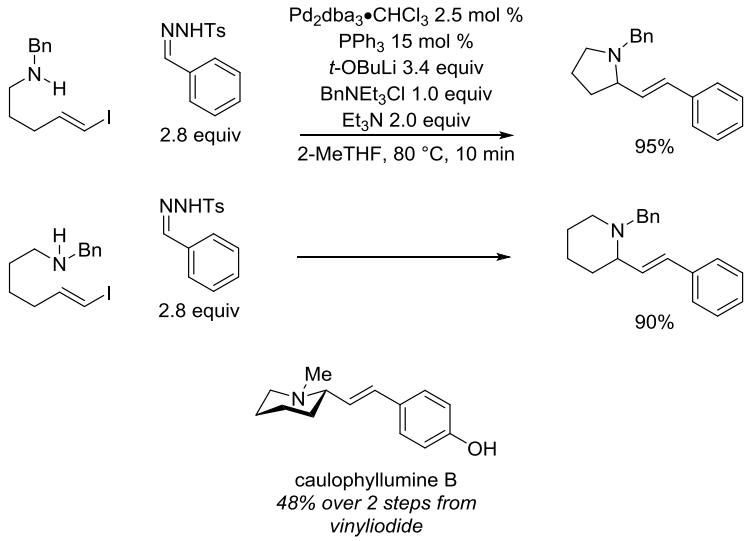
Figure 2-6: General Catalytic Cycle for Carbenylative Cyclization



Palladium-Catalyzed Carbenylative Cyclizations with Heteroatom Nucleophiles

Carbenylative cyclization reactions are an excellent method for the synthesis of *N*-allyl substituted heterocycles. In 2012 Khanna and co-workers from the Van Vranken lab disclosed an elegant palladium-catalyzed carbenylative cyclization between benzaldehyde *N*-tosylhydrazone and *E*-vinyliodides with pendant benzyl amine nucleophiles, affording substituted pyrrolidines and piperidines in high yields (Figure 2-7).[8] In most cases the amines were substituted with benzyl groups; however *N*-methyl substituted vinyl iodides were also diligent coupling partners. This reaction was utilized to synthesize piperidine natural product caulophyllumine B.

Figure 2-7: Synthesis of *N*-allyl Pyrrolidines and Piperidines



Palladium-catalyzed carbenylative cyclizations have also been used to construct isochromene, chromeno[4,3-*b*]chromene derivatives, and spiroacetal enol ether derivatives (Figure 2-8).[9] For example, in 2014 Yin and co-workers reported a palladium-catalyzed carbenylative cyclization reaction involving aryl bromides and furfural *N*-tosylhydrazones with pendant hydroxypropyl groups as coupling partners. Dearomatization of the furan ring may occur through palladium-catalyzed carbenylative insertion followed by equilibration of several allylpalladium(II) intermediates (Figure 2-9). Bamford-Stevens elimination of furfural *N*-

tosylhydrazones **L** generates diazo **M** which reacts with arylpalladium(II) bromide generating palladium(II) carbene species **N**. Migratory of the aryl ligand in **N** to the carbene ligand furnishes η^1-allylpalladium **O**. Dearomatization of the furan ring occurs upon equilibration of η^1-allylpalladium **P** to η^3-allylpalladium **N** via the intermediacy of η^3-allylpalladium **Q** and η^1-allylpalladium **R**. The η^3-allylpalladium moiety in **R** is ultimately trapped by the pendant hydroxypropyl group yielding spiroacetal enol ether product **S** and releasing palladium(0) back into the catalytic cycle.

Figure 2-8: Carbenylative Cyclizations with Oxygen Nucleophiles

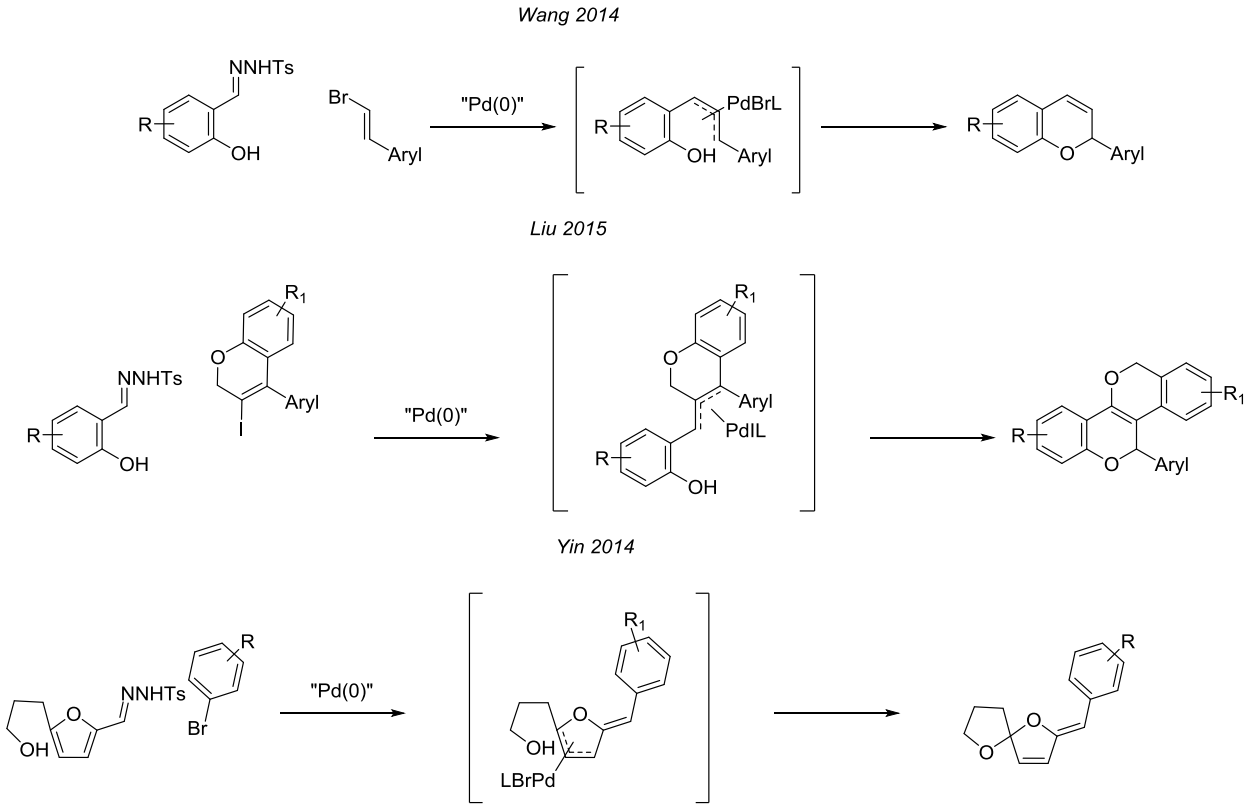
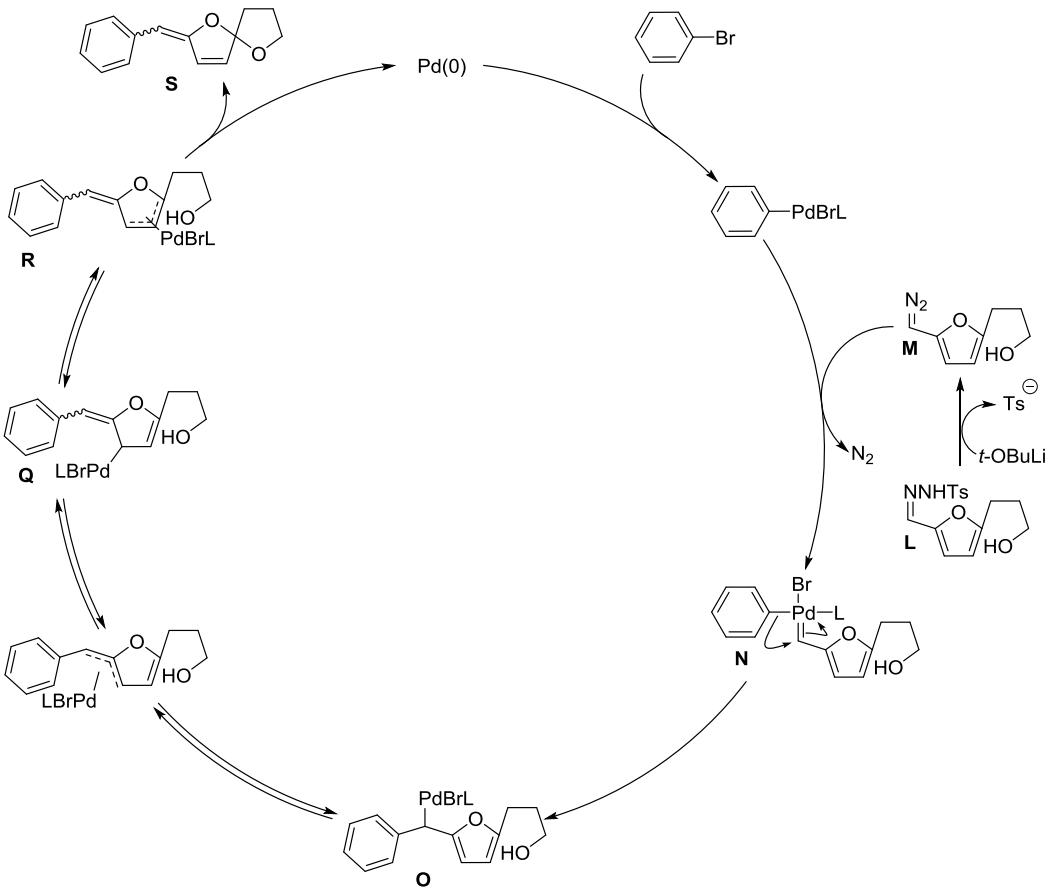


Figure 2-9: Synthesis Spiroacetal Enol Ethers via Palladium-Catalyzed Carbenylative Cyclization

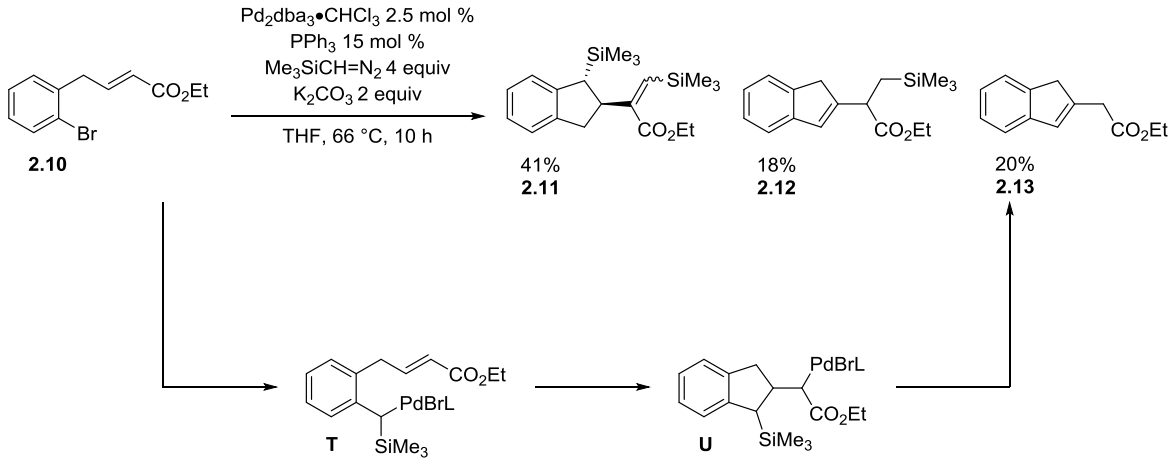


Palladium-Catalyzed Carbenylative Cyclizations with Carbon Nucleophiles

All of the preceding examples of palladium-catalyzed carbenylative insertions have followed the general pattern of: (1) a palladium(II) carbene undergoing migration of a *cis* aryl or vinyl group to the carbene carbon, (2) equilibration of the incipient η^1-palladium complex to its electrophilic η^3-palladium isomer, and (3) cyclization by attack of a pendant nucleophile on the η^3-palladium complex. A different approach to carbenylative cyclizations was reported in 2008 by Romas Kudirka from the Van Vranken group.[10] Alkylpalladium(II) species generated after migratory insertion were used to carbopalladate pendant olefins. Kudirka successfully employed this strategy to synthesize indenylsilanes via a carbenylative cyclization involving

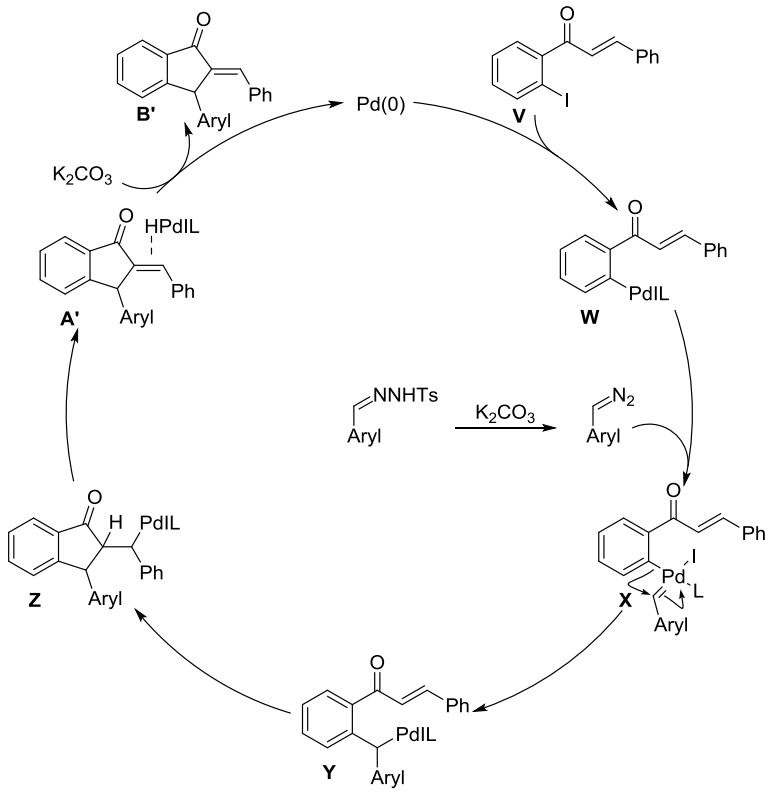
trimethylsilyldiazomethane and arylhalides tethered with olefins (Figure 2-10). Benzylpalladium intermediate **T** undergoes facile intramolecular carbopalladation with its tethered olefin forming the new indane ring. Alkylpalladium species **U** was found to be very susceptible to overinsertion of trimethylsilyldiazomethane. Overinsertion followed by β-hydride elimination afforded silylindane **2.11** as a mixture of *E/Z* isomers in 41% yield. Indenes **2.12** and **2.13** are a result of the protodesilylation of intermediate indenylsilanes, a facile process inherent with these species.[11]

Figure 2-10: Indenylsilanes Generated via Carbenylative Cyclization



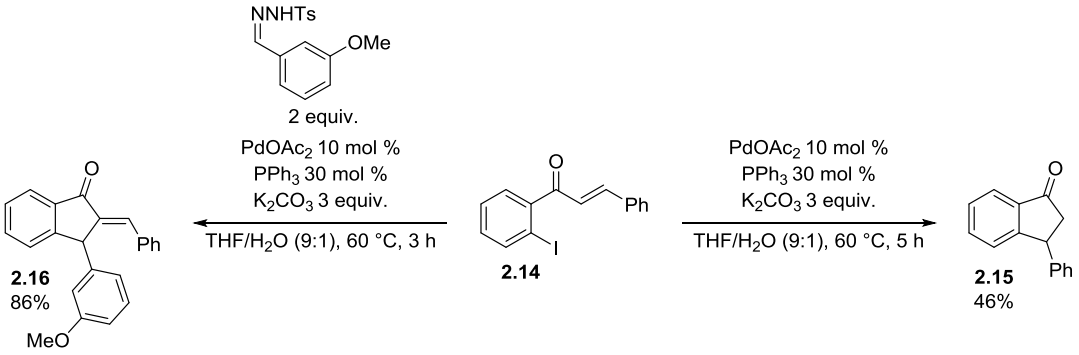
In 2015 Sekar and co-workers reported a very similar carbenylative cyclization reaction employing *N*-tosylhydrazones and 2-iodochalcones.[12] Oxidative addition of palladium(0) into aryl halide **V** followed by carbene formation results in palladium(II) carbene **X** (Figure 2-11). Migratory insertion of the aryl ligand into the carbene carbon of **X** generates η^1-benzylpalladium species **Y**. Intramolecular carbopalladation followed by β-hydride elimination produces alkenyl indanone **B'**.

Figure 2-11: Synthesis of 2-Arylindanones via Carbenylative Cyclization



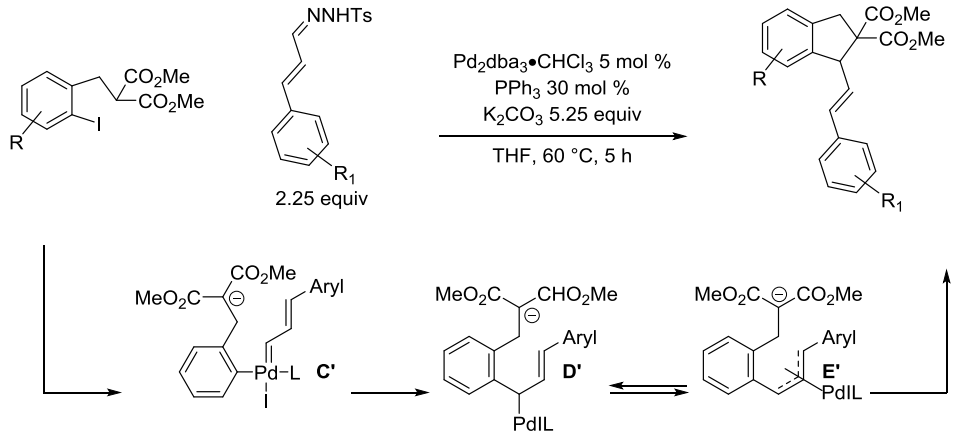
This work was an important contribution to the field of palladium-catalyzed carbenylative cyclizations because it showed that under typical reaction conditions, formation of palladium(II) carbenes outcompetes intramolecular cyclization (Figure 2-12). In the absence of *N*-tosylhydrazone, aryl iodide **2.14** afforded indanone **2.15** in 46% yield when subjected to the reaction conditions. Conversely, the expected product **2.16** was formed in 86% yield over three hours when 2 equiv of *N*-tosylhydrazone was used. These data suggest that formation of palladium(II) carbenes is a fast process.

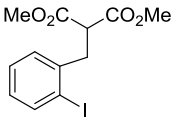
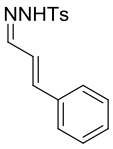
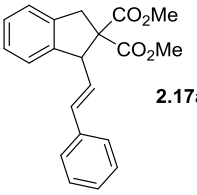
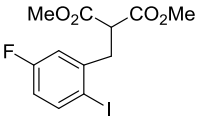
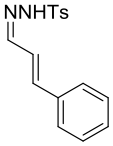
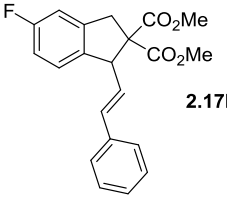
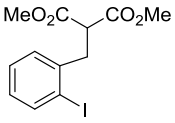
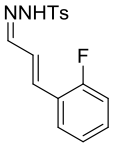
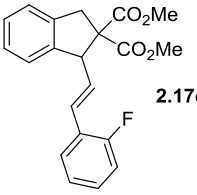
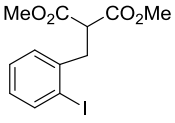
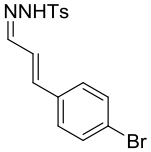
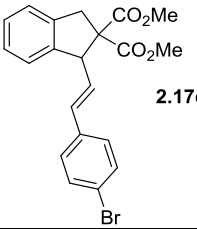
Figure 2-12: Palladium-Carbene Formation Outcompetes Carbopalladation



In 2013 Liang and co-workers reported the synthesis of 1-vinylindanes using aryl iodides with pendant malonate nucleophiles and cinnamaldehyde derived *N*-tosylhydrazones, extending the scope of carbenylative cross-coupling reactions.[13] The optimized reaction conditions utilized potassium carbonate as a base and a similar catalyst system as was used by Khanna and co-workers in their 2012 synthesis of pyrrolidine derivatives via carbenylative amination (Figure 2-13).[14] Palladium carbene **C'** undergoes migratory insertion generating η^1-allylpalladium species **D'** which then isomerizes to electrophilic η^3-allylpalladium intermediate ***E'***. Malonate anion on **E'** is poised to attack the pendant η^3-allylpalladium and form the desired indane ring system. The reaction tolerates substitution on both the hydrazone and aryl iodide coupling partners (**2.17a-d**).

Figure 2-13: Synthesis of 1-Vinyl Indanes through Carbenylative Cross-Coupling

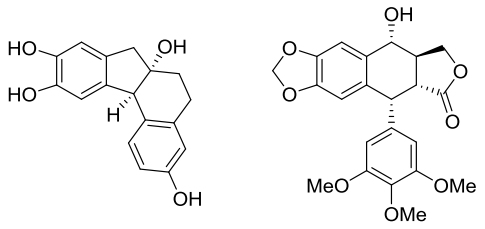


aryl iodide	*N*-tosylhydrazone	product	yield
		 **2.17a**	72%
		 **2.17b**	96%
		 **2.17c**	48%
		 **2.17d**	74%

Although an important contribution to the field of carbenylative cross-couplings, the 1-vinylindane products disclosed by Liang and co-workers do not constitute a particularly exciting or biologically relevant class of products. Unlike 1-vinylindanes, 1-arylindanes and 1-

aryltetralins are motifs found in a large amount of biologically active lignin natural products and semi-synthetic drugs (Figure 2-14).[15] Access to these ring systems via a carbenylative cross-coupling cascade reaction may be envisioned to take place through a η^3-benzylpalladium intermediate. η^3-benzylpalladium species are more reactive than their allyl counterparts and have yet to be utilized in carbenylative cross-couplings.

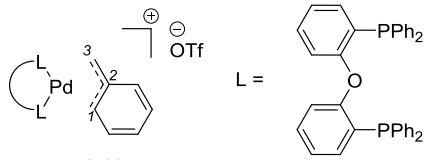
Figure 2-14: Biologically Relevant 1-Arylindanes and 1-Aryltetralins



Generation of η^3-Benzylpalladium Intermediates

Isomerization of η^1-allylpalladium to η^3-allylpalladium requires the breaking of a C-C pi system. Contrastingly, the isomerization of η^1-benzylpalladium to η^3-benzylpalladium requires the breaking of a C-C pi system in addition to loosing aromatic stabilization, a penalty of 36 kcal/mol.[16] Reacquisition of aromaticity is the reason why η^3-benzylpalladium intermediates act as powerful electrophiles. In exchange for the breaking of aromaticity in an aryl ligand, the metal center increases its d electron count and coordination number, a process which is thermodynamically favorable when the metal center is coordinately unsaturated.[17] In 2006 Johns and co-workers reported the crystal structure of cationic η^3-benzylpalladium/bis[2-(diphenylphosphino)phenyl]ether (DPEphos) complex **2.18** (Figure 2-15).[18] The C-Pd bond distances are all different in this complex, ranging from 2.408 Å in the Pd-C_1 bond to 2.102 Å in the Pd-C_3 bond. The asymmetry in Pd-C bond lengths suggests each carbon of the benzyl ligand can display varying degrees of electrophilicity.

Figure 2-15: Structure of η^3-Benzylpalladium/DPEphos Complex

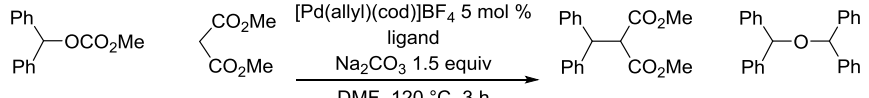


2.18

Pd - C_1 = 2.408 Å
Pd - C_2 = 2.275 Å
Pd - C_3 = 2.102 Å

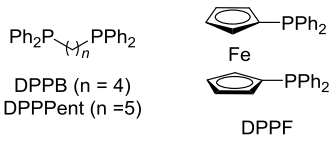
Traditionally, η^3-benzylpalladium intermediates have been accessed through the ionization of benzylic leaving groups such as benzyl chlorides, benzyl acetates, benzyl carbonates, and benzyl phosphates.[19] These intermediates have been intercepted with various nucleophiles such phenoxides, amines, sulfinates, and malonates.[20] In all instances, substitution occurred at the benzylic carbon of the η^3-benzylpalladium complex, thus regenerating aromaticity in the benzyl species. Kuwano and Kusano found bidentate phosphine ligands promoted the palladium-catalyzed nucleophilic substitution of diarylmethyl carbonates (Figure 2-16). No diarylmethane **2.20** was observed when triphenylphosphine was used a ligand however, Cy-Xantphos provided diarylmethane **2.20** in 31% yield along with 3% of the bis-arylether side product **2.21**.

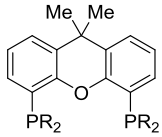
Figure 2-16: Ligand Screen for the Synthesis of Diarylmethanes



2.19 1.5 equiv **2.20** **2.21**

ligand mol %	yield **2.20**	yield **2.21**
PPh_3 12 %	0 %	6 %
DPPB 5 %	1 %	12 %
DPPPent 5 %	2 %	13 %
DPPF 5 %	2 %	23 %
Xantphos 5 %	10 %	26 %
Cy-Xantphos 5 %	31 %	3 %

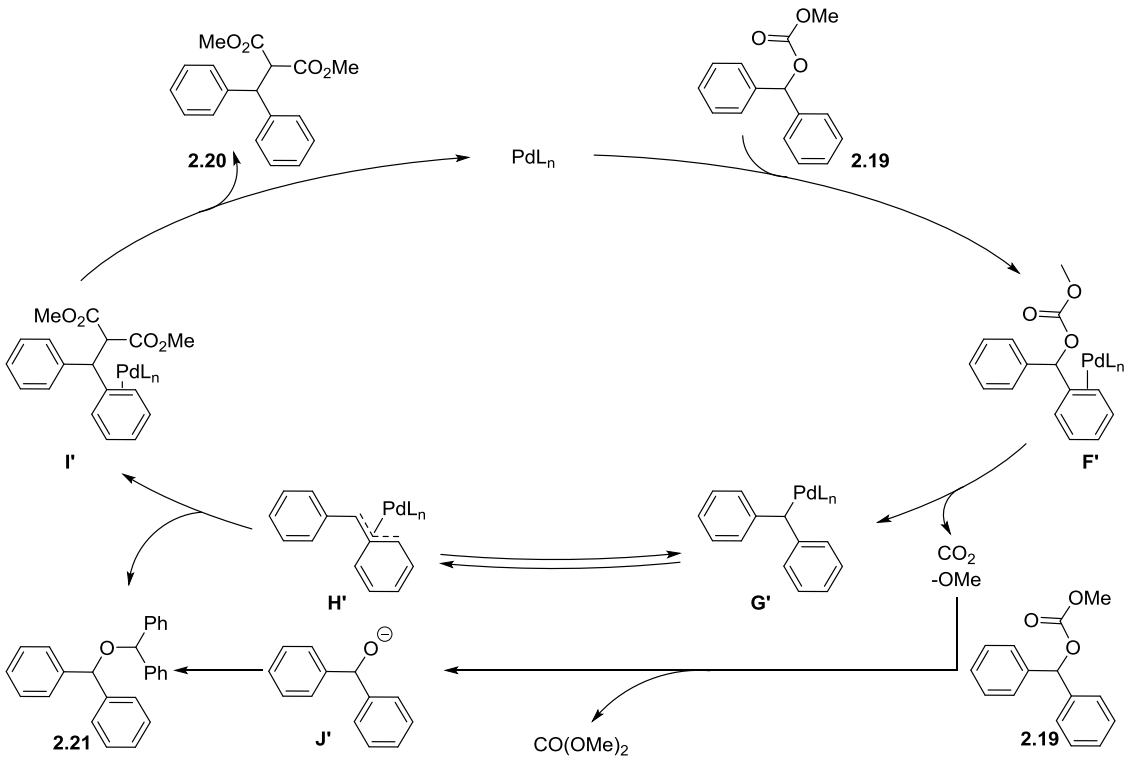




Xantphos (R = Ph)
Cy-Xantphos (R = Cy)

A plausible catalytic cycle begins with coordination of palladium to the aryl ring of carbonate **2.19** (Figure 2-17). Oxidative addition affords η^1-benzylpalladium species **G'** while extruding CO_2 and methoxide. Equilibration of **G'** to η^3-benzylpalladium **H'** and attack by malonate anion affords dirarylmethane product **2.20** and releases palladium(0) back into the catalytic cycle. Formation of bis-aryl ether **2.21** may arise from solvolysis of carbonate **2.19**. Methoxide formed after oxidative addition of palladium may undergo nucleophilic substitution with another equivalent of **2.19** producing dimethoxy carbonate and bis-benzyl alkoxide **J'** which subsequently intercepts η^3-benzylpalladium intermediate **H'** leading to bis-aryl ether **2.21**. The authors speculate the bulky substituents on the bidentate phosphine ligand of palladium prevent attack by the sterically encumbered alkoxide **J'** while allowing the smaller malonate to attack.

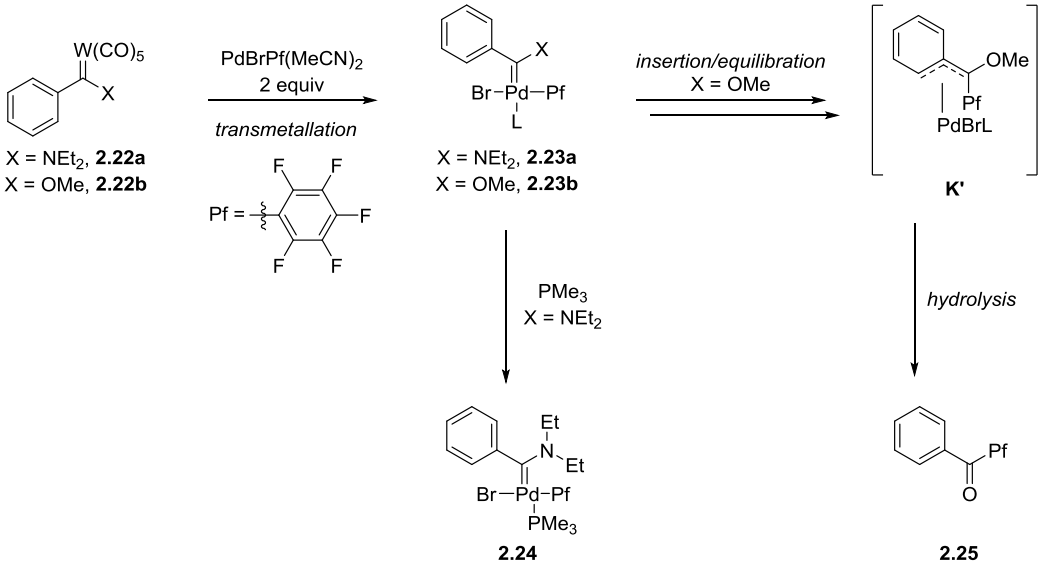
Figure 2-17: Plausible Mechanistic Cycle for Formation of Diarylmethanes



In 2002 Albeniz and co-workers showed it was possible to access η^3-benzylpalladium intermediates through carbene insertion.[21] Arylpalladium(II) carbenes were synthesized via transmetallation of palladium(II) salts with tungsten carbenes, a common method for metal carbene synthesis in organometallic chemistry (Figure 2-18).[22] Arylcarbene **2.24** was stable to isolation and the X-ray crystal structure revealed the Pd-carbene carbon bond length to be 2.030 Å, a value in line with other palladium(II) carbene structures. The carbene and aryl ligands in **2.24** are arranged in a *cis* orientation around the metal center and both ligands are situated perpendicularly to the palladium coordination plane. The geometry of the carbene and aryl ligands around the palladium suggests migratory insertion should be a facile process. Indeed, when the diethylamino substituent of the carbene ligand was replaced with a methoxy group in **2.22b**, no palladium(II) carbene complex could be isolated. Migratory insertion leading to η^3-benzylpalladium intermediate **K'** was extremely fast. Formation of η^3-benzylpalladium **K'** was

observable spectroscopically due to the observation of the high-field shift of the aryl proton involved in η^3-benzyl isomerism (δ = 5.55 ppm).[23] The authors suggest η^3-benzylpalladium **K'** is attacked at the benzylic carbon by methanol (present as a by-product) affording an intermediate ketal, which ultimately hydrolyzes to benzophenone **2.25** by the action of advantageous water found in their NMR tubes. The extreme reactivity of arylpalladium(II) carbenes suggests these species could be utilized at intermediates in a catalytic manifold.

Figure 2-18: Isolation and Reactivity of Arylpalladium(II) Carbenes



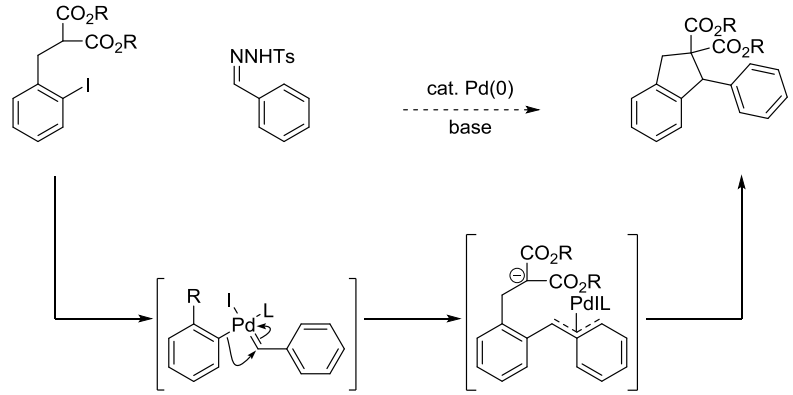
The pioneering work by Kuwano and Albeniz presented in this section shows it is possible to generate η^3-benzylpalladium species through migratory insertion of palladium carbenes and trap them with various nucleophiles. With this precedent in hand, it is possible to envision generating the privileged structures of 1-arylindanes and 1-aryltetralins through a palladium-catalyzed carbenylative cross-coupling sequence.

Results and Discussion

Optimization and Synthesis of 1-arylindanes and 1-aryltetralins

Albeniz and co-workers demonstrated that aryl ligands bound to palladium(II) carbenes undergo migratory insertion ultimately generating η^3-benzylpalladium species, while Kuwano and co-workers showed that it is possible to attack η^3-benzylpalladium intermediates with malonate anions.[24,25] With these pioneering studies in mind, we thought it possible to intercept the η^3-benzylpalladium intermediate formed after migratory insertion from a palladium(II) carbene with an intramolecular anionic malonate nucleophile, leading to 1-arylindane (Figure 2-19).

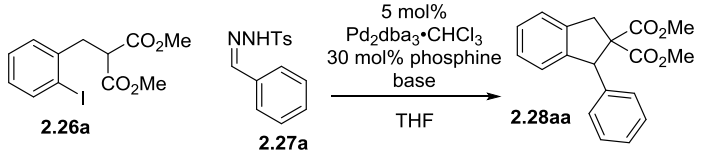
Figure 2-19: Access to 1-Arylindanes via Carbenylative Cyclization



Initially, we explored the carbenylative cyclization of dimethyl (2-iodobenzyl) malonate **2.26a** using the *N*-tosylhydrazone **2.27a** derived from benzaldehyde as a precursor to phenyldiazomethane. Adopting the conditions developed by Avinesh Khanna for carbenylative cyclizations involving benzaldehyde *N*-tosylhydrazone and amine nucleophiles,[8] we were able to obtain a promising 45% yield of 1-phenylindane **2.28a** (Table 2-1, entry 4). Weaker bases such as triethylamine, potassium carbonate, and potassium phosphate resulted in only trace amounts of product (entries 1-3). Use of potassium *tert*-butoxide decreased the solubility of the reactants resulting in a heterogeneous mixture at the beginning of the reaction, however slightly higher

yields were obtained (entry 5). The solubility of the *N*-tosylhydrazone anion and the reaction temperature are important factors that determine the rate at which phenyldiazomethane is generated in the reaction mixture. Better results were obtained at lower temperatures and lower hydrazone loadings, with the optimum temperature being 60 °C (entries 6 -8). Electron-deficient phosphine tris(4-fluorophenyl)phosphine was slightly better than triphenylphosphine in terms of reaction time and yield (entries 8 and 9). Reaction times were significantly decreased by preforming the sodium enolate and sodium *N*-tosylhydrazone salt with sodium hydride (entry 10).

Table 2-1: Initial Optimization of Carbenylative Cyclization



2.26a **2.27a** **2.28aa**

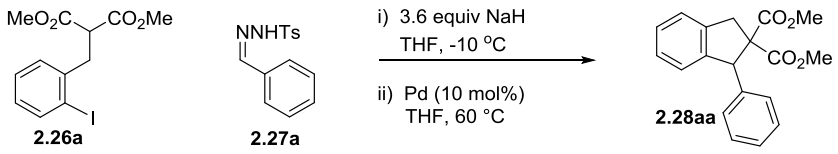
Entry	Ligand	**2.27a** (equiv.)	Base (equiv.)	T (°C)	Time (h)	Yield **2.28aa** [a]
1	Ph_3P	4	NEt_3(5.2)	66	24	trace
2	Ph_3P	4	K_2CO_3(5.2)	66	6	trace
3	Ph_3P	4	K_3PO_4(5.2)	66	7	trace
4	Ph_3P	4	*t*-BuOLi (5.2)	66	5	45%
5	Ph_3P	4	*t*-BuOK (5.2)	66	5	54%[b]
6	Ph_3P	2	*t*-BuOK (3.2)	50	20	68%
7	Ph_3P	1.5	*t*-BuOK (2.7)	50	22	60%
8	Ph_3P	2	*t*-BuOK (3.2)	60	6	73%
9	$(4\text{-FPh})_3P$	2	*t*-BuOK (3.2)	60	4	75%
10[c]	$(4\text{-FPh})_3P$	2	NaH (3.2)	60	1.5	75%

[a] NMR yields versus dimethoxybenzene as an internal standard
[b] isolated yield
[c] Na salts of **2.26a** and **2.27a** preformed with NaH before addition of catalyst

The yield was further increased by switching to a palladium(II) precatalyst and increasing the sodium hydride loading. Tomilov and co-workers have shown that diazo compounds are able to reduce palladium(II) halide salts to palladium(0) in the absence of phosphine ligands.[26] A brief screen of ligands favored phosphines with less donor ability (Table 2-2, entries 1-3). Tris(4-trifluoromethylphenyl)phosphine and tri(2-furyl) phosphine gave comparable yield to tris(4-

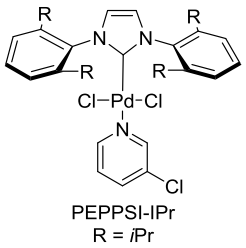
fluorophenyl)phosphine, so the less expensive tris(4-fluorophenyl)phosphine was preferred (entries 5 and 6). Tris(4-fluorophenyl)phosphine has been used effectively in a number of palladium-catalyzed transformations where a more electron deficient metal complex is desired.[27] When the reaction was run with bidentate phosphine dppf, indane **2.28aa** was isolated in only 15% along with 48% recovered starting material **X** (entry 7). Other catalysts such as Buchwald's X-phos palladacycle and the PEPPSI NHC system only provided a few turnovers along with a significant amount of recovered starting material (entries 8 and 9). The reaction also tolerated other palladium pre-catalysts such as palladium acetate and palladium chloride (entries 10 and 11). Under the optimized conditions using 3.6 equiv of NaH and 2 equiv of N-tosylhydrazone **2.27a**, indane **2.28aa** was formed in 86% yield in 1.5 hour (entry 3), a slightly lower yield (79%) was obtained using 5 mol % of the palladium catalyst (entry 4).

Table 2-2: Optimization of Ligand and Palladium Source

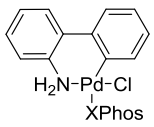


Entry	Pd source	Ligand (mol%)	Time (h)	Yield 2.28aa[a]	% 2.26a[a]
1	$PdCl_2(MeCN)_2$	Ph_3P (40%)	1.5	71%	0%
2	$PdCl_2(MeCN)_2$	$(4\text{-}MeOC_6H_4)_3P$ (40%)	2.0	76%	0%
3	$PdCl_2(MeCN)_2$	$(4\text{-}FC_6H_4)_3P$ (40%)	1.5	86%	0%
4[b]	$PdCl_2(MeCN)_2$	$(4\text{-}FC_6H_4)_3P$ (20%)	3.0	79%	0%
5	$PdCl_2(MeCN)_2$	$(4\text{-}F_3CC_6H_4)_3P$ (40%)	1.5	87%	0%
6	$PdCl_2(MeCN)_2$	$(2\text{-furyl})_3P$ (40%)	1.5	87%	0%
7	$PdCl_2(MeCN)_2$	dppf (20%)	1.0	15%	48%
8	Buchwald G2	X-Phos (10%)	1.0	23%	35%
9	PEPPSI	IPr (10%)	1.5	9%	59%
10	$Pd(OAc)_2$	$(4\text{-}F_3CC_6H_4)_3P$ (40%)	1.5	81%	0%
11	$PdCl_2$	$(4\text{-}F_3CC_6H_4)_3P$ (40%)	3.5	28%	51%

[a] NMR yields determined by comparison with an internal standard.
[b] 5 mol% Pd



PEPPSI-IPr
R = *i*Pr

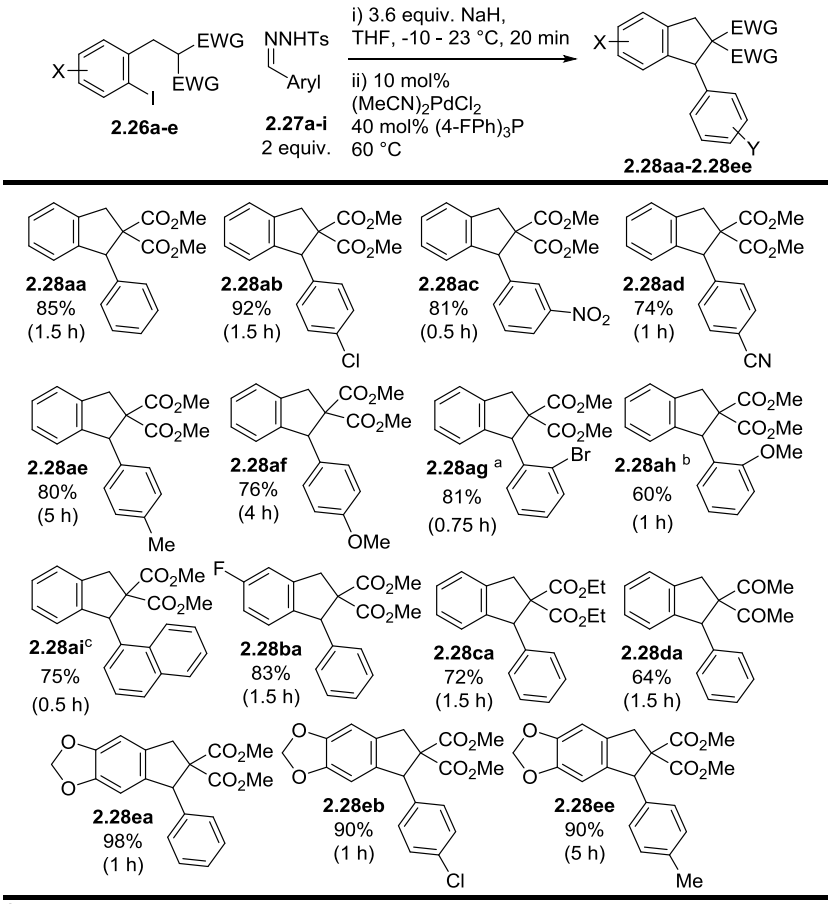


Buchwald G2
XPhos

Using the optimized conditions, we set out to explore the scope of this powerful cyclization reaction (Figure 2-20). We first examined *N*-tosylhydrazones to evaluate the

functional group compatibility of the reaction. Aryl bromides and chlorides were tolerated without competing oxidative addition (**2.28ab 2.28ag**). Electron-withdrawing groups were also tolerated (**2.28ac and 2.28ad**). If formation of an η^3-benzylpalladium intermediate is a limiting factor in the reaction, then one would expect better results for insertion of 1-naphthylmethylidene over phenylmethylidene (**2.28aa** versus **2.28ai**), but the yield was slightly lower when the hydrazone derived from 1-naphthaldehyde was used. However, the partial solubility of the *N*-tosylhydrazone anion is a critical factor for the success of the reaction and may lead to some of the observed differences in yields and rates. *N*-Tosylhydrazones generate aryldiazomethanes at a slower rate when the arene group is electron-rich as evidenced by the longer reaction time for formation of indane **2.28af**.[28] We then looked to varying the (2-iodobenzyl)malonate. Both oxygen and fluorine substituents are tolerated on the aryl halide (**2.28ba and 2.28ea**). In fact, the methylenedioxyphenyl iodide **2.26e** afforded indane in almost quantitative yield (**2.28ea**). Other types of stabilized enolates were also effective in the reaction (**2.28ca and 2.28da**).

Figure 2-20: Scope of Carbenylative Cyclization for Formation of 1-Arylindanes



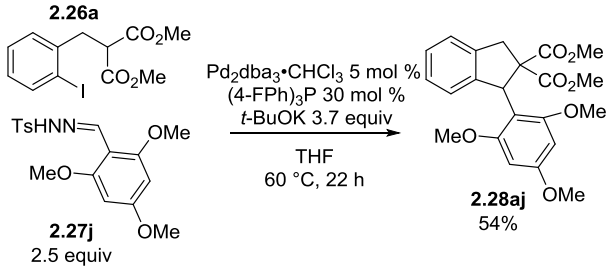
[a] Isolated as a chromatographically inseparable 9:1 mixture of indane **2.28ag** and aryl iodide **2.26a**.

[b] 3.0 equiv *N*-tosylhydrazone, 4.6 equiv NaH.

[c] 4.0 equiv *N*-tosylhydrazone, 5.6 equiv NaH.; NMR yield versus dimethoxybenzene as an internal standard.

Rapid decomposition of ortho-substituted *N*-tosylhydrazones necessitates additional equivalents of hydrazone and base to achieve full conversion of aryl iodide (**2.28ag, 2.28ah, and 2.28ai**). Generally, ortho groups seem to accelerate the rate of the reaction. The sterically demanding, electron-rich *N*-tosylhydrazone **2.27j** afforded none of the desired product under the optimized conditions (Figure 2-21). Interestingly, formation of potassium enolate using a one pot procedure resulted in 54% yield of highly hindered indane **2.28aj**. Perhaps potassium chelation of 2-methoxy substituted *N*-tosylhydrazones is an important factor in this cyclization reaction.

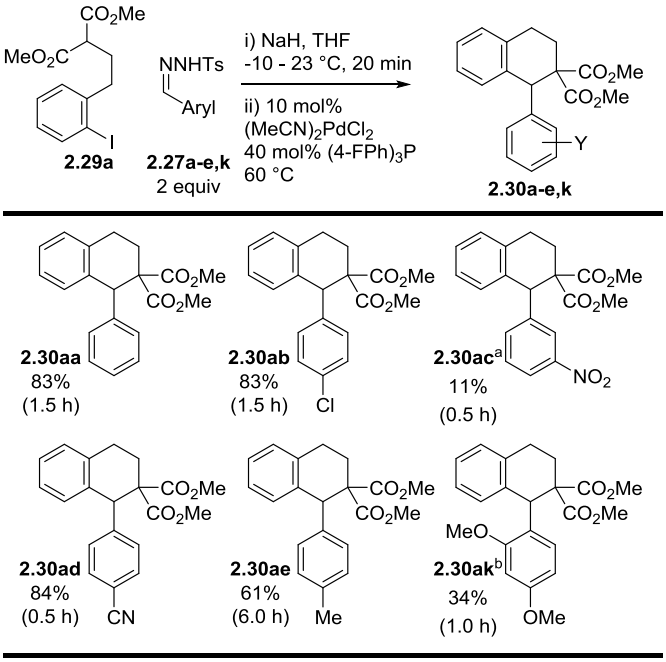
Figure 2-21: Insertion of a Highly Hindered Benzylidene Group



Buoyed by the success of carbenylative insertion for making indanes, we next turned to the formation of tetralins (Figure 2-22). The yields and reaction times for 1-aryltetralin formation are comparable to the yields and reaction times for 1-arylindane formation, suggesting that the benzylic alkylation step is not limiting the yield. The 3-nitroaryltetralin derivative **2.30ac** appeared to work well by TLC analysis (complete conversion of aryl iodide) but proved difficult to separate from impurities using chromatography and was purified by recrystallization, reducing the isolated yield.

The facile synthesis of 1-aryltetralins is particularly exciting due to the prominence of this ring system in many lignin derived bioactive compounds. In 1981 Curran and co-workers synthesized tetralone **2.30bl** through an elegant three-component cyclization reaction in 76% yield (Figure 2-23).[29] Synthesis of (±)-podophyllotoxin was completed in 6 steps from tetralone intermediate **2.30bl**. We sought to apply our carbenylative cyclization reaction towards the synthesis of Curran's tetralone intermediate **2.30bl.** This cyclization is challenging due to competing 5-*O*-*exo* cyclization, a known pathway in similar palladium-catalyzed carbonylative cyclizations reported by Shibasaki and co-workers.[6] However, when aryliodide **2.29b** and *N*-tosylhydrazone **2.27l** were subjected to our conditions, the desired product was isolated in 50% yield, further highlighting the utility of this carbenylative cyclization (Figure 2-24).

Figure 2-22: Scope of Carbenylative Cyclization for Formation of 1-Aryltetralins



[a] Yield after recrystallization.

[b] 4.0 equiv *N*-tosylhydrazone, 5.6 equiv NaH.

Figure 2-23: Curran and Co-worker's 1981 Synthesis of Tetralone **2.30bl**

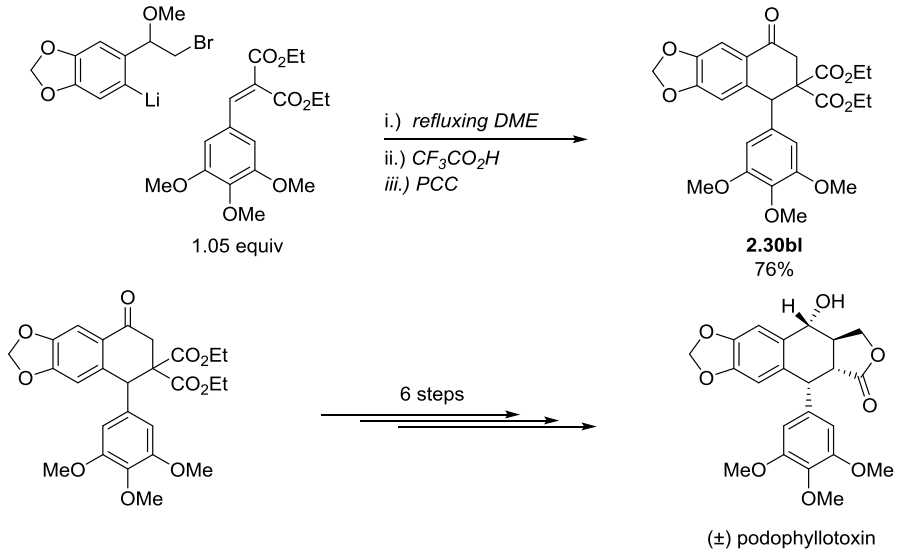
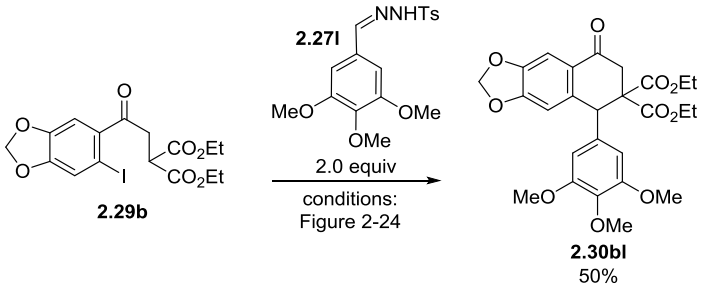
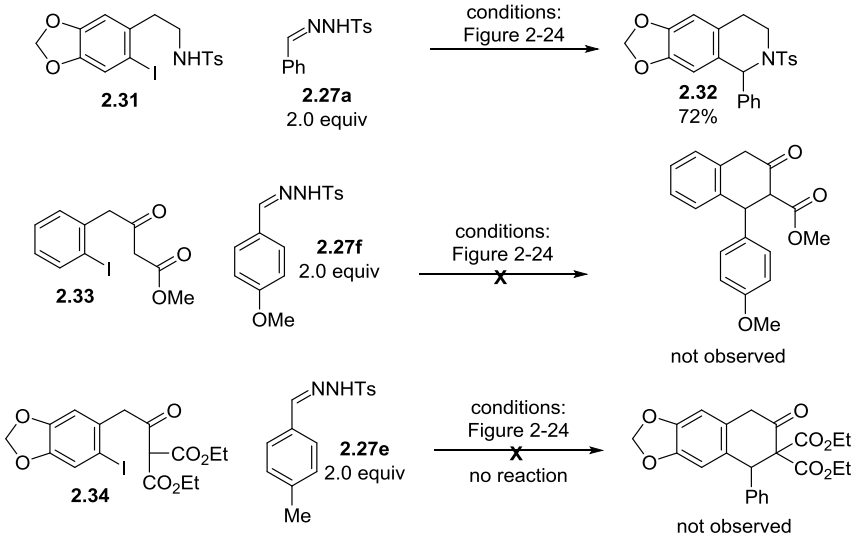


Figure 2-24: Synthesis of Tetralone **2.30bl** via Carbenylative Cyclization



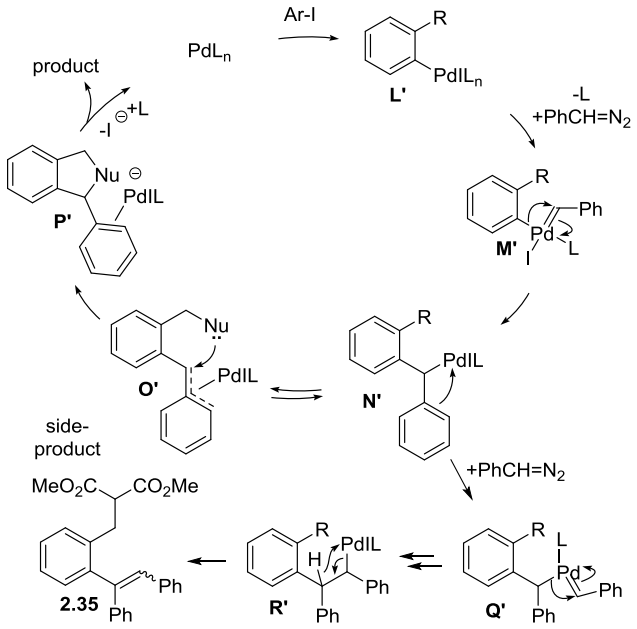
We briefly examined other nucleophiles besides 2-(iodobenzyl) and 2-(iodohomobenzyl) malonates. Tosylamine **2.31** was successfully coupled with *N*-tosylhydrazone **2.26a** affording 1-aryltetrahydroisoquinoline **2.32** in 69% yield, extending the scope of this carbenylative cyclization towards the synthesis of heterocyclic ring systems (Figure 2-25). Unfortunately β-keto ester **2.33** did not form the desired tetralone product, most likely due to competitive 6-*O*-*exo* cyclization. A similar observation was made by Negeshi and co-workers in their study of palladium-catalyzed carbonylative cyclizations.[4] No reaction was observed when β-keto malonate **2.34** was subjected to the standard conditions.

Figure 2-25: Carbenylative Cyclizations with Various Nucleophiles



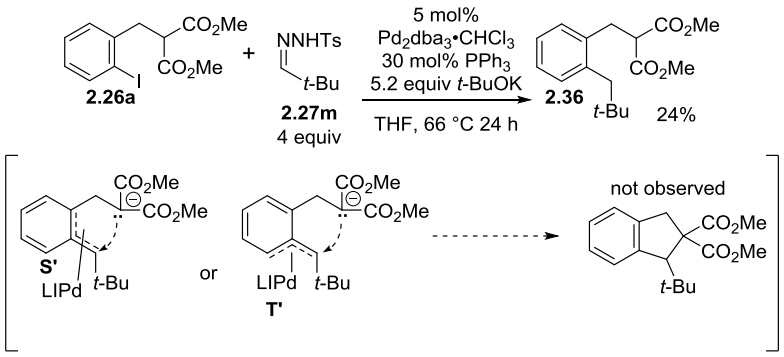
Our mechanistic rationale for the reaction involves addition of the diazo compound to arylpalladium iodide **L'** to form an arylpalladium carbene intermediate **M'** (Figure 2-26). Migratory insertion would generate η^1-benzylpalladium iodide intermediate **N'**. Direct cross-coupling of the enolate with the η^1-benzylpalladium moiety in intermediate **N'** would require a highly unfavorable reductive elimination that is not likely to be facile under our reactions conditions.[30] The η^1-benzylpalladium iodide **N'** has two choices. Kuwano and co-workers have shown that benzhydrylpalladium intermediates couple with malonates through an outer-sphere attack on the η^3-benzyl ligand, so it is expected that the structurally analogous η^3-benzhydrylpalladium intermediate **O'** can undergo 5-exo-trig cyclization through an outer-sphere mechanism to generate product.[20b] Other types of η^3-benzylpalladium complexes are possible, but 5-endo-trig ring closures onto analogous η^3-allylpalladium intermediates are strongly disfavored.[31] Alternatively, η^1-benzylpalladium intermediate **N'** can insert another carbene followed by rapid β-hydride elimination to afford a stilbene side product **2.35**.[32] Stilbene **2.35** was the major side-product identified in this reaction, in some cases forming in 10% yield. Hydrodepalladation, a known side-reaction occurring with malonates and arylpalladium intermediates such as **L'** under basic conditions, was also observed.[5,18] We do not observe any tetralin from the η^3-benzylpalladium complex derived from the cyclization of **R'**.

Figure 2-26: Proposed Mechanism for Carbenylative Cyclization and Formation of Side Products



To probe the intermediacy of η^3-benzylpalladium intermediates other than **O'** we attempted to carry out the reaction with the *N*-tosylhydrazone **2.27m**, derived from pivaldehyde (Figure 2-27), under potassium enolate conditions. Insertion product **2.36** was isolated in low yield, but none of the desired indane was observed, suggesting that η^3-benzylpalladium intermediates **S'** and **T'** are not viable intermediates. Hydride reduced product **2.36** may stem from hydrodepalladation of an intermediate η^1-benzylpalladium species. Isolation of product **2.36** inspired us to investigate other carbenylative cyclization reactions involving aliphatic *N*-tosylhydrazones (*vida infra*).

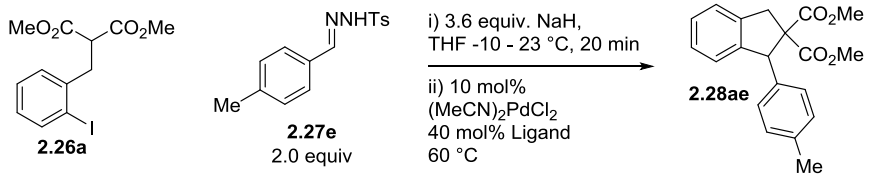
Figure 2-27: Evidence against Alternative η^3-Benzylpalladium Intermediates



Progress towards Asymmetric Induction

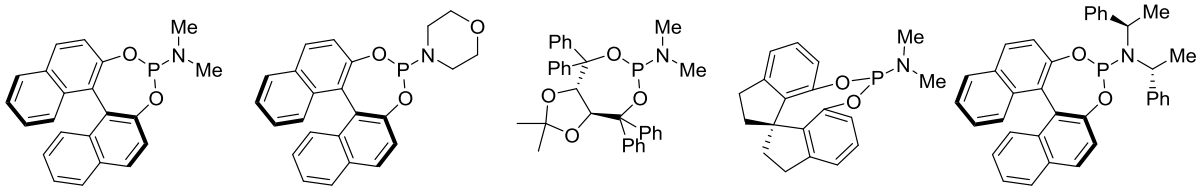
Control of the new sp^3 stereocenter generated in this carbenylative cyclization was examined. We began our investigation by examining the effect chiral phosphoramidites have on the reaction (Table 2-3). Phosphoramidites have previously been successfully employed as ligands in asymmetric palladium-catalyzed allylic alkylations and aminations.[33] Reaction with BINOL derived phosphoramidite **L1** afforded indane product **2.28ae** in 63% yield and 11% *ee* (Table 2-3, entry 1). Spirocyclic phosphoramidite **L4** gave slightly higher *ee* while significantly lowering the reaction yield (entry 4).

Table 2-3: Carbenylative Cyclization with Phosphoramidite Ligands



Entry	Ligand (40 mol%)	Time (h)	% 2.28ae[a]	% 2.26a[a]	ee[b]
1	**L1**	6	63	0	11
2	**L2**	16	13	25	0
3	**L3**	6	44	27	0
4	**L4**	9	6	25	21
5	**L5**	6	59	0	0

[a] NMR yields determined by comparison with an internal standard.
[b] *ee* determined by chiral HPLC



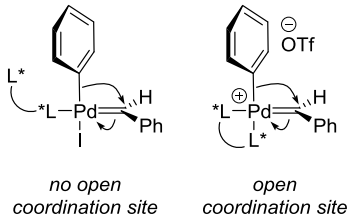
L1 **L2** **L3** **L4** **L5**

The low levels of enantiocontrol observed with monodentate phosphoramidite ligands led us to pursue alternate strategies towards controlling the stereocenter formed in the carbenylative cyclization reaction. Overman and co-workers have shown that cationic palladium intermediates are critical in achieving high levels of enantioselection in asymmetric Heck cyclizations.[34] Ionization of vinyl or arylpalladium halides with silver salts generates cationic palladium(II) species,[35] however silver salts have been shown to decompose *N*-tsoylhydrazones in previous carbenylative cyclizations run by our group.[36]

Aryl triflates offer an alternative method for accessing cationic arylpalladium(II) intermediates. Replacing aryl iodides with aryl triflates in our reaction would allow us to access cationic arylpalladium(II) intermediates without the addition of problematic silver salts. Cationic arylpalladium(II) intermediates contain an open coordination site that can accommodate chiral

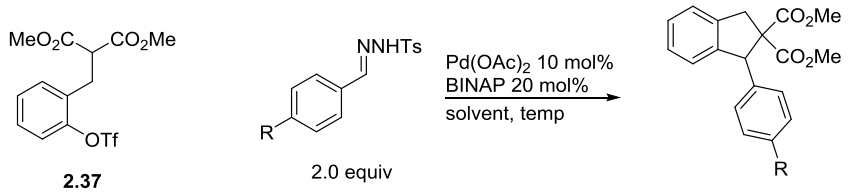
bidentate phosphine ligands such as BINAP, creating an asymmetric environment around the metal center and hopefully influencing the enantiodetermining migratory insertion step (Figure 2-28). Furthermore, Shibasaki and co-workers have demonstrated high levels of asymmetric induction in intramolecular Heck cyclizations yielding 1-vinyltetralins utilizing aryl triflates and bidentate chiral phosphines as ligands for palladium.[37]

Figure 2-28: Model for Asymmetric Induction with Aryltriflates



Subjecting aryltriflate **2.37** and *N*-tosylhydrazone **2.27f** to the standard sodium enolate conditions did not afford any product. At this stage it was clear that a separate optimization was required in order to successfully utilize aryl triflates as coupling partners in our carbenylative cyclization reaction (table 2-4). Toluene was required in order to observe any product at all, other non-protoic solvents were not suitable (entries 1-3). Lithium *tert*-butoxide was superior to other bases screened as well (entries 4-6). The reaction with the *N*-tosylhydrazone derived from paramethylbenzaldehyde **2.27e** was much faster compared to 4-MeO (entries 2 and 7). This hydrazone was chosen as the coupling partner in the ligand screen due to convenience.

Table 2-4: Initial Optimization with Aryl Triflate **2.37**



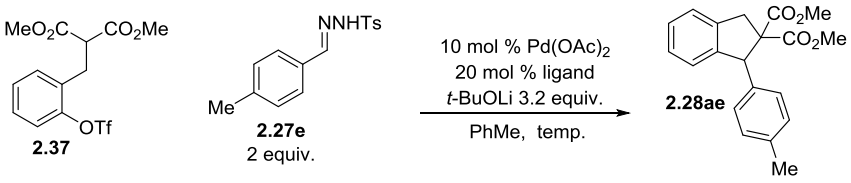
Entry	Solvent	R	Base (equiv)	Temp. °C	Time (h)	Yield indane[a]
1	1,4 dioxane	R = OMe	*t*-BuOLi (3.2)	90	1	0
2	PhMe	R = OMe	*t*-BuOLi (3.2)	110	1	12
3	DMA	R = OMe	*t*-BuOLi (3.2)	130	1	0
4	PhMe	R = OMe	Cs_2CO_3 (3.2)	110	1	0
5	PhMe	R = OMe	*t*-BuOK (3.2)	110	1	<2
6	PhMe	R = OMe	K_2CO_3(3.2)	110	22	<2
7	PhMe	R = Me	*t*-BuOLi (3.2)	110	0.25	15

[a] NMR yields determined by comparison with an internal standard

Modest asymmetric induction was observed when *R*-BINAP was used as a ligand at 110 °C (Table 2-5, entry 1). Decreasing the temperature of the reaction gave a modest boost in enantioselectivity, with the best results coming at 70 °C (entries 1-4). As expected, the intensities in of the enantiomer peaks in the HPLC chromatogram switched when the opposite stereoisomer of BINAP was used (entry 3). Dimethoxy BINAP derivative **L6** can also form a 7-memebred ring chelate with palladium, however it performed worse than BINAP as ligand for our reaction (entries 4 and 5). *R*-DIOP afforded the indane product in slightly higher yield and enantiomeric purity (entries 4 and 6). Running the reaction at 50 °C with *R*-DIOP as a ligand extended the reaction time but did not demonstrate a significant improvement in yield or enantioselectivity (entry 7). BINAP, DIOP, and **L6** ligands form a 7-memebred ring chelate when bound to palladium. Ligands that could form 5, 7 or 8 membered ring were also examined (entries 8-10). Electron-rich ferrocene derived phosphine **L8** afforded the indane product in 21% yield and 50% *ee*, proving a superior ligand to electron-deficient phosphine **L9**(entries 9 and 10). P-chiral

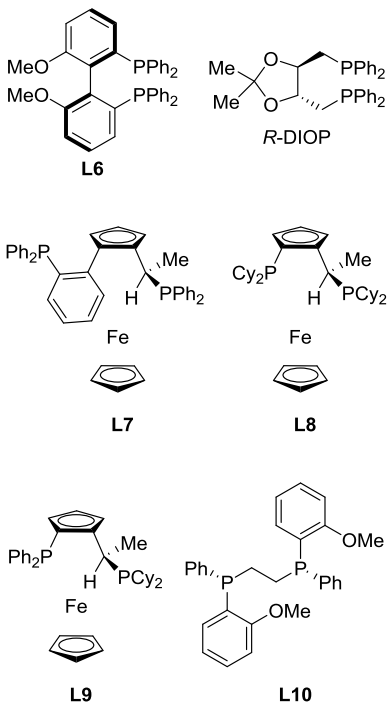
bidentate phosphine **L10** was not suitable for this reaction (entry 11). It appears ligands which can form a 7-membered ring chelate with palladium provide the highest yield and *ee*, however the correlation is modest at best.

Table 2-5: Ligand and Temperature Screen in Asymmetric Carbene Insertions



Entry	Ligand (mol%)	T (°C)	Time (h)	Yield indane[a]	*ee*[b]
1	*R*-BINAP	110	0.25	15	34
2	*R*-BINAP	90	0.75	11	37
3	*S*-BINAP	90	0.75	11	-43
4	*R*-BINAP	70	5	15	47
5	**L6**	70	5	13	7
6	*R*-DIOP	70	5	26	52
7	*R*-DIOP	50	24	18	56
8	**L7**	70	20	11	11
9	**L8**	70	24	21	50
10	**L9**	70	24	5	12
11	**L10**	70	8	10	7

[a] NMR yields determined by comparison with an internal standard.
[b] ee determined by chiral HPLC



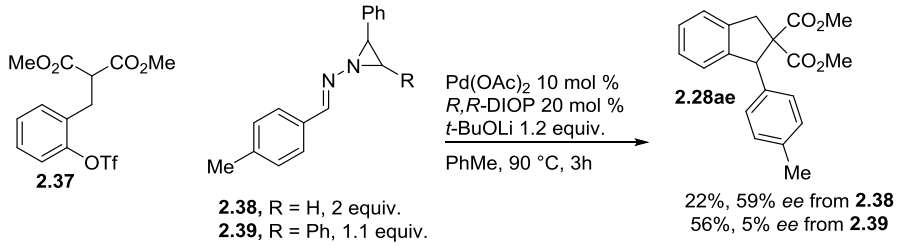
Attempts to account for the mass balance of aryl triflate **2.37** at the end of the reaction were not successful. TLC analysis revealed a significant buildup of baseline polar compounds: oligomerization or polymerization is suspected. ESI mass spectrometry also revealed peaks consistent with dehydropalladation of arylpalladium(II) intermediates.

Alternative Sources of Diazo Compounds

N-Tosylhydrazones generate stoichiometric amounts of sulfinate anion upon Bamford-Stevens decomposition, and sulfinates are known ligands for palladium.[38] *N*-Aziridinylimines offer an alternate approach to generating diazo compounds.[39] Upon heating, *N*-aziridinylimines

decompose to diazo compounds and either styrene or stilbene (depending on the substitution of the aziridine ring). Employing *N*-aziridinylimines instead of *N*-tosylhydrazones in our carbenylative cyclization would allow us to study the reaction without interference of sulfinate salts. When *N*-aziridinylimine **2.38** was used a diazo precursor, indane product **2.28ae** was isolated in 22% yield and 59% *ee* (Figure 2-29). Phenyl substituted *N*-aziridinylimine **2.39** increased the yield of indane product (the highest observed in any reaction with aryltriflate), unfortunately this came at the cost of extremely diminished enantioselectivity. *N*-Aziridinylimines **2.38** generates stilbene as a byproduct of diazo formation, which could in theory serve as a ligand for palladium.

Figure 2-29: *N*-Aziridinylimines Serve as Palladium-Carbene Precursors



Conclusion

In summary, we have developed a palladium-catalyzed carbenylative cyclization reaction that generates 1-arylindanes and 1-aryltetralins in good yields. The reaction generates sp^3 centers through a mechanism involving the alkylation of an η^3-benzylpalladium complex. Attempts at influencing asymmetric induction with chiral bidentate ligands were met with lower yields and modest enantioselectivities. For the first time *N*-aziridinylimines have been used as carbene precursors in palladium-catalyzed reactions but proved to be less efficient than metalated sulfonylhydrazones. Overall, the intramolecular carbenylative cross-coupling of aryl halides with stabilized enolates offers a powerful approach to complex natural products with interesting biological activity.

References

[1] Vlaar, T.; Ruijter, E.; Maes, B. U. W.; Orru, R. "Palladium-Catalyzed Migratory Insertion of Isocyanides: An Emerging Platform in Cross-Coupling Chemistry" *Angew. Chem., Int. Ed.* **2013**, *52*, 7084 – 7097.

[2] Selected examples of Pd-catalyzed carbonylative cross-couplings: (a) Wu, X,-F.; Sundararaju, B.; Neumann, H.; Dixneuf, P. H.; Beller, M. "A General Palladium-Catalyzed Carbonylative Sonogashira Coupling of Aryl Triflates" *Chem. Eur. J.* **2011**, *17*, 106 – 110. (b) Campo, M. A.; Larock, R. C. "Synthesis of Fluoren-9-ones by the Palladium-Catalyzed Cyclocarbonylation of o-Halobiaryls" *J. Org. Chem.*, **2002**, *67*, 5616 – 5620. (c) Kaganovsky, L.; Gelman, D.; Rueck-Braun, K. "Trans-Chelating Ligands in Palladium-Catalyzed Carbonylative Coupling and Methoxycarbonylation of Aryl Halides" *J. Organomet.Chem.* **2010**, *695*, 260 – 266. (d) Lindh, J,; Fardost, A.; Almeida, M.; Nilsson, P "Convenient Stille Carbonylative Cross-Couplings Using Molybdenum Hexacarbonyl" *Tetrahedron Lett.* **2010**, *18*, 2470 – 2472. (e) O'Keefe, B. M.; Simmons, N.; Martin. S. F. "Carbonylative Cross-Coupling of ortho-Disubstituted Aryl Iodides. Convenient Synthesis of Sterically Hindered Aryl Ketones" *Org. Lett.* **2008**, *10*, 5301 – 5304.

[3] Knight, S. D.; Overman, L. E.; Pairaudeau, G. "Synthesis Applications of Cationic Aza-Cope Rearrangements. 26. Enantioselective Total Synthesis of (-)-Strychnine" *J. Am. Chem. Soc.* **1993**, *115*, 9293 – 9294.

[4] Negeshi, E.-I.; Coperet, C.; Sugihara, T.; Shimoyama, I.; Zhang, Y. "Palladium-Catalyzed Carbonylative Cyclization via Trapping of Acylpalladium Derivatives with Internal Enolates. Its Scope and Factors Affecting C-to-O Ratio" *Tetrahedron* **1994**, *50*, 425 – 436.

[5] Negeshi, E.-I.; Zhang, Y.; Shimoyama, I.; Wu, G. "Carbonylative Cyclization via Intramolecular Trapping of Acylmetal Derivatives by Carbon Nucleophiles Catalyzed by Late Transition Metals" *J. Am. Chem. Soc.* **1989**, *111*, 8018 – 8020.

[6] Uozumi, Y.; Mori, E.; Mori, M.; Shibasaki, M. "Incorporation of Molecular Nitrogen into Organic Compounds. IV. Novel Lactam Synthesis by Nitrogenation of Enol Lactones" *J. Organomet. Chem.* **1990**, *399*, 93 – 102.

[7] van Leeuwen, P. W. N. M.; Zuideveld, M. A.; Swennenhuis, B. H. G.; Freixa, Z.; Kamer, P. C. J.; Goubitz, K.; Fraanje, J.; Lutz, M.; Spek, A. L. "Alcoholysis of Acylpalladium(II) Complexes Relevant to the Alternating Copolymerization of Ethene and Carbon Monoxide and the Alkoxycarbonylation of Alkenes: the Importance of Cis-Coordinating Phosphines" *J. Am. Chem. Soc.* **2003**, *125*, 5523 – 5539.

[8] Khanna, A.; Maung, C.; Johnson, K. R.; Luong, T. T.; Van Vranken, D. L. "Carbenylative Amination with *N*-tosylhydrazones" *Org. Lett.* **2012**, *14*, 3233 – 3235.

[9] (a) Xia, Y.; Xia, Y.; Zhang, Y.; Wang, J. "Palladium-Catalyzed Coupling of *N*-tosylhydrazones and β-bromostyrene Derivatives: New Approach to 2*H*-Chromenes" *Org. Biomol. Chem.* **2014**, *12*, 9333 – 9336. (b) Shang, S. X.; Li, N. T.; Siyang, H. X.; Liu, P. N. "Palladium-Catalyzed Tandem Carbene Migratory Insertion and Intramolecular Cyclization: Synthesis of Chromeno[4,3-b]chromene Compounds" *J. Org. Chem.* **2015**, *80*, 4808 – 4815. (c) Yin, B.; Zhang, X.; Liu, J.; Li., X.; Jiang, H. "Practical

Access to Spiroacetal Enol Ethers via Nucleophilic Dearomatization of 2-Furylmethylenepalladium Halides Generated by Pd-Catalyzed Coupling of Furfural Tosylhydrazones with Aryl Halides" *Chem. Commun.* **2014**, *50*, 8113 – 8116.

[10] Kudirka, R.; Van Vranken, D. L. "Cyclization Reactions Involving Palladium-Catalyzed Carbene Insertion into Aryl Halides" *J. Org. Chem.* **2008**, *73*, 3585 – 3588.

[11] Earborn, C.; Walton, D. R. M.; "Remarkable Brönsted Type Correlation for Base Cleavage of Carbon-Silicon Bonds. Kinetic Isotope Effects for Interaction of Carbanions with Methanol" *J. Chem. Soc., Chem. Commun.* **1975**, 937 – 939.

[12] Arunprasath, D.; Muthupandi, P.; Sekar, G. "Palladium-Catalyzed Intermolecular Carbene Insertion Prior to Intramolecular Heck Cyclization: Synthesis of 2‑Arylidene-3-aryl-1- indanones" *Org. Lett.* **2015**, 5448 – 5451.

[13] Ye, Y.-Y.; Zhou, P.-X.; Luo, J.-Y.; Zhong, M.-J.; Liang, Y.-M. "Palladium-Catalyzed Insertion of α,β-Unsaturated *N*-tosylhydrazones and Trapping with Carbon Nucleophiles" *Chem. Commun.* **2013**, *49*, 10190 – 10192.

[14] Both studies employed $Pd_2dba_3 \bullet CHCl_3/PPh_3$ as a catalyst in ethereal solvents

[15] (a) Prat, L.; Mojovic, L.; Levacher, V.; Dupas, G.; Queguiner, G.; Bourguignon, J. "Deracemization of Diarylmethanes via Lateral Lithiation-Protonation Sequences by Means of Sparteine" *Tetrahedron: Asymmetry* **1998**, *9*, 2509 − 2516. (b) Saxena, D. B. "Phenyl Indane from *Acorus Calamus*" *Phytochemistry* **1986**, *25*, 553 − 555. (c) Ishii, H.; Koyama, H.; Hagiwara, K.; Miura, T.; Xue, G.; Hashimoto, Y.; Kitahara, G.; Aida, Y.; Suzuki, M. "Synthesis of and Biological Evaluation of Deoxy-hematoxylin Derivatives as a Novel Class of Anti-HIV-1 Agents" *Bioorg. Med. Chem. Lett.* **2012**, *22*, 1469 − 1474. (d) Vitale, M.; Prestat, G.; Lopes, D.; Madec, D.; Kammerer, C.; Poli, G.; Girnita, L. "New Picropodophylin Analogs via Palladium-Catalyzed Allylic Alkylation-Hiyama Cross-Coupling Sequences" *J. Org. Chem.* **2008**, *73*, 5795 − 5805.

[16] Wheland, G. W. Resonance in Organic Chemistry; Wiley: New York, 1955.

[17] Kuwano, R. "Catalytic Transformations of Benzylic Carboxylates and Carbonates" *Synthesis* **2009**, 1049 – 1061.

[18] Johns, A. M.; Utsunomiya, M.; Incarvito, C. D.; Hartwig, J. F. "A Highly Active Palladium Catalyst for Intermolecular Hydroamination. Factors that Control Reactivity and Additions of Functionalized Anilines to Dienes and Vinylarenes" *J. Am. Chem. Soc.* **2006**, *128*, 1828 – 1839.

[19] (a) Legros, J.-Y.; Toffano, M.; Fiaud, J.-C. "Palladium-Catalyzed Substitution of Esters of Naphthlmethanols, 1-Naphthylethanols, and Analogues by Sodium Dimethyl Malonate. Stereoselective Synthesis from Enantiomerically Pure Substrates" *Tetrahedron* **1995**, *51*, 3235 – 3246. (b) Kuwano, R.; Kusano, H. "Palladium-Catalyzed Nucleophilic Substitution of Diarylmethyl Carbonates with Malonates Carbanions" *Chem. Lett.* **2007**, *36*, 528 – 529. (c) McLaughlin, M. "Suzuki-Miyaura Cross-Coupling of Benzylic Phosphates with Arylboronic Acids" *Org. Lett.* **2005**, *7*, 4875 – 4878.

[20] (a) Kuwano, R.; Kusano, H. "Benzyl Protection of Phenols under Neutral Conditions: Palladium-Catalyzed Benzylations of Phenols" *Org. Lett.* **2008**, *10*, 1979 – 1982. (b) Kuwano, R.; Kondo, Y.; Matsuyama, Y. "Palladium-Catalyzed Nucleophilic Benzylic Substitutions of Benzylic Esters" *J. Am. Chem. Soc.* **2003**, *125*, 12104 – 12105. (c) Kuwano, R.; Kondo, Y.; Shirahama, T. "Transformation of Carbonates into Sulfones at the Benzylic Position via Palladium-Catalyzed Benzylic Substitution" *Org. Lett.* **2005**, *7*, 2973 – 2975. (d) Legros, J.-Y.; Fiaud, J.-C. "Palladium-Catalyzed Nucleophilic

Substitution of Naphthylmethyl and 1-Naphthylethyl Esters" *Tetrahedron Lett.* **2002**, *33*, 2509 – 2510.

[21] Albeniz, A. C.; Espinet, P.; Manrique, R.; Perez-Mateo, A. "Observation of the Direct Products of Migratory Insertion in Aryl Palladium Carbene Complexes and Their Subsequent Hydrolysis" *Angew. Chem.* **2002**, *114*, 2469 – 2472.

[22] Liu, S.-T.; Reddy, K. R. "Carbene Transfer Reactions Between Transition-Metal Ions" *Chem. Soc. Rev.* **1999**, *28*, 315 – 322.

[23] Albeniz, A. C.; Espinet, P.; Lin, Y.-S. "Involvement of Intramolecular Hydride Transfer in the Formation of Alkanes from Palladium Alkyls" *Organometallics* **1997**, *16*, 4030 – 4032.

[24] Albeniz, A. C.; Espinet, P.; Lin, Y.-S. "Involvement of Intramolecular Hydride Transfer I n the Formation of Alkanes from Palladium Alkyls" *Organometallics* **1997**, *16*, 4030 – 4032.

[25] Kuwano, R.; Kusano, H. "Palladium-Catalyzed Nucleophilic Substitution of Diarylmethyl Carbonates with Malonates Carbanions" *Chem. Lett.* **2007**, *36*, 528 – 529.

[26] Tomilov, Y. V.; Kostitsyn, A. B.; Shulishov, E. V.; Nefedov, O. M. " Palladium(II)-Catalyzed Cyclopropanation of Simple Allyoxy and Allylamino Compounds and of 1-Oxy-1,3-butadienes with Diazomethane" *Synthesis*, **1990**, 246 - 248.

[27] Rahman, M. M.; Liu, H. Y.; Eriks, K.; Prock, A. "Quantitative Analysis of Ligand Effects. Part 3. Separation of Phosphorus(III) Ligands into Pure Sigma-Donors and Sigma-Donor/Pi-Acceptors. Comparison of Basicity and Sigma-Donicity" *Organometallics*. **1989**, 8, 1 – 7.

[28] Davies, H. W.; Schwarz, M. "The Effects of Hydrogen Bonding on the Absorption Spectra of Some Substituted Benzaldehyde Tosylhydrazone Anions" *J. Org. Chem*. **1965**, *30*, 1242 – 1244.

[29] Kende, A. S.; King, M. L.; Curran, D. P. "Total Synthesis of (±)-4'-Demethyl-4-epipodophyllotoxin by Insertion-Cyclization" *J. Org. Chem*. **1981**, *46*, 2826 – 2828.

[30] (a) Beare, N. A.; Hartwig, J. F. "Palladium-Catalyzed Arylation of Malonates and Cyanoesters Using Sterically Hindered Trialkyl- and Ferrocenyldialkylphosphine Ligands" *J. Org. Chem*. **2002**, *67*, 541 − 555. (b) Wolkowski, J. P.; Hartwig, J. F. "Generation of Reactivity from Typically Stable Ligands: C-C Bond-Forming Reductive Elimination from Aryl Palladium(II) Complexes of Malonate Anions" *Angew. Chem., Int. Ed*. **2002**, *41*, 4289 − 4291.

[31] (a) Hashimoto, S.; Shinoda, T.; Ikegami, S. "A Novel Lithium Iodide-Promoted Vinylcyclopropane-Cyclopentene Rearrangement: Efficient Synthesis of Bicyclo[3.3.0]oct-6-en-2-one, Versatile Building Block for Polycyclopentanoid Natural Products" *Tetrahedron Lett*. **1986**, *27*, 2885 − 2888. (b) Thorimbert, S.; Malacria, M. "Silicon Effect Favoring the Formation of a Cyclopentene via Palladium-Catalyzed 5-Endo-trig Cyclisation" *Tetrahedron Lett*. **1998**, *39*, 9659 − 9660.

[32] (a) Greenman, K. L.; Van Vranken, D. L. "Palladium-Catalyzed Carbene Insertion into Benzyl Bromides" *Tetrahedron* **2005**, *61*, 6438 − 6441. (b) Yu, W.-Y.; Tsoi, Y.-T.; Zhou, Z.; Chan, A. S. C. "Palladium-Catalyzed Cross Coupling Reaction of Benzyl Bromides with Diazoesters for Stereoselective Synthesis of (*E*)-α,β-Diarylacrylates" *Org.Lett*. **2009**, *11*, 469 − 472.

[33] (a) Shi, C.; Ojima, I. "Asymmetric Synthesis of 1-Vinyltetrahydroisoquinoline through Pd-Catalyzed Intramolecular Allylic Amination" *Tetrahedron* **2007**, *63*, 8563 – 8570. (b)

Chapsal, B. D.; Ojima, I. "Total Synthesis of Enantiopure (+)-γ-Lycorane Using Highly Efficient Pd-Catalyzed Asymmetric Allylic Alkylation" *Org. Lett.* **2006**, *7*, 1395 – 1398.

[34] Carpenter, N. E.; Kucera, D. J.; Overman, L. E. "Palladium-Catalyzed Polyene Cyclizations of Trienyl Triflates" *J. Org. Chem.* **1989**, *54*, 5846 – 5848.

[35] Dounay, A. B.; Overman, L. E. "The Asymmetric Intramolecular Heck Reaction in Natural Product Total Synthesis" *Chem. Rev.* **2003**, *103*, 2945 – 2963.

[36] Khanna, A. Harnessing the Reactivity of Palladium Carbenes. Ph.D. Dissertation, University of California, Irvine, 2013.

[37] Takemoto, T.; Sodeoka, M.; Sasai, H.; Shibasaski, M. "Catalytic Asymmetric Synthesis of Benzylic Quaternary Carbon Centers. An Efficient Synthesis of (-)-eptazocine" *J. Am. Chem. Soc.* **1993**, *115*, 8477 – 8478.

[38] Palladium(II) has been shown to catalyze the desulfinative coupling of aryl sulfinate salts with various electrophiles: (a) Li, Y.; Yang, W.; Cheng, G.; Yang, D. "Palladium-Catalyzed *syn*-Stereocontrolled Ring-Opening of Oxabicyclic Alkenes with Sodium Arylsulfinates" *J. Org. Chem.* **2016**, *81*, 4744 – 4750.
(b) Liu, J.; Zhou, X.; Rao, H.; Xiao, F.; Li, C.-J.; Deng, G.-J. "Direct Synthesis of Aryl Ketones by Palladium-Catalyzed Desulfinative Addition of Sodium Sulfinates to Nitriles" *Chem. Eur. J.* **2011**, *17*, 7996 – 7999.
(c) Zhou, X.; Luo, J.; Liu, J.; Peng, S.; Deng, G.-J. "Pd-Catalyzed Desulfinative Heck Coupling with Dioxygen as the Terminal Oxidant" *Org. Lett.* **2011**, *13*, 1432 – 1435.

[39] Kirmse, W. "Reactive Intermediates from *N*-Aziridinylimines" *Eur. J. Org. Chem.* **1998**, 201 – 212.

Experimental Section

General Procedures

Unless otherwise noted, ^{1}H and ^{13}C NMR spectral data were recorded at room temperature in a Bruker 500 or 600 MHz spectrometer equipped with a cryoprobe. The NMR data are reported as follows: chemical shift in ppm, multiplicity (br = broad, app = apparent, s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet), coupling constants (Hz), and integration. All spectra were calibrated to tetramethylsilane (0.00 ppm). The NMR data are reported as follows: chemical shift in ppm, multiplicity (br = broad, app = apparent, s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet), coupling constants (Hz), and integration.

All reactions were monitored by thin-layer chromatography (TLC). Analytical TLC was performed using EMD Reagents 0.25 mm silica gel 60-F plates. $KMnO_4$ and *p*-anisaldehyde

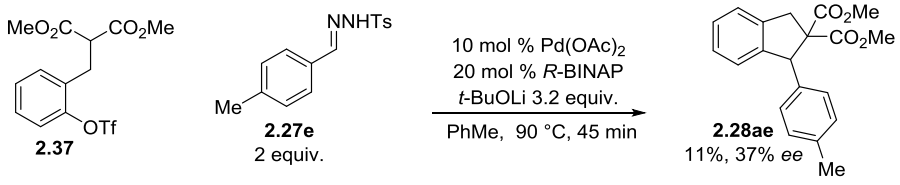
stains were used for TLC visualization. "Flash" chromatography on silica gel was performed using Silicycle silica gel (40-63 μm).

Melting points were taken on an electrothermal melting point apparatus using a mercury thermometer and are uncorrected. Infrared spectrometric data were recorded on a Thermo Scientific iD5 ATR (Nicolet iS5) Spectrometer. All reactions were carried out under an atmosphere of nitrogen in glassware that was evacuated and back-filled with nitrogen three times. Alcohol precursors of aryl iodides **2.26b**, **2.26d**, and **2.29a** were prepared from the commercially available carboxylic acids following the procedure of Quach and coworkers.[1] *N*-tosylhydrazones were prepared following the procedure of Kabalka and co-workers.[2] Aryl iodide **2.33** was prepared according to the procedure of Negeshi and co-workers.[3] Unless otherwise noted, all reagents were commercially obtained and, where appropriate, purified prior to use. THF, Et_2O, and CH_2Cl_2 were dried by filtration through alumina according to the procedure of Grubbs and co-workers.[3]

Enantiomeric excess was determined by HPLC. Waters Acrodisc filters were used to filter HPLC samples (P/N WAT200520). A Chiralcel Technologies normal phase CHIRALCEL OD-H (0.46cmØ × 25cm) chiral column was used on a Shimadzu Prominence Modular HPLC instrument. The instrument comprises two solvent delivery units (LC-20AD), a UV-VIS detector (SPD-20AV), an on-line degassing unit (DGU-20A-5R), and a system controller (CBM-20A LITE w/network switch). Analysis was performed on LabSolutions software version 5.52 copyright of Shimadzu Corporation.

Representative HPLC Traces

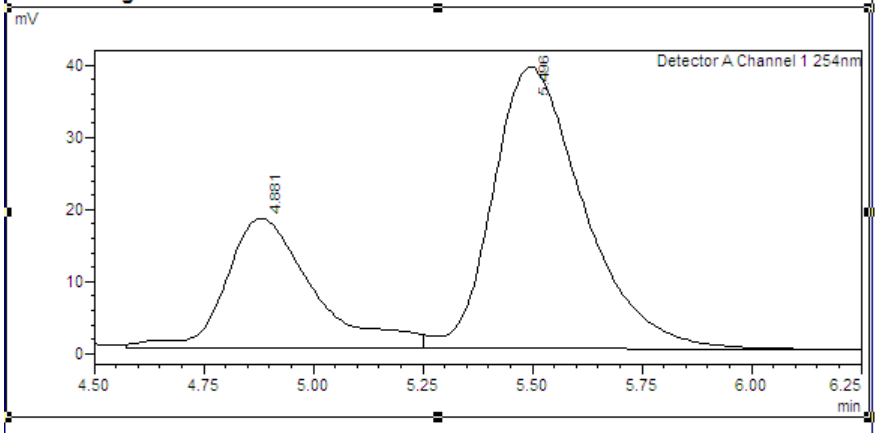
Representative HPLC traces are shown below for compound **2.28ae** synthesized from Aryl triflate **2.38** utilizing *R*-BINAP and and *S*-BINAP ligands. The *ee* was measured utilizing the Shimadzu HPLC instrument using a chiral stationary phase [Chiralcel OD-H, 2-propanol/hexanes = 1/99, 1.5 mL/min, λ = 254 nm]. With *R*-BINAP t_R = 4.88 min (minor) and 5.50 min (major).



==== Shimadzu LabSolutions Analysis Report ====

Sample Name	: Chiracel ODH eg-3-258 1% 1.5mL/min		
Sample ID	: eg-3-258		
Data Filename	: eg-3-279.lcd		
Method Filename	: indane.lcm		
Batch Filename	:		
Vial #	: 1-1	Sample Type	: Unknown
Injection Volume	: 10 uL		
Date Acquired	: 10/31/2014 7:41:19 PM	Acquired by	: Admin
Date Processed	: 10/31/2014 7:51:22 PM	Processed by	: Admin

<Chromatogram>

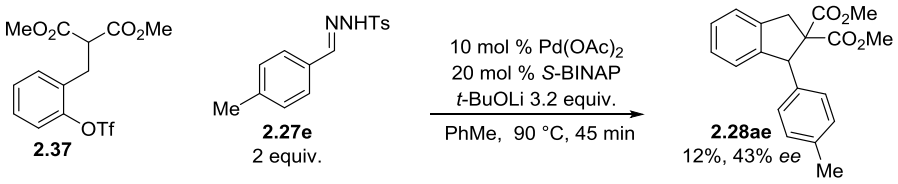


<Peak Table>

Detector A Channel 1 254nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	4.881	249614	17976	30.629		M	
2	5.496	565341	39047	69.371		V M	

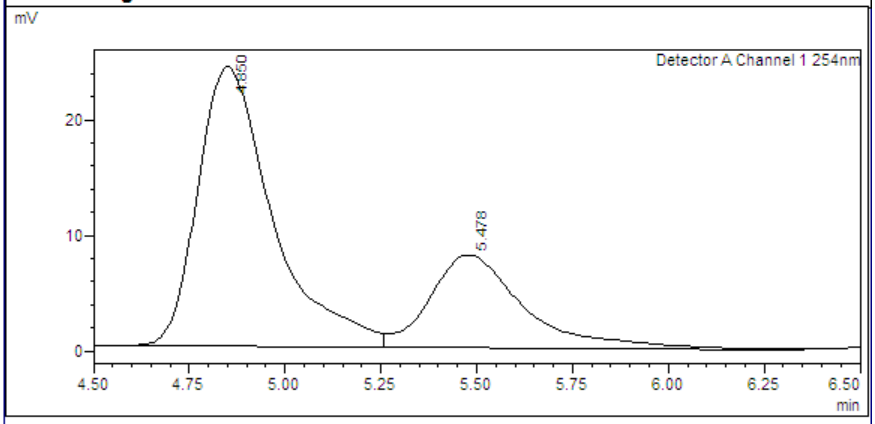
With *S*-BINAP t_R = 4.85 min (major) and 5.48 min (minor).



==== Shimadzu LabSolutions Analysis Report ====

Sample Name	: Chiracel ODH eg-3-264 1% 1.5mL/min		
Sample ID	: eg-3-264		
Data Filename	: eg-3-261.lcd		
Method Filename	: shutdown method.lcm		
Batch Filename	:		
Vial #	: 1-1	Sample Type	: Unknown
Injection Volume	: 10 uL		
Date Acquired	: 10/30/2014 4:49:02 PM	Acquired by	: Admin
Date Processed	: 10/30/2014 4:59:04 PM	Processed by	: Admin

<Chromatogram>



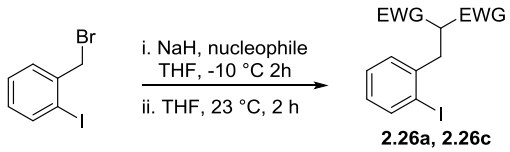
<Peak Table>

Detector A Channel 1 254nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	4.850	327014	24183	70.688		M	
2	5.478	135603	7964	29.312		V M	

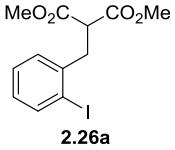
Synthesis of 2-iodoaryl malonates, 2.26a-d and 2.29.

General procedure for the synthesis of 2-iodoaryl malonates 2.26a and 2.26c:



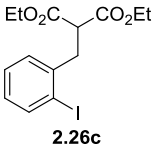
A flame-dried round-bottom flask was charged with 60% NaH dispersion in mineral oil (5.0 equiv), and a stir bar. The flask was fitted with a septum and purged with nitrogen. The

round-bottom flask was cooled to −10 ^{o}C in a brine-ice bath and THF was added leading to a 2.1 M solution of NaH. Malonate nucleophile (5.0 equiv) was added dropwise to the stirred reaction mixture resulting in formation of a white suspension. Then, 2-iodobenzyl bromide (1.0 equiv) was added dropwise to the stirred reaction mixture as a 1.7 M solution in THF. The reaction was removed from the brine-ice bath and allowed to warm to 23 ^{o}C while stirring. The reaction was stirred at 23^{o}C until the 2-iodobenzyl bromide was no longer detectable by TLC. The reaction mixture was quenched with saturated $NH_4Cl_{(aq)}$ and extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried ($NaSO_4$), filtered, and concentrated *in vacuo*. The desired monoalkylated malonate was isolated by flash chromatography on silica gel.



2.26a

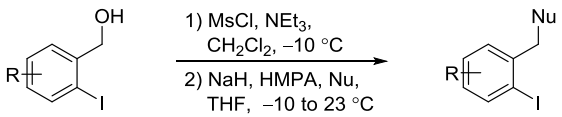
Dimethyl 2-(2-iodobenzyl) malonate, 2.26a. Following the general procedure, a solution of 2-iodobenzyl bromide (1.00 g, 3.37 mmol) in THF (4 mL) was added dropwise to a mixture of 60% NaH (0.673 g, 16.8 mmol) and dimethyl malonate (1.9 mL, 17 mmol) in THF (8 mL) at –10 ^{o}C. After 3 h, 2-iodobenzyl bromide was no longer detectable by TLC (1:3 EtOAc/hexanes). The reaction mixture was quenched with saturated $NH_4Cl_{(aq)}$ (30 mL) and extracted with 3 x 30 mL of CH_2Cl_2. The combined organic phases were washed with 30 mL of brine, dried ($NaSO_4$), filtered, and concentrated *in vacuo* to afford a clear oil. Purification by flash chromatography on silica gel (1:9 EtOAc/hexanes) provided dimethyl 2-(2-iodobenzyl) malonate **2.26a** as a white solid (1.08 g, 92%). ^{1}H and ^{13}C matched reported spectroscopic data.[5] R_f = 0.55 (15:85 EtOAc/hexanes).



2.26c

Diethyl 2-(2-iodobenzyl)malonate, 2.26c. Following the general procedure, a solution of 2-iodobenzyl bromide (0.703 g, 2.37 mmol) in THF (4.5 mL) was added dropwise to a solution of 60% NaH (0.474 g, 11.8 mmol) and diethyl malonate (1.90 g, 11.8 mmol) in THF (5 mL) at –10 °C. Upon completion, the reaction was quenched according to general procedure to afford a clear oil. Purification by flash chromatography on silica gel (1:9 EtOAc/hexanes) provided 2-iodobenzyl diethylmalonate **2.26c** as a clear oil (0.630 g, 71%). ^{1}H and ^{13}C matched reported spectroscopic data (0.630 g, 71%).[6] R_f = 0.65 (15:85 EtOAc/hexanes).

General procedure for the synthesis of 2-iodoaryl malonates 2.26b, 2.26d, and 2.29:

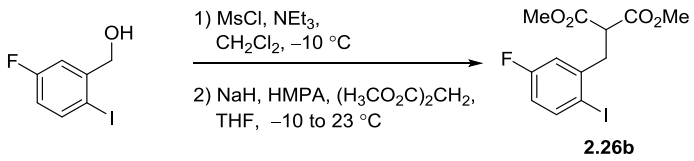


Mesylation: A flame-dried 10 mL, 2-necked, round-bottom flask equipped with a short-stem vacuum adapter and rubber septum was charged with the corresponding 2-iodobenzyl

alcohol (1 equiv), a stir bar, and CH_2Cl_2 (0.2 M in alcohol). The solution was cooled to –10 ^oC in a brine-ice bath and stirred before adding triethylamine (1.6 equiv). After 10 min, methanesulfonyl chloride (1.2 equiv) was added producing a pale yellow solution. The reaction was left to stir until the corresponding 2-iodobenzyl was no longer detectable by TLC (1:3 EtOAc/hexanes). The reaction mixture was then transferred to a separatory funnel and washed with 20 mL of H_2O, 20 mL of 1N HCl, 20 mL of $NaHCO_3$, and 20 mL of brine. The organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford the corresponding crude mesylate, which was then used directly in the following alkylation step without further purification.

Alkylation: A flame-dried 25 mL, 2-necked, round-bottom flask equipped with a short-stem vacuum adapter and rubber septum was charged with 60% NaH (2 equiv), and a stir bar. The flask was cooled to –10 ^oC in a brine-ice bath, and charged with THF (1.7 M in NaH) and hexamethylphosphoroamide (HMPA) (2 equiv). Dimethyl malonate (2.2 equiv) was added dropwise via syringe over 5 min resulting in a homogeneous pale yellow solution. After 25 min, a solution of crude mesylate (1 equiv) in THF (2.4 M in mesylate) was added dropwise via syringe over 1 min. The reaction was warmed to 23 ^oC and left stirring until the mesylate was no longer detectable by TLC (1:3 EtOAc/hexanes). The reaction mixture was quenched with saturated $NH_4Cl_{(aq)}$ (15 mL), transferred to a separatory funnel, and washed with 3 x 20 mL of Et_2O. The combined organic phases were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford product, which was then purified by flash chromatography on silica gel.

Example Procedure: Dimethyl 2-(5-fluoro-2-iodobenzyl)malonate, 2.26b.



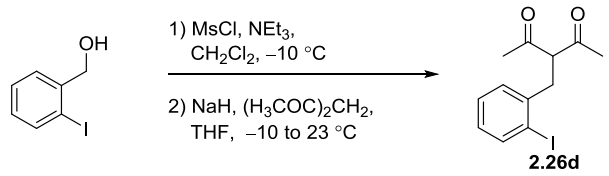
2.26b

A flame-dried 10 mL, 2-necked round-bottom flask equipped with a short-stem vacuum adapter and rubber septum was charged with 5-fluoro-2-iodobenzyl alcohol (0.702 g, 2.79 mmol) and a stir bar. The flask was charged with CH_2Cl_2 (14 mL), cooled to –10 ^oC in a brine-ice bath, and triethylamine (0.65 mL, 4.6 mmol) was added while stirring. After 10 min, methanesulfonyl chloride (0.26 mL, 3.3 mmol) was added, producing a pale yellow solution. After 45 min, benzyl alcohol starting material was no longer detectable by TLC (1:3 EtOAc/hexanes). The reaction mixture was transferred to a separatory funnel and washed with 20 mL of H_2O, 20 mL of 1N HCl, 20 mL of $NaHCO_3$, and 20 mL of brine. The organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford 0.873 g of a grey solid. The crude mesylate was used directly in the following alkylation step without further purification.

A flame-dried 25 mL, 2-necked round-bottom flask equipped with a short-stem vacuum adapter and rubber septum was charged with 60% NaH (0.207 g, 5.18 mmol), and a stir bar. The flask cooled was to –10 ^oC in a brine-ice bath, and charged with THF (3 mL) and HMPA (0.84 mL, 4.9 mmol). Dimethyl malonate (0.62 mL, 5.3 mmol) was added dropwise via syringe over 5 min resulting in a homogeneous pale yellow solution. After 25 min, a solution of crude mesylate (0.800 g, 2.42 mmol) in THF (1 mL) was added dropwise via syringe over 1 min. The reaction was removed from the brine-ice bath and warmed to 23 ^oC while stirring. After 4.5 h, mesylate was no longer detectable by TLC (1:3 EtOAc/hexanes). The reaction mixture was quenched with 15 mL of saturated $NH_4Cl_{(aq)}$, transferred to a separatory funnel, and washed with 3 x 20 mL of Et_2O. The combined organic phases were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to

afford a clear oil. The oil was purified by flash chromatography on silica gel (1:19 EtOAc/hexanes) to yield dimethyl 2-(5-fluoro-2-iodobenzyl) malonate **2.26b** as a white solid (0.454 g, 51%). R_f = 0.51 (1:4 EtOAc/hexanes); mp = 69–71 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (dd, *J* = 8.6, 5.7 Hz, 1H), 6.99 (dd, *J* = 9.5, 2.8 Hz, 1H), 6.71 (td, *J* = 8.3, 2.8 Hz, 1H), 3.82 (t, *J* = 7.7 Hz, 1H), 3.73 (s, 6H), 3.31 (d, *J* = 7.8 Hz, 2H)); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.7, 140.8, 140.7, 117.9, 117.7, 116.3, 116.2, 52.8, 51.3, 39.3; IR (thin film) 2953, 1732, 1575, 1403, 1232 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{12}H_{12}FIO_4Na$ $(M + Na)^+$ 388.9662, found 388.9656.

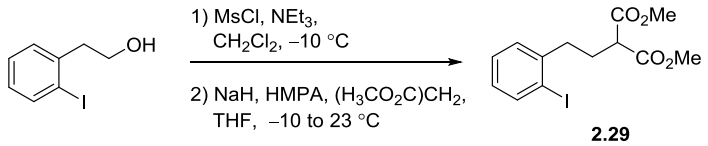
3-(2-iodobenzyl)pentane-2,4-dione, 2.26d.



2.26d

Following the general procedure, a solution of crude mesylate (2.00 g, 6.41 mmol) in THF (3 mL) was added dropwise to a mixture of 60% NaH (3.21 g, 32.0 mmol) and pentane-2,4-dione (3.3 mL, 32 mmol) in THF (25 mL) at –10 °C. (**Note:** No HMPA was used and the 2-necked round-bottom was fitted with a reflux condenser.) Then, the reaction mixture was removed from the brine-ice bath and heated at 66 °C. After 3 h, mesylate was no longer detectable by TLC (1:3 EtOAc/hexanes). The reaction was quenched and worked up according to the general procedure resulting in yellow oil. Purification by flash chromatography on silica gel (1:2 PhMe/hexanes) afforded 3-(2-iodobenzyl)pentane-2,4-dione **2.26d** as a brown solid (1.29 g, 64%). ^{1}H and ^{13}C matched reported spectroscopic data.[7] R_f = 0.52 (15:85 EtOAc/hexanes).

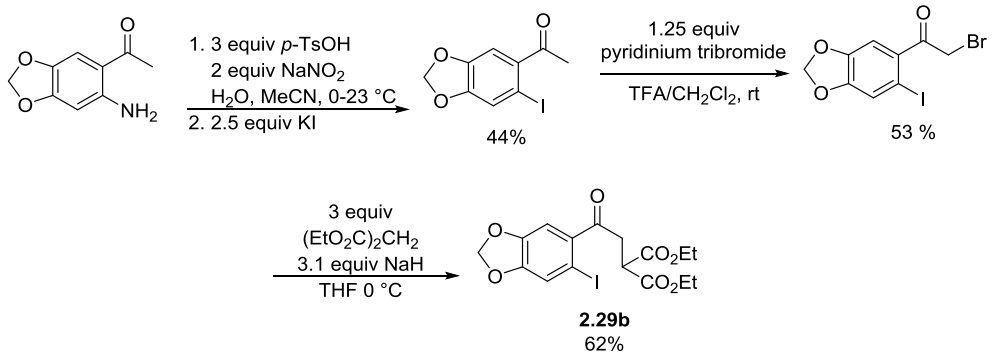
Dimethyl 2-(2-iodophenethyl) malonate, 2.29.

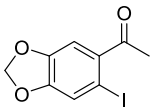


Following the general procedure, a solution of crude mesylate (2.00 g, 6.13 mmol) in THF (3 mL) was added dropwise to a solution of 60% NaH (0.736 g, 18.4 mmol), HMPA (3.2 mL, 18.4 mmol), and dimethylmalonate (2.1 mL, 18 mmol) in THF (7 mL) at –10 °C. (**Note:** The 2-necked round-bottom was fitted with a reflux condenser). The reaction was removed from the brine-ice bath and heated at 66 °C. After 16 h, mesylate was no longer detectable by TLC (15:85 EtOAc/hexanes). The reaction was quenched and worked up according to the general procedure resulting in yellow oil. Purification by flash chromatography on silica gel (1:9 EtOAc/hexanes) afforded malonate **2.29** as a pale yellow oil (0.454 g, 51%). ^{1}H and ^{13}C matched matching the reported spectroscopic data (0.454 g, 51%).[8] R_f = 0.70 (15:85 EtOAc/hexanes).

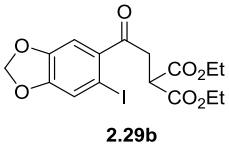
Synthesis of 2-iodoaryl malonate 2.29b.

Dimethyl 2-((6-iodobenzo[d][1,3]dioxol-5-yl)methyl) malonate **2.26e** was prepared using the following synthetic route:





Synthesis of 1-(6-iodobenzo[d][1,3]dioxol-5-yl)ethan-1-one. 1-(6-iodobenzo[d][1,3]dioxol-5-yl)ethan-1-one was synthesized according to the procedure of Sangeetha and co-workers.[9] Spectroscopic data matched known reported data.[9]



2.29b

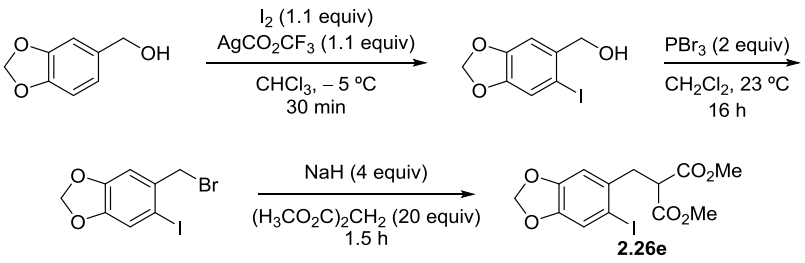
Synthesis of diethyl 2-(2-(6-iodobenzo[d][1,3]dioxol-5-yl)-2-oxoethyl)malonate 2.29b. Aryl iodide **2.29b** was synthesized following a modified procedure from Ziegler and co-workers.[$] Briefly, a 25 mL 2-neck round-bottom flask was equipped with a stir bar, flame-dried, and charged with aryl iodide 1-(6-iodobenzo[d][1,3]dioxol-5-yl)ethan-1-one (0.300 g, 1.03 mmol). The round-bottom flask was evacuated and backfilled with N_2 three times before being charged with DCM (6.1 mL) and TFA (0.04 mL, 0.52 mmol). To the yellow solution was added pyridinium tribromide (0.363 g, 1.14 mmol) in four portions over four hours. The flask was wrapped in aluminum foil during the reaction to exclude light. After 10 h, starting material was no longer detectable by TLC (100% PhMe). The crude reaction mixture was quenched with sat. $NaHCO_3$ (6 mL) and stirred until gas ceased evolving. The crude reaction mixture was transferred to a separatory funnel and washed once with 6 mL of 1N aq. HCl. The aqueous layer was extracted with 1 x 12 mL of DCM and the combined organic phases were washed with 1 x 20 mL of brine, dried over Na_2SO_4, and concentrated *in vacuo.* The resulting yellow oil was immediately purified by flash chromatography (1:9 hexanes/PhMe) to afford α-bromoketone as a clear oil (0.203 g, 0.55 mmol). R_f = 0.55 (100% PhMe).

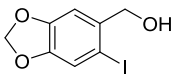
A flame-dried 25 mL, 2-necked round-bottom flask equipped with a short-stem vacuum adapter and rubber septum was charged with 60% NaH (0.066 g, 1.65 mmol), and a stir bar. The flask cooled was to –10 ^oC in a brine-ice bath, and charged with THF (4.5 mL). Diethyl malonate (0.272 g, 1.65 mmol) was added dropwise via syringe over 5 min resulting in white slurry. After

25 min, a solution of α-bromoketone from the previous step (0.203 g, 0.55 mmol) in THF (1 mL) was added dropwise via syringe over 1 min. The reaction was removed from the brine-ice bath and warmed to 23 ^{o}C while stirring. After 4.5 h, α-bromoketone was no longer detectable by TLC (1:3 EtOAc/hexanes). The reaction mixture was quenched with 15 mL of saturated $NH_4Cl_{(aq)}$, transferred to a separatory funnel, and washed with 3 x 20 mL of Et_2O. The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo* to afford a clear oil. The oil was purified by flash chromatography on silica gel (1:9 EtOAc/hexanes) to yield dimethyl diethyl 2-(2-(6-iodobenzo[d][1,3]dioxol-5-yl)-2-oxoethyl)malonate **2.29b** as a clear oil (0.153 g, 62%). R_f = 0.51 (1:4 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (s, 1H), 7.15 (s, 1H), 6.05 (s, 2H), 4.27-4.19 (m, 4H), 4.06 (t, *J* = 7.2 Hz, 1H), 3.45 (d, *J* = 7.2 Hz, 2 H), 1.29 (t, *J* = 7.13 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.5, 168.8, 150.6, 148.3, 135.5, 120.7, 109.2, 102.4, 81.5, 61.9, 47.5, 40.2, 14.1; HRMS (ESI): *m/z* calcd for $C_{16}H_{17}O_7INa$ $(M + Na)^+$ 470.9917, found 470.9906.

Synthesis of 2-iodoaryl malonate 2.26e.

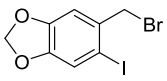
Dimethyl 2-((6-iodobenzo[d][1,3]dioxol-5-yl)methyl) malonate **2.26e** was prepared using the following synthetic route:



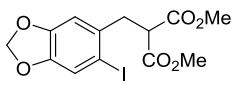


2-Iodo-4,5-methylenedioxy benzyl alcohol. A flame-dried 200 mL round-bottom flask was covered with aluminum foil and charged with piperonyl alcohol (3.00 g, 19.7 mmol), $AgOCOCF_3$ (weighed in the dark) (4.80 g, 22.0 mmol), and a stir bar. The

flask was charged with $CHCl_3$ (20 mL) and cooled to –5 °C in an brine-ice bath. Finely ground I_2 (5.50 g, 18.0 mmol) was dissolved in $CHCl_3$ (25 mL) and added dropwise via syringe over 5-10 min yielding a yellow mixture. Residual I_2 was added to the flask via spatula (rubber septum was removed briefly). After 0.5 h, piperonyl alcohol starting material was no longer detectable by TLC (1:4 EtOAc/hexanes). The reaction mixture was filtered through tightly packed Celite to remove silver salts. The Celite pad was rinsed with $CHCl_3$ (150 mL) and the filtrate was washed with 200 mL of $Na_2S_2O_3$, dried ($MgSO_4$), filtered, and concentrated *in vacuo.* The resulting crude solid was purified by flash chromatography (0–20 % EtOAc/hexanes) to afford benzyl alcohol as a white solid (5.09 g, 93%). ^1H and ^{13}C matched reported spectroscopic data.[5] R_f = 0.20 (1:4 EtOAc/hexanes).



5-(bromomethyl)-6-iodobenzo[d][1,3]dioxole. Benzyl bromide was prepared according to literature procedure.[6] Briefly, benzyl alcohol from the previous step (0.81 g, 2.9 mmol) and CH_2Cl_2 (29 mL, 0.1 M in alcohol) was added to a 50 mL, flame-dried round-bottom flask. The resulting mixture was stirred until alcohol **7** was completely dissolved. PBr_3 (0.55 mL, 5.8 mmol) was added dropwise to afford a pale yellow solution and the solution was left to stir for 16 h. The reaction mixture was then concentrated *in vacuo*, washed with 25 mL of saturated $NaHCO_{3(aq)}$, and extracted with 3 x 45 mL of CH_2Cl_2. The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo* to afford a white solid. Recrystallization from Et_2O afforded white needles of benzyl bromide (0.52 g, 52%). ^1H and ^{13}C matched reported spectroscopic data.[6] R_f = 0.5 (1:4 EtOAc/hexanes).

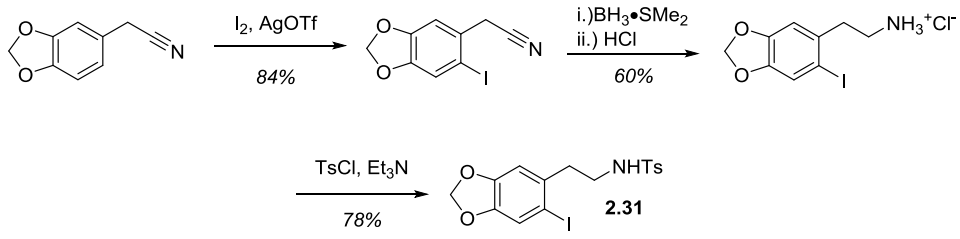


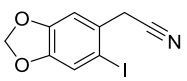
2.26e

Dimethyl 2-((6-iodobenzo[*d*][1,3]dioxol-5-yl)methyl)malonate, 2.26e. A flame-dried 500 mL, round-bottom flask was charged with benzyl bromide from the previous step (4.25 g, 12.5 mmol), a stir bar, and dimethyl malonate (50 mL), and then cooled to 0°C while stirring. Then, 60% NaH (2.00 g, 0.440 mmol) was added in three separate portions over 15 min. After 1.5 h, bromide **8** was no longer detectable by TLC (1:4 EtOAc/hexanes). The reaction mixture was quenched with 100 mL of saturated $NH_4Cl_{(aq)}$, transferred to a separatory funnel, and the aqueous phase was extracted with 3 x 100 mL of CH_2Cl_2. The combined organic phases were washed with 100 mL of brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. A vacuum distillation was performed to remove excess dimethylmalonate. The resulting yellow oil was purified by flash chromatography on silica gel (0–10% EtOAc/hexanes) to afford malonate **2.26e** as a white solid (4.68 g, 95%); R_f = 0.36 (1:3 EtOAc/hexanes); mp = 76–78 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (s, 1H), 6.75 (s, 1H), 5.94 (s, 2H), 3.77 (t, *J* = 8.0 Hz, 1H), 3.72 (s, 6H), 3.24 (d, *J* = 8.0 Hz, 2H); ^{13}C (125 MHz, $CDCl_3$) δ 169.0, 148.5, 147.6, 133.4, 118.9, 110.6, 101.8, 88.1, 52.8, 51.9, 39.3; IR (thin film) 2952, 1731, 1474, 1225, 1035, 930 cm^{-1}; HRMS (EI+): *m/z* calculated for $C_{13}H_{13}IO_6Na$ $(M + Na)^+$ 414.9655, found 414.9667.

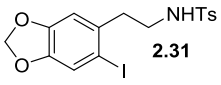
Synthesis of tosyl amine 2.31.

Tosyl amine **2.31** was prepared using the following synthetic route:





Synthesis of 2-(6-iodobenzo[d][1,3]dioxol-5-yl)acetonitrile. 1-(6-iodobenzo[d][1,3]dioxol-5-yl)ethan-1-one was synthesized according to the procedure of Johannes and co-workers.[10] Spectroscopic data matched known reported data.[10]



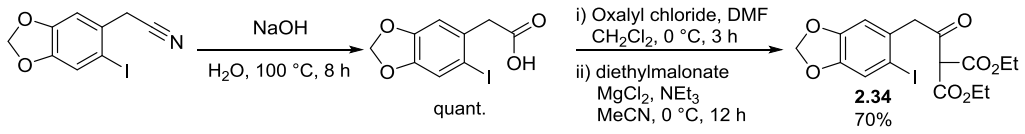
Synthesis of N-(2-(6-iodobenzo[d][1,3]dioxol-5-yl)ethyl)-4-methylbenzenesulfonamide 2.31. A flame-dried 10 mL two neck conical flask was charged with aryl iodide from the previous step (143 mg, 0.5 mmol), and a magnetic stir bar. The flask was equipped with a reflux condenser and purged and backfilled with nitrogen three times, fitted with a rubber septum, and charged with THF resulting in a clear solution. The flask was submersed in an ice bath and cooled to 0 °C while stirring for 10 min. A $BH_3 \bullet SMe_2$ solution (2M in THF, 0.7 mL, 1.43 mmol) was added via syringe over 30 min. The reaction was allowed to stir at 0 °C for another 30 min before being submerged in a hot oil bath and refluxed for 22 h. The reaction was allowed to cool to rt and the crude reaction mixture was carefully added dropwise via syringe to a separate flask containing 10 mL of MeOH cooled to 0 °C in an ice bath. The crude reaction mixture was stirred for 30 min while warming to rt and then concentrated *in vacuo* affording a clear oil. The oil was redissolved in 10 mL of MeOH and concentrated *in vacuo* again affording a sticky white solid. The solid was taken up in 5 mL of 0.5 N aq. HCl and refluxed for 1 h before being transferred to a separatory funnel while still hot. The crude mixture was allowed to cool to rt in the separatory funnel and extracted with 3 x 25 mL of Et_2O. The aqueous phase was made basic by addition of 15% w/v aq. NaOH (10 mL) and extracted with 3 x 25 mL of Et_2O (Note: vigorous agitation is required in order to coax the freebase into the ethereal phase). The combined organic phases were washed with 75 mL of brine, dried over Na_2SO_4, and concentrated *in vacuo* down to a volume of roughly 2 mL. Treatment with a freshly prepared concentrated ethereal HCl solution precipitated out a white

solid which was filtered and washed with cold hexanes affording the phenethylamine salt as a white solid (98.3 mg, 60%).

A flame-dried 5 mL round-bottomed flask was charged with phenethylamine salt from the previous step (50 mg, 0.15 mmol) and a magnetic stir bar. The flask was backfilled with nitrogen three times, fitted with a rubber septum, and charged with DCM (1.5 mL) at rt resulting in a cloudy suspension. The flask was charged with Et_3N (63 μL, 0.46 mmol) and stirred for 15 min at rt resulting in a clear solution. The septum was removed and *p*-methyltoluene sulfonylchloride (35 mg, 0.18 mmol) was added in one batch. The septum was replaced and the reaction was stirred at rt for 12 h. The reaction was taken up in H_2O (1.5 mL) and the aquaeous phase was extracted with 3 x 2 mL of DCM. The organic phase was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* affording yellow oil. The oil was purified by flash chromatography on silica gel (1:3 EtOAc/hexanes) affording tosylamine **2.31** as a clear oil (53 mg, 78%). R_f = 0.5 (40% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.1 Hz, 2 H), 7.28 (d, *J* = 8.0, 2H), 7.15 (s, 1H), 6.64 (s, 1H), 5.93 (s, 2H), 4.70 (t, *J* = 6 Hz, 1H), 3.15 (q, *J* = 6.8 Hz, 2H), 2.81 (t, *J* = 7.1 Hz, 2H), 2.42 (s, 3H).

Synthesis of β-ketomalonate 2.34.

β-ketomalonate **2.34** was prepared using the following synthetic route:

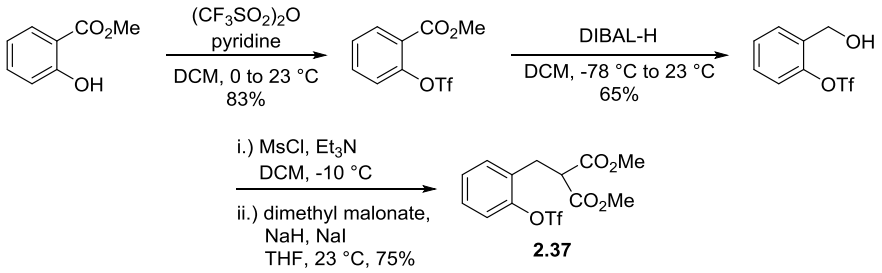


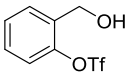
Synthesis of diethyl 2-(2-(6-iodobenzo[d][1,3]dioxol-5-yl)acetyl)malonate 2.34. A flame-dried 25 mL round-bottom flask was charged with **2-(6-iodobenzo[d][1,3]dioxol-5-yl)acetic acid** and a magnetic stir-bar. The flask was backfilled with nitrogen three times, fitted with a rubber septum, and charged with PhMe (9 mL) at rt resulting in a cloudy suspension. Oxalyl chloride

(0.28 mL, 3.22 mmol) was added dropwise via syringe followed by DMF (10 μL, 0.134 mmol) resulting in a color change to yellow and effervescence. The reaction was stirred for 3 h before being concentrated *in vacuo* affording viscous yellow oil. A separate flame-dried 25 mL round-bottom flask was charged with recently dried $MgCl_2$ (0.255 g, 2.68 mmol) and a magnetic stir bar. MeCN (2.7 mL) was added via syringe under an atmosphere of N_2 followed by diethyl malonate (0.41 mL, 2.68 mmol) and Et_3N (0.74 mL, 5.36 mmol) resulting in a clear homogenous solution. The reaction was cooled to 0°C in an ice bath and stirred for 30 min. The acid chloride was taken up in MeCN (2.7 mL) and added dropwise via syringe to the flask containing malonate nucleophile at 0 °C. The reaction was allowed to warm to rt and stirred for 12 resulting in a yellow slurry and complete consumption of diethyl malonate as judged by TLC. The reaction was cooled to 0 °C and quenched with 1.6 mL of a 5 M aq. HCl solution. The crude reaction mixture was stirred for 5 min while warming to rt and then transferred to a separatory funnel and extracted with 3 x 5 mL of Et_2O, dried over Na_2SO_4, and concentrated *in vacuo*. The resulting yellow oil was purified by silica gel flash chromatography (10% EtOAc/hexanes) to afford β-ketomalonate **2.34** as a pale yellow oil (0.839g, 70%) (1.1:1 keto/enol). R_f = 0.50 (1:4 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ keto tautomer: 7.25 (s, 1H), 6.74 (s, 1H), 5.97 (s, 2H), 4.57 (s, 1H), 4.31-4.25 (m, 4H), 4.05 (s, 2H), 1.34-1.29 (m, 6 H), enol tautomer: 13.60 (s, 1H), 7.25 (s, 1H), 6.86 (s, 1H), 5.96 (s, 1H), 4.31-4.25 (m, 4H), 3.92 (s, 1H), 1.34-1.29 (m, 6 H); ^{13}C (125 MHz, $CDCl_3$) δ 195.8, 179.7, 171.2, 165.8, 164.5, 148.7, 148.6, 148.0, 147.6, 131.9, 130.0, 118.7, 118.6, 110.8, 110.0, 101.9, 101.8, 101.0, 89.3, 88.8, 64.8, 62.5, 61.7, 61.3, 53.3, 44.5, 29.8, 14.2, 14.1; HRMS (ESI): *m/z* calcd for $C_{16}H_{17}IO_7Na$ $(M + Na)^+$ 470.9917, found 470.9901.

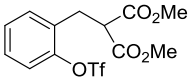
Synthesis of Aryl Triflate 2.37.

Aryl triflate **2.37** was prepared using the following synthetic route





Synthesis of 2-(hydroxymethyl)phenyl trifluoromethanesulfonate. 2-(hydroxymethyl)phenyl trifluoromethanesulfonate was synthesized according to the procedure of Echavarren and co-workers.[11] Spectroscopic data matched known reported data.[11]



2.37

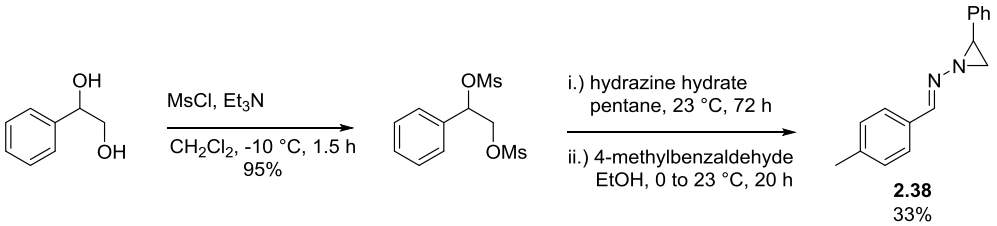
Synthesis of dimethyl 2-(2-(((trifluoromethyl)sulfonyl)oxy)benzyl)malonate 2.37. A flame-dried 5 mL, round-bottom flask equipped with a short-stem vacuum adapter was charged with a magnetic stir bar, DCM (2.5 mL), and 2-(hydroxymethyl)phenyl trifluoromethanesulfonate (64 mg, 0.25 mmol). The flask was cooled to -10 °C and charged with Et_3N (43 mg, 0.42 mmol) and stirred for 15 min after which MsCl(34 mg, 0.3 mmol) was added dropwise via syringe. The reaction was stirred at -10 °C for one hour at which time TLC analysis indicated all starting material was consumed (40% EtOAc/hexanes). The crude reaction mixture transferred to a separatory funnel and washed with 1 x 3 mL of water, 1 x3 mL of brine, dried over Na_2SO_4, and concentrated *in vacuo* affording a clear viscous oil (71 mg, with a purity of >95% by ^{1}HNMR. This material was used immediately in the following alkylation step.

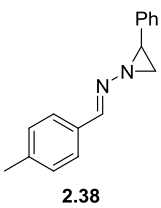
A flame-dried 5 mL, round-bottom flask was equipped with a short-stem vacuum adapter and charged with 60% NaH (18 mg, 0.46 mmol) and a magnetic stir bar. The flask was purged and backfilled with nitrogen three times before being fitted with a rubber septum. THF (1 mL)

was added and the suspension was cooled to –0 °C in a brine-ice bath. Dimethyl malonate (60 mg, 0.46 mmol) was added dropwise via syringe as solution in THF (0.5 mL) and the reaction was stirred for 30 min after which benzyl mesylate from the previous step (61 mg, 0.18 mmol) was added dropwise via syringe as a solution in THF (0.5 mL). The reaction was allowed to warm to rt, the septum removed, and NaI (27 mg, 0.18 mmol) was added in one batch resulting in a cloudy green suspension. The septum was replaced and the reaction was stirred under N_2 for 3 h. TLC analysis indicated complete consumption of starting material (25% EtOAc/hexanes). The reaction was diluted with 3 mL of Et_2O and transferred to a separatory funnel, washed with 1 x 10 mL water, washed with 1 x 10 mL brine, dried over Na_2SO_4, and concentrated *in vacuo* affording a yellow oil. The oil was purified by flash chromatography on silica gel (2% EtOAc/PhMe) to afford aryl triflate **2.37** as a clear oil (78 mg, 75%). R_f = 0.40 (1:4 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.29 (m, 4H), 3.76 (t, *J* = 7.7 Hz, 1H), 3.71 (s, 3H), 3.33 (d, *J* = 7.8 Hz, 2H); ^{13}C (125 MHz, $CDCl_3$) δ 168.6, 148.0, 131.9, 130.5, 129.1, 128.5, 121.5, 52.8, 51.5, 29.2; HRMS (ESI): *m/z* calcd for $C_{13}H_{13}F_3O_7SNa$ $(M + Na)^+$ 393.0232, found 393.0226.

Synthesis of *N*-Aziridinylhydrazones 2.38 and 2.39.

N-aziridinylhydrazone **2.38** was prepared using the following synthetic route:

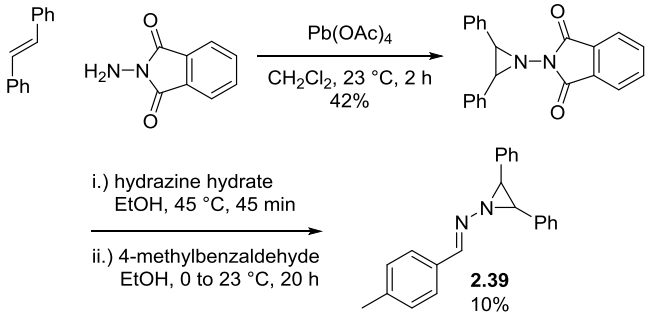


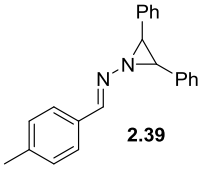


Synthesis of (E)-N-(2-phenylaziridin-1-yl)-1-(p-tolyl)methanimine 2.38. (*E*)-N-(2-phenylaziridin-1-yl)-1-(p-tolyl)methanimine was prepared following the

procedure reported by Mahoney and co-workers.[12] R_f = 0.80 (1:4 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.51 (s, 1H), 7.54 (d, *J* = 8.0 Hz, 2H), 7.35-7.23 (m, 5H), 7.18 (d, *J* = 8.0 Hz, 2H), 3.13 (dd, *J* = 7.7, 4.9 Hz, 1H), 2.57 (d, *J* = 7.8 Hz, 1H), 2.44 (d, *J* = 4.9 Hz, 1H), 2.36 (s, 3H); ^{13}C (125 MHz, $CDCl_3$) δ 159.3, 140.7, 138.6, 131.2, 129.4, 128.4, 127.5, 127.3, 126.4, 44.2, 40.7, 21.5; HRMS (ESI): *m/z* calcd for $C_{16}H_{16}N_2Na$ $(M + H)^+$ 237.1392, found 237.237.1399.

N-aziridynlhydrazone **2.39** was prepared using the following synthetic route:

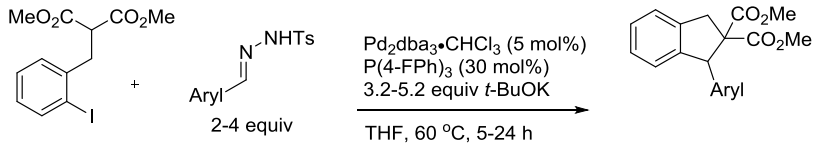




Synthesis of (E)-N-(2,3-diphenylaziridin-1-yl)-1-(p-tolyl)methanimine 2.39. (E)-N-(2,3-diphenylaziridin-1-yl)-1-(p-tolyl)methanimine was prepared following the procedure of O'Leary and co-workers.[13]

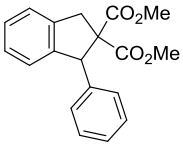
Procedures for Palladium-Catalyzed Insertion and Cyclization of η^3-Benzhydrylpalladium Intermediates

General procedure A: Synthesis of 2.28aa, 2.28ai, 2.28aj.



A flame-dried 5 mL, pear-shaped flask was charged with $Pd_2dba{\bullet}CHCl_3$ (5 mol%), tris(4-fluorophenyl)phosphine (30 mol%), and a stir bar. The flask was purged and backfilled

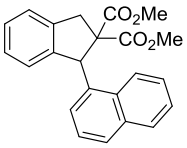
with nitrogen three times, fitted with a rubber septum, and charged with THF. The mixture was stirred for 10 min resulting in a clear yellow solution. A separate flame-dried 5 mL, round-bottom flask equipped with a short-stem vacuum adapter was charged with aryl iodide (1.0 equiv), *N*-tosylhydrazone (2–4 equiv), potassium *tert*-butoxide (*t*-BuOK, 3.2–5.2 equiv), and a stir bar. The flask was purged and backfilled with nitrogen three times. Under a stream of nitrogen, the yellow catalyst solution was added to the flask containing aryl iodide. The flask containing catalyst solution was washed with THF three times and the washes were added to the flask containing aryl iodide. The reaction mixture was heated at 60 °C by immersing it in a hot oil bath up to the level of the flask contents. The stirred reaction was monitored by TLC to check for depletion of aryl iodide. Upon completion of reaction, the flask was cooled to 23 ^{o}C, diluted with Et_2O, and passed through a plug of silica. The plug of silica was rinsed three times with Et_2O and the filtrate was concentrated *in vacuo.* The resulting oil was then purified by flash chromatography on silica gel to afford the target indane compounds.



2.28aa

Example Procedure: Dimethyl 1-phenyl-1,3-dihydro-2H-indene-2,2-dicarboxylate, 2.28aa. A flame-dried 5 mL, pear-shaped flask was charged with $Pd_2dba{\bullet}CHCl_3$ (5.2 mg, 0.0050 mmol), tris(4-fluorophenyl)phosphine (9.5 mg, 0.030 mmol), and a stir bar. The flask was purged and backfilled with nitrogen three times, fitted with a rubber septum, and charged with THF (0.8 mL). The mixture was stirred for 10 min resulting in a clear yellow solution. A separate flame-dried 5 mL, round-bottom flask equipped with a short-stem vacuum adapter was charged with aryl iodide **2.26a** (34.8 mg, 0.10 mmol), *N*-tosylhydrazone **2.27a** (54.9 mg, 0.20 mmol), *t*-BuOK (35.9 mg, 0.32 mmol), and a stir bar. The flask was purged and backfilled with nitrogen three times. Under a stream of nitrogen, the

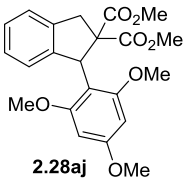
catalyst solution was added to the flask containing aryl iodide **2.26a**. The flask containing catalyst solution was washed with THF (3 x 0.4 mL) and the washes were added to the reaction. The reaction mixture was heated at 60 °C. After 5 h, aryl iodide **2.26a** was no longer detectable by TLC (15:85 EtOAc/hexanes). After cooling to 23 ^{o}C, the crude reaction mixture was diluted with 5 mL of Et_2O and passed through a plug of silica. The plug of silica was washed with 3 x 100 mL of Et_2O and the filtrate was concentrated *in vacuo.* The resulting orange oil was then purified by flash chromatography on silica gel (1:19 EtOAc/hexanes) to afford indane **2.28aa** as a white solid (18.6 mg, 60%). R_f = 0.60 (15:85 EtOAc/hexanes); mp = 71–77 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29–7.15 (m, 6H), 7.08–7.02 (m, 3H), 5.37 (s, 1H), 4.02 (d, *J* = 16.8 Hz, 1H), 3.75 (s, 3H), 3.37 (d, *J* = 16.8 Hz, 1H), 3.21 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.2, 169.8, 143.4, 140.0, 139.9, 129.3, 128.1, 127.5, 127.3, 127.2, 125.3, 124.1, 66.4, 56.8, 53.0, 52.1, 39.7; IR (thin film) 3050, 1731, 1254 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{19}H_{18}O_4Na$ $(M + Na)^+$ 333.1103, found 333.1099.



2.28ai

Dimethyl 1-(naphthalen-1-yl)-1,3-dihydro-2H-indene-2,2-dicarboxylate, 2.28ai. Following procedure A, the following amounts of reagents were used: *N*-tosylhydrazone **2.27i** (129.8 mg, 0.40 mmol), *t*-BuOK (58.3 mg, 0.52 mmol). The product was purified by flash chromatography on silica gel (1:19 EtOAc/hexanes) to afford the indane product **2.28ai** as a white solid (18.3 mg, 51%). R_f = 0.58 (15:85 EtOAc/hexanes); mp = 79–81 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.53 (d, *J* = 8.6 Hz, 1H), 7.83 (d, *J* = 7.6 Hz, 1H), 7.83 (d, *J* = 7.6 Hz, 1H), 7.58 (ddd, *J* = 8.5, 6.9, 1.5 Hz, 1H), 7.49 (ddd, *J* = 8.1, 6.9, 1.1 Hz, 1H) 7.32 (d, *J* = 7.6 Hz, 1H), 7.28–7.24 (m, 2H), 7.19 (t, *J* = 7.4 Hz, 1H), 7.02 (d, *J* = 7.6 Hz, 1H), 6.70 (dd, *J* = 7.3, 1.1Hz, 1H), 6.42 (s, 1H), 4.17 (d, *J* = 17.0 Hz, 1H), 3.79 (s, 3H), 3.52 (d, *J* =

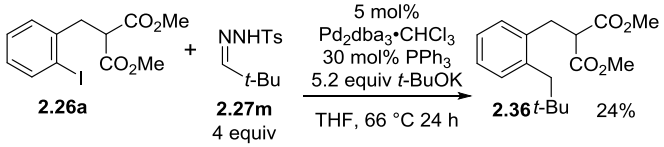
17.1 Hz, 1H), 2.69 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.5, 169.6, 144.5, 140.2, 137.0, 133.7, 132.3, 128.5, 127.8, 127.7, 127.6, 127.4, 125.9, 125.5, 125.4, 125.3, 124.4, 124.2, 66.2, 53.2, 51.6, 51.0, 40.1; IR (thin film) 3015, 1730, 1435, 1253 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{23}H_{20}O_4Na$ $(M + Na)^+$ 383.1259, found 383.1259.



2.28aj

Dimethyl 1-(2,4,6-trimethoxyphenyl)-1,3-dihydro-2H-indene-2,2-dicarboxylate, 2.28aj. Following procedure A, the following amounts of reagents were used: *N*-tosylhydrazone **2.27j** (91.1 mg, 0.25 mmol), *t*-BuOK (41.5 mg, 0.37 mmol). The product was purified by flash chromatography on silica gel (2:3 CH_2Cl_2/PhMe) to afford the indane product **2.28aj** as a white solid (21.6 mg, 54%). R_f = 0.38 (1:2 EtOAc/hexanes); mp = 179–184 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 (d, *J* = 7.5 Hz, 1H), 7.08 (dt, *J* = 20.9, 7.3 Hz, 2H), 6.90 (d, *J* = 7.3 Hz, 1H), 6.16 (s, 1H), 6.01 (s, 1H), 5.94 (bs, 1H), 4.27 (d, *J* = 16.6 Hz, 1H), 3.90 (s, 3H), 3.76 (s, 3H), 3.73 (s, 3H), 3.33 (d, *J* = 16.7 Hz, 1H), 3.29 (s, 3H), 3.27 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.3, 170.4, 160.1, 159.8, 159.0, 144.7, 140.4, 126.5, 126.1, 123.8, 123.2, 111.6, 91.3, 90.9, 64.4, 56.5, 55.3, 55.2, 53.0, 51.9, 45.7, 41.4; IR (thin film) 2980, 1731, 1606, 1457, 1249 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{22}H_{24}O_7Na$ $(M + Na)^+$ 423.1420, found 423.1404.

Synthesis of Dimethyl 2-(2-neopentylbenzyl) malonate, 2.36.

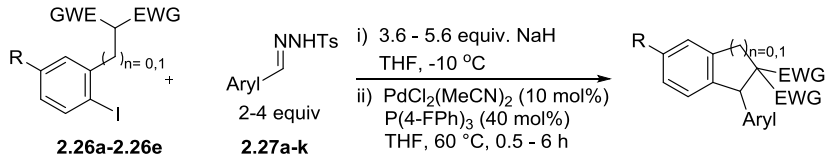


2.26a **2.27m** 4 equiv **2.36**

A flame-dried 5 mL, pear-shaped flask was charged with $Pd_2dba{\bullet}CHCl_3$ (5.2 mg, 0.0050 mmol), triphenylphosphine (7.8 mg, 0.03 mmol), and a stir bar. The flask was purged and backfilled with nitrogen three times, fitted with a rubber septum, and charged with THF (0.8 mL). The mixture was stirred for 10 min resulting in a clear yellow solution. A separate flame-

dried 5 mL, round-bottom flask equipped with a reflux condenser and containing aryl iodide **2.26a** (34.8 mg, 0.10 mmol), *N*-tosylhydrazone **2.27m** (101.7 mg, 0.40 mmol), *t*-BuOK (58.3 mg, 0.52 mmol), and a stir bar was purged and backfilled with nitrogen three times. Under a stream of nitrogen, the catalyst solution was added to the flask containing aryl iodide **2.26a**. The flask containing catalyst solution was washed with THF (3 x 0.4 mL) and the washes were added to the reaction. The reaction mixture was heated at 66 °C by immersing it in a hot oil bath up to the level of the flask contents. After 24 h, the reaction was cooled to 23 ^{o}C, diluted with 5 mL of Et_2O, and passed through a plug of silica. The plug of silica was washed with 3 x 100 mL of Et_2O and the filtrate was concentrated *in vacuo*. The resulting orange oil was then purified by flash chromatography on silica gel (1:99 EtOAc/PhMe) followed by another column (2:98 EtOAc/hexanes) to afford malonate **2.36** as a clear oil (7.0 mg, 24%). R_f = 0.60 (15:85 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.12 (s, 4H), 3.69 (s, 6H), 3.64 (t, *J* = 7.7 Hz, 1H), 3.31 (d, *J* = 7.7 Hz, 2H), 2.60 (s, 2H), 0.93 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.4, 137.9, 136.6, 132.1, 129.1, 126.2, 126.0, 53.2, 52.6, 44.9, 32.9, 32.0, 29.7; IR (thin film)) 2952, 1736, 1392, 1363 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{17}H_{24}O_4Na$ $(M + Na)^+$ 315.1572, found 315.1580.

General procedure B: Synthesis of remaining Indanes and Tetralins.



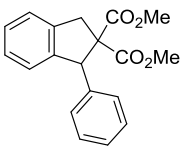
A flame-dried 5 mL, pear-shaped flask was charged with $PdCl_2(MeCN)_2$ (10 mol%), tris(4-fluorophenyl)phosphine (40 mol%), and a stir bar. The flask was purged and backfilled with nitrogen three times and then fitted with a rubber septum. THF was added and the mixture was stirred for 10 min, resulting in a clear yellow solution.

A separate flame-dried 5 mL, pear-shaped flask containing aryl iodide (1.0 equiv), *N*-tosylhydrazone, and a stir bar was purged and backfilled with nitrogen three times and fitted with a rubber septum. THF was added and the mixture was stirred for 10 min resulting in a clear solution.

A separate flame-dried 15 mL, round-bottom flask was equipped with a short-stem vacuum adapter and charged with 60% NaH and a stir bar. The flask was purged and backfilled with nitrogen three times before being fitted with a rubber septum. THF was added and the suspension was cooled to −10 ^{o}C in a brine-ice bath. Under a stream of nitrogen, the solution of aryl iodide and *N*-tosylhydrazone in THF was added dropwise via syringe over 5 min to the 15 mL round-bottom flask containing a stirring NaH suspension. During the course of addition, a white solid precipitated out of solution. The flask containing aryl iodide and *N*-tosylhydrazone was washed twice with THF and the washes were added to the 15 mL flask.

The reaction flask was taken out of the brine-ice bath and warmed to 23 ^{o}C while stirring for 20 min. Under a stream of nitrogen, the yellow catalyst solution was added to the reaction flask. The flask containing catalyst solution was washed twice with THF and the washes were added to the reaction. The reaction mixture was heated at 60 °C by immersing it in a hot oil bath up to the level of the flask contents. The stirred reaction was monitored by TLC to check for depletion of aryl iodide.

Upon consumption of aryl iodide, the reaction mixture was cooled to 23 ^{o}C, diluted with Et_2O, and passed through a plug of silica. The plug of silica was washed with Et_2O and the filtrate was concentrated *in vacuo*. The resulting crude mixtures were then purified by flash chromatography on silica gel to afford the target indane and tetralin compounds.



2.28aa

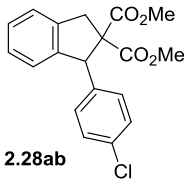
Example Procedure: Dimethyl 1-phenyl-1,3-dihydro-2H-indene-2,2-dicarboxylate, 2.28aa. A flame-dried 5 mL, pear-shaped flask was charged with $PdCl_2(MeCN)_2$ (5.2 mg, 0.02 mmol), tris(4-fluorophenyl)phosphine (25.3 mg, 0.08 mmol), and a stir bar. The flask was purged and backfilled with nitrogen three times and then fitted with a rubber septum. THF (2 mL) was then added and the mixture was stirred for 10 min, resulting in a clear yellow solution.

A separate flame-dried 5 mL, pear-shaped flask containing aryl iodide **2.26a** (69.6 mg, 0.20 mmol), *N*-tosylhydrazone **2.27a** (109.7 mg, 0.40 mmol), and a stir bar was purged and backfilled with nitrogen three times and fitted with a rubber septum. THF (2 mL) was added and the mixture was stirred for 10 min resulting in a clear solution.

A separate flame-dried 15 mL, round-bottom flask was equipped with a short-stem vacuum adapter and charged with 60% NaH (28.6 mg, 0.72 mmol) and a stir bar. The flask was purged and backfilled with nitrogen three times and fitted with a rubber septum. THF (2 mL) was added and the suspension was cooled to −10 ^{o}C in a brine-ice bath. The solution of aryl iodide **2.26a** and *N*-tosylhydrazone **2.27a** in THF (2 mL) was then added dropwise via syringe over 5 min to the 15 mL flask containing a stirring NaH suspension. During the course of addition, a white solid precipitated out of solution. The flask containing aryl iodide **2.26a** and *N*-tosylhydrazone **2.27a** was washed with THF (2 x 1 mL) and the washes were added to the 15 mL flask.

The flask was then warmed to 23 °C and stirred for 20 min. Under a stream of nitrogen, the yellow catalyst solution was added to the reaction. The flask containing catalyst solution was washed with THF (2 x 1 mL) and the washes were added to the reaction. The reaction mixture was heated at 60 °C. After 1.5 h, aryl iodide **2.26a** was no longer detectable by TLC (15:85 EtOAc/hexanes).

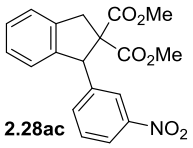
The reaction mixture was cooled to 23 °C, diluted with 15 mL of Et_2O, and passed through a plug of silica. The plug of silica was washed with 3 x 100 mL of Et_2O and the filtrate was concentrated *in vacuo*. The resulting orange oil was then purified by flash chromatography on silica gel (1:99 EtOAc/PhMe) followed by another column (1:9 EtOAc/hexanes) to afford indane **2.28aa** as white solid (53.3 mg, 86%). R_f = 0.60 (15:85 EtOAc/hexanes); mp = 71–77 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29–7.15 (m, 6H), 7.08–7.02 (m, 3H), 5.37 (s, 1H), 4.02 (d, *J* = 16.8 Hz, 1H), 3.75 (s, 3H), 3.37 (d, *J* = 16.8 Hz, 1H), 3.21 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.2, 169.8, 143.4, 140.0, 139.9, 129.3, 128.1, 127.5, 127.3, 127.2, 125.3, 124.1, 66.4, 56.8, 53.0, 52.1, 39.7; IR (thin film) 3050, 1731, 1254 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{19}H_{18}O_4Na$ $(M + Na)^+$ 333.1103, found 333.1099.



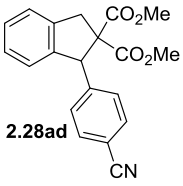
2.28ab

Dimethyl 1-(4-chlorophenyl)-1,3-dihydro-2H-indene-2,2-dicarboxylate, 2.28ab. Following procedure B, the following amounts of reagents were used: aryl iodide **2.26a** (69.6 mg, 0.20 mmol), *N*-tosylhydrazone **2.27b** (123 mg, 0.40 mmol), 60% NaH (28.6 mg, 0.72 mmol). The product was purified by flash chromatography on silica gel (1:19 EtOAc/hexanes) to afford indane product **2.28ab** as a white solid (63.4 mg, 92%). R_f = 0.60 (15:85 EtOAc/hexanes); mp = 108–111 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29–7.20 (m, 4H), 7.17 (d, *J* = 7.4 Hz, 1H), 7.04–6.95 (m, 3H), 5.35 (s, 1H), 3.98 (d, *J* = 16.9 Hz, 1H), 3.75 (s, 3H), 3.37 (d, *J* = 16.9 Hz, 1H), 3.26 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ

172.2, 169.9, 143.1, 140.2, 138.6, 133.3, 130.9, 128.4, 128.0, 127.7, 125.3, 124.5, 66.5, 56.3, 53.2, 52.4, 39.9; IR (thin film) 2923, 1731, 1490, 1458, 1251 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{19}H_{17}ClO_4Na$ $(M + Na)^+$ 367.0713, found 367.0706.

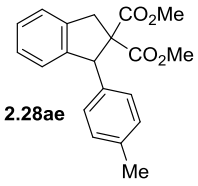


Dimethyl 1-(3-nitrophenyl)-1,3-dihydro-2H-indene-2,2-dicarboxylate, 2.28ac. Following procedure B, the following amounts of reagents were used: aryl iodide **2.26a** (69.6 mg, 0.20 mmol), *N*-tosylhydrazone **2.27c** (127.7 mg, 0.40 mmol), 60% NaH (28.6 mg, 0.72 mmol). The product was purified by flash chromatography on silica gel (1:99 EtOAc/PhMe) to afford indane product 3ac as a yellow oil (57.7 mg, 81%). R_f = 0.31 (1:4 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (d, *J* = 6.7 Hz, 1H), 8.02 (s, 1H), 7.43–7.26 (m, 4H), 7.21 (bs, 1H), 7.00 (d, *J* = 6.8 Hz, 1H), 5.49 (s, 1H), 4.00 (d, *J* = 16.8 Hz, 1H), 3.78 (s, 3H), 3.43 (d, *J* = 16.9 Hz, 1H), 3.26 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.6, 169.4, 148.1, 142.1, 141.8, 140.2, 135.4, 129.1, 128.2, 127.7, 125.0, 124.5, 124.3, 122.5, 66.5, 56.2, 53.2, 52.3, 39.6; IR (thin film) 3029, 2952, 1730, 1528, 1433, 1351, 1249 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{19}H_{17}NO_6Na$ $(M + Na)^+$ 378.0954, found 378.0951.



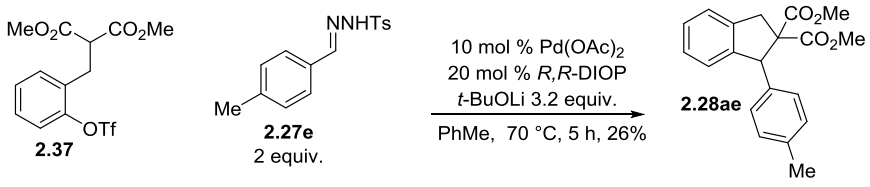
Dimethyl 1-(4-cyanophenyl)-1,3-dihydro-2H-indene-2,2-dicarboxylate, 2.28ad. Following procedure B, the following amounts of reagents were used: aryl iodide **2.26a** (69.6 mg, 0.20 mmol), *N*-tosylhydrazone **2.27d** (119.7 mg, 0.40 mmol), 60% NaH (28.6 mg, 0.72 mmol). The product was purified by flash chromatography on silica gel (1:9 EtOAc/hexanes) followed by another column (1:49 EtOAc/PhMe) to afford indane product **2.28ad** as a white solid (49.9 mg, 74%). R_f = 0.23 (15:85 EtOAc/hexanes); mp 146–150 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.3 Hz, 2H), 7.33–7.13 (m, 5H), 6.97 (d, *J* = 7.6 Hz, 1H), 5.43 (s, 1H), 3.99 (d, *J* = 16.9 Hz, 1H), 3.77 (s, 3H), 3.41 (d, *J* = 16.9 Hz, 1H), 3.23 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.7, 169.4, 145.6, 141.9, 140.2, 131.9, 130.2,

128.1, 127.6, 125.1, 124.4, 118.7, 111.2, 66.4, 56.6, 53.2, 52.2, 39.8; IR (thin film) 3028, 2958, 2228, 1726, 1604, 1434, 1241 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{20}H_{17}NO_4Na$ $(M + Na)^+$ 358.1055, found 358.1053.



Dimethyl 1-(p-tolyl)-1,3-dihydro-2H-indene-2,2-dicarboxylate, 2.28ae. Following procedure B, the following amounts of reagents were used: aryl iodide **2.26a** (73.2 mg, 0.20 mmol), *N*-tosylhydrazone **2.27e** (115.3 mg, 0.40 mmol), 60% NaH (28.6 mg, 0.72 mmol). The product was purified by flash chromatography on silica gel (1:19 EtOAc/hexanes) to afford indane **2.28ae** as a brown oil (51.6 mg, 80%). R_f = 0.60 (15:85 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29–7.25 (m, 1H), 7.22 (t, *J* = 7.4 Hz, 1H), 7.16 (t, *J* = 7.1 Hz, 1H), 7.03 (d, *J* = 7.3 Hz, 3H), 6.93 (d, *J* = 7.8 Hz, 2H), 5.32 (s, 1H), 4.01 (d, *J* = 16.8 Hz, 1H), 3.74 (s, 3H), 3.36 (d, *J* = 16.8 Hz, 1H), 3.25 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.2, 169.9, 143.7, 139.9, 136.8, 136.7, 129.1, 128.8, 127.4, 127.3, 125.2, 124.1, 66.4, 56.4, 52.9, 52.1, 39.6, 21.1; IR (thin film) 3024, 2950, 2843, 1731, 1512, 1432, 1245 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{20}H_{20}O_4Na$ $(M + Na)^+$ 347.1259, found 347.1257.

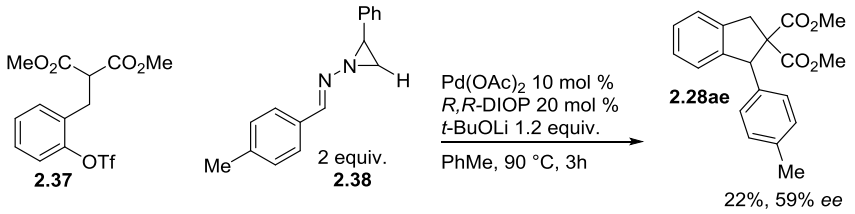
Alternative synthesis of dimethyl 1-(p-tolyl)-1,3-dihydro-2H-indene-2,2-dicarboxylate, 2.28ae from aryl triflate 2.37 and *N*-tosylhydrazone 2.27e.



A flame-dried 5 mL, pear-shaped flask was charged with aryl triflate **2.37** (74 mg, 0.2 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), *R,R*-DIOP (20 mg, 0.04 mmol), *N*-tosylhydrazone **2.27e** (115 mg, 0.4 mmol), lithium *tert*-butoxide (51 mg, 0.64 mmol), and a stir bar. The flask was purged and backfilled with nitrogen three times, fitted with a rubber septum, and charged with

PhMe (4 mL). The reaction mixture was heated at 70 °C by immersing it in a hot oil bath up to the level of the flask contents. After 5 h, the reaction was cooled to 23 °C, diluted with 5 mL of PhMe, and passed through a plug of silica. The plug of silica was washed with 3 x 100 mL of PhMe and the filtrate was concentrated *in vacuo.* The resulting orange oil was then purified by flash chromatography on silica gel (2.5% EtOAc/hexanes) to afford indane **2.28ae** as a brown oil (18 mg, 26%). The *ee* was measured utilizing the Shimadzu HPLC instrument using a chiral stationary phase [Chiralcel OD-H, 2-propanol/hexanes = 1/99, 1.5 mL/min, λ = 254 nm], t_R = 4.70 min (minor), 5.50 min (major)

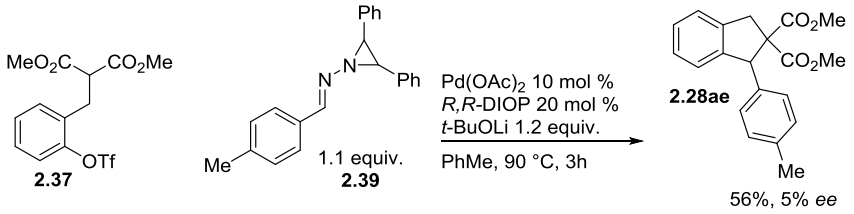
Alternative synthesis of dimethyl 1-(p-tolyl)-1,3-dihydro-2H-indene-2,2-dicarboxylate, 2.28ae from aryl triflate 2.37 and *N*-aziridinylhydrazone 2.38.



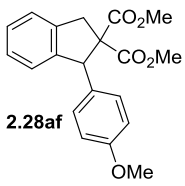
A flame-dried 5 mL, pear-shaped flask was charged with aryl triflate **2.37** (37 mg, 0.1 mmol), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), *R,R*-DIOP (10 mg, 0.02 mmol), *N*-aziridinylhydrazone **2.38** (47 mg, 0.2 mmol), lithium *tert*-butoxide (9 mg, 0.11mmol), and a stir bar. The flask was purged and backfilled with nitrogen three times, fitted with a rubber septum, and charged with PhMe (2 mL). The reaction mixture was heated at 90 °C by immersing it in a hot oil bath up to the level of the flask contents. After 3 h, the reaction was cooled to 23 °C, diluted with 5 mL of PhMe, and passed through a plug of silica. The plug of silica was washed with 3 x 100 mL of PhMe and the filtrate was concentrated *in vacuo.* The resulting orange oil was then purified by flash chromatography on silica gel (2.5% EtOAc/hexanes) to afford indane **2.28ae** as a brown oil (18 mg, 22%). The *ee* was measured utilizing the Shimadzu HPLC instrument using a chiral

stationary phase [Chiralcel OD-H, 2-propanol/hexanes = 1/99, 1.5 mL/min, λ = 254 nm], t_R = 4.70 min (minor), 5.50 min (major).

Alternative synthesis of dimethyl 1-(p-tolyl)-1,3-dihydro-2H-indene-2,2-dicarboxylate, 2.28ae from aryl triflate 2.37 and *N*-aziridinylhydrazone 2.39.

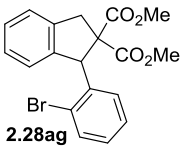


A flame-dried 5 mL, pear-shaped flask was charged with aryl triflate **2.37** (37 mg, 0.1 mmol), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), *R,R*-DIOP (10 mg, 0.02 mmol), *N*-aziridinylhydrazone **2.39** (34 mg, 0.11 mmol), lithium *tert*-butoxide (9 mg, 0.11mmol), and a stir bar. The flask was purged and backfilled with nitrogen three times, fitted with a rubber septum, and charged with PhMe (2 mL). The reaction mixture was heated at 90 °C by immersing it in a hot oil bath up to the level of the flask contents. After 3 h, the reaction was cooled to 23 ^oC, diluted with 5 mL of PhMe, and passed through a plug of silica. The plug of silica was washed with 3 x 100 mL of PhMe and the filtrate was concentrated *in vacuo.* The resulting orange oil was then purified by flash chromatography on silica gel (2.5% EtOAc/hexanes) to afford indane **2.28ae** as a brown oil (19 mg, 56%). The *ee* was measured utilizing the Shimadzu HPLC instrument using a chiral stationary phase [Chiralcel OD-H, 2-propanol/hexanes = 1/99, 1.5 mL/min, λ = 254 nm], t_R = 4.70 min (minor), 5.50 min (major).



Dimethyl 1-(4-methoxyphenyl)-1,3-dihydro-2H-indene-2,2-dicarboxylate, 2.28af. Following procedure B, the following amounts of reagents were used:

aryl iodide **2.26a** (69.6 mg, 0.20 mmol), *N*-tosylhydrazone **2.27f** (121.6 mg, 0.40 mmol), 60% NaH (28.6 mg, 0.72 mmol). The product was purified by flash chromatography on silica gel (1:49 EtOAc/PhMe) followed by another column (15:85 EtOAc/hexanes) to afford indane product **2.28af** as a yellow oil (51.7 mg, 76%). R_f = 0.43 (15:85 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28–7.24 (m, 1H), 7.22 (t, *J* = 7.4 Hz, 1H), 7.17 (t, *J* = 7.3 Hz, 1H), 7.03 (d, *J* = 7.5 Hz, 1H), 6.98 (d, *J* = 8.6 Hz, 2H), 6.77 (d, *J* = 8.8 Hz, 2H), 5.32 (s, 1H), 3.99 (d, *J* = 16.7 Hz, 1H), 3.75 (s, 6H), 3.35 (d, *J* = 16.9 Hz, 1H), 3.26 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.5, 170.1, 158.9, 143.9, 140.1, 132.1, 130.5, 127.7, 127.5, 125.4, 124.3, 113.6, 66.6, 56.2, 55.4, 53.2, 52.3, 39.8; IR (thin film) 2953, 1731, 1511, 1250 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{20}H_{20}O_5Na$ $(M + Na)^+$ 363.1208, found 363.1207.



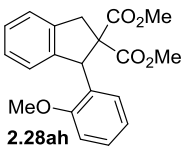
2.28ag

Dimethyl 1-(2-bromophenyl)-1,3-dihydro-2H-indene-2,2-dicarboxylate, 2.28ag. Following procedure B, the following amounts of reagents were used: aryl iodide **2.26a** (69.6 mg, 0.20 mmol), *N*-tosylhydrazone **2.27g** (141.0 mg, 0.40 mmol), 60% NaH (28.6 mg, 0.72 mmol). The product was purified by flash chromatography on silica gel (1:99 EtOAc/PhMe) followed by another column (1:19 EtOAc/hexanes) resulting in 67.8 mg of a yellow oil comprised of a chromatographically inseparable 7:93 mixture of aryl iodide **2.26a** and indane **2.28ag**.

To remove aryl iodide **2.26a**, a flame-dried 5 mL, round-bottom flask was charged with 95% NaH (1.0 mg, 0.05 mmol), a stir bar, and THF (1 mL). The flask was cooled to –10 ^{o}C in a brine-ice bath and a solution of the 7:93 **2.26a/2.28ag** oil in THF (1 mL) was added dropwise with a syringe over 5 min to the reaction. After 20 min, a solution of benzyl bromide (7.5 mg,

0.05 mmol) in THF (0.5 mL) was added to the reaction. The flask was taken out of the brine-ice bath and warmed to 23 °C while stirring.

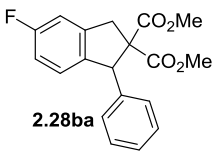
After 3 h, the reaction mixture was quenched with 5 mL of saturated $NH_4Cl_{(aq)}$, transferred to a separatory funnel, and extracted with 10 mL of Et_2O. The organic phase was washed with 10 mL of H_2O, dried ($NaSO_4$), and concentrated *in vacuo*. The resulting oil was taken up in 0.5 mL of hot EtOAc and dripped into 10 mL of cold hexanes. The solution was placed in a 0 °C freezer overnight and indane **2.28ag** precipitated as a white solid (29.3 mg, 38%). R_f = 0.55 (15:85 EtOAc/hexanes); mp = 95–99 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.27 (d, *J* = 7.4 Hz, 1H), 7.22 (t, *J* = 7.4 Hz, 1H), 7.16 (t, *J* = 7.3 Hz, 1H), 7.08 (td, *J* = 7.5, 1.0 Hz, 1H), 7.04–7.00 (m, 2H), 6.60 (dd, *J* = 7.8, 1.6 Hz, 1H), 6.04 (s, 1H), 4.17 (d, *J* = 17.2 Hz, 1H), 3.76 (s, 3H), 3.45 (d, *J* = 17.3 Hz, 1H), 3.28 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.8, 169.6, 144.2, 140.4, 139.6, 132.7, 130.7, 128.6, 127.7, 127.4, 125.3, 124.3, 65.6, 55.2, 53.1, 52.0, 40.2; IR (thin film) 2952, 1734, 1435, 1273 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{19}H_{17}BrO_4Na$ $(M + Na)^+$ 411.0208, found 411.0198.



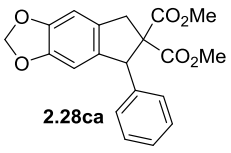
2.28ah

Dimethyl 1-(2-methoxyphenyl)-1,3-dihydro-2H-indene-2,2-dicarboxylate, 2.28ah. Following procedure B, the following amounts of reagents were used: aryl iodide **2.26a** (69.6 mg, 0.20 mmol), *N*-tosylhydrazone **2.27h** (152.2 mg, 0.5 mmol), 60% NaH (36.8 mg, 0.92 mmol). The product was purified by flash chromatography on silica gel (1:99 EtOAc/PhMe) followed by another column (15:85 EtOAc/hexanes) to afford indane **2.28ah** as a white solid (40.7 mg, 60%). R_f = 0.43 (15:85 EtOAc/hexanes); mp = 99–103 °C; ^{1}H NMR (600 MHz, toluene-d_8, 100 °C) δ 7.05–6.87 (m, 6H), 6.62 (t, *J* = 7.4 Hz, 1H), 6.57 (d, *J* = 8.1 Hz, 1H), 6.08 (bs, 1H), 4.25 (d, *J* = 16.7 Hz, 1H), 3.42 (s, 3H), 3.40 (d, *J* = 16.9 Hz, 1H), 3.00 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.4, 170.0, 157.2, 144.4, 139.9, 129.9,

129.2, 128.3, 127.3, 127.1, 125.1, 124.0, 120.3, 110.4, 55.6, 52.9, 52.0, 40.4; IR (thin film) 2953, 1733, 1435, 1251, 1218 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{20}H_{20}O_5Na$ $(M + Na)^+$ 363.1208, found 363.1201.

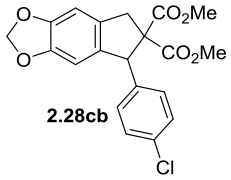


Dimethyl 5-fluoro-1-phenyl-1,3-dihydro-2H-indene-2,2-dicarboxylate, 2.28ba. Following procedure B, the following amounts of reagents were used: aryl iodide **2.26b** (73.2 mg, 0.20 mmol), *N*-tosylhydrazone **2.27a** (109.7 mg, 0.40 mmol), 60% NaH (28.6 mg, 0.72 mmol). The product was purified by flash chromatography on silica gel (1:99 EtOAc/PhMe) to afford indane **2.28ba** as a white solid (54.5 mg, 83%). R_f = 0.50 (1:4 EtOAc/hexanes); mp = 97–99 ^oC; ^1H NMR (500 MHz, $CDCl_3$) δ 7.31–7.15 (m, 3H), 7.05 (d, *J* = 6.9 Hz, 2H), 6.97 (d, *J* = 7.2 Hz, 2H), 6.87 (t, *J* = 8.0 Hz, 1H), 5.31 (s, 1H), 4.00 (d, *J* = 17.1 Hz, 1H), 3.76 (s, 3H), 3.35 (d, *J* = 17.1 Hz, 1H), 3.21 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.9, 169.5, 163.6, 161.7, 142.2, 142.1, 139.6, 139.0, 138.9, 129.2, 128.1, 127.4, 126.5, 126.4, 114.6, 114.5, 111.2, 111.0, 66.9, 56.0, 53.1, 52.1, 39.6; IR (thin film) 3026, 2952, 1731, 1601, 1454, 1246 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{19}H_{17}FO_4Na$ $(M + Na)^+$ 351.1009, found 351.1006.

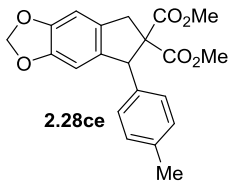


Dimethyl 5-phenyl-5,7-dihydro-6H-indeno[5,6-d][1,3]dioxole-6,6-dicarboxylate, 2.28ca. Following procedure B, the following amounts of reagents were used: aryl iodide **2.26c** (39.2 mg, 0.10 mmol), *N*-tosylhydrazone **2.27a** (54.9 mg, 0.20 mmol), 60% NaH (14.4 mg, 0.36 mmol). The product was purified by flash chromatography on silica gel (0–5% EtOAc/hexanes) to afford indane product **2.28ca** as a peach colored solid (34.9 mg, 98%). R_f = 0.34 (1:4 EtOAc/hexanes); mp = 144–146 ^oC; ^1H NMR (500 MHz, $CDCl_3$)

δ 7.25–7.20 (m, 3H), 7.04 (d, *J* = 7.0 Hz, 2H), 6.72 (s, 1H), 6.48 (s, 1H), 5.92 (d, , *J* = 4.0 Hz, 2H), 5.22 (s, 1H), 3.91 (d, *J* = 16.5 Hz, 1H), 3.76 (s, 3H), 3.25 (d, *J* = 16.5 Hz, 1H), 3.21 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.3, 169.7, 147.7, 147.5, 139.9, 136.3, 132.7, 129.3, 128.2, 127.5, 105.7, 104.6, 101.3, 67.1, 56.5, 53.1, 52.2, 39.4; IR (thin film) 2951, 1731, 1496, 1278, 1231 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{20}H_{18}O_6Na$ $(M + Na)^+$ 377.1001, found 377.1006.

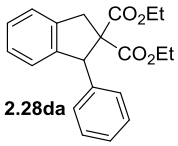


Dimethyl 5-(4-chlorophenyl)-5,7-dihydro-6H-indeno[5,6-d][1,3]dioxole-6,6-dicarboxylate, 2.28cb. Following procedure B, the following amounts of reagents were used: aryl iodide **2.26c** (39.2 mg, 0.10 mmol), *N*-tosylhydrazone **2.27b** (61.8 mg, 0.20 mmol), 60% NaH (14.4 mg, 0.36 mmol). The product was purified by flash chromatography on silica gel (2:23 EtOAc/hexanes) to afford indane product **2.28cb** as a peach colored solid (35.1 mg, 90%). R_f = 0.42 (1:4 EtOAc/hexanes); mp = 159–161 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 (d, *J* = 8.5 Hz, 2H), 6.99 (d, *J* = 8.0 Hz, 2H), 6.71 (s, 1H), 6.43 (s, 1H), 5.92 (d, *J* = 4.0 Hz, 2H), 5.20 (s, 1H), 3.88 (d, *J* = 17.0 Hz, 1H), 3.76 (s, 3H), 3.27 (s, 3H), 3.24 (d, *J* = 16.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.0, 169.5, 147.8, 147.6, 138.5, 135.7, 133.2, 132.7, 130.6, 128.3, 105.4, 104.6, 101.3, 66.9, 55.8, 53.1, 52.3, 39.3; IR (thin film) 2952, 1732, 1235, 1090, 939 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{20}H_{17}ClO_6Na$ $(M + Na)^+$ 411.0611, found 411.0592.



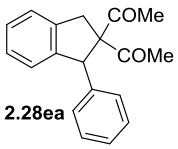
Dimethyl 5-(p-tolyl)-5,7-dihydro-6H-indeno[5,6-d][1,3]dioxole-6,6-dicarboxylate, 2.28ce. Following procedure B, the following amounts of reagents were used: aryl iodide **2.26c** (39.2 mg, 0.10 mmol), *N*-tosylhydrazone **2.27e** (57.7 mg, 0.20 mmol), 60% NaH (14.4 mg, 0.36 mmol). The product was purified by flash chromatography on silica gel (0–5% EtOAc/hexanes) to afford the indane product **2.28ce** as a peach colored solid (31.1 mg, 90%). R_f = 0.42 (1:4 EtOAc/hexanes); mp =

128–130 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.03 (d, *J* = 8.0 Hz, 2H), 6.91 (d, *J* = 7.5 Hz, 2H), 6.71 (s, 1H), 6.47 (s, 1H), 5.91 (d, *J* = 4.0 Hz, 2H), 5.17 (s, 1H), 3.90 (d, *J* = 16.5 Hz, 1H), 3.75 (s, 3H), 3.25 (s, 3H), 3.24 (d, *J* = 16.5 Hz, 1H), 2.28 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.3, 169.7, 147.6, 147.4, 137.0, 136.7, 136.5, 132.6, 129.0, 128.8, 105.6, 104.5, 101.2, 67.0, 56.1, 53.0, 52.1, 39.2, 21.1; IR (thin film) 2952, 1732, 1031, 925 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{21}H_{20}O_6Na$ $(M + Na)^+$ 391.1158, found 391.1164.



2.28da

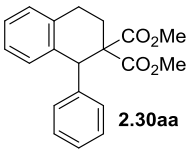
Diethyl 1-phenyl-1,3-dihydro-2H-indene-2,2-dicarboxylate, 2.28da. Following procedure B, the following amounts of reagents were used: aryl iodide **2.26d** (75.2 mg, 0.20 mmol), *N*-tosylhydrazone **2.27a** (109.7 mg, 0.40 mmol), 60% NaH (28.6 mg, 0.72 mmol). The product was purified by flash chromatography on silica gel (1:99 EtOAc/PhMe) to afford indane **2.28da** as a white solid (48.9 mg, 72%). R_f = 0.75 (15:85 EtOAc/hexanes); mp = 67–71°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (d, *J* = 7.5 Hz, 1H), 7.23-7.15 (m, 5H), 7.08 (d, *J* = 6.8 Hz, 2H), 7.03 (d, *J* = 7.5 Hz, 1H), 5.36 (s, 1H), 4.26 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.17 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.04 (d, *J* = 16.9 Hz, 1H), 3.78 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.51 (dq, *J* = 10.7, 7.2 Hz, 1H), 3.36 (d, *J* = 16.9 Hz, 1H), 1.24 (t, *J* = 7.1, 3H), 0.87 (t, *J* = 7.1, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.8, 169.5, 143.8, 140.2, 140.1, 129.4, 128.1, 127.5, 127.3, 127.2, 125.3, 124.2, 66.3, 61.7, 61.2, 56.7, 39.9, 14.1, 13.6; IR (thin film) 3047, 2980, 1727, 1244 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{21}H_{22}O_4Na$ $(M + Na)^+$ 361.1416, found 361.1412.



2.28ea

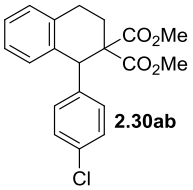
1,1'-(1-phenyl-2,3-dihydro-1H-indene-2,2-diyl)bis(ethan-1-one), 2.28ea. Following procedure B, the following amounts of reagents were used: aryl iodide **2.26e** (63.2 mg, 0.20 mmol), *N*-tosylhydrazone **2.27a** (109.7 mg, 0.40 mmol), 60% NaH (28.6

mg, 0.72 mmol). The product was purified by flash chromatography on silica gel (1:19 EtOAc/hexanes) followed by another column (1:99 EtOAc/PhMe) to afford indane **2.28ea** as a white solid (35.5 mg, 64%). R_f = 0.44 (15:85 EtOAc/hexanes); mp = 151–154 ^oC; ^1H NMR (500 MHz, $CDCl_3$) δ 7.30–7.11 (m, 6H), 7.08 (d, *J* = 7.3 Hz, 2H), 7.01 (d, *J* = 7.5 Hz, 1H), 5.39 (s, 1H), 4.14 (d, , *J* = 17.0 Hz, 1H), 3.20 (d, *J* = 17.0 Hz, 1H), 2.20 (s, 3H), 1.65 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.4, 203.3, 143.5, 139.4, 137.8, 128.1, 127.6, 126.5, 126.4, 126.3, 124.2, 123.3, 79.2, 53.6, 36.5, 27.6, 25.8; IR (thin film) 3028, 2951, 1731, 1697, 1454, 1212 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{19}H_{18}O_2Na$ $(M + Na)^+$ 301.1205, found 301.1204.

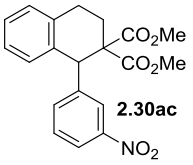


2.30aa

Dimethyl 1-phenyl-3,4-dihydronaphthalene-2,2(1H)-dicarboxylate, 2.30aa. Following procedure B, the following amounts of reagents were used: aryl iodide **2.29a** (72.4 mg, 0.20 mmol), *N*-tosylhydrazone **2.27a** (109.7 mg, 0.40 mmol), 60% NaH (28.6 mg, 0.72 mmol). The product was purified by flash chromatography on silica gel (1:99 EtOAc/PhMe) followed by another column (1:19 EtOAc/hexanes) to afford **2.30aa** as a white solid (53.7 mg, 83%). R_f = 0.70 (15:85 EtOAc/hexanes); mp = 150–154 ^oC; ^1H NMR (500 MHz, $CDCl_3$) δ 7.23–7.14 (m, 3H), 7.11 (app d, *J* = 3.9 Hz, 2H), 7.06 (dt, *J* = 7.7, 3.9 Hz, 1H), 7.00–6.91 (m, 3H), 4.97 (s, 1H), 3.71 (s, 3H), 3.52 (s, 3H), 3.01 (dd, *J* = 17.6, 4.9 Hz, 1H), 2.68 (ddd, *J* = 17.9, 12.8, 5.7 Hz, 1H), 2.42 (td, *J* = 13.6, 5.7 Hz, 1H), 2.34 (dd, *J* = 13.9, 6.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 170.4, 142.0, 137.1, 134.1, 130.6, 129.9, 128.5, 128.0, 127.0, 126.5, 126.3, 58.9, 52.8, 52.1, 48.3, 25.8, 22.9; IR (thin film) 3025, 2951, 2844, 1734, 1432, 1223 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{20}H_{20}O_4Na$ $(M + Na)^+$ 347.1259, found 347.1252.

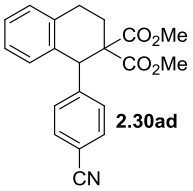


Dimethyl 1-(4-chlorophenyl)-3,4-dihydronaphthalene-2,2(1H)-dicarboxylate, 2.30ab. Following procedure B, the following amounts of reagents were used: aryl iodide **2.29a** (72.4 mg, 0.20 mmol), *N*-tosylhydrazone **2.27b** (123.5 mg, 0.40 mmol), 60% NaH (28.6 mg, 0.72 mmol). The product was purified by flash chromatography on silica gel (1:99 EtOAc/PhMe) followed by another column (1:19 EtOAc/hexanes) to afford **2.30ab** as a white solid (59.6 mg, 78%). R_f = 0.70 (15:85 EtOAc/hexanes); mp = 140–142 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 (d, *J* = 8.5 Hz, 2H), 7.11 (bs, 2H), 7.08–7.05 (m, 1H), 6.92–6.88 (m, 3H), 4.94 (s, 1H), 3.71 (s, 3H), 3.54 (s, 3H), 3.03–2.98 (m, 1H), 2.67 (ddd, *J* = 18.0, 11.1, 7.2 Hz, 1H), 2.38–2.33 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 170.2, 140.6, 136.7, 134.0, 133.0, 131.2, 130.5, 128.6, 128.2, 126.6, 126.5, 58.8, 52.9, 52.3, 47.6, 25.7, 22.8; IR (thin film) 2954, 1734, 1490, 1404, 1233 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{20}H_{19}ClO_4Na$ $(M + Na)^+$ 381.0869, found 381.0870.

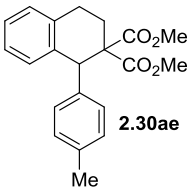


Dimethyl 1-(3-nitrophenyl)-3,4-dihydronaphthalene-2,2(1H)-dicarboxylate, 2.30ac. Following procedure B, the following amounts of reagents were used: aryl iodide **2.29a** (72.4 mg, 0.20 mmol), *N*-tosylhydrazone **2.27c** (127.8 mg, 0.40 mmol), 60% NaH (28.6 mg, 0.72 mmol). The product was purified by flash chromatography on silica gel (1:49 EtOAc/PhMe) followed by another column (15:85 EtOAc/hexanes). The resulting oil was dissolved in 0.5 mL of hot EtOAc, dripped into 10 mL of cold hexanes, and placed in a 0 ^{o}C freezer overnight. The resulting precipitate was filtered and dried *in vacuo* affording the product **2.30ac** as a white solid (8.0 mg, 11%). R_f = 0.36 (1:4 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.2 Hz, 1H), 7.92 (bs, 1H), 7.39 (t, *J* = 8.0 Hz, 1H), 7.27–7.21 (m, 1H), 7.16 (bs, 2H), 7.12–7.05 (m, 1H), 6.91 (d, *J* = 7.6 Hz, 1H), 5.10 (s, 1H), 3.73 (s, 3H), 3.60 (s, 3H), 3.06 (dd, *J* = 17.7, 5.6 Hz, 1H), 2.71 (ddd, *J* = 18.0, 12.9, 5.5 Hz, 1H),

2.43–2.24 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6, 170.0, 148.0, 144.2, 136.2, 135.6, 134.2, 130.4, 129.1, 128.9, 127.0, 126.9, 124.6, 122.3, 58.7, 53.1, 52.5, 47.9, 25.6, 22.8; IR (thin film) 3004, 1735, 1529, 1345, 1274 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{20}H_{19}NO_6Na$ $(M + Na)^+$ 392.1110, found 392.1100.

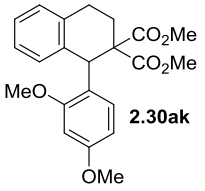


Dimethyl 1-(4-cyanophenyl)-3,4-dihydronaphthalene-2,2(1H)-dicarboxylate, 2.30ad. Following procedure B, the following amounts of reagents were used: aryl iodide **2.29a** (72.4 mg, 0.20 mmol), *N*-tosylhydrazone **2.27d** (119.7 mg, 0.40 mmol), 60% NaH (28.6 mg, 0.72 mmol). The product was purified by flash chromatography on silica gel (1:49 EtOAc/PhMe) followed by another column (15:85 EtOAc/hexanes) to afford product **2.30ad** as a yellow solid (58.7 mg, 84%). R_f = 0.16 (1:4 EtOAc/hexanes); mp = 109–111 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.1 Hz, 2H), 7.14–7.07 (m, 5H), 6.88 (d, *J* = 7.7 Hz, 1H), 5.02 (s, 1H), 3.72 (s, 3H), 3.53 (s, 3H), 3.03 (dd, *J* = 17.6, 5.0 Hz, 1H), 2.69 (ddd, *J* = 17.9, 13.0, 5.4 Hz, 1H), 2.41–2.48 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 170.0, 147.6, 135.8, 134.2, 131.9, 130.8, 130.5, 128.9, 126.9, 126.8, 118.7, 111.1, 58.8, 53.1, 52.4, 48.3, 25.7, 22.9; IR (thin film) 2954, 2223, 1735, 1435, 1227 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{21}H_{19}NO_4Na$ $(M + Na)^+$ 372.1212, found 372.1207.

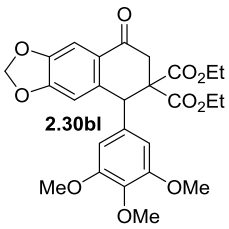


Dimethyl 1-(p-tolyl)-3,4-dihydronaphthalene-2,2(1H)-dicarboxylate, 2.30ae. Following procedure B, the following amounts of reagents were used: aryl iodide **2.29a** (72.4 mg, 0.20 mmol), *N*-tosylhydrazone **2.27e** (115.3 mg, 0.40 mmol), 60% NaH (28.6 mg, 0.72 mmol). The product was purified by flash chromatography on silica gel (1:99 EtOAc/PhMe) followed by another column (15:85 EtOAc/hexanes) to afford product **2.30ae** as a clear oil (41.0 mg, 61%). R_f = 0.70 (15:85 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.10 (d, *J* = 3.9 Hz, 2H), 7.05 (dt, *J* = 7.8, 4.0 Hz, 1H), 7.00 (d, *J* = 7.9 Hz, 2H),

6.95 (d, *J* = 7.7 Hz, 1H), 6.85 (d, *J* = 7.9 Hz, 2H), 4.93 (s, 1H), 3.70 (s, 3H), 3.54 (s, 3H), 3.00 (dd, *J* = 17.1, 4.6 Hz, 1H), 2.67 (ddd, 17.8, 12.8, 5.5 Hz, 1H), 2.44–2.32 (m, 2H), 2.26 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3, 170.4, 139.0, 137.4, 136.6, 134.0, 130.6, 129.8, 128.8, 128.4, 126.5, 126.2, 58.9, 52.8, 52.1, 47.9, 25.8, 22.9, 21.0; IR (thin film) 2953, 1735, 1404, 1272 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{21}H_{22}O_4Na$ $(M + Na)^+$ 361.1416, found 361.1404.

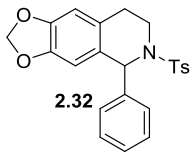


Dimethyl 1-(2,4-dimethoxyphenyl)-3,4-dihydronaphthalene-2,2(1H)-dicarboxylate, 2.30ak. Following procedure B, the following amounts of reagents were used: aryl iodide **2.29a** (72.4 mg, 0.20 mmol), *N*-tosylhydrazone **2.27k** (267.5 mg, 0.80 mmol), 60% NaH (44.8 mg, 1.12 mmol). The product was purified by flash chromatography on silica gel (1:99 EtOAc/PhMe) resulting in a yellow oil. The oil was further purified by preparatory thin layer chromatography (1:49:50 MeOH/CH_2Cl_2/hexanes) to afford **2.30ak** as a yellow oil (25.8 mg, 34%). R_f = 0.22 (1:3 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.10–7.00 (m, 3H), 6.92 (d, *J* = 7.6 Hz, 1H), 6.57 (d, *J* = 8.5 Hz, 1H), 6.39 (s, 1H), 6.30 (d, *J* = 8.4 Hz, 1H), 5.45 (s, 1H), 3.79 (s, 3H), 3.73 (s, 3H), 3.69 (s, 3H), 3.50 (s, 3H), 2.98 (dd, *J* = 17.6, 5.3 Hz, 1H), 2.70 (ddd, 17.6, 12.8, 5.5 Hz, 1H), 2.48 (td, *J* = 13.5, 6.0 Hz, 1H), 2.30 (dd, *J* = 13.8, 5.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.7, 171.0, 159.5, 157.7, 138.5, 134.1, 132.6, 130.4, 128.3, 126.3, 125.9, 123.2, 104.0, 97.8, 58.1, 55.4, 55.1, 52.6, 52.0, 39.8, 25.7, 23.7; IR (thin film) 2953, 1733, 1540, 1324, 1225 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{22}H_{24}O_6Na$ $(M + Na)^+$ 407.1471, found 407.1463.



Diethyl 8-oxo-5-(3,4,5-trimethoxyphenyl)-7,8-dihydronaphtho[2,3-d][1,3]dioxole-6,6(5H)-dicarboxylate 2.30bl. Following procedure B, the

following amounts of reagents were used: aryl iodide **2.29b** (44.5 mg, 0.10 mmol), *N*-tosylhydrazone **2.27l** (72.9 mg, 0.2 mmol), 60% NaH (14.4 mg, 0.36 mmol). The product was purified by flash chromatography on silica gel (1:3 EtOAc/hexanes) to afford a mixture **2.30bl** and azine (9:1 tetralone **2.30bl**/azine) as a yellow solid. (24.5 mg, 50%). R_f = 0.20 (1:9 EtOAc/PhMe); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (s, 1H), 6.64 (s, 1H), 6.23 (s, 2H), 6.02 (s, 2H), 5.05 (s, 1H), 4.17-4.00 (m, 4H), 3.80 (s, 3H), 3.73 (s, 6H), 3.27 (d, *J* = 18.1 Hz, 1H), 3.22 (d, *J* = 17.9 Hz, 1H), 1.18 (t, *J* = 7.1 Hz, 3H), 1.14 (t, *J* = 7.1, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.1, 169.5, 168.0, 153.4, 153.1, 147.9, 140.5, 137.6, 132.9, 129.5, 128.8, 126.3, 108.8, 106.8, 105.5, 102.1, 62.4, 62.0, 60.8, 59.9, 56.1, 49.8, 38.4, 13.9, 13.8; HRMS (ESI): *m/z* calcd for $C_{26}H_{28}O_{10}Na$ $(M + Na)^+$ 523.1580, found 523.1570.



2.32

5-phenyl-6-tosyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinoline 2.32. Following procedure B, the following amounts of reagents were used: tosyl amine **2.31** (52.6 mg, 0.12 mmol), *N*-tosylhydrazone **2.27a** (64.7 mg, 0.24 mmol), 60% NaH (17 mg, 0.43 mmol). The product was purified by flash chromatography on silica gel (1:9 EtOAc/hexanes) to afford product **2.32** as a clear oil (34.6 mg, 72%). R_f = 0.66 (40% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.2 Hz, 2H), 7.29-7.24 (m, 5H), 7.20 (d, *J* = 7.9 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 2H), 6.43 (s, 1H), 6.11 (s, 1H), 5.91 (d, *J* = 3.9 Hz, 2H), 3.73 (dd, *J* = 14.3, 5.3 Hz, 1H), 3.24 (ddd, *J* = 14.7, 10.9, 4.5 Hz, 1H), 2.57 (ddd, *J* = 16.8, 11.0, 6.2 Hz, 1H), 2.44 (ddd, *J* = 16.9, 5.0, 2.6 Hz, 1H), 2.35 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.7, 146.0, 143.0, 141.4, 137.7, 129.3, 128.7, 128.2, 127.6, 127.0, 108.4, 108.0, 100.9, 59.1, 38.8, 26.7, 21.5; HRMS (ESI): *m/z* calcd for $C_{23}H_{21}NO_4SNa$ $(M + Na)^+$ 430.1089, found 430.1095.

Experimental References

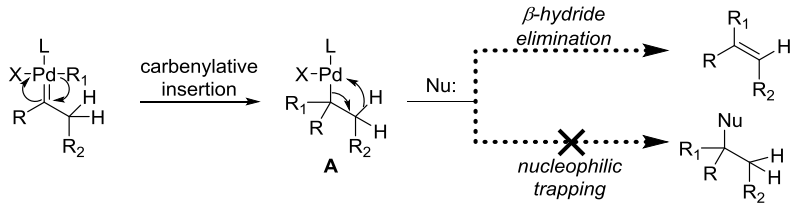
1. Furkert, D. P.; Brimble, M. A.; Quach, R. *Tetrahedron Lett.* **2013**, *54*, 5865 – 5868.
2. Maddox, J. T.; Bogas, E.; Kelley S. W.; Kabalka, G. W. *J. Org. Chem.* **1997**, *62*, 3688 – 3695.
3. Negeshi, E.-I.; Coperet, C.; Sugihara, T.; Shimoyama, I.; Zhang, Y. *Tetrahedron* **1994**, *50*, 425 – 436.
4. Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518 – 1520.
5. Bi, H.-P.; Guo, L.-N.; Duan, X.-H.; Gou, F.-R.; Huang, S.-H.; Liu, X.-Y.; Liang, Y.-M. *Org. Lett.* **2007**, *9*, 397 – 400.
6. Cossy, J.; Tresnard, L.; Pardo, D. G. *Eur. J. Org. Chem.* **1999**, 1925 – 1933.
7. Ruiz, J.; Ardeo, A.; Ignacio, R.; Sotomayor, N.; Lete, E. *Tetrahedron* **2005**, *61*, 3311 – 3324.
8. Mukai, C.; Kuroda, N.; Ukon, R.; Itoh, R. *J. Org. Chem.* **2005**, *70*, 6282 – 6290.
9. Sangeetha, S.; Muthupandi, P.; Sekar, G. *Org. Lett.* **2015**, *17*, 6006 – 6009.
10. Johannes, M.; Altmann, K,-H. *Org. Lett.* **2012**, *14*, 3752 – 3755.
11. Echavarren, A. M.; Stille, J. K. *J. Am. Chem. Soc.* **1988**, *110*, 1557 – 1565.
12. Mahoney, S. J.; Fillion, E. *Chem. Eur. J.* **2012**, *18*, 68 – 71.
13. O'Leary, M. A.; Wege, D. *Tetrahedron* **1981**, *37*, 801 – 811.

Chapter 3: Carbenylative Amination of Vinyl Iodides via Palladium Alkylidene Intermediates

Introduction

Palladium-catalyzed carbenylative insertions generate a stereogenic center when an alkyl ligand migrates to the sp^2 center of the carbene moiety. Preserving the stereocenter formed after migratory insertion has proven extremely challenging, especially when alkylidene derivatives with hydrogens adjacent to the carbene are employed as carbene precursors. The stereocenter is lost due to rapid β-hydride elimination from an alkylpalladium(II) intermediate such as species **A** (Figure 3-1). In the majority of cases, β-hydride elimination outcompetes any attempts at intercepting alkylpalladium(II) intermediates with nucleophiles.

Figure 3-1: Loss of Stereogenic Center Due to β-Hydride Elimination

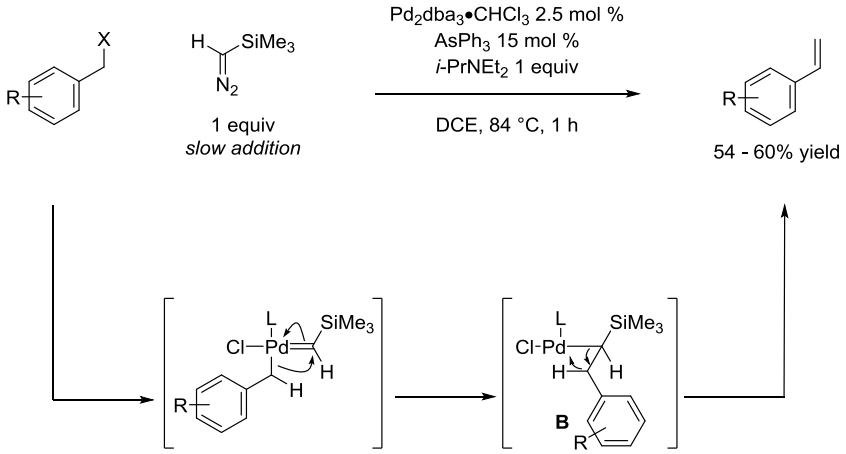


Palladium Alkylidene complexes that undergo β-hydride Elimination after Migratory Insertion

In 2001 our lab reported one of the earliest examples of olefin synthesis through a palladium-catalyzed carbenylative insertion process.[1] Alkylpalladium(II) species **B,** formed after a second carbene insertion, underwent β-hydride elimination and subsequent protodesilylation affording styrene derivatives in modest yields (Figure 3-2). This reaction utilized trimethylsilyldiazomethane as the carbene precursor. In 2007 Barluenga and co-workers reported the first use of *N*-tosylhydrazones as carbene precursors in a palladium-catalyzed carbenylative

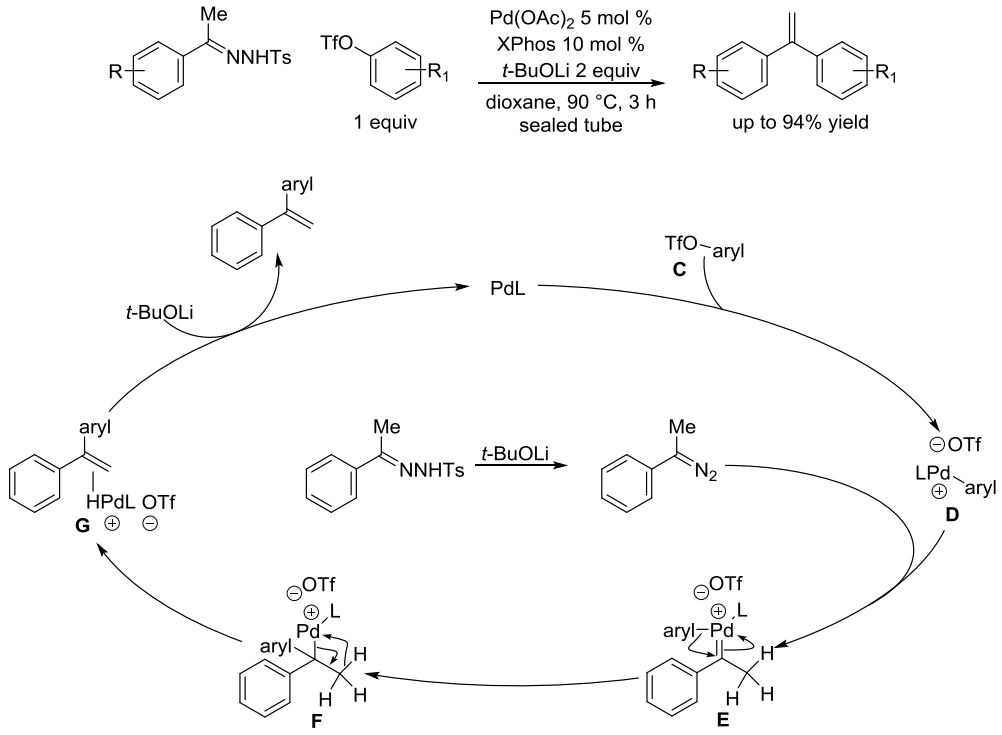
cross-coupling.[2] Since that time *N*-tosylhydrazones have increasingly become the carbene precursor of choice in palladium-catalyzed carbenylative insertion reactions.[3]

Figure 3-2: β-hydride Elimination Generates Styrenes



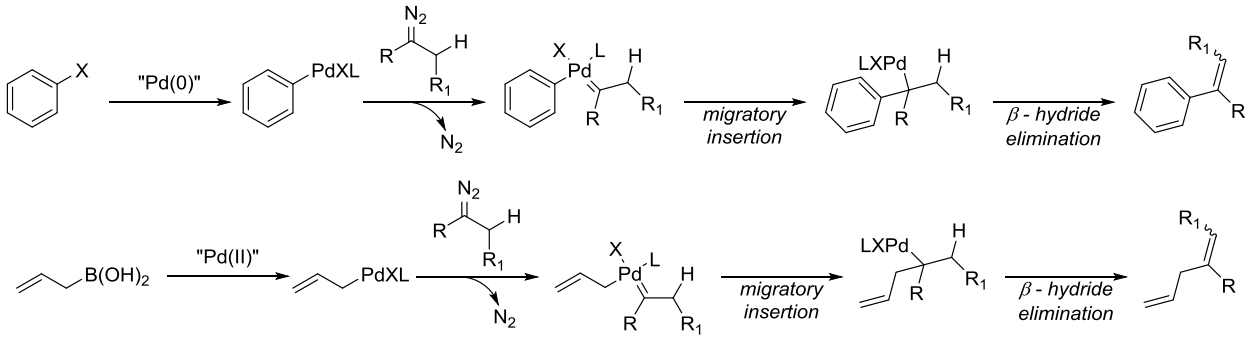
In 2009 Alami and co-workers reported an elegant palladium-catalyzed carbenylative cross-coupling for the synthesis of 1,1-diarylethylenes related to *iso*combretastatin A-4,[4] a potent tubulin polymerization inhibitor.[5] Aryltriflates and various polyoxygenated *N*-tosylhydrazones were coupled utilizing $Pd(OAc)_2$/XPhos as a catalyst and lithium *tert*-butoxide as base. A plausible catalytic cycle begins with oxidative addition of palladium(0) to form an arylpalladium(II) species, followed by ionization of triflate anion to afford cationic palladium(II) intermediate **D (**Figure 3-3).[6] Formation of palladium(II) carbene **E** followed by migratory insertion affords alkylpalladium(II) intermediate **F**. β-Beta hydride elimination followed by deprotonation of hydridopalladium **G** with lithium *tert*-butoxide produces the 1,1-diarylethylene product while releasing monoligated palladium(0) back into the catalytic cycle. Similar palladium-catalyzed carbenylative insertion processes have been developed for the synthesis of highly substituted olefins and polyenes.[7]

Figure 3-3: Plausible Catalytic Cycle for Formation of 1,1-Diarylethylenes



The preceding examples accessed alkylpalladium(II) intermediates via oxidative addition of aryl**,** allyl, or benzylic (pseudo)halides followed by migratory insertion. Another approach is to start from palladium(II) and transmetallate the alkyl group onto the metal center before forming the palladium(II) carbene (Figure 3-4).[8] From this point the typical sequence of migratory insertion and β-hydride elimination provides olefin product. In most of these cases, an external oxidant is required to reoxidize palladium(0) formed after β-hydride elimination.

Figure 3-4: Strategies to Access Palladium(II) Carbenes which Ultimately Undergo β-Hydride Elimination



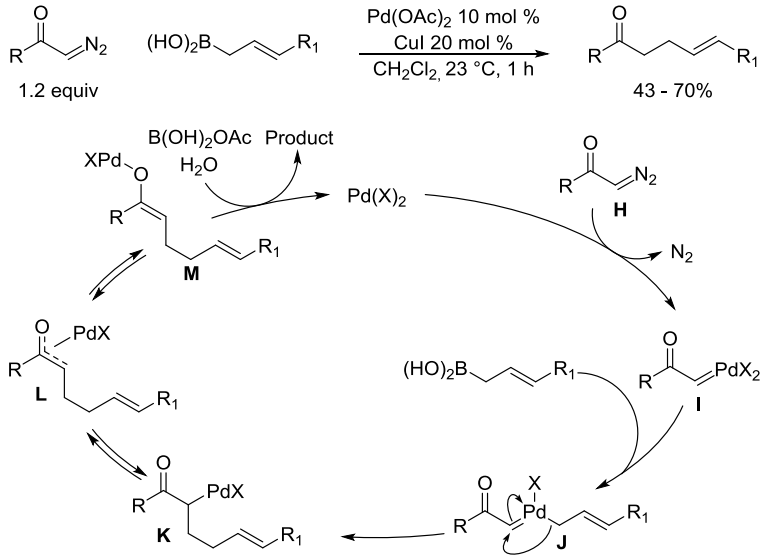
Palladium Alkylidene Complexes that Resist β-Hydride Elimination after Migratory Insertion

Examples of palladium alkylidenes that resist β-hydride elimination after migratory insertion are relatively rare. When the migratory group on the palladium(II) carbene is carbon monoxide or isonitrile the migratory insertion process generates a ketene or ketimine instead of an sp^3 alkyl group so β-hydride elimination is suppressed.[9] Some three-component palladium-catalyzed carbenylative coupling reactions can avoid β-hydride elimination through rapid isomerization of palladium between η^1 and η^3 forms. Alkylpalladium species that have the potential to equilibrate to η^3-allyl, oxa-allyl, or aza-allyl can be intercepted before β-hydride elimination can occur.

In 2016 Szabó and co-workers reported a novel palladium-catalyzed carbenylative cross-coupling of allylboronic acids and α-diazoketones.[10] The resulting linear γ,δ-unsaturated ketones produced from this reaction contain a new C(sp^3)-C(sp^3) bond. This important study showed it was possible to avoid β-hydride elimination by sequestering palladium as a palladium enolate. Interestingly, the authors suggest that this reaction is redox neutral, with palladium remaining in a +2 oxidation state throughout the catalytic cycle. A plausible catalytic cycle begins with

formation of palladium(II) carbene species **I** from α-diazoketone **H** (Figure 3-5). Transmetallation of the allyl group from allylboronic acid starting material onto the metal center affords palladium(II) carbene intermediate **J.** The authors speculate that copper iodide additive assists with the transmetallation step, noting that yields were 20% lower without the additive. Migratory insertion of the allyl ligand to the carbene carbon in **J** generates alkylpalladium(II) species **K**. Remarkably, β-hydride elimination and enone formation is suppressed in favor of equilibration to η^3-oxa-allylpalladium(II) species **L**. Further equilibration to palladium enolate **M** followed by protonation affords the γ,δ-unsaturated ketone product. Formation of water may arise from dehydration of boronic acid species present in the reaction.[11]

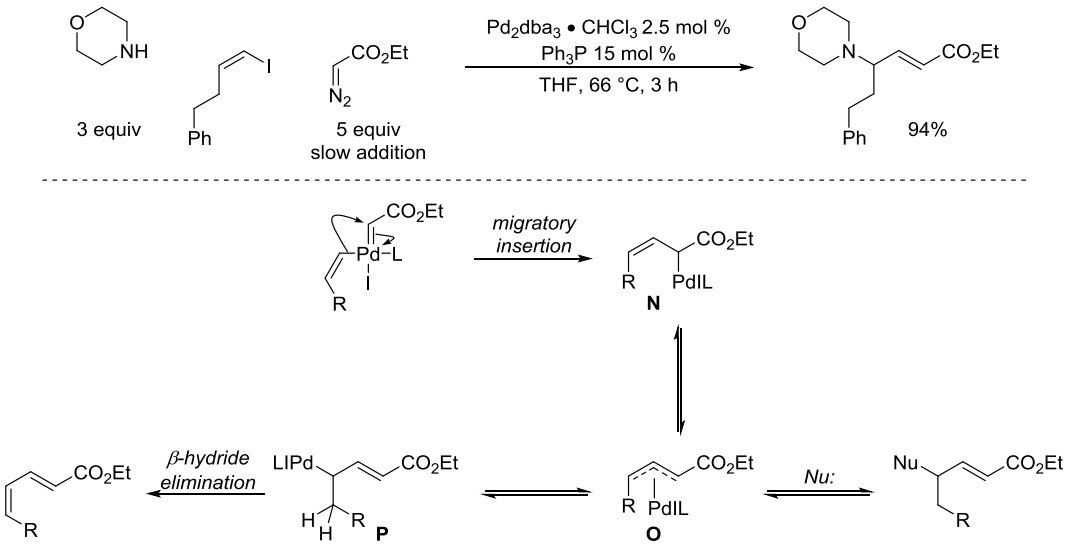
Figure 3-5: Proposed Catalytic Cycle for γ,δ-Unsaturated Ketone Formation



Our lab has developed three-component cross-coupling reactions involving vinyl iodides, nucleophiles and carbene precursors.[12] In some cases β-hydride elimination was avoided due to nucleophilic trapping of η^3-allylpalladium. For example in 2009 Kudirka and others from our group reported a palladium-catalyzed insertion of α-diazoesters into vinyl halides to generate α,β-unsaturated γ-amino esters.[13] The key step in this reaction was the nucleophilic trapping of

η^3-allylpalladium species **O** (Figure 3-6). Migratory insertion generates a η^1-allylpalladium species **N** which is incapable of β-hydride elimination; however equilibration to η^1-allylpalladium **P** does present the opportunity for palladium to undergo β-hydride elimination. Kudirka and co-workers demonstrated that nucleophilic attack is a faster process than equilibration/β-hydride elimination. Other cyclic secondary amines such as piperdine and pyrrolidine were shown to be competent nucleophiles in this reaction. Slow addition of the α-diazoester was essential for achieving high yields. Bolus addition of the diazo drastically lowered the yield of product, presumably due to reaction with allylamine product or catalyst deactivation. Interestingly, diazopropionate was also a competent coupling partner in this reaction and γ-amino esters product was isolated in 53% yield as a 2:1 mixture of *E* and *Z* isomers. The lower yields are likely due to β-hydride elimination after migratory insertion.

Figure 3-6: Palladium-Catalyzed Insertion of α-Diazoesters into Vinyl Halides to Generate α,β-Unsaturated γ-Amino Esters



In 2015, we demonstrated that aliphatic carbene precursors with adjacent hydrogens can effectively participate in three-component palladium-catalyzed carbenylative cross-coupling reactions of vinyl iodides while avoiding β-hydride elimination.[14]

Results and Discussion

In 2014 we reported a rare example of palladium alkylidenes participating in a carbenylative coupling reaction.[15] Pivaldehyde *N*-tosylhydrazone **3.1a** was employed as the carbene precursor in this reaction (Figure 3-7). Inspired by this result, I hypothesized that hydrazone **3.1a** could be utilized a carbene precursor in the intramolecular carbenylative amination reaction developed by my co-worker Avinash Khanna.[11b] Prior to that, the group had never carried out insertions reactions of aliphatic alkylidene groups; instead only *N*-tosylhydrazones derived from benzaldehyde or cinnamaldehyde derivatives were used as carbene precursors (Figure 3-8). Gratifyingly, the reaction afforded pyrrolidine **3.3a** in 68% yield, demonstrating that aliphatic *N*-tosylhydrazones can be successfully utilized as carbene precursors in carbenylative amination reactions. The major side-product generated in this reaction was known pyrrolidine dimer (~10%).[16]

Figure 3-7: Palladium Alkylidenes Undergo Migratory Insertion

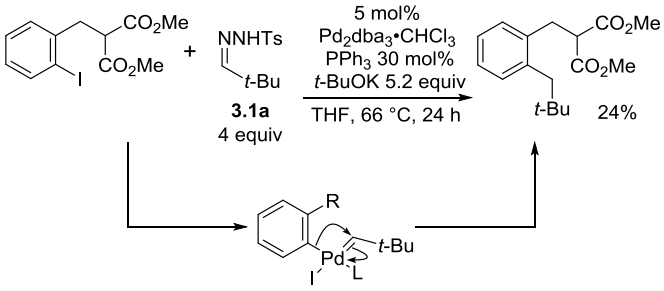
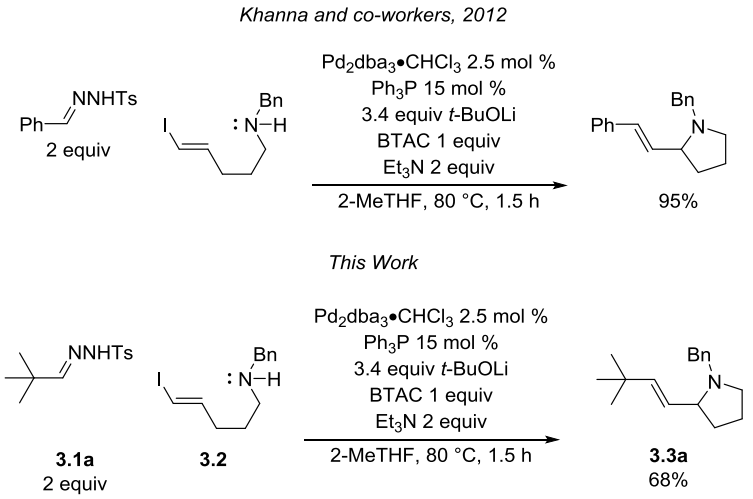


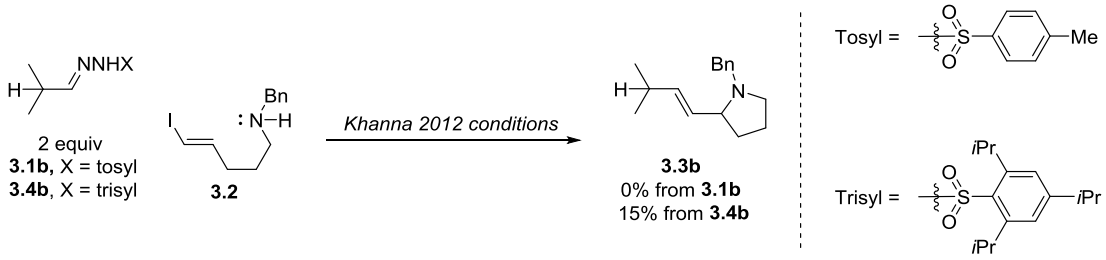
Figure 3-8: Carbenylative Amination with Aliphatic *N*-Tosylhydrazone



Along with my co-workers Udara Premachandra, Thi Nguyen, and Chengtian Shen, we further extended the scope of palladium-catalyzed carbenylative aminations by showing that alkylidenes with α-hydrogens can successfully participate in these reactions. When isobutyraldehyde *N*-tosylhydrazone **3.1b** and ω-aminovinyl iodide **3.2** were subjected to the reaction conditions developed by Khanna, none of the desired cyclized product was isolated. Instead, pyrrolidine dimer was isolated in 15% yield along with 68% recovered starting vinyl iodide (Figure 3-9). The lithium salt of *N*-tosylhydrazone **3.1b** was rather insoluble under these reaction conditions, suggesting a low effective concentration of carbene precursor in the reaction mixture. In order to increase the concentration of carbene precursor, isobutyraldehyde *N*-trisylhydrazone **3.4b** was employed in place of *N*-tosylhydrazone **3.1b**. This substitution resulted in a 15% isolated yield of desired pyrrolidine product **3.3b**. *N*-trisylhydrazones are known to generate diazo compounds faster than their *N*-tosylhydrazone counterparts.[17] In addition, the lithium salt of *N*-trisylhydrazone **3.4b** displayed better solubility under the reaction conditions. The combination of better solubility along with faster diazo generation probably resulted in a higher concentration of carbene precursor in the reaction medium, favoring the carbenylative

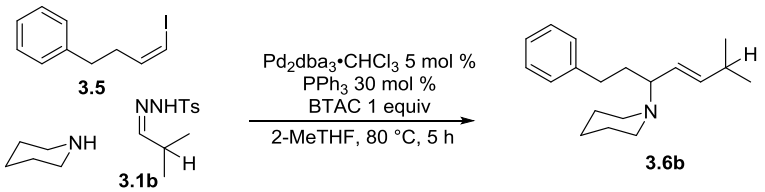
coupling reaction. The reaction was further optimized by doubling the catalyst loading, doubling Et_3N concentration from 2 to 4 equiv, and increasing the lithium *tert*-butoxide concentration from 3.4 equiv to 3.6 equiv. These changes resulted in a 91% yield of pyrrolidine product **3.3b** as well as decrease in reaction time from 1.5 hours to only 10 minutes.

Figure 3-9: *N*-trisylhydrazones Serve as Carbene Precursors



We next turned our attention to development of a three-component carbenylative amination reaction involving carbene precursors with α-hydrogens, vinyl iodides, and amines (Table 3-1). Under the conditions optimized for intramolecular trapping with vinyl iodide **3.2**, none of the desired allylamine **3.6ab** was observed. Under these conditions, trisylhydrazone **3.4b** was too reactive as a carbene source. When *N*-tosylhydrazone **3.1b** was used along with 4 equiv of piperidine, the desired allylamine **3.6ab** was obtained in 44% yield (Table 3-1, entry 2). The triethylamine additive can be omitted from the reaction conditions (entry 1). Increasing the piperidine concentration had a beneficial effect on yield up to 5 equiv; 10 equiv of piperidine did not increase the yield significantly (entries 2-4). Under the optimized conditions, 5 equiv of piperidine was used and the amounts of *N*-tosylhydrazone and lithium *tert*-butoxide were increased, leading to a 75% isolated yield of the carbenylative amination product **3.6ab** (entry 5). When the *E* isomer of vinyl iodide **3.5a** was employed in the reaction, the product was obtained in lower yield (55%) (Figure 3-10). Previously, it had been shown that *Z*-vinyl iodides and *E*-vinyl iodides give comparable yields in intramolecular carbenylative aminations.[11b]

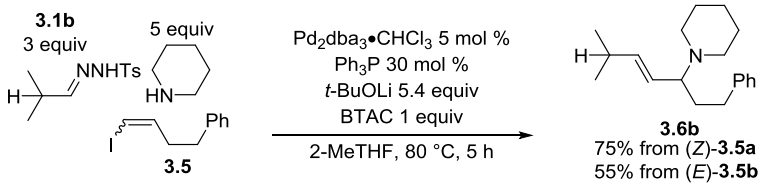
Table 3-1: Optimization of Three-Component Coupling



entry	equiv of **3.1b**	equiv of *t*-BuOLi	equiv of piperidine	yield of **3.6ab**
1[a]	2	3.6	4	0%
2	2	3.6	4	44%
3	2	3.6	5	66%
4	2	3.6	10	68%
5	3	5.4	5	75%
6	4	7.2	5	60%

[a] 4 equiv Et_3N added.

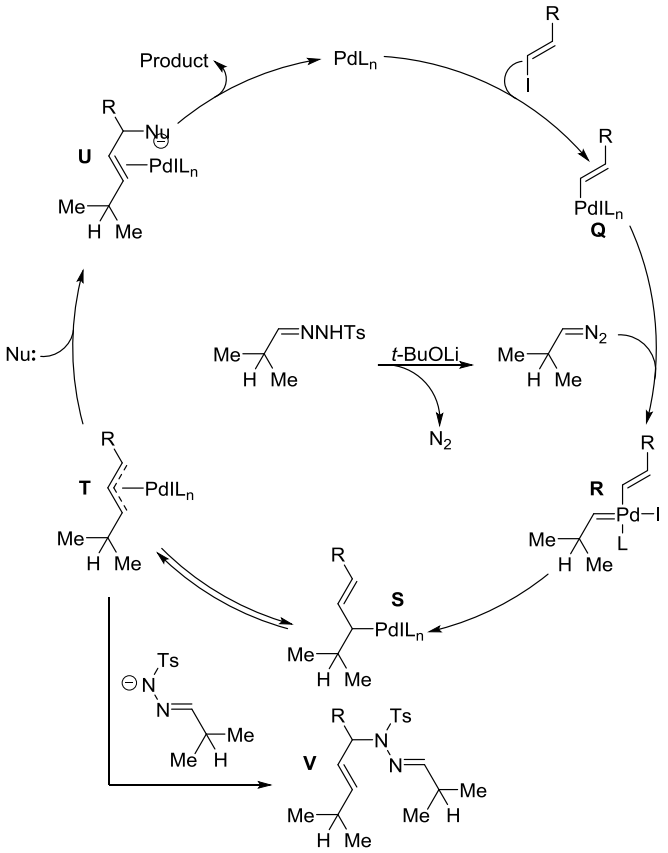
Figure 3-10: Three-Component Carbenylative Amination with Alkylidene Precursor



A plausible catalytic cycle begins with oxidative addition of palladium(0) to form a vinyl palladium species Q, which may then react with the diazo compound to yield palladium(II) carbene **R**. Migratory insertion of the vinyl ligand affords η^1-allylpalladium(II) species **S** which equilibrates to its η^3-allylpalladium(II) isomer **T**. Nucleophilic attack on intermediate **T** and subsequent dissociation affords allylamine product.

The sulfonylhydrazone anions compete with other nucleophiles in the reaction by attacking the η^3-allylpalladium intermediate **T**.[18] Formation of *N*-allylated hydrazone **V** accounts for 20−30% of the mass balance based on NMR of the crude reaction mixtures. In the absence of a nucleophile, a mixture of diene products, resulting from β-hydride elimination of η^1-allylpalladium(II) **S**, was observed along with adduct *N*-allyl adduct **V** (22%).

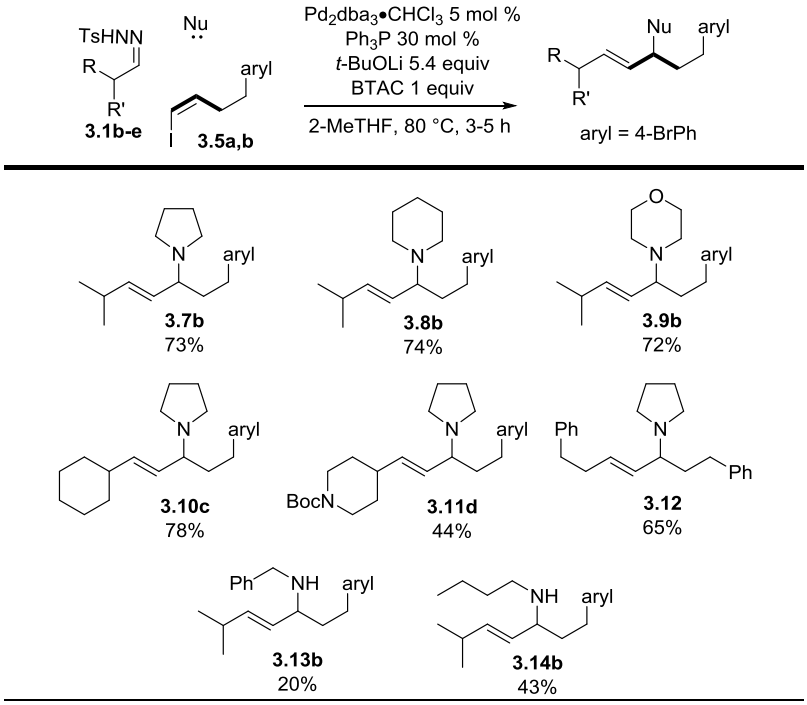
Figure 3-11: Plausible Catalytic Cycle for Carbenylative Amination with Alkylidene Precursors



Next we examined the substrate scope by varying the amine and aliphatic *N*-tosylhydrazone (Figure 3-12). The reaction worked well with cyclic secondary amines, a trend observed in previous palladium-catalyzed carbenylative aminations.[12a,13] Pyrrolidine, piperidine, and morpholine all afforded allyl amine products in good yields (**3.7b-3.9b**). Primary amines such butylamine and benzylamine resulted in modest yields of product (**3.14b** and **3.13b**). High chemoselectivity was demonstrated in all the reactions; products resulting from oxidative addition across the C-Br bond were not observed. Next, we explored the compatibility of various alkyl *N*-tosylhydrazones. The *N*-tosylhydrazone derived from cyclohexanecarboxaldehyde reacted smoothly under our conditions, furnishing product in 78% yield (**3.10c**). Unfortunately, *N*-Boc derivative **3.11d** afforded product in lower yield (44%). The carbenylative coupling of

vinyliodide **3.5a** and hydrazone **3.1f** results in a symmetrical η^3-allylpalladium species. Reaction of this species with pyrrolidine afforded product in 65% yield (**3.12**).

Figure 3-12: Substrate Scope of Three Component Coupling



Conditions: 3 equiv hydrazone, 5 equiv amine, aryl = 4-BrPh

Conclusion

In conclusion, unstabilized alkylidene groups are shown to participate in palladium catalyzed carbenylative amination reactions, without β-hydride elimination, and with high efficiency for both intramolecular and intermolecular processes. Good yields are obtained under conditions that minimize competing processes such as addition of metalated hydrazones to η^3-allylpalladium complexes. *N*-Trisylhydrazones are shown to give superior results relative to *N*-tosylhydrazones when faster rates of participation are needed from the alkylidene precursor. A three-component carbenylative amination reaction was developed which afforded allylamines in high yields for a number of substrates.

References

[1] Greenman, K. L.; Carter, D. S. Van Vranken, D.L. "Palladium-catalyzed Insertion Reactions of Trimethylsilyldiazomethane" *Tetrahedron* **2001**, *57*, 5219 – 5225.

[2] Barluenga, J.; Morriel, P.; Valdes, C.; Aznar, F. "*N*-Tosylhydrazones as Reagents for Cross-Coupling Reactions: A Route to Polysubstituted Olefins" *Angew. Chem. Int. Ed.* **2007**, *46*, 5587 – 5590.

[3] Barluenga, J.; Valdés, C. "Tosylhydrazones: New Uses for Classic Reagents in Palladium-Catalyzed Cross-Coupling and Metal-Free Reactions" *Angew. Chem. Int. Ed.* **2011**, *50*, 7486 – 7500.

[4] Patani, G. A.; LaVoie, E. J.; "Bioisosterism: A Rational Approach in Drug Design" *Chem. Rev.* **1996**, *96*, 3147 – 3176.

[5] Tréguier, B.; Abdallah, H.; Provot, O.; Brion, J.-D. Alami, M. "Expeditious Synthesis of 1,1-diarylethylenes Related to *Iso*combretastatin A-4 (*iso*CA-4) via Palladium-Catalyzed Arylation of *N*-tosylhydrazones with Aryl Triflates" *Tetrahedron Lett.* **2009**, *50*, 6549 – 6552.

[6] Wolfe, J. P.; Buchwald, S. L. "Palladium-Catalyzed Amination of Aryl Triflates" *J. Org. Chem.* **1997**, *62*, 1264 – 1267.

[7] (a) Zhao, X.; Wu, G.; Yan, C.; Lu, K.; Li, H.; Zhang, Y.; Wang, J. "Microwave-Assisted, Pd(0)-Catalyzed Cross-Coupling of Diazirines with Aryl Halides" *Org. Lett*. **2010**, *12*, 5580 – 5583.

(b) Ojha, D. P.; Prabhu, K. R.; "Palladium Catalyzed Coupling of Tosylhydrazones with Aryl and Heteroaryl Halides in the Absence of External Ligands: Synthesis of Substituted Olefins" *J. Org. Chem.* **2012**, *77*, 11027 – 11033.

(c) Rasolofonjatovo, E.; Provot, O.; Hamze, A.; Rodrigo, J.; Bignon, J.; Wdzieczak-Bakala, J.; Desravines, D.; Dubois, J.; Brion, J.-D.; Alami, M. "Conformationally Restricted Naphthalene Derivatives Type isocombretastatin A-4 and Isoerianin Analogues: Synthesis, Cytotoxicity and Antitubulin Activity" *Eur. J. Med. Chem.* **2012**, *52*, 22 – 32.

(d) Ganapathy, D.; Sekar, G. "Efficient Synthesis of Polysubstituted Olefins Using Stable Palladium Nanocatalyst: Applications in Synthesis of Tamoxifen and Isocombretastatin A4" **2014**, *16*, 3856 – 3859.

(e) Renko, D.; Provot, O.; Rasolofonjatovo, E.; Bignon, J.; Rodrigo, J.; Dubois, J.; Brion, J.-D.; Hamze, A.; Alami, M. "Rapid Synthesis of 4-arylchromenes from ortho-Substituted Alkynols: A Versatile Access to Restricted Isocombretastatin A-4 Analogues as Antitumor Agents" *Eur. J. Med. Chem.* **2015**, *90*, 834 – 835.

(f) Florentino, L.; Aznar, F.; Valdés, C. "Synthesis of Polysubstituted Isoquinolines through Cross-Coupling Reactions with α-Alkoxytosylhydrazones" *Org. Lett.* **2012**, *14*, 2323 – 2325.

(g) Zhou, Y.; Ye, F.; Wang, X.; Xu, S.; Zhang, Y.; Wang, J. "Synthesis of Alkenylphosphonates through Palladium-Catalyzed Coupling of α-Diazo Phosphonates with Benzyl or Allyl Halides" *J. Org. Chem.* **2015**, *80*, 6109 – 6118.

(h) Khelifi, I.; Naret, T.; Renko, D.; Hamze, A.; Bernadet, G.; Bignon, J.; Lenoir, C.; Dubois, J.; Brion, J,-D.; Provot, O.; Alami, M. "Design, Synthesis and Anticancer Properties of *Iso*CombretaQuinolines as Potent Tubulin Assembly Inhibitors" *Eur. J. Med. Chem.* **2017**, *127*, 1025 – 1034.

[8] (a) Peng, C.; Wang, Y.; Wang, J. "Palladium-Catalyzed Cross-Coupling of α-Diazocarbonyl Compounds with Arylboronic Acids" *J. Am. Chem. Soc.* **2008**, *130*, 1566 – 1567.
(b) Tsoi, Y.-T.; Zhou, Z.; Chan, A. S. C.; Yu, W.-Y. "Palladium-Catalyzed Oxidative Cross-Coupling Reaction of Arylboronic Acids with Diazoesters for Stereoselective Synthesis of (E)-α,β-Diarylacrylates" *Org. Lett.* **2010**, *12*, 4506 – 4509.
(c) Zhao, X.; Jing, J.; Lu, K.; Zhang, Y.; Wang, J. "Pd-Catalyzed Oxidative Cross-Coupling of *N*-Tosylhydrazones with Arylboronic Acids" *Chem. Commun.* **2010**, *46*, 1724 – 1726.
(d) Zeng, X.; Cheng, G.; Shen ,J.; Cui, X. "Palladium-Catalyzed Oxidative Cross-Coupling of *N*-Tosylhydrazones with Indoles: Synthesis of *N*-Vinylindoles" *Org. Lett.* **2013**, *15*, 3022 – 3025.
(e) Xia, Y.; Xia, Y.; Liu, Z.; Zhang, Y.; Wang, J. "Palladium-Catalyzed Cross-Coupling Reaction of Diazo Compounds and Vinyl Boronic Acids: An Approach to 1,3-Diene Compounds" *J. Org. Chem.* **2014**, *79*, 7771 – 7717.

[9] (a) Zhang, Z.; Liu, Y.; Ling, L.; Li, Y.; Dong, Y.; Gong, M.; Zhao, X.; Zhang, Y.; Wang, J. "Pd-Catalyzed Carbonylation of Diazo Compounds at Atmospheric Pressure: A Catalytic Approach to Ketenes" *J. Am. Chem. Soc.* **2011**, *133*, 4330 – 4341.
(b) Zhou, F.; Ding, K.; Cai, Q. ""Palladium-Catalyzed Amidation of *N*-Tosylhydrazones with Isocyanides" *Chem. Eur. J.* **2011** , *17*, 12268 – 12271.
(c) Zhang, Z.; Liu, Y.; Gong, M.; Zhao, X.; Zhang, Y.; Wang, J. "Palladium-Catalyzed Carbonylation/Acyl Migratory Insertion Sequence" Angew. Chem., Int. Ed. 2010, 49, 1139 – 1142.

[10] Belhomme, M.-C.; W, Dong.; Szabó, K. "Formation of C(sp3)−C(sp3) Bonds by Palladium Catalyzed Cross-Coupling of α‑Diazoketones and Allylboronic Acids" *Org. Lett.* **2016**, *18*, 2503 – 2506.

[11] Raducan, M.; Alam, R.; Szabó, K. "Palladium-Catalyzed Synthesis and Isolation of Functionalized Allylboronic Acids: Selective, Direct Allylboration of Ketones" *Angew. Chem., Int. Ed.* **2012**, *51*, 13050 – 13053.

[12] (a) Devine, S. K. J.; Van Vranken, D. L. "Palladium-Catalyzed Carbene Insertion into Vinyl Halides and Trapping with Amines" *Org. Lett.* **2007**, *9*, 2047 – 2049.
(b) Khanna, A.; Maung, C.; Johnson, K. R.; Luang, T. T.; Van Vranken, D. L. "Carbenylative Amination with *N*-Tosylhydrazones" *Org. Lett.* **2012**, *14*, 3233 – 3235.

[13] Kudirka, R.; Devine, S. K. J.; Adams, C. S.; Van Vranken, D. L. "Palladium-Catalyzed Insertion of α-Diazoesters into Vinyl Halides To Generate α,β-Unsaturated γ-Amino Esters" *Angew. Chem., Int. Ed.* **2009**, *48*, 3677 – 3680.

[14] Premachandra, I. D. U. A.; Nguyen, T. A.; Shen, C.; Gutman, E. S.; Van Vranken, D. L. "Carbenylative Amination and Alkylation of Vinyl Iodides via Palladium Alkylidene Intermediates" *Org. Lett.* **2015**, *17*, 5464 – 5467.

[15] Gutman, E. S.; Arredondo, V.; Van Vranken, D. L. "Cyclization of η^3-Benzylpalladium Intermediates Derived from Carbene Insertion" *Org. Lett.* **2014**, 5498 – 5501.

[16] Khanna, A.; Premachandra, I. D. U. A.; Sung, P. D.; Van Vranken, D. L. "Pd-Catalyzed Bis-cyclization/Dimerization Reactions of ω-Aminovinyl Halides" *Org. Lett.* **2013**, *15*, 3694 – 3697.

[17] Rosiak, A.; Hoenke, C.; Christoffers, J. "Synthesis of 3-Phenyl-4-piperidones from Acetophenone by Shapiro and Aza-Michael Reactions and Their Further Derivatization" *Eur. J. Org. Chem.* **2007**, 4376 – 4382.

[18] (a) Nun, P.; Martin, C.; Martinez, J.; Lamaty, F. "Solvent-Free Synthesis of Hydrazones and their Subsequent *N*-Alkylation in a Ball-mill" *Tetrahedron* **2011**, *67*, 8187 – 8194. (b) Kong, Y.; Zhang, W.; Tang, M.; Wang, H. "*N*-Alkylation of Tosylhydrazones in the Presence of Triphenylphoshine" *Tetrahedron* **2013**, *69*, 7487 – 7491.

Experimental Section

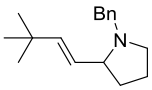
Unless otherwise noted, ^{1}H and ^{13}C NMR spectral data were recorded at room temperature in a Bruker 500 or 600 MHz spectrometer equipped with a cryoprobe. The NMR data are reported as follows: chemical shift in ppm, multiplicity (br = broad, app = apparent, s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet), coupling constants (Hz), and integration. All spectra were calibrated to tetramethylsilane (0.00 ppm). NMR data was processed using Mestrelab Research MestReNova 11.0.2 software, using automatic phasing and baseline correction.

All reactions were monitored by thin-layer chromatography (TLC). Analytical TLC was performed using EMD Reagents 0.25 mm silica gel 60-F plates. Preparative layer chromatography (PLC) was performed using EMD Millipore PLC Plates F254, 500 μm thick, 200 × 200 mm, 60 Å pore size (EM1.05744.0001). $KMnO_4$ and *p*-anisaldehyde stains were used for TLC visualization. "Flash" chromatography on silica gel was performed using Agela Scientific Flash Silica sorbent (40-63 μm) silica gel of 230-400 mesh (CS605025-P). Infrared spectroscopic data were acquired using a PerkinElmer Spectrum Two IR Spectrometer.

Chemical names found in the supporting information were generated using PerkinElmer ChemBioDraw Ultra 13.0 software. Spectral data for substrates that have no identifying number (those from the supplementary reactions) have been provided after the spectral data of all numbered compounds reported in the paper.

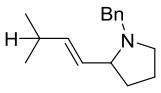
Materials

All reactions were evacuated, backfilled with nitrogen, and carried out under an atmosphere of nitrogen. Unless otherwise noted, all reagents were commercially obtained and used without prior purification. Toluene, THF, Et_2O, and CH_2Cl_2 were dried by filtration through alumina according to the procedure of Grubbs and co-workers.[1] *N*-sulfonylhydrazones were prepared following the procedure of Kabalka and co-workers.[2] All other solvents used were purified according to the Purification of Laboratory Chemicals book.[3]



3.3a

(E)-1-Benzyl-2-(3,3-dimethylbut-1-en-1-yl)pyrrolidine, **3.3a.** Following the procedure for intramolecular carbenylation by Khanna, *et al*,[4] vinyl iodide **3.2** (45.2 mg, 0.150 mmol) and *N*-tosylhydrazone **3.1a** (0.130 g, 0.420 mmol) were used to give pyrrolidine **3.3b** (24.9 mg, 68%) as a yellow oil. Rf = 0.24 (10:90 EtOAc/Hex). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.62 (app d, *J* = 4.4 Hz, 3H), 7.23 (sext, *J* = 4 Hz, 1H), 5.63 (d, *J* = 15.6 Hz, 1H), 5.28 (dd, *J* = 15.6, 8.4 Hz, 1H), 3.98 (d, *J* = 12.9 Hz, 1H), 3.04 (d, *J* = 12.9 Hz, 1H), 2.93 (dt, *J* = 9.2, 2.2 Hz, 1H), 2.69 (q, *J* = 8.4 Hz, 1H), 2.09 (q, *J* = 8.85 Hz, 1H), 1.95-1.90 (m, 1H), 1.80-1.72 (m, 1H), 1.71-1.58 (m, 3H), 1.02 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.6, 139.8, 129.1, 128.2, 127.1, 126.7, 67.9, 58.1, 53.4, 32.9, 31.8, 29.8, 21.9; IR (thin film) 2957, 2786, 1454, 1362 cm^{-1} ; HRMS (ESI): *m/z* calc'd for $C_{17}H_{25}NH$ $(M+H)^+$ 244.2065, found 244.2074.



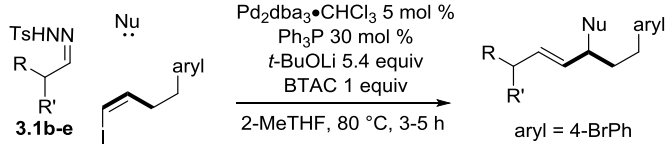
3.3b

(E)-1-benzyl-2-(3-methylbut-1-en-1-yl)pyrrolidine, 3.3b. An oven-dried 5 mL pear-shaped flask was charged with Pd_2dba_3•$CHCl_3$ (5.4 mg, 0.0071 mmol), PPh_3 (11.0 mg, 0.042 mmol), and a stir bar. The flask was fitted with a septum and purged with nitrogen. 2-MeTHF (0.2 mL) was added, and the brown slurry was then stirred for 20 min at

room temperature to give a clear yellow catalyst solution. Meanwhile, a separate oven-dried 5 mL round-bottom flask containing of *N*-trisylhydrazone **3.4b** (98.6 mg, 0.280 mmol), benzyltriethylammonium chloride (31.9 mg, 0.140 mmol), lithium *tert*-butoxide base (40.4 mg, 0.504 mmol), and a stir bar. The reaction vessel was evacuated and backfilled with N_2 three times, and then capped with a septum. A solution of the vinyl iodide **3.2** (42.1 mg, 0.140 mmol) in 0.2 mL of 2-MeTHF was transferred from a pear-shaped flask by syringe to the dry reagents in the round-bottom flask. The residual vinyl iodide in the pear-shaped flask was transferred to the reaction vessel using 2x0.15 mL 2-MeTHF. Triethylamine (78 µL, 0.560 mmol) was added to the round-bottom flask. Finally, the catalyst solution was transferred to the reaction vessel via syringe, the remaining catalyst solution was transferred 2x0.2 mL 2-MeTHF. The reaction vessel was fitted with a reflux condenser and capped with a septum. The reaction vessel was immersed in a 80 °C oil bath up to the level of the flask contents, and the stirred slurry rapidly reached reflux temperature. The reaction reached completion within 10 min and was allowed to cool to room temperature; then 2 mL 1% (w/v) aq. NaOH was added to the reaction vessel. The mixture was extracted with 3x5 mL EtOAc and the combined organic extracts were washed with brine, dried with Na_2SO_4, and concentrated in vacuo. The crude reaction mixture was purified by silica gel chromatography (10:85:5 EtOAc/Hex/Et_3N) to provide pyrrolidine **3.3b** (29.0 mg, 91%), as a brown oil. R_f = 0.6 (20:79:1 EtOAc/Hexanes/Et_3N). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43-7.07 (m, 5H), 5.59 (dd, *J* = 15.3, 6.4 Hz, 1H), 5.33 (dd, *J* = 15.3, 8.3 Hz, 1H), 4.01 (d, *J* = 13 Hz, 1H), 3.04 (d, *J* = 12.9 Hz, 1H), 2.93 (t, *J* = 8.4, 1H), 2.70 (dd, *J* = 16.0, 8.0 Hz, 1H), 2.32-2.29 (m, 1H), 2.09-2.06 (m, 1H), 1.92-1.89 (m, 1H), 1.76-1.60 (m, 3H), 1.00-0.99 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 132.5, 129.3, 129.0, 128.7, 128.2, 128.1, 127.0, 67.8, 57.7, 53.1, 31.6, 30.9,

22.6, 22.5, 21.8; IR (thin film) 2959, 1681, 1455, 1364 cm^{-1} ; HRMS (ESI): *m/z* calc'd for $C_{16}H_{23}NH$ $(M+H)^+$ 230.1909, found 230.1902.

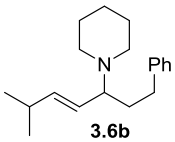
General procedure for intermolecular carbenylation:



An oven-dried 5 mL pear-shaped flask was charged with Pd_2dba_3•$CHCl_3$ (5.0 mol%), PPh_3 (30 mol%), and a stir bar. The flask was fitted with a septum and purged with nitrogen. 2-MeTHF was added to make a 0.01 M solution, and the brown slurry was then stirred for 20 min at room temperature to give a clear yellow catalyst solution. Meanwhile, a separate oven-dried 5 mL round-bottom flask containing of *N*-tosylhydrazone (3.0 equiv), benzyltriethylammonium chloride (1.0 equiv), lithium *tert*-butoxide base (5.4 equiv), and a stir bar was evacuated and back-filled with N_2 three times, and then capped with a septum. A solution of the vinyl iodide (1.0 equiv, 0.5 M in 2-MeTHF) was transferred from a pear-shaped flask by syringe to the dry reagents in the round-bottom flask. The residual vinyl iodide in the pear-shaped flask was transferred to the reaction vessel using 2x0.15 mL 2-MeTHF. Next, amine (5.0 equiv) was added to the round-bottom flask.

Finally, the catalyst solution was transferred to the reaction vessel via syringe, the remaining catalyst solution was transferred using 2x0.2 mL 2-MeTHF. The reaction vessel was fitted with a reflux condenser and capped with a septum. The reaction vessel was immersed in an 80 °C oil bath up to the level of the flask contents, and the stirred slurry rapidly reached reflux temperature. The reaction was monitored by thin layer chromatography (20:79:1 EtOAc/hex/Et_3N) to check for depletion of the vinyl iodide. The reactions reached completion between ca. 3 and 5 h depending on *N*-tosylhydrazone. Upon consumption of the vinyl iodide,

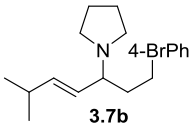
the reaction was allowed to cool to room temperature and 1% (w/v) aq. NaOH was added to the reaction vessel. The mixture was extracted with EtOAc three times and the combined organic extracts were washed with brine, dried with Na_2SO_4, and concentrated in vacuo. The pyrrolidine was purified by silica gel chromatography.



3.6b

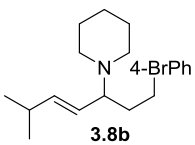
(*E*)-1-(6-methyl-1-phenylhept-4-en-3-yl)piperidine, 3.6b. An oven-dried 5 mL pear-shaped flask was charged with Pd_2dba_3•$CHCl_3$ (8.6 mg, 0.008 mmol), PPh_3 (13.1 mg, 0.050 mmol), and a stir bar. The flask was fitted with a septum and purged with nitrogen. 2-MeTHF (0.2 mL) was added, and the brown slurry was then stirred for 20 min at room temperature to give a clear yellow catalyst solution. Meanwhile, a separate oven-dried 5 mL round-bottom flask containing of *N*-tosylhydrazone **3.1b** (0.12 g, 0.499 mmol), benzyltriethylammonium chloride (46.2 mg, 0.166 mmol), lithium *tert*-butoxide base (72.2 mg, 0.899 mmol), and a stir bar was evacuated and back-filled with N_2 three times, and then capped with a septum. A solution of the (Z)-(4-iodobut-3-en-1-yl)benzene **3.5a** (43.0 mg, 0.167 mmol) in 0.2 mL of 2-MeTHF was transferred from a pear-shaped flask by syringe to the dry reagents in the round-bottom flask. The residual vinyl iodide in the pear-shaped flask was transferred to the reaction vessel using 2x0.15 mL 2-MeTHF. Next, piperidine (82 µL, 0.833 mmol) was added to the roundbottom flask. Finally, the catalyst solution was transferred to the reaction vessel via syringe, the remaining catalyst solution was transferred 2x0.2 mL 2-MeTHF. The reaction vessel was fitted with a reflux condenser and capped with a septum. The reaction vessel was immersed in a 80 °C oil bath up to the level of the flask contents, and the stirred slurry rapidly reached reflux temperature. The reaction reached completion within 10 min and was allowed to cool to room temperature; then 2 mL 1% (w/v) aq. NaOH was added to the reaction vessel. The mixture

was extracted with 3x10 mL EtOAc and the combined organic extracts were washed with brine, dried with Na_2SO_4, and concentrated in vacuo. The crude reaction mixture was purified by silica gel chromatography (10:85:5 EtOAc/Hex/Et_3N) to provide of pyrrolidine **3.6b** (29.0 mg, 75%), as a yellow oil. R_f = 0.45 (10:90:5 EtOAc/Hexanes/Et3N). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37-7.21 (m, 2H), 7.20-7.08 (m, 3H), 5.47 (dd, *J* = 15.4, 6.6 Hz, 1H), 5.30 (dd, *J* = 15.4, 8.9 Hz, 1H), 2.73-2.69 (m, 1H), 2.65-2.59 (m, 1H), 2.56-2.45 (m, 3H), 2.42-2.26 (m, 3H), 2.07- 1.82 (m, 1H), 1.83-1.64 (m, 1H), 1.64-1.47 (m, 4H), 1.46-1.33 (m, 2H), 1.02 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.8, 141.5, 128.5, 128.3, 125.6, 125.5, 67.5, 50.6, 34.4, 33.0, 31.2, 26.4, 24.9, 22.9, 22.8; IR (thin film) 2929, 2856, 2791, 1495, 1453, 1101 cm^{-1}; HRMS (ESI): *m/z* calc'd for $C_{19}H_{29}NH$ $(M+H)^+$ 272.2378, found 272.2384.



3.7b

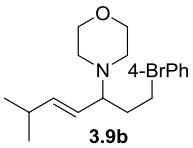
(*E*)-1-(1-(4-bromophenyl)-6-methylhept-4-en-3-yl)pyrrolidine, 3.7b. Following the general procedure for intermolecular carbenylation, vinyl iodide **3.5b** (51.2 mg, 0.136 mmol) gave **3.7b** (32.0 mg, 70 %) as a yellow oil. R_f = 0.43 (10:90:5 EtOAc/Hex/Et3N). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.3 Hz, 2H), 7.04 (d, *J* = 8.3 Hz, 2H), 5.50 (dd, *J* = 15.4, 6.6 Hz, 1H), 5.31(ddd, *J* = 15.4, 8.9, 0.6 Hz, 1H), 2.64-2.41 (m, 6H), 2.35-2.29 (m, 1H), 2.01-1.94 (m, 1H), 1.75-1.65 (m, 6H), 1.01 (dd, *J* = 6.8, 3.3 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.6, 140.7, 131.3, 130.3, 127.9, 119.4, 67.1, 51.6, 35.7, 31.9, 31.0, 23.2, 22.7; IR (thin film) 2957, 2867, 2782, 1487, 1458, 1361, 1121, 1071, 1011 cm^{-1}; HRMS (ESI): *m/z* calc'd for $C_{18}H_{26}BrNH$ $(M+H)^+$ 336.1327, found 336.1330.



3.8b

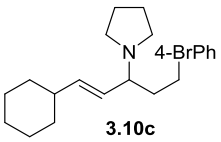
(*E*)-1-(1-(4-bromophenyl)-6-methylhept-4-en-3-yl)piperidine, 3.8b. Following the general procedure for intermolecular carbenylation, vinyl iodide

3.5b (49.7 mg, 0.132 mmol) gave **3.8b** (34.0 mg, 74%) as a yellow oil. R*f* = 0.45 (10:90:5 EtOAc/Hex/Et_3N). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42- 7.33 (m, 2H), 7.04 (d, *J* = 8.3 Hz, 2H), 5.44 (dd, *J* = 15.4, 6.6 Hz, 1H), 5.31- 5.25 (m, 1H), 2.68-2.65 (m, 1H), 2.61-2.56 (m, 1H), 2.50-2.45 (m, 3H), 2.33-2.29 (m, 3H), 1.94-1.86 (m, 1H), 1.71-1.61 (m, 1H), 1.61-1.48 (m, 4H), 1.43-1.35 (m, 2H), 1.01 (dd, *J* = 6.7, 2.1 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.7, 141.6, 131.3, 130.3, 125.4, 119.3, 67.2, 50.6, 34.2, 32.4, 31.2, 26.5, 24.9, 22.9, 22.8; IR (thin film) 2929, 2855, 2791, 1660, 1487, 1452, 1095, 1071, 1011 cm^{-1} ; HRMS (ESI): *m/z* calc'd for $C_{19}H_{28}BrNH$ $(M+H)^+$ 350.1483, found 350.1482.



3.9b

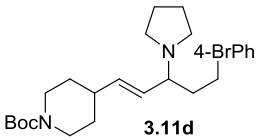
(*E*)-4-(1-(4-bromophenyl)-6-methylhept-4-en-3-yl)morpholine, 3.9b. Following the general procedure for intermolecular carbenylation, vinyl iodide **3.5b** 14 (47.6 mg, 0.126 mmol) gave **3.9b** (31.9 mg, 72%) as a colorless oil. R_f = 0.41 (10:90:5 EtOAc/Hex/Et_3N). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40-7.36 (m, 2H), 7.04 (d, *J* = 8.3 Hz, 2H), 5.44 (dd, *J* = 15.5, 6.6 Hz, 1H), 5.31-5.25 (ddd, *J* = 15.5, 6.6, 1.2 Hz, 1H), 3.76-3.62 (m, 4H), 2.68-2.58 (m, S15 2H), 2.58-2.46 (m, 3H), 2.43-2.37 (m, 2H), 2.36-2.29 (m, 1H), 1.97-1.87 (m, 1H), 1.70-1.61 (m, 1H), 1.01 (dd, *J* = 6.8, 1.1 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.4, 141.4, 131.4, 130.3, 125.0, 119.4, 67.4, 67.0, 50.1, 33.6, 32.0, 31.2, 22.8, 22.7; IR (thin film) 2954, 2853, 2810, 1487, 1452, 1117, 1071, 1011 cm^{-1}; HRMS (ESI): *m/z* calc'd for $C_{18}H_{26}BrNOH$ $(M+H)^+$ 352.1276, found 352.1278.



3.10c

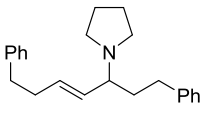
(*E*)-1-(5-(4-bromophenyl)-1-cyclohexylpent-1-en-3-yl)piperidine, 3.10c. Following the general procedure for intermolecular carbenylation, vinyl iodide **3.5b** (53.9 mg, 0.160 mmol) gave **3.10c** (47.0 mg, 78%) as a yellow oil. R_f = 0.59 (5:95:3

EtOAc/Hex/Et_3N). ^1H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.2 Hz, 2H), 7.33-7.24 (d, *J* = 8.1 Hz, 2H), 5.48 (dd, *J* = 15.5, 6.6 Hz, 1H), 5.31 (dd, *J* = 15.4, 8.9 Hz, 1H), 2.70-2.31 (m, 8H), 1.99-1.94 (m, 2H), 1.80-1.60 (m, 9H), 1.35-1.00 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.6, 139.6, 131.3, 130.3, 128.3, 119.3, 67.2, 51.6, 40.6, 35.7, 33.2, 33.3, 31.9, 26.2, 26.1, 23.2; IR (thin film) 2921, 1652, 1487, 1447, 1122, 1072, 1011 cm^{-1} ; HRMS (ESI): *m/z* calc'd for $C_{21}H_{30}BrNH$ $(M+H)^+$ 376.1640, found 376.1637.



3.11d

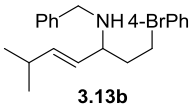
***tert*-Butyl (*E*)-4-(5-(4-bromophenyl)-3-(piperidin-1-yl)pent-1-en-1-yl)piperidine-1-carboxylate, 3.11d.** Following the general procedure for intermolecular carbenylation, vinyl iodide **3.5b** (49.9 mg, 0.148 mmol) gave **3.11b** (35.3 mg, 44%) as a yellow oil. Rf = 0.27 (10:90:5 EtOAc/Hex/Et3N). 1 H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.4 Hz, 2H), 7.03 (d, *J* = 8.4 Hz, 2H), 5.49 (dd, *J* = 15.5, 6.4 Hz, 1H), 5.38 (dd, *J* = 15.7, 8.7 Hz, 1H), 4.10 (m, 2H), 2.82- 2.69 (m, 2H), 2.63-2.40 (m, 7H), 2.19-2.12 (m, 1H), 2.02-1.96 (m, 1H), 1.75-1.67 (m, 6H), 1.46 (s, 9H), 1.35-1.27 (m, 3H); 13C NMR (125 MHz, $CDCl_3$) δ 154.9, 141.3, 137.5, 131.4, 130.2, 129.6, 119.4, 79.4, 67.0, 51.6, 38.8, 35.4, 32.0, 31.8, 29.8, 28.5, 23.2; IR (thin film) 2927, 2853, 1689, 1422, 1364, 1274, 1231, 1162 cm-1 ; HRMS (ESI): m/z calc'd for C25H37BrN2O2H (M+H)+ 477.2117, found 477.2126.



3.12

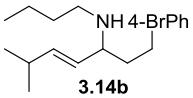
(*E*)-1-(1,8-diphenyloct-4-en-3-yl)piperidine, 3.12. Following the general procedure for intermolecular carbenylation, vinyl iodide **3.5a** (49.0 mg, 0.190 mmol) gave **3.12** (34.3 mg, 65%) as a yellow oil. R_f = 0.39 (10:90:5 EtOAc/Hex/Et_3N). ^1H NMR (500 MHz, $CDCl_3$) δ 7.28-7.25 (m, 4H), 7.20-7.13 (m, 6H), 5.56 (dt, *J* = 15.4, 6.7 Hz, 1H), 5.41-5.37 (m, 1H), 2.75-2.72 (m, 2H), 2.62-2.56 (m, 2H), 2.48-2.39 (m, 5H), 2.00-1.94 (m, 1H), 1.73-

1.67 (m, 4H), 1.63 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.7, 141.8, 132.2, 128.5, 128.4, 128.33, 128.30, 125.8, 125.6, 67.3, 51.6, 35.83, 35.80, 34.1, 32.4, 23.2; IR (thin film) 2925, 2782, 1603, 1495, 1454 cm^{-1} ; HRMS (ESI): *m/z* calc'd for $C_{23}H_{29}NH$ $(M+H)^+$ 320.2378, found 320.2379.



3.13b

(*E*)-*N*-benzyl-1-(4-bromophenyl)-6-methylhept-4-en-3-amine, 3.13b. Following the general procedure for intermolecular carbenylation, vinyl iodide **3.5b** (148 mg, 0.440 mmol) gave **3.13b** (33.7 mg, 21%) as a colorless oil. R_f = 0.9 (20:79:1 EtOAc/Hex/Et_3N). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (d, *J* = 8.4 Hz, 2H), 7.32-7.22 (m, 5H), 7.23 (d, *J* = 8.4 Hz, 2H), 5.50 (dd, *J* = 15.4, 6.7 Hz, 1H), 5.19 (ddd, *J* = 15.4, 8.5, 1 Hz, 1H), 3.80 (d, *J* = 13.2 Hz, 1H), 3.62 (d, *J* = 13.2, 1H), 2.96 (m, 1H), 2.57 (m, 2H), 2.37-2.30 (m, 1H), 1.81-1.74 (m, 1H), 1.71-1.64 (m, 1H), 1.02 (dd, *J* = 6.8, 3.2 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.4, 140.8, 140.7, 131.4, 130.2, 129.2, 128.4, 128.3, 126.9, 119.4, 59.7, 51.2, 37.5, 31.8, 31.0, 22.74, 22.70; IR (thin film) 2923, 1727, 1488, 1454, 1288, 1105, 1072, 1011 cm^{-1} ; HRMS (ESI): *m/z* calc'd for $C_{21}H_{26}BrNH$ $(M+H)^+$ 372.1327, found 372.1328.



3.14b

(*E*)-1-(4-bromophenyl)-*N*-butyl-6-methylhept-4-en-3-amine, 3.14b. Following the general procedure for intermolecular carbenylation, vinyl iodide **3.5b** (53.9 mg, 0.143 mmol) gave **3.14b** (20.9 mg, 43%) as a yellow oil. R_f = 0.41 (10:90:5 EtOAc/Hex/Et_3N). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.0 Hz, 2H), 7.04 (d, *J* = 7.9 Hz, 1H), 5.49 (dd, *J* = 15.4, 6.6 Hz, 1H), 5.14 (dd, *J* = 15.4, 8.4 Hz, 1H), 2.93-2.88 (m, 1H), 2.67-2.49 (m, 2H), 2.46-2.41(m, 2H), 2.36-2.27 (m, 1H), 1.81-1.74 (m, 1H), 1.68-1.60 (m, 1H), 1.47-1.38 (m, 2H), 1.35-1.29 (m, 2H), 1.01 (d, *J* = 6.6 Hz, 6H), 0.9 (t, *J* = 7.2 Hz, 4H); ^{13}C NMR

(125 MHz, $CDCl_3$) δ 141.2, 131.4, 130.3, 119.4, 66.9, 60.6, 46.7, 31.8, 31.0, 22.69, 22.64, 20.5, 14.0; IR (thin film) 2956, 2926, 2867, 1488, 1464, 1072, 1012 cm^{-1} ; HRMS (ESI): *m/z* calc'd for $C_{18}H_{28}NBrH$ $(M+H)^+$ 338.1483, found 338.1496.

Experimental References

1 A. B. Pangborn, M. A. Giardello, R. H. Grubbs, R. K. Rosen, F. J. Timmers, *Organometallics* **1996**, *15*, 1518.

2 W. L. F. Armarego, C. L. L. Chai, *Purification of Laboratory Chemicals*; Elsevier, 2013.

3 Maddox, J. T.; Bogas, E.; Kelley S. W.; Kabalka, G. W. *J. Org. Chem.* **1997**, *62*, 3688 − 3695.

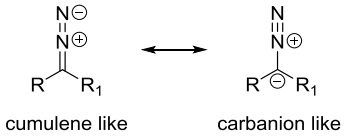
4 Khanna, A.; Maung, C.; Johnson, K. R.; Luang, T. T.; Van Vranken, D. L. *Org. Lett.* **2012**, *14*, 3233 – 3235.

Chapter 4: Enantioselective Palladium-Catalyzed Carbene Insertion into the N-H Bonds of Aromatic Heterocycles

Introduction

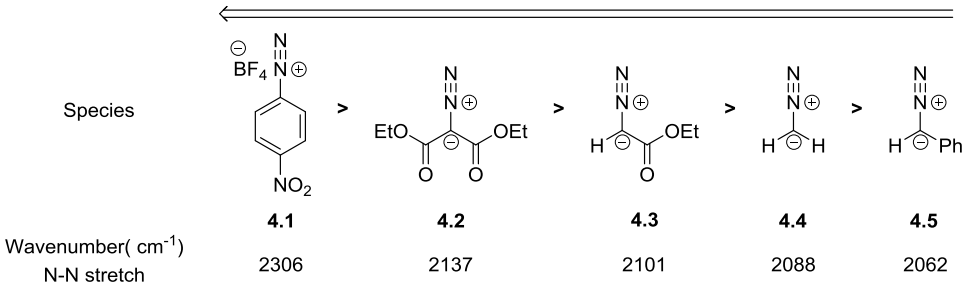
Organic chemistry is built upon the manipulation of highly reactive functional groups; few of which are as reactive as the diazo compound. Two resonance structures are drawn to depict the diazo compound (Figure 4-1). One resonance structure places the formal negative charge on the carbon while the other resonance depiction puts the formal negative charge on the terminal nitrogen of the diazo.

Figure 4-1: Resonance Forms of a Generic Diazo Compound



The identity of the R and R_1 substituent on the diazo compound determines which resonance form is the most realistic depiction for each particular compound. Electron-withdrawing groups (EWG) bound to the carbon atom stabilize the negative charge, increasing the carbanion like character of the diazo while electron-donating groups (EDG) have the opposite effect.[1] The carbanion resonance form also implies triple bond character between the two nitrogen atoms. The degree of triple bond character is correlated with the frequency of the N-N stretch seen in the IR spectra of these species. Appending EWG to the carbon atom increases the wavenumber of the diagnostic N-N stretch seen in diazo compounds and in the related diazonium species (Figure 4-2).

Figure 4-2: EWG Increase N-N Triple Bond Character in Diazo and Diazonium Species[2]



When more electron withdrawing substituents are attached, an increase in carbanion-like character is observed for diazo compounds. For example, the N-N stretching frequency of aryl diazonium salt **4.1** (2306 cm^{-1}) is not far off the Raman absorption of diatomic nitrogen (2330 cm^{-1}), a pure N-N triple bond.[4] Diethyl 2-diazomalonate **4.2**, ethyl diazoacetate **4.3**, and diazomethane **4.4** continue to display the same trend. Curiously, phenyl diazomethane **4.5** has a lower wavenumber N-N stretch than even unsubstituted diazomethane **4.4**. This may be because the phenyl substituent helps stabilize cationic character on the diazo equally as well as anionic character, thus providing little net stabilization.[4]

Diazo compounds behave quite differently in reactions depending on the IR frequency of their N-N stretching absorption (i.e., whether they are cumulene like or carbanion like). The thermodynamic driving force behind the reactivity of the diazo functional group is the extrusion of nitrogen gas. The entropic driving force for blowing off N_2 gas is so strong in fact, that the diazo starting material is left with an unfilled valence shell, characteristic of that enigmatic creature; the carbene. Work in our lab has focused on intercepting diazo compounds with transition-metal catalysts and probing the reactivity of the incipient metal carbenes. The carbenylative reactions studied by our group to date have involved oxidative addition with an aryl, vinyl, or benzyl halide. None of these reactions proceeded with both high yield and high levels of asymmetric induction. The ability of palladium to catalyze highly enantioselective

insertion reactions between stabilized diazo compounds and heteroatom-hydrogen bonds has garnered increasing levels of attention in recent years. This chapter describes recent developments in enantioselective palladium-catalyzed X-H insertion reactions of stabilized diazo compounds. In addition, the development of a highly stereoselective N-H insertion reaction of aryldiazoacetates and carbazole as well as its application towards the synthesis of a bioactive carbazole derivative are described herein.[3]

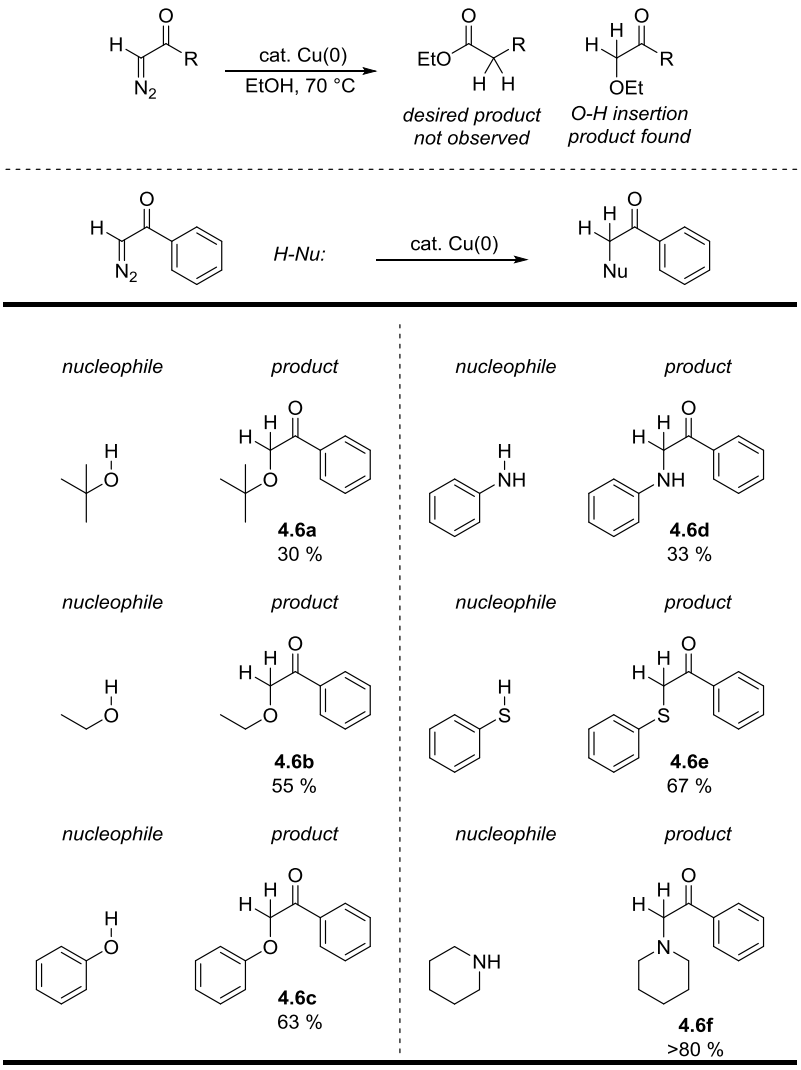
Heteroatom-H Insertion Reactions of Metal Carbenes

The discovery of metal-catalyzed X-H insertions must be credited to Peter Yates. Yates observed that copper was a poor catalyst for the Wolff rearrangement of α-diazoketones in protic solvents.[4] Instead of generating the desired rearrangement product, Yates found that copper catalyzes the direct insertion of the diazo compound into the O-H bond of the ethanol solvent (Figure 4-3). This transformation was observed with various other nucleophiles. Treatment of α-diazoacetophenone solutions in *tert*-butanol or ethanol with copper/bronze alloy afforded α-alkoxyacetophenones in 30% and 55% yield respectively (Figure 4-3, **4.6a** and **4.6b**). The much less basic phenol afforded α-phenoxyacetophenone **4.6c** in 63% yield. Similar products were obtained with aniline (**4.6d**, 33%) and thiophenol (**4.6e**, 67% yield). In the case of phenol and aniline, products arising from a formal C-H insertion of α-diazoacetophenone (electrophilic aromatic substitution) were obtained. Piperidine was also shown to partake in this reaction, affording α-aminoacetophenone derivative **4.6e** in over 80% yield.

Curiously, interest in this powerful insertion reaction was limited in the decades following the seminal publication by Yates.[5] It was not until the discovery of rhodium(II) acetate-catalyzed carbene insertion reactions that interest in the X-H insertion process was

reawakened. Rapoport and co-workers reported the construction of 5 and 6-membered heterocycles utilizing an intramolecular variant of the Yates reaction with rhodium acetate.[6]

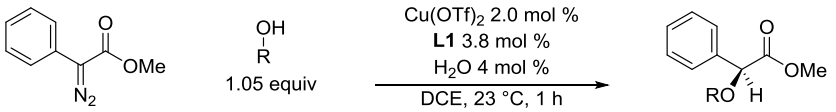
Figure 4-3: Copper-Catalyzed Insertion of α-diazoacetophenone into various Nucleophiles



In 2006 Fu and co-workers reported the first highly enantioselective O-H insertion reaction of alcohols and α-diazo-α-phenylacetates.[7] Asymmetric induction was achieved utilizing a copper/bisazaferrocene catalyst system (Table 4-1). They observed that addition of water to the reaction was essential in achieving high enantioselectivity. When water was omitted from their reaction, product yields remained intact, however, the *ee* dropped precipitously. Substitution of the alcohol alkyl chain impacted yields and *ee*. 2-trimethylsilylethanol reacts in excellent yield

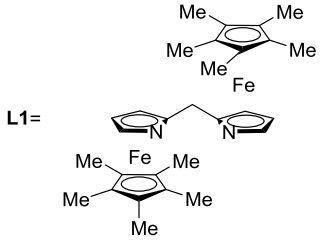
and *ee* while *tert*-butyl alcohol was a poor substrate for the reaction (entries 5 and 4). 2,2,2-trifluoroethanol does not undergo insertion, presumably due to the poor nucleophilicity of the alcohol (entry 6). Cyclopropanation was not observed when allyl alcohol was subjected to the reaction conditions (entry 9).

Table 4-1: Asymmetric O-H Insertion of Diazo Compounds



entry	R =	% yield	% ee	entry	R =	% yield	% ee
1	Me	86	69	6	CH_2CF_3	<2	nd
2	Et	85	87	7	Bn	86	77
3	*i*-Pr	76	68	8	*p*-methoxybenzyl	87	82
4	*t*-Bu	<2	nd	9	allyl	77	27
5	CH_2CH_2TMS	94	90	10	Ph	56	11

L1=



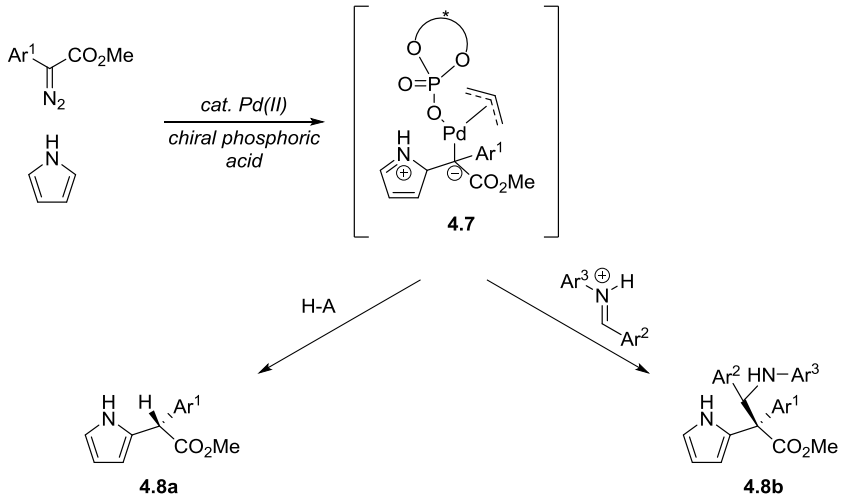
Since the initial report by Fu in 2006, a multitude of reports have documented the transition-metal catalyzed X-H insertion reaction of diazo compounds, many asymmetric.[8]

Enantioselective Palladium-Catalyzed X-H insertion Reactions with Diazo Compounds

Palladium has also proven to be an efficient metal for enantioselective C-H and X-H insertion reactions with diazo compounds. In 2013, Hu and co-workers reported an elegant palladium-catalyzed asymmetric three-component reaction of pyrroles, α-diazo-α-arylacetates, and imines (Figure 4-4).[9] This reaction employed chiral phosphoric acids as co-catalysts, affording 2-substituted pyrroles in moderate yields but high diastereoselectivity and enantioselectivity. Zwitterionic palladium intermediate **4.7** is believed to form after electrophilic aromatic substitution with pyrrole. Zwitterion **4.7** was successfully intercepted with iminium ions to afford substituted pyrrole derivatives such as **4.8b**. In the absence of iminium ion, formal C-H insertion product **4.8a** was observed. List and co-workers have spearheaded the development of palladium phosphate catalyst systems and demonstrated their utility in highly

enantioselective allylic alkylation reactions.[10] However, the work of Wu and co-workers represents the first demonstration of a highly enantioselective palladium carbene mediated insertion process.

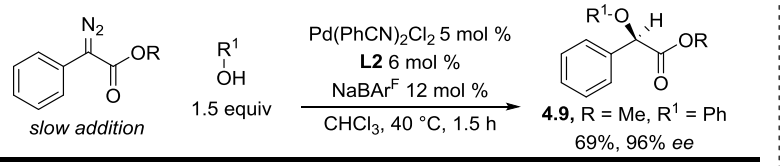
Figure 4-4: Trapping of Zwitterionic Intermediates Generated after Insertion



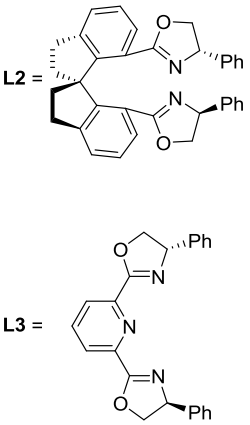
The year 2014 saw major advances in the field of palladium-catalyzed X-H insertion reactions. Zhu and co-workers reported a highly enantioselective O-H insertion reaction of phenols (Table 4-2).[11] The Zhu reaction achieved high yields and *ee*s through chiral spiro-bis(oxazoline) ligand **L2**. α-Aryl-α-diazoesters were used as palladium carbene precursors. Use of sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate ($NaBAr^F$) as an additive increased yields and decreased reaction time. When the reaction was run in the absence of $NaBAr^F$, a significant increase reaction time was observed (11 vs 1.5 h) (entry 1). The authors also observed side-products stemming from O-H insertion of H_2O, prompting addition of molecular sieves into the reaction. This change further increased the yield of the desired phenol O-H insertion product (69 vs 83%) (entry 2). Palladium(II) pre-catalysts were found to more effective than other metals in the O-H insertion reaction. Palladium(0) pre-catalyst $Pd(dba)_2$ increased the reaction time and lowered the enantioselectivity of the reaction (Table 4-2, entry 3). Use of Ph-Pybox ligand **L3**

decreased the yields and *ee* of the product (entry 4). *n*-Butanol and H_2O also underwent O-H insertion, however with lower yields and enantioselectivity (entries 5 and 6).

Table 4-2: Enantioselective O-H Insertion of Alcohols and H_2O

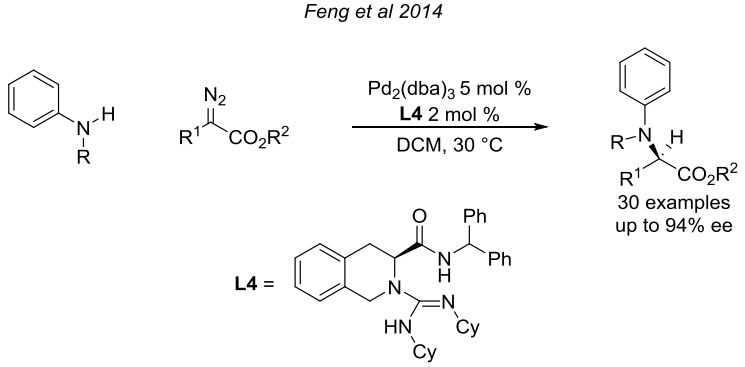


entry	deviation from standard conditions	t(h)	% yield	% *ee*
1	no $NaBAr^F$	11	47	92
2	mol. sieves added	2	83	98
3	M = $Pd(dba)_2$	3.5	54	0
4	Ligand = **L3**	2	74	19
5	R^1 = *n*-Bu	2	74	72
6	R^1 = H	1	64	36



The same year, Feng and co-workers developed an asymmetric palladium-catalyzed N-H insertion reaction of anilines (Figure 4-5).[12] This system utilized a palladium(0) pre-catalyst (Pd_2dba_3●$CHCl_3$) along with a chiral guanidine co-catalyst **L4**. α-Alkyl-α-diazoesters were used as palladium carbene precursors in this reaction.

Figure 4-5: Enantioselective N-H Insertion of Anilines



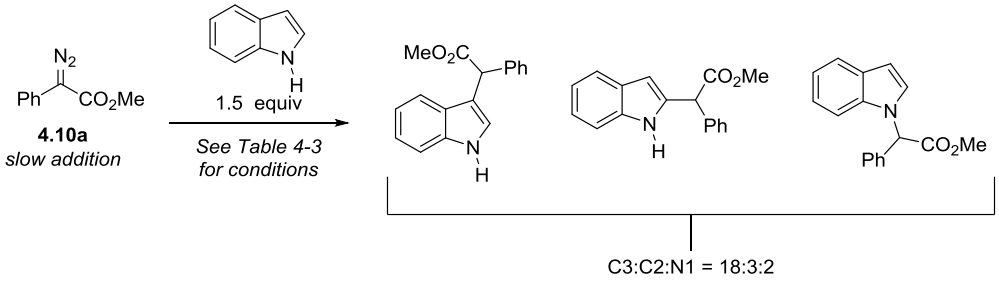
In 2015 Zhou and co-workers reported a palladium-catalyzed C-H functionalization of *N*-protected indoles.[13] The reaction utilized a palladium(II) pre-catalyst and a chiral bipyridine ligand. High yields and enantioselectivity were achieved in this reaction, however the authors did

not attempt the reaction with unprotected indoles. The remainder of this chapter describes the development of a palladium-catalyzed enantioselective carbene insertion into the N-H bond of aromatic heterocycles to obtain α-(*N*-indolyl)-α-arylesters and α-(*N*-carbazolyl)-α-arylesters, using α-diazo-α-arylacetates as palladium carbene precursors. The reaction was applied towards the synthesis of a bioactive carbazole derivative in a concise manner.

Results and Discussion

We began our study by examining the intrinsic regioselectivity of unprotected indole under O-H insertion conditions reported by Zhu and co-workers (Figure 4-6).[11] Using methyl phenyldiazoacetate **4.10a** as the palladium carbene precursor, alkylation at the C3, C2, and N1 positions was observed in an 18:3:2 ratio. While C-H insertion at the C3 and C2 position of indole is favored, N-H insertion is a viable process.

Figure 4-6: C3 and C2 C-H Insertion Dominates over N-H Insertion with Unprotected Indole

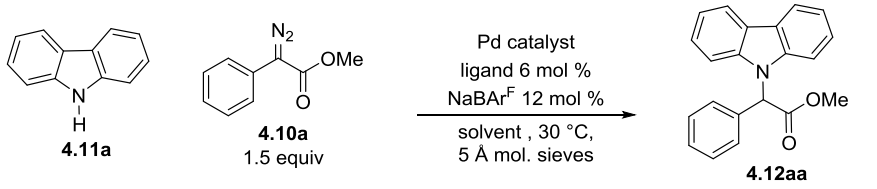


Next, we turned our attention to optimizing the N-H insertion of carbazole derivatives.[14] The bulk of this optimization was performed by my co-worker Vanessa Arredondo. When unsubstituted carbazole **4.11a** was subjected to the O-H insertion conditions reported by Zhu and co-workers,[11] N-H insertion product α-(*N*-carbozolyl)-α-phenylacetate **4.12aa** was isolated in 64% yield and 83% *ee* (Table 4-3, entry 1). Use of chiral guanidine **L4** and a palladium(0) pre-catalyst (conditions similar to Feng and co-workers N-H insertion of anilines[12]) afforded N-H insertion product **4.12aa** in quantitative yield, however the *ee* plummeted to 5 % (entry 2).

Evidently, both palladium(II) and palladium(0) species are competent pre-catalysts for this N-H insertion reaction, however high levels of asymmetric induction were only achieved with palladium(II). Presumably, the metal catalyst is not redox active acting to form an electrophilic palladium carbene species. Switching to a carbazole/diazo ratio of 1:1.5 and bolus addition of diazo **4.10a** resulted in an 88% yield of **4.12aa** and 76% *ee* (entry 3). A ligand screen revealed tri-coordinate *i*-Pr PyBox **L8** as superior to other ligands screened (entries 4-8). The bidentate phosphine BINAP ligand **L5** completely shut down the reaction and no N-H insertion product was observed. Ligands with sp^2 hybridized nitrogen atoms such as bisoxazolines and bipyridine derivatives are ubiquitous in transition-metal catalyzed X-H insertion processes of diazo compounds.[8a] Bidentate bisoxazoline **L6** afforded product in high yield but with only 15% *ee*. Tri-coordinate bisoxazoline ligands **L7** and **L8** both afforded products in high yield and high enantioselectivity, however tripod ligand **L7** required extended reaction time (16 h) compared to PyBox ligand **L8** (2 h). Excluding $NaBAr^F$ dramatically slowed down the reaction and lowered the yield; starting materials were present even after 96 h (entry 9). The sodium cation may be extracting halide from the $PdCl_2$ pre-catalyst to produce a highly reactive cationic palladium species. Similar results were observed in copper(I) chloride-catalyzed N-H insertion reactions when $NaBAr^F$ was excluded.[15] Extended reaction times were observed with lower catalyst loading, however high yields and enantioselectivity were still observed even at 0.5 mol% palladium loading (entry 10 and 11). Other non-coordinating solvents such as 1,2-dichloroethane and toluene worked well, however THF completely halted the reaction altogether (entries 12-14). The optimum conditions for the N-H insertion reaction of carbazole **4.11a** with diazo **4.10a** are those which are outlined in entry 8. Parenthetically, these conditions are: **4.11a**/**4.10a** ratio of

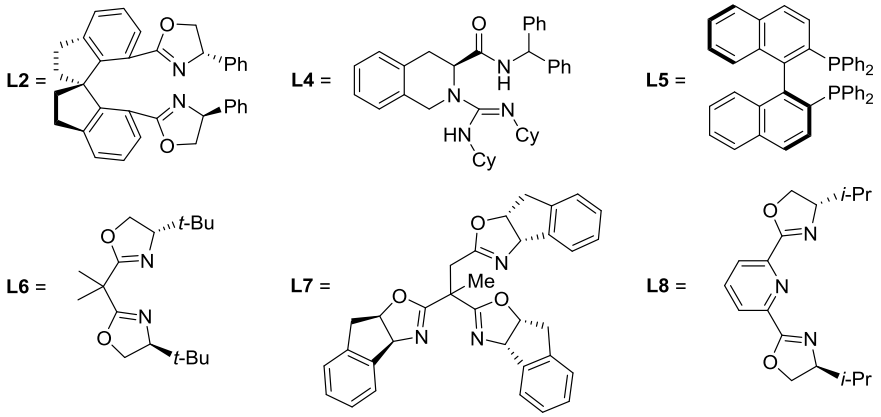
1:1.5 and bolus addition of diazo **4.10a**, 5 mol% palladium loading, 6 mol% *i*-Pr PyBox ligand **L8,** 12 mol% $NaBAr^F$, 30 °C in chloroform along with the addition of 5 Å molecular sieves.

Table 4-3: Optimization of N-H Insertion withCarbazole **4.11a**



Entry	Pd Source[(c)]	Pd (mol%)	Solvent	Ligand	t(h)	% yield[(d)]	% *ee*
1[(a)]	1	5	$CHCl_3$	**L2**	2	64	83
2[(b)]	2	10	CH_2Cl_2	**L4**	5	100	5
3	1	5	$CHCl_3$	**L2**	2	88	76
4	1	5	$CHCl_3$	**L4**	2	85	13
5	1	5	$CHCl_3$	**L5**	2	0	nd
6	1	5	$CHCl_3$	**L6**	2	94	15
7	1	5	$CHCl_3$	**L7**	16	94	90
8	1	5	$CHCl_3$	**L8**	2	99	97
9[(e)]	1	5	$CHCl_3$	**L8**	96	34	nd
10	1	1	$CHCl_3$	**L8**	4	98	97
11	1	0.5	$CHCl_3$	**L8**	20	91	95
12	1	5	DCE	**L8**	4	95	95
13	1	5	PhMe	**L8**	4	100	96
14	1	5	THF	**L8**	4	0	nd

[(a)] Zhu's O-H insertion conditions, [(b)] 2 equiv of diazo, no $NaBAr^F$, mol. sieves.
[(c)] 1 = $Pd(PhCN)_2Cl_2$, 2 = $Pd_2(dba)_3$, [(d)] Isolated yield, [(e)] No $NaBAr^F$

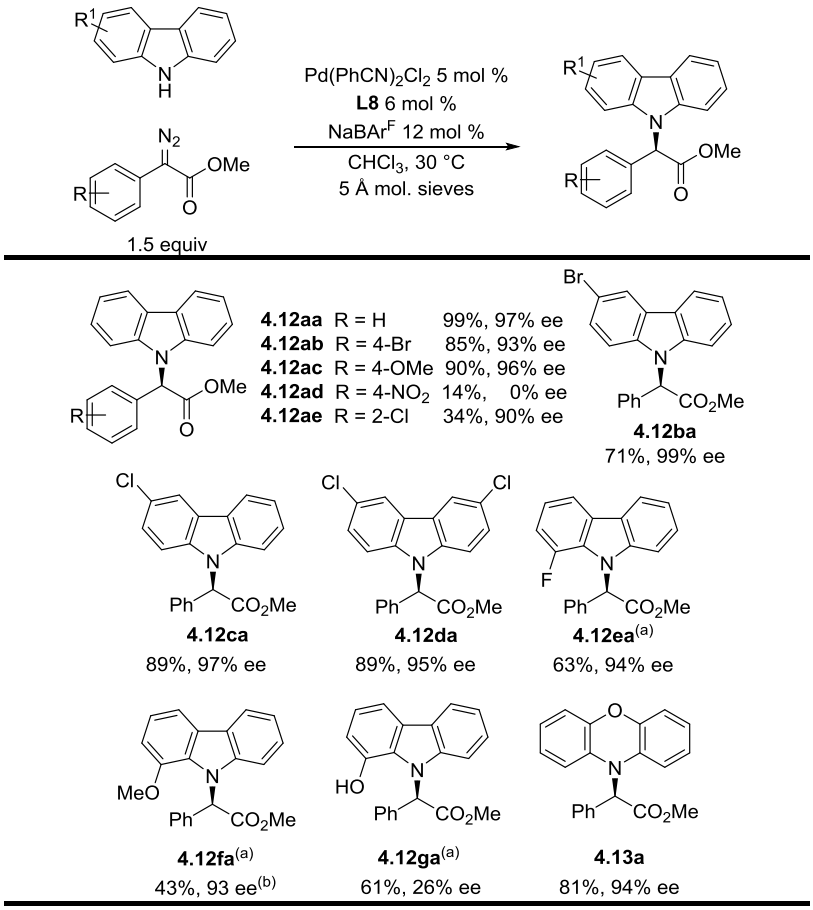


With the optimized conditions in hand, Stanley Hiew, Vanessa Arredondo, and I proceeded to examine the substrate scope of this N-H insertion reaction with respect to carbazole and diazo compound (Figure 4-7). Electron-donating groups on the aryl ring of the diazo

compound accelerated the reaction, with product **4.12ac** forming in 30 minutes with high yields and enantioselectivity. Diazo compound **4.10d**, with a *para*-nitro substituent was a poor substrate for this reaction. Heating the reaction at 55 °C for 24 only afforded N-H insertion product **4.12ad** in 14% yield. Perhaps unsurprisingly, product **4.12ad** was isolated as the racemate due to the increased acidity of the α-protons and its susceptibility towards epimerization. *ortho*-Chloro substitution on the aryl ring of the diazo lowered the yield significantly, with product **4.12ae** isolated in only 34% yield, however enantioselectivity remained high (90% *ee*). Bromine substitution is tolerated on the diazo compound (**4.12ab**) and carbazole (**4.12ba**), however slightly lower yields were observed possibly due to catalyst deactivation stemming from oxidative addition processes. Enantioselectivity remained high with bromine substitution. Electron-withdrawing groups were tolerated on the carbazole. Chlorine substituted carbazoles reacted in high yield and enantioselectivity furnishing N-H insertion products **4.12ca** and **4.12da**. Carbazoles with substituents at the one position were problematic, probably due to steric crowding in the transition state of the carbene insertion step. My co-worker Stanley Hiew was responsible for the optimization of the reactions involving 1-substituted carbazoles. Products **4.12ea**-**4.12ga** were isolated in yields below 30% under the standard conditions. 1-Substituted carbazoles necessitated increased catalyst and additive loading, increased temperature, and slow addition of diazo compound via syringe pump. Above 40 °C, competitive formation of fumarate side products was observed. Slow addition of diazo reduced fumarate formation, although up to two equivalents were required. Under these harsher conditions, 1-fluoro and 1-methoxy N-H insertion products **4.12ea** and **4.12fa** were isolated in 63% and 43% yield respectively. High levels of asymmetric induction were observed as well. With hindered 1-methoxycarbazole, the corresponding product **4.12fa** was accompanied by an inseparable mixture of C-H insertion

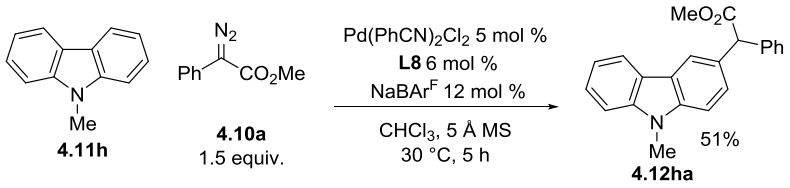
products, presumably due to reaction with the electron-rich aromatic ring. Indeed, when 9-*N*-methylcarbazole **4.12h**, was subjected to the reaction conditions, the C3−H insertion product **4.13ha** was obtained in 51 % yield (Figure 4-8).[16] With 1-hydroxycarbazole, the N-H insertion product **4.12ga** was obtained in up to 61 % yield and 4:1 selectivity over the O-H insertion product.[8d] The *ee* for **4.12ga** was highly variable (0 to 49 %) depending on reaction conditions. Carbazole-like substrates such as phenoxazine also worked well, affording **4.13a** in 81 % yield and 94 % *ee*, but with some C-H insertion products.

Figure 4-7: Reaction Scope with Substitution on the Carbazole and Diazo Compound



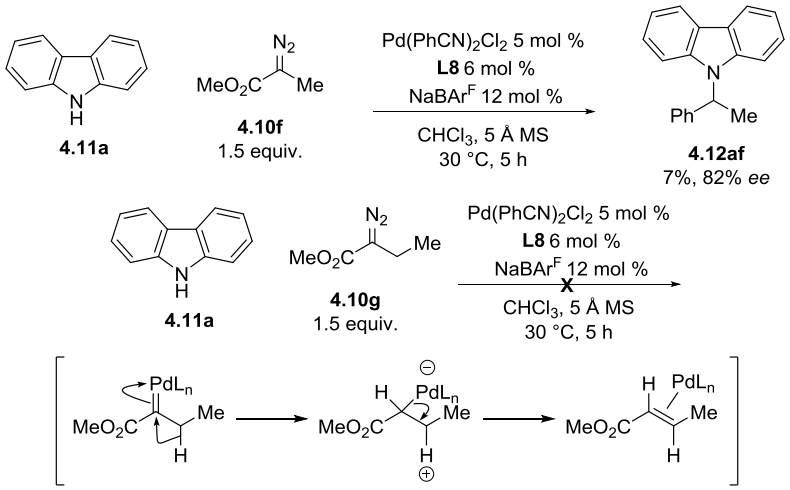
[a] 10 mol% Pd, 12 mol% L8, 24 mol% NaBAr^F, 8 h slow addition of diazo.
[b] *ee* determined for the corresponding alcohol.

Figure 4-8: C-H Insertion Reaction of 9-*N*-Methylcarbazole



α-Alkyl-α-diazoesters were poor substrates due to palladium-catalyzed decomposition (Figure 4-9). α-Diazopropanoate **4.10f** did afford a scant amount of N-H insertion product **4.12af,** with 7% yield and 82% *ee*. Methyl α-diazobutanoate **4.10g** formed (*E*)- and (*Z*)-methylcrotonate as major products. A 1,2 hydride shift into the carbenic center of the palladium carbene may be responsible for the formation of crotonates in the reaction.

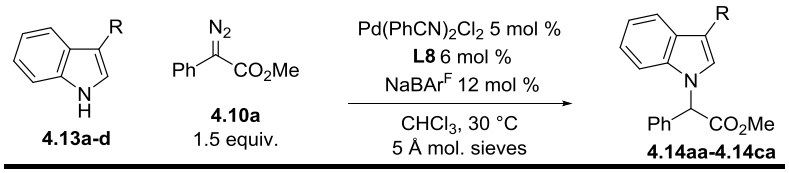
Figure 4-9: N-H Insertion with α-Alkyl-α-Diazoesters



We revisited unsubstituted indole using the conditions optimized for carbazole. Once more, indole **4.13a** gave primarily C3−H insertion product, with double-insertion at the N1 and C3 position as the major by-product (Figure 4-10). Blocking the C3 position led to preferential insertion at N1. Increasing bulk at the C3 position improved selectivity for N1 over C2 insertion (**4.14aa**<**4.14ba**<**4.14ca**). Other *N*-heterocycles besides carbazole derivatives were investigated as substrates for the N-H insertion reaction. 4-Methylpyrazole afforded coupled product in low

yields and no enantioselectivity (Figure 4-11) along with a large amount of unreacted starting material. Other *N*-heterocycles with sp^2 hybridized nitrogen atoms gave similar results. We suspect these *N*-heterocycles are competing with the bis(oxazoline) **L8** for coordination to the palladium center and deactivating the catalyst. Aliphatic amines were briefly investigated. Piperidine afforded product **4.16a** in 40 % yield. Derivative **4.17a** and P2Y12 antagonist **4.17e** ((±)-clopidogrel) were obtained in 59 % and 79 % yield, respectively. Aliphatic amines are basic enough to racemize the products; the *ee* of carbazole product **4.12aa** declined to 25 % after 2 h under the reaction conditions with 50 mol % piperidine.

Figure 4-10: N-H Insertion of Indole Derivatives



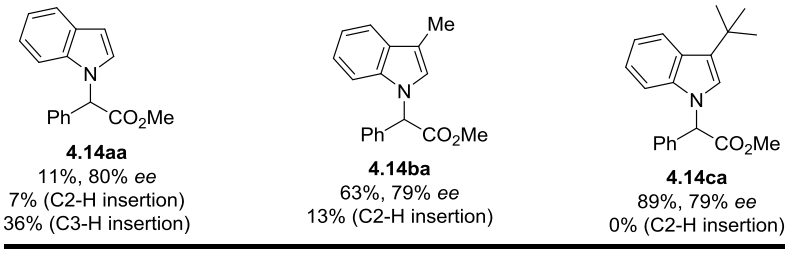
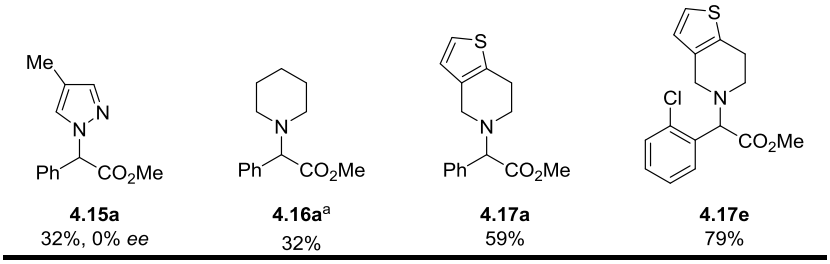


Figure 4-11: N-H Insertion of *N*-heterocycles



Conditions: See Figure 4-10

[a] No ligand

We applied the N-H insertion reaction towards the synthesis of the core of 5-HT6 receptor antagonist **4.19** (Figure 4-12). Oxazinocarbazole **4.18** was synthesized by DIBAL-H

reduction of **4.12fa** to the alcohol, mesylation, and a one-step thermal cyclization/dealkylation. This concise synthesis highlights the powerful palladium-catalyzed N-H insertion reaction described herein, avoiding a lengthy synthesis of oxazinocarbazoles that involves a late-stage Fischer indolization.[17] Alternatively, a shorter albeit lower yielding synthetic route was explored utilizing in situ generation of alkyltriflate followed by cyclization to form the six-membered ring of oxazinocarbazole **19** (Figure 4-13). Neither route suffered from racemization of the newly formed stereocenter.

Figure 4-12: Synthesis of the core of 5-HT6 Receptor Antagonist **4.19**

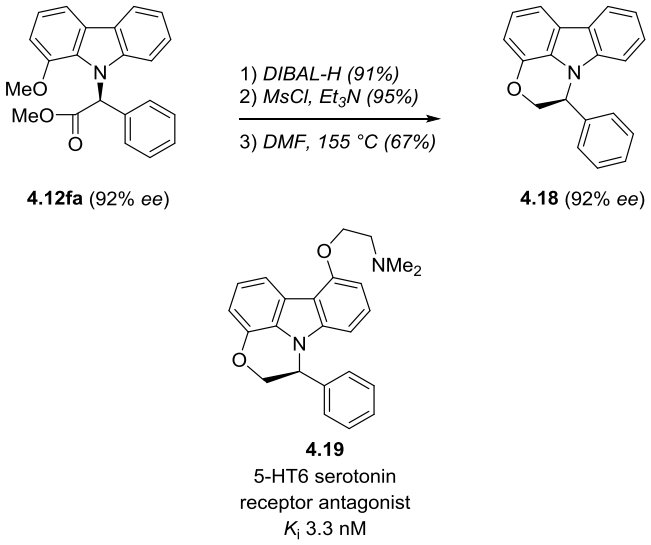
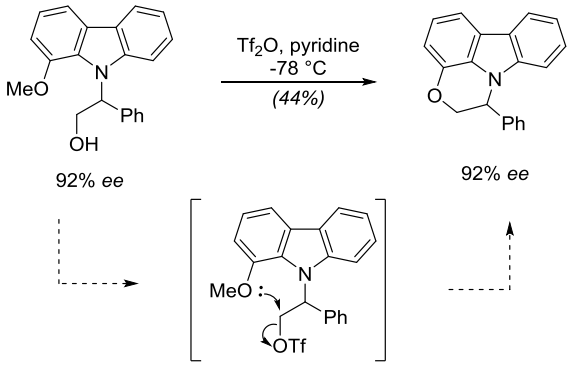


Figure 4-13: Alternate Cyclization Procedure



Conclusion

In summary, we report an enantioselective palladium-catalyzed carbene insertion into the N-H bonds of aromatic heterocycles using (S,S)-*iPr*-PyBOX and a palladium(II) precatalyst. Products were obtained in good to excellent yields and up to 99 % *ee*. A product of the reaction was carried through a series of further transformations without erosion of *ee* to synthesize the core of a potent pharmacophore.

References

[1] Regitz, M.; Maas, G. *Diazo Compounds: Properties and Synthesis*; Academic Press Inc.: Orlando, 1986; Chapter 1.

[2] Spectroscopic studies of diazo compounds and aryl diazonium salts: (a) Aroney, M.; Le Fèvre, R. J. W.; Werner, R. L. "Infrared Absorption of Characteristic of Diazonium Cations" *J. Chem. Soc.* **1955**, 276.
(b) Yates, P.; Shapiro, B. L.; Yoda, N.; Fugger, J. "Aliphatic Diazo Compounds. III. Infrared Spectra" *J. Am. Chem. Soc.* **1957**, *79*, 5756 – 5760.
(c) Foffani, A.; Pecile, C.; Ghersetti, S. "Infrared Intensity Measurements of Diazo Compounds" *Tetrahedron* **1960**, *11*, 285 – 289.
(d) Regitz, M.; Liedhegener, A. "Reaktionen aktiver Methylenverbindungen mit Aziden, XII. Synthese von Diacyl-diazomethanen durch Diazogruppen-Übertragung" *Chem. Ber.* **1966**, *99*, 3128 – 3147. (e) Regitz, M.; Menz. F. "Reaktionen CH-aktiver Verbindungen mit Aziden, XXI. Entformylierende Diazogruppen-Übertragung - ein neuer Weg zu α-Diazo-ketonen, -aldehyden und –carbonsäureestern" *Chem. Ber.* **1968**, *101*, 2622 – 2632.

[3] Arredondo, V.; Hiew, S. C.; Gutman, E. S.; Premachandra, I. D. U. A.; Van Vranken, D. L. "Enantioselective Palladium-Catalyzed Carbene Insertion into the N-H Bonds of Aromatic Heterocycles" *Angew. Chem. Int. Ed.* **2017**, *56*, 4156 – 4159.

[4] Yates, P. "The Copper-Catalyzed Decomposition of Diazoketones" *J. Am. Chem. Soc.* **1952**, *74*, 5376 – 5381.

[5] (a) Saegusa, T.; Ito, Y.; Kobayashi, S.; Hirota, K.; Shimizu, T. "Synthetic Reactions by Complex Catalysts. VIII. Copper-Catalyzed Reactions of Thiol and Alcohol with Diazoacetate" *J. Org. Chem.* **1968**, *33*, 544 – 547.
(b) Paulissen, R.; Reimlinger, H.; Hayez, E.; Hubert, A. J.; Teyssié, P. "Transition Metal Catalyzed Reactions of Diazo Compounds. II Insertion in the Hydroxylic Bond" *Tetrahedron Lett.* **1973**, 2233 – 2236.
(c) Paulissen, R.; Hayez, E.; Hubert, A. J.; Teyssié, P. "Transition Metal Catalyzed Reactions of Diazo Compounds. III A One-Step Synthesis of Substituted Furanes and Esters." *Tetrahedron Lett.* **1974**, 607 – 608.
(d) McKervey, M. A.; Ratananukul, P. "Regiospecific Synthesis of α-(Phenylthio)ketones via Rhodium(II) Acetate Catalysed Addition of Thiophenol to α-Diazoketones" *Tetrahedron Lett.* **1982**, *23*, 2509 – 2512.

[6] Moyer, M. P.; Feldman, P. L.; Rapoport, H. "Intramolecular N-H, O-H, and S-H Insertion Reactions. Synthesis of Heterocycles from α-Diazo β-Keto Esters" *J. Org. Chem.* **1985**, *50*, 5223 – 5230.

[7] Maier, T. C.; Fu, G. C. "Catalytic Enantioselective O-H Insertion Reactions" *J. Am. Chem. Soc.* **2006**, *128*, 4594 – 4595.

[8] Review of transition-metal-catalyzed enantioselective X-H insertion: (a) Zhu, S.-F.; Zhou, Q.-L. 'Transition-Metal-Catalyzed Enantioselective Heteroatom-Hydrogen Bond Insertion Reaction" *Acc. Chem. Res.* **2012**, *45*, 1365 – 1377, and references therein.
Cu-catalyzed examples: (b) Tishinov, K.; Fei, N.; Gillingham, D. "Cu(I)-Catalysed N–H Insertion in Water: a New Tool for Chemical Biology" *Chem. Sci.* **2013**, *4*, 4401 – 4406.
(c) Le Maux, P.; Carrié, D.; Jéhan, P.; Simonneaux, G. "Asymmetric O–H Insertion Reaction of Carbenoids Catalyzed by Chiral Bicyclo Bisoxazoline Copper(I) and (II) Complexes" *Tetrahedron* **2016**, *72*, 4671 – 4675.
(d) Ramakrishna, K.; Sivasankar, C. "Synthesis of Aminobenzoic Acid Derivatives via Chemoselective Carbene Insertion into the −NH Bond Catalyzed by Cu(I) Complex" *J. Org. Chem.* **2016**, *81*, 6609 – 6616.
Fe-Catalyzed examples: (e) Xu, X.; Li, C.; Tao, Z.; Pan, Y. "Hemin-Catalyzed, Cyclodextrin-Assisted Insertion of Carbenoids into N–H Bonds." *Adv. Synth. Catal.* **2015**, *357*, 3341 – 3345.
(f) Mbuvi, H. M.; Klobukowski, E. R.; Roberts, G. M.; Woo, L. K. "O-H Insertion and Tandem N-H Insertion/Cyclization Reactions using an Iron Porphyrin as Catalyst with Diazo Compounds as Carbene Sources" *J. Porphyrins Phthalocyanins* **2010**, *14*, 284.
(g) Ma, C.; Xing, D.; Zhai, C, Che, J.; Liu, Wang, J.; Hu, W. "Iron Porphyrin-Catalyzed Three-Component Reaction of Ethyl Diazoacetate with Aliphatic Amines and β,γ-Unsaturated α-Keto Esters" *Org. Lett.* **2013**, *15*, 6140 – 6143.
Rh-catalyzed examples: (h) Nicolle, S. M.; Hayes, C. J.; Moody, C. J. "Alkyl Halide-Free Heteroatom Alkylation and Epoxidation Facilitated by a Recyclable Polymer-Supported Oxidant for the In-Flow Preparation of Diazo Compounds" *Chem. Eur. J.* **2015**, *21*, 4576 – 4579.
(h) Xu, B.; Zhu, S.-F.; Zuo, X.-D.; Zhang, Z.-C.; Zhou, Q.-L "Enantioselective N-H Insertion Reaction of α-Aryl α-Diazoketones: An Efficient Route to Chiral α-Aminoketones" *Angew. Chem. Int. Ed.* **2014**, *53*, 3913 – 3916.
(i) Tan, F.; Liu, X.; Hao, X.; Tang, Y.; Lin, L.; Feng, X. "Asymmetric Catalytic Insertion of α-Diazo Carbonyl Compounds into O–H Bonds of Carboxylic Acids" *ACS Catal.* **2016**, *6*, 6930 – 6934.
Ru-catalyzed examples: (j) Li, M.; Chu, R.; Chen, J.; Wu, X.; Zhao, Y.; Liu, S.; Hu, W. "Enantioselective Formal [3 + 1 + 1] Cycloaddition Reaction by Ru(II)/Iminium Cocatalysis for Construction of Multisubstituted Pyrrolidines" *Org. Lett.* **2017**, *19*, 1290 – 1293.
(k) Deng, Q.-H.; Xu, H.-W.; Yuen, A. W.-H.; Xu, Z.-J.; Che, C.-M. "Ruthenium-Catalyzed One-Pot Carbenoid N−H Insertion Reactions and Diastereoselective Synthesis of Prolines" *Org. Lett.* **2008**, *10*, 1529 – 1532.

[9] Zhang, D.; Qiu, H.; Jiang, L.; Lu, F.; Ma, C.; Hu, W. "Enantioselective Palladium(II) Phosphate Catalyzed Three-Component Reactions of Pyrrole, Diazoesters, and Imines" *Angew. Chem. Int. Ed.* **2013**, *52*, 13356 – 13360.

[10] Mukherjee, S.; List, B. "Chiral Counteranions in Asymmetric Transition-Metal Catalysis: Highly Enantioselective Pd/Brønsted Acid-Catalyzed Direct α-Allylation of Aldehydes" *J. Am. Chem. Soc.* **2007**, *129*, 11336 – 11337.

[11] Xie, X.-L.; Zhu, S.-F.; Guo, J.-X.; Cai, Y.; Zhou, Q.-L. "Enantioselective Palladium-Catalyzed Insertion of α-Aryl-α-diazoacetates into the O-H Bonds of Phenols" *Angew. Chem. Int. Ed.* **2014**, *126*, 3022 – 3025.

[12] Zhu, Y.; Liu, X.; Dong, S.; Zhou, Y.; Li, W.; Lin, L.; Feng, X. "Asymmetric N-H Insertion of Secondary and Primary Anilines under the Catalysis of Palladium and Chiral Guanidine Derivatives" *Angew. Chem. Int. Ed.* **2014**, *53*, 1636 – 1640.

[13] Gao, X.; Wu, B.; Huang, W.-X.; Chen, M.-W.; Zhou, Y.-G. "Enantioselective Palladium-Catalyzed C-H Functionalization of Indoles Using an Axially Chiral 2,2'-Bipyridine Ligand" *Angew. Chem. Int. Ed.* **2015**, *127*, 12124 – 12128.

[14] Reaction optimization performed by my co-workers Vanessa Arredondo and Udara Premachandra.

[15] Liu, B.; Zhu, S.-F.; Zhang, W.; Chen, C.; Zhou, Q.-L. "Highly Enantioselective Insertion of Carbenoids into N-H Bonds Catalyzed by Copper Complexes of Chiral Spiro Bisoxazolines." *J. Am. Chem. Soc*. **2007**, *129*, 5834 – 5835.

[16] Examples of transition metal catalyzed C-H insertion of anilines: (a) Yang, J,-M.; Cai, Y.; Zhu, S.-F.; Zhou, Q.-L. "Iron-Catalyzed Arylation of α-aryl-α-diazoesters" *Org. Biomol. Chem.* **2016**, *14*, 5516 – 5519.
(b) Tayama, E.; Ishikawa, M.; Iwamoto, H.; Hasegawa, E. "Copper(II)-Acid Co-Catalyzed Intermolecular Substitution of Electron-Rich Aromatics with Diazoesters" *Tetrahedron Lett.* **2012**, *53*, 5159 – 5161.
(c) Tayama, E.; Yanaki, T.; Iwamoto, H.; Hasegawa, E. "Copper(II) Triflate Catalyzed Intermolecular Aromatic Substitution of *N*,*N* –Disubstituted Anilines with Diazo Esters" *Eur. J. Org. Chem.* **2010**, 6719 – 6721.

[17] "Oxazinocarbazoles for the Treatment of CNS Diseases": R. E. Tenbrink, US 6821970(B2), Nov. 23, 2004.

Experimental Section

Unless otherwise noted, ^{1}H and ^{13}C NMR spectral data were recorded at room temperature in a Bruker 500 or 600 MHz spectrometer equipped with a cryoprobe. The NMR data are reported as follows: chemical shift in ppm, multiplicity (br = broad, app = apparent, s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet), coupling constants (Hz), and integration. All spectra were calibrated to tetramethylsilane (0.00 ppm). NMR data was processed using Mestrelab Research MestReNova 11.0.2 software, using automatic phasing and baseline correction.

All reactions were monitored by thin-layer chromatography (TLC). Analytical TLC was performed using EMD Reagents 0.25 mm silica gel 60-F plates. Preparative layer chromatography (PLC) was performed using EMD Millipore PLC Plates F254, 500 μm thick, 200 × 200 mm, 60 Å pore size (EM1.05744.0001). $KMnO_4$ and *p*-anisaldehyde stains were used for TLC visualization. "Flash" chromatography on silica gel was performed using Agela Scientific Flash Silica sorbent (40-63 μm) silica gel of 230-400 mesh (CS605025-P). Infrared spectroscopic data were acquired using a PerkinElmer Spectrum Two IR Spectrometer.

Enantiomeric excess was determined by HPLC. Waters Acrodisc filters were used to filter HPLC samples (P/N WAT200520). A Chiralcel Technologies normal phase CHIRALPAK AD (0.46cmØ × 25cm) chiral column was used on an Agilent Technologies Series 1100 HPLC instrument. The instrument comprises a series 1100 auto-sampler, a series 1100 binary pump system, a series 1100 diode array detector, and a series 1100 colcom. Data analysis was performed using ChemStation for LC 3D systems Rev. B.04.01.

A Chiralcel Technologies normal phase CHIRALCEL OD-H (0.46cmØ × 25cm) chiral column was used on a Shimadzu Prominence Modular HPLC instrument. The instrument comprises two solvent delivery units (LC-20AD), a UV-VIS detector (SPD-20AV), an on-line degassing unit (DGU-20A-5R), and a system controller (CBM-20A LITE w/network switch). Analysis was performed on LabSolutions software version 5.52 copyright of Shimadzu Corporation.

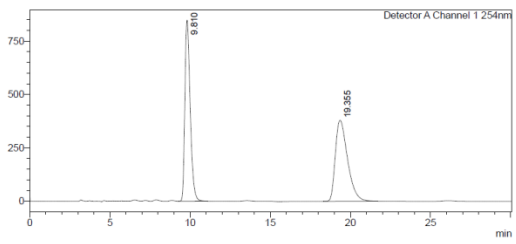
Chemical names found in the supporting information were generated using PerkinElmer ChemBioDraw Ultra 13.0 software. Spectral data for substrates that have no identifying number (those from the supplementary reactions) have been provided after the spectral data of all numbered compounds reported in the paper.

Materials

All reactions were evacuated, backfilled with nitrogen, and carried out under an atmosphere of nitrogen. Unless otherwise noted, all reagents were commercially obtained and used without prior purification. Indole **4.14a**, 3-methylindole **4.14b** were commercially available and used without prior purification. Toluene, THF, Et_2O, and CH_2Cl_2 were dried by filtration through alumina according to the procedure of Grubbs and co-workers.[1] All other solvents used were purified according to the Purification of Laboratory Chemicals book.[2]

Representative HPLC Traces

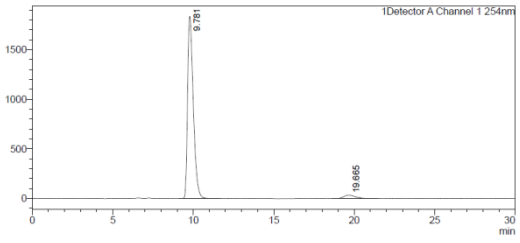
Representative HPLC traces are shown below for racemic and chiral compound **4.12aa**. Information including choice of chiral column, eluent, flow rate, and enantiomeric excess are provided in the Analytical Data section of the supporting information.



Peak Table

Detector A Channel 1 254nm

Peak#	Ret. Time	Area	Conc.	Mark	Area%
1	9.810	19668736	49.682	M	49.682
2	19.355	19920681	50.318	M	50.318
Total		39589417			100.000

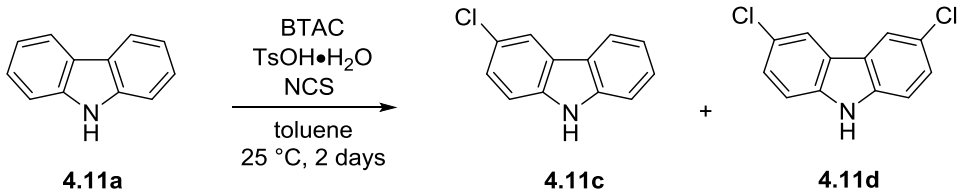


<Peak Table>

Detector A Channel 1 254nm

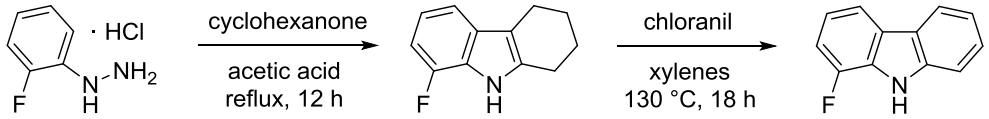
Peak#	Ret. Time	Height	Conc.	Area	Area%	Unit	Mark
1	9.781	1836172	96.446	45368762	96.446		M
2	19.665	32990	3.554	1671767	3.554		M
Total		1869161		47040530	100.000		

Synthesis of Carbazole and Indole Substrates



4.11a **4.11c** **4.11d**

3-chloro-9*H*-carbazole (4.11c) and **3,6-Dichloro-9*H*-carbazole (4.11d)** were synthesized according to a previously reported procedure by Chen and co-workers, with minor modification.[3] A flame-dried 100 mL round-bottom flask equipped with stir bar was charged with carbazole (95%, 1.0 g, 6.0 mmol), benzyltriethylammonium chloride (0.063 g, 0.30 mmol), and *p*-toluenesulfonic acid monohydrate (0.57 g, 3.0 mmol). The flask was then charged with toluene (30 mL) and allowed to stir open to air for 2 days. *N*-Chlorosuccinimide (1.6 g, 12.0 mmol) was added in four portions over two days. The reaction mixture was poured into saturated $NaHCO_3$ (100 mL) and the aqueous phase was extracted with ether (3 × 75 mL). The combined organic phase was washed with de-ionized water (3 × 75 mL), dried over Na_2SO_4, and concentrated *in vacuo* to obtain a yellow oil. The crude product was purified by flash chromatography on silica gel (15% EtOAc/hexanes) to afford **3-chloro-9*H*-carbazole 4.11c** as a tan solid (92 mg, 8%) as well as **3,6-Dichloro-9*H*-carbazole 4.11d** as a tan solid (0.680 g, 48%). Spectroscopic data for both compounds matched known reported data.[4]



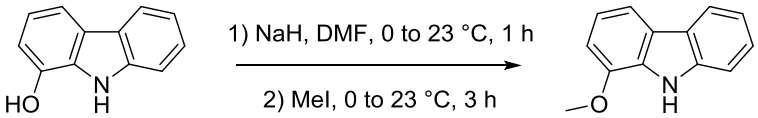
4.11e

1-fluoro-9*H*-carbazole (4.11e) was synthesized in two steps according to literature procedure with minor modification.[5]

Step 1: A 100 mL round-bottom flask was charged with 2-fluorophenylhydrazine hydrochloride (3.0 g, 18.5 mmol), cyclohexanone (2.3 mL, 22.2 mmol), and acetic acid (30 mL). The flask was fitted with a reflux condenser and the reaction mixture heated at reflux for 12 h. The mixture was cooled to room temperature, diluted with H_2O (250 mL), and extracted with ether (3 × 100 mL). The combined organic layers were washed with H_2O (3 × 75 mL) and brine (75 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (1st column = 50% ether/hexanes; 2nd column = 10% ether/hexanes). Pure fractions were combined and concentrated *in vacuo* to obtain 8-fluoro-2,3,4,9-tetrahydro-1*H*-carbazole as white cubic crystals (569 mg, 3.0 mmol, 16%). R_f = 0.81 (50% ether/hexanes); R_f = 0.43 (10% ether/hexanes). ^{1}H NMR data agrees with previously reported values.[6] ^{13}C and IR have not been reported. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (br s, 1H), 7.21 (app d, *J* = 7.8 Hz, 1H), 7.00 – 6.92 (m, 1H), 6.86 – 6.77 (m, 1H), 2.83 – 2.58 (m, 4H), 2.00 – 1.75 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) 149.2 (d, *J* = 242.4 Hz), 134.9, 131.6 (d, *J* = 5.5 Hz), 123.5 (d, *J* = 12.6 Hz), 119.3 (d, *J* = 6.2 Hz), 113.5 (d, *J* = 3.1 Hz), 111.0, 106.1 (d, *J* = 16.4 Hz), 23.2, 23.14, 23.08, 21.0; IR (ATR) 3380, 2931, 2848, 1232, 774, 725 cm^{-1}; HRMS (ESI): m/z calculated for $C_{12}H_{11}FN$ [M − Na]$^-$ 188.0876, found 188.0870.

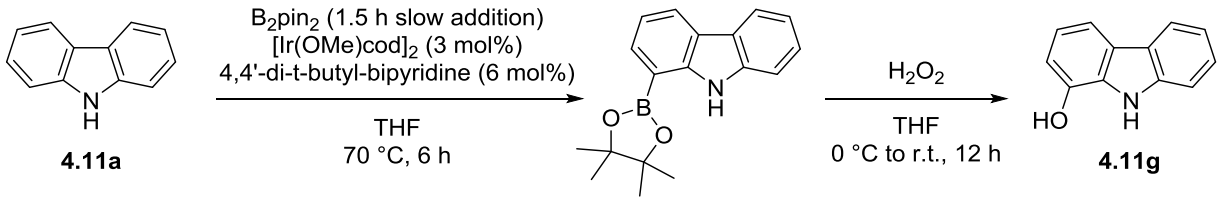
Step 2: An oven-dried 50 mL round-bottom flask equipped with stir bar was charged with 8-fluoro-2,3,4,9-tetrahydro-1*H*-carbazole (500 mg, 2.61 mmol), chloranil (1.41 g, 5.74 mmol), and anhydrous xylenes (15 mL). The flask was fitted with a reflux condenser and then submerged in a 130 °C oil bath for 18 h. The reaction mixture was cooled to room temperature, diluted with ether (150 mL), and washed with aqueous NaOH (0.5 M, 2 × 75 mL), H_2O (75 mL), and brine (75 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (1st column = 25% DCM/hexanes; 2nd column

= 8% ether/hexanes) to obtain **1-fluoro-9*H*-carbazole 4.11e** as a white solid (318 mg, 1.72 mmol, 66%). Spectroscopic data matched known reported data.[5] R_f = 0.28 (25% DCM/hexanes); R_f = 0.32 (8% ether/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (br s, 1H), 8.06 (d, *J* = 7.8 Hz, 1H), 7.85 – 7.80 (m, 1H), 7.48 – 7.41(m, 2H), 7.30 – 7.22 (m, 1H), 7.18 – 7.10 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.1 (d, *J* = 242.8 Hz), 139.5, 127.5 (d, *J* = 13.1 Hz), 126.8 (d, *J* = 5.7 Hz), 126.5, 123.2 (d, *J* = 2.7 Hz), 120.6, 120.0, 119.7 (d, *J* = 5.9 Hz), 116.0 (d, *J* = 3.4 Hz), 111.1, 110.9 (d, *J* = 16.2 Hz); HRMS (ESI): m/z calculated for $C_{12}H_7FN$ $[M-Na]^-$ 184.0563, found 184.0555.



4.11g **4.11f**

1-methoxy-9*H*-carbazole (4.11f) was synthesized according to a patented procedure.[7] A 250 mL oven-dried round bottom flask was charged with 9*H*-carbazol-1-ol **4.11g** (850 mg, 4.64 mmol) and anhydrous DMF (50 mL). The flask was cooled in an ice-water bath for 10 min while stirring. To the flask was added in a single portion NaH (60 wt%, 240 mg, 6.0 mmol). The reaction was warmed to room temperature and stirred for one hour. Next, the flask was again cooled in an ice-water bath for 10 min and iodomethane (375 μL, 6.0 mmol) was added. The reaction was warmed to room temperature and stirred for 3 h. Work-up and purification according to literature procedure yielded **1-methoxy-9*H*-carbazole 4.11f** as a beige solid (801 mg, 88%). Spectroscopic data matched known reported data.[8,9]

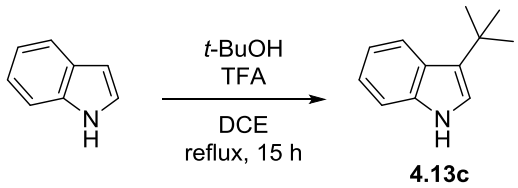


9*H*-carbazol-1-ol (1g) was synthesized according to a two-step procedure by Sperry and co-workers, with modifications.[10]

Step 1: A oven-dried 500 mL round-bottom flask was charged with carbazole **4.11a** (6 g, 36.0 mmol), 4,4'-di-*tert*-butyl-bipyridine (193 mg, 0.72 mmol), $[Ir(OMe)cod]_2$ (238 mg, 0.36 mmol), and dry THF (200 mL). The mixture was stirred at room temperature for 10 minutes until a dark red, homogeneous solution was obtained. The flask was submerged in a 70 °C oil bath. Bis(pinacolato)-diboron (3.04 g, 12.0 mmol) was dissolved in dry THF (20 mL) and this solution was added over 1.5 h using a syringe pump. After addition, the reaction mixture was stirred at 70 °C for an additional 4.5 h, for a total reaction time of 6 h. The reaction mixture was cooled to room temperature and concentrated *in vacuo*. The crude product was purified by flash chromotography on silica gel using 8% EtOAc/hexanes, concentrated, and dried *in vacuo* to obtain 1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-9*H*-carbazole as a white solid (1.86 g, 26%). R_f = 0.43 (8% EtOAc/hexanes); ^{1}H NMR[10] and ^{13}C NMR[11] spectroscopic data match previously reported data. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.15 (s, 1H), 8.18 (d, *J* = 8.2 Hz, 1H), 8.07 (d, *J* = 7.8 Hz, 1H), 7.86 (dd, *J* = 7.2, 1.2 Hz, 1H), 7.49 (d, *J* = 8.1 Hz, 1H), 7.41 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H), 7.28 – 7.18 (m, 2H), 1.42 (s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.1, 139.3, 132.8, 125.7, 123.7, 122.9, 122.3, 120.3, 119.1, 118.7, 110.6, 84.0, 25.0.

Step 2: 1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-9*H*-carbazole) (1.80 g, 6.13 mmol) was dissolved in THF (75 mL). The reaction was cooled in an ice-water bath for 10 min while stirring. Into the flask was syringed 30 wt % aqueous hydrogen peroxide (1.9 mL, 18.4 mmol).

The mixture was allowed to warm to room temperature and stirred for 12 h. The mixture was concentrated *in vacuo*, purified by flash chromatography on silica gel using 30% EtOAc/hexanes, concentrated, and dried *in vacuo* to obtain a light brown solid. The solid was recrystallized from hot benzene under nitrogen. Upon cooling to room temperature, a few drops of hexanes were added to initiate crystallization. The mother liquor was removed via syringe, and the solid washed twice with cold hexanes. The solid was dried *in vacuo* to obtain 9*H*-carbazol-1-ol **4.11g** as flaky white crystals (920 mg, 82%). R_f = 0.28 (30% EtOAc/hexanes). Spectroscopic data matched known reported data.[12] ^{13}C NMR data has not been reported. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (s, 1H), 8.07 (d, *J* = 8.3 Hz, 1H), 7.70 (d, *J* = 7.9 Hz, 1H), 7.52 – 7.40 (m, 2H), 7.25 (ddd, *J* = 8.0, 7.0, 1.2 Hz, 1H), 7.09 (t, *J* = 7.8 Hz, 1H), 6.84 (dd, *J* = 7.6, 0.7 Hz, 1H), 5.00 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 141.0, 139.4, 129.0, 126.0, 125.3, 123.6, 120.6, 119.7, 119.5, 113.3, 111.0, 110.7.

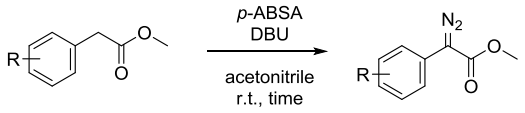


4.13c

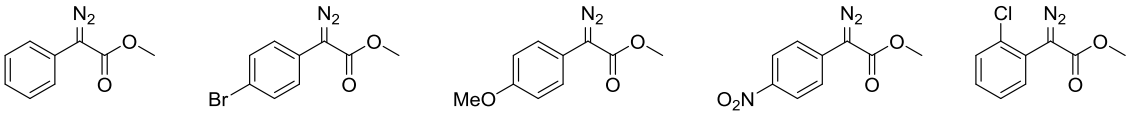
3-(*tert*-butyl)-1*H*-indole 4.13c was synthesized according to a patented procedure.[13] Indole (3.0 g, 25.6 mmol) was used to obtain compound **4.13c** as an amorphous pale pink solid (312 mg, 7%). Pure compound **4.13c** containing residual toluene (<5 mol %) was isolated following three rounds of flash chromatography on silica gel (1st column = 10% EtOAc/hexanes; 2nd column = gradient 5→10% EtOAc/hexanes; 3rd column = 40% toluene/hexanes). R_f = 0.32 (10% EtOAc/hexanes); R_f = 0.22 (5% EtOAc/hexanes); R_f = 0.31 (40% toluene/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.70 (br s, 1H), 7.30 (dd, *J* = 8.1, 1.0 Hz, 1H), 7.16 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1H), 7.09 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 6.86 (d, *J* = 2.5 Hz,

1H), 1.45 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.1, 126.7, 125.8, 121.4, 121.2, 119.2, 118.7, 111.3, 31.6, 30.7; IR (ATR): 3394, 2962, 2863, 1616, 1459, 1360, 1123, 1100, 737 cm^{-1}.

Synthesis of α-Aryl-α-Diazoesters



Aryldiazoacetates 4.10a-4.10e were synthesized according to a patented procedure.[14] An oven-dried round-bottom flask equipped with stir bar was charged with the aryl acetate (1.0 equiv) and *p*-acetamidebenzenesulfonylazide (1.1 equiv). Dry acetonitrile was added to obtain a 0.25 M solution in aryl acetate. The flask was cooled in an ice-water bath for 10 minutes while stirring. A 1.5 M solution of DBU (1.2 equiv) in acetonitrile was syringed into the flask. The flask was allowed to warm to room temperature and stirred until aryl acetate was no longer detected by TLC. Next, the reaction mixture was diluted with three times its volume of ether, then washed sequentially with 50 mL each of saturated aqueous NH_4Cl and H_2O (× 2). The organic layer was dried with Na_2SO_4, concentrated, and purified by flash chromatography on silica gel to afford the aryldiazoacetate product.



4.10a **4.10b** **4.10c** **4.10d** **4.10e**

Synthesis and characterization for **4.10a** has been previously reported.[15] ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.5 Hz, 2H), 7.38 (t, *J* = 8.0 Hz, 2H), 7.18 (t, *J* = 7.4 Hz, 1H), 3.86 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.6, 128.9, 125.8, 125.5, 123.9, 52.0.

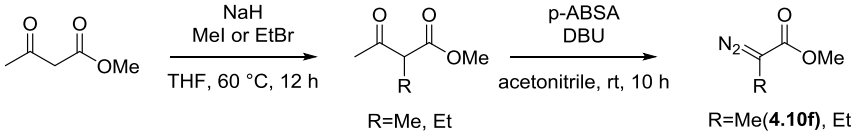
Synthesis and characterization for **4.10b** has been previously reported.[15] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.7 Hz, 2H), 7.36 (d, *J* = 8.7 Hz, 2H), 3.87 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.2, 132.0, 125.3, 124.7, 119.3, 52.1.

Synthesis and characterization for **4.10c** has been previously reported.[15] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, *J* = 9.0 Hz, 2H), 6.95 (d, *J* = 9.0 Hz, 2H), 3.85 (s, 2H), 3.81 (s, 3H).

Synthesis and characterization for **4.10d** has been previously reported.[16] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (d, *J* = 9.1 Hz, 2H), 7.67 (d, *J* = 9.1 Hz, 2H), 3.91 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.1, 145.0, 133.8, 124.3, 123.1, 52.4.

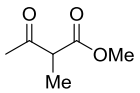
Synthesis and characterization for **4.10e** has been previously reported.[15] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.42 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.32 (td, *J* = 7.6, 1.5 Hz, 1H), 7.28 (dd, *J* = 7.9, 1.8 Hz, 1H), 3.84 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.9, 133.8, 132.3, 130.1, 129.6, 127.1, 123.9, 52.3.

Synthesis of α-Alkyl-α-Diazoesters



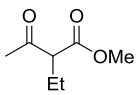
α-Alkyl-α-diazoesters compounds were synthesized from methyl acetoacetate in two steps. A previously reported procedure for the first step was used with some modification.[17]

Step 1: An oven-dried 100 mL round-bottom flask equipped with stir bar was evacuated and backfilled with argon. The flask was charged with NaH (60% dispersion in mineral oil, 0.48 g, 12 mmol, 1.2 equiv) and THF (25 mL). The suspension was cooled in an ice-water bath for 10 minutes while stirring. A solution of methyl acetoacetate (1.75 g, 15 mmol, 1.5 equiv) in THF (5



mL) was then added to the flask over 10 minutes. The flask was warmed to room temperature and stirred for 30 minutes. Iodomethane (1.42 g, 10 mmol, 1.0 equiv) was then added and the flask submerged in a 60 °C oil bath for 12 h. After 12 h, the flask was cooled in an ice-water bath for 10 minutes, and saturated aqueous NH_4Cl (15 mL) was added. The mixture was diluted with ether (30 mL) and H_2O (30 mL). The resulting layers were separated and the aqueous layer extracted with additional ether (50 mL). The organic layers were combined and washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The resulting oil was further purified by silica gel chromatography (30% ether/hexanes) to obtain methyl 2-methyl-3-oxobutanoate (methyl 2-methylacetoacetate) as a colorless oil (678 mg, 52%). Spectroscopic data was consistent with previous reports.[18]

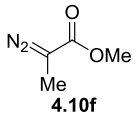
methyl 2-methyl-3-oxobutanoate: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.77 (s, 3H), 3.55 (q, *J* = 7.2 Hz, 1H), 2.27 (s, 3H), 1.38 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 203.6, 171.0, 53.4, 52.4, 28.5, 12.8.



methyl 2-ethyl-3-oxobutanoate: Methyl 2-ethyl-3-oxobutanoate was synthesized as outlined in Step 1 above, except ethyl bromide (1.09 g, 10 mmol, 1.0 equiv) was used instead of iodomethane. The product was obtained as a colorless oil (1.02 g, 71 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.74 (s, 3H), 3.36 (t, *J* = 7.4 Hz, 1H), 2.23 (s, 3H), 2.00 – 1.81 (m, 2H), 0.94 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.3, 170.3, 61.2, 52.3, 28.9, 21.7, 11.9.

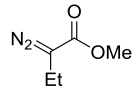
Step 2:[14] An oven-dried round-bottom flask equipped with stir bar was charged with methyl 2-methyl-3-oxobutanoate (622 mg, 4.78 mmol, 1.0 equiv), *p*-acetamidebenzenesulfonylazide (1.26 g, 5.25 mmol, 1.1 equiv), and dry acetonitrile (15 mL). The flask was cooled in an ice-water bath for 10 minutes while stirring. A solution of DBU (872 mg, 5.73 mmol, 1.2 equiv) in dry

acetonitrile (5 mL) was then syringed into the flask. The flask was allowed to warm to room temperature and stirred for 10 h. The reaction mixture was diluted with ether (60 mL) and then washed with saturated aqueous NH_4Cl (30 mL) and brine (30 mL). The organic layer was dried over Na_2SO_4, concentrated, and purified by flash chromatography (10% ether/hexanes) to obtain methyl 2-diazopropanoate as a yellow oil (263 mg, 48%). The product was volatile, so was concentrated to ~2 mL *in vacuo* and the remaining solvent evaporated under a gentle stream of argon. Spectroscopic data was consistent with previous reports.[19]



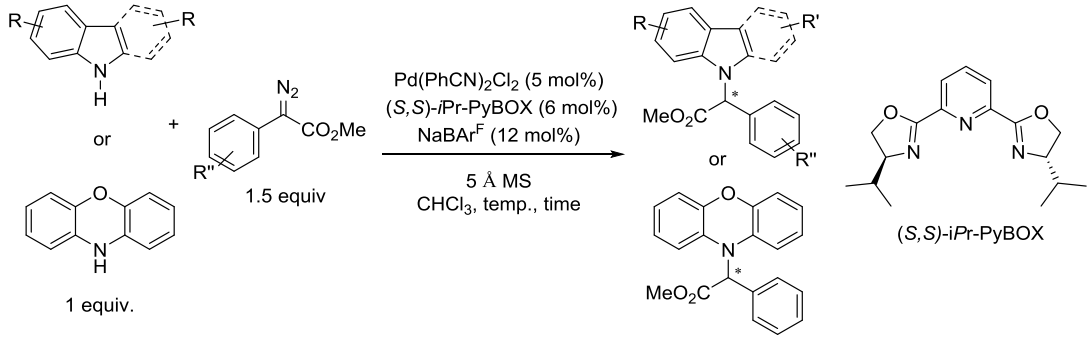
4.10f

methyl 2-diazopropanoate 4.10f: ^{1}H NMR (500 MHz; $CDCl_3$) 3.77 (3H, s), 1.97 (3H, s); ^{13}C NMR (125 MHz $CDCl_3$) δ 52.0, 8.5. Resonances from C=N_2 and C=O not observed.



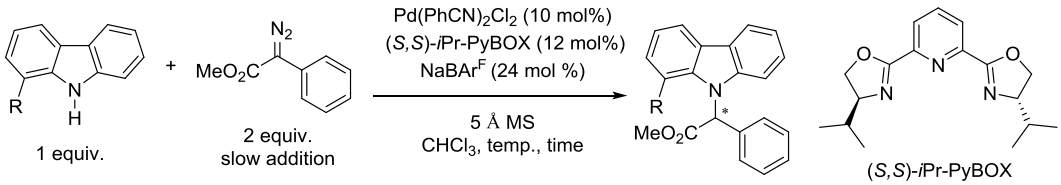
methyl 2-ethyl-3-oxobutanoate: Methyl 2-diazobutanoate was synthesized as outlined in Step 2 above, except methyl 2-ethyl-3-oxobutanoate (912 mg, 6.33 mmol, 1.0 equiv) was used instead of methyl 2-methyl-3-oxobutanoate and all other reagents scaled proportionally. The product was obtained as a yellow oil (620 mg, 76 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.76 (s, 3H), 2.36 (q, J = 7.5 Hz, 2H), 1.14 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 51.9, 16.6, 12.0. Resonances from C=N_2 and C=O not observed.

General Experimental Procedure A: Palladium-Catalyzed Insertion with *N*-Heterocycles



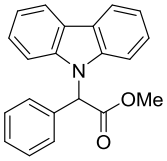
To a flame-dried round-bottom flask equipped with stirbar was added the heterocycle substrate (1 equiv), $Pd(PhCN)_2Cl_2$ (5 mol %), (*S*,*S*)-*i*Pr-PyBOX (6 mol %), $NaBAr^F$ (12 mol %), and 5 Å MS (approximately 1 g/mmol of the heterocycle). To a separate flame-dried pear-shaped flask was added the diazo substrate (1.5 equiv). Both flasks were evacuated for 10 min and backfilled with nitrogen gas. Distilled $CHCl_3$ (stored over 4 Å MS) was added to the round-bottom flask to obtain a heterocycle concentration of 200 mM. The round-bottom flask was submerged in an oil bath of specified temperature for 5 min (see Analytical Data section below for reaction temperature). The diazo substrate was dissolved in $CHCl_3$ to obtain a 750 mM solution, and this solution was transferred in one portion to the round-bottom flask. Additional $CHCl_3$ was used to rinse the pear-shaped flask and ensure complete transfer of the diazo and to achieve a final heterocycle concentration of 75 mM. The reaction was stirred until consumption of either the heterocycle or diazo as determined by TLC (see Analytical Data section for reaction time). Upon completion, the reaction flask was cooled to room temperature and diluted with $CHCl_3$. The mixture was filtered through a pad of Celite which was then washed three times with $CHCl_3$. The filtrate was concentrated and the residue purified via column chromatography. A slightly modified procedure was used for aliphatic amine substrates, please refer to the Analytical Data section.

General Experimental Procedure B: Palladium-Catalyzed Insertion with 1-Substituted Carbazoles



To a flame-dried round-bottom flask equipped with stir-bar was added the 1-substituted carbazole (1 equiv), $Pd(PhCN)_2Cl_2$ (10 mol %), (*S*,*S*)-*i*-Pr-PyBOX (12 mol %), $NaBAr^F$ (24 mol %), and 5 Å MS (approximately 1g/mmol of carbazole). To a separate flame-dried pear-shaped flask was added the diazo substrate (2 equiv). Both flasks were evacuated for 10 min, and backfilled with nitrogen gas. To the round-bottom flask was added $CHCl_3$ to obtain a 100 mM solution with respect to the carbazole substrate. The diazo substrate was dissolved in $CHCl_3$ to obtain a 300 mM solution. The round-bottom flask was submerged in an oil bath for 5 min (see Analytical Data section below for reaction temperature) and the diazo solution added over 8 hours using a syringe pump. After addition, the reaction was stirred for some additional time (see Analytical Data section) until consumption of either the 1-substituted carbazole or diazo as determined by TLC. Upon completion, the reaction mixture was cooled to room temperature and diluted with $CHCl_3$. The mixture was filtered through a pad of Celite which was then washed three times with $CHCl_3$. The filtrate was concentrated and the residue purified via column chromatography.

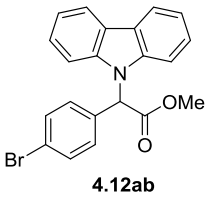
Analytical Data



4.12aa

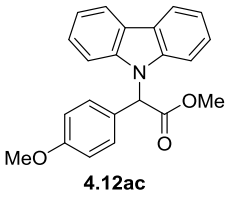
Methyl 2-(9*H*-carbazol-9-yl)-2-phenylacetate (4.12aa): Example using general procedure A. A flame-dried, 5 mL round-bottom flask equipped with stir bar was charged with 9*H*-carbazole **4.11a** (31.4 mg, 0.19 mmol, 1 equiv), $Pd(PhCN)_2Cl_2$ (3.6 mg, 0.009 mmol, 5 mol%), (*S*,*S*)-iPr-PyBOX (3.4 mg, 0.01 mmol, 6 mol%), $NaBAr^F$ (20 mg, 0.02 mmol, 12 mol%), and 5 Å MS (190 mg). To a separate flame-dried pear-shaped flask was added methyl 2-diazo-2-phenylacetate **4.10a** (49.6 mg, 0.28 mmol, 1.5 equiv). Both flasks were evacuated for 10 min and backfilled with nitrogen gas. Distilled $CHCl_3$ (1.1 mL) was added to the round-bottom flask to obtain a carbazole concentration of 200 mM. The round-bottom flask was submerged in an 30 °C oil bath for 5 min while stirring. Next, the diazo substrate was dissolved in $CHCl_3$ (0.4 mL) to obtain a 750 mM solution, and this solution was transferred in one portion to the round-bottom flask. Additional $CHCl_3$ (1.0 mL) was used to rinse the pear-shaped flask and ensure complete transfer of the diazo and to achieve a final heterocycle concentration of 75 mM. The reaction mixture was stirred for 2 h at 30 °C at which point carbazole was no longer detected by TLC. The crude product was purified by flash chromatography on silica gel (5% ether/hexanes) to obtain compound **4.12aa** as a pale beige solid (55.6 mg, 99%, 97% e*e*). R_f = 0.37 (20% ether/hexanes); The *ee* was measured utilizing the Shimadzu HPLC instrument using a chiral stationary phase [Chiralcel OD-H, 2-propanol/hexanes = 8/92, 1.0 mL/min, λ = 254 nm], t_R = 9.50 min (major), 19.04 min (minor); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (dd, *J* = 8.0, 1.2 Hz, 2H), 7.36 (td, *J* = 7.5, 7.1, 1.2 Hz, 2H), 7.34 – 7.30 (m, 3H), 7.27 – 7.26 (m, 2H), 7.25 – 7.21 (m, 4H), 6.62 (s, 1H), 3.78 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.8, 140.2, 134.0, 128.7, 128.3, 127.4, 125.8, 123.5, 120.3, 119.7,

110.1, 60.3, 52.8; IR (ATR) 3036, 2920, 2851, 1741, 1449, 1205 cm^{-1}. HRMS (ESI): m/z calculated for $C_{21}H_{17}NO_2Na$ $[M + Na]^+$ 338.1157, found 338.1144.



4.12ab

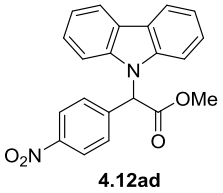
Methyl 2-(4-bromophenyl)-2-(9*H*-carbazol-9-yl)acetate (4.12ab): Using general procedure A, 9*H*-carbazole **4.11a** (95%, 21.1 mg, 0.12 mmol) was reacted with methyl 2-(4-bromophenyl)-2-diazoacetate **4.10b** (45.9 mg, 0.18 mmol) for 8 h. The crude product was purified by flash chromatography on silica gel (20% ether/hexanes) to obtain compound **4.12ab** as pale yellow solid (40.4 mg, 85%, 93% *ee*). R_f = 0.31 (20% ether/hexanes); The *ee* was measured utilizing the Shimadzu HPLC instrument using a chiral stationary phase [Chiralcel OD-H, 2-propanol/hexanes = 8/92, 1.0 mL/min, λ = 254 nm], t_R = 9.78 min (major), 19.67 min (minor); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (d, *J* = 7.7 Hz, 2H), 7.43 (d, *J* = 8.6 Hz, 2H), 7.38 (t, *J* = 7.2 Hz, 2H), 7.30 – 7.19 (m, 4H), 7.10 (d, *J* = 8.4 Hz, 2H), 6.52 (s, 1H), 3.75 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.3, 140.0, 133.0, 131.8, 129.1, 125.9, 123.6, 122.5, 120.4, 120.0, 109.9, 59.6, 52.9; IR (ATR): 3061, 2949, 1745, 1483, 1451, 1198, 1171, 996, 749, 724 cm^{-1}; HRMS (ESI): m/z calculated for $C_{21}H_{16}BrNO_2Na$ $[M + Na]^+$ 416.0262, found 416.0247.



4.12ac

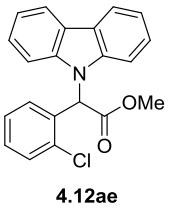
Methyl 2-(9*H*-carbazol-9-yl)-2-(4-methoxyphenyl)acetate (4.12ac): Using general procedure A, 9*H*-carbazole **4.11a** (95%, 21.1 mg, 0.12 mmol) was reacted with methyl 2-diazo-2-(4-methoxyphenyl)acetate **4.10c** (37.1 mg, 0.18 mmol) for 30 min. The crude product was purified by flash chromatography on silica gel (1st column = 15% ether/hexanes; 2nd column = 25% ether/hexanes) to obtain compound **4.12ac** as a pale orange solid (37.3 mg, 90%, 96% *ee*). R_f = 0.15 (15% ether/hexanes); R_f = 0.29 (25%

ether/hexanes); The *ee* was measured utilizing the Shimadzu HPLC instrument using a chiral stationary phase [Chiralcel OD-H, 2-propanol/hexanes = 12/88, 1.0 mL/min, λ = 254 nm], t_R = 11.45 min (major), 21.95 min (minor);^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, *J* = 7.6 Hz, 2H), 7.36 (t, *J* = 7.2 Hz, 2H), 7.30 – 7.20 (m, 4H), 7.16 (d, *J* = 8.8 Hz, 2H), 6.84 (d, *J* = 8.8 Hz, 2H), 6.57 (s, 1H), 3.78 (s, 3H), 3.76 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.1, 159.5, 140.2, 128.7, 125.9, 125.8, 123.5, 120.3, 119.7, 114.0, 110.2, 59.8, 55.3, 52.7; IR (ATR): 3010, 2951, 2837, 1743, 1612, 1598, 1512, 1450, 1175, 750, 722.7 cm^{-1}; HRMS (ESI): m/z calculated for $C_{22}H_{19}NO_3Na$ $[M + Na]^+$ 368.1263, found 368.1256.



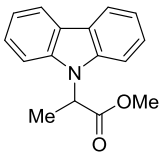
4.12ad

Methyl 2-(9*H*-carbazol-9-yl)-2-(4-nitrophenyl)acetate (4.12ad): Using general procedure A, 9*H*-carbazole **4.11a** (95%, 21.1 mg, 0.12 mmol) was reacted with methyl 2-diazo-2-(4-nitrophenyl)acetate **4.10d** (39.8 mg, 0.18 mmol) at 55 °C for 30 h. The crude product was purified by flash chromatography on silica gel using (1st column = 50% ether/hexanes; 2nd column = 70% DCM/hexanes) to obtain compound **4.12ad** as pale yellow solid (6.1 mg, 14%, 0% *ee*). R_f = 0.44 (50% ether/hexanes); R_f = 0.39 (70% DCM/hexanes); The *ee* was measured utilizing the Shimadzu HPLC instrument using a chiral stationary phase [Chiralcel OD-H, 2-propanol/hexanes = 15/85, 1.0 mL/min, λ = 254 nm], t_R = 16.91 min (equal), 24.08 min (equal);^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (t, *J* = 8.0 Hz, 4H), 7.44 – 7.35 (m, 4H), 7.29 (t, *J* = 7.5 Hz, 2H), 7.21 (d, *J* = 8.3 Hz, 2H), 6.61 (s, 1H), 3.76 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.7, 147.8, 141.1, 139.8, 128.5, 126.2, 123.8, 123.7, 120.6, 120.3, 109.6, 59.5, 53.2; IR (ATR): 3050, 2952, 1743, 1520, 1451, 1344, 1203, 750, 723 cm^{-1}; HRMS (ESI): m/z calculated for $C_{21}H_{15}N_2O_4$ $[M - H]^-$ 359.1032, found 359.1041.



4.12ae

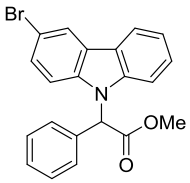
Methyl 2-(9*H*-carbazol-9-yl)-2-(2-chlorophenyl)acetate (4.12ae): Using general procedure A, 9*H*-carbazole **4.11a** (95%, 16.7 mg, 0.095 mmol) was reacted with methyl 2-(2-chlorophenyl)-2-diazoacetate **4.10e** (31.5 mg, 0.15 mmol) at 30 °C for 2.5 h. The crude product was purified by flash chromatography on silica gel (4% EtOAc/hexanes) to afford compound **4.12ae** as a clear oil (11.3 mg, 34%, 87% *ee*). R_f = 0.65 (25% EtOAc/hexanes); The *ee* was measured utilizing the Shimadzu HPLC instrument using a chiral stationary phase [Chiralcel OD-H, 2-propanol/hexanes = 1/99, 1.0 mL/min, λ = 254 nm], t_R = 22.60 min (major), 24.84 min (minor); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (d, *J* = 7.7 Hz, 2H), 7.46 (d, *J* = 8.4 Hz, 1H), 7.41 (t, *J* = 7.2 Hz, 2H), 7.34 – 7.26 (m, 5H), 7.16 – 7.11 (m, 2H), 6.77 (s, 1H), 3.76 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.7, 140.3, 134.1, 132.7, 129.9, 128.4, 127.0, 126.1, 123.5, 120.4, 120.0, 109.5, 59.1, 53.1; IR (ATR) 2923, 2852, 1746, 1451, 747 cm^{-1}; HRMS (ESI): *m/z* calculated for $C_{21}H_{16}ClNO_2Na$ $[M + Na]^+$ 372.0767, found 372.0760.



4.12af

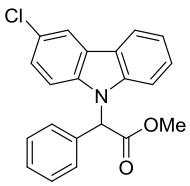
methyl 2-(9*H*-carbazol-9-yl)propanoate (4.12af): Using general procedure A, carbazole **4.11a** (25.1 mg, 0.15 mmol) was reacted with methyl 2-diazopropanoate **4.10f** (25.7 mg, 0.23 mmol) at 30 °C for 14 h. The resulting red oil was purified by flash chromatography on silica gel (10% ether/hexanes) followed by preparative thin-layer chromatography (10% acetone/hexanes) to afford methyl 2-(9H-carbazol-9-yl)propanoate as a white film (2.7 mg, 7%, 82% *ee*). R_f = 0.32 (10% acetone/hexanes); The *ee* was measured utilizing Shimadzu HPLC instrument using a chiral stationary phase [Chiralcel OD-H, 2-propanol/hexanes = 7.5/92.5, 1.0 mL/min, λ = 254 nm], t_R = 15.53 min (major), 16.82 min (minor); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (dt, *J* = 7.8, 1.0 Hz, 2H), 7.45 (ddd, *J* = 8.3, 7.1, 1.2

Hz, 2H), 7.37 (d, *J* = 8.2 Hz, 2H), 7.25 (t, *J* = 7.4 Hz, 2H), 5.43 (q, *J* = 7.3 Hz, 1H), 3.69 (s, 3H), 1.83 (d, *J* = 7.3 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.6, 139.5, 129.5, 125.8, 123.4, 120.5, 119.4, 109.1, 52.7, 52.0, 15.4; IR (ATR) 3048, 2925, 1740, 1453, 1236, 1226, 748, 722 cm^{-1}; HRMS (ESI): m/z calculated for $C_{16}H_{15}NO_2Na$ $[M + Na]^+$ 276.1000, found 276.0994.



4.12ba

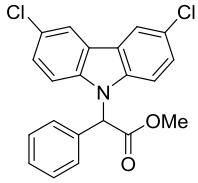
Methyl 2-(3-bromo-9*H*-carbazol-9-yl)-2-phenylacetate (4.12ba): Using general procedure A, 3-bromo-9*H*-carbazole **4.11b** (97%, 73.5 mg, 0.29 mmol) was reacted with methyl 2-diazo-2-phenylacetate **4.10a** (79.3 mg, 0.45 mmol) at 30 °C for 7 h. The crude product was purified by flash chromatography on silica gel (15% EtOAc/hexanes) to obtain compound **4.12ba** as a clear oil (81.9 mg, 71%, 99% *ee*). R_f = 0.41 (20% EtOAc/hexanes); The *ee* was measured utilizing the Shimadzu HPLC instrument using a chiral stationary phase [Chiralcel OD-H, 2-propanol/hexanes = 8/92, 1.0 mL/min, λ = 254 nm], t_R = 8.90 min (major), 13.75 min (minor); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (d, *J* = 1.9 Hz, 1H), 8.06 (d, *J* = 7.7 Hz, 1H), 7.43 – 7.39 (m, 2H), 7.35 – 7.32 (m, 3H), 7.29 – 7.26 (m, 2H), 7.21 – 7.19 (m, 2H), 7.07 (d, *J* = 8.7 Hz, 1H), 6.58 (s, 1H), 3.79 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.5, 140.6, 138.7, 133.6, 128.8, 128.5, 128.4, 127.3, 126.6, 125.4, 123.0, 122.5, 120.5, 120.2, 112.7, 112.1, 110.1, 60.4, 52.8; IR (ATR) 3056, 2950, 1745, 1444, 1270, 1201, 731 cm^{-1}; HRMS (ESI): *m/z* calculated for $C_{21}H_{16}BrNO_2Na$ $[M + Na]^+$ 416.0262, found 416.0262.



4.12ca

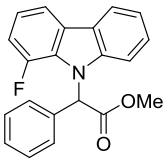
Methyl 2-(3-chloro-9*H*-carbazol-9-yl)-2-phenylacetate (4.12ca): Using general procedure A, 3-chloro-9*H*-carbazole **4.11c** (24.0 mg, 0.12 mmol) was reacted with methyl 2-diazo-2-phenylacetate **4.10a** (31.4 mg, 0.18 mmol) at 30 °C for 2 h. The crude product was purified by flash chromatography on silica gel (25% ether/hexanes) to obtain compound **4.12ca** as a clear oil (33.6 mg, 89%, 97% *ee*). R_f =

0.46 (30% ether/hexanes); The *ee* was measured utilizing the Shimadzu HPLC instrument using a chiral stationary phase [Chiralcel OD-H, 2-propanol/hexanes = 8/92, 1.0 mL/min, λ = 254 nm], t_R = 8.46 min (major), 12.35 min (minor); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 – 8.03 (m, 2H), 7.40 (t, *J* = 7.4 Hz, 1H), 7.35 – 7.25 (m, 6H), 7.21 – 7.17 (m, 2H), 7.11 (d, *J* = 8.8 Hz, 1H), 6.58 (s, 1H), 3.78 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.5, 140.8, 138.4, 133.6, 128.8, 128.5, 127.3, 126.5, 125.8, 125.3, 124.8, 122.6, 120.5, 120.1, 120.0, 111.6, 110.1, 60.4, 52.8; IR (ATR) 3063, 2924, 2951, 1745, 1473, 1446, 1201, 745 cm^{-1}; HRMS (ESI): *m/z* calculated for $C_{21}H_{16}ClNO_2Na$ $[M + Na]^+$ 372.0767, found 372.0759.



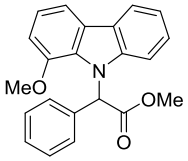
4.12da

Methyl 2-(3,6-dichloro-9*H*-carbazol-9-yl)-2-phenylacetate (4.12da): Using general procedure A, 3,6-dichloro-9*H*-carbazole **4.11d** (22.6 mg, 0.10 mmol) was reacted with methyl 2-diazo-2-phenylacetate **4.10a** (25.3 mg, 0.14 mmol) for 30 °C at 3.5 h. The crude product was purified by flash chromatography on silica gel (30% ether/hexanes) to obtain compound **4.12da** as a clear oil (32.8 mg, 89%, 95% *ee*). R_f = 0.41 (30% ether/hexanes); The *ee* was measured utilizing the Shimadzu HPLC instrument using a chiral stationary phase [Chiralcel OD-H, 2-propanol/hexanes = 2/98, 1.5 mL/min, λ = 254 nm], t_R = 9.40 min (minor),10.29 min (major); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, *J* = 2.1 Hz, 2H), 7.35 – 7.31 (m, 5H), 7.19 – 7.17 (m, 2H), 7.15 (d, *J* = 8.8 Hz, 2H), 6.54 (s, 1H), 3.80 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.3, 139.0, 133.3, 128.9, 128.7, 127.2, 126.6, 125.7, 123.8, 120.2, 111.5, 60.6, 52.9; IR (ATR) 2952, 2921, 1745, 1474, 1434, 1203, 864, 792, 734 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{21}H_{15}Cl_2NO_2Na$ $[M + Na]^+$ 406.0378, found 406.0382.



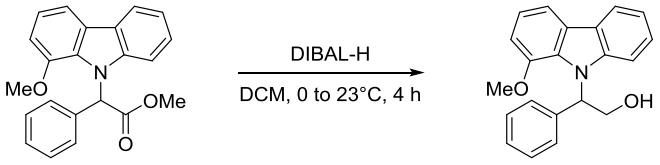
4.12ea

Methyl 2-(1-fluoro-9*H*-carbazol-9-yl)-2-phenylacetate (4.12ea): Example using general procedure B. A flame-dried, 5 mL round-bottom flask equipped with stir bar was charged with 1-fluoro-9*H*-carbazole **4.11e** (38.3 mg, 0.21 mmol, 1 equiv), $Pd(PhCN)_2Cl_2$ (7.6 mg, 0.020 mmol, 10 mol%), (*S*,*S*)-*i*Pr-PyBOX (7.2 mg, 0.024 mmol, 12 mol%), $NaBAr_F$ (42.5 mg, 0.048 mmol, 24 mol%), and 5 Å MS (196 mg). To a separate flame-dried pear-shaped flask was added methyl 2-diazo-2-phenylacetate **4.10a** (74.0 mg, 0.42 mmol, 2 equiv). Both flasks were evacuated for 10 min and backfilled with nitrogen gas. Distilled $CHCl_3$ (2.1 mL) was added to the round-bottom flask to obtain a 100 mM solution with respect to 1-fluoro-9*H*-carbazole. The diazo substrate was dissolved in $CHCl_3$ (1.4 mL) to obtain a 300 mM solution. The round-bottom flask was submerged in a 43 °C oil bath and stirred for 5 min. Then, the diazo solution was added to the reaction mixture over 8 hours via syringe pump, followed by 2.5 h additional stirring. The crude product was purified by flash chromatography on silica gel (15% ether/hexanes) to obtain compound **4.12ea** as a white solid (43.1 mg, 63%, 94% *ee*). R_f = 0.32 (15% ether/hexanes); The *ee* was measured utilizing the Shimadzu HPLC instrument using a chiral stationary phase [Chiralcel OD-H, 2-propanol/hexanes = 8/92, 1.0 mL/min, λ = 254 nm], t_R = 6.68 min (major), 9.78 min (minor);^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, *J* = 7.8 Hz, 1H), 7.92 – 7.84 (m, 1H), 7.37 – 7.26 (m, 6H), 7.26 – 7.20 (m, 3H), 7.19 (m, 3H), 3.78 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.8, 149.4 (d, *J* = 241.9 Hz), 140.3, 134.9, 128.5, 128.2, 127.9 (d, *J* = 8.0 Hz), 127.4, 127.3 (d, *J* = 4.7 Hz), 126.4, 123.7 (d, *J* = 2.0 Hz), 120.4, 120.2, 120.1 (d, *J* = 6.8 Hz), 116.1 (d, *J* = 3.4 Hz), 112.4 (d, *J* = 19.6 Hz), 111.3, 61.7 (d, *J* = 7.9 Hz), 52.8; IR (ATR): 3070, 2943, 1744, 1574, 1457, 1431, 1338, 1211, 748, 736 cm^{-1}; HRMS (ESI): m/z calculated for $C_{21}H_{16}FNO_2Na$ $[M + Na]^+$ 356.1063, found 356.1081.



4.12fa

Methyl 2-(1-methoxy-9*H*-carbazol-9-yl)-2-phenylacetate (4.12fa): Using general procedure B, 1-methoxy-9*H*-carbazole **4.11f** (700 mg, 3.55 mmol) was reacted with methyl 2-diazo-2-phenylacetate **4.10a** (1.25 g, 7.10 mmol) at 40 °C. The diazo solution was added via syringe pump over 8 h, followed by 1 h additional stirring. The crude product was purified by flash chromatography on silica gel (1st column = 30% ether/hexanes; 2nd column = 30% ether/hexanes) to obtain compound **4.12fa** as a colorless oil that solidifies upon drying *in vacuo* (529 mg, 43%). R_f = 0.31 (toluene); R_f = 0.38 (30% ether/hexanes); The *ee* was determined by analyzing the reduced product (see next paragraph). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (d, *J* = 7.8 Hz, 1H), 7.73 (d, *J* = 7.8 Hz, 1H), 7.47 (br, 1H), 7.35 – 7.23 (m, 6H), 7.21 – 7.15 (m, 2H), 7.11 (d, *J* = 8.3 Hz, 1H), 6.93 (d, *J* = 7.9 Hz, 1H), 3.86 (s, 3H), 3.71 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4, 146.7, 140.1, 135.9, 129.8, 128.3, 127.7, 127.5, 125.6, 125.3, 123.8, 120.2, 120.2, 119.6, 113.1, 111.2, 107.8, 61.5, 55.6, 52.5; IR (ATR): 3058, 2950, 2838, 1740, 1579, 1455, 1430, 1261, 1204, 1014, 735 cm^{-1}; HRMS (ESI) m/z calculated for $C_{22}H_{19}NO_3Na$ $[M + Na]^+$ 368.1263, found 368.1255.

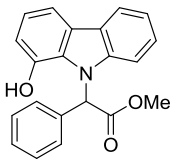


4.12fa

4.12fa-OH, 93% *ee*

Reduction of **4.12fa** to obtain **2-(1-methoxy-9*H*-carbazol-9-yl)-2-phenylethan-1-ol (4.12fa-OH)**: An oven-dried 100 mL round-bottom flask equipped with stir bar was charged with compound **4.12fa** (293 mg, 0.85 mmol, 1 equiv), evacuated, backfilled with nitrogen, and sealed with a rubber septum. Through the septum was injected dry CH_2Cl_2 (20 mL). The flask

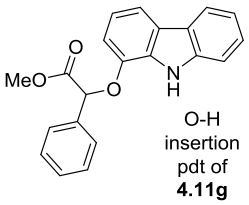
was submerged in an ice-water bath for 10 min while stirring. Through the septum was injected DIBAL-H (2.6 mL, 1 M in hexanes, 2.55 mmol, 3 equiv). The ice-water bath was allowed to warm to room temperature and the reaction stirred for 4 h. Next, the flask was cooled again for 10 min in an ice-water bath. Methanol (0.5 mL) was added dropwise to quench unreacted DIBAL-H. The reaction mixture was diluted with ether (25 mL). To the mixture was added a saturated solution of sodium potassium tartrate (5 mL) and stirred vigorously at room temperature for 2 h. The ether layer was collected. Additional ether (30 mL) was added to the aqueous layer and the mixture stirred vigorously for 15 min. The ether layers were combined and concentrated. The crude product was purified by flash chromatography on silica gel (30% EtOAc/hexanes) to obtain compound **4.12fa-OH** (246 mg, 91%, 93% *ee*). R_f = 0.41 (30% EtOAc/hexanes); The *ee* was measured utilizing the Shimadzu HPLC instrument using a chiral stationary phase [Chiralcel OD-H, 2-propanol/hexanes = 50/50, 0.5 mL/min, λ = 254 nm], t_R = 14.07 min (major), 44.20 min (minor); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, *J* = 7.9 Hz, 1H), 7.70 (d, *J* = 7.8 Hz, 1H), 7.52 – 6.67 (m, 11H), 4.62 – 4.41 (m, 2H), 3.82 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.7, 138.8, 130.7, 128.5, 127.1, 126.4, 125.3, 124.2, 120.3, 119.9, 119.3, 113.0, 112.1, 108.1, 62.9, 60.3, 55.7; IR (ATR): 3343 (br), 3054, 2932, 2835, 1576, 1454, 1427, 1328, 1259, 1217 cm^{-1}. HRMS (ESI): m/z calculated for $C_{21}H_{19}NO_2Na$ $[M + Na]^+$ 340.1313, found 340.1325.



4.12ga

Methyl 2-(1-hydroxy-9*H*-carbazol-9-yl)-2-phenylacetate (4.12ga): Using general procedure A, 9*H*-carbazol-1-ol **4.11g** (55.0 mg, 0.30 mmol) was reacted with methyl 2-diazo-2-phenylacetate **4.10a** (79.2 mg, 0.45 mmol) at 40 °C for 5 h. The crude product was purified by flash chromatography on silica gel (1st column = 30%

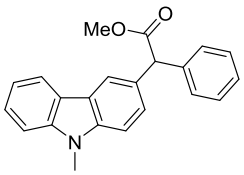
ether/hexanes; 2nd column = 50% ether/hexanes) to obtain compound **4.12ga** as a white solid (60.8 mg, 61%, 26% *ee*). R_f = 0.15 (30% ether/hexanes); R_f = 0.33 (50% ether/hexanes); The *ee* was measured utilizing the Shimadzu HPLC instrument using a chiral stationary phase [Chiralcel OD-H, 2-propanol/hexanes = 10/90, 1.0 mL/min, λ = 254 nm], t_R = 12.10 min (major), 36.38 min (minor); ^{1}H NMR (500 MHz, acetone-d_6) 9.08 (br, 1H), 8.08 (d, *J* = 7.8 Hz, 1H), 7.76 (s, 1H), 7.69 (dd, *J* = 7.8, 0.9 Hz, 1H), 7.38 (d, *J* = 7.6 Hz, 2H), 7.35 – 7.18 (m, 5H), 7.18 – 7.10 (m, 1H), 7.06 (t, *J* = 7.7 Hz, 1H), 6.96 (dd, *J* = 7.7, 0.9 Hz, 1H), 3.73 (s, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 170.9, 144.5, 141.1, 137.5, 130.1, 129.0, 128.7, 128.4, 126.5, 126.2, 124.9, 121.2, 120.9, 120.2, 113.1, 112.8, 112.4, 62.1, 52.7; IR (ATR): 3413 (br), 3057, 2951, 1722, 1585, 1455, 1338, 1268, 1215, 742 cm^{-1}; HRMS (ESI): m/z calculated for $C_{21}H_{17}NO_3Na$ $[M + Na]^+$ 354.1106, found 354.1113. The other by-product is the competitive O–H insertion product for which characterization is below.



O-H insertion pdt of **4.11g**

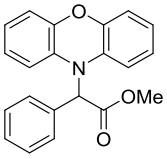
Methyl 2-((9H-carbazol-1-yl)oxy)-2-phenylacetate (O–H insertion product of **4.11g**): Using general procedure A, 9H-carbazol-1-ol **4.11g** (55.0 mg, 0.30 mmol) was reacted with methyl 2-diazo-2-phenylacetate **4.10a** (79.2 mg, 0.45 mmol) at 40 °C for 5 h. The crude product was purified by flash chromatography on silica gel (1st column = 30% ether/hexanes; 2nd column = 50% ether/hexanes) to obtain the title compound as a colorless oil (14.9 mg, 15%). R_f = 0.33 (30% ether/hexanes); R_f = 0.52 (50% ether/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.65 (br, 1H), 8.04 (d, *J* = 7.8 Hz, 1H), 7.72 (d, *J* = 7.8 Hz, 1H), 7.65 (d, *J* = 6.6 Hz, 2H), 7.54 – 7.36 (m, 5H), 7.24 – 7.17 (m, 1H), 7.08 (t, *J* = 7.8 Hz, 1H), 6.84 (d, *J* = 7.8 Hz, 1H), 5.82 (s, 1H), 3.75 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 143.3, 139.4, 135.5, 130.6, 129.2, 128.9, 127.2, 125.9, 125.0,

123.5, 120.5, 119.5, 119.4, 114.4, 111.0, 109.3, 79.7, 52.7; IR (ATR): 3414 (br), 3060, 2952, 1743, 1577, 1455, 1234, 1099, 743 cm^{-1}; HRMS (ESI): m/z calculated for $C_{21}H_{17}NO_3Na$ $[M + Na]^+$ 354.1106, found 354.1114.



4.12ha

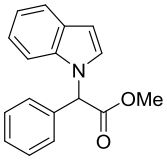
Methyl 2-(9-methyl-9*H*-carbazol-3-yl)-2-phenylacetate (4.12ha): Using general procedure A, 9-methylcarbazole **4.11h** (36.2 mg, 0.20 mmol) was reacted with methyl 2-diazo-2-phenylacetate **4.10a** (52.8 mg, 0.30 mmol) at 30 °C for 5 h. The crude product was purified by flash chromatography on silica gel (15% EtOAc/hexanes) to obtain compound **4.12ha** as a red oil (33.5 mg, 51%). R_f = 0.46 (20% EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 8.06 – 8.05 (m, 2H), 7.48 – 7.43 (m, 2H), 7.38 – 7.31 (m, 6H), 7.27 – 7.24 (m, 1H), 7.21 (t, *J* = 7.5 Hz, 1H), 5.24 (s, 1H), 3.83 (s, 3H), 3.77 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.6, 141.3, 140.2, 139.5, 129.0, 128.5, 127.1, 126.4, 125.8, 122.9, 122.6, 120.4, 120.3, 118.9, 108.6, 108.5, 57.0, 52.3, 29.1; IR (ATR) 3026, 2948, 1732, 1602, 1494, 1471, 1146, 730 cm^{-1}; HRMS (ESI): *m/z* calculated for $C_{22}H_{19}NO_2Na$ $[M + Na]^+$ 352.1313, found 352.1326.



4.13a

Methyl 2-(10*H*-phenoxazin-10-yl)-2-phenylacetate (4.13a): Using general procedure A, phenoxazine (19.8 mg, 0.11 mmol) was reacted with methyl 2-diazo-2-phenylacetate **4.10a** (28.6 mg, 0.16 mmol) at 30 °C for 15 min. The crude product was purified by flash chromatography on silica gel (10% ether/hexanes) to obtain compound **4.13a** as a white solid (36.5 mg, 81%, 94% *ee*). R_f = 0.59 (20% ether/hexanes); The *ee* was measured utilizing the Shimadzu HPLC instrument using a chiral stationary phase [Chiralcel OD-H, 2-propanol/hexanes = 2/98, 1.0 mL/min, λ = 254 nm], t_R = 7.86 min (major),

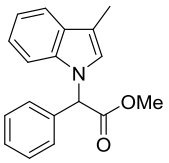
9.53 min (minor); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.1 Hz, 2H), 7.37 (t, *J* = 7.4 Hz, 2H), 7.34 – 7.31 (m, 1H), 6.79 (dd, *J* = 7.8, 1.6 Hz, 2H), 6.75 (td, *J* = 7.6, 1.5 Hz, 2H), 6.70 (td, *J* = 7.6, 1.7 Hz, 2H), 6.36 (dd, *J* = 7.9, 1.4 Hz, 2H), 5.71 (s, 1H), 3.76 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.3, 146.8, 133.8, 133.3, 128.6, 128.0, 127.7, 123.4, 122.1, 115.7, 114.2, 64.0, 52.9; IR (ATR) 3056, 2922, 1744, 1484, 1207, 1131 cm^{-1}; HRMS (ESI): *m/z* calculated for $C_{21}H_{17}NO_3Na$ $[M + Na]^+$ 354.1106, found 354.1113.



4.14aa

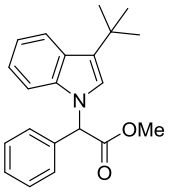
Methyl 2-(1*H*-indol-1-yl)-2-phenylacetate (4.14aa): Using general procedure A, indole **4.13a** (70.2 mg, 0.60 mmol) was reacted with methyl 2-diazo-2-phenylacetate **4.10a** (158.6 mg, 0.90 mmol). The general procedure was modified so that the reaction was halted 15 minutes after adding the diazo solution, with indole only partially reacted. The reaction mixture was immediately diluted with $CHCl_3$ (2 mL) and filtered through a pad of celite. (Longer reaction times led to products resulting from over-insertion). The crude product was purified by flash chromatography on silica gel (8% ether/hexanes) to obtain compound **4.14aa** as a colorless oil (17.4 mg, 11%, 80% *ee*). The ratio of N1-H/C2-H/C3-H insertion at 15 min was 1.0:0.8:3.0 as determined by ^{1}H NMR analysis. R_f = 0.49 (20% ether/hexanes); The *ee* was measured utilizing the Shimadzu HPLC instrument using a chiral stationary phase [Chiralcel OD-H, 2-propanol/hexanes = 3/97, 1.0 mL/min, λ = 254 nm], t_R = 11.29 min (major), 12.62 min (minor); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.63 (dt, *J* = 7.9, 0.9 Hz, 1H), 7.41 – 7.36 (m, 3H), 7.36 – 7.31 (m, 3H), 7.22 (t, *J* = 8.3 Hz, 1H), 7.16 – 7.10 (m, 2H), 6.53 (d, *J* = 3.3 Hz, 1H), 6.26 (s, 1H), 3.80 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.1, 136.4, 134.6, 129.1, 129.0, 128.8, 128.06, 126.7, 121.9, 121.2, 120.1, 109.0, 102.5, 62.0, 52.8; IR

(ATR) 3030, 952, 2923, 1745, 1457, 1310, 1197, 1168, 737 cm^{-1}; HRMS (ESI): *m/z* calculated for $C_{17}H_{15}NO_2Na$ $[M + Na]^+$ 288.1000, found 288.1013.



4.14ba

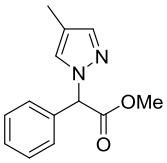
Methyl 2-(3-methyl-1*H*-indol-1-yl)-2-phenylacetate (4.14ba): Using general procedure A, 3-methylindole **4.13b** (98%, 13.4 mg, 0.1 mmol) was reacted with methyl 2-diazo-2-phenylacetate **4.10a** (26.4 mg, 0.15 mmol) at 30 °C for 1 h. The general procedure was modified slightly so that the 3-methylindole solution was stirred at 30 °C for 15 min instead of 5 min before adding the diazo solution. The crude product was purified by flash chromatography on silica gel (5% ether/hexanes) to obtain compound **4.14ba** as an off-white oil (17.5 mg, 63%, 79% *ee*). R_f = 0.35 (10% ether/hexanes); The *ee* was measured utilizing the Agilent HPLC instrument using a chiral stationary phase [Chiralpak AD, 2-propanol/hexanes = 5/95, 1.0 mL/min, λ = 254 nm], t_R = 6.38 min (major), 7.52 min (minor); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, *J* = 7.8 Hz, 1H), 7.41 – 7.36 (m, 3H), 7.34 – 7.28 (m, 3H), 7.21 (t, *J* = 7.4 Hz, 1H), 7.14 (t, *J* = 7.4 Hz, 1H), 6.88 (s, 1H), 6.21 (s, 1H), 3.79 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.3, 136.8, 134.9, 129.1, 129.0, 128.8, 128.0, 124.1, 121.9, 119.4, 119.2, 111.6, 108.8, 77.3, 77.0, 76.8, 61.7, 52.7, 9.7; IR (ATR) 3030, 2918, 1747, 1459, 1194, 1169 cm^{-1}; HRMS (ESI): *m/z* calculated for $C_{18}H_{17}NO_2Na$ $[M + Na]^+$ 302.1157, found 302.1145.



4.14da

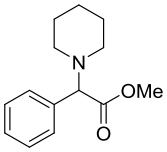
Methyl 2-(3-(tert-butyl)-1*H*-indol-1-yl)-2-phenylacetate (4.14da): Using general procedure A, 3-(*tert*-butyl)-1*H*-indole **4.14d** (20.5 mg, 0.12 mmol) was reacted with methyl 2-diazo-2-phenylacetate **4.10a** (31.3 mg, 0.18 mmol) for 4 h. The crude product was purified by flash chromatography on silica gel (10% ether/hexanes) to obtain compound **4.14da** as a white solid (33.8 mg, 89%, 79% *ee*); R_f = 0.33

(10% ether/hexanes); The *ee* was measured utilizing the Shimadzu HPLC instrument using a chiral stationary phase [Chiralcel OD-H, 2-propanol/hexanes = 0.3/99.7, 1.0 mL/min, λ = 254 nm], t_R = 14.27 min (minor), 15.54 min (major); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.0 Hz, 1H), 7.41 – 7.34 (m, 3H), 7.33 – 7.29 (m, 3H), 7.18 (t, *J* = 7.2 Hz, 1H), 7.11 (t, *J* = 7.2 Hz, 1H), 6.87 (s, 1H), 6.21 (s, 1H), 3.80 (s, 3H), 1.40 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.2, 137.6, 134.9, 129.0, 128.8, 128.0, 126.9, 126.4, 121.8, 121.6, 121.4, 119.1, 109.2, 61.8, 52.7, 31.6, 30.7; IR (ATR) 2953, 1749, 1462, 1197, 1166, 736 cm^{-1}; HRMS (ESI): m/z calculated for $C_{21}H_{22}BrNO_2Na$ $[M + Na]^+$ 344.1627, found 344.1638.



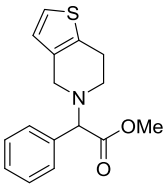
4.15a

Methyl 2-(4-methyl-1*H*-pyrazol-1-yl)-2-phenylacetate (4.15a): Using general procedure A, 4-methyl-1*H*-pyrazole (22.3 mg, 0.27 mmol) was reacted with methyl 2-diazo-2-phenylacetate **4.10a** (22.3 mg, 0.41 mmol) at 55 °C for 30 h. The crude product was purified by flash chromatography on silica gel (1st column = 20% ether/hexanes; 2nd column = 50% ether/hexanes) to obtain compound **4.15a** as a white solid (20.3 mg, 32%, 0% *ee*); R_f = 0.35 (50% ether/hexanes); The *ee* was measured utilizing the Shimadzu HPLC instrument using a chiral stationary phase [Chiralcel OD-H, 2-propanol/hexanes = 8/92, 1.0 mL/min, λ = 254 nm], t_R = 9.56 min (equal), 19.38 min (equal); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 – 7.35 (m, 6H), 7.14 (s, 1H), 6.16 (s, 1H), 3.80 (s, 3H), 2.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.7, 140.5, 134.0, 129.3, 129.2, 128.4, 127.9, 116.6, 67.8, 52.9, 890; IR (ATR) 2950, 1740, 1432, 1210, 978, 742 cm^{-1}; HRMS (ESI): m/z calculated for $C_{13}H_{14}N_2O_2Na$ $[M + Na]^+$ 253.0953, found 253.0957.



4.16a

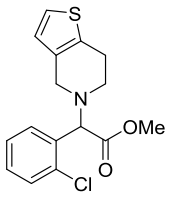
Methyl 2-phenyl-2-(piperidin-1-yl)acetate (4.16a): A flame-dried, 5 mL round-bottom flask equipped with stir bar was charged with $Pd(PhCN)_2Cl_2$ (3.3 mg, 0.009 mmol, 5 mol %), $NaBAr_F$ (18.7 mg, 0.021 mmol, 12 mol %), and 5Å MS (170 mg). To a separate flame-dried, 5 mL pear-shaped flask was added methyl 2-diazo-2-phenylacetate **4.10a** (45.7 mg, 0.26 mmol, 1.5 equiv). Both flasks were evacuated for 10 min and backfilled with nitrogen gas. Distilled $CHCl_3$ (1.1 mL) was added to the flask containing catalyst and stirred for 5 min at 30 °C. Piperidine (21 μmL, 0.21 mmol, 1 equiv) was injected into the flask via syringe. Next, $CHCl_3$ (0.3 mL) was added to the flask containing methyl 2-diazo-2-phenylacetate. Additional $CHCl_3$ (0.9 mL) was used to ensure complete transfer of the diazo substrate. The flask was stirred at 30 °C for 48 h. Then, the reaction mixture was cooled to room temperature and diluted with $CHCl_3$. The mixture was filtered through a pad of Celite and washed three times with $CHCl_3$. The filtrate was concentrated and the residue purified by flash chromatography on silica gel (10% EtOAc/hexanes) to obtain compound **4.16a** as a clear oil (16.2 mg, 40%); R_f = 0.43 (20% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, J = 7.2 Hz, 2H), 7.35 – 7.28 (m, 3H), 3.97 (s, 1H), 3.68 (s, 3H), 2.44 – 2.27 (m, 4H), 1.59 (p, J = 5.5 Hz, 4H), 1.43 (p, J = 6.2 Hz, 2H);^{13}C NMR (125 MHz, $CDCl_3$) δ 172.4, 136.1, 128.8, 128.5, 128.2, 75.0, 52.5, 52.0, 25.7, 24.3; IR (ATR) 2926, 2851, 1736, 1453, 1152, 747, 697 cm^{-1}; HRMS (ESI): *m/z* calculated for $C_{14}H_{19}NO_2Na$ $[M + Na]^+$ 256.1313, found 256.1304.



4.17a

Methyl 2-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)-2-phenylacetate (4.17a): A flame-dried, 10 mL round-bottom flask equipped with stir bar was charged with $Pd(PhCN)_2Cl_2$ (4.1 mg, 0.011 mmol, 5 mol %), (*S*,*S*)-*i*Pr-PyBOX (3.9 mg, 0.013 mmol, 6 mol %), $NaBAr_F$ (23.0 mg, 0.026 mmol, 12 mol %), and 5Å MS (200 mg). To a second

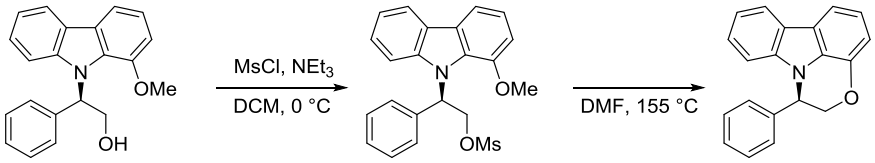
flame-dried, 5 mL pear-shaped flask was added methyl 2-diazo-2-phenylacetate **4.10a** (57.0 mg, 0.32 mmol, 1.5 equiv). To a third flame-dried, 5 mL pear-shaped flask was added 4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (30.0 mg, 0.22 mmol, 1 equiv). All three flasks were evacuated for 10 min and backfilled with nitrogen gas. Distilled $CHCl_3$ (0.9 mL) was added to the flask containing catalyst and the resulting solution stirred for 5 min at 25 °C. Next, $CHCl_3$ (0.5 mL) was added to the flask containing 4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine; the resulting solution was added via syringe to the catalyst solution. Additional $CHCl_3$ (0.5 mL) was used to ensure complete transfer of the pyridine substrate and the reaction mixture stirred for an additional 5 min at 30 °C. Finally, $CHCl_3$ (0.5 mL) was used to dissolve methyl 2-diazo-2-phenylacetate and the resulting solution transferred to the reaction mixture. Additional $CHCl_3$ (0.5 mL) was used to ensure complete transfer of the diazo substrate. The reaction was stirred at 30 °C for 18 h. The reaction mixture was cooled to room temperature, diluted with $CHCl_3$, and filtered through a pad of Celite. The pad was washed three times with $CHCl_3$. The filtrate was concentrated and the residue purified by flash chromatography on silica gel (8% EtOAc/hexanes) to obtain compound **4.17a** as a clear oil (36.8 mg, 60%). R_f = 0.57 (20% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (dd, *J* = 7.8, 1.6 Hz, 2H), 7.38 – 7.32 (m, 3H), 7.05 (d, *J* = 5.1 Hz, 1H), 6.65 (d, *J* = 5.2 Hz, 1H), 4.30 (s, 1H), 3.72 (s, 3H), 3.64 (app d, *J* = 14.3 Hz, 1H), 3.60 (app d, *J* = 14.3 Hz, 1H), 2.92 – 2.76 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.0, 135.9, 133.3, 133.2, 128.8, 128.7, 128.5, 125.2, 122.7, 72.9, 52.1, 51.0, 48.3, 25.3; IR (ATR) 2949, 2921, 2841, 1737, 1651, 1453, 1433, 1162, 732, 697 cm^{-1}; HRMS (ESI): *m/z* calculated for $C_{16}H_{17}NO_2SNa$ $[M + Na]^+$ 310.0878, found 310.0869.



4.17e

Methyl 2-(2-chlorophenyl)-2-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)acetate (4.17e) (± clopidogrel): A flame-dried, 10 mL round-bottom flask equipped with stir bar was charged with $Pd(PhCN)_2Cl_2$ (5.7 mg, 0.015 mmol, 5 mol %), (*S*,*S*)-*i*Pr-PyBOX (5.4 mg, 0.018 mmol, 6 mol %), $NaBAr_F$ (32.0 mg, 0.036 mmol, 12 mol %), and 5Å MS (300 mg). To a second flame-dried, 5 mL, pear-shaped flask was added methyl 2-(2-chlorophenyl)-2-diazoacetate **4.10a** (94.5 mg, 0.45 mmol, 1.5 equiv). To a third flame-dried, 5 mL pear-shaped flask was added 4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (42.0 mg, 0.30 mmol, 1 equiv). All three flasks were evacuated for 10 min and backfilled with nitrogen gas. Distilled $CHCl_3$ (1.2 mL) was added to the flask containing catalyst and the resulting solution stirred for 5 min at 30 °C. Next, $CHCl_3$ (0.7 mL) was added to the flask containing 4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine; the resulting solution was added via syringe to the round-bottom flask. Additional $CHCl_3$ (0.7 mL) was used to ensure complete transfer of the pyridine substrate, and the reaction mixture stirred for an additional 5 min at 25 °C. Finally, $CHCl_3$ (0.7 mL) was used to dissolve the diazo substrate and the resulting solution transferred to the reaction mixture. Additional $CHCl_3$ (0.7 mL) was used to ensure complete transfer of the diazo substrate.The reaction was stirred at 30 °C for 15 h. The reaction mixture was cooled to room temperature, diluted with $CHCl_3$, and filtered through a pad of Celite pad. The pad was washed three times with $CHCl_3$. The filtrate was concentrated and the residue purified by flash chromatography on silica gel (15% ether/hexanes) to obtain compound **4.17e** as a pale yellow oil (76.6 mg, 79%). R_f = 0.40 (20% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (dd, *J* = 7.4, 2.2 Hz, 1H), 7.41 (dd, *J* = 7.4, 1.9 Hz, 1H), 7.32 – 7.26 (m, 2H), 7.06 (d, *J* = 5.2 Hz, 1H), 6.67 (d, *J* = 5.1 Hz, 1H), 4.92 (s, 1H), 3.76 (d, *J* = 14.3 Hz, 1H), 3.63 (d, *J* = 14.2 Hz, 1H), 2.88 (s, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.3, 134.7, 133.8, 133.29, 133.26, 130.0,

129.8, 129.4, 127.2, 125.2, 122.7, 67.9, 52.2, 50.7, 48.3, 25.5; IR (ATR) 2951, 2921, 2844, 1738, 1433, 1164, 752 cm^{-1}; HRMS (ESI): *m/z* calculated for $C_{16}H_{16}ClNO_2SNa$ $[M + Na]^+$ 344.0488, found 344.0472.



4.12fa-OH 92% ee **4.12fa-OMS** **4.18** 92% ee

2-(1-methoxy-9*H*-carbazol-9-yl)-2-phenylethan-1-ol (4.12fa-OMS) was prepared from the **4.12fa-OH** by adapting reaction conditions from a patented procedure.[25] A solution of **2-(1-methoxy-9*H*-carbazol-9-yl)-2-phenylethan-1-ol 4.12fa-OH** (20 mg, 0.06 mmol, 1.0 equiv) in DCM (1.1 mL) was treated with NEt_3 (17.5 μL, 0.13 mmol, 2 equiv) at 0 °C. Mesyl chloride (7.3 μL, 0.09 mmol, 1.5 equiv) was then added and the resulting solution was stirred for 20 min at 0 °C. The reaction was quenched with saturated sodium bicarbonate aqueous solution (2 mL). The resulting mixture was extracted with DCM (3 × 10 mL) and the combined organic layers were dried with Na_2SO_4. The organic layer was concentrated and purified by flash chromatography on silica gel (20% EtOAc/hexanes) to afford 2-(1-methoxy-9H-carbazol-9-yl)-2-phenylethyl methanesulfonate **4.12fa-OMS** as a white solid (24 mg, 95%). R_f = 0.22 (toluene); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.05 (d, *J* = 7.8 Hz, 1H), 7.72 (d, *J* = 7.8 Hz, 1H), 7.43 – 7.25 (br m, 6H), 7.20 (t, *J* = 7.8 Hz, 3H), 7.11 – 6.61 (br s, 2H), 5.52 – 4.91 (br m, 2H), 3.94 (br s, 3H), 2.31 (br s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 146.7, 137.1, 130.4, 128.80 127.7, 126.3, 125.6, 120.5, 119.7, 113.0, 112.3, 108.2, 68.6, 57.1, 55.7, 37.0; IR (ATR) 3029, 2634, 1453, 1428, 1356, 1329, 1260, 1218, 1172 cm^{-1}; HRMS (ESI): *m/z* calculated for $C_{22}H_{21}NO_4SNa$ $[M + Na]^+$ 418.1089, found 418.1092.

1-phenyl-1,2-dihydro-[1,4]oxazino[2,3,4-jk]carbazole (4.18): Compound **4.18** was synthesized by heating **4.12fa-OMS** (12.1 mg, 0.031 mmol, 1 equiv) at 155 °C in DMF (0.5 mL) for 8 h. After 8 h, the reaction was allowed to cool to room temperature then diluted with de-ionized H_2O (1 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with H_2O (3 × 10 mL) and dried with Na_2SO_4. The resulting organic layers were concentrated and purified using preparative layer chromatography (5% EtOAc/Hexanes) to afford compound **4.18** as a pale white film (6 mg, 67%, 92% *ee*). R_f = 0.58 (30% EtOAc/Hexanes). The *ee* was measured utilizing the Shimadzu HPLC instrument using a chiral stationary phase [Chiralcel OD-H, 2-propanol/hexanes = 5/95, 1.0 mL/min, λ = 254 nm], t_R = 8.57 min (major), 14.94 min (minor); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.09 (dt, *J* = 7.7, 0.9 Hz, 1H), 7.70 (dd, *J* = 7.9, 0.7 Hz, 1H), 7.38 – 7.31 (m, 3H), 7.24 – 7.20 (m, 1H), 7.20 – 7.17 (m, 3H), 7.15 (d, *J* = 7.8 Hz, 1H), 6.98 (dd, *J* = 7.8, 0.7 Hz, 1H), 6.80 (dd, *J* = 8.0, 1.0 Hz, 1H), 5.51 (dd, *J* = 5.5, 3.4 Hz, 1H), 4.63 (dd, *J* = 11.3, 3.4 Hz, 1H), 4.52 (dd, *J* = 11.3, 5.5 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 142.6, 139.2, 136.9, 129.0, 128.9, 128.6, 127.1, 125.5, 123.9, 122.8, 121.2, 119.9, 119.4, 113.4, 110.3, 109.8, 71.8, 56.6; IR (ATR) 3057, 2920, 1636, 1587, 1500, 1450, 1234, 742 cm^{-1}; HRMS (ESI): *m/z* calculated for $C_{20}H_{15}NOH$ [M + H] 286.1232, found 286.1227.

Alternative route to 1-phenyl-1,2-dihydro-[1,4]oxazino[2,3,4-*jk*]carbazole (4.18) from 4.12fa-OH:

A flame-dried 5 mL, single-necked, round-bottom flask equipped with a rubber septum and magnetic stir bar was charged with 2-(1-methoxy-9*H*-carbazol-9-yl)-2-phenylethan-1-ol **4.12fa-OH** (20.0 mg, 0.06 mmol). The flask was purged and backfilled with nitrogen three times, charged with dry DCM (0.5 mL), cooled to –78 °C in a dry ice/acetone bath, and charged with pyridine (12 μL, 0.07 mmol) while stirring. After 10 min, Tf_2O (5.6 μL, 0.07 mmol) was added

via syringe. The reaction mixture was stirred at –78 °C for 45 min and then allowed to warm to room temperature over 1 h. Half-saturated aqueous ammonium chloride (5 mL) was then added, and the resulting mixture was extracted with DCM (3 × 5 mL). The combined organic layers were washed with brine (1 × 25 mL), dried over Na_2SO_4, and concentrated *in vacuo* to afford a yellow oil. The oil was purified by flash chromatography on silica gel (3% EtOAc/hexanes) to afford compound **4.18** as a pale white film (7.7 mg, 43%, 93% *ee*).

Experimental References

1 A. B. Pangborn, M. A. Giardello, R. H. Grubbs, R. K. Rosen, F. J. Timmers, *Organometallics* **1996**, *15*, 1518.

2 W. L. F. Armarego, C. L. L. Chai, *Purification of Laboratory Chemicals*; Elsevier, 2013.

3 J. Chen, X. Xiong, Z. Chen, J. Huang, *Syn. Lett.* **2015**, *26*, 2831.

4 a) S. M. Bonesi, R. Erra-Balsells, *J. Heterocyclic Chem.* **1997**, *34*, 877; b) S. M. Bonesi, M. A. Ponce, R. Erra-Balsells *J. Heterocyclic Chem.* **2005**, *42*, 867.

5 F. L. Allen, H. Suschitzky, *J. Chem. Soc.* **1953**, 3845.

6 C. Jing, H. Yongzhou, *Synth. Commun.* **2006**, *36*, 1485.

7 G. Balasubramanian, L. A. Gharat, A. D. Lakdawala, R. R. Anupindi. Novel Tricyclic Compounds Useful for the Treatment of Inflammatory and Allergic Disorders: Process for Their Preparation and Pharmaceutical Compositions Containing Them. WO/2004/037805 A1, May 6, **2004**.

8 T. Martin, C. J. Moody, *J. Chem. Soc. Perkin Trans. 1* **1988**, 235.

9 L. Ackermann, A. Althammer, P. Mayer, *Synthesis* 2009, *20*, 3493; b) L. Ackermann, A. Althammer, *Angew. Chem. Int. Ed.* **2007**, *46*, 1627.

10 A. Eastabrook, C. Wang, E. Davison, J. Sperry, *J. Org. Chem.* **2015**, *80*, 1006.

11 D. W. Robbins, T. A. Boebel, J. F. Hartwig, *J. Am. Chem. Soc.* **2010**, *132*, 4068.

12 T. Martin, C. J. Moody, *J. Chem. Soc., Perkin Trans. 1* **1988**, 235.

13 A. J. Rebecca, A. A Kudzovi, G. K Matthew, G. G. Stuart, H. S. Andrew, P. J. Hoogestraat, J. W. Dennis, Jr., S. D. Lynn. CB1 Modulator Compounds. WO/2005/066126 (A1), **2005**.

14 H. M. Davies, S. Chennamadhavuni, T. J. Martin, S. R. Childers. Cyclopropyl Derivatives and Methods of Use. WO/2012/145234, **2012**.

15 E. Yayama, S. Saito, *Synlett* **2015**, *26*, 1880.

16 W.-W. Chan, S.-H. Yeung, Z. Zhou, A. S. C. Chan, W.-Y. Yu, *Org. Lett.* **2010**, *12*, 604.

17 L. Gao, B. Kang, D. Ryu, *J. Am. Chem. Soc*. **2013**, *135*, 14556.

18 M. Lee, D. Kim, *Bioorg. Med. Chem*. **2002**, *10*, 913.

19 H. E. Bartrum, D. C. Blakemore, C. J. Moody, C. J. Hayes, C.J. *Chem. Eur. J.*, **2011**, *17*, 9586.

20 J. A. Morales-Sernaa, A. Veraa, E. Paleoa, E. García-Ríosa, R. Gaviñoa, G. García de la Morab, J. Cárdenas, *Synthesis* **2010**, *24*, 4261.

21 S. Muthusamy, M. Sivaguru, *Org. Lett.* **2014**, *16*, 4248.

[22] W.-W. Chan, S.-H. Yeung, Z. Zhou, A. S. C. Chan, W.-Y. Yu, *Org. Lett.* **2010**, *12*, 604.
[23] C.-L. K. Lee, T.-P. Loh, *Org. Lett.* **2005**, *7*, 2965.
[24] X. L. Xie, S. F. Zhu, J. X. Guo, Y. Cai, Q. L. Zhou, *Angew. Chem. Int. Ed.* **2014**, *53*, 2978; *Angew. Chem.* **2014**, *126*, 3022.
[25] L. Li, C. Beaulieu, D. Guay, C. Sturino, Z. Wang. Fluoro-Methanesulfonyl-Substituted Cycloalkanoindoles and their use as Prostaglandin d2 Antagonists. WO/2004/103970 (A1), May 18, **2004**.

Chapter 5: Using Machine Learning to Help Identify Unknown Side-Products in Organic Reactions with the Reaction Predictor System

Introduction

The ability to accurately predict the outcome of chemical reactions has been sought after since the beginnings of modern synthetic organic chemistry. The complex interplay of factors which determine reactivity (molecular orbitals, Coulombic interactions, sterics, solvation, concentration, and temperature) makes this problem seemingly intractable. Synthetic organic chemists rely on their understanding of frontier molecular orbital theory along with knowledge of the reaction conditions to simplify the problem and decide the most likely outcome of a reaction. Chemical reactions can generate mixtures of products because the starting materials can react in various combinations and often contain multiple sites of reactivity. Chemical analysis of a crude reaction mixture can sometimes reveal the identity of desired products, however unknown side-products are usually left uncharacterized because they stem from vast and/or unexpected patterns of reactivity. A system is needed that can match analytical data with the potential products resulting from the reaction of user inputted starting materials.

The advent of computers in the middle part of the previous century gave hope to scientists that computer algorithms could be designed which accurately and reliably predict the most likely products of a reaction along with every conceivable side-product. Computational chemists have developed robust methods for approximating the potential energy surface of a chemical reaction and this insight has revolutionized our understanding of chemistry. Unfortunately, due to the complexity of the underlying wave functions used to describe chemical systems, electronic structure calculations require intense computing power and exhibit poor turnover.[1] Typically the user has to restrict reactants to an geometrical approximation of a

desired transition state in order to identify a precise transition state geometry as opposed to seemingly random chemical events. In order to avoid the pitfalls inherent to identification of transition states with electronic structure calculations, predictive systems based on empirical rules have been developed. These systems attempt to codify the knowledge of human experts into a list of rules which govern the making and breaking of bonds under specified reaction conditions. This approach offers faster results and less computational cost compared to quantum mechanical based reaction prediction systems. However, rules-based systems for prediction of reaction outcomes are extremely difficult to scale requiring the curation of new rules by human experts. In addition, a rules-based system is limited by what the user already knows i.e., it will never be able to predict a novel elementary reaction step because no such reaction has been encoded into the system.

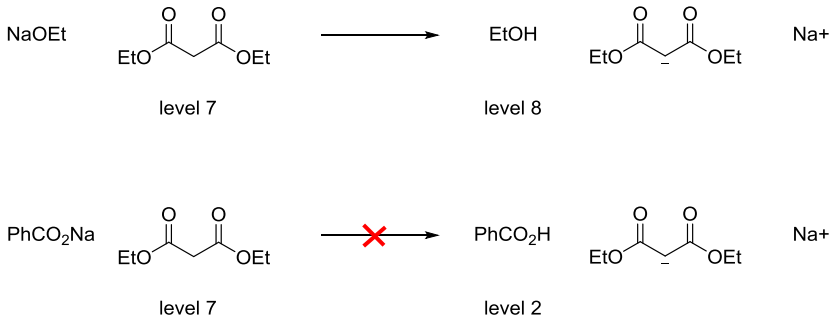
This chapter summarizes a select number of software systems which have been developed for the prediction of chemical reactions. In addition, the development of a unique machine-learning based chemical reaction prediction algorithm called Reaction Predictor and its use in helping identify unknown side-products from organic reactions will be described.

Rules-Based Reaction Prediction Systems

Programs which rely on a set of heuristics gleaned from experts in order to predict a reaction outcome are defined as knowledge-based systems. Many such programs have been developed for the prediction of mammalian metabolism and environmental degradation of pollutants.[2] One of the earliest attempts at designing a system which could accurately predict the outcome of synthetic organic reactions was CAMEO (Computer-Assisted Mechanistic Evaluation of Organic Reactions) developed by Jorgenson and co-workers from 1980 to 1995.[3] CAMEO is a suite of six mechanism-based computer modules designed to predict the outcomes

of chemical reactions: a basic/nucleophilic module, an acidic/electrophilic module, a pericyclic module, oxidation-reduction module, free radical module, and carbene module. Some modules, such as the pericyclic module and the basic/nucleophilic module, were based on elementary single-step reactions. For example, the base-catalyzed module considers any carbon-heteroatom bond or carbon-carbon multiple bond as a functional group (Figure 5-1). Functional groups were grouped into different acidity levels depending on the pK_a of the protons they contain. The base-catalyzed module would only predict proton transfers if the conjugate acid was in a lower acidity level. Interactions between nucleophiles and electrophiles worked in a similar way. The base-catalyzed module would only predict a bond forming event between nucleophile and electrophile if the conjugate acid of the nucleophile was no more than one acidity level below the conjugate acid of the leaving group. Other modules, such as the oxidation-reduction module, were based on multi-step processes. The user had to specify the chemical reactivity module they wanted to utilize in order to predict the outcome of the desired reaction. Development of CAMEO was discontinued in 1995.

Figure 5-1: Reaction Prediction Based on Acidity Levels in CAMEO



A similar system called EROS (Elaboration of Reactions for Organic Synthesis) was reported by Gasteiger and co-workers in 1987.[4] EROS was a knowledge-based system which simulated chemical reactions. Given the chemical structures of starting materials and the reaction conditions (biochemical, synthetic, concentrations, etc) EROS could generate a list of plausible

product structures. EROS employed a set of user-defined rules for chemical reactions as well as kinetic and thermodynamic information for reaction modeling. The user could apply the system to sequential reactions in order to generate a tree list of intermediates and products. Like other knowledge-based systems, the predictive power of EROS was limited to what had been entered into its knowledge base by the users.

The degradation of small molecule therapeutics is of vital interest to pharmaceutical companies and regulatory agencies alike. The International Conference on Harmonization of technical requirements for registration of pharmaceuticals for human use (ICH) puts forth guidelines for stability testing of new drug substances and products.[5] The results of these stability studies inform scientists on the degradation profile, safety, and analytical methods required for characterization of a new drug substance. A reaction prediction system called DELPHI (Degradant Expert Leading to Pharmaceutical Insight) was developed by Pole and co-workers at Pfizer in order to predict the most likely degradation products of a drug substance.[6] DELPHI used a set of expert rules for functional group transformations. DELPHI was able to rank the intrinsic reactivity of functional groups and reactions between functional groups. Although DELPHI was not designed to think in terms of elementary reaction steps, it could predict some of the detectable intermediates in the degradation pathway as well as the end products. Development of DELPHI was discontinued at Pfizer in 2012 however, private development of a system based on DELPHI, now called Zeneth, is still taking place.[7]

Zeneth is a reaction prediction platform designed for predicting potential degradation products of small molecule pharmaceuticals. The system utilizes a knowledge base populated with known degradation pathways. Users must input new rules in order to expand the knowledge base. The knowledge base scientist must assign a likelihood of a reaction occurring under

various conditions. The reasoning engine generates a list of likely products based on reaction conditions and the similarity of the starting material to a known compound in the knowledge base. Features include reactive site prediction and a description of relative likelihood of product generation. The user must specify what kind of chemical degradation the drug will be subjected to. The degradation types are modeled on the experimental guidelines set worth by the ICH and predict a compounds vulnerability to oxidative, hydrolytic, thermal, and photochemical stress. 27 drug compounds containing a wide array of functional groups were entered into the Zeneth system in order to predict their degradation products. Parameters were chosen so that each compound would be subjected to each forced degradation condition. Zeneth was able to predict the chemical structures of 104 out of 191 (54%) experimentally observed degradation products. Possible reasons for the failed structural assignments included: (1) the relevant transformation has not been entered into the reaction library; (2) the system was not able to correctly identify a relvant functional group due to unique substitution; (3) the predicated likelihood of a transformation occurring was judged to low by the Zeneth reasoning engine; (4) the degradation pathway requires too many steps to reach the product and the system truncated the search before it could be reached; (5) there were too many predicted branches on the search tree and the system truncated the results.

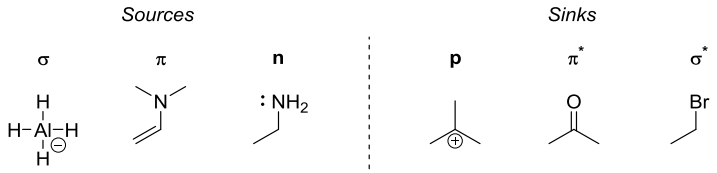
The problems encountered with the Zeneth system represent the major issues hampering knowledge-based reaction prediction systems. Transformations which are not encoded into the library of the system will never be proposed. Machine learning at the level of elementary mechanistic reaction steps offers a unique solution to many of these problems.

Machine Learning Based Reaction Prediction Systems

Machine learning is ubiquitous in today's society. From facial recognition to self-driving automobiles, machine learning is inserting itself into the everyday lives of citizens. Surprisingly, one of the earliest implementations of machine-learning was a program developed in the late 1960s which attempted to predict the outcomes of unimolecular fragmentation reactions in EI mass spectrometry.[8] The DENDRAL system consisted of two programs: Heuristic DENDRAL and Meta DENDRAL. Heuristic DENDRAL would accept an input molecular mass and construct a list of possible structures based on atomic masses and rules for chemical bonding. Meta DENDRAL was a machine learning system that could be trained with EI mass spectra. It generated rules for gas-phase unimolecular fragmentation reactions in EI mass spectrometry. Together, the components of the DENDRAL system were designed to deduce the structure of a molecular ion in an EI mass spectrum of an unknown compound. A user could enter additional structural constraints to reduce the number of matching structures.

Recently, a plethora of machine-learning based reaction prediction systems have been reported.[9] The majority of these systems only consider the overall transformation and attempt to match the reaction to a similar example present in their training set. In 2011 Baldi and co-workers reported Reaction Predictor, a machine learning based reaction prediction system which takes a mechanistic approach towards predicting the outcome of organic reactions.[10] The system treats all bond forming and bond breaking events as interactions between sources and sinks. These sources and sinks are based on the six canonical filled and unfilled orbitals of frontier molecular orbital theory (HOMO/LUMO interactions) (Figure 5-2).

Figure 5-2: Sources and Sinks Used in Reaction Predictor



The user interacts in one of two different modes: Single Step mode and Pathway mode (for predicting multi-step mechanisms). In Single Step mode the flow of the system can be broken up into five stages (Figure 5-3): (i) the user inputs the reactants and conditions; (ii) Reaction Predictor identifies every possible source and sink present among the reactants; (iii) algorithms rank the most plausible sources and sinks found in the reactants based on similarity to reactions entered in the training set; (iv) the system generates reactions by combining the selected sources and sinks; and finally (e) algorithms rank the pairwise source-sink interactions generated in the previous step. This approach mirrors reactive site prediction present in rules-based reaction prediction programs such as BEPPE, SOPHIA, and ROBIA.[11]

Figure 5-3: Reaction Prediction Framework

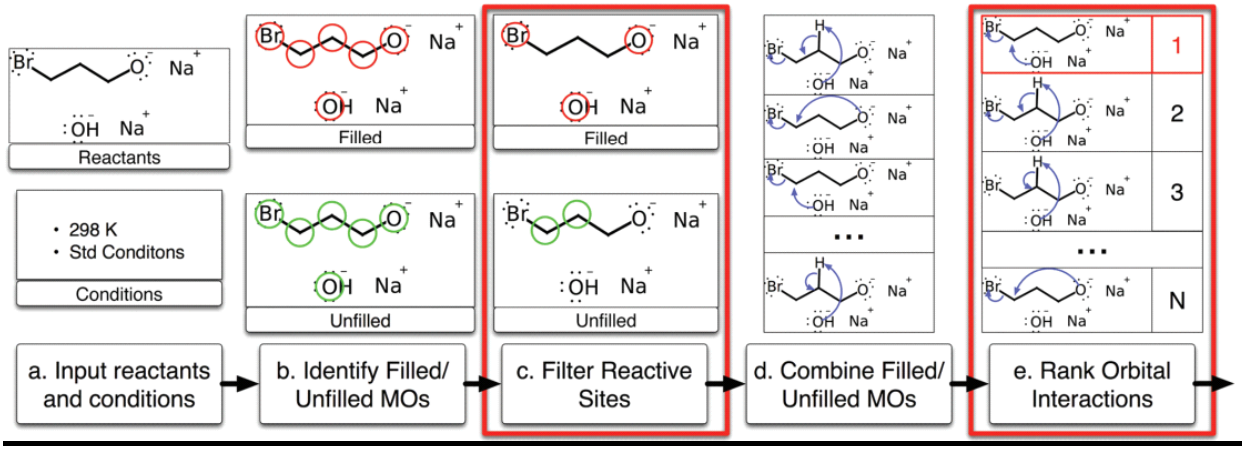
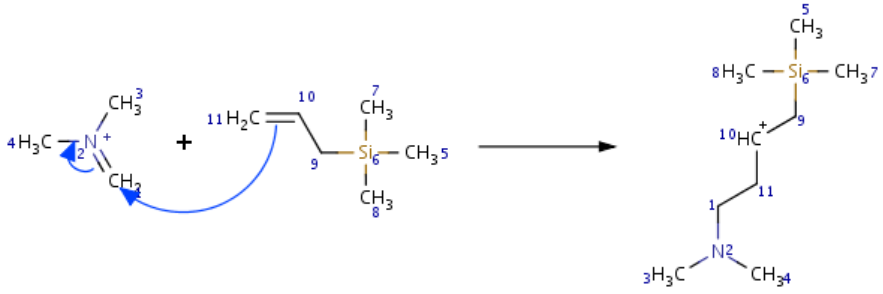


Figure taken from Kayala, M. et al. *J. Chem. Inf. Model.* **2011**, *51*, 2209

Machine learning is used to train both the source/sink prediction and the ranking of source-sink combinations. Reaction Predictor "learns" from the reactions in a carefully curated training set. Expansion of the training set is non-trivial because there is no existing database of

elementary reaction steps, each training reaction must be encoded into a text-based format called SMIRKS.[12] SMIRKS is based on the widely used SMILES (Simplified Molecular Input Line Entry System) system for representing complex molecular structures in text format. SMIRKS is used to represent chemical transformations between reactants and products and allows for atom mapping and arrow-pushing mechanisms (Figure 5-4). The last line of the SMIRKS string pictured below indicates the flow of electrons i.e., the π electrons between atoms 10 and 11 are attacking π* of the imine bond which contains atoms 1 and 2. In addition, the lexicon of the final line (10,11=1,11), designates the new bond will form between atoms 11 and 1. The semicolon located in the middle of the line (10,11=1,11;1,2=2) allows the system to concatenate electron flow arrows, essential in most arrow pushing mechanisms. This line of code also indicates that the electrons will ultimately end on nitrogen atom 2. The information contained in the arrow pushing code is how reaction predictor identifies reactive sites on molecules (sources and sinks). The more related examples of a source type or sink type in the training set, the better the system becomes at predicting those reactive sites in a user query.

Figure 5-4: Translation of a Lewis Structure Based Arrow-Pushing Mechanism into a SMIRK String



[CH3:3][N+:2](=[CH2:1])[CH3:4].[CH3:5][Si:6]([CH3:7])([CH3:8])[CH2:9][CH:10]=[CH2:11]
>>[CH3:3][N:2]([CH3:4])[CH2:1][CH2:11][CH+:10][CH2:9][Si:6]([CH3:5])([CH3:7])[CH3:8]
10,11=1,11;1,2=2

Our lab began collaborating with the Baldi group in 2015 in order to further develop Reaction Predictor. Since we began our partnership we have added over 10,000 novel reactions

to the training set related to modern synthetic organic chemistry. Included in the expansion were reactions dealing with palladium catalysis, a first for the system. In addition to expanding the training set we have also been optimizing the system to match unknown peaks in crude ESI mass spectra to molecular structures. The capability to match peaks in crude ESI spectra to plausible products generated by Reaction Predictor should greatly enhance the rate of reaction discovery and optimization in our laboratory.

Results and Discussion

Given a set of reactants and conditions, Reaction Predictor must consistently rank the most likely reactions at the top of the list of plausible reactions generated in order to realize its full potential. The biggest obstacle preventing this is the system's failure to identify relevant sources and sinks while filtering reactive sites. Reaction Predictor utilizes an inductive machine learning algorithm to select reactive sites as well as rank their combinations thus; expanding the number of diverse reactions included in the training set should increase its predictive capability.

Expanding the Training Set

The initial training set for Reaction Predictor was taken from an on-line tutorial system called Reaction Explorer (a rules based reaction prediction system developed by the Baldi group prior to Reaction Predictor).[13] The original training data set only included reactions covered in a sophomore organic chemistry course - rudimentary reactants with few combinations of functional groups –and included separate training sets for polar reactions, radical reactions, and pericyclic reactions (with two sets of sources and two sets of sinks). The system worked reasonably well with reactants of low complexity but performance was poor for complex substrates and reactions involving second and third row atoms. The system was not set up to

handle main group organometallics. We set out to address these limitations and turn Reaction Predictor into a valuable research tool.

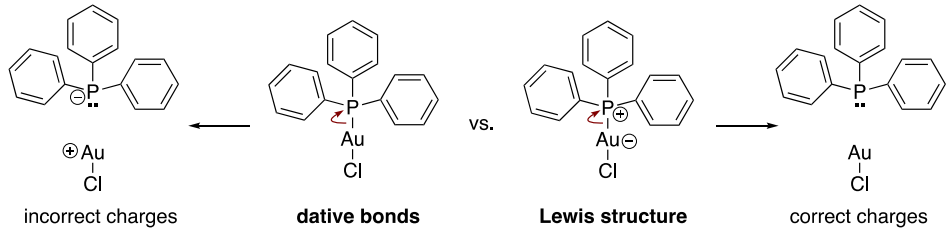
The original training set of 5,686 SMIRKS-encoded reactions overemphasized certain reactions such as S_N2 and electrophilic aromatic substituion. Professor Van Vranken culled 884 implausible, improbable, redundant, and anti-pedagogical reactions from the initial training set. We added 5,300 new training reactions representing a broad spectrum of modern synthetic organic chemistry, but mostly focused on polar reactions, bringing up the size of the training set to 10,050 reactions. More recently, we have written Python scripts capable of generating over a million combinatorial variants of common reaction types.

Reaction Predictor was not initially trained with reactions involving transition metal catalysis. Transition metal catalyzed reactions, particularly those involving palladium, are ubiquitous in modern synthetic organic chemistry. To that end, we authored 879 new SMIRKS covering a wide array of elementary reactions common among the transition metals. Included in these were SMIRKS describing association/disassociation, oxidative addition, carbopalladation, aminopalladation, oxypalladation, transmetallation, reductive elimination, β-hydride elimination, and most importantly to the interests of our group, palladium carbene formation and migratory insertion.

Chemists typically depict bonds between transition metals and ligands using dative bonds. Dative bonds are a useful alternative to the corresponding Lewis structure representations as ylides when dealing with organometallics because dative bonds reduce the number of formal charges. For example, in a Lewis structure representation of (Ph3P)AuCl, the phosphorus atom would have a formal charge of +1 and the gold atom would have a formal charge of -1. Unfortunately, arrow-pushing leads to incorrect formal charges when applied to dative bonds.

We used Lewis structure representations when writing SMIRKS reactions of transition metals so that arrow-pushing would give the correct formal charges (Figure 5-5).

Figure 5-5: Depiction of Metal-Ligand Bonding in Novel SMIRKS



Before training the Reaction Predictor for transition metal mediated processes, it was necessary to improve the predictive ability for polar organic reactions including those involving second and third row atoms. Once optimized the system will be trained on the 879 transition metal SMIRKS we have written.

We have developed a set of 52 complex diagnostic chemical transformations in order to test the predictive performance of the systems single-step feature. These reactions were taken from the literature and represent most of the HOMO/LUMO (source/sink) interactions encountered in polar organic reaction mechanisms. Every iteration of a source (σ bond, π bond, or lone pair) attacking a sink (empty p orbital, π*, σ*) is represented in this diagnostic set. Some interactions are over-represented such as reactions where π serves as a source or π* serves as sink. Reaction Predictor will not be trained with these diagnostic test reactions; instead they will be used to gauge the ability of the system to accurately predict sources and sinks and ranking source-sink pairings.

Using Pathway Search to Help Identify Unknowns in Chemical Reactions

Our main interest in Reaction Predictor is using it to help identify unknown side products generated in the reactions run by our group. Electrospray ionization (ESI) mass spectrometry allows us to gain a qualitative understanding of the products being generated in our crude reaction mixtures. Entering in peaks from ESI spectra as targets in Reaction Predictor's pathway search feature generates a list of plausible products, as well as pathways to reach those products from the starting materials (Table 5-1).[14] Previous versions of pathway search only accepted structures as targets for the search. Changing the target parameter to accept masses instructs the system to perform a tree-like search of possible reaction pathways that lead to a product that matches the target mass.

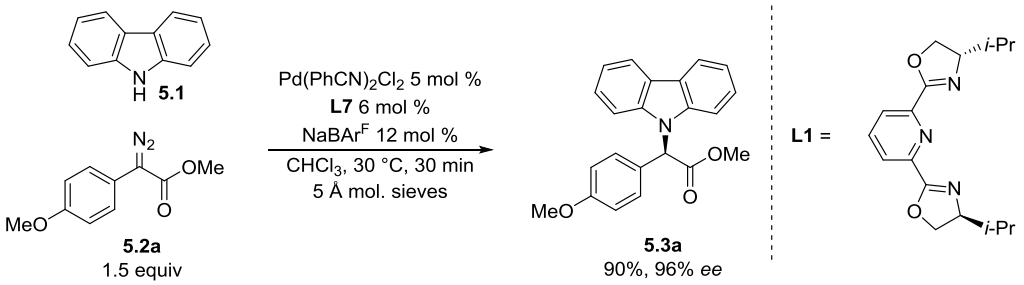
Table 5-1: Description of Parameters Used in Pathway Search Mode

Search Parameter	Description
Reactants	SMILES representation of starting materials
Target	Molecular weight of unknown from ESI
Minimum Score	Minimum score for a reaction to be considered
Search Depth	Maximum depth for search tree
Branching Factor	Maximum number of results considered for each step (top N)

We are primarily interested in the chemistry of palladium carbenes. Although Reaction Predictor is not currently capable of handling most organometallic chemistry, we decided to use the system to help us identify side-products in the palladium-catalyzed enantioselective N-H insertion reaction described in chapter 4.[15] We anticipated that Reaction Predictor may still generate some plausible structures via non-palladium mediated mechanisms. Reaction of

carbazole **5.1** with α-aryl-α-diazoester **5.2a** afforded the desired N-H insertion product **5.3a** in 90% yield and 96% *ee* (Figure 5-6).

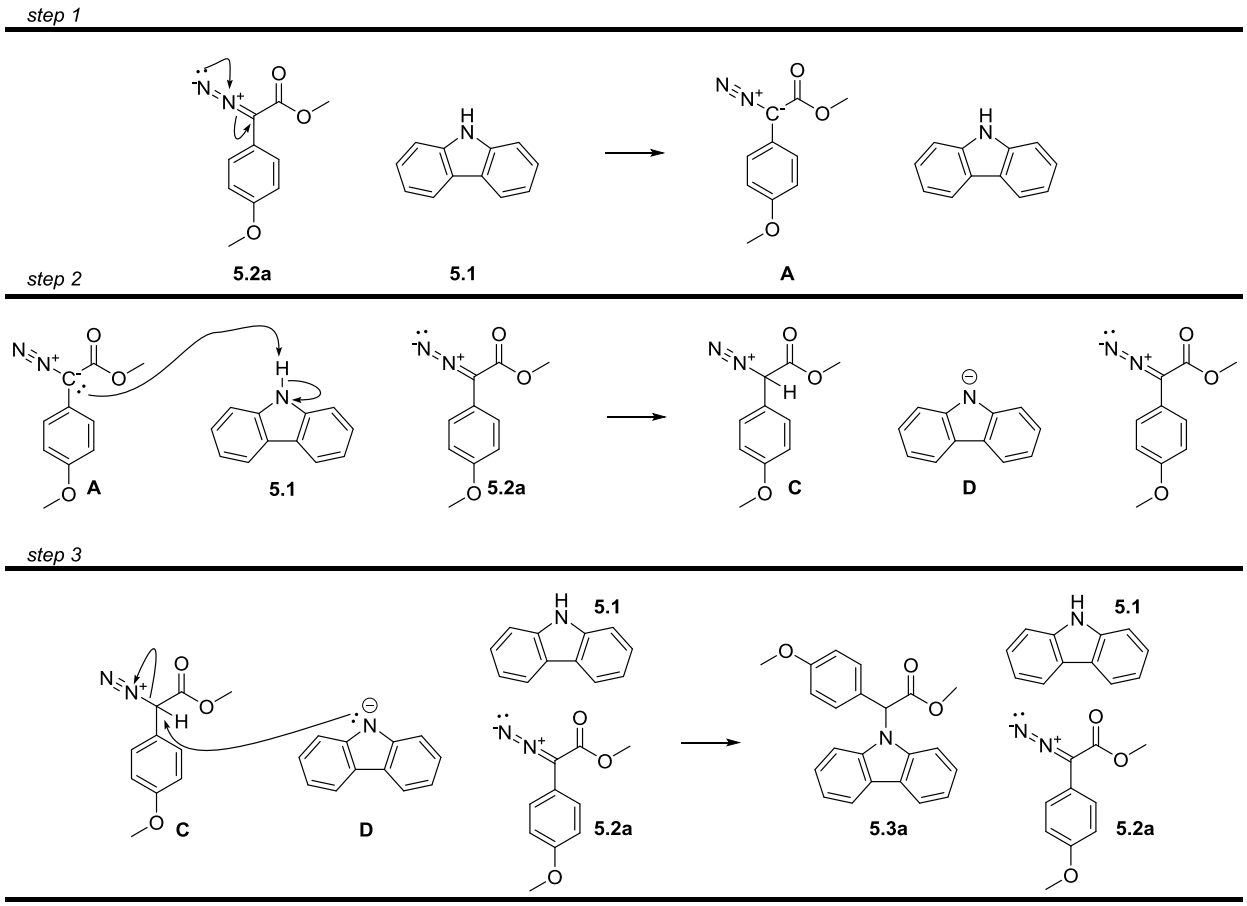
Figure 5-6: N-H Insertion of Carbazole **5.1** with α-Aryl-α-Diazoester **5.2a**



We entered in a mass of 345.11 as a target in pathway search along with the reactants pictured below (Figure 5-7). This mass corresponds to the desired N-H insertion product **5.3a.** Often times the *m/z* peaks observed in ESI correspond to a compound plus a sodium ion or proton. We manually subtract the masses of sodium ions or protons from the ESI peaks before we enter in a target mass in pathway search. Reaction Predictor generated three structures matching 345.11, one of which was the N-H insertion product **5.3a**. Pathway search found a three step mechanism for generation of N-H insertion product **5.3a** from the entered starting materials and target mass (Figure 5-7). Currently, Reaction Predictor treats arrow pushing mechanisms between resonance structures as discrete reactions. In addition, the system automatically reenters an equivalent of starting material into the next step of the reaction tree if it has been changed in the previous step, ensuring certain reaction side-products such as dimers and oligomers are considered. Step one shows the interconversion of cumulene like resonance form of diazo **5.2a** to its carbanion like structure **A**. The second step uses the carbanion carbon of **A** to deprotonate the N-H bond of carbazole **5.1**. Finally, carbazole anion **D** attacks diazonium species **C** generating N-H insertion product **5.3a**. In reality, N-H insertion is a palladium-catalyzed

process; however as a proof of concept this result displays the potential of utilizing Reaction Predictor as tool in structure identification and reaction development.

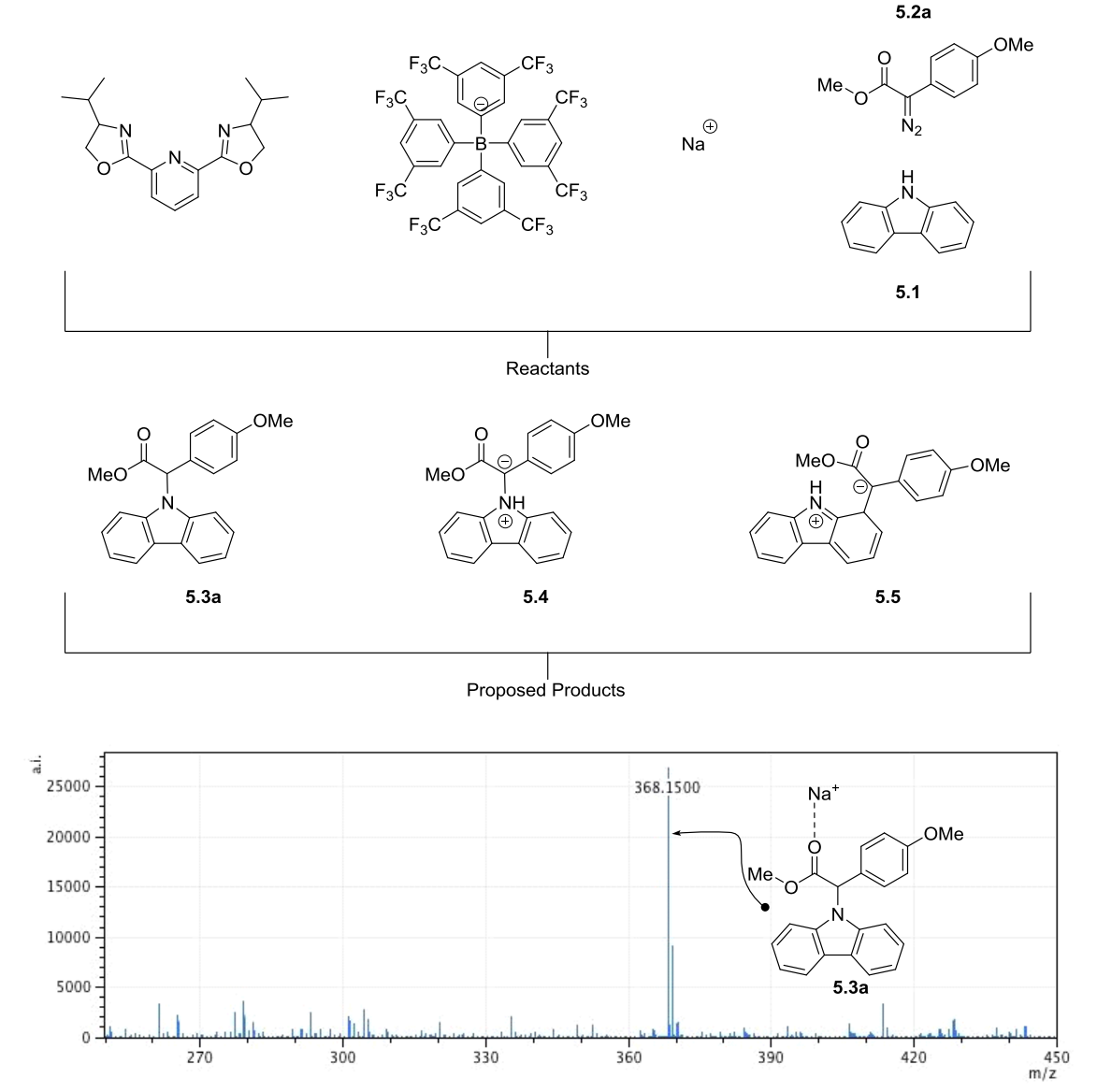
Figure 5-7: Pathway Proposed for Generation of N-H Insertion Product **5.3a**



$NaBAr^F$ and **L1** omitted for clariity

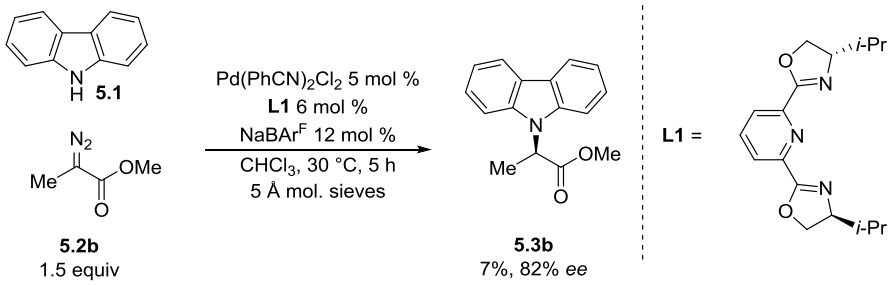
Proposed structure **5.4** is merely a tautomer of the N-H insertion product **5.3a**. Structure **5.5** represents a tautomer of a plausible product stemming from C-H insertion (electrophilic aromatic substitution) of diazo compound with carbazole. We have observed similar regioisomeric C-H insertion products in other palladium-catalyzed N-H insertion products.[16]

Figure 5-8: Product Identification Using Reaction Predictor



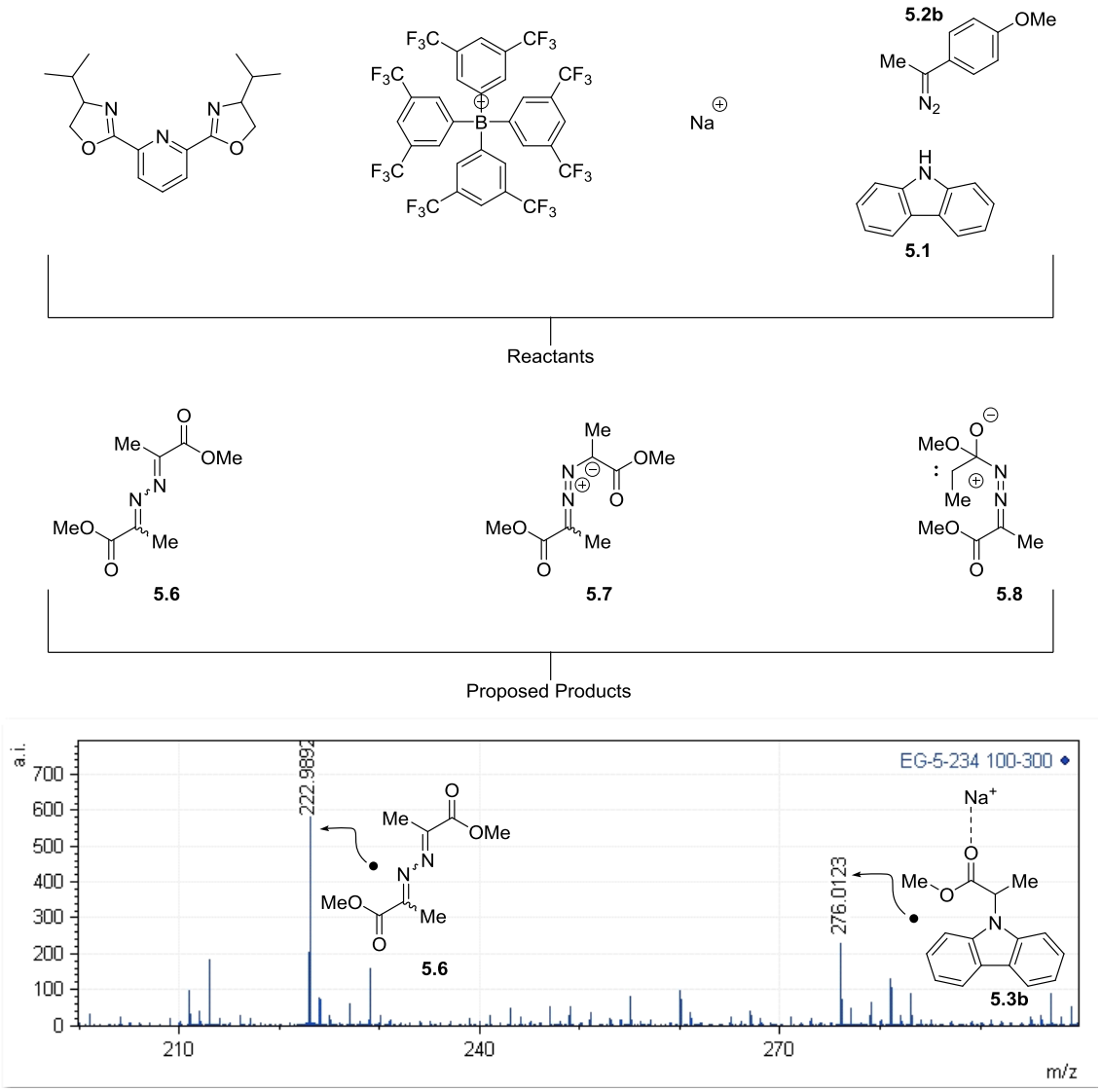
Next, we returned to a much lower yielding palladium-catalyzed N-H insertion reaction between carbazole **5.1** and α-alkyl-α-diazoester **5.2b**. This particular reaction only resulted in 7% yield of the desired N-H insertion product **5.3b (**Figure 5-9). Most of diazo compound **5.2b** was consumed in the first 30 minutes of the reaction, leaving behind a large amount of unreacted carbazole.

Figure 5-9: N-H Insertion of Carbazole **5.1** with α-Alkyl-α-Diazoester **5.2b**



The ESI spectra of the crude reaction mixture showed two prominent peaks (*m/z* = 222.99 and 276.01). The mass corresponding to *m/z* = 276.01 matches the isolated N-H insertion product **5.3b**. The mass corresponding to *m/z* = 222.99 was entered as a target into pathway search after correcting for sodium ion and proton (Figure 5-10). Reaction Predictor returned three plausible structures for this mass. Azine **5.6** is a common side-product observed in reactions of diazo compounds. N-H insertion conditions typically favor formation of fumarate via dimerization of diazo compound,[17] however azine formation is plausible.[18] Proposed product **5.7** is simply a resonance structure of azine **5.6**. Carbene **5.8** is a highly unlikely structure, however it does showcase the system's ability to consider many diverse reaction mechanisms when arriving at a target structure.

Figure 5-10: Side-Product Identification Using Reaction Predictor



Parameters: target = 199.99, minimum score = 5, search depth = 10, branching =25

Conclusion

In conclusion, a reaction prediction program based on inductive machine learning called Reaction Predictor has been trained and applied towards identification of plausible reaction products in ESI spectra. Over 800 transition metal based training reactions have been written. In addition, over 10,000 new complex training reactions have been written and added to the training set. The Reaction Predictor pathway search feature has been customized to match products to

unknown *m/z* peaks in ESI spectra. Pathway search was applied towards unknown identification in palladium-catalyzed N-H insertion reactions.

References

[1] Benkö, G.; Flamm, C.; Stadler, P. F. "A Graph-Based Toy Model of Chemistry." *J. Chem. Inf. Model.* **2003**, *43*, 1085 – 1093.

[2] (a) Klopman, G.; Dimayagu, M.; Talafous, J. META. 1. "A Program for the Evaluation of Metabolic Transformation of Chemicals." *J. Chem. Inf. Comput. Sci.* **1994**, *34*, 1320 – 1325.
(b) Talafous, J.; Sayre, L. M.; Mieyal, J. J.; Klopman, G. "META. 2. A Dictionary Model of Mammalian Xenobiotic Metabolism." *J. Chem. Inf. Comput. Sci.* **1994**, *34*, 1326 – 1333.
(c) Testa, B.; Balmat, A.-L.; Long, A.; Judson, P. "Predicting Drug Metabolism-an Evaluation of the Expert System METEOR." *Chem. Biodiversity* **2005**, *2*, 872 – 885.
(d) Wipke, W. T.; Ouchi, G. I.; Chou, J. T. Computer-Assisted Prediction of Metabolism, in Structure–Activity Correlation as a Predictive Tool in Toxicology: Fundamentals, Methods, and Applications; Golberg, L., Ed.; Hemisphere; Washington, DC, 1983; pp 24.
(e) Jaworska, J.; Dimitrov, S.; Nikolova, N.; Mekenyan, O. "Probabilistic Assessment of Biodegradability Based on Metabolic Pathways: CATABOL System." *SAR QSAR Environ. Res.* **2002**, *13*, 307 – 323.
(f) Kyeng Hou, B.; Wackett, L. P.; Ellis, L. B. M. "Predicting Microbial Catabolism: a Functional Group Approach." *J. Chem. Inf. Comput. Sci.* **2003**, *43*, 1051 – 1057.
(g) Tebes-Stevens, C.; Patel, J. M.; Jones, W. J.; Weber, E. J. "Prediction of Hydrolysis Products of Organic Chemicals under Environmental pH Conditions" *Environ. Sci. Technol.* **2017**, *51*, 5008 – 5016.

[3] (a) Module 1: Salatin, T. D. ; Jorgensen, W. L. "Computer Assisted Mechanistic Evaluation of Organic Reactions. l. Overview." *J. Org. Chem.* **1980**, *45*, 2043 – 2051.
(b) Module 2: Roos-Kozel, B. L.; Jorgensen, W. L. "Computer Assisted Mechanistic Evaluation of Organic Reactions, 2. Perception of Rings, Aromaticity, and Tautomers." *J. Chem. Inf. Comput. Sci.* **1981**, *21*, 101 – 111.
(c) Module 3: Salatin, T. D.; McLaughlin, D.; Jorgensen, W. L. "Computer-Assisted Mechanistic Evaluation of Organic Reactions, 3. Ylid Chemistry and the Organometallic Chemistry of Li, Mg, and Lithium Cuprates." *J. Org. Chem.* **1981**, *46*, 5284 – 5294.
(d) Module 4: Peishoff, C. E.; Jorgensen, W. L. "Computer-Assisted Mechanistic Evaluation of Organic Reactions. 4. Organosilicon Chemistry." *J. Org. Chem.* **1983**, *48*, 1970 – 1979.
(e) Module 7: Schmidt, J. A.; Jorgensen, W. L. "Computer Assisted Mechanistic Evaluation of Organic Reactions. 7. Six Electron Cycloadditions." *J. Org. Chem.* **1983**, *48*, 3923 – 3941.
(f) Module 9: Peishoff, C. E.; Jorgensen, W. L. "Computer-Assisted Mechanistic Evaluation of Organic Reactions, 9. Reactions of Unsaturated Electrophiles Including Nucleophilic Aromatic Substitution." *J. Org. Chem.* **1985**, *50*, 1056 – 1068.

(g) Module 10: Peishoff, C. E.; Jorgensen, W. L. "Computer-Assisted Mechanistic Evaluation of Organic Reactions, 10. Stereochemistry." *J. Org. Chem.* **1985**, *50*, 3174 – 3184.

(h) Module 11: Bures, M. G.; Roos-Kozel, B. L.; Jorgensen, W. L. "Computer-Assisted Mechanistic Evaluation of Organic Reactions, 11. Electrophilic Aromatic Substitution." *J. Org. Chem.* **1985**, *50*, 4490 – 4498.

(i) Module 12: Gushurst, A. J.; Jorgensen, W. L. "Computer-Assisted Mechanistic Evaluation of Organic Reactions, 12. pKa Predictions for Organic Compounds in DMSO." *J. Org. Chem.* **1986**, *51*, 3513 – 3522.

(j) Module 14: Gushurst, A. J.; Jorgensen, W. L. "Computer-Assisted Mechanistic Evaluation of Organic Reactions, 14. Reactions of Sulfur and Phosphorus Ylides, Iminophosphoranes, and P=X-Activated Anions." *J. Org. Chem.* **1988**, *53*, 3397 – 3408.

(k) Module 15: Bures, M. G.; Jorgensen, W. L. "Computer-Assisted Mechanistic Evaluation of Organic Reactions. 15. Heterocycle Synthesis." *J. Org. Chem.* **1988**, *53*, 2504 – 2520.

(l) Module 17: Laird, E. R.; Jorgensen, W. L. "Computer-Assisted Mechanistic Evaluation of Organic Reactions. 17. Free Radical Chain Reactions." *J. Org. Chem.* **1990**, *55*, 9 – 27.

(m) Module 18: Paderes, G. D.; Metivier, P.; Jorgensen, W. L. "Computer-Assisted Mechanistic Evaluation of Organic Reactions. 18. Reductions with Hydrides." *J. Org. Chem.* **1991**, *56*, 4718 – 4733.

(n) Module 20: Paderes, G. D.; Jorgensen, W. L. "Computer-Assisted Mechanistic Analysis of Organic Reactions. 20. Ene and Retro-ene Chemistry." *J. Org. Chem.* **1992**, *57*, 1904 – 1916.

(o) Module 22: Gothe, S. A.; Helson, H. E.; Houdaverdis, I.; Lagerstedt, I.; Sinclair, S.; Jorgensen, W. L. "Computer Assisted Mechanistic Evaluation of Organic Reactions. 22. The Generation and Use of Three-Dimensional Structures." *J. Org. Chem.* **1993**, *58*, 5081 – 5094.

(p) Module 23: Sinclair, S.; Jorgensen, W. L. "Computer Assisted Mechanistic Evaluation of Organic Reactions. 23. Dissolving Metal Reductions with Lithium in Liquid Ammonia Including the Birch Reduction." *J. Org. Chem.* **1994**, *59*, 762 – 772.

(q) Module 24: Helson, H. E.; Jorgensen, W. L. "Computer Assisted Mechanistic Evaluation of Organic Reactions, 24. Carbene Chemistry." *J. Org. Chem.* **1994**, *59*, 3841 – 3856.

(r) Module 25: Helson, H. E.; Jorgensen, W. L. "Computer Assisted Mechanistic Evaluation of Organic Reactions, 25. Structure Diagram Positioning." *J. Chem. Inf. Comput. Sci*. **1994**, *34*, 962 – 971.

(s) Module 26: Fleischer, J. M.; Gushurst, A. J.; Jorgensen, W. L. "Computer Assisted Mechanistic Evaluation of Organic Reactions, 26. Diastereoselective Additions: Cram's Rule." *J. Org. Chem.* **1995**, *60*, 490 – 498.

[4] Gasteiger, J.; Hutchings, M. G.; Christoph, B.; Gann, L.; Hiller, C.; Loew, P.; Marsili, M.; Saller, H.; Yuki. "A New Treatment of Chemical Reactivity: Development of EROS (Elaboration of Reactions for Organic Synthesis), an Expert System for Reaction Prediction and Synthesis Design." *Topics. Curr. Chem.* **1987**, *137*, 19 – 73.

[5] ICH. Q1A(R2): *Stability Testing of New Drug Substances and Products* (Second Revision). February 6, 2003.

http://www.ich.org/fileadmin/Public_Web_Site/ICH/_Products/Guidlines/Quality/Q1A_R2/Step4/Q1A_R2/Step4/Q1A_R2_Guidlines.pdf

[6] Pole, D. L.; Ando, H. Y.; Murphey, S. T. "Prediction of Drug Degradants Using DELPHI: An Expert System for Focusing Knowledge" *Mol. Pharmaceutics*, **2007**, *4*, 539 – 549.

[7] Kleinman, M. H.; Baertschi, S. W.; Alsante, K. M.; Reid, D. L.; Mowery, M. D.; Shimanovich, R.; Foti, C.; Smith, W. K.; Reynolds, D. W.; Nefliu, M.; Ott, M. A. "In Silico Prediction of Pharmaceutical Degradation Pathways: A Benchmarking Study." *Mol. Pharmaceutics* **2014**, *11*, 4179 – 4188.

[8] (a) Lederberg, J.; Sutherland, G. L.; Buchanan, B. G.; Feigenbaum, E. A.; Robertson, A. V.; Duffield, A. M; Djerassi, C. "Applications of Artificial Intelligence for Chemical Inference. I. The Number of Possible Organic Compounds. Acyclic Structures Containing C, H, 0, and N." *J. Am. Chem. Soc.* **1969**, *91*, 2973 – 2977.

(b) Duffield, A. M.; Robertson, A. V.; Djerassi, C.; Buchanan, B. G.; Sutherland, G. L.; Feigenbaum, E. A.; Lederberg, J. "Applications of artificial intelligence for chemical inference. II. Interpretation of low-resolution mass spectra of ketones." *J. Am. Chem. Soc.* **1969**, *91*, 2977 – 2981.

(c) Lindsay, R. K.; Buchanan, B. G.; Feigenbaum, E. A.; Lederberg. J. *Applications of Artificial Intelligence for Organic Chemistry: The DENDRAL Project*; McGraw-Hill Book Company: New York, 1980.

[9] (a) Gelernter, H.; Rose, J. R.; Chen, C. "Building and refining a knowledge base for synthetic organic chemistry via the methodology of inductive and deductive machine learning." *J. Chem. Inf. Model.* **1990**, *30*, 492 − 504.

(b) Ramakrishnan, R.; Dral, P. O.; Rupp, M.; von Lilienfeld, O. A. "Big Data Meets Quantum Chemistry Approximations: The Δ-Machine Learning Approach" *J. Chem. Theory Comput*., **2015**, *11*, 2087 – 2096.

(c) Wei, J. N.; Duvenaud, D.; Aspuru-Guzik, A. "Neural Networks for the Prediction of Organic Chemistry Reactions" *ACS Cent. Sci.* **2016**, *2*, 725 – 732.

(d) Segler, M. H. S.; Waller, M. P. "Modelling Chemical Reasoning to Predict and Invent Reactions" *Chem. Eur. J.* **2017**, *23*, 6118 – 6128.

(e) Coley, C. W.; Barzilay, R.; Jaakkola, T. S.; Green, W. H.; Jensen, K. F. "Prediction of Organic Reaction Outcomes Using Machine Learning" *ACS Cent. Sci.* **2017**, *3*, 434 – 443.

[10] Kayala, M .A.; Azencott, C. A.; Chen, J. H.; Baldi, P. "Learning to Predict Chemical Reactions" *J. Chem. Inf. Model.* **2011**, *51*, 2209 – 2222.

[11] (a) Sello, G. "Reaction prediction: the suggestions of the Beppe program" *J. Chem. Inf. Model.* **1992**, *32*, 713 – 717.

(b) Satoh, H.; Funatsu, K. "SOPHIA, a Knowledge Base-Guided Reaction Prediction System - Utilization of a Knowledge Base Derived from a Reaction Database." *J. Chem. Inf. Model.* **1995**, *35*, 34 – 44.

(c) Socorro, I. M.; Taylor, K.; Goodman, J. M. "ROBIA: A Reaction Prediction Program." *Org. Lett.* **2005**, *7*, 3541 – 3544.

[12] James, C. A.; Weininger, D.; Delany, J. *Daylight Theory Manual*; Daylight Chemical information Systems, Inc.: Laguna Niguel, CA, 2004; http://daylight.com/dayhtml/doc/theory/index.html. Accessed May, 2017).

[13] (a) Chen, J. H.; Baldi, P. "No electron left behind: a rule-based expert system to predict chemical reactions and reaction mechanisms." *J. Chem. Inf. Model.* **2009**, *49*, 2034 – 2043.
(b) Kayala, M. A.; Baldi, P. "Reaction Predictor: Prediction of Complex Chemical Reactions at the Mechanistic Level Using Machine Learning" *J. Chem. Inf. Model.* **2012**, *52*, 2526 – 2540.
(c) J.H. Chen, P. Baldi. "Synthesis Explorer: A Chemical Reaction Tutorial System for "Organic Synthesis Design and Mechanism Prediction" *J. Chem. Educ.* **2008**, *85*, 1699 – 1703.

[14] Reaction Predictor Webserver: Pathway ReactionPredictor. http://reactions.igb.uci.edu/rxnpred/path (accessed May 26, 2017).

[15] Arredondo, V.; Hiew, S. C.; Gutman, E. S.; Premachandra, I. D. U. A.; Van Vranken, D. L. "Enantioselective Palladium-Catalyzed Carbene Insertion into the N-H Bonds of Aromatic Heterocycles" *Angew. Chem. Int. Ed.* **2017**, *56*, 4156 – 4159.

[16] C-H insertion was observed at the 4 position of the carbazole

[17] See chapter four.

[18] Regitz, M.; Maas, G. *Diazo Compounds: Properties and Synthesis*; Academic Press Inc.: Orlando, 1986; Chapter 1.

Experimental Section

Materials

All reactions were evacuated, backfilled with nitrogen, and carried out under an atmosphere of nitrogen. Unless otherwise noted, all reagents were commercially obtained and used without prior purification. Toluene, THF, Et_2O, and CH_2Cl_2 were dried by filtration through alumina according to the procedure of Grubbs and co-workers.[1] All other solvents used were purified according to the Purification of Laboratory Chemicals book.[2] Synthesis and characterization of compounds **5.2a**, **5.2b**, **5.3a**, and **5.3b** can be found in the experimental section of chapter 4.[3] An aliquot taken from the crude reaction mixtures was diluted to a concentration of 0.1 mM in methanol and submitted for mass spec. Mass spectral data were obtained using a Waters ESI LC-TOF Micromass LCT operated in flow injection analysis mode. Mass Spectral data was processed using Waters MassLynx 4.0.

Diagnostic Reactions

Source	Sink	SMIRK
l.p. O	empty orb Ti	CCC(CC1CCCCC1)C=[O:10].CC(C)(C)OC(=C)O[Si](C)(C)C.Cl[Ti:20](Cl)(Cl)Cl>>CCC(CC1CCCCC1)C=[O+:10][Ti-:20](Cl)(Cl)(Cl)Cl.CC(C)(C)OC(=C)O[Si](C)(C)C 10=20
l.p. O	empty orb Si	CCC(CC1CCCCC1)C(CC(=[O+][Si:20](C)(C)C)OC(C)(C)C)[O-:10].Cl[Ti](Cl)(Cl)Cl>>CCC(CC1CCCCC1)C2CC(=[O+][Si-:20](C)(C)(C)[O:10]2)OC(C)(C)C.Cl[Ti](Cl)(Cl)Cl 10=20
l.p. N	empty orb P	[CH3:1][N:2]([CH3:3])[P+:4]1([O:21][C:16]2=[C:15]([O:14]1)[CH:20]=[CH:19][CH:18]=[CH:17]2)[N:5]=[N:6][N-:7][C:8]3=[CH:9][CH:10]=[CH:11][CH:12]=[CH:13]3>>[CH3:1][N:2]([CH3:3])[P:4]12([N:5]=[N:6][N:7]1[C:8]3=[CH:9][CH:10]=[CH:11][CH:12]=[CH:13]3)[O:21][C:16]4=[C:15]([O:14]2)[CH:20]=[CH:19][CH:18]=[CH:17]4 7=4
reverse	ionization	CCC(CC1CCCCC1)C(CC(=O)OC(C)(C)C)[O+:21]([Si](C)(C)C)[Ti-:20](Cl)(Cl)(Cl)Cl>>CCC(CC1CCCCC1)C(CC(=O)OC(C)(C)C)[O:21][Si](C)(C)C.Cl[Ti:20](Cl)(Cl)Cl 20,21=21
reverse	ionization	[H:1][O+:2]([Li:15])[CH:3]1[CH2:4][CH2:5][CH:6]([CH2:11][C:12]1([CH3:13])[CH3:14])[C:7]([CH3:8])([CH3:9])[CH3:10].[OH-:16]>>[H:1][O:2][CH:3]1[CH2:4][CH2:5][CH:6]([CH2:11][C:12]1([CH3:13])[CH3:14])[C:7]([CH3:8])([CH3:9])[CH3:10].[Li+:15].[OH-:16] 15,2=2
reverse	ionization	CCC(CC1CCCCC1)C2CC(=[O+:21][Si-:20](O2)(C)(C)C)OC(C)(C)C.Cl[Ti](Cl)(Cl)Cl>>CCC(CC1CCCCC1)C(CC(=[O:21])OC(C)(C)C)O[Si:20](C)(C)C.Cl[Ti](Cl)(Cl)Cl 20,21=21
reverse	ionization	[Li+].CCC1=C(C=CC(=C1)[CH:20](C(C)C)[OH2+:21])C.CCC(C)C(CCC1CCCC1)C(=O)[O-].[Br-]>>[Li+].CCC1=C(C=CC(=C1)[CH+:20]C(C)C)C.CCC(C)C(CCC1CCCC1)C(=O)[O-].[OH2:21].[Br-] 20,21=21
l.p. S	pi*C=CC=O	[CH:5]1=[CH:6][CH:7]=[CH:8][C:2](=[S:1])[CH:3]=[CH:4]1.[CH:11]1=[CH:12][C:14](=[O:15])[O:13][C:10]1=[O:9]>>[CH-:12]1[CH:11]([C:10](=[O:9])[O:13][C:14]1=[O:15])[S+:1]=[C:2]2[CH:3]=[CH:4][CH:5]=[CH:6][CH:7]=[CH:8]2 1=11;11,12=12
l.p. N	pi*C=O	C1=CC2=C(C=C1)C3=C(C2COC(=O)NC[C:20](=[O:21])Cl)C=CC=C3.C1=C(C=C(C(=C1)[NH2:10])I)Cl.C(=O)([O-])[O-].[K+]>>C1=CC2=C(C=C1)C3=C(C2COC(=O)NC[C:20]([NH2+:10]C4=CC=C(C=C4I)Cl)([O-:21])Cl)C=CC=C3.C(=O)([O-])[O-].[K+] 10=20;20,21=21
l.p. C	alkyne pi*	CC1=CC=C(C=C1)C[N+]#[C-:10].C1=C[C:20]#[C:21]C=C1>>CC1=CC=C(C=C1)C[N+]#[C:10][C:20]2=[C-:21]C=CC=C2 10=20;20,21=21
reverse l.p. O	sigma* CO+	CCCC(CCO)C1CCCCC1.CC[OH+:21][C:20]1(CC2CCCCC2CO1)[OH:10]>>CCCC(CCO)C1CCCCC1.CC[OH:21].C1CCC2CO[C:20](=[OH+:10])CC2C1 10=20;20,21=21
reverse l.p. N	sigma* CO+	CCCCCNCC1=C(C=CC=C1)CC=O.CCCCC[N:10]1CC2=C(C[CH:20]1[OH2+:21])C=CC=C2>>CCCCCNCC1=C(C=CC=C1)CC=O.CCCCC[N+:10]1=[CH:20]CC2=C(C1)C=CC=C2.[OH2:21] 10=20;20,21=21
reverse lp O	sigma* CO	CS(=O)(=O)[O-].C1CC[C:20]2(C(=CCC[O:10]2)C1)[OH2+:21]>>CS(=O)(=O)[O-].C1CC[C:20]2=[O+:10]CCC=C2C1.[OH2:21] 10=20;20,21=21
reverse l.p. N	sigma* CBr+	[BH3-]C#N.C[N:10]1CCC(C2[CH:20]1[Br+:21]2)(CCCC3=CC=CC=C3)C4=C(C=CC(=C4)OC)OC.[Na+]>>[BH3-]C#N.C[N+:10]1=[CH:20]C(C(CC1)(CCCC2=CC=CC=C2)C3=C(C=CC(=C3)OC)OC)[Br:21].[Na+] 10=20;20,21=21
l.p o	sigma C-Cl	CC[O:21][C:20]1(CN(CC2=C(N1)C=CC(=C2)Cl)C(=O)OC(C)(C)C)[O-:10]>>CC[O-:21].CC(C)(C)OC(=O)N1CC2=C(C=CC(=C2)Cl)N[C:20](=[O:10])C1 10=20;20,21=21
l.p. C	sigma* CBr	[Li+].CCCC.CN1CC[C-:10](C=C1)C2=C(C=CC(=C2)OC)OC.C1=CC=C(C=C1)CC[CH2:20][Br:21]>>[Li+].CCCC.CN1CC[C:10](C=C1)([CH2:20]CCC2=CC=CC=C2)C3=C(C=CC(=C3)OC)OC.[Br-:21] 10=20;20,21=21
l.p. O	nitrile pi*	C[C:20]#[N+:21]C1C(CC2=C1C=CC=C2)[OH:10]>>C[C:20]1=[N:21]C2C(CC3=C2C=CC=C3)[OH+:10]1 10=20;20,21=21
reverse l.p. N	sigma* C-O (forms nitrilium)	COC1=C(C=C(C=C1)CC/[N:10]=[C:20](\C2=CC=C(C=C2)Br)/[O:21]P(=O)(Cl)Cl)OC>>COC1=C(C=C(C=C1)CC[N+:10]#[C:20]C2=CC=C(C=C2)Br)OC.[O-:21]P(=O)(Cl)Cl 10=20;20,21=21
l.p. O-	sigma* CCl	CCCC(C(C)CC)C(C)C(CC)C[O-:10].[CH2:20](/C=C/Cl)[Cl:21]>>CCCC(C(C)CC)C(C)C(CC)C[O:10][CH2:20]/C=C/Cl.[Cl-:21] 10=20;20,21=21
pi CC	empty orb C	[CH3:1][CH2:2][CH2:3][CH2:4][C:5]1=[CH:6][CH:7]=[CH:8][S:9]1.[CH3:10][C+:11]([CH3:12])[C:13]1=[CH:14][CH:15]=[CH:16][CH:17]=[CH:18]1.[F:19][P-:20]([F:21])([F:22])([F:23])([F:24])[F:25]>>[CH3:1][CH2:2][CH2:3][CH2:4][C:5]1=[CH:6][CH+:7][CH:8]([S:9]1)[C:11]([CH3:12])([CH3:10])[C:13]2=[CH:18][CH:17]=[CH:16][CH:15]=[CH:14]2.[F:25][P-:20]([F:24])([F:22])([F:19])([F:23])[F:21] 7,8=8,11

reverse sigma C-Sn-	empty p(C)	[B-:10]([O:9][CH:8]([CH:14]([CH3:36])[CH+:15][CH2:16][Sn-:17]([CH2:24][CH2:25][CH2:26][CH3:27])([CH2:28][CH2:29][CH2:30][CH3:31])([CH2:32][CH2:33][CH2:34][CH3:35])[O+:18]([B:19]([F-:21])([F:20])[F:22])[CH3:23])[CH:7]([CH3:37])[CH:6]1[CH:4]([CH2:3][CH:2]([CH:39]([O:38]1)[O:40][CH:41]([CH3:42])[CH3:43])[CH3:1])[CH3:5])([F:11])([F:12])[F:13]>>[B-:10]([O:9][CH:8]([CH:14]([CH3:36])[CH:15]=[CH2:16])[CH:7]([CH3:37])[CH:6]1[CH:4]([CH2:3][CH:2]([CH:39]([O:38]1)[O:40][CH:41]([CH3:42])[CH3:43])[CH3:1])[CH3:5])([F:11])([F:12])[F:13].[B:19]([O+:18]([CH3:23])[Sn:17]([CH2:24][CH2:25][CH2:26][CH3:27])([CH2:28][CH2:29][CH2:30][CH3:31])[CH2:32][CH2:33][CH2:34][CH3:35])([F-:21])([F:22])[F:20] 17,16=16,15
pi CC	pi* C=CC=O	[Li+].CCCCI.CC(C)(C)O[C:22](=[O:23])[CH:21]=[CH:20]CCCCI.CC(C)(C)O[C:11](=[CH:10]C1CCCC1)[O:12]>>[Li+].CCCCI.CC(C)(C)O[C:22](=[CH:21][CH:20](CCCCI)[CH:10](C1CCCC1)[C:11](=[O:12])OC(C)(C)C)[O-:23] 10,11=10,20;12=11;20,21=21,22;22,23=23
pi CC	pi* C=O+	CCC(CC1CCCCC1)[CH:20]=[O+:21][Ti-](Cl)(Cl)(Cl)Cl.CC(C)(C)O[C:11](=[CH2:10])[O:12][Si](C)(C)C>>CCC(CC1CCCCC1)[CH:20]([CH2:10][C:11](=[O+:12][Si](C)(C)C)OC(C)(C)C)[O-:21][Ti-](Cl)(Cl)(Cl)Cl 10,11=10,20;12=11;20,21=21
reverse l.p. O	sigma C-C	[CH3:13][CH2:12][C+:11]1[CH2:10][CH2:9][O:8][CH:7]([CH2:14]1)[CH3:6].[O-:4][S:2](=[O:3])(=[O:5])[F:1]>>[CH3:13][CH2:12][C:11](=[CH2:14])[CH2:10][CH2:9][O+:8]=[CH:7][CH3:6].[O-:4][S:2](=[O:3])(=[O:5])[F:1] 8=7;7,14=14,11
pi CC	alkyne pi*	CCOC(=O)[C:10]1=[C:11](CC2=CC(=C(C=C21)OC)OC)[O-:12].C1OC2=C[C:20]#[C:21]C=C2O1>>CCOC(=O)[C:10]1([C:11](=[O:12])CC2=CC(=C(C=C21)OC)OC)[C:20]3=[C-:21]C=C4C(=C3)OCO4 10,11=10,20;12=11;20,21=21
reverse l.p. N	sigma* C-O	CCC(C#N)[C:20](=[N-:10])[O:21][P+:22](Cl)(Cl)Cl.Cl>>CCC(C#N)[C:20]#[N:10].[O:21]=[P-:22](Cl)(Cl)Cl.Cl 10=20;20,21=21,22
pi CC	sigma* C-I	[Li][O:12]/[C:11](=[CH:10]\C(CCCCI)C(C1CCCC1)C(=O)OC(C)(C)C)/OC(C)(C)C.CCC[CH2:20][I:21]>>[Li][O+:12]=[C:11]([CH:10]([CH2:20]CCC)C(CCCCI)C(C1CCCC1)C(=O)OC(C)(C)C)OC(C)(C)C.[I-:21] 10,11=10,20;12=11;20,21=21
pi CC	sigma* C-O	[Li][OH+]C(C)(C)C.CC1(C([C:10]2=[C:11](CCC=C2O1)[O-:12])[CH2:20][O:21]S(=O)(=O)C(F)(F)F)C>>[Li][OH+]C(C)(C)C.CC1(C2[C:10]3([C:11](=[O:12])CCC=C3O1)[CH2:20]2)C.C(F)(F)(F)S(=O)(=O)[O-:21] 10,11=10,20;12=11;20,21=21
reverse l.p. Br-	sigma* CCC+	[B:31]([OH:30])([F:32])([F:33])[F:34].[CH3:1][CH2:2][CH2:3][CH2:4][N+:5]([CH2:6][CH2:7][CH2:8][CH3:9])([CH2:10][CH2:11][CH2:12][CH3:13])[CH2:14][CH2:15][CH2:16][CH3:17].[CH3:28][C+:27]1[CH2:29][C:19](=[O:18])[C:20](=[CH:23][C:24]12[CH2:25][CH2:26]2)[C:21]#[N:22].[Br-:35]>>[B:31]([OH:30])([F-:32])([F:33])[F:34].[CH3:17][CH2:16][CH2:15][CH2:14][N+:5]([CH2:10][CH2:11][CH2:12][CH3:13])([CH2:6][CH2:7][CH2:8][CH3:9])[CH2:4][CH2:3][CH2:2][CH3:1].[CH3:28][C:27]1=[C:24]([CH:23]=[C:20]([C:19](=[O:18])[CH2:29]1)[C:21]#[N:22])[CH2:26][CH2:25][Br:35] 35=25;25,24=24,27
alkyne pi	empty orb C	C1C[CH+:20]CCC[C:10]#[C:11]C1.C1=CC(=CC=C1C(=O)[O-])[N+](=O)[O-]>>C1C[C+:11]=[C:10]2CCC[CH:20]2C1.C1=CC(=CC=C1C(=O)[O-])[N+](=O)[O-] 10,11=10,20
reverse sigma C-Si-	empty orb C=C+	[CH3:23][CH:22]([CH3:24])[O:21][C:20]1=[C:25]([C:17]([C:19]1=[O:30])([C+:16]=[C:6]([Si-:7]([CH3:13])([CH3:14])([CH3:15])[O+:8]=[CH:9][N:10]([CH3:11])[CH3:12])[I:5])[OH:18])[O:26][CH:27]([CH3:28])[CH3:29].[N+:2](=[O:4])([O-:1])[O-:3]>>[CH3:23][CH:22]([CH3:24])[O:21][C:20]1=[C:25]([C:17]([C:19]1=[O:30])([C:16]#[C:6][I:5])[OH:18])[O:26][CH:27]([CH3:28])[CH3:29].[CH3:11][N:10]([CH3:12])[CH:9]=[O+:8][Si:7]([CH3:13])([CH3:14])[CH3:15].[N+:2](=[O:4])([O-:1])[O-:3] 7,6=6,16
alkyne pi	pi* CO	C[C:10]#[C:11]CC(C1=CC=CC=C1)[O+:21]=[CH:20]C2=CC=C(C=C2)[N+](=O)[O-].O=S([O-])(C(F)(F)F)=O>>O=S([O-])(C(F)(F)F)=O.C[C:10]1=[C+:11]CC(C2=CC=CC=C2)[O:21][CH:20]1C3=CC=C(C=C3)[N+](=O)[O-] 10,11=10,20;20,21=21
reverse l.p. O-	sigma* C-C=C+	CCCC[N+](CCCC)(CCCC)CCCC.O=C(C)[O-].[CH3:8][O:9][C:10]1=[CH:11][CH:12]=[C:13]([CH:20]=[CH:21]1)[C+:14]=[C:15]([C:17](=[O:19])[O-:18])[I:16].[CH2:3]1[CH2:4][C:6](=[O:7])[NH:5][C:2]1=[O:1]>>CCCC[N+](CCCC)(CCCC)CCCC.O=C(C)[O-].[CH3:8][O:9][C:10]1=[CH:11][CH:12]=[C:13]([CH:20]=[CH:21]1)[C:14]#[C:15][I:16].[CH2:3]1[CH2:4][C:6](=[O:7])[NH:5][C:2]1=[O:1].[C:17](=[O:18])=[O:19] 18=17;17,15=15,14
alkyne pi	sigma* Br-Br	CC(CCC[C:11]#[CH:10])(C(=O)OC)C(=O)OCC1=CC=CC=C1.[Br:20][Br:21]>>CC(CCC[C+:11]=[CH:10][Br:20])(C(=O)OC)C(=O)OCC1=CC=CC=C1.[Br-:21] 10,11=10,20;20,21=21
reverse		CCCCC(=[CH+:20])CCC.C(F)(F)(F)S(=O)(=O)[O-:10].IC1=CC=CC=C1>>IC1=CC=CC=C1.CCCCC(=[CH:20][O:10]S(=O)(=O)C(F)(F)F)CCC 10=20
sigma C-Mg	empty orb B	[B:20](OCCCC)(OCCCC)OCCCC.C=C[CH2:10][Mg:11]Br>>[B-:20]([CH2:10]C=C)(OCCCC)(OCCCC)OCCCC.[Mg+:11]Br 10,11=10,20
sigma CLi	pi* C=CC=O	[Li:11][CH2:10]CCC[CH:20]=[CH:21][C:22](=[O:23])OC(C)(C)C.CCCCI>>[Li+:11].CCCCI.CC(C)(C)O[C:22](=[CH:21][CH:20]1[CH2:10]CCC1)[O-:23] 10,11=10,20;20,21=21,22;22,23=23
reverse sigma C-C	empty orb Zn	[CH3:1][CH2:2][O:3][C:4]1([CH2:10][CH2:11]1)[O:5][Si:6]([CH3:7])([CH3:8])[CH3:9].[Cl:12][Zn:13][Cl:14]>>[CH3:1][CH2:2][O:3][C:4](=[O+:5][Si:6]([CH3:7])([CH3:8])[CH3:9])[CH2:11][CH2:10][Zn-:13]([Cl:12])[Cl:14] 5=4;4,10=10,13
sigma C-Cu	alkyne pi*	CCO[C:22](=[O:23])[C:21]#[C:20]C1=CC=CC=C1.C1=CC=C(C=C1)C[CH2:10][Cu:11]>>CCO[C:22](=[C:21]=[C:20]([CH2:10]CC1=CC=CC=C1)C2=CC=CC=C2)[O-:23].[Cu+:11] 10,11=10,20;20,21=21,22;22,23=23

sigma CLi	sigma* CBr	[Li:11][CH:10]1C=CC=C1.CC1=C(C(=CC=C1)C)OCCCCC[CH2:20][Br:21]>>[Li+:11].CC1=C(C(=CC=C1)C)OCCCCC[CH2:20][CH:10]2C=CC=C2.[Br-:21] 10,11=10,20;20,21=21
sigma C-Mg	sigma CO*	CC1=CC=C(C=C1)S(=O)(=O)OCC2[CH2:20][O:21]2.C=C[CH2:10][Mg:11]Br>>CC1=CC=C(C=C1)S(=O)(=O)OCC([CH2:20][CH2:10]C=C)[O-:21].[Mg+:11]Br 10,11=10,20;20,21=21
l.p. n	sigma* CH(E2,alkane)	[H:20][CH:21]1CC2CC(N(C2C[CH:22]1[Br:23])C(=O)OCC3=CC=CC=C3)C(=O)OC.C1CCC2=[N:10]CCCN2CC1>>[H:20][N+:10]1=C2CCCCCN2CCC1.COC(=O)C1CC2C[CH:21]=[CH:22]CC2N1C(=O)OCC3=CC=CC=C3.[Br-:23] 10=20;20,21=21,22;22,23=23
l.p. C	sigma* CH(E2, alkene)	[H:20]/[C:21](=[CH:22]\[Br:23])/CC1C2C(C(O1)N3C=NC4=C(N=CN=C43)NC5CCCC5)OC(O2)(C)C.CC(C)(C)[O:10][K]>>[H:20][O+:10](C(C)(C)C)[K].CC1(OC2C(OC(C2O1)N3C=NC4=C(N=CN=C43)NC5CCCC5)C[C:21]#[CH:22])C.[Br-:23] 10=20;20,21=21,22;22,23=23
pi CC	sigma* CH	[H:20][CH:21]([C:22](=[O:23])OC)C(=O)OCC1=CC=CC=C1.[Li][O:12]/[C:11](=[CH:10]\C(=O)OC)/OCC1=CC=CC=C1>>[H:20][CH:10](C(=O)OC)[C:11](=[O+:12][Li])OCC1=CC=CC=C1.CO[C:22](=[CH:21]C(=O)OCC1=CC=CC=C1)[O-:23] 10,11=10,20;12=11;20,21=21,22;22,23=23
sigma CLi	sigma* HN	[H:1][N:2]([N:21]=[C:22]1[CH2:31][CH2:30][CH2:29][CH2:28][CH:23]1[CH2:24][CH2:25][CH:26]=[CH2:27])[S:3]([C:5]#[C:6][C:7]#[C:8][C:9]#[C:10][C:11]#[C:12][C:13]#[C:14][C:15]#[C:16][C:17]#[C:18][CH3:19])([O-:4])[O-:20].[Li:34][CH:33]([CH3:32])[CH2:35][CH3:36]>>[H:1][CH:33]([CH3:32])[CH2:35][CH3:36].[Li+:34].[CH3:19][C:18]#[C:17][C:16]#[C:15][C:14]#[C:13][C:12]#[C:11][C:10]#[C:9][C:8]#[C:7][C:6]#[C:5][S:3]([N-:2][N:21]=[C:22]1[CH2:31][CH2:30][CH2:29][CH2:28][CH:23]1[CH2:24][CH2:25][CH:26]=[CH2:27])([O-:4])[O-:20] 33,34=1,33;2,1=2
sigma CLi	sigma* HC	[H:20][CH:21]1[CH:22]=[C:23](CCN1C)C2=C(C=CC(=C2)OC)OC.[Li:11][CH2:10]CCC>>[H:20][CH2:10]CCC.[Li+:11].CN1CC[C-:23]([CH:22]=[CH:21]1)C2=C(C=CC(=C2)OC)OC 10,11=10,20;20,21=21,22;22,23=23
sigma Si-H	empty orb C	[H:23][Si-:24]([CH2:32][CH3:33])([CH2:34][CH3:35])([CH2:36][CH3:37])[O:25][C:26](=[O:31])[C:27]([F:28])([F:29])[F:30].[CH3:19][C+:20]([CH3:21])[CH3:22].[CH:12]1=[CH:11][C:10]2=[C:9]([CH:14]=[CH:13]1)[NH:8][CH:7]=[C:6]2[CH2:5][CH:4]([C:2](=[O:1])[OH:3])[NH:15][C:16](=[O:18])[OH:17]>>[H:23][C:20]([CH3:19])([CH3:21])[CH3:22].[CH3:37][CH2:36][Si:24]([CH2:32][CH3:33])([CH2:34][CH3:35])[O:25][C:26](=[O:31])[C:27]([F:29])([F:28])[F:30].[CH:12]1=[CH:11][C:10]2=[C:9]([CH:14]=[CH:13]1)[NH:8][CH:7]=[C:6]2[CH2:5][CH:4]([C:2](=[O:1])[OH:3])[NH:15][C:16](=[O:18])[OH:17] 23,24=20,23
sigma C-H	empty orb C	[H:21][C:20]1([CH2:19][CH2:18][C:16]2([CH:15]1[CH2:14][CH2:13][CH:12]3[C:10]2([CH2:9][CH2:8][CH:7]4[C:5]3([CH2:4][CH2:3][CH:2]([C:30]4([CH3:31])[CH3:32])[OH:1])[CH3:6])[CH3:11])[CH3:17])[C+:22]([CH3:23])[CH2:24][CH2:25][CH:26]=[C:27]([CH3:28])[CH3:29]>>[H:21][C:22]([CH3:23])([CH2:24][CH2:25][CH:26]=[C:27]([CH3:28])[CH3:29])[C+:20]1[CH2:19][CH2:18][C:16]2([CH:15]1[CH2:14][CH2:13][CH:12]3[C:10]2([CH2:9][CH2:8][CH:7]4[C:5]3([CH2:4][CH2:3][CH:2]([C:30]4([CH3:31])[CH3:32])[OH:1])[CH3:6])[CH3:11])[CH3:17] 20,21=21,22
sigma H-B-	pi* C=N+	[H:10][BH2:11]C#N.C[N+:21]1=[CH:20]C(C(CC1)(CCCC2=CC=CC=C2)C3=C(C=CC(=C3)OC)OC)Br.[Na+]>>[H:10][CH:20]1C(C(CC[N:21]1C)(CCCC2=CC=CC=C2)C3=C(C=CC(=C3)OC)OC)Br.[BH2:11]C#N.[Na+] 10,11=10,20;20,21=21
sigma H-Al-	pi* C=O	[H:10][AlH3:11].[Li][O+:21]=[C:20]1CCC(CC1(C)C)C(C)(C)C>>[H:10][C:20]1(CCC(CC1(C)C)C(C)(C)C)[O:21][Li].[AlH3:11] 10,11=10,20;20,21=21
sigma C-H	pi* C=C	[H:33][C:32]1([C:26](=[C:24]([N:23]([C:41](=[C:35]1[C:36](=[O:40])[O:37][CH2:38][CH3:39])[CH3:42])[H:22])[CH3:25])[C:27](=[O:31])[O:28][CH2:29][CH3:30])[H:34].[CH:7]1=[CH:6][CH:5]=[C:4]([CH:9]=[CH:8]1)[N:3]2[C:10]3=[CH:11][CH:12]=[CH:13][CH:14]=[C:15]3[C:16](=[C:17]([C:18]#[N:19])[C:20]#[N:21])[C:2]2=[O:1]>>[H:33][C+:32]1[C:26](=[C:24]([N:23]([C:41](=[C:35]1[C:36](=[O:40])[O:37][CH2:38][CH3:39])[CH3:42])[H:22])[CH3:25])[C:27](=[O:31])[O:28][CH2:29][CH3:30].[H:34][C:17]([C:18]#[N:19])([C:20]#[N:21])[C:16]1[C:15]2=[CH:14][CH:13]=[CH:12][CH:11]=[C:10]2[N:3]([C:2]1=[O:1])[C:4]3=[CH:5][CH:6]=[CH:7][CH:8]=[CH:9]3 34,32=17,34;17,16=16
sigma Al-H	alkyne pi* CN	[H:16][Al:17]([H:18])([H:19])[H:20].[CH3:1][O:2][C:3]1=[CH:4][C:5]2=[C:6]([CH:10]=[CH:11][CH:12]=[C:13]2[CH:14]=[CH:15]1)[CH2:7][C:8]#[N:9]>>[H:16][C:8](=[N-:9])[CH2:7][C:6]1=[C:5]2[CH:4]=[C:3]([CH:15]=[CH:14][C:13]2=[CH:12][CH:11]=[CH:10]1)[O:2][CH3:1].[H:20][Al:17]([H:19])[H:18] 17,16=16,8;8,9=9
sigma B-H	sigma*	[H:10][B:11](CC)(CC)CC.[Li+].C1CCC[CH:20](CCC1)[Br:21]>>[H:10][CH:20]1CCCCCCC1.[Li+].[B:11](CC)(CC)CC.[Br-:21] 10,11=10,20;20,21=21

Experimental References

[1] A. B. Pangborn, M. A. Giardello, R. H. Grubbs, R. K. Rosen, F. J. Timmers, *Organometallics* **1996**, *15*, 1518.

[2] W. L. F. Armarego, C. L. L. Chai, *Purification of Laboratory Chemicals*; Elsevier, 2013.

[3] Arredondo, V.; Hiew, S. C.; Gutman, E. S.; Premachandra, I. D. U. A.; Van Vranken, D. L. *Angew. Chem. Int. Ed.* **2017**, *56*, 4156 – 4159.

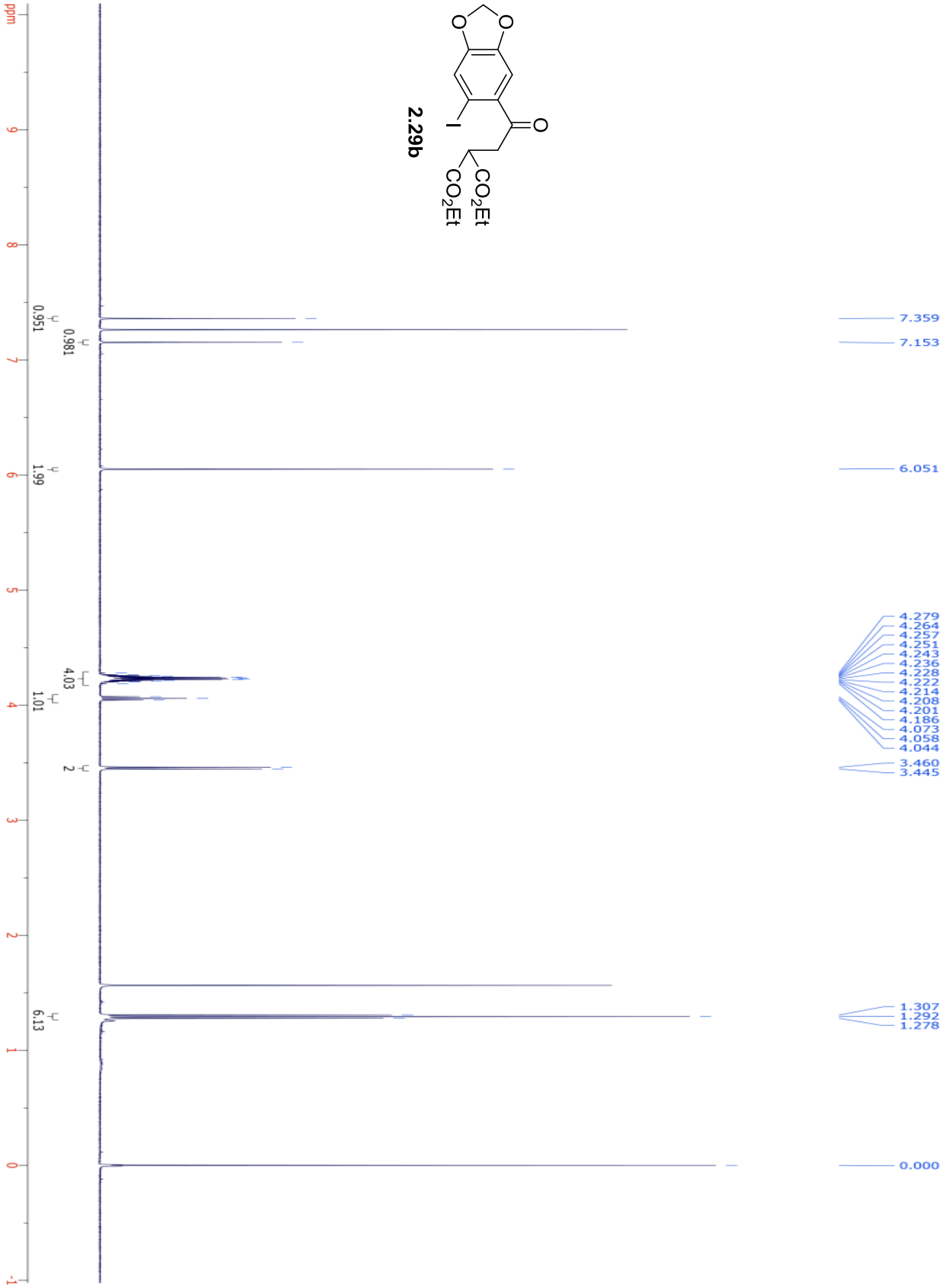
Appendix

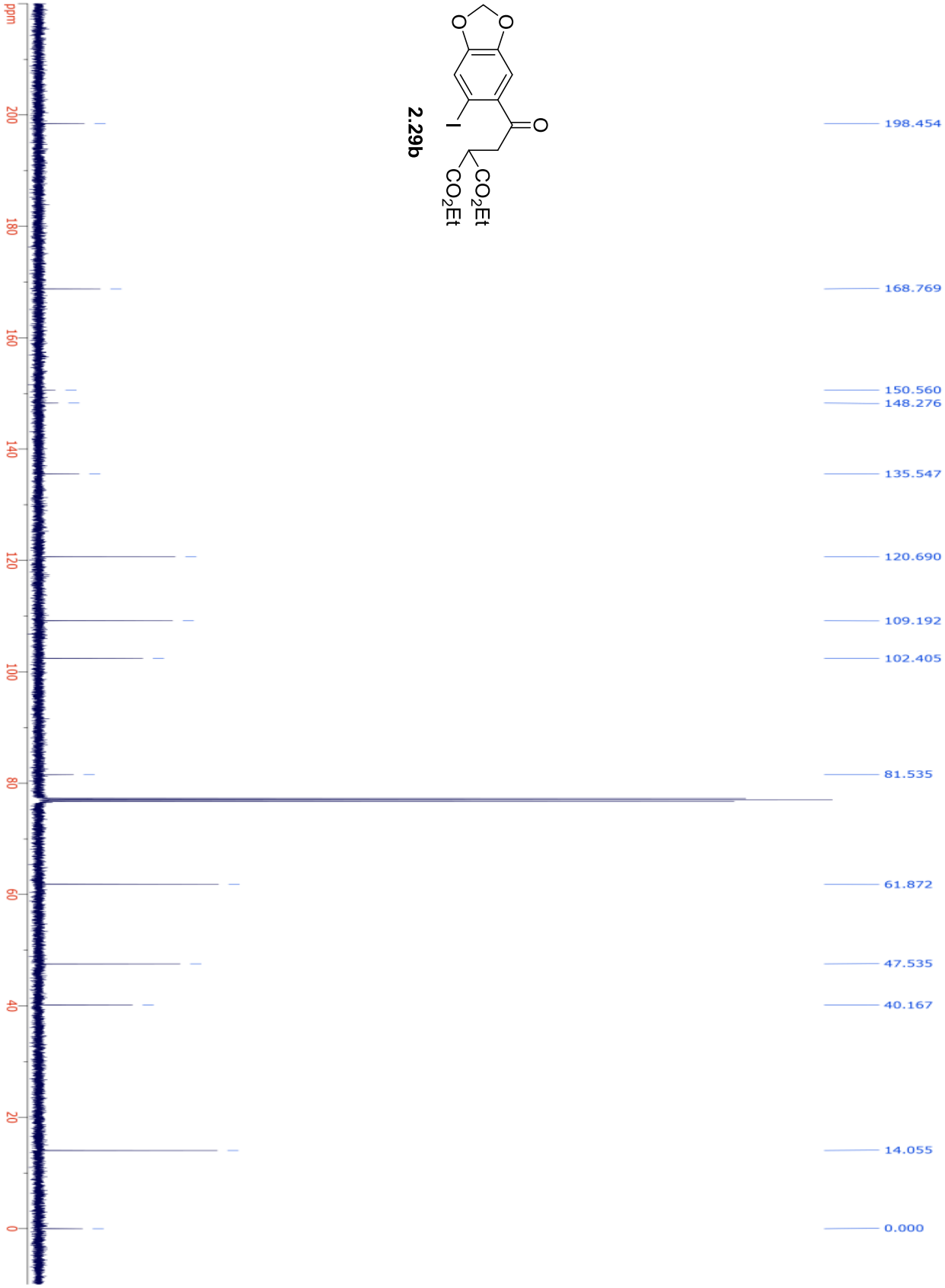
The following section contains spectral data for unpublished compounds found in Chapter 2. Spectral data for the remainder of the compounds described in this work can be found online in the supplementary information of the following published work.

Chapter 2: Gutman, E. S.; Arredondo, V.; Van Vranken, D. L. "Cyclization of η^3-Benzylpalladium Intermediates Derived from Carbene Insertion" *Org. Lett.* **2014**, 5498 – 5501.

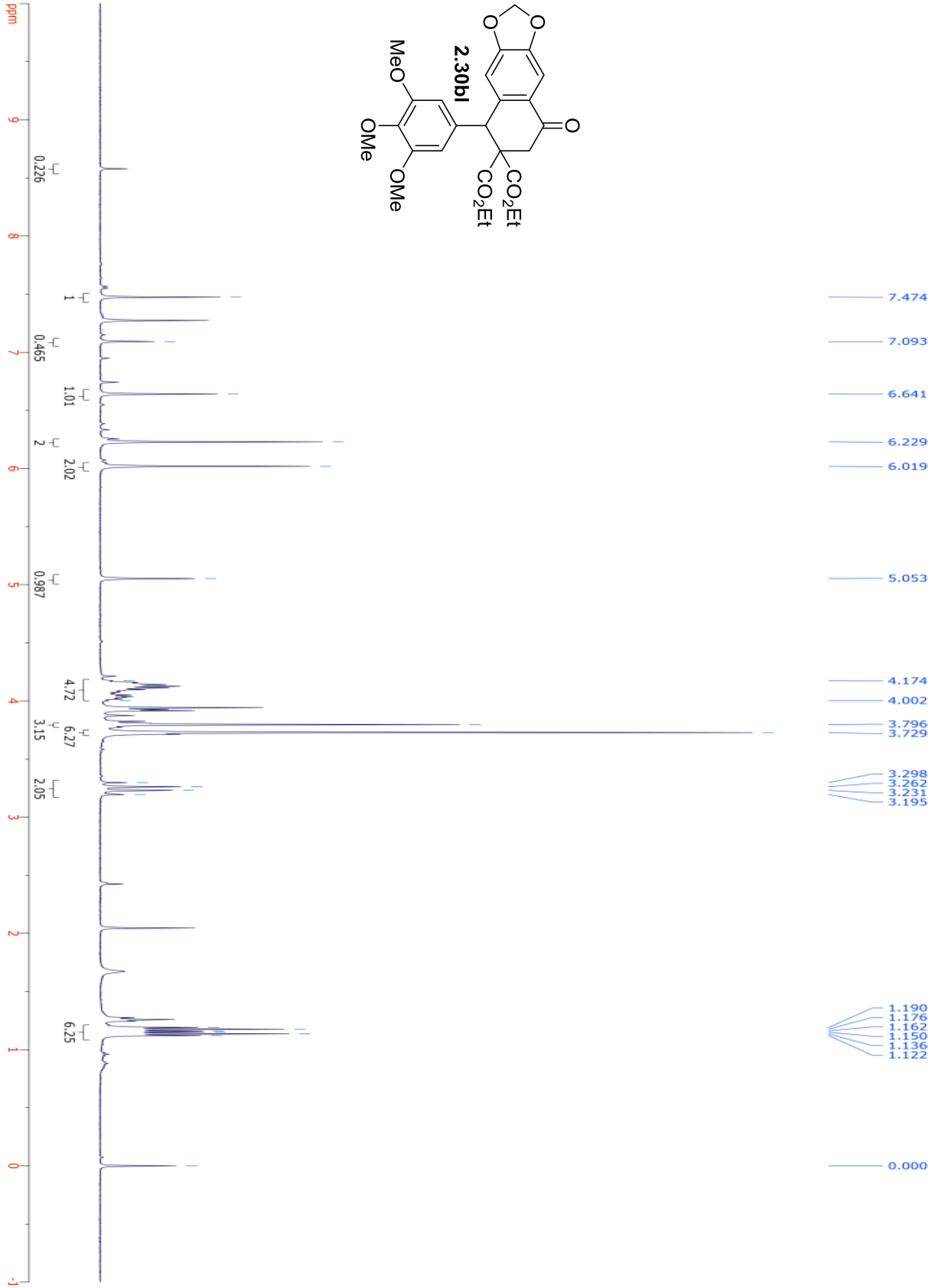
Chapter 3: Premachandra, I. D. U. A.; Nguyen, T. A.; Shen, C.; Gutman, E. S.; Van Vranken, D. L. "Carbenylative Amination and Alkylation of Vinyl Iodides via Palladium Alkylidene Intermediates" *Org. Lett.* **2015**, *17*, 5464 – 5467.

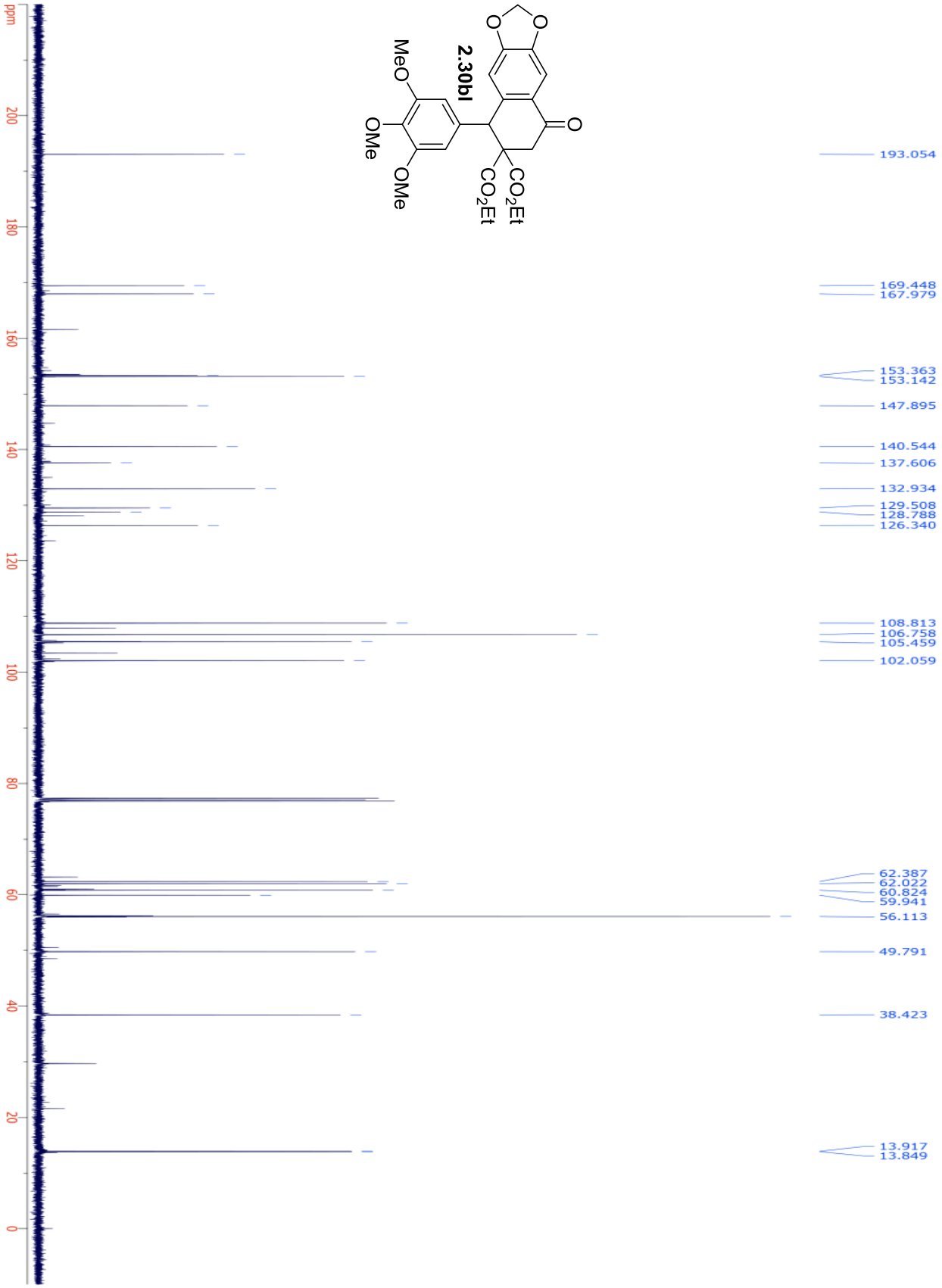
Chapter 4: Arredondo, V.; Hiew, S. C.; Gutman, E. S.; Premachandra, I. D. U. A.; Van Vranken, D. L. "Enantioselective Palladium-Catalyzed Carbene Insertion into the N-H Bonds of Aromatic Heterocycles" *Angew. Chem. Int. Ed.* **2017**, *56*, 4156 – 4159.

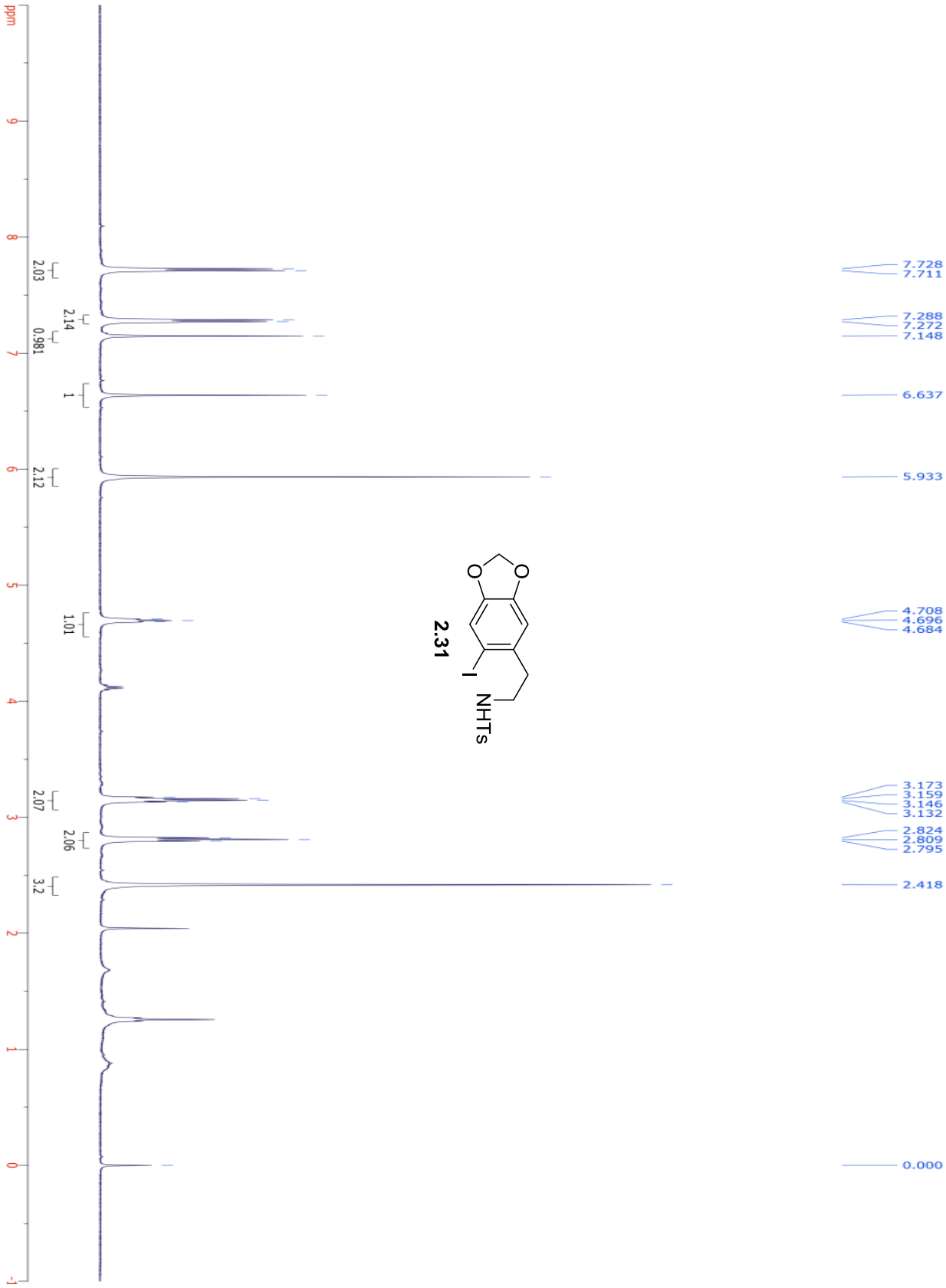

2.29b
ppm
7.359
7.153
6.051
4.279
4.264
4.257
4.251
4.243
4.236
4.228
4.222
4.214
4.208
4.201
4.186
4.073
4.058
4.044
3.460
3.445
1.307
1.292
1.278
0.000
0.951
0.981
1.99
4.03
1.01
2
6.13

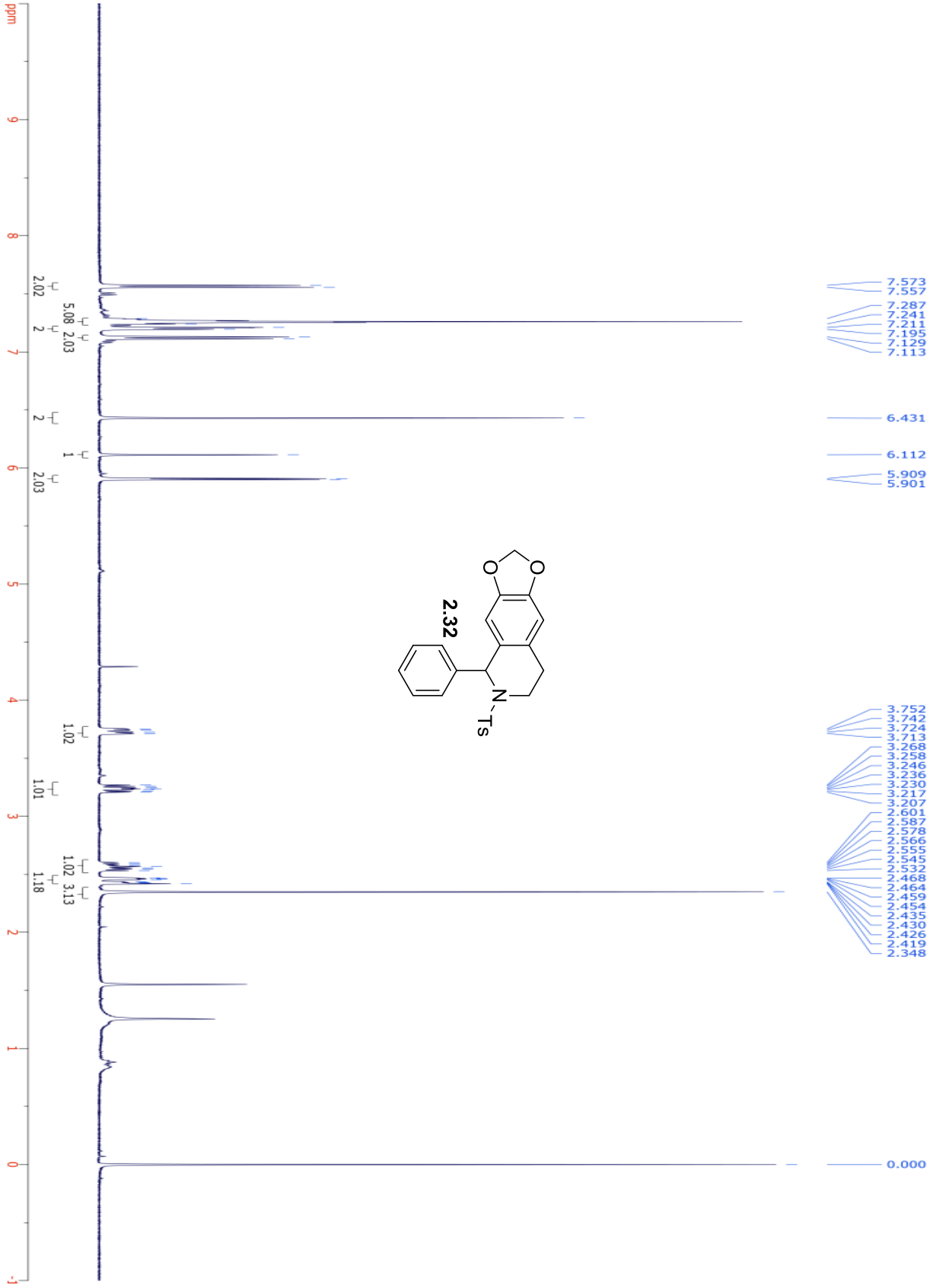

ppm
200
180
160
140
120
100
80
60
40
20
0
198.454
168.769
150.560
148.276
135.547
120.690
109.192
102.405
81.535
61.872
47.535
40.167
14.055
0.000
O
O
O
I
CO2Et
CO2Et

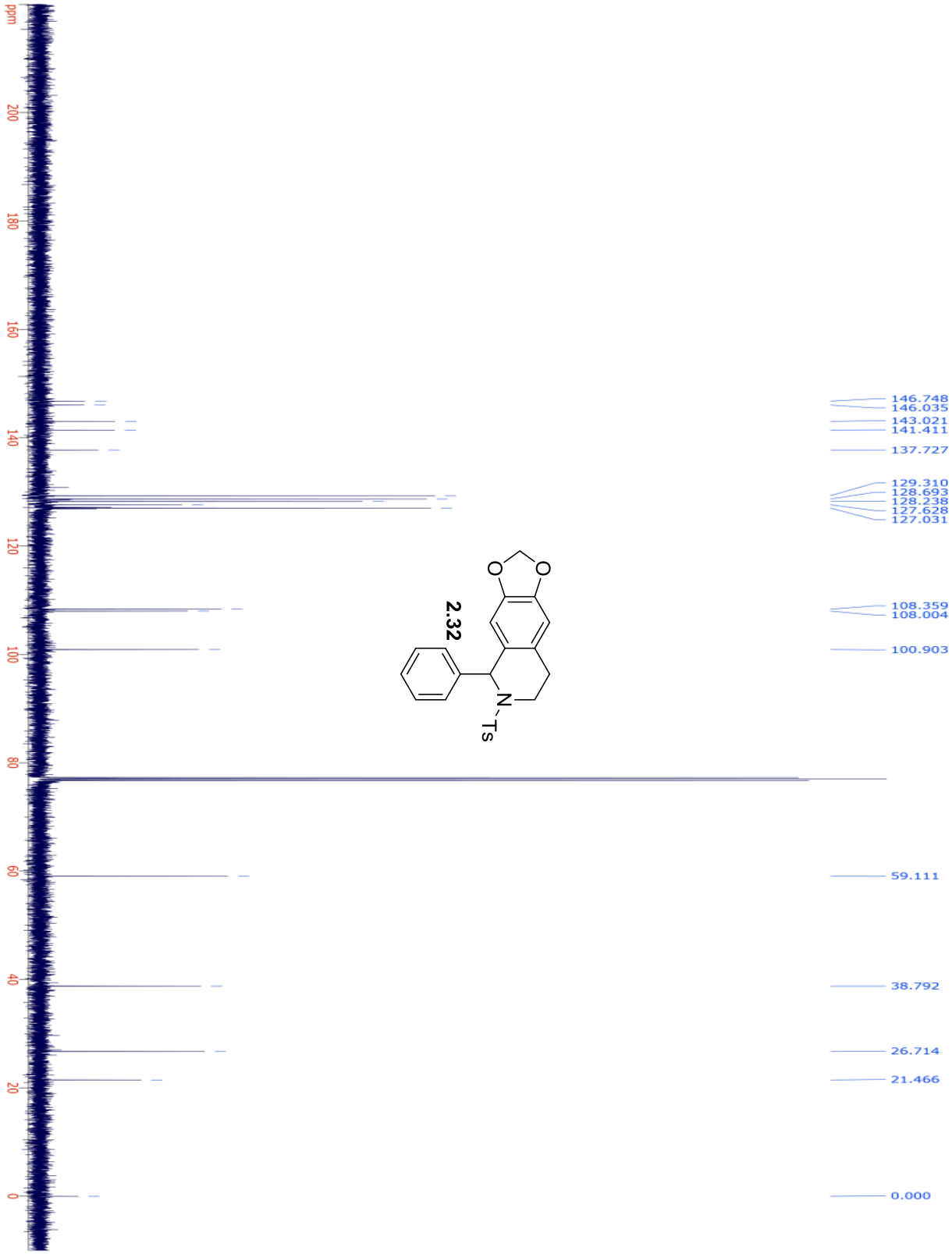
2.29b

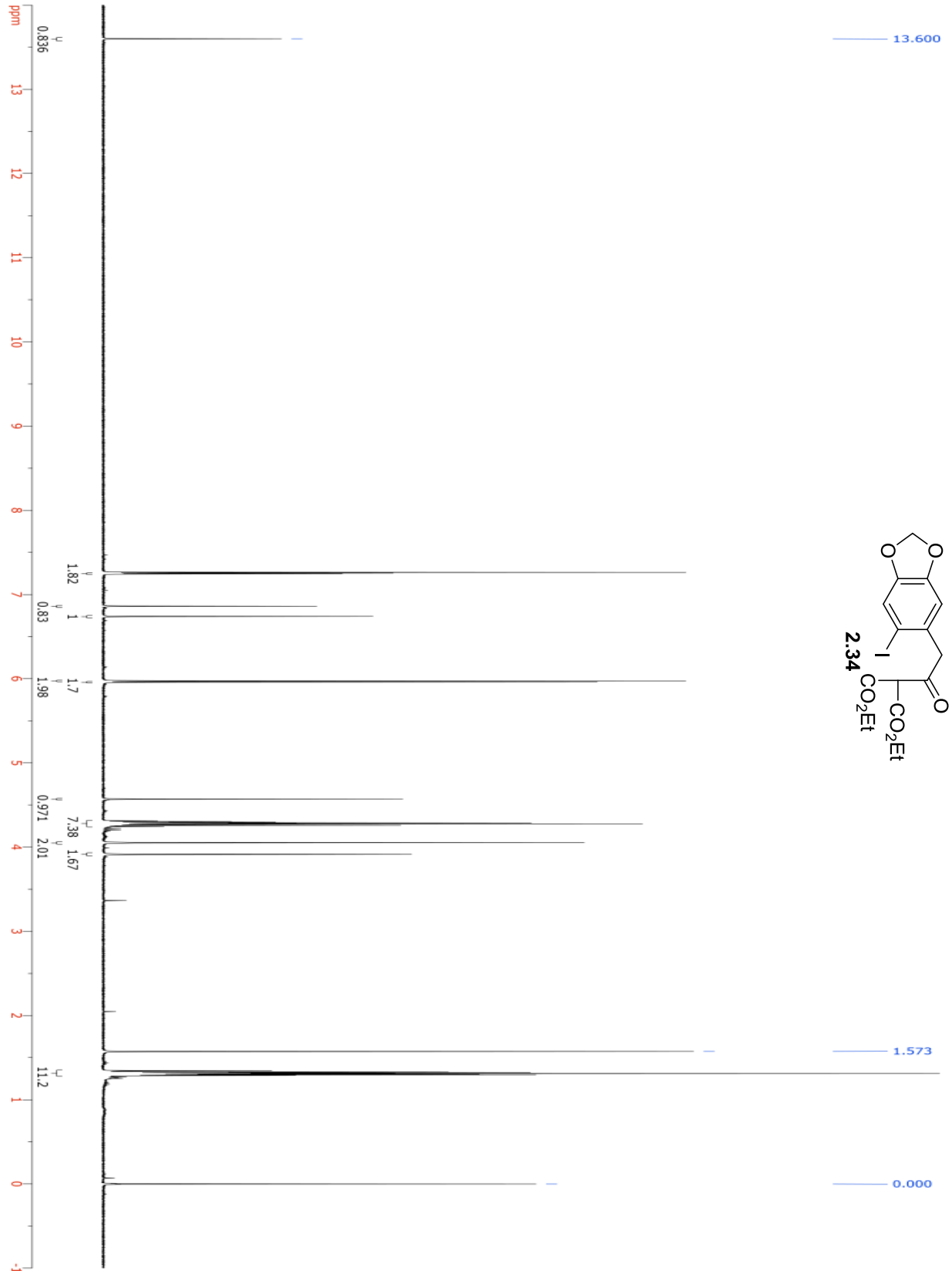

2.30bl
MeO
OMe
OMe
O
O
O
O
CO2Et
CO2Et
ppm
9
8
7
6
5
4
3
2
1
0
-1
0.226
1
0.465
1.01
2
2.02
0.987
4.72
3.15
6.27
2.05
6.25
7.474
7.093
6.641
6.229
6.019
5.053
4.174
4.002
3.796
3.729
3.298
3.262
3.231
3.195
1.190
1.176
1.162
1.150
1.136
1.122
0.000

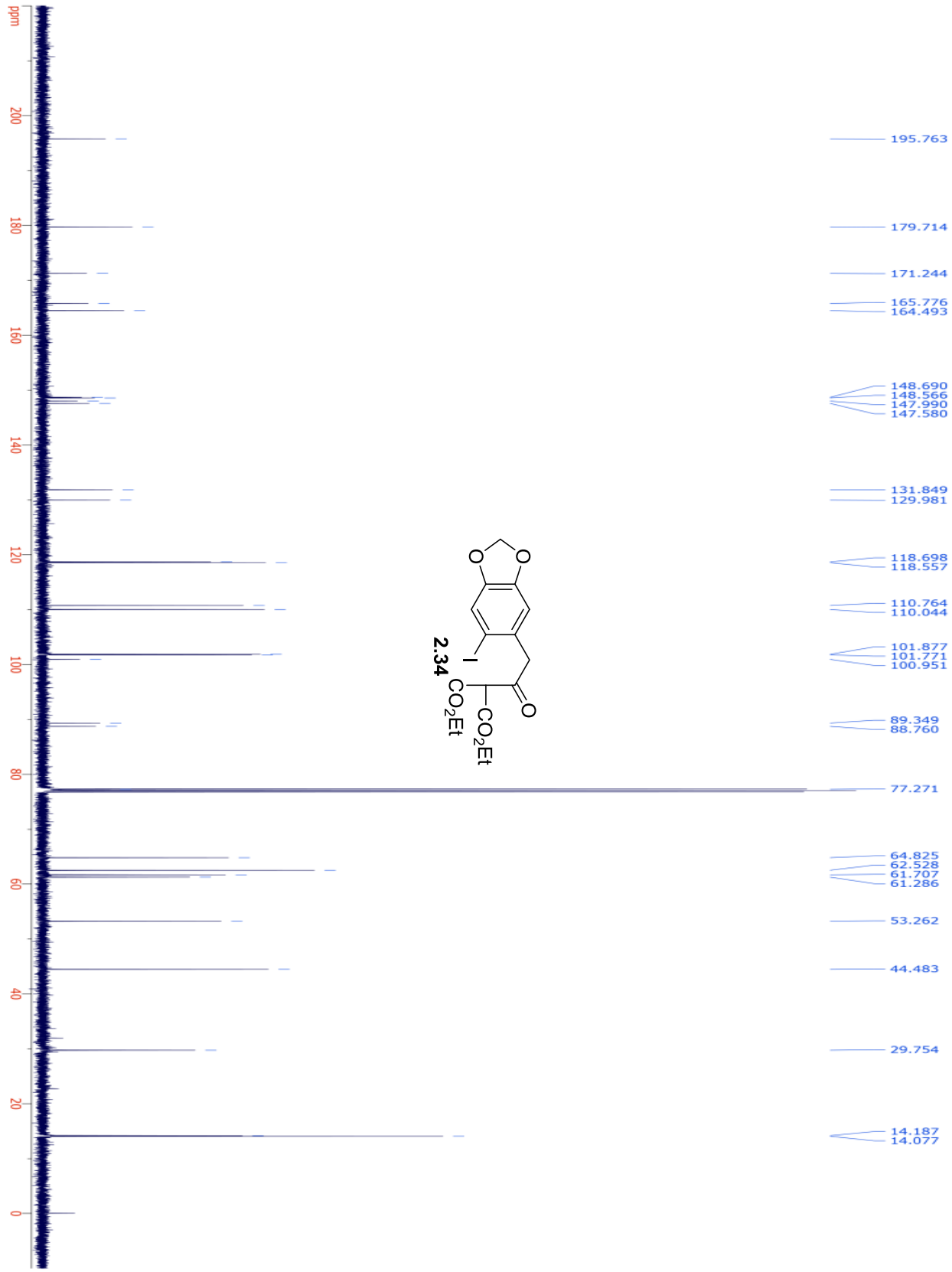

2.30bl
MeO
OMe
OMe
O
O
O
O
CO2Et
CO2Et
ppm
200
180
160
140
120
100
80
60
40
20
0
193.054
169.448
167.979
153.363
153.142
147.895
140.544
137.606
132.934
129.508
128.788
126.340
108.813
106.758
105.459
102.059
62.387
62.022
60.824
59.941
56.113
49.791
38.423
13.917
13.849

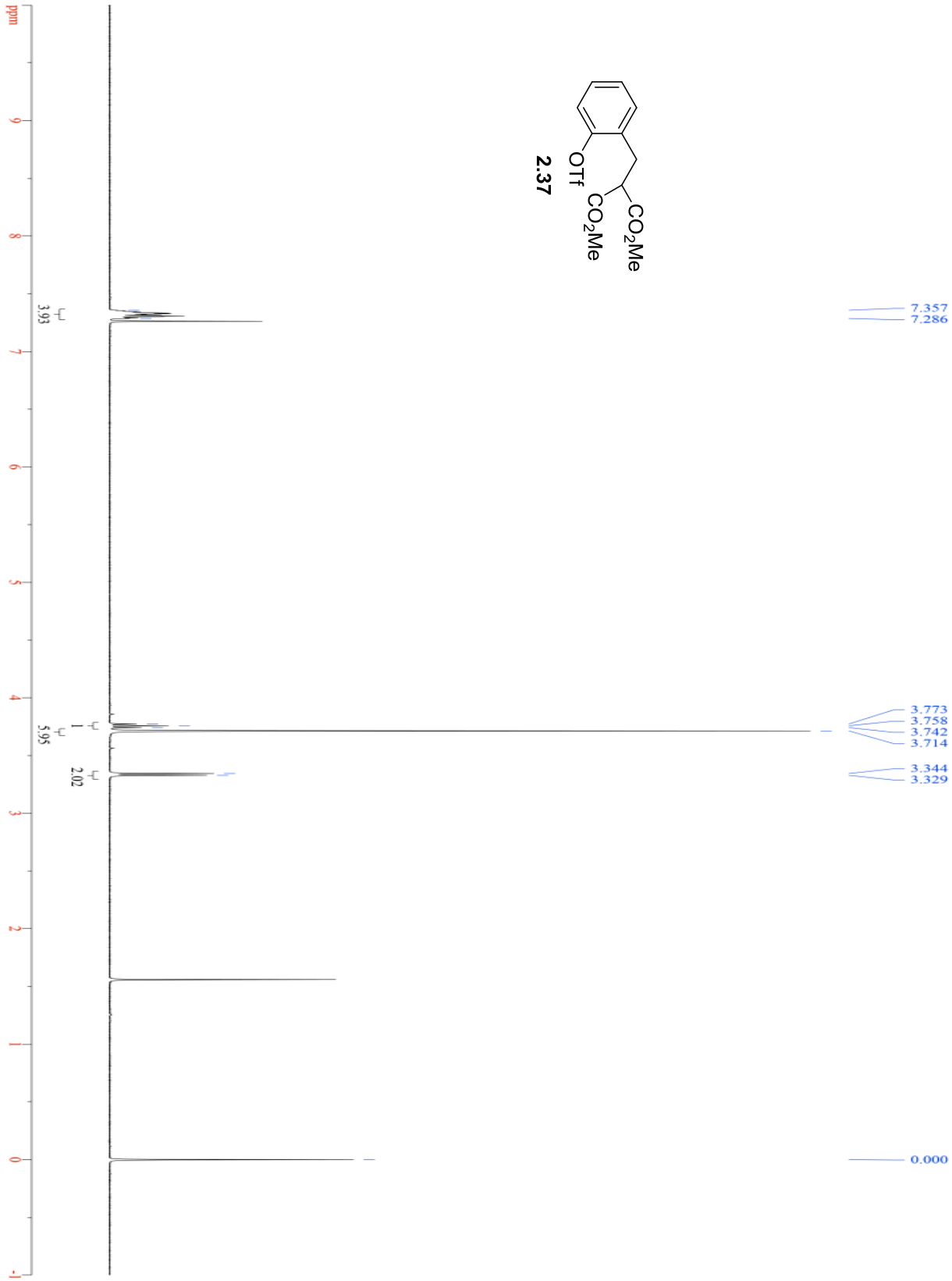

ppm
9
8
7
6
5
4
3
2
1
0
-1
2.03
2.14
0.981
1
2.12
1.01
2.07
2.06
3.2
7.728
7.711
7.288
7.272
7.148
6.637
5.933
4.708
4.696
4.684
3.173
3.159
3.146
3.132
2.824
2.809
2.795
2.418
0.000
2.31
O
O
I
NHTs

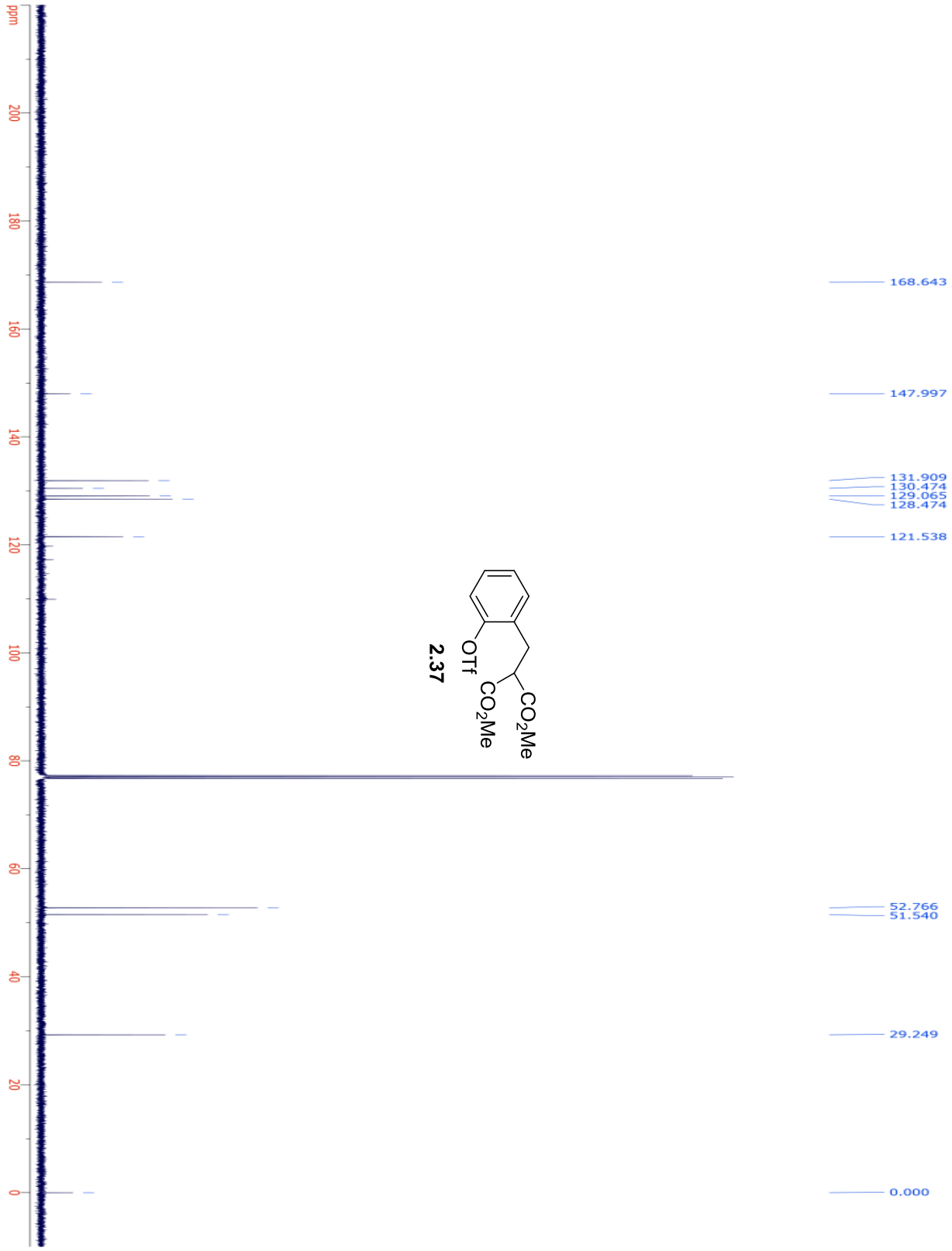

ppm
9
8
7
6
5
4
3
2
1
0
-1
2.02
5.08
2.03
2
2
1
2.03
1.02
1.01
1.02
3.13
1.18
7.573
7.557
7.287
7.241
7.211
7.195
7.129
7.113
6.431
6.112
5.909
5.901
3.752
3.742
3.724
3.713
3.268
3.258
3.246
3.236
3.230
3.217
3.207
2.601
2.587
2.578
2.566
2.555
2.545
2.532
2.468
2.464
2.459
2.454
2.435
2.430
2.426
2.419
2.348
0.000
2.32
O
O
N
Ts

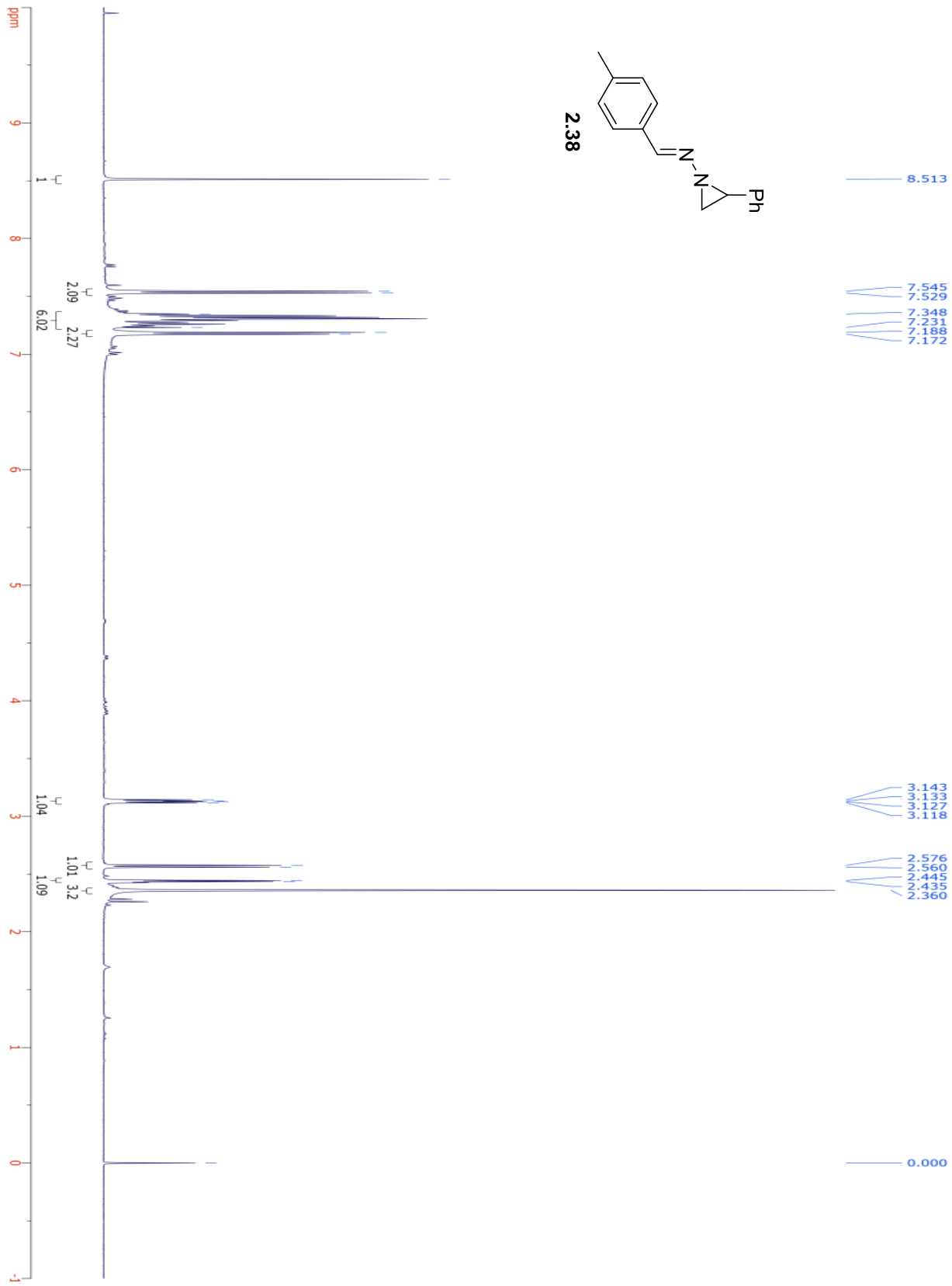

ppm
200
180
160
140
120
100
80
60
40
20
0
146.748
146.035
143.021
141.411
137.727
129.310
128.693
128.238
127.628
127.031
108.359
108.004
100.903
59.111
38.792
26.714
21.466
0.000
2.32
O
O
N
Ts

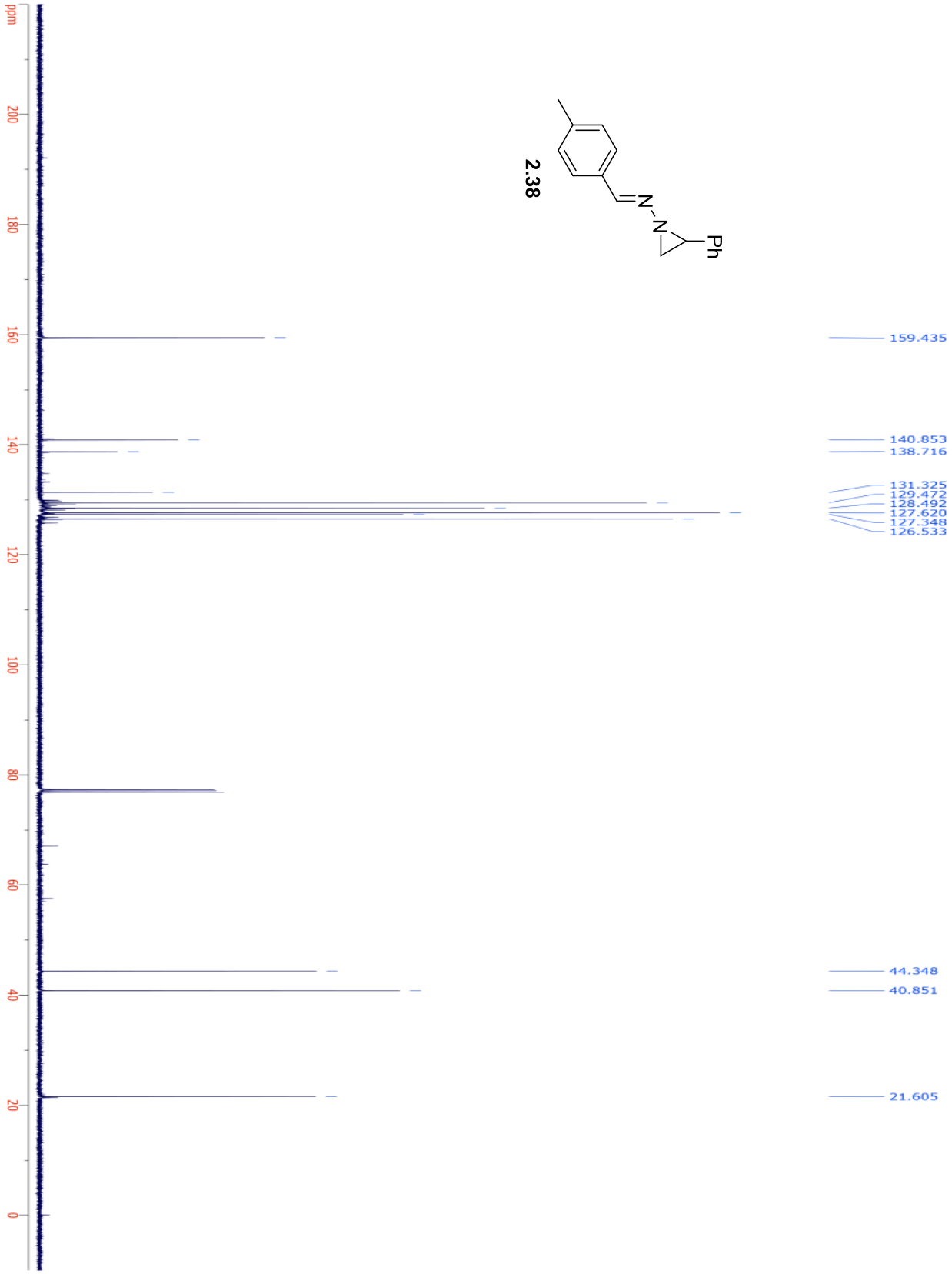

ppm
13.600
1.573
0.000
0.836
1.82
1
0.83
1.98
1.7
0.971
7.38
1.67
2.01
11.2
2.34
I
CO2Et
CO2Et
O
O
O


ppm
200
180
160
140
120
100
80
60
40
20
0
195.763
179.714
171.244
165.776
164.493
148.690
148.566
147.990
147.580
131.849
129.981
118.698
118.557
110.764
110.044
101.877
101.771
100.951
89.349
88.760
77.271
64.825
62.528
61.707
61.286
53.262
44.483
29.754
14.187
14.077
2.34
I
CO2Et
CO2Et
O
O
O


ppm
9
8
7
6
5
4
3
2
1
0
-1
3.93
1
5.95
2.02
7.357
7.286
3.773
3.758
3.742
3.714
3.344
3.329
0.000
OTf
CO2Me
CO2Me
2.37


ppm
200
180
160
140
120
100
80
60
40
20
0
168.643
147.997
131.909
130.474
129.065
128.474
121.538
52.766
51.540
29.249
0.000
OTf
CO2Me
CO2Me
2.37


2.38
Ph
8.513
7.545
7.529
7.348
7.231
7.188
7.172
3.143
3.133
3.127
3.118
2.576
2.560
2.445
2.435
2.360
0.000
ppm


ppm
200
180
160
140
120
100
80
60
40
20
0
2.38
N
N
Ph
159.435
140.853
138.716
131.325
129.472
128.492
127.620
127.348
126.533
44.348
40.851
21.605