Palladium-Catalyzed Alkene Difunctionalization Reactions: Synthesis of Functionalized Heterocycles and Mechanistic Investigation

by

Janelle Kathryn Kirsch

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Doctoral Committee:

Professor John P. Wolfe, Chair
Professor John Montogmery
Associate Professor Pavel Nagorny
Assistant Professor Alison R. H. Narayan

Janelle K. Kirsch

jakirsch@umich.edu

ORCID iD: 0000-0003-4230-9068

Dedication

To everyone who helped me get here – Thank you

To Brinkley – I will see you on the Rainbow Bridge

Acknowledgements

I am not sure I could have had a better PI for my graduate school career than Professor John P. Wolfe. John always made time and answered his office door when I knocked looking for help and guidance. I will never forget his eagerness to help me analyze an NMR, show me how to use/fix an instrument or the glove box, or help me set up a reaction that no one in lab has run before. I think John's motivations are 50% he is just that kind and excited about chemistry and 50% he just really misses lab and will take any chance he can get to stop working at his computer. This became very apparent when John came back into lab to help Evan and I on a teaching lab project. Long story short, we needed to do a large scale synthesis and didn't have enough time/ "man power" to get it done and John volunteered to help get it done. However, after not working in lab for 10+ years, nothing was where John thought it should be. Watching John look around lab for the glassware he needed was one of the funniest things I will remember about grad school. John's love for chemistry and his almost encyclopedia knowledge of it has been, and will continue to be, inspiring for me. Thank you for allowing me to be part of The Pack.

Professor Jeff Johnson at Hope College has been the most important mentor of my life. Jeff never pushed me to go to grad school, but I *never* would have gone without his amazing guidance. I don't remember interacting with Jeff much before I started working on my orgo 2 lab "special project," but Jeff's superb reputation preceded him and I'm so thankful that I was able to work for and learn from him. Jeff taught me so much and

continues to answer the call if I need advice or need to complain about grad school life. And of course, he taught me one of the most important skills, how to play Kubb.

Jeff also had an awesome group culture that allowed me to build my friend circle at Hope and connect me to the ever-growing list of group alumni. Theme week during summer research was the best and I love seeing the tradition continue through reading the yearly newsletter! Thanks to Joey, Sarah, Erik, Kimbo, James, and Patrick for being great friends and/or mentors.

Thank you to all my teachers and Professors over the years both inside and outside of STEM for helping me grow and develop as a student and person. Especially thank you to Mr. Mooney, Ms. Wright, Mrs. Hessling, Mr. & Mrs. Lapine, Mrs. Sorenson, Ms. Murdock, and of course Mrs. Wood and Mrs. Pleiness for that awesome year of Preschool.

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Thank you to all the undergraduate students I've interacted with at the University of Michigan either through teaching or in the Wolfe lab. Thank you to the undergraduate students I've mentored over the years including Dali, Mike, Mason, and Jenna. You have all made me a better teacher, mentor, and chemist and I will always be so proud of you all! I especially want to thank Jenna & Mason, who I spent the most time with; I am eternally grateful for all your contributions to the projects I have worked on.

Thank you to my lab mate Elsa. I'm really happy that we could bond over our love for Disney, gossip, organization, and exasperation over some crazy thing that Evan was doing. I have a lot of great memories of sitting in your desk area, including helping/talking about your wedding! I'm grateful that I was able to watch you go through the departmental

requirements and learn from you in the lab. I will forever appreciate all our long talks, the advice you have given me, and of course all the amazing baking you brought into lab.

Thank you to Evan my “work husband.” I cannot believe I’m such good friends with “that one first-year that wears Green Bay cheesehead earmuffs,” but I’m honestly super lucky to have you as a friend and lab mate. You’ve always been unbelievably supportive, kind, and willing to help me with whatever I need. I do miss Doritos and Dominos pizza Evan, but I’m happy you’re living a healthier lifestyle now. You’re one of the most motivated people I know working like crazy in the lab day in and day out and rarely complain about your 20 spot columns. Hopefully, we can go fishing sometime and continue to debate whether college football or the NFL is better.

I would like to thank my college friends Lauren, Michael, Amber, Liz, and Amy for being supportive and great friends during my graduate school career. Thank you for all the chats, texts, and visits over the years where I could complain about grad school and also be thankful of the career path I had chosen. Amber and Liz, thank you for asking me to be a part of your weddings! Barrows, thank you for our “monthly” chats and help with random excel or word questions! Messer, thank you for coming to visit on my birthday every year and going golfing in the summer. I can’t wait for our next margarita pitcher!

Thank you to all the older Stephenson/Schindler ladies for inviting myself and other ladies in my year to social events. It really meant a lot of have a strong culture of women doing great chemistry and supporting one another in the department.

Thank you, Becky, for becoming such a great friend over the years. I couldn’t have made it through all of the departmental requirements and the job hunt without your expertise! I continue to look up to you and hope I will be just as successful as you.

Amie and Annabel, I literally have no idea what I would have done without you two! Amie, thank you for being a great rotation buddy! Thank you for studying with me practically every night after our dinner at Panera. Shout out to Caleb for all the rides home after studying in Chem late. Annabel, thank you for being my climbing buddy and pushing me to be active throughout grad school and always being my tailgate, football seat, and bar hopping buddy! Your motivation and positive attitude have always been something I've tried to emulate. Thank you both for always being willing to read over documents, listen to practice talks, study together, celebrate together, and video chat during Covid-19 for hours on end! I am so happy and thankful to have you both as my grad school colleagues and friends!

Thank you to my Grandparents and many Aunts, Uncles, and Cousins for your love and support. Yes, I am almost done with school!! Especially thank you to Kerri, Kevin, Charlotte, and Sadie for your love, support, advice, "play-dates", home-cooked meals, and washer/dryer.

Thank you to my parents, Mike & Kathy, siblings, Andy & Angie, Jolene & Jimmy, and Jacqueline & Brayden, and my nephew, Harvey. I will never be able to say thank you enough for all your love and support. I am sure you never understood why I wanted to go to grad school or what it entailed, but you were always my biggest cheerleaders. Thank you. Thank you. Thank you.

Thank you to the best dog Brinkley. I love you and miss you so much! Seeing you was my favorite part about going home; my chemistry problems didn't matter when you needed a good belly rub. I'll see you on the Rainbow Bridge.

Thank you to Brandon; I’m so lucky to have found you. You’ve been there to support me, encourage me, celebrate my accomplishments, laugh with me, and hug me when I cry. I’m so happy to have you as my adventure partner for the next stage of my life.

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List of Schemes

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List of Abbreviations

A ..... angstrom

α ..... alpha

acac ..... acetylacetone

acac [$Pd(acac)_2$] ..... acetylacetonate

acac-F_6 ..... hexafluoroacetylacetonate

app ..... apparent

aq ..... aqueous

Ar ..... aryl (when bound to another atom)

β ..... beta

Boc ..... *tert*-butyloxycarbonyl

Bn ..... benzyl

br. ..... Broad

Bz ..... benzoyl

ca ..... circa

calcd ..... calculated

CN ..... cyano

Cp ..... cyclopentadienyl

Cy ..... cyclohexyl

°C ..... degrees Celsius

d ..... doublet

dba ..... dibenzylideneacetone

DCM ..... dichloromethane/methylene chloride

dd ..... doublet of doublets

ddd ..... doublet of doublet of doublets

ddt ..... doublet of doublet of triplets

DMF ..... dimethylformamide

DMSO ..... dimethylsulfoxide

dppf ..... 1,1'-bis(diphenylphosphino)ferrocene

dr ..... diastereomeric ratio

eh 2-ethylhexanoate

equiv ..... equivalents

eq ..... equation

er ..... enantiomeric ratio

ESI ..... electrospray ionization

Et ..... ethyl

EtOH ..... ethanol

(g) ..... gas

h ..... hour(s)

HFIP ..... hexafluoroisopropanol

HRMS ..... high resolution mass spectrometry

IR ..... infrared spectroscopy

LiHMDS/KHMDS ..... lithium/potassium hexamethyldisilazide

J ..... coupling constant

L_n/L ..... general ligand

M ..... molar (mol/L)

m ..... multiplet

mCPBA ..... *meta*-chloroperoxybenzoic acid

Me ..... methyl

MeOH ..... methanol

m.p. ..... melting point

MS ..... molecule sieve

Ms ..... mesyl

MTBE ..... methyl *tert*-butyl ether

NBS ..... *N*-bromosuccinimide

NMR ..... nuclear magnetic resonance

Nuc/Nuc-H ..... nucleophile

OAc ..... acetate

OMe ..... methoxy

O^{t}Bu ..... *tert*-butoxide

OTf ..... triflate

p ..... para

Pd ..... palladium

Pd/C ..... palladium on carbon

pent ..... pentet

PG/P ..... protecting group

Ph ..... phenyl

PMP ..... para-methoxyphenyl

prep TLC ..... preparative thin-lay chromatography

q ..... quartet

rbf ..... round-bottom flask

rt ..... room temperature

s ..... singlet

satd. ..... Saturated

t ..... triplet

t ..... tert

^{t}-butyl/^{t}-Bu ..... *tert*-butyl

TEA ..... triethylamine

TEMPO 2,2,6,6-tetramethyl-1-piperidinyloxy

Tf ..... triflyl

TFA [Pd(TFA)$_2$] ..... trifluoroacetate

TFA ..... trifluoroacetic acid

Tf_2O ..... triflic anhydride

THF ..... tetrahydrofuran

TLC ..... thin-layer chromatography

TMS ..... trimethylsilyl

Ts ..... tosyl

T. S ..... transition state

R ..... general functional group

X ..... general halide, counterion, or atom

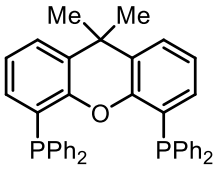
Y ..... general heteroatom

Z ..... general atom or substitution

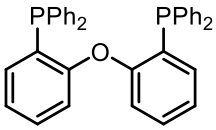
List of Ligands

The ligands drawn in this section are referenced by name throughout this dissertation. They are illustrated here for the reader's convenience.

Other Phosphine Ligands

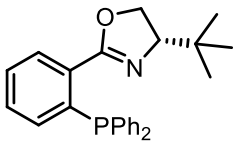


Xantphos

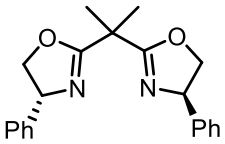


DPE-Phos

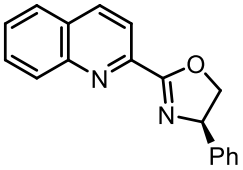
Phox, Box, PyBox, and Quinox Ligands



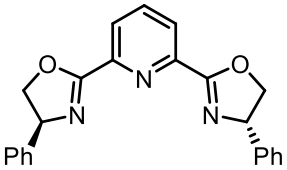
(*S*)-*t*-BuPhox



(*R*)-Ph-Box

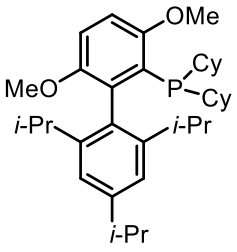


(*R*)-Ph-Quinox

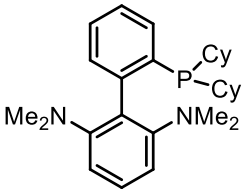


2,6-Bis[(4*S*)-4-phenyl-2-oxazolinyl]pyridine

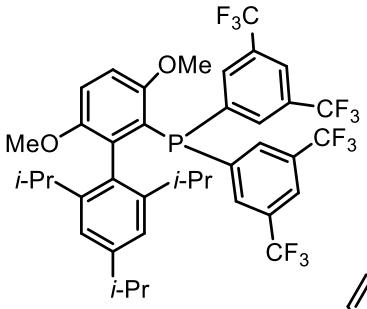
Buchwald Ligands



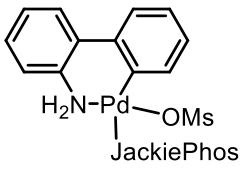
BrettPhos



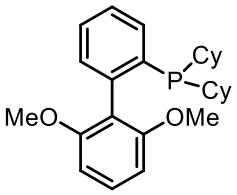
CPhos



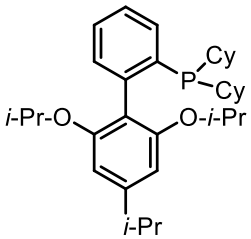
JackiePhos



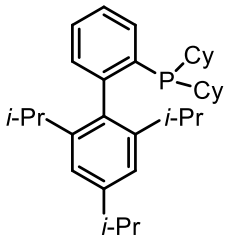
JackiePhos Pd G3



SPhos



RuPhos



XPhos

Abstract

Alkene difunctionalization reactions have allowed chemists to rapidly increase the complexity of molecules in a single transformation. This dissertation focuses on the development of Pd-catalyzed alkene difunctionalization for the synthesis of carbocycles, cyclic ureas and guanidines, and lactams. These reactions form two new bonds and a ring in a single step, providing new and important methodology for the synthesis of functionalized heterocycles.

Early work in the Wolfe lab, described in Chapter 1 of this dissertation, laid the groundwork for the synthesis of heterocycles via Pd-catalyzed alkene difunctionalization reactions where a nucleophile with a tethered alkene is coupled with an exogenous electrophile. In later work, this three-component reaction was altered to instead have the nucleophile be the external piece. In Chapter 2, my work in this field is described, in which indole and pyrrole derivatives are coupled with aryl or alkenyl triflates bearing tethered alkenes to afford 3-cyclopentylindole derivatives. The products of this reaction are formed in moderate to good yields with excellent >20:1 diastereoselectivity when employing alkenyl triflates as the coupling partner. The mechanism of this transformation is proposed to proceed via a Pd(0)/Pd(II) catalytic cycle.

My work has also involved the development of Pd-catalyzed alkene diamination reactions; the progress by others in this field is described in Chapter 3. My studies on alkene diamination involved the coupling of *O*-acylated hydroxylamine derivatives with guanidines or ureas bearing pendant alkenes. These reactions produced cyclic guanidine

and urea products bearing attached dialkylaminomethyl groups. The initial work on this transformation is detailed in Chapter 4. The products were formed in good to excellent yields with three different amine electrophiles. Additionally, we found the reaction proceeded with up to 7:1 dr favoring *anti*-addition to the double bond. The imperfect stereocontrol results from competing *syn*-aminopalladation vs *anti*-aminopalladation.

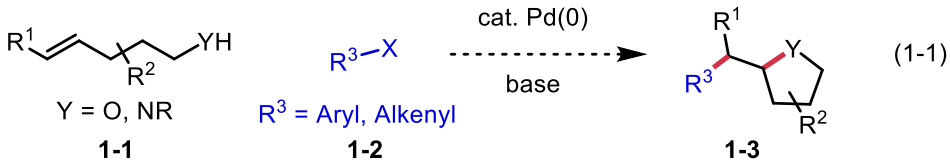
Further studies on the scope and mechanism of these new Pd-catalyzed alkene diamination reactions are described in Chapter 5. Through NMR studies and isolation and characterization of side products, we discovered that our initially proposed Pd(0)/Pd(II) catalytic cycle is not operating. We have evidence to suggest the diamination reaction is proceeding through a Pd(II)/Pd(IV) catalytic cycle. Additionally, control experiments revealed that acac, not the phosphine ligand JackiePhos, is the critical ligand for Pd in this transformation. From these discoveries, we have been able to utilize acac-derived ligands to promote previously difficult or unsuccessful reactions for the formation of cyclic ureas, guanidines, and lactams. In addition, unexpected reactions, as well as efforts to develop an *in situ* preparation of the electrophiles, are also described.

Chapter 1

Introduction to Palladium-Catalyzed Alkene Difunctionalization Reactions

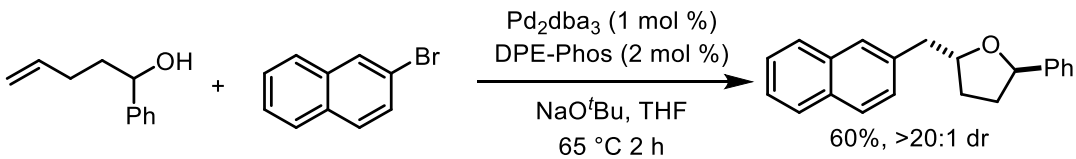
1.1 Palladium-Catalyzed Alkene Difunctionalization Reactions that Proceed via *Syn*-Nucleopalladation

Difunctionalization of alkenes is a powerful tool in organic synthesis due to the ability to form two new bonds in a single transformation.[1] This rapidly increases the complexity of a molecule allowing for intricate molecules to be synthesized in fewer steps. The Wolfe group has focused on Pd-catalyzed alkene difunctionalization reactions since the early days of the lab.[2] In general, these reactions combine a heteroatom nucleophile



(1-1)

(oxygen or nitrogen) that contain a tethered alkene (**1-1**) and an external electrophile (an aryl or alkenyl halide or triflate) (**1-2**) in the presence of a Pd-catalyst and a base to produce a product in which a ring, one C-C bond and one C-heteroatom bond are formed (**1-3**, eq 1-1). The first related publication from the Wolfe group was in 2004, the synthesis of tetrahydrofurans from aryl bromides and γ-hydroxy alkenes (eq 1-2).[3] This method was

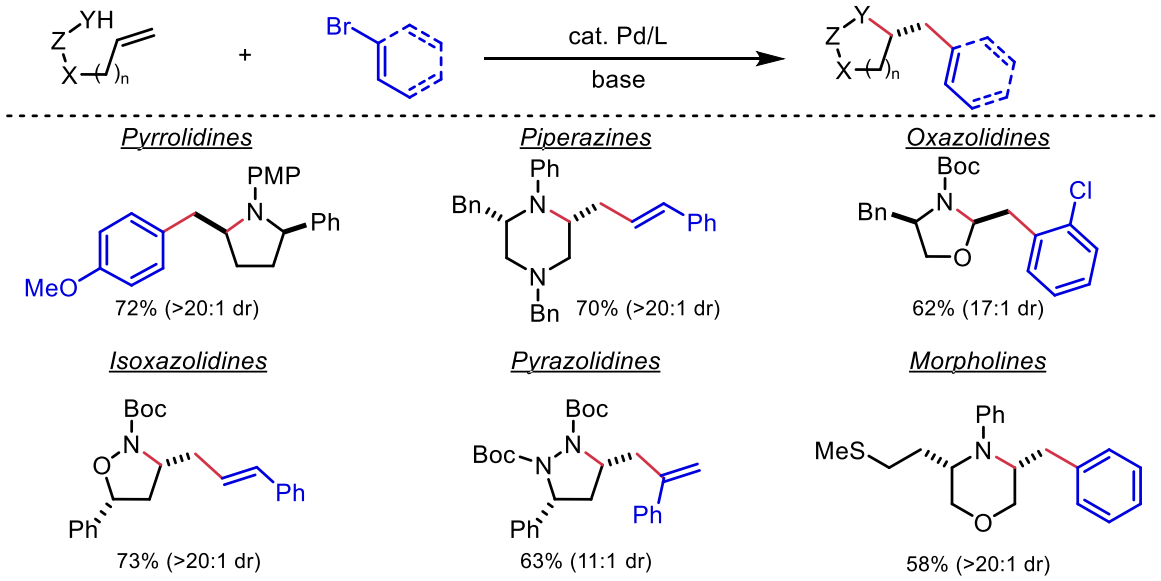


(1-2)

extended to the synthesis of other heterocycles including pyrrolidines, piperazines, oxazolidines, isoxazolidines, pyrazolidines, and morpholines (Scheme 1-1).[2a,4] These

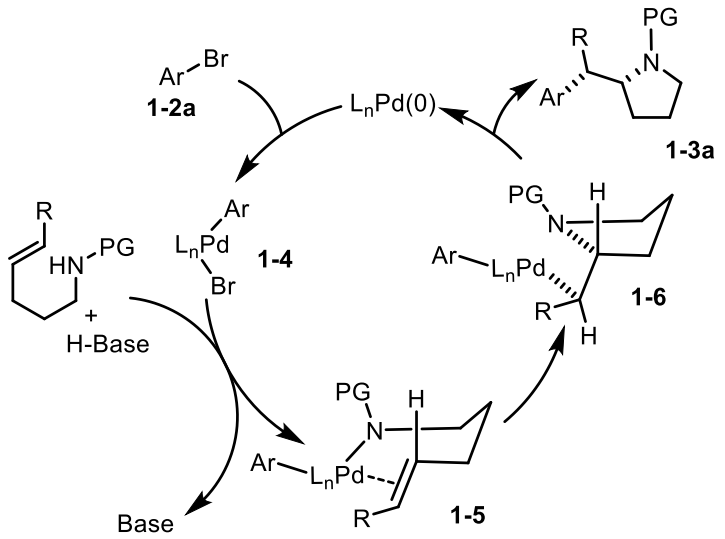
types of heterocycles are of interest to the Wolfe group due to their prevalence in many biologically active molecules.[5]

Scheme 1-1: Selected Examples of Heterocycles Prepared Through Pd-Catalyzed Alkene Difunctionalization



These reactions are proposed to proceed through a Pd(0)/Pd(II) catalytic cycle (Scheme 1-2). The Pd(0) species is initially oxidized by aryl-halide **1-2a** to Pd(II). The Pd

Scheme 1-2: Proposed Catalytic Cycle with *Syn*-Aminopalladation

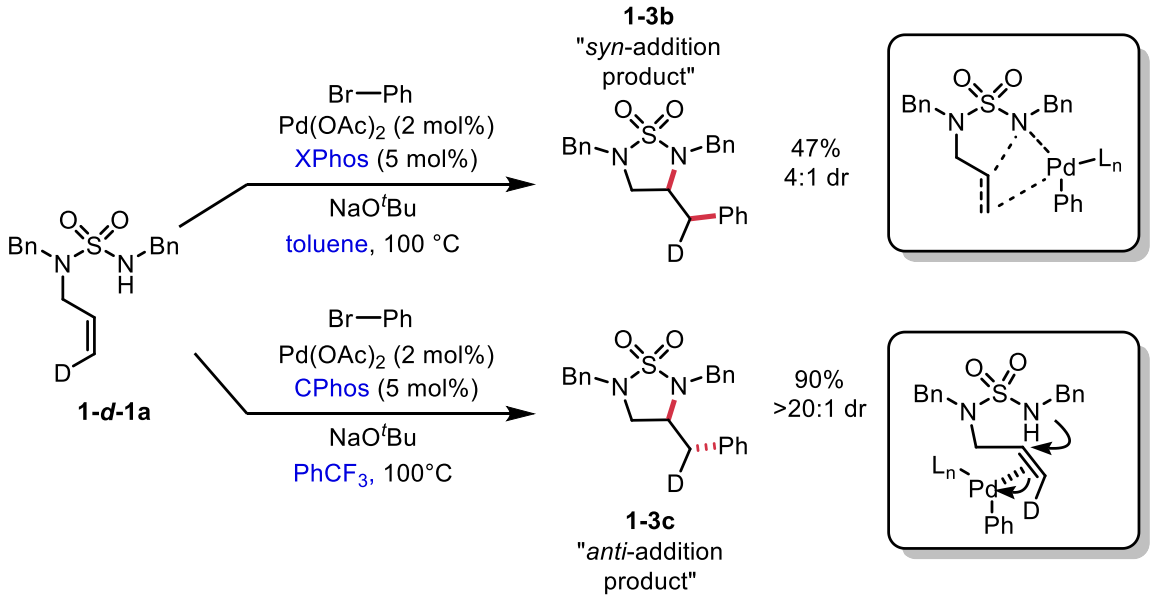


intermediate **1-4** then coordinates to the amine and alkene as shown in **1-5**. *Syn*-aminopalladation occurs so that the C-N and C-Pd bonds formed are *syn* to each other in **1-6**. Following reductive elimination, substituted pyrrolidine **1-3a** is formed concurrently with the regeneration of the Pd(0) catalyst.

1.2 *Syn*- vs *Anti*-Nucleopalladation Pathways

The Pd-catalyzed alkene difunctionalization reaction was later expanded upon in the lab to include *N*-allylsulfamides.[6] However, the authors were surprised when they explored the stereospecificity of this reaction. Unlike analogous reactions conducted previously in the lab, when **1-*d*-1a** was used in this reaction the authors isolated the *anti*-product in >20:1 dr (Scheme 1-3, **1-3b**). However, they found they could favor the formation of the *syn*-product (**1-3c**) by changing the reaction conditions from XPhos and toluene to CPhos and $PhCF_3$.

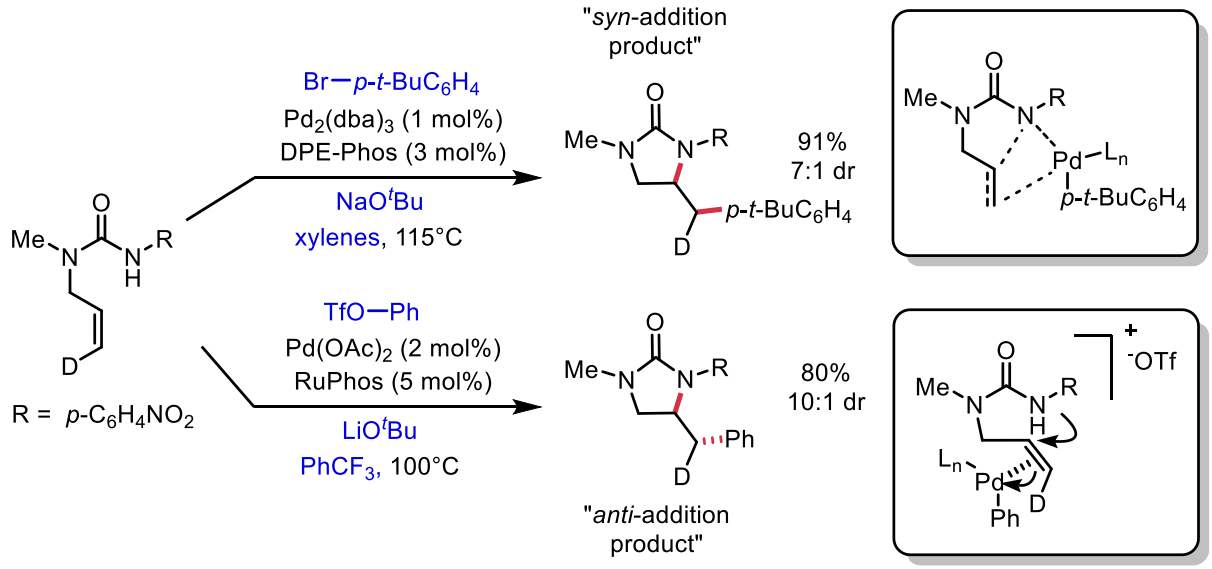
Scheme 1-3: *Syn*- vs *Anti*-Aminopalladation with *N*-Allylsulfamides



In the *syn*-aminopalladation pathway, the Pd is coordinated to the nucleophilic nitrogen prior to the aminopalladation step (Scheme 1-3). Whereas in the *anti*-aminopalladation pathway, the Pd is not coordinated to the nucleophilic nitrogen prior to

the aminopalladation and therefore the Pd and nitrogen form bonds on opposite faces of the alkene giving the relative *anti* stereochemistry. Overall, reaction conditions that favor a cationic Pd generally favor the *anti*-aminopalladation pathway. This trend was also observed when *N*-allylureas are used in the reaction (Scheme 1-4). Changing (i) the counterion of the electrophile to a less coordinating triflate, (ii) the counterion of the base to Li, and (iii) to the more polar solvent results in the *anti*-addition product being favored. The discovery of the *anti*-aminopalladation pathway in our alkene difunctionalization reactions allowed our lab to develop further methods in this field.

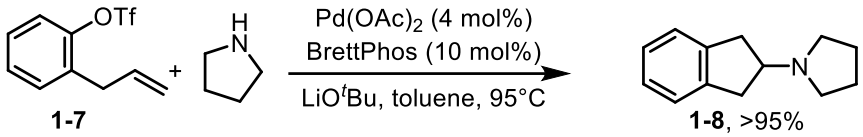
Scheme 1-4: *Syn*- vs *Anti*-Aminopalladation with *N*-Allylureas



1.3 Palladium-Catalyzed Alkene Difunctionalization with Exogenous Nucleophiles

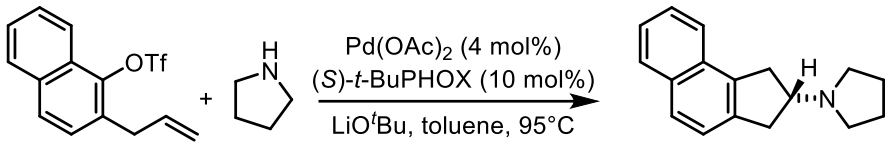
With the discovery that these types of alkene difunctionalizations can occur through an *anti*-nucleopalldation pathway, former group member Derick White was interested in changing the arrangement of the three required components – alkene, nucleophile, and electrophile – in a manner that would provide access to carbocycles. Carbocycles are commonly found in biologically active molecules such as steroids[7] and terpenes[8], which are vastly important molecules for both animals and plants. As shown in eq 1-1 these

reactions traditionally consist of a nucleophile with a tethered alkene and an exogenous electrophile. When the conditions were changed to employ an electrophile containing a tethered alkene coupled with an exogenous nucleophile the transformation proceeded exceedingly well to form carbocyclic product **1-8** (eq 1-3).[9] Aryl triflate (**1-7**) was coupled



1-7 **1-8**, >95% (1-3)

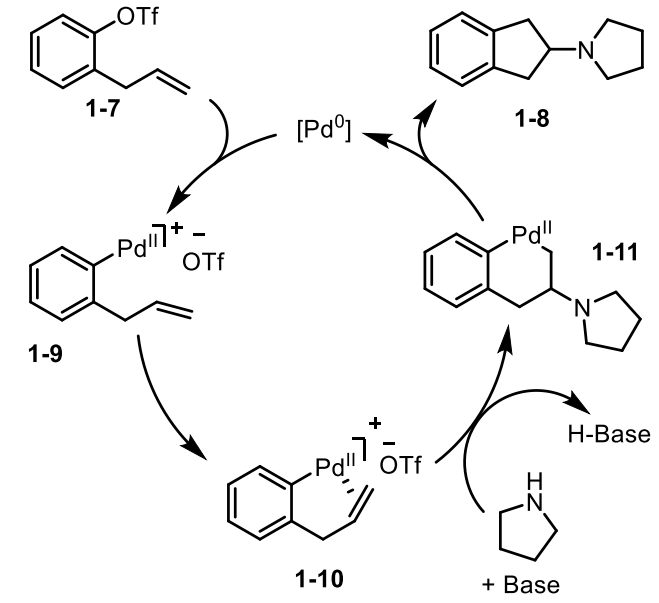
with pyrrolidine with Pd catalysis to form one C-C bond, one C-N bond, and a ring in a single transformation in quantitative yields (eq 1-3). The authors were able to extend this to asymmetric reactions to yield products in excellent yield and er (eq 1-4). The



98%, >99:1 er (1-4)

mechanism of this reaction is proposed to involve a Pd(0)/Pd(II) catalytic cycle(Scheme 1-5). After initial oxidation to the carbon-triflate bond, Pd associates to the alkene (**1-9** to **1-10**). *Anti*-aminopalldation and deprotonation then occur followed by reductive

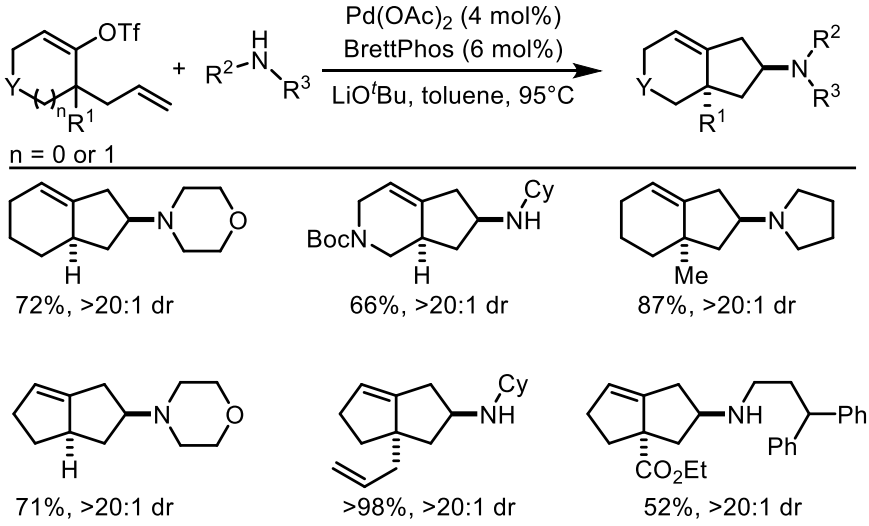
Scheme 1-5: Proposed Catalytic Cycle



elimination to form **1-8**.

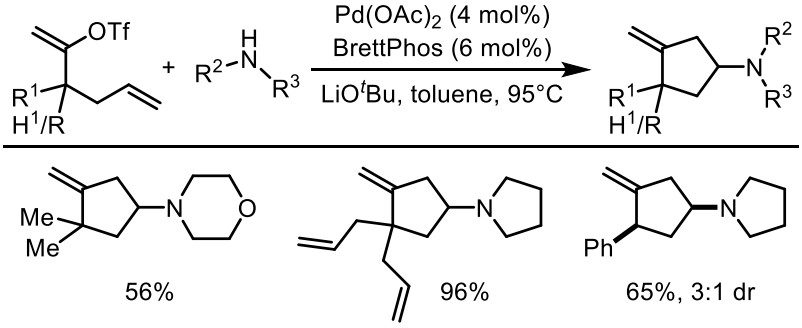
Following this initial publication, the scope was expanded beyond the use of aryl triflates.[10] With various amine nucleophiles, this reaction is tolerant of six- and five-membered alkenyl triflates, ones containing heterocycles or containing a second allyl chain, and acyclic ones (Scheme 1-6-7). The products from these reactions are formed

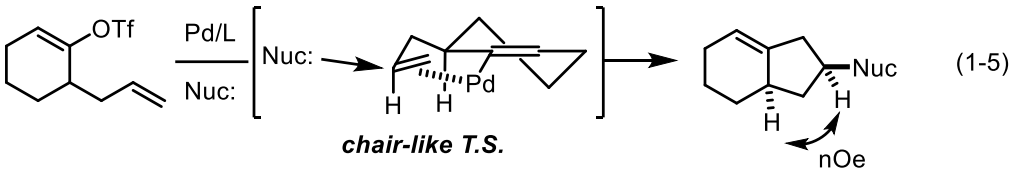
Scheme 1-6: Selected Scope of Alkenyl Triflates and Amine Nucleophiles



in good to excellent yields and excellent diastereoselectivities. It is proposed that the high observed diastereoselectivities is due to a highly structured chair-like transition state in which the alkene is positioned to avoid unfavorable 1,3-diaxial strain (eq 1-5).

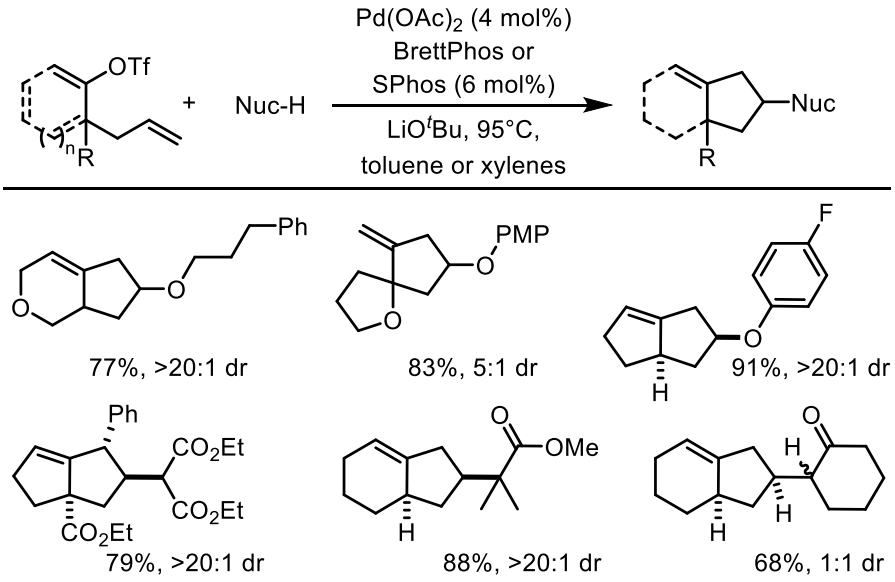
Scheme 1-7: Selected Scope of Acyclic Alkenyl Triflates and Amine Nucleophiles





The scope was then expanded to include alcohol and stabilized carbanion nucleophiles (Scheme 1-8).[11] These reactions again proved to be successful with aryl and alkenyl triflates. Additionally, the authors found the stabilized carbanion nucleophiles to be tolerant of internal alkenes yielding products in >20:1 dr. When carbanions containing epimerizable protons are employed, a 1:1 mixture of diastereomers is formed that are epimeric at the stereocenter adjacent to the carbonyl. (Scheme 1-8). These reactions are proposed to undergo a mechanism similar to the one shown in Scheme 1-5.

Scheme 1-8: Selected Scope of Alcohol and Carbanion Nucleophiles



1.4 Conclusion

The alkene difuctionalization reactions discussed in this chapter allow for the rapid formation of heterocycles and carbocycles via Pd-catalysis. The recent development of

the *anti*-nucleopalladation pathway allowed for the development of new alkene difunctionalization reactions in which the nucleophile, rather than the electrophile, is the exogenous piece. This has allowed for the formation of substituted carbocycles in which a ring is formed in addition to (i) one C-C bond and one C-N bond (ii) one C-C bond and one C-O bond or (iii) two C-C bonds. The ability to form highly substituted heterocycles and carbocycles in a single step continues to be a major focus of our lab today and my work in this area will be described in Chapter 2.

References

(1) (a) Togni, A.; Grutzmacher, H. Eds. *Catalytic Heterofunctionalization*; Wiley-VCH: Weinheim, 2001. (b) Beller, M.; Seayad, J.; Tillack, A.; Jiao, H. *Angew. Chem. Int. Ed.* **2004**, *43*, 3368.

(2) For recent reviews, see: (a) Schultz, D. M.; Wolfe, J. P. *Synthesis* **2012**, *44*, 351. (b) Wolfe, J. P. *Top. Heterocycl. Chem.* **2013**, *32*, 1. (c) Garlets, Z. J.; White, D. R.; Wolfe, J. P. *Asian J. Org. Chem.* **2017**, *6*, 636. (d) White, D. R.; Bornowski, E. C.; Wolfe, J. P. *Isr. J. Chem.* **2020**, *60*, doi.org/10.1002/ijch.201900108.

(3) Rossi, M. A.; Wolfe, J. P. *J. Am. Chem. Soc.* **2004**, *126*, 1620.

(4) (a) Ney, J. E.; Wolfe, J. P. *Angew. Chem. Int. Ed.* **2004**, *43*, 3605. (b) Nakhla, J. S.; Wolfe, J. P. *Org. Lett.* **2007**, *9*, 3279. (c) Giampietro, N. C.; Wolfe, J. P. *J. Am. Chem. Soc.* **2008**, *130*, 12907. (d) Lemen, G. S.; Giampietro, N. C.; Hay, M. B.; Wolfe, J. P. *J. Org. Chem.* **2009**, *74*, 2533. (e) Leathen, M. L.; Rosen, B. R.; Wolfe, J. P. *J. Org. Chem.* **2009**, *74*, 5107. (f) Ward, A. F.; Wolfe, J. P. *Org. Lett.* **2011**, *13*, 4728.

(5) (a) Cheng, T.-J. R.; Chan, T.-H.; Tsou, E.-L.; Chang, S.-Y.; Yun, W.-Y.; Yang, P.-J.; Wu, Y.-T.; Cheng, W.-C. *Chem. Asian J.* **2013**, *8*, 2600. (b) Xu, G.; Yang, X.; Jiang, B.; Lei, P.; Liu, X.; Wang, Q.; Zhang, X.; Ling, Y. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 1849. (c) Hong, X.-W.; Zhou, Y.-Q.; Bai, C.-B.; Wang, N.-X.; Xing, Y.; Zhang, W.; Wang, Y.-J.; Lan, X.-W.; Xie, Y.; Li, Y.-H. *Molecules*, **2015**, *20*, 17208. (d) Ram, V. J.; Sethi, A.; Nath, M.; Pratap, R. Five-Membered Heterocycles. *The Chemistry of Heterocycles: Nomenclature and Chemistry of Three-to-Five Membered Heterocycles*, 1; Elsevier:, 2019. (e) Berthet, M.; Cheviet, T.; Dujardin, G.; Parrot, I.; Martinez, J. *Chem. Rev.* **2016**,

116, 15235. (f) Zhong, C.; Wang, Y.; O'Herin, C.; Young, D. W. *ACS Catal.* **2013**, *3*, 643.

(6) Fornwald, R. M.; Fritz, J. A.; Wolfe, J. P. *Chem. Eur. J.* **2014**, *20*, 8782.

(7) Brueggemeier, R. W.; Li, P.-K. Fundamentals of Steroid Chemistry and Biochemistry. In *Burger's Medicinal Chemistry and Drug Discovery*, 7; Abraham, D. J.; Rotella, D. P. Eds.; Wiley, 2010.

(8) Jaeger, R.; Cuny, E. *Natural Product Communications* **2016**, *11*, 1373.

(9) White, D. R.; Hutt, J. T.; Wolfe, J. P. *J. Am. Chem. Soc.* **2015**, *137*, 11246.

(10) White, D. R.; Wolfe, J. P. *Chem. Eur. J.* **2017**, *23*, 5419.

(11) (a) White, D. R.; Herman, M. I.; Wolfe, J. P. *Org. Lett.* **2017**, *19*, 4311. (b) White, D. R.; Hinds, E. M.; Bornowski, E. C.; Wolfe, J. P.; *Org. Lett.* **2019**, *21*, 3813. (c) Bornowski, E. C.; Hinds, E. M.; White, D. R.; Nakamura, Y.; Wolfe, J. P. *Org. Process Res. Dev.* **2019**, *23*, 1610.

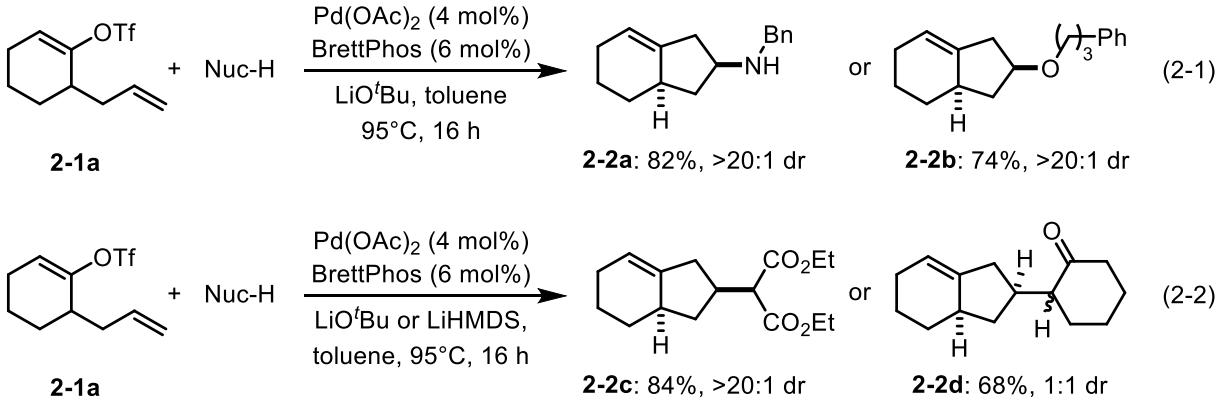
Chapter 2

Palladium-Catalyzed Alkene Carboheteroarylation Reactions for the Synthesis of 3-Cyclopentylindole Derivatives

2.1 Introduction

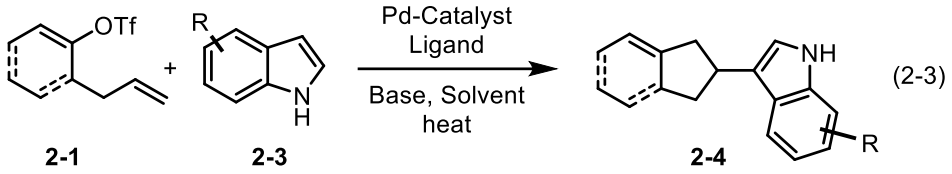
Over the past 14 years, our group has focused on the development of a number of new Pd-catalyzed alkene difunctionalization reactions.[1] Recently, we have described a new class of alkene difunctionalization reactions between aryl/alkenyl triflates (e.g., **2-1a**) bearing a tethered alkene, and exogenous amine or alcohol nucleophiles.[2] These transformations afford products such as **2-2a-b** in high yield with high diastereoselectivity, and generate a carbon-carbon bond, a carbon-heteroatom bond, and a carbocyclic ring in one step (eq 2-1). Following the report of these reactions, we sought to explore these reactions with carbon atom nucleophiles, such as malonates, ketones, and esters (eq 2-2).[3] High yields and diastereoselectivities were observed when using stabilized carbanion nucleophiles except in the cases when an epimerizable proton at a stereocenter was present. In these cases, the product is obtained in a 1:1 dr (**2-2d**).

Previous work



To further explore the scope of this method, we sought to examine transformations of heteroaromatic nucleophiles, such as indole (eq 2-3). These species

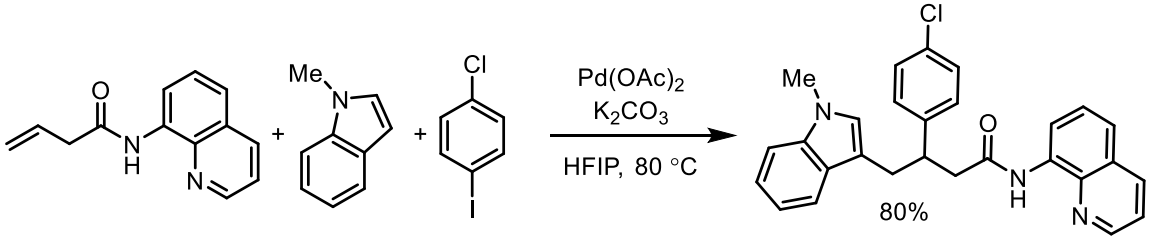
This work



(2-3)

are inherently less nucleophilic than amines, alkoxides/phenoxides, or stabilized carbanions and have been shown to act as either C-nucleophiles or N-nucleophiles under appropriate conditions in Pd-catalyzed indole alkylation/arylation reactions (eq 2-4-5).[4,5]

Engle 2016[4f]



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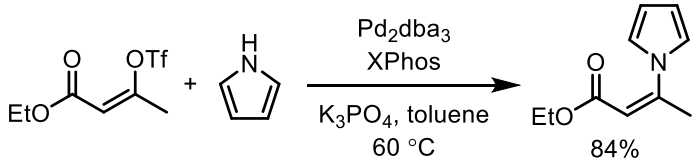
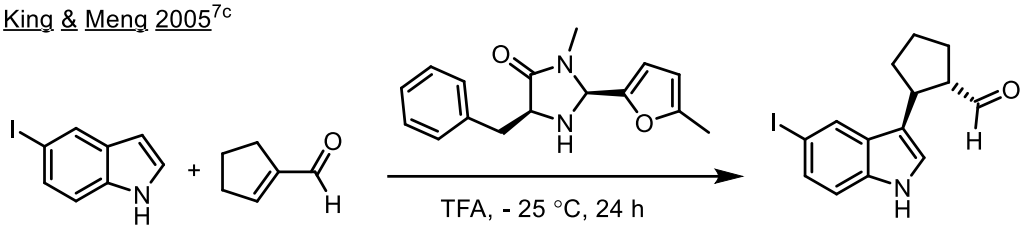
Movassaghi 2005[5b]



(2-5)

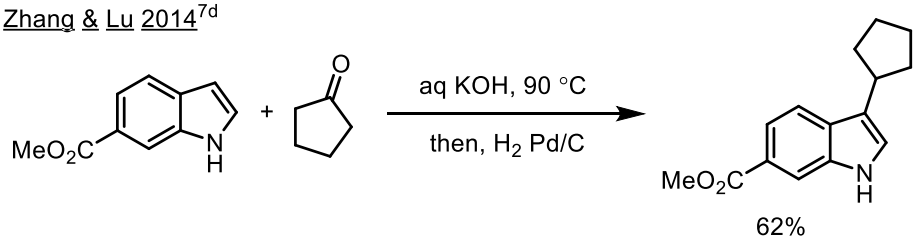
The reduction in reactivity, in addition to the possibility of product mixtures, gave us an interesting challenge for expanding the scope of Pd-catalyzed alkene difunctionalization reactions. Additionally, we took interest in synthesizing molecules containing indole due to its prevalence in natural products and pharmaceutical targets. Observed bioactivity of indole derivatives including anti-inflammatory, -cancer, -fungal, and -bacterial activity.[6] Others have constructed similar 3-cyclopentylindole derivatives using methods that typically involve either conjugate addition of indoles to α,β-unsaturated carbonyl compounds or condensation of indoles with cyclopentanones (eq 2-6-7).[7] For example, King and Meng employ a chiral imidazolidinone catalyst to form a precursor to a selective

King & Meng 2005[7c]



(2-6)

Zhang & Lu 2014[7d]



(2-7)

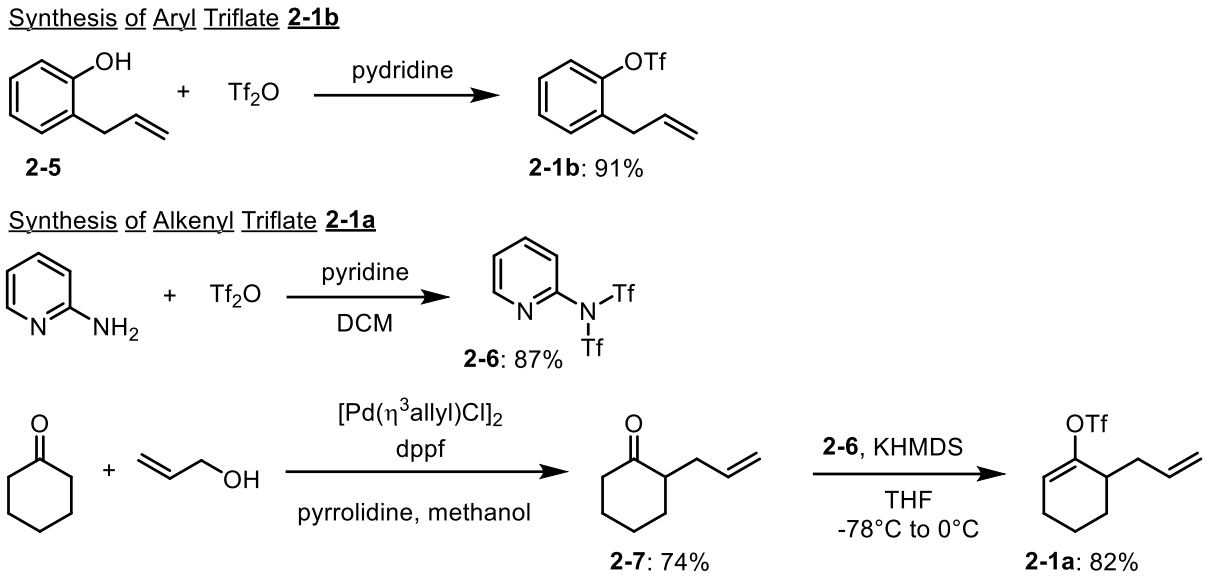
serotonin reuptake inhibitor 1 via conjugate addition (eq 2-6). Zhang and Lu form the desired precursor for their Hepatitus C virus polymerase inhibitor via condensation of their indole with cyclopentanone followed by reduction with Pd/C (eq 2-7). Nevertheless, we believe our Pd-catalyzed alkene difunctionalization method will build upon previous literature by allowing for the rapid construction of complex molecules due to the formation of two carbon-carbon bonds and a ring in a single transformation (eq 2-3).

2.2 Optimization of Reaction Conditions

The synthesis of the aryl and alkenyl triflates (**2-1a-h**) were conducted using previously reported routes (Scheme 2-1).[2a-c] **2-1b** is easily synthesized from **2-5** and trifluorormethanesulfonic anhydride in the presence of pyridine. The synthesis of alkenyl triflate **2-1a** requires the use of a more polar triflating reagent **2-6**, an analog of Comins' reagent, which can be prepared in one step from commercially available 2-aminopyridine and trifluorormethanesulfonic anhydride. Once in hand, the synthesis of **2-1a** is completed with a Tsuji-Trost allylation of cyclohexanone, and then formation of the enol-triflate.

With the limitations mentioned previously in mind, we studied various conditions in attempts to promote the alkene difunctionalization with heteroaromatic nucleophiles. In

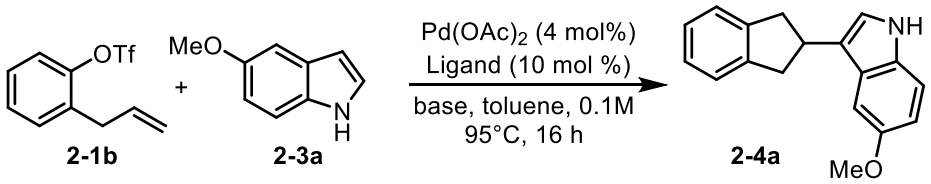
Scheme 2-1: Representative Examples of Substrate Synthesis



preliminary studies, we examined the Pd/BrettPhos-catalyzed reaction of 2-allylphenyl triflate (**2-1b**) with 5-methoxyindole (**2-3a**) because these conditions generally provided satisfactory results with amine and alcohol nucleophiles. This reaction afforded 25% of the C3-alkylated product **2-4a** as judged by ^{1}H NMR analysis of the crude reaction mixture (Table 2-1, entry 1). We did not observe the formation of the *N*-alkylated product. Other Buchwald-type biaryl phosphine ligands were screened and XPhos was found to give the best yield relative to conversion to product (entries 2-3). Increasing the temperature to 105 °C resulted in a slightly improved 40% yield (entry 4). Changing the counterion of the *tert*-butoxide base to Na or K, or changing the base to LiHMDS led to a decrease in yield due to the formation of a number of unidentified side products (entries 5-7). However, when the reaction concentration was increased to 1 M the desired product was generated in 62% yield (entry 8).

Despite some improvement during the initial optimization studies, the yields proved to be difficult to consistently reproduce. During the optimization studies, these

Table 2-1: Optimization Studies



2-1b **2-3a** **2-4a**

Entry	Ligand	Base	Conversion (%)	Yield (%)[b]
1	BrettPhos	LiO^{t}Bu	75	25
2	RuPhos	LiO^{t}Bu	75	Trace
3	XPhos	LiO^{t}Bu	25	25
4	XPhos	LiO^{t}Bu	85	40[c]
5	XPhos	NaO^{t}Bu	>95	<50[c,d]
6	XPhos	KO^{t}Bu	>95	0[c]
7	XPhos	LiHMDS	65	5[c]
8	XPhos	LiO^{t}Bu	>95	62[d]

[a]Conditions: 1.0 equiv 1b, 1.2 equiv 3a, 4 mol % Pd(OAc)2, 10 mol % ligand, 1.4 equiv base, toluene (0.1 M), 95 °C,16 h. [b]Yields were determined by ^{1}H NMR analysis using phenanthrene as an internal standard. [c]The reaction was conducted at 105 °C. [d]This material contains ca 30% of an unidentified side product. [e]The reaction was conducted at 1 M concentration.

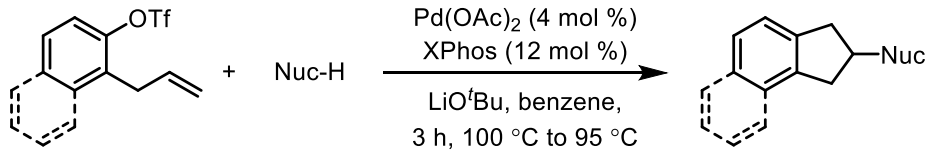
reactions were conducted in glass vials with screw caps and heated in a metal heating block. When we increased the reaction concentration to 1 M, we began to notice that the solvent would completely evaporate after the 16 hour reaction time in some of the vials. While in other vials, conducted under the same conditions, solvent remained. We observed that the reactions where the solvent had evaporated resulted in higher yields than the reactions with remaining solvent. We reasoned that transformations of the weakly nucleophilic indoles might be improved by omitting the solvent; however, when

the reactions were conducted with no solvent, we obtained unsatisfactory results. It seemed the difference in the outcomes for these two sets of conditions (evaporation vs. neat) may be due to a need for solvent during the catalyst activation process. When reactions were carried out in the absence of solvent, very little liquid is present in the reaction mixture (typically only the aryl/alkenyl triflate substrate). It is possible in the absence of solvent that catalyst activation is inefficient due to the poor solubility of the precatalyst and ligand resulting in possible decomposition of the precatalyst (precipitation of unligated Pd). The decomposition may occur at rates that are comparable to or greater than ligation and catalyst activation. As such, we developed a protocol in which the reactions were conducted in benzene as the solvent (1 M) in a round bottom flask equipped with a short-path distillation head. After all reagents were mixed in the reaction vessel, the mixture was heated to 100 °C for 15-30 minutes while the benzene solvent was removed via distillation. The reaction temperature was then decreased to 95 °C while the reaction stirred for an additional three hours. This protocol provided consistent and reproducible results with a variety of substrates, and allowed us to decrease the reaction time significantly from ~16 h to ~3.5 h.

2.3 Reaction Scope and Limitations

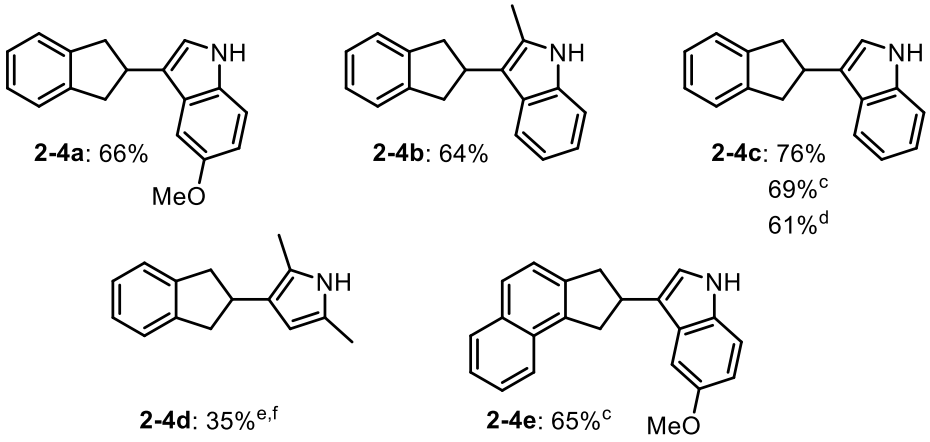
With the optimized conditions in hand, we examined the reactivity of 2-allylphenyl triflate **2-1b** or 1-allyl-2-naphthyl triflate **2-1c** with several different aromatic heterocycles (Scheme 2-2). The coupling of **2-1b** proceeded smoothly with 5-methoxyindole, 2-methylindole, and indole to afford **2-4a**-**c**, and **2-1c** was coupled with 5-methoxyindole in good yield (**4e**). In the synthesis of **2-4c**, use of 6 mol % XPhos provided comparable results to those obtained with 12 mol % XPhos on both our standard 0.5 mmol scale and

Scheme 2-2: Reaction of Aryl Triflates



2-1b: 2-allylphenyl triflate
2-1c: 1-allyl-2-naphthyl triflate

2-4a-e



2-4a: 66%

2-4b: 64%

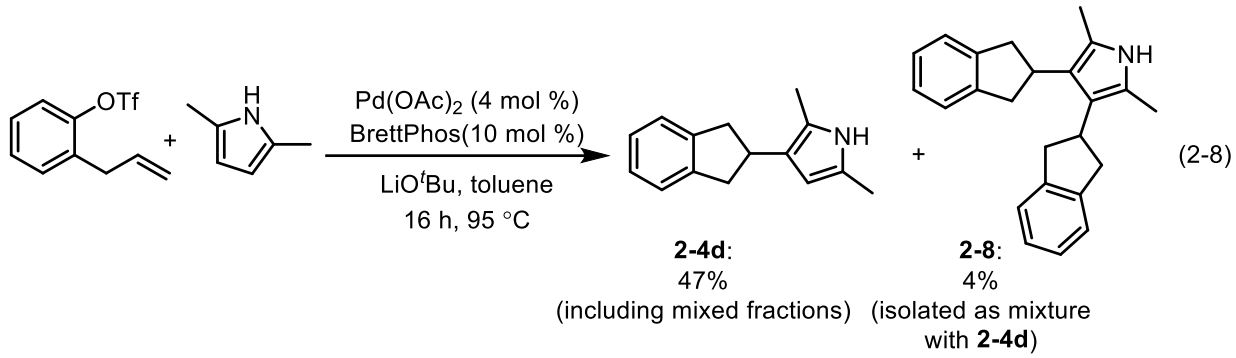
2-4c: 76%
69%[c]
61%[d]

2-4d: 35%[e,f]

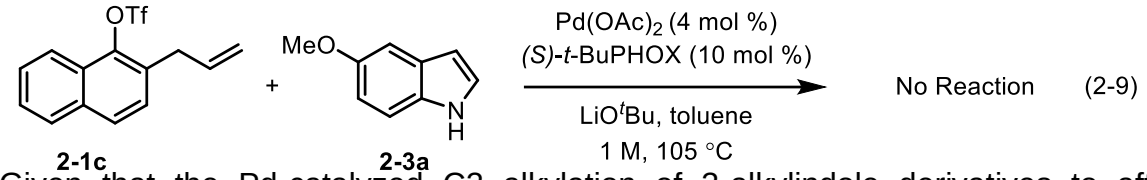
2-4e: 65%[c]

[a]Conditions: 1.0 equiv of **2-1**, 1.2 equiv of nucleophile, 4 mol % $Pd(OAc)_2$, 12 mol % XPhos, 1.4 equiv of Li*O*^{t}Bu, benzene (1M), 100-95 °C, 3 h. [b]Yields are isolated yields (average of two or more runs). [c]The reaction was conducted with 6 mol % XPhos. [d]The reaction was conducted on a 1 mmol scale with 6 mol % XPhos. [e]The reaction was conducted with 10 mol% BrettPhos in toluene solvent (0.1M) with a 16h reactions time. [f]JLM conducted one of the reaction experiments used for the averaged yield reported.

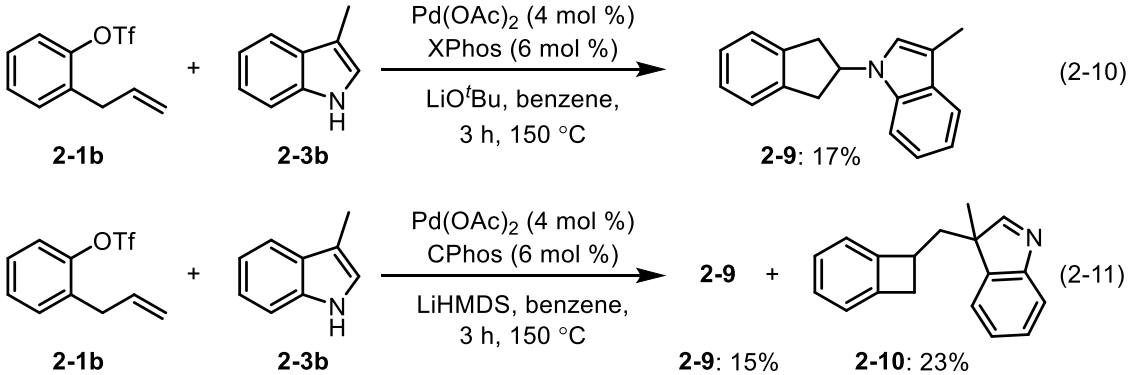
a slightly larger 1 mmol scale. Use of 2,5-Dimethylpyrrole as the nucleophile produces the desired product **2-4d** in up to 80% yield as determined by ^{1}H NMR analysis of the crude reaction mixture. However, compound **2-4d** is extremely air-sensitive, and a low isolated yield of 35% was obtained due to partial oxidation/decomposition during purification.[8] Additionally, a second product was observed in low yields that, based on GC/MS and ^{1}H NMR analysis we have tentatively assigned as an over-alkylated 2,5-dimethylpyrrole derivative bearing 2-indanyl groups at both the C3 and C4 positions (**2-8**, eq 2-8**)**.[9] Efforts to employ N-alkyl indoles, benzofuran, or benzothiophene as the



nucleophile failed to provide the desired products. This suggests the substrate N–H proton is required to achieve the desired reactivity and may be removed prior to the reaction of the indole with the intermediate palladium complex **2-12** (see below in Scheme 2-5). Additionally, attempts to conduct enantioselective reactions of **2-1c** with indole nucleophiles have thus far been unsuccessful (eq 2-9).[10]

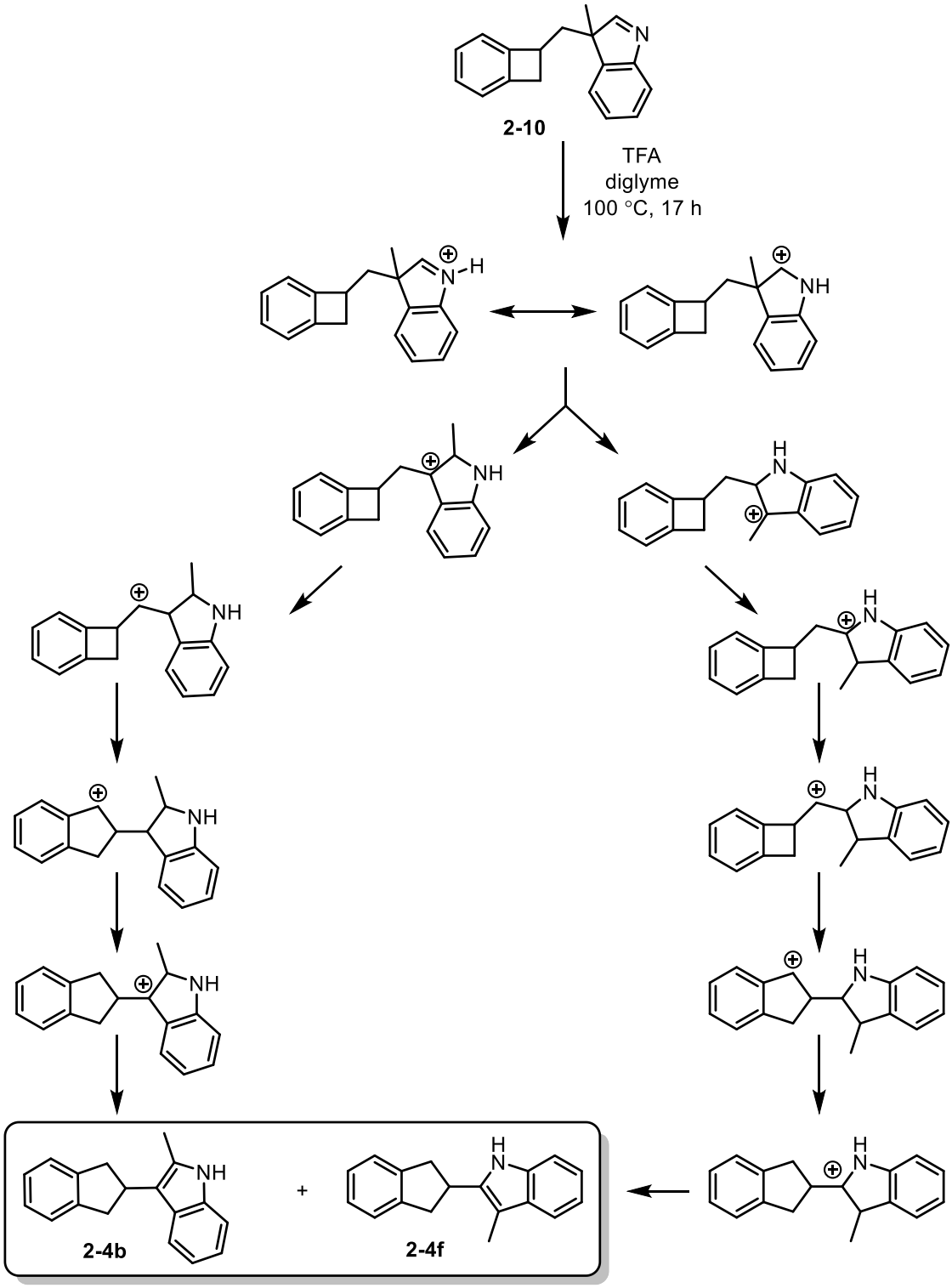


Given that the Pd-catalyzed C3 alkylation of 3-alkylindole derivatives to afford products bearing a quaternary carbon center is well-established,[11] we examined the coupling of **2-1b** with 3-methylindole (**2-3b**). Our optimized conditions led to no reaction, but when the mixture was heated to 150 °C, the formation of *N*-alkylindole product **2-9** was observed, albeit in low yield (eq 2-10). While attempting to further optimize this reaction, we found that use of CPhos as ligand and LiHMDS as base produced a mixture



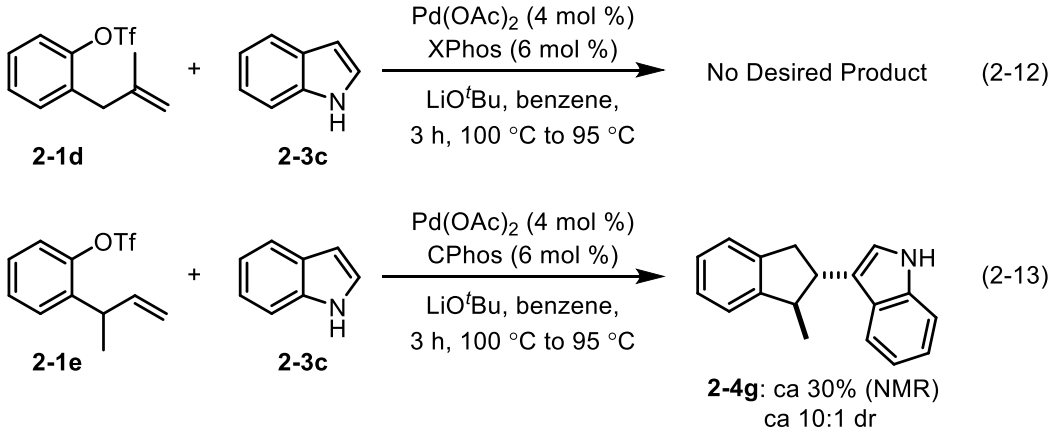
of **2-9** along with an unexpected 5-exo cyclization/C3-alkylation product **2-10** (eq 2-11).[12] We attempted to establish the relative stereochemistry of **2-10** converting it to a bicyclic

Scheme 2-3: Proposed Mechanism for Formation of **2-4b** & **2-4f**



derivative through Friedel-Crafts cyclization for use in nOe experiments, but this instead led to products **2-4b** and **2-4f** resulting from carbocation rearrangements (Scheme 2-3). Further efforts to optimize the selectivity and yields of either **2-9** or **2-10** have thus far been unsuccessful.

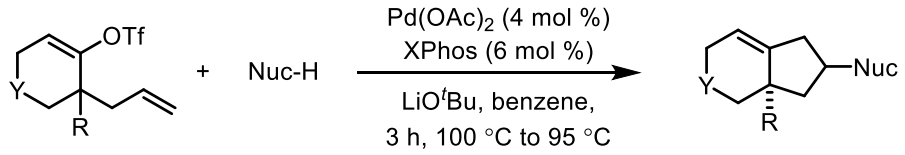
We also examined the effect of substitution along the allyl group on reactivity, and found the transformations are quite sensitive to substrate steric properties. A 2-allylphenyltriflate derivative bearing a methyl group at the internal alkene carbon atom (**2-1d**) proved to be unreactive (eq 2-12). In contrast, substrate **2-1e** that contains an allylic methyl group was transformed to **2-4g** in 30% NMR yield with good diastereoselectivity (eq 2-13). However, compound **2-4g** proved to be inseparable from unreacted **2-3c**, and a 1:1 mixture of **2-4g**:**2-3c** was obtained in low yield after chromatography (ca 13% of **2-4g** was obtained based on the mixture). Efforts to assign the stereochemistry through ^{1}H NMR nOe experiments provided ambiguous data and therefore the stereochemistry of **2-4g** has been tentatively assigned as *trans* based on analogy to previously reported reactions in our lab.[13]



Since our prior studies have shown that both aryl and alkenyl triflate electrophiles can be coupled with various nucleophiles (e.g., eq 2-1-2, **2-1a** –> **2-2a-d**),[2b-c,3] we explored the use of alkenyl triflate electrophiles **2-1a** and **2-1f-h** in reactions with indoles (Scheme

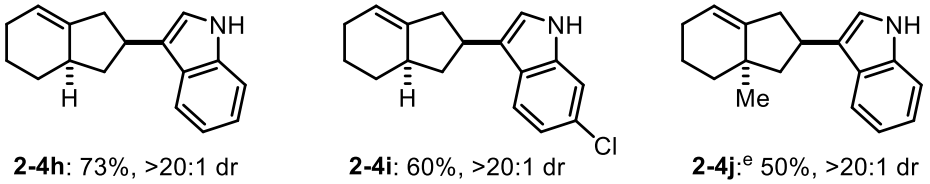
2-4). We were pleased to find that these electrophiles were successfully coupled with indole and 6-chloroindole to afford **2-4h-i** in good yields with high diastereoselectivity. Although the presence of a methyl group at the allylic position of aryl triflate **2-1e** was not well tolerated, substrate **2-1f**, which contains a methyl group at the homoallylic position, was coupled with indole in 50% yield (**2-4j**, >20:1 dr).[14] In addition, substrates **2-1g-h** that contain heteroatoms in their backbones were transformed to products **2-4k-l** in low to moderate yields with good (10 to >20:1) diastereoselectivities. Given the hazards associated with the use of benzene, we also briefly examined alternative solvents for these transformations. Use of 2-methyl THF in the coupling of **2-1a** with indole afforded

Scheme 2-4: Reaction of Alkenyl Triflates



2-1a: Y = CH_2, R = H; **2-1f**: Y = CH_2, R = Me;
2-1g: Y = NBoc, R = H; **2-1h**: Y = O, R = H

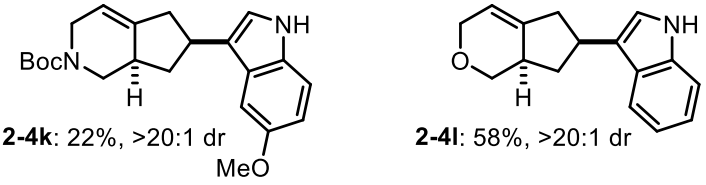
2-4h-l



2-4h: 73%, >20:1 dr
64%, >20:1 dr[c]
48%, >20:1 dr[d]

2-4i: 60%, >20:1 dr

2-4j:[e] 50%, >20:1 dr



2-4k: 22%, >20:1 dr

2-4l: 58%, >20:1 dr

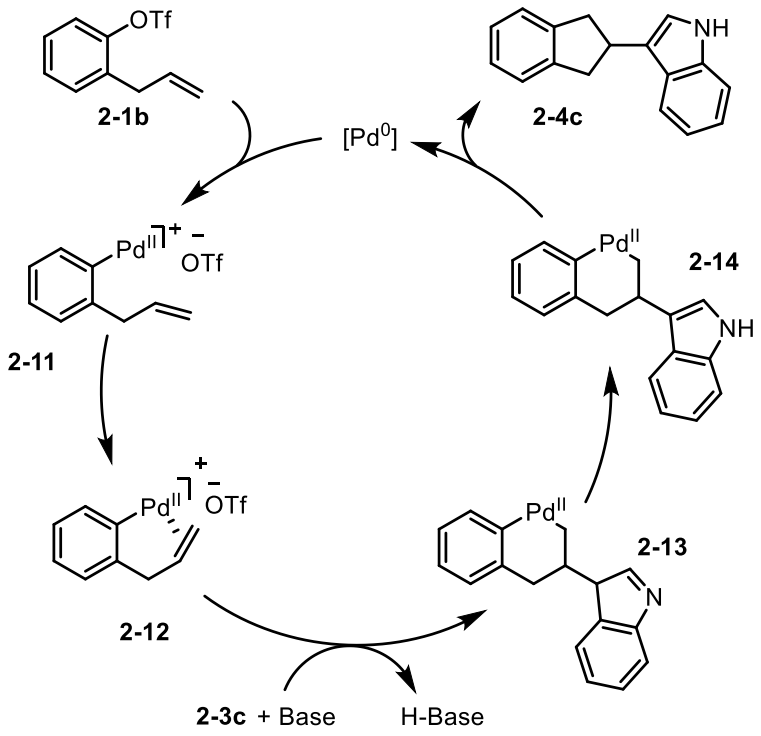
[a]Conditions: 1.0 equiv of **2-1**, 1.2 equiv of nucleophile, 4 mol % $Pd(OAc)_2$, 6 mol % XPhos, 1.4 equiv of LiO^{t}Bu, benzene (1M), 100-95 °C, 3h. [b]Yields are isolated yields (average of two or more runs). [c]The reaction was conducted using 2-methyl THF in place of benzene as a solvent, with an initial temperature of 110 °C. [d]The reaction was conducted using toluene in place of benzene as a solvent, with an initial temperature of 130 °C. [e]JLM conducted both of the reaction experiments that were used for the averaged yield reported.

the desired product **2-4h** in 64% yield, which is comparable to the 73% yield obtained with benzene. In contrast, use of toluene as solvent required a significantly higher temperature for the distillation step (130 °C), and the desired product was obtained in 48% yield. However, the excellent >20:1 diastereoselectivites were retained when using these alternative solvents.

2.4 Proposed Catalytic Cycle

Our current mechanistic hypothesis for this transformation is illustrated in Scheme 2-5, and is similar to that for reactions involving amine, alcohol, or stabilized carbanion nucleophiles.[2,3] The catalytic cycle is initiated by reduction of the Pd(II) precatalyst to Pd(0), followed by oxidative addition of the triflate electrophile (e.g., **2-1b**) to afford cationic Pd(II) species **2-11**. Coordination of the alkene to the Pd-center affords **2-12**, in which the alkene is rendered electrophilic at the internal alkene carbon. A sequence involving deprotonation of the indole followed by a Friedel-Crafts-like *anti-*

Scheme 2-5: Proposed Catalytic Cycle



carbopalladation gives the 6-membered palladacycle **2-13**, which is converted to **2-14** upon tautomerization of the 3*H* indole to a 1*H* indole. Reductive elimination from **2-14** leads to formation of the second C–C bond to afford the product (**2-4c**) with concomitant regeneration of the active Pd(0) catalyst. It is also possible that the tautomerization of the 3*H* indole to the 1*H* indole occurs after reductive elimination.

2.5 Conclusion

In conclusion, we have developed a new Pd-catalyzed alkene difunctionalization reaction that effects intramolecular arylation and intermolecular heteroarylation of the alkene. This reaction forms two carbon-carbon bonds in one step to afford 3-cyclopentylindole derivatives in good yield and high diastereoselectivity. We only observed alkylation at the C-3 position of the indole and pyrrole derivatives under the optimized reaction conditions. Unfortunately, this method is thus far not applicable to N-alkyl indoles and other heteroaromatic compounds.

The work described in this chapter was published in *The Journal of Organic Chemistry*[15] and was adapted with permission from Kirsch, J. K.; Manske, J. L. Wolfe, J. P. Pd-Catalyzed Alkene Carboheteroarylation Reactions for the Synthesis of 3-Cyclopentylindole Derivatives. *J. Org. Chem.*, **2018**, *83*, 13568.

2.6 Experimental

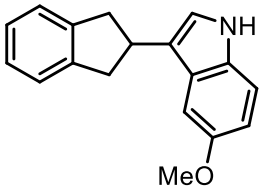
General: All reactions were carried out under a nitrogen atmosphere using oven or flame-dried glassware. All palladium sources and reagents were obtained from commercial

sources and used without further purification unless otherwise noted. Aryl and alkenyl triflate substrates **2-1a**,[2b] **2-1b-c**,[2a] **2-1d-e**,[2c] and **2-1f-h**[2b] were prepared according to previously reported procedures. Toluene was purified using a GlassContour solvent system. Benzene was purified by distillation from calcium hydride under a nitrogen atmosphere. 2,5-Dimethylpyrrole was distilled from calcium hydride under a nitrogen atmosphere and stored in a re-sealable Schlenk tube in the glove box. Anhydrous 2-methyltetrahydrofuran was obtained from commercial sources and was used without further purification. All yields refer to isolated compounds that are estimated to be ≥95% pure as judged by ^{1}H NMR analysis unless otherwise noted. *The yields reported in the experimental section describe the result of a single experiment, whereas yields reported in Schemes 2-2 & 2-4 and equations 2-10–11 are average yields of two or more experiments. Thus, the yields reported in the experimental section may differ from those shown in Schemes 2-2 & 2-4 and equations 2-10–11.*

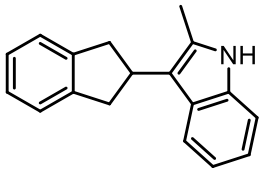
Synthesis and Characterization of Products

General Procedure for Pd-Catalyzed Alkene Difunctionalization Reactions. A flame-dried round bottom flask equipped with a stirbar was cooled under a stream of N_2 and charged with $Pd(OAc)_2$ (4 mol %), XPhos (12 mol %), the appropriate nucleophile (0.6 mmol, 1.2 equiv), and lithium *tert*-butoxide (0.7 mmol, 1.4 equiv). The tube was purged with N_2 and a solution of the appropriate aryl or alkenyl triflate (0.5 mmol, 1.0 equiv) in benzene (0.5 mL, 1M) was added. A short path distillation apparatus was attached to the flask, and the mixture was heated to 100-105 ^{o}C until the benzene had been removed by distillation. The reaction temperature was decreased to 95 ^{o}C and stirring was continued for 3 h. The mixture was cooled to rt, satd. NH_4Cl (aq) (2 mL) was added and the mixture

was transferred to a separatory funnel. The layers were separated, the aqueous layer was extracted with EtOAc (3 mL x 2), then the organic layers were combined, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was then purified by flash chromatography on silica gel.

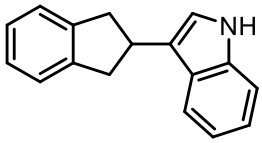


3-(2,3-Dihydro-1*H*-inden-2-yl)-5-methoxy-*1H*-indole (2-4a). The general procedure was used for the coupling of 5-methoxyindole (88.3 mg, 0.6 mmol) and **2-1b** (133.1 mg, 0.5 mmol). The crude product was purified by flash chromatography on silica gel (100% DCM) to afford 89.1 mg (68%) of the title compound as a light pink oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (s, 1 H), 7.30–7.24 (m, 3 H), 7.21– 7.16 (m, 2 H), 7.02 (dd, *J* = 18.2, 2.4 Hz, 2 H), 6.86 (dd, *J* = 8.8, 2.4 Hz, 1 H), 3.91 (pent, *J* = 8.2 Hz, 1 H), 3.83 (s, 3 H), 3.43 (dd, *J* = 15.4, 8.0 Hz, 2 H), 3.16 (dd, *J* = 15.4, 8.3 Hz, 2 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.9, 143.6, 132.0, 127.5, 126.4, 124.6, 121.2, 120.3, 112.2, 112.0, 101.7, 56.1, 40.0, 37.1. IR (film) 3414, 2935, 2831, 1623, 1581, 1481 cm^{-1}; HRMS (ESI^+) m/z: $[M + H]^+$ Calcd for $C_{18}H_{18}NO$ 264.1383; Found 264.1385.



3-(2,3-Dihydro-1*H*-inden-2-yl)-2-methyl-1*H*-indole (2-4b). The general procedure was used for the coupling of 2-methylindole (78.7 mg, 0.6 mmol) and **2-1b** (133.1 mg, 0.5 mmol). The crude product was purified by flash chromatography on silica gel (100% DCM)

to afford 79.7 mg (64%) of the title compound as a white solid, m.p. 158–159 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (s, 1 H), 7.44 (d, *J* = 7.9 Hz, 1 H), 7.32–7.24 (m, 3 H), 7.24 –7.19 (m, 2 H), 7.13–7.07 (m, 1 H), 7.02–6.95 (m, 1 H), 3.89 (p, *J* = 9.3 Hz, 1 H), 3.45 (dd, *J* = 15.9, 9.8 Hz, 2 H), 3.22 (dd, *J* = 15.9, 8.8 Hz, 2 H), 2.42 (s, 3 H). ^{13}C (126 MHz, $CDCl_3$) δ 143.9, 135.7, 130.7, 127.4, 126.4, 124.6, 121.0, 119.5, 119.0, 114.5, 110.5, 39.7, 36.7, 12.3. IR (film) 3391, 2932, 2844 cm^{-1}; HRMS (ESI^+) m/z: $[M + H]^+$ Calcd for $C_{18}H_{18}N$ 248.1434; Found 248.1430.

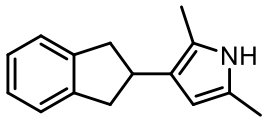


3-(2,3-Dihydro-1*H*-inden-2-yl)-1*H*-indole (2-4c). The general procedure was used for the coupling of indole (70.3 mg, 0.6 mmol) and **2-1b** (133.1 mg, 0.5 mmol). The crude product was purified by flash chromatography on silica gel (5% hexanes in DCM) to afford 89.0 mg (76%) of the title compound as a pale yellow solid, m.p. 80–83 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (s, 1 H), 7.66 (d, *J* = 7.9 Hz, 1 H), 7.38 (d, *J* = 8.1 Hz, 1 H), 7.30–7.24 (m, 2 H), 7.24–7.14 (m, 3 H), 7.12 (app t, *J* = 7.2 Hz, 1 H), 7.02 (d, *J* = 1.6 Hz, 1 H), 3.96 (pent, *J* = 8.3 Hz, 1 H), 3.43 (dd, *J* = 15.3, 8.0 Hz, 2 H), 3.19 (dd, *J* = 15.3, 8.6 Hz, 2 H). ^{13}C (126 MHz, $CDCl_3$) δ 143.5, 136.8, 127.1, 126.4, 124.6, 122.2, 120.4, 120.3, 119.6, 119.4, 111.3, 40.1, 37.1. IR (film) 3416, 3046, 2976, 2842, 1456 cm^{-1}; HRMS (ESI^+) m/z: $[M + H]^+$ Calcd for 234.1277 $C_{17}H_{16}N$; Found 234.1275.

3-(2,3-Dihydro-1*H*-inden-2-yl)-1*H*-indole (2-4c). The general procedure was used for the coupling of indole (70.3 mg, 0.6 mmol) and **2-1b** (133.1 mg, 0.5 mmol) except using 6 mol % of XPhos (14.3 mg, 0.03 mmol) rather than 12 mol %. The crude product was

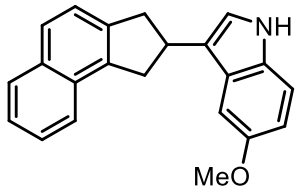
purified by flash chromatography on silica gel (5% hexanes in DCM) to afford 81.2 mg (70%) of the title compound as a pale yellow solid, m.p. 80–83 °C). Spectroscopic data were identical to those reported above.

3-(2,3-Dihydro-1*H*-inden-2-yl)-1*H*-indole (2-4c). The general procedure was used for the coupling of indole (140.6 mg, 1.2 mmol) and **2-1b** (266.2 mg, 1.0 mmol). The crude product was purified by flash chromatography on silica gel (5% hexanes in DCM) to afford 143.1 mg (61%) of the title compound as a pale-yellow solid, m.p. 80–83 °C. Spectroscopic data were identical to those reported above.

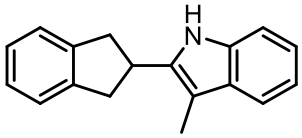


3-(2,3-Dihydro-1*H*-inden-2-yl)-2,5-dimethyl-1*H*-pyrrole (2-4d).[8] A flame-dried Schlenk tube equipped with a stirbar was cooled under a stream of N_2 and charged with $Pd(OAc)_2$ (0.0045g, 4 mol %), BrettPhos (0.0268g, 10 mol %), and lithium *tert*-butoxide (0.0560g, 0.7 mmol). The tube was purged with N_2 (g) and 4.5 mL of toluene and a solution of **2-1b** (133.1 mg, 0.5 mmol) in toluene (0.5 mL) was added. 2,5-Dimethylpyrrole (61 µL, 0.6 mmol) was added directly to the reaction mixture via syringe, then the reaction mixture was heated to 95 °C with stirring for 16 h. The mixture was then cooled to rt, satd. NH_4Cl (aq) (5 mL) was added, the mixture was transferred to a separatory funnel, and the layers were separated. The aqueous layer was extracted with EtOAc (3 mL x 2), then the organic layers were combined, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was then purified by flash chromatography on silica gel (5% EtOAc in hexanes) to afford 41.0 mg (39%) of the title compound as a yellow solid, m.p. 91–94 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 7.41 (s, 1 H), 7.25–7.17 (m, 2 H), 7.17–7.10 (m, 2 H), 5.72

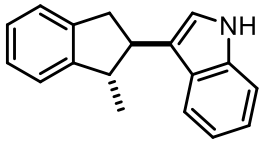
(d, *J* = 2.8 Hz, 1 H), 3.52 (tt, *J* = 9.6, 8.0 Hz, 1 H), 3.16 (dd, *J* = 15.3, 7.9 Hz, 2 H), 2.95 (dd, *J* = 15.3, 9.6 Hz, 2 H), 2.20 (s, 6 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.9, 126.2, 125.2, 124.3, 122.7, 121.9, 104.4, 41.2, 37.7, 13.1, 11.3. IR (film) 3331, 2896, 2839 cm^{-1}; HRMS (ESI^+) m/z: $[M + H]^+$ Calcd for $C_{15}H_{18}N$ 212.1434; Found 212.1432.



3-(2,3-Dihydro-1*H*-cyclopenta[*a*]naphthalen-2-yl)-5-methoxy-1*H*-indole (2-4e). The general procedure was used for the coupling of 5-methoxyindole (88.3 mg, 0.6 mmol) and **2-1c** (158.1 mg, 0.5 mmol) except using 6 mol % of XPhos (14.3 mg, 0.03 mmol) rather than 12 mol %. The crude product was purified by flash chromatography on silica gel (100% DCM) to afford 106.2 mg (68%) of the title compound as a white foam. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (dd, *J* = 7.8, 1.3 Hz, 1 H), 7.84–7.76 (m, 2 H), 7.73 (d, *J* = 8.3 Hz, 1 H), 7.49 (ddd, *J* = 8.3, 6.8, 1.5 Hz, 1 H), 7.43 (dd, *J* = 8.2, 6.3 Hz, 2 H), 7.24 (d, *J* = 3.3 Hz, 1 H), 7.02 (dd, *J* = 3.7, 2.4 Hz, 2 H), 6.86 (dd, *J* = 8.8, 2.4 Hz, 1 H), 4.16–4.04 (m, 1 H), 3.81 (dd, *J* = 15.8, 8.4 Hz, 1 H), 3.75 (s, 3 H), 3.62 (dd, *J* = 15.7, 8.4 Hz, 1 H), 3.46 (dd, *J* = 15.8, 7.4 Hz, 1 H), 3.35 (dd, *J* = 15.8, 7.4 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.9, 140.4, 138.8, 132.8, 132.0, 130.6, 128.6, 127.4, 127.1, 126.1, 124.9, 124.4, 123.5, 121.2, 120.8, 112.2, 112.0, 101.7, 56.0, 41.1, 38.4, 36.5. IR (film) 3420, 3052, 2930, 2832, 1625, 1582 cm^{-1}; HRMS (ESI^+) m/z: $[M + H]^+$ Calcd for $C_{22}H_{20}NO$ 314.1539; Found 314.1537.

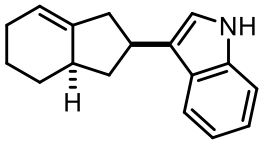


2-(2,3-dihydro-1H-inden-2-yl)-3-methyl-1H-indole (2-4f). Trifluoroacetic acid (10.1 µL, 0.13 mmol, 1 equiv) was added to a mixture of diglyme (0.2 mL, 0.66M) and **2-10** (32.7 mg, 0.13 mmol, 1 equiv). Smoking of the solution was observed. The solution was heated to 100 °C for 17 h. $NaHCO_3$ (aq) solution (1 mL) and ether (1 mL) were added. The layers were separated, and the aqueous layer was extracted 2x with ether. The combined organic layers were dried with sodium sulfate and filtered. The crude product was purified by flash chromatography on silica gel (1% EtOAc in Hexanes) to afford 15.5 mg (47%) of the title compound and 1.8 mg of **2-4b** (isolated separately). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (s, 1H), 7.50 (dd, *J* = 6.9, 1.9 Hz, 1H), 7.33 – 7.27 (m, 2H), 7.24 (dd, *J* = 5.6, 3.3 Hz, 2H), 7.21 – 7.18 (m, 1H), 7.14 – 7.05 (m, 2H), 4.03 – 3.91 (m, 1H), 3.41 (dd, *J* = 15.8, 8.3 Hz, 2H), 3.11 (dd, *J* = 15.8, 6.7 Hz, 2H), 2.31 (s, 3H).^{13}C (126 MHz, $CDCl_3$) δ 142.5, 138.1, 135.1, 129.2, 127.0, 124.8, 121.4, 119.2, 118.3, 110.4, 106.7, 39.8, 36.1, 8.8.



3-(1-Methyl-2,3-dihydro-1H-inden-2-yl)-1H-indole (2-4g). The general procedure was used for the coupling indole (70.3 mg, 0.6 mmol) and **2-1e** (140.1 mg, 0.5 mmol) except using 6 mol % of XPhos (14.3 mg, 0.03 mmol) rather than 12 mol %. The crude product was purified by flash chromatography on silica gel (3% EtOAc in hexanes) to afford 38.2 mg as an inseparable mixture of the title compound and indole as a yellow oil. Of this mixture, ca. 16.0 mg (13%) was the title compound, based on ^{1}H NMR analysis of the mixture. The title compound was obtained as a ca 10:1 mixture of diastereomers. The

relative stereochemistry of the major isomer has tentatively been assigned as *trans* based on the outcome of a prior reaction of this substrate with a phenol nucleophile,[2c] but efforts to unambiguously assign stereochemistry by nOe have been unsuccessful. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (s, 1 H), 7.69–7.64 (m, 1 H), 7.46–7.38 (m, 1 H), 7.28 (d, *J* = 7.3 Hz, 1H), 7.27–7.19 (m, 3 H), 7.17–7.05 (m, 3 H), 3.57–3.44 (m, 1 H), 3.43–3.32 (m, 2 H), 3.27–3.17 (m, 1 H), 1.39 (d, *J* = 6.8 Hz, 3 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.1, 143.0, 136.9, 127.3, 126.5, 124.4, 123.3, 122.2, 120.9, 120.0, 119.3, 118.8, 111.4, 46.8, 45.8, 39.7, 18.3. IR (film) 3415, 3056, 2956 cm^{-1}; HRMS (ESI^+) m/z: $[M + H]^+$ Calcd for $C_{18}H_{18}N$ 248.1434; Found 248.1432.

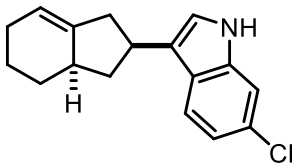


3-(2,3,3a,4,5,6-Hexahydro-1*H*-inden-2-yl)-1*H*-indole (2-4h). The general procedure was used for the coupling of indole (70.3 mg, 0.6 mmol) and **2-1a** (135.1 mg, 0.5 mmol) except 6 mol % of XPhos (14.3 mg, 0.03 mmol) was used instead of 12 mol %. The crude product was purified by flash chromatography on silica gel (5% EtOAc in hexanes) to afford 87.4 mg (74%, >20:1 dr) of the title compound as a yellow solid, m.p. 91–93 °C). ^{1}H NMR (500 MHz, C_6D_6) δ 7.73 (d, *J* = 7.8 Hz, 1H), 7.28 – 7.17 (m, 2H), 7.07 (d, *J* = 8.0 Hz, 1H), 6.54 (s, 1H), 6.48 – 6.45 (m, 1H), 5.49 – 5.43 (m, 1H), 3.43 – 3.20 (m, 1H), 3.04 – 2.89 (m, 1H), 2.57 – 2.44 (m, 1H), 2.33 – 2.19 (m, 2H), 2.10 – 2.01 (m, 2H), 2.00 – 1.92 (m, 1H), 1.83 – 1.67 (m, 1H), 1.57 – 1.34 (m, 2H), 1.20 – 1.00 (m, 1H). ^{13}C NMR (126 MHz, C_6D_6) δ 144.3, 137.3, 122.2, 120.9, 120.1, 119.7, 119.4, 117.8, 111.4, 42.2, 41.5, 38.2, 35.0, 29.4, 25.8, 23.1, one carbon signal is missing due to accidental equivalence.

IR (film) 3414, 3055, 2920, 2852 cm^{-1}; HRMS (ESI^+) m/z: $[M + H]^+$ Calcd for $C_{17}H_{20}N$ 238.1596; Found 238.1592.

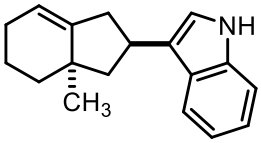
3-(2,3,3a,4,5,6-Hexahydro-1*H*-inden-2-yl)-1*H*-indole (2-4h). The general procedure was used for the coupling of indole (70.3 mg, 0.6 mmol) and **2-1a** (135.1 mg, 0.5 mmol) except 6 mol % of XPhos (14.3 mg, 0.03 mmol) was used instead of 12 mol %, and the reaction was carried out in 2-methyl THF solvent with an initial temperature of 110 °C.. The crude product was purified by flash chromatography on silica gel (5% EtOAc in hexanes) to afford 76.7 mg (64%, >20:1 dr) of the title compound as a yellow solid, m.p. 91–93 °C). Spectroscopic data were identical to those reported above.

3-(2,3,3a,4,5,6-Hexahydro-1*H*-inden-2-yl)-1*H*-indole (2-4h). The general procedure was used for the coupling of indole (70.3 mg, 0.6 mmol) and **2-1a** (135.1 mg, 0.5 mmol) except 6 mol % of XPhos (14.3 mg, 0.03 mmol) was used instead of 12 mol %, and the reaction was carried out in toluene solvent with an initial temperature of 130 °C. The crude product was purified by flash chromatography on silica gel (5% EtOAc in hexanes) to afford 57.2 mg (48%, >20:1 dr) of the title compound as a yellow solid, m.p. 91–93 °C). Spectroscopic data were identical to those reported above.



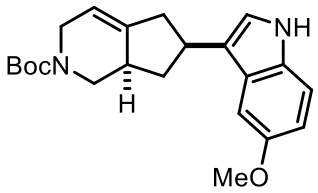
6-Chloro-3-(2,3,3a,4,5,6-hexahydro-1*H*-inden-2-yl)-1*H*-indole (2-4i). The general procedure was used for the coupling of 6-chlorolindole (91.0 mg, 0.6 mmol) and **2-1a** (135.1 mg, 0.5 mmol) except 6 mol% of XPhos (14.3 mg, 0.03 mmol) was used instead of 12 mol %. The crude product was purified by flash chromatography on silica gel (5%

EtOAc in hexanes) to afford 81.9 mg (60%, >20:1 dr) of the title compound as a yellow solid, m.p. 86–90 °C). ^{1}H NMR (400 MHz, C_6D_6) δ 7.40 (d, *J* = 8.5 Hz, 1H), 7.21 – 7.12 (m, 2H), 7.07 (d, *J* = 1.9 Hz, 1H), 6.35 (s, 1H), 5.47 (s, 1H), 3.28 – 3.07 (m, 1H), 2.89 (dd, *J* = 16.7, 10.1 Hz, 1H), 2.43 – 2.32 (m, 1H), 2.32 – 2.12 (m, 2H), 2.12 – 2.00 (m, 2H), 1.99 – 1.90 (m, 1H), 1.84 – 1.70 (m, 1H), 1.58 – 1.41 (m, 1H), 1.32 (q, *J* = 11.4 Hz, 1H), 1.18 – 1.02 (m, 1H). ^{13}C NMR (126 MHz, C_6D_6) δ 144.0, 137.4, 126.3, 121.0, 120.9, 120.4, 120.0, 118.0, 111.4, 42.1, 41.3, 38.0, 34.7, 29.3, 25.8, 23.0, one carbon signal is missing due to accidental equivalence. IR (film) 3424, 2920, 2852 cm^{-1}; HRMS (ESI$^+$) m/z: [M + H]$^+$ Calcd for $C_{17}H_{19}ClN$ 272.1201; Found 272.1191.

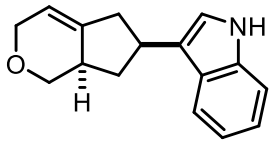


3-(3a-Methyl-2,3,3a,4,5,6-hexahydro-1*H*-inden-2-yl)-1*H*-indole (2-4j).[14] The general procedure was used for the coupling of indole (70.3 mg, 0.6 mmol) and **2-1f** (142.1mg, 0.5 mmol) except 6 mol% of XPhos (14.3 mg, 0.03 mmol) was used instead of 12 mol %. The crude product was purified by flash chromatography on silica gel (5% EtOAc in hexanes) to afford 63.1 mg (50%, >20:1 dr) of the title compound as a pale-yellow solid, m.p. 84–87ºC). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.63 (d, *J* = 7.9 Hz, 1H), 7.35 (dd, *J* = 8.2, 1.0 Hz, 1H), 7.18 (ddd, *J* = 8.2, 7.0, 1.3 Hz, 1H), 7.09 (ddd, *J* = 8.1, 7.0, 1.1 Hz, 1H), 6.97 (d, *J* = 2.2 Hz, 1H), 5.37 (s, 1H), 3.94 – 3.52 (m, 1H), 3.16 – 2.96 (m, 1H), 2.53 – 2.31 (m, 1H), 2.12 (dd, *J* = 11.9, 7.0 Hz, 1H), 2.08 – 1.98 (m, 2H), 1.86 – 1.78 (m, 1H), 1.73 – 1.67 (m, 2H), 1.62 (t, *J* = 11.6 Hz, 1H), 1.38 – 1.28 (m, 1H), 1.16 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.2, 137.0, 127.1, 122.0, 121.9, 119.9, 119.8, 119.1, 117.4, 111.3, 49.4, 41.5, 37.3, 36.5, 31.8, 25.5, 24.6, 19.1. IR (film) 3392, 2965, 2928, 2868,

2838, 1455 cm^{-1}; HRMS (ESI^+) m/z: $[M + H]^+$ Calcd for $C_{18}H_{22}N$ 252.1747; Found 252.1749.

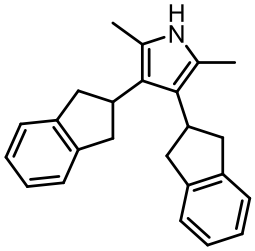


***tert*-Butyl 6-(5-methoxy-1*H*-indol-3-yl)-1,3,5,6,7,7a-hexahydro-2*H*-cyclopenta[*c*] pyridine-2-carboxylate (2-4k).** The general procedure was used for the coupling of 5-methoxyindole (88.3 mg, 0.6 mmol) and **2-1g** (185.7 mg, 0.5 mmol) except 6 mol% of XPhos (14.3 mg, 0.03 mmol) was used instead of 12 mol %. The crude product was purified by flash chromatography on silica gel (5% EtOAc in hexanes) to afford 61.1 mg (33%, >20:1 dr) of the title compound as a yellow foam. ^1H NMR (500 MHz, Toluene-d_8) δ 7.28 (s, 1 H), 7.05–6.93 (m, 3 H), 6.52 (s, 1 H), 5.16 (s, 1 H), 4.79–4.07 (m, 2 H), 3.60 (s, 3 H), 3.52–3.42 (m, 1 H), 3.22 (s, 1 H), 2.90–2.71 (m, 1 H), 2.44 (s, 1 H), 2.38–2.20 (m, 2 H), 2.08–2.01 (m, 1 H), 1.50 (s, 9H), 1.26–1.14 (m, 1 H). ^{13}C NMR (126 MHz, Toluene-d_8) δ 154.8, 144.4, 143.6, 132.9, 121.0, 120.9, 120.0, 115.6, 114.9, 112.7, 112.5, 102.4, 79.5, 55.8, 47.6–46.1 (m), 44.5–43.8 (m), 41.8, 41.6, 38.0, 37.9, 35.7, 29.0, the observed complexity is due to rotamers. IR (film) 3326, 2930, 2857, 1695, 1669 cm^{-1}; HRMS (ESI^+) m/z: $[M + H]^+$ Calcd for $C_{22}H_{29}N_2O_3$ 369.2173; Found 369.2175.

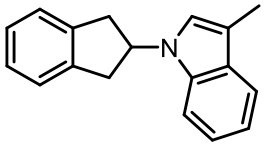


3-(1,3,5,6,7,7a-Hexahydrocyclopenta[*c*]pyran-6-yl)-1*H*-indole (2-4l). The general procedure was used for the coupling of indole (70.3 mg, 0.6 mmol) and **2-1h** (136.1 mg, 0.5 mmol). The crude product was purified by flash chromatography on silica gel (10%

EtOAc in hexanes) to afford 69.5 mg (58%, 10:1 dr) of the title compound as a yellow solid, m.p. 176–179 ºC). ^{1}H NMR (500 MHz, C_6D_6) δ 7.65 (d, *J* = 7.8 Hz, 1H), 7.28 – 7.18 (m, 2H), 7.07 (d, *J* = 8.0 Hz, 1H), 6.56 (s, 1H), 6.41 (s, 1H), 5.22 (s, 1H), 4.30 – 4.13 (m, 2H), 4.07 – 3.96 (m, 1H), 3.32 – 3.18 (m, 1H), 3.06 (t, *J* = 10.0 Hz, 1H), 2.96 – 2.79 (m, 1H), 2.71 – 2.59 (m, 1H), 2.50 – 2.32 (m, 1H), 2.11 – 1.83 (m, 1H), 1.21 (q, *J* = 11.7 Hz, 1H). ^{13}C NMR (126 MHz, C_6D_6) δ 142.3, 137.2, 127.9, 122.3, 120.3, 120.1, 119.7, 119.5, 117.1, 111.5, 69.6, 65.4, 41.1, 37.6, 36.6, 34.9. IR (film)[16] 3253, 2966, 2924, 2856, 2744, 2718, 2709, 2702 cm^{-1}; HRMS (ESI^+) m/z: $[M + H]^+$ Calcd for $C_{16}H_{18}NO$ 240.1383; Found 240.1383.

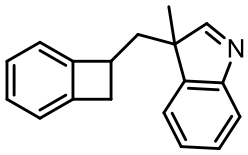


3,4-bis(2,3-dihydro-1H-inden-2-yl)-2,5-dimethyl-1H-pyrrole (2-8).[9] Following the synthesis of **2-4d, 2-8** was obtained (4.3 mg, 4%) as a mixture with **2-4d** (8.4 mg) While we did not collect full characterization data, we have tentatively assigned the structure as shown above. ^{1}H NMR Data (mixture) and GC/MS data are provided below in section **2.8**.



3-(2,3-Dihydro-1*H*-inden-2-yl)-5-methoxy-1*H*-indole (2-9). The general procedure was used for the coupling of 3-methylindole (78.7 mg, 0.6 mmol) and **2-1b** (133.1 mg, 0.5 mmol) except 6 mol% of XPhos (14.3 mg, 0.03 mmol) was used instead of 12 mol %, and

the reaction was stirred at 150 ºC for 3 h rather than 95 °C. The crude product was purified by flash chromatography on silica gel (10% DCM in hexanes) to afford 26.0 mg (21%) of the title compound as a light pink oil. This material was judged to be ca 85% pure by ^{1}H NMR analysis. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (d, *J* = 7.8 Hz, 1 H), 7.39 (d, *J* = 8.3 Hz, 1 H), 7.34–7.22 (m, 5 H), 7.18–7.12 (m, 1 H), 6.86 (d, *J* = 1.3 Hz, 1 H), 5.39–5.21 (m, 1 H), 3.54 (dd, *J* = 16.2, 7.8 Hz, 2 H), 3.32 (dd, *J* = 16.2, 5.7 Hz, 2 H), 2.31 (s, 3 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.0, 136.2, 129.0, 127.1, 124.8, 122.5, 121.5, 119.2, 118.9, 110.7, 109.5, 55.7, 40.0, 9.8. IR (film) 3044, 2917, 2853 cm^{-1}; HRMS (ESI^+) m/z: $[M + H]^+$ Calcd for $C_{18}H_{18}N$ 248.1434; Found 248.1434.

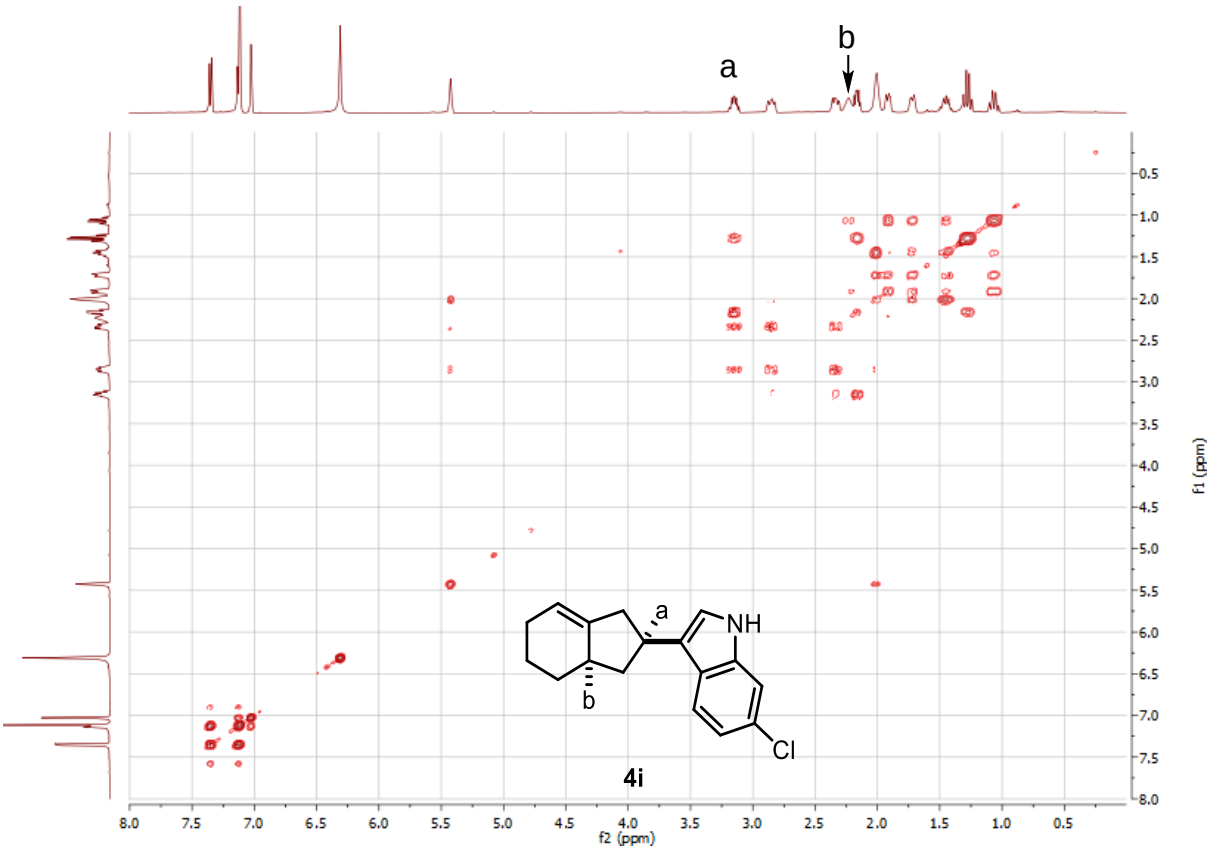


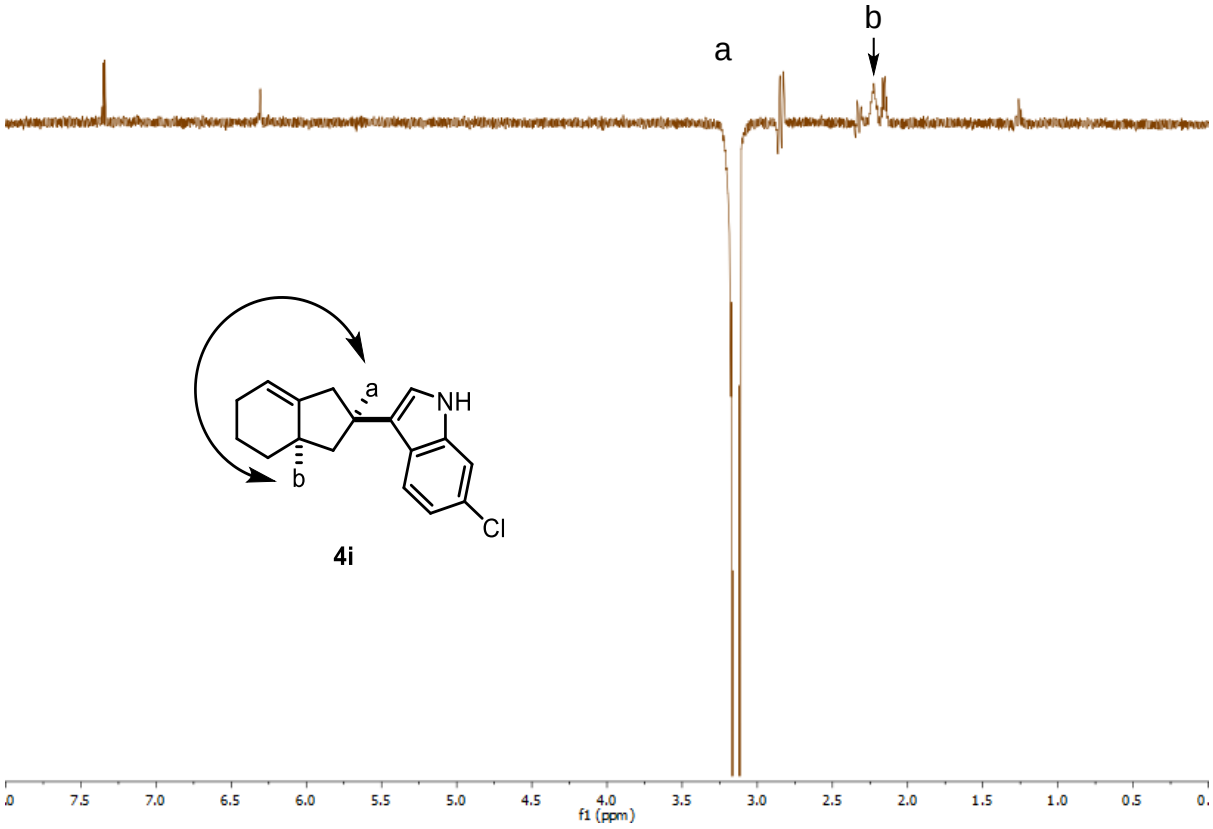
3-(Bicyclo[4.2.0]octa-1,3,50trien-7-ylmethyl)-3-methyl-3*H*-indole (2-10). The general procedure was used for the coupling of 3-methylindole (78.7 mg, 0.6 mmol) and **2-1b** (133.1 mg, 0.5 mmol) except using 6 mol% of CPhos (13.1 mg, 0.03 mmol) as ligand, LiHMDS (0.1171 g, 0.7 mmol) as base, and the reaction was stirred at 150 ºC for 3 h instead of 95 °C. The crude product was purified by flash chromatography on silica gel (10% DCM in hexanes then 20% EtOAc in hexanes) to afford 23.3 mg (19%, 85% purity) of **2-9** and 32.7 mg (26%, >20:1 dr) of the title compound (isolated separately) as an orange oil. Data for **2-9** are provided above, and data for **2-10** are as follows. Although **2-10** was generated with high diastereoselectivity, we have been unable to establish the relative stereochemistry. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (s, 1 H), 7.66 (d, *J* = 7.7 Hz, 1 H), 7.40–7.32 (m, 2 H), 7.30–7.23 (m, 1 H), 7.18–7.02 (m, 4 H), 3.10 (dd, *J* = 15.4, 8.2

Hz, 1 H), 2.99 (ddd, *J* = 17.7, 9.6, 8.2 Hz, 1 H), 2.81–2.67 (m, 2 H), 2.44 (dd, *J* = 15.9, 9.6 Hz, 1 H), 1.47 (s, 3 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.1, 155.0, 143.2, 142.5, 142.2, 128.1, 126.6, 126.5, 126.5, 124.5, 124.5, 122.3, 121.4 59.2, 45.4, 35.5, 35.2, 19.3. IR (film) 3021, 2934, 2245 cm^{-1}; HRMS (ESI^+) m/z: $[M + H]^+$ Calcd for $C_{18}H_{18}N$ 248.1434; Found 248.1434.

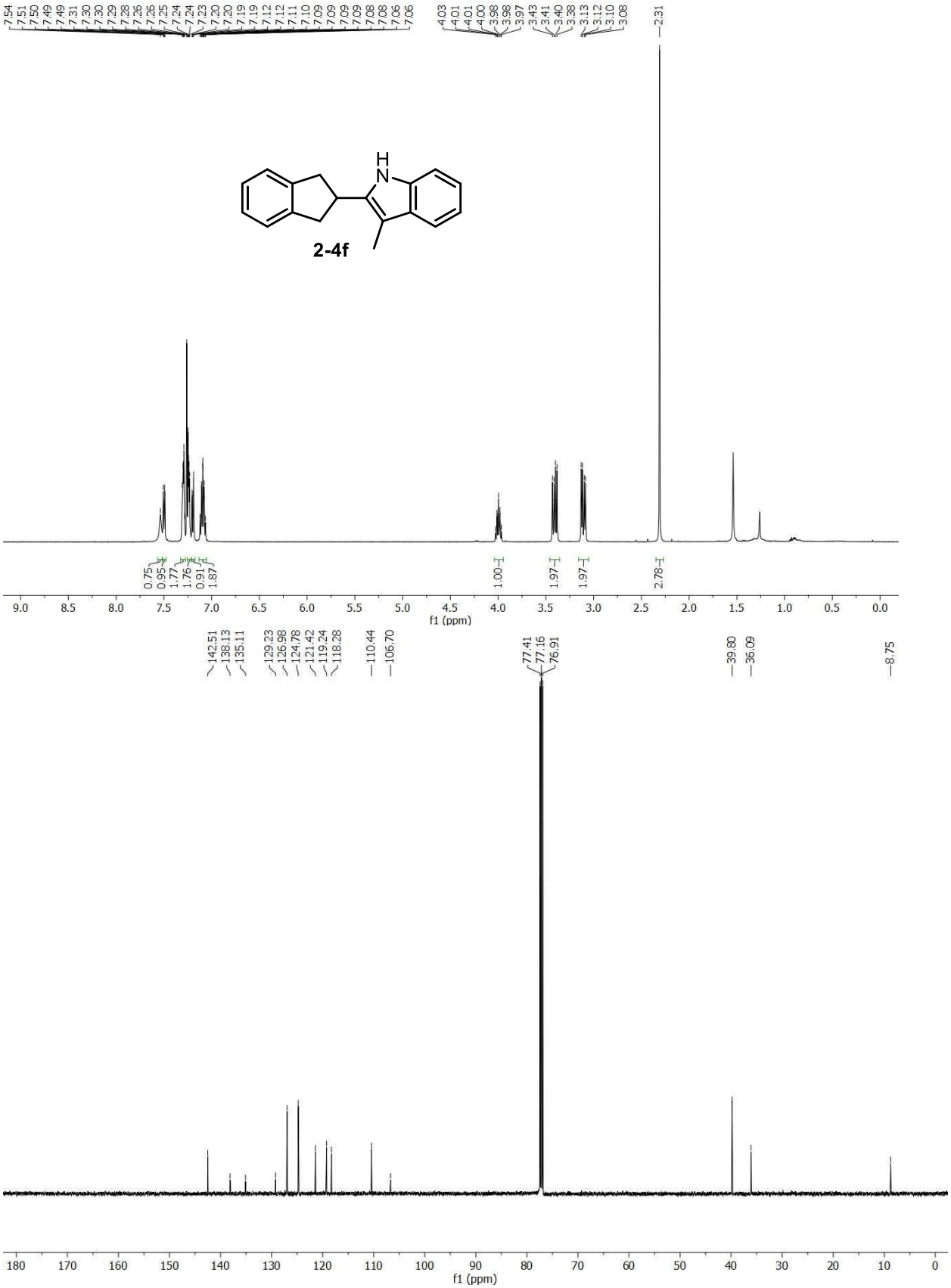
Assignment of relative stereochemistry for 2-4h-l.

The relative stereochemistry of **2-4i** was assigned using 2D COSY and 1D NOESY analysis. The key nOe signals are shown below. Structurally related products **2-4h** and **2-4j-l** were assigned based on analogy to **4i**.




a
b
a
b
NH
Cl
4i
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

2.7 Unpublished Spectra


7.54
7.51
7.50
7.49
7.49
7.31
7.30
7.30
7.29
7.28
7.26
7.26
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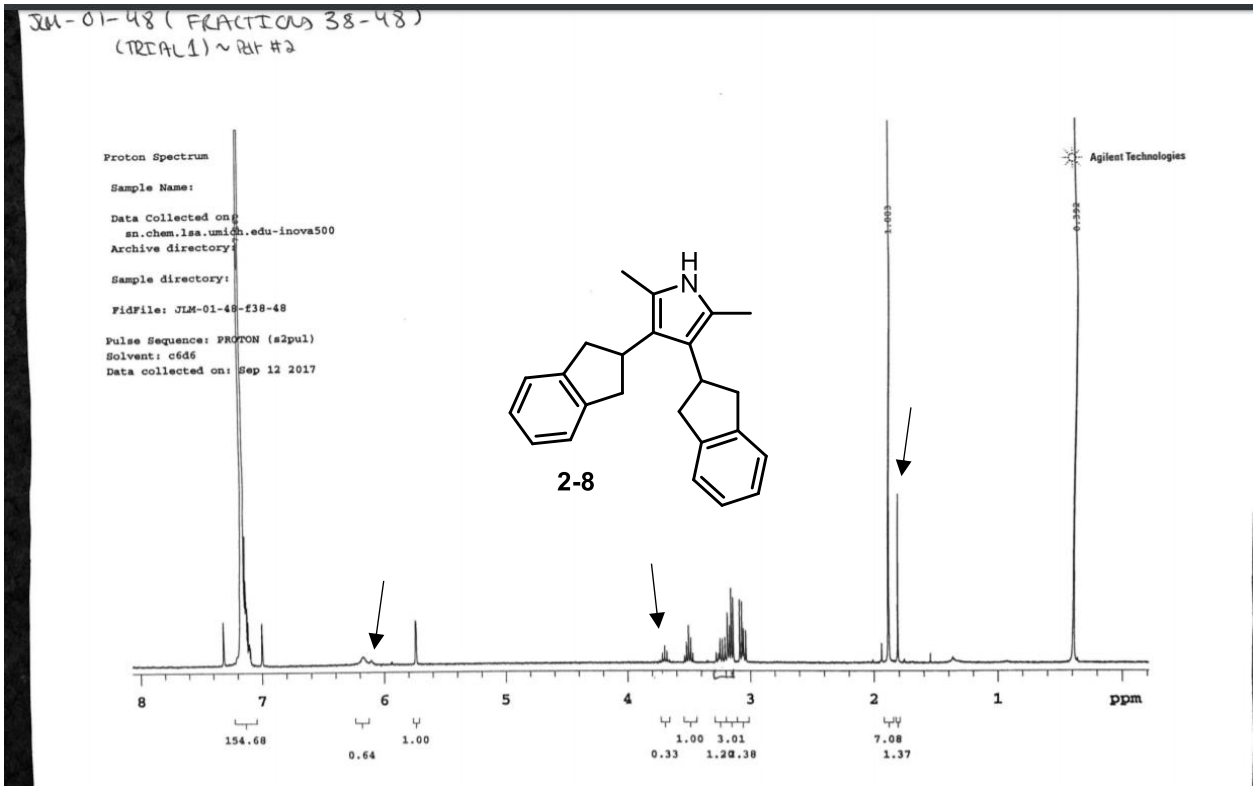
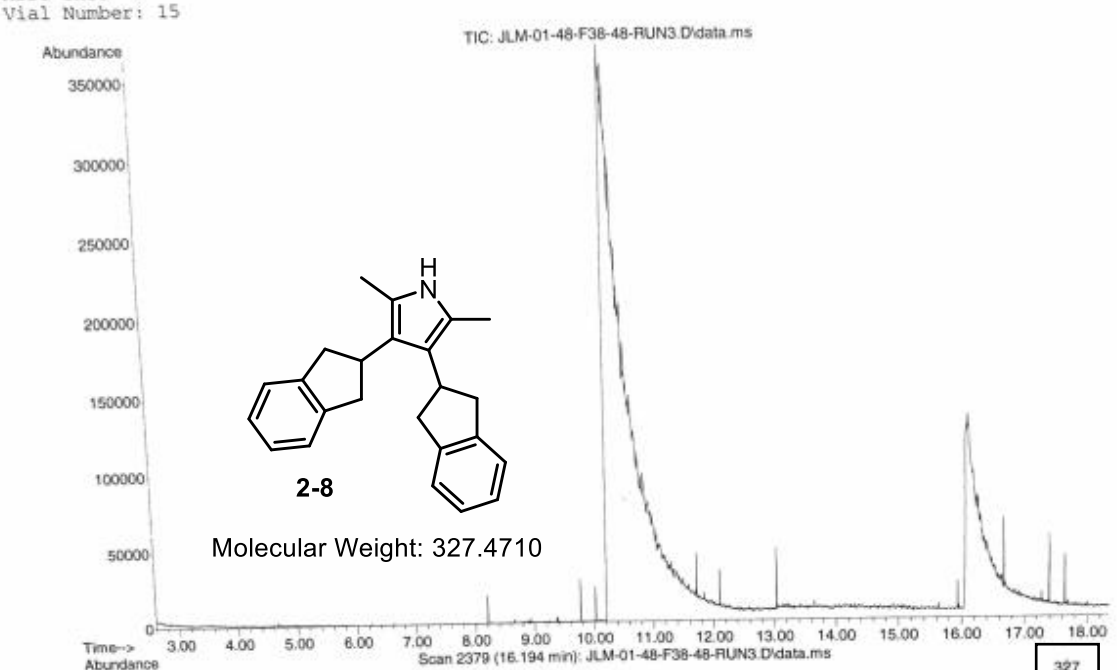
7.24
7.24
7.23
7.20
7.20
7.19
7.19
7.12
7.12
7.11
7.10
7.09
7.09
7.09
7.09
7.08
7.08
7.06
7.06
4.03
4.01
4.01
4.00
3.98
3.98
3.97
3.43
3.41
3.40
3.38
3.13
3.12
3.10
3.08
2.31
H
N
2-4f
0.75
0.95
1.77
1.76
0.91
1.87
1.00
1.97
1.97
2.78
f1 (ppm)
142.51
138.13
135.11
129.23
126.98
124.78
121.42
119.24
118.28
110.44
106.70
77.41
77.16
76.91
39.80
36.09
8.75
f1 (ppm)


JLM-01-48 (FRACTIONS 38-48)
(TRIAL 1) ~ PDT #2
Proton Spectrum
Sample Name:
Data Collected on:
sn.chem.lsa.umich.edu-inova500
Archive directory:
Sample directory:
FidFile: JLM-01-48-f38-48
Pulse Sequence: PROTON (s2pul)
Solvent: c6d6
Data collected on: Sep 12 2017
Agilent Technologies
H
N
2-8
8
7
6
5
4
3
2
1
ppm
154.68
0.64
1.00
0.33
1.00
3.01
1.20
1.38
7.08
1.37

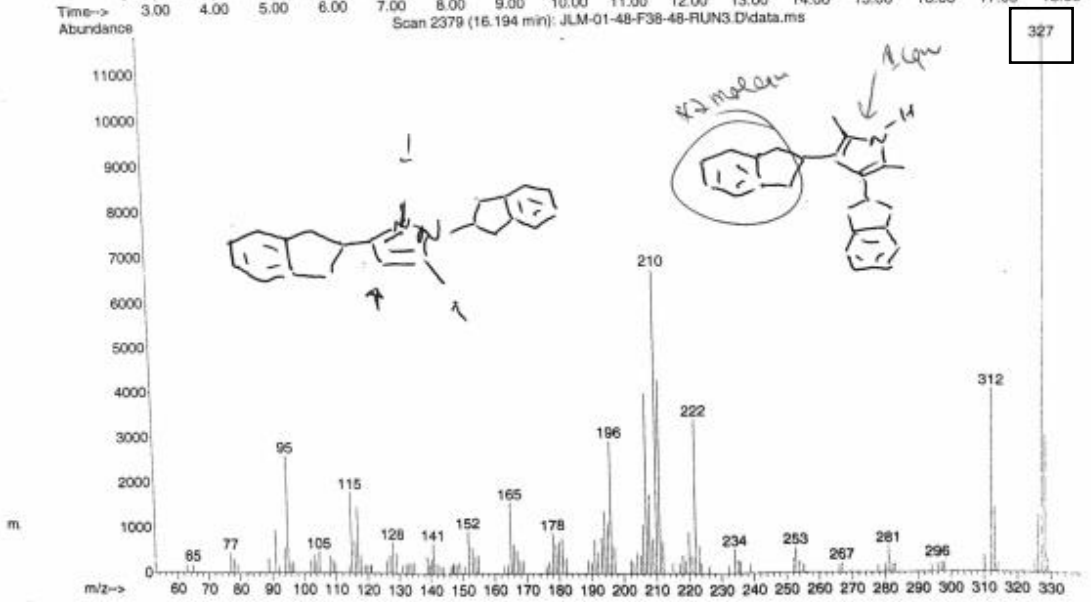
:C:\msdchem\1\DATA\Annabel\JLM-01-48-...

File :C:\msdchem\1\DATA\Annabel\JLM-01-48-F38-48-RUN3.D
Operator : AQA
Acquired : 21 Sep 2017 13:27 using AcqMethod TESTRAMP-FILAMENT2.M
Instrument : GC
Sample Name: JLM-01-48-F38-48-RUN3
Misc Info :
Vial Number: 15



2-8

Molecular Weight: 327.4710



References

(1) For recent reviews, see: J. M. Takacs, X. Jiang, Curr. Org. Chem. 2003, 7, 369. (d) White, D. R.; Bornowski, E. C.; Wolfe, J. P. *Isr. J. Chem.* **2020**, *60*, doi.org/10.1002/ijch.201900108.

(2) (a) White, D. R.; Hutt, J. T.; Wolfe, J. P. *J. Am. Chem. Soc.* **2015**, *137*, 11246. (b) White, D. R.; Wolfe, J. P. *Chem. Eur. J.* **2017**, *23*, 5419. (c) White, D. R.; Herman, M. I.; Wolfe, J. P. *Org. Lett.* **2017**, *19*, 4311.

(3) (a) White, D. R.; Hinds, E. M.; Bornowski, E. C.; Wolfe, J. P.; *Org. Lett.* **2019**, *21*, 3813. (b) Bornowski, E. C.; Hinds, E. M.; White, D. R.; Nakamura, Y.; Wolfe, J. P. *Org. Process Res. Dev.* **2019**, *23*, 1610.

(4) For selected examples of Pd-catalyzed C3-alkylation, alkenylation, or arylation of N-H indoles, see: (a) Yamaguchi, M.; Suzuki, K.; Sato, Y.; Manabe, K. *Org. Lett.* **2017**, *19*, 5388. (b) Lane, B. S.; Brown, M. A.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 8050. (c) Grimster, N. P.; Gauntlett, C.; Godfrey, C. R. A.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 3125. (d) Trost, B. M.; Quancard, J. *J. Am. Chem. Soc.* **2006**, *128*, 6314. (e) Zhu, Y.; Rawal, V. H. *J. Am. Chem. Soc.* **2012**, *134*, 111. (f) Liu, Z; Zeng, T.; Yang, K. S.; Engle, K. M. *J. Am. Chem. Soc.* **2016**, *138*, 15122.

(5) For selected examples of Pd-catalyzed N-alkylation, alkenylation, or arylation of N-H indoles, see: (a) Old, D. W.; Harris, M. C.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 1403. (b) Movassaghi, M.; Ondrus, A. E. *J. Org. Chem.* **2005**, *70*, 8638. (c) Chen, L. -Y.; Yu, X. -Y.;

Chen, J. -R.; Feng, B.; Zhang, H.; Qi, Y. -H.; Xiao, W. -J. *Org. Lett.* **2015**, *17*, 1381. (d) Trost, B. M.; Krische, M. J.; Berl, V.; Grenzer, E. M. *Org. Lett.* **2002**, *4*, 2005.

(6) (a) Fu, L. *Top Heterocycl Chem*, **2010**, *26*, 1-488. (b) Corsello, M. A.; Kim, J. Garg, N. K. *Chem. Sci.*, **2017**, *8*, 5836. (c) Melander, R. J.; Minvielle, M. J.; Melander, C. *Tetrahedron*, **2014**, *70*, 6363. (d) Stempel, E.; Gaich, T. *Acc. Chem. Res.*, **2016**, *49*, 2390.

(7) For representative examples, see: (a) Rizzo, J. R.; Alt, C. A.; Zhang, T. Y. *Lett.* **2008**, *49*, 6749. (b) King, H. D.; Meng, Z.; Deskus, J. A.; Sloan, C. P.; Gao, Q.; Beno, B. R.; Kozlowski, E. S.; LaPaglia, M. A.; Mattson, G. K.; Molski, T. F.; Taber, M. T.; Lodge, N. J.; Mattson, R. J.; Macor, J. E. *J. Med. Chem.* **2010**, *53*, 7564. (c) King, H. D.; Meng, Z.; Denhart, D.; Mattson, R.; Kimura, R.; Wu, D.; Gao, Q.; Macor, J. E. *Org. Lett.* **2005**, *7*, 3437. (d) Zhang, Y.; Lu, B. Z.; Li, G.; Rodriguez, S.; Tan, J.; Wei, H. -X.; Liu, J.; Roschangar, F.; Ding, F.; Zhao, W.; Qu, B.; Reeves, D.; Grinberg, N.; Lee, H.; Heckmann, G.; Niemeier, O.; Brenner, M.; Tsantrizos, Y.; Beaulieu, P. L.; Hossain, A.; Yee, N.; Farina, V.; Senanyake, C. H. *Org. Lett.* **2014**, *16*, 4558.

(8) JLM conducted one of the reaction experiments used for the averaged yield reported.

(9) JLM isolated the described over-alkylated 2,5-dimethylpyrrole derivative while JKK and JLM characterized and assigned the structure. A small amount was isolated and full characterization was not obtained.

(10) Although the reaction conditions reported in eq 2-9 are not the optimized conditions reported in Scheme 2-2, these reaction conditions produced the desired product in ~45% crude yield when using XPhos for the ligand.

(11) For representative examples, see reference 4.

(12) For related 5- or 6-exo Heck/C–H heteroarylation reactions between 1-bromo-2-oxyallyl benzene derivatives and aromatic heterocycles, see: René, O.; Lapointe, D.; Fagnou, K. *Org. Lett.* **2009**, *11*, 4560.

(13) See reference 2c.

(14) JLM conducted both of the reaction experiments that were used for the averaged yield reported.

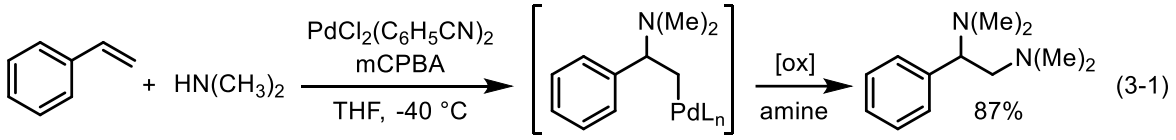
(15) Kirsch, J. K.; Manske, J. L. Wolfe, J. P. *J. Org. Chem.*, **2018**, *83*, 13568.

(16) JLM conducted a reaction and isolated **2-4l** which was used for IR characterization.

Chapter 3
Introduction to Late-Transition-Metal-Catalyzed Alkene Diamination Reactions

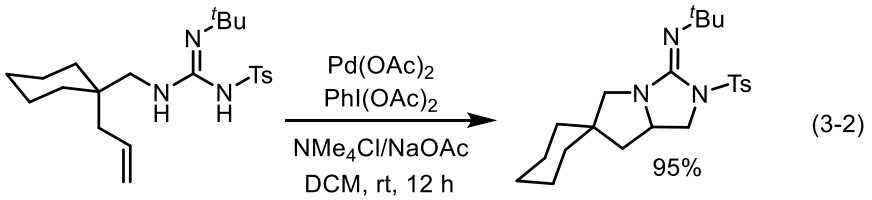
3.1 Diamination Reactions via Palladium Catalysis and Additional Oxidant

Pd-catalyzed alkene diamination has been explored since the late 1970s when Bäckvall reported a stoichiometric Pd method in which diamination occurs across an alkene in the presence of an oxidant in up to 87% yield (eq 3-1).[1] In this report, Bäckvall proposes a Pd(II) intermediate that is oxidized to Pd(IV) (by either mCPBA, Br_2, NBS, or $Pb(OAc)_2$) followed by a Sn2-like reductive elimination to form the product.



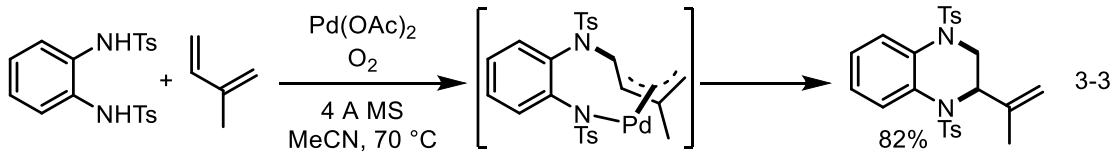
(3-1)

More recent work by Muñiz has demonstrated the ability to perform diamination reactions with catalytic amounts of Pd.[2] They perform intramolecular diaminations to form 5-5, 6-5, or 7-5 fused rings of cyclic ureas and guanidines (eq 3-2). This method requires the use of $PhI(OAc)_2$ as an oxidant and is proposed to go through a Pd(II)/Pd(IV) cycle. The authors also report using Cu as a "transient oxidant" instead of employing hypervalent iodine.[2b]



(3-2)

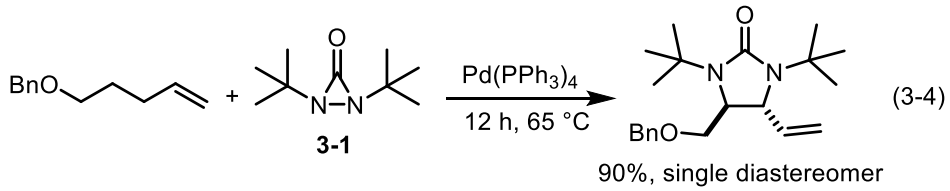
Diamination of dienes has also been studied to yield cyclic ureas and tetrahydroquinoxalines (eq 3-3).[3] However these mechanisms are proposed to go through a Pd(II)-π-allyl intermediate. These reactions still require the use of an external oxidant which can take the form of benzoquninone, O_2, or O_2 and Cu.



3-3

3.2 Diamination Reactions via Palladium Catalysis with Nitrogen-Centered Electrophiles

Further discoveries in the field have found conditions for Pd-catalyzed diamination reactions with nitrogen-centered electrophiles. In 2007 Shi reported the use of di-*t*-butyldiaziridinone (**3-1**) as a nitrogen-centered electrophile for diamination of dienes[4] and then followed up that work with a report of diamination of terminal olefins at the allylic and homoallylic positions (eq 3-4).[5] In both cases, the cyclic urea is obtained as a single diastereomer. The reaction is proposed to go through a Pd(0)/Pd(II) cycle with a Pd(II)-π-allyl intermediate similar to mechanisms proposed by Lloyd-Jones/Booker-Milburn and Zhang.[3] The urea can be removed with TFA and concentrated HCl to give the diamine. However, the use of this single nitrogen source limits the ability to produce a range of heterocycles.

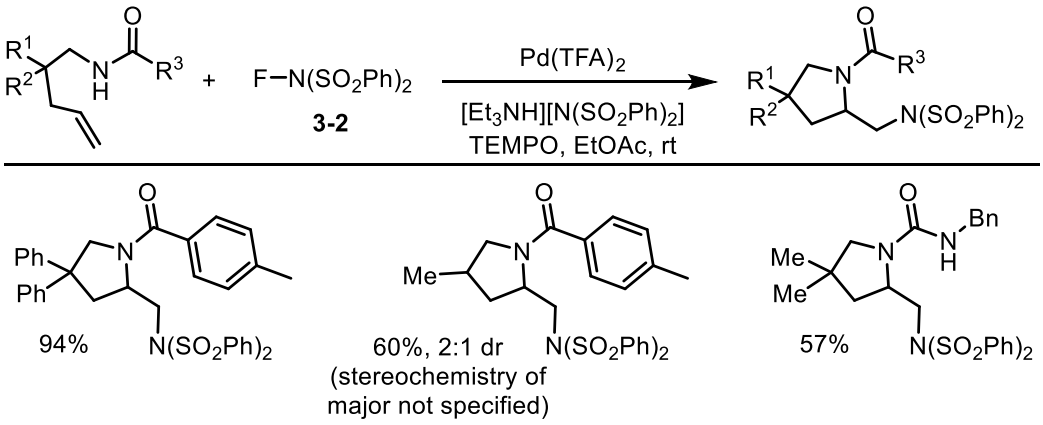


(3-4)

In 2009, Michael reported another method for Pd-catalyzed alkene diamination, but instead uses *N*-fluorobenzenesulfonimide (**3-2**) as the nitrogen-centered electrophile and

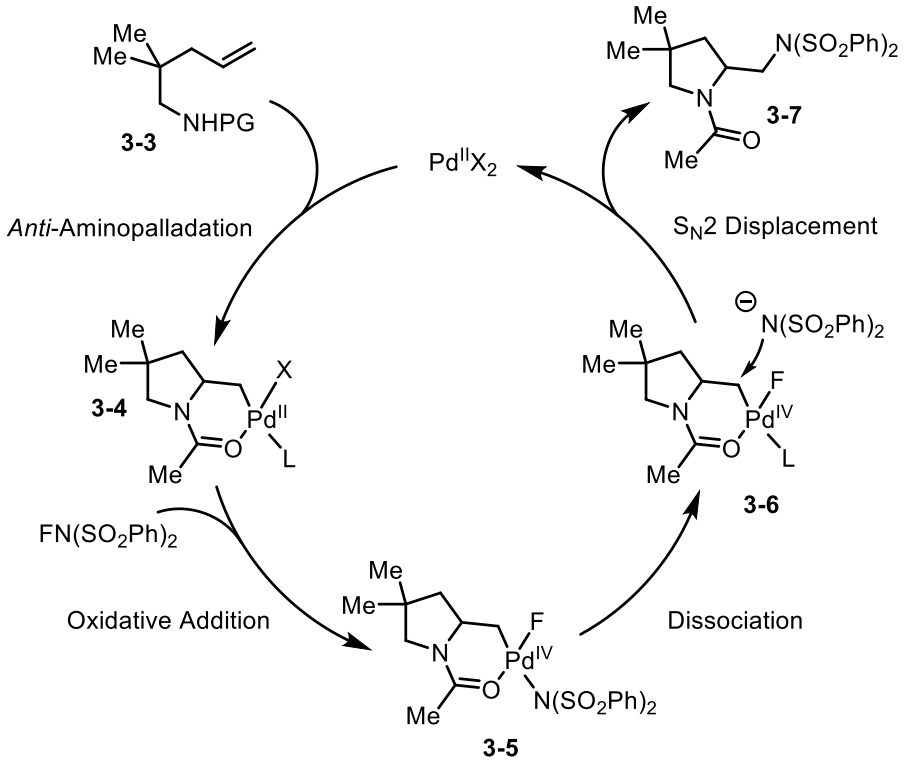
an amide with a tethered alkene to form lactam products (Scheme 3-1).[6] They were also able to optimize conditions to promote asymmetric diamination using (*R*)-Ph-Quinox as the ligand to give up to 96% ee.[7] A limitation of this work is the use of a single nitrogen source as it limits the ability to access a wide array of products in a single transformation. The benzenesulfonimide groups can be removed from the product to allow for further functionalization; however, this requires harsh conditions in which the methylbenzoyl protecting group is removed along with both benzenesulfonimide groups (H_2SO_4, 135 °C, 3 days). One of the benzenesulfonimide groups can be removed while leaving the amide intact, but the compound must be refluxed in EtOH/KOH for 18 hours.

Scheme 3-1: Selected Scope of Michael Pd-Catalyzed Diamination



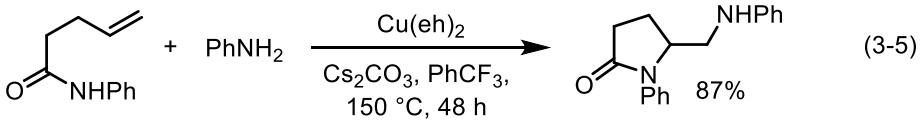
In a follow-up publication, the authors completed a number of experiments to determine the stereochemical outcomes for the aminopalladation and reductive elimination steps.[8] These experiments allow the authors to propose that the reaction proceeds through a Pd(II)/Pd(IV) catalytic cycle (Scheme 3-2). The cycle begins with *anti*-aminopalladation with **3-3** to give **3-4**, followed by oxidative addition of *N*-fluorobenzenesulfonimide. The nitrogen anion then dissociates from **3-5** and subsequent Sn2-like reductive elimination from **3-6** yields **3-7**.

Scheme 3-2: Proposed Mechanism for Michael Pd-Catalyzed Diamination



3.3 Diamination Reactions via Copper Catalysis

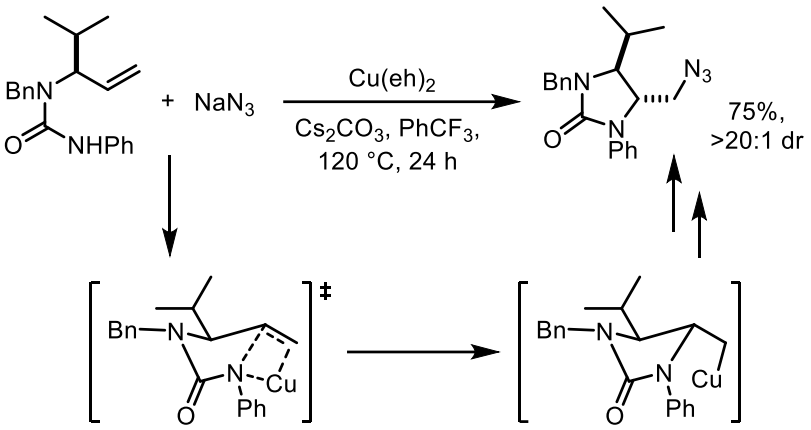
Besides Pd-catalysis, Cu catalysis has also been widely studied for the synthesis of diaminated products. Chemler has reported the synthesis of α-amino substituted cyclic ureas and sulfamides, indolines, pyrrolidines, lactams, and isoxazolidines (eq 3-5).[9]



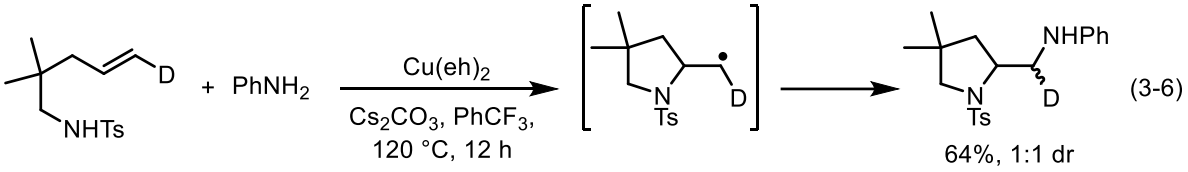
(3-5)

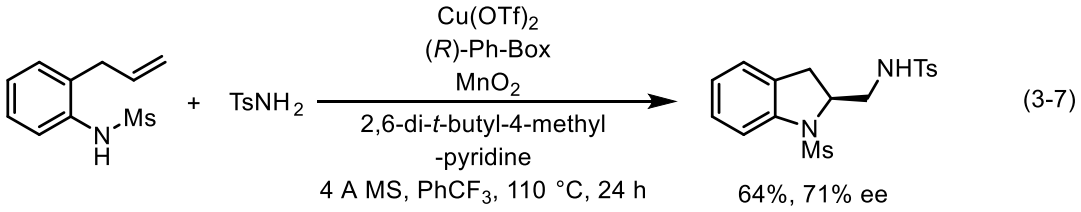
These reactions generally provided better results with electron-deficient anilines or sodium azide as the amine nucleophiles. Electron-rich or neutral anilines and secondary amines generally resulted in lower yields. They observed high diastereoselectivity for allylic substituted ureas due to a highly structured transition state (Scheme 3-3). A limitation of this work is the requirement for either super stoichiometric amounts of Cu or the addition of MnO_2 as a stoichiometric oxidant. Additionally, they found that these

Scheme 3-3: Chemler Cu-Catalyzed Diamination

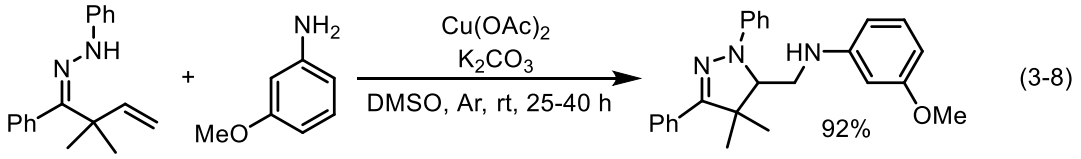


reactions are not stereospecific, likely due to the formation of a radical during the catalytic cycle (eq 3-6). The authors also conducted this reaction with a chiral ligand to yield the product in up to 71% ee (eq 3-7).





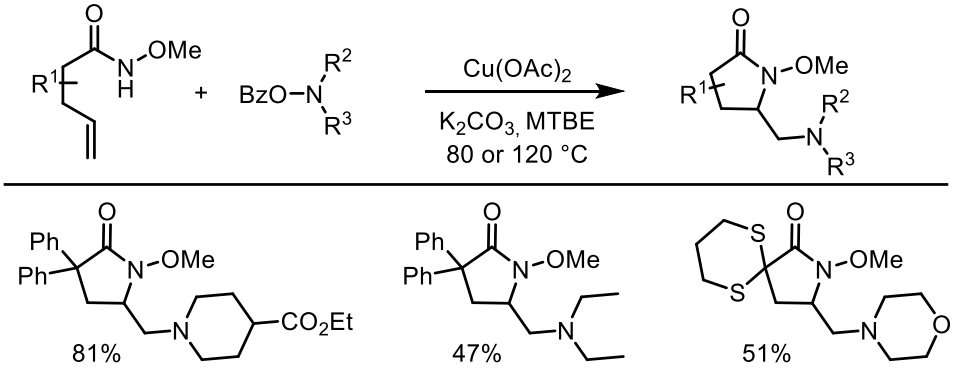
Li detailed examples of alkene diamination reactions of hydrozones with tethered alkenes coupled and amines via Cu catalysis (eq 3-8).[10] Anilines with electron-donating and electron-withdrawing groups are tolerated (79-92% yield) and aliphatic amines are also tolerated in moderate to good yields. This method is interesting due to the absence



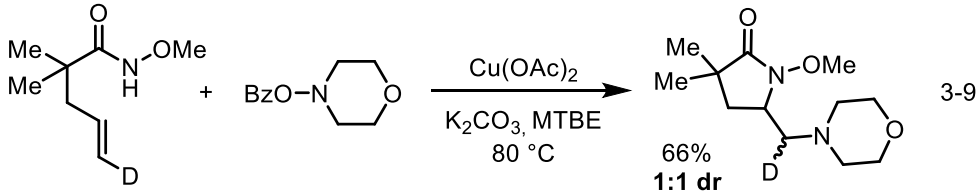
of an obvious oxidant. The authors propose that DMSO is acting as the oxidant for Cu(I) to Cu(II).

Wang reports a diamination method via Cu catalysis in which O-acylated hydroxylamine derivatives are used as nitrogen-centered electrophiles and coupled with homoallylic amides (Scheme 3-4).[11] The electrophiles are synthesized from their amine

Scheme 3-4: Selected Scope of Wang Diamination



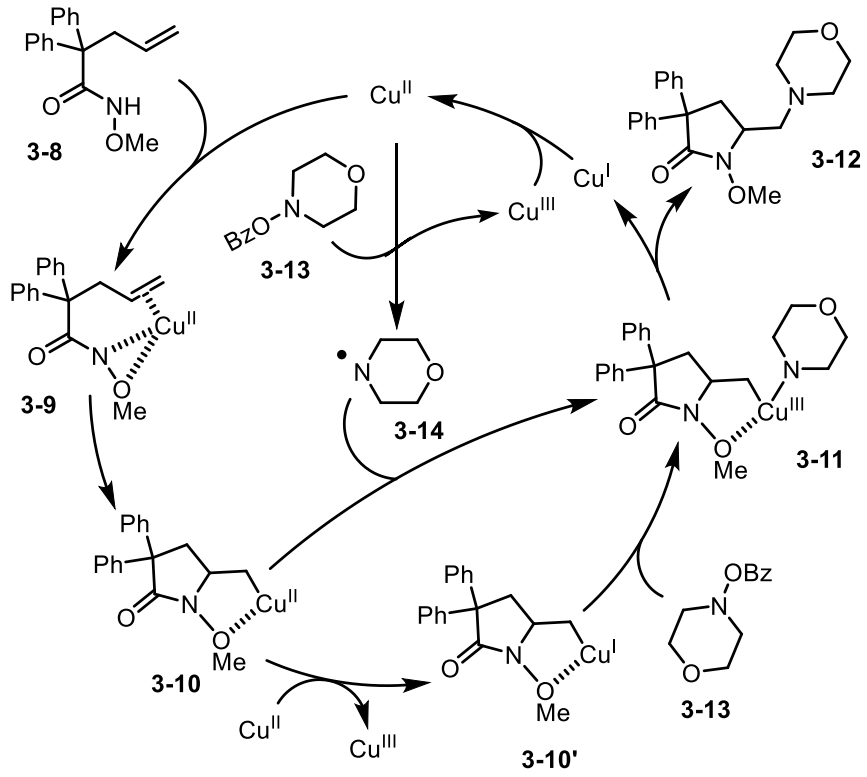
precursors allowing for a wide array of products to be formed. However, the method requires α-substitution on the amide to instill the Thorpe-Ingold effect.[12] When a single stereoisomer of the deuterium-labeled homoallyic amide is used, they obtain a 1:1 mixture of diastereoisomers (eq 3-9). This lack of stereospecificity is likely due to the radical nature of the Cu catalysis as observed in the work by Chemler.



The proposed mechanism (Scheme 3-5) begins with association of the Cu(II) species to the alkene, nitrogen, and oxygen of **3-8** to yield **3-9** followed by aminocupration. **3-10** combines with amino radical **3-14** to from Cu(III) intermediate **3-11** and reductive elimination yields **3-12** and Cu(I). The Cu(I) can be oxidized by Cu(III) that is formed by the reduction of **3-13**. There is a second proposed pathway in which **3-10** is reduced by

Cu(II) to form Cu(III) and **3-10'**. From here, **3-10'** can undergo oxidative addition with **3-13** and then follow the same pathway previously discussed from **3-11**.

Scheme 3-5: Proposed Mechanism for Wang Cu-Catalyzed Diamination



3.4 Conclusion

Pd- and Cu-catalyzed alkene diamination reactions have been reported for the synthesis of heterocycles including ureas, guanidines, lactams, tetrahydroquinoxalines, and isoxazolidines, among others. These methods have suffered from (i) the requirements for the use of external oxidants such as hypervalent iodine, Cu, O_2, or Mn, (ii) the use of limited sources of nitrogen-centered electrophiles such as **3-1** or **3-2**, and (iii) lack of stereospecificity. We were interested in building upon these diamination methods in our own lab using Pd-catalysis. The results of this work thus far are detailed in Chapters 4 & 5.

References

(1) Bäckvall, J.-E. *Tetrahedron Lett.* **1978**, *19*, 163.

(2) (a) Streuff, J. Hövelmann, C. H.; Nieger, M.; Muñiz, K. *J. Am. Chem. Soc.* **2005**, *127*, 14586. (b) Muñiz, K.; Martinez, C. *J. Org. Chem.* **2013**, *78*, 2168. (c) Muniz, K.; Hovelmann, C. H.; Streuff, J.; Campos-Gomez, E. *Pure Appl. Chem.* **2008**, *80*, 1089. (d) Muniz, K.; Hovelmann, C. H.; Streuff, J. *J. Am. Chem. Soc.* **2008**, *130*, 763.

(3) (a) Booker-Milburn, K. I.; Lloyd-Jones, G. C.; Bar, G. L. J. *J. Am. Chem. Soc.* **2005**, *127*, 7308. (b) Wu, Z.; Wen, K.; Zhang, J.; Zhang, W. *Org. Lett.* **2017**, *19*, 2813.

(4) Du, H.; Zhao, B.; Shi, Y. *J. Am. Chem. Soc.* **2007**, *129*, 762.

(5) Du, H.; Yuan, W.; Zhao, B.; Shi, Y. *J. Am. Chem. Soc.* **2007**, *129*, 7496.

(6) Sibbald, P. A.; Michael, F. E. *Org. Lett.*, **2009**, *11*, 1147.

(7) Ingalls, E. L.; Sibbald, P. A.; Kaminsky, W.; Michael, F. E. *J. Am. Chem. Soc.* **2013**, *135*, 8854.

(8) Sibbald, P. A.; Rosewall, C. F.; Swartz, R. D.; Michael, F. E. *J. Am. Chem. Soc.* **2009**, *131*, 15945.

(9) (a) Sequeira, F. C.; Turnpenny, B. W.; Chemler, S. R. *Angew. Chem. Int. Ed.* **2010**, *49*, 6365. (b) Khoder, Z. M.; Wong, C. E.; Chemler. S. R. *ACS Catal.* **2017**, *7*, 4775.

(10) Chen, M.; Wang, L.-J.; Ren, P.-X.; Hou, X.-Y.; Fang, Z.; Han, M.-N.; Li, W. *Org. Lett.* **2018**, *20*, 510.

(11) Shen, K.; Wang. Q. *Chem. Sci.* **2015**, *6*, 4279.

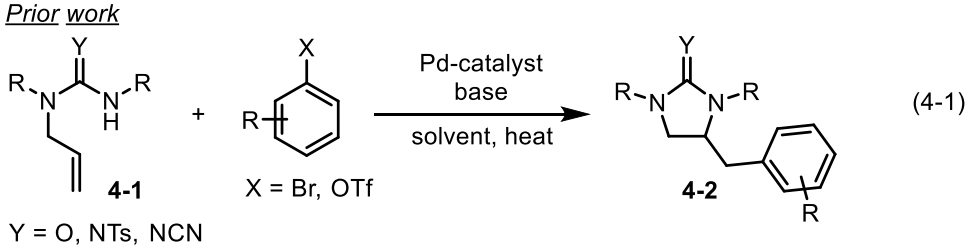
(12) (a) Beesley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc. Trans.* **1915**, *107*, 1080. (b) Jung, M. E.; Piizzi, G. *Chem. Rev.* **2005**, *105*, 1735.

Chapter 4

Palladium-Catalyzed Alkene Diamination Reactions of Nitrogen Electrophiles. Synthesis of Cyclic Guanidines and Ureas Bearing Dialkylaminomethyl Groups.

4.1 Introduction

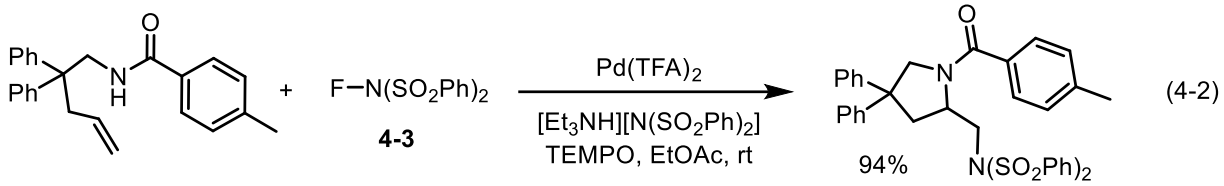
Over the past fourteen years, our group has reported a series of Pd-catalyzed alkene difunctionalization reactions between aryl or alkenyl halides or triflates and alkenes bearing pendant nucleophiles.[1] For example, treatment of an *N*-allyl urea or guanidine derivative (**4-1**) with an aryl halide or triflate affords heterocyclic product **4-2** in good yield (eq 4-1).[2] These transformations are effective with a broad range of nucleophiles, the reactions are stereospecific with respect to alkene geometry, and substrates bearing substituents on the alkene or the alkyl tether are generally transformed with good to excellent levels of diastereoselectivity. Despite the utility of these transformations, to date, all reactions have involved the use of carbon-centered electrophiles, which leads to the formation of one C–C bond and one carbon-heteroatom bond during the alkene addition.



(4-1)

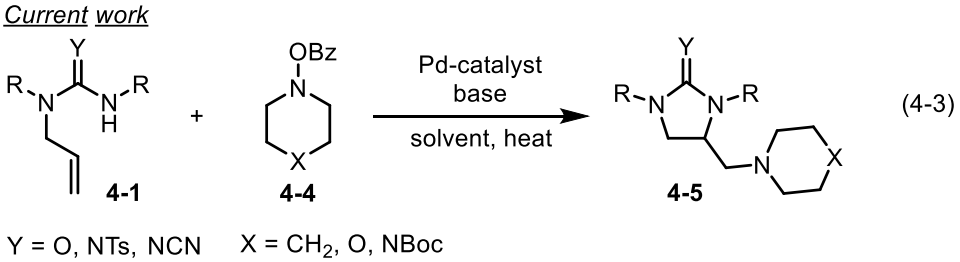
When we surveyed the literature for other types of electrophiles employed, we took interest in work reported by Forrest Michael in 2009 in which they use *N*-fluorobenzenesulfonimide (**4-3**) as a nitrogen-centered electrophile (eq 4-2).[3,4] This

electrophile gives diaminated heterocyclic products via Pd catalysis in up to 94% yield, but the method suffers due to the use of a singular electrophile.



(4-2)

In addition to **4-3**, the use of O-acylated hydroxylamine derivatives as nitrogen-centered electrophiles (**4-4**) in metal-catalyzed reactions has attracted considerable attention.[5] We were interested in investigating the utility of these electrophiles in Pd-catalyzed heterocycle-forming alkene diamination reactions,[6,7,8] which we felt could proceed through a mechanism related to the mechanism for our Pd-catalyzed alkene carboamination reactions (eq 4-3). These transformations would provide heterocyclic products bearing an appended dialkylaminomethyl group (**4-5**), which are subunits

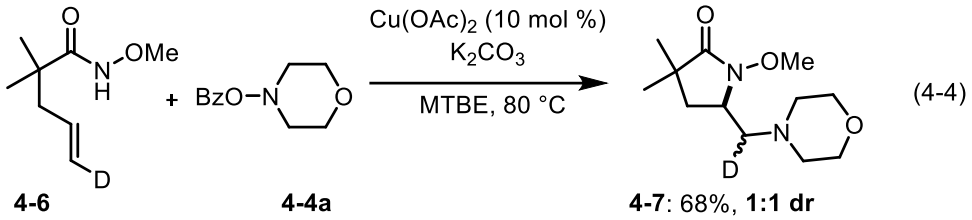


(4-3)

displayed in some biologically active compounds.[9] We initially proposed that the final step in the alkene diamination catalytic cycle would likely be an $sp^3C–sp^3N$ bond-forming reductive elimination from an alkylpalladium complex, which is a very rare organometallic transformation,[10] and was expected to be challenging to achieve. However, recent studies on alkane C–H functionalization with these electrophiles suggested that this reductive elimination step may be possible.[10a,11] In addition, related Cu-catalyzed reactions reported by Wang[12,13,14] are thus far not stereospecific with respect to alkene geometry due to the radical character of an intermediate alkylcopper complex (eq 4-4). Thus, it

appeared that the Pd-catalyzed process could have advantages over the Cu-catalyzed reactions, as our Pd-catalyzed alkene carboamination reactions are stereospecific, and we anticipated the new diamination reactions would also be stereospecific.

Wang 2015[10]



(4-4)

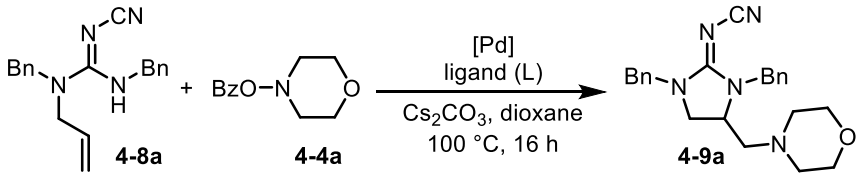
4-6 **4-4a** **4-7**: 68%, **1:1 dr**

The work described in this chapter is comprised of both the author's (JKK) and Luke J. Peterson's contributions. LJP conducted early reaction optimization (Table 4-1, entries 1-10), reaction scope (Table 4-2, Table 4-3, entries 1-4), alkene addition stereochemistry (Table 3-4), and synthesis of starting materials. We have decided to include LJP's results in this dissertation to give the reader the full story about this transformation.

4.2 Optimization of Reaction Conditions and Precatalyst Studies

In order to explore the feasibility of Pd-catalyzed alkene diamination reactions involving nitrogen electrophiles, we first examined the coupling of **4-8a** with morpholino benzoate (**4-4a**) to afford cyclic guanidine product **4-9a** (Table 4-1).[15,16] Initially, we employed catalysts derived from $Pd(OAc)_2$ and the ligands DPE-Phos, CPhos, and XantPhos, as these ligands provided good to excellent results in alkene carboamination reactions of **4-8a** and related nucleophiles.[1,2] No desired product was obtained with the CPhos or XantPhos ligands, but we were gratified to find that use of DPE-Phos led to the formation of the desired product in a measurable, but low yield (entries 1-3). The mass

Table 4-1: Optimization Studies



entry	[Pd]	ligand (L)	catalyst loading	yield (%)[b]
1	$Pd(OAc)_2$	DPE-Phos	2 mol % [Pd] 4 mol % L	13[e]
2	$Pd(OAc)_2$	CPhos	2 mol % [Pd] 8 mol % L	0[e]
3	$Pd(OAc)_2$	XantPhos	2 mol % [Pd] 8 mol % L	0[e]
4	$Pd(OAc)_2$	$P(C_6F_5)_3$	2 mol % [Pd] 8 mol % L	30[e]
5	$Pd_2(dba)_3$	$P(C_6F_5)_3$	4 mol % [Pd] 16 mol % L	0[e]
6	$Pd(TFA)_2$	$P(C_6F_5)_3$	4 mol % [Pd] 16 mol % L	40[e]
7	$Pd(acac)_2$	$P(C_6F_5)_3$	4 mol % [Pd] 16 mol % L	60[e]
8	$Pd(acac)_2$	$P[C_6H_3\text{-}3,5\text{-}CF_3)_2]_3$	4 mol % [Pd] 16 mol % L	80[e]
9	$Pd(acac)_2$	JackiePhos	4 mol % [Pd] 16 mol % L	95[e]
10	**$Pd(acac)_2$**	**JackiePhos**	**4 mol % [Pd] 16 mol % L**	**95[c,e]**
11	$Pd_2(dba)_3$	JackiePhos	4 mol % [Pd] 16 mol % L	0[c]
12	$Pd(acac)_2$	JackiePhos + dba	4 mol % [Pd] 16 mol % L 6 mol % dba	25[c]
13	G3-JackiePhos	JackiePhos	4 mol % [Pd] 16 mol % L	<5[c]
14	G3-JackiePhos	no added ligand	4 mol % [Pd]	5[c]
15	G3-JackiePhos	JackiePhos + acac	4 mol % [Pd] 16 mol % L 8 mol % acac	35[c]

[a]Conditions: 1.0 equiv **4-8a**, 4.0 equiv **4-4a**, 2 equiv Cs_2CO_3, [Pd], ligand (L), dioxane (0.1M), 100 °C, 16 h. [b]Yields were determined by ^1H NMR using 1,10-phenanthroline as an internal standard. [c]The reaction was conducted using 3 equiv **4-4a** instead of 4 equiv. [d]The reaction was conducted with 12 mol % added JackiePhos (plus the 4 mol % of JackiePhos bound to the G3 complex).[e]Experiments conducted by LJP.

balance in these transformations consisted predominantly of unreacted starting material. Subsequently, we turned our attention to electron-poor monodentate phosphines, as ligands such as $P(C_6F_5)_3$ have provided good results in other Pd-catalyzed transformations of nitrogen electrophiles,[11a,17] and it seemed that the electron-poor ligand may accelerate the $sp^3C–sp^3N$ bond-forming reductive elimination step.[18] Use of $P(C_6F_5)_3$ as ligand resulted in an improved 30% yield of **4-9a** (entry 4), and after surveying several palladium sources, we found that use of $Pd(acac)_2$ led to a further increase to 60% yield (entry 7). The combination of $P[3,5\text{-}(CF_3)_2C_6H_3]_3$ as ligand and $Pd(acac)_2$ as precatalyst was even better, with **4-9a** generated in 80% yield (entry 8). Finally, we examined the biarylphosphine JackiePhos, which contains two $3,5\text{-}(CF_3)_2C_6H_3$ groups on the phosphorous atom and has previously been shown to promote challenging $sp^2C–N$ bond-forming reductive elimination;[19] we were delighted to obtain a 95% NMR yield of **4-9a** (entry 9). With this catalyst system we were able to decrease the amount of electrophile used from 4 equiv to 3 equiv, but use of 2 equiv or less of the electrophile resulted in diminished yields (entry 10).

Once the satisfactory conditions were in hand, we conducted a few additional experiments to further examine the influence of precatalyst structure on yield. Although the $Pd(acac)_2$/JackiePhos catalyst system provided excellent results (entry 10), use of $Pd_2(dba)_3$ as a precatalyst for this reaction completely inhibited product formation (entries 5 & 11). Addition of 6 mol % dba to the otherwise optimal conditions (entry 12) resulted in the formation of **4-9a** in only 25% yield. Use of the Buchwald G3-JackiePhos catalyst precursor in place of $Pd(acac)_2$ failed to produce significant amounts of the desired product (≤ 5%, entries 13–14). However, when 8 mol % acac (2,4-pentanedione) was

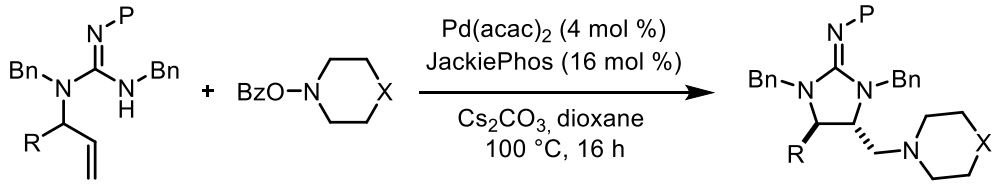
added to a reaction in which the G3-JackiePhos complex was used as precatalyst, **4-9a** was generated in 35% yield. These results indicate that: (a) the failure of $Pd_2(dba)_3$ to serve as a viable precatalyst is probably due to inhibition by the dba ligand rather than the zerovalent oxidation state of that complex; and (b) acac plays a key role in these reactions. Initially, we suggested the role of acac was to either facilitate reactivity of an intermediate along the catalytic cycle, or to inhibit catalyst deactivation. However, subsequent discoveries, described in Chapter 5, revealed that acac is the true ligand for palladium, rather than JackiePhos.

4.3 Reaction Scope

We explored the scope of the Pd-catalyzed coupling reactions of *N*-cyano and *N*-tosylguanidine substrates **4-8a-d** with several different electrophiles. As shown in Table 4-2[20], these transformations are effective with *O*-benzoylhydroxylamine electrophiles derived from morpholine (**4-3a**), piperidine (**4-3b**), and *N*-boc piperazine (**4-3c**). However, efforts to employ an acyclic electrophile derived from *N*-methyl benzylamine led to the formation of a complex mixture of products. Reactions of substrates **4-8c-d** bearing an allylic methyl group proceeded to afford **4-9f**-**h** in good yield and moderate diastereoselectivity (3:1 dr). These diastereoselectivities are comparable to those obtained in analogous Pd-catalyzed carboamination reactions of **4-8c**-**d** with aryl bromides.[2a] Attempts to employ substrates bearing either 1,1- or 1,2-disubstituted alkenes have thus far been unsuccessful.

We also briefly explored the coupling of urea substrates **4-10a-c** to afford **4-11a-f**. As shown in Table 4-3[21], the reactions of **4-10a** proceeded smoothly with electrophiles derived from morpholine **4-3a** (90% yield on a 0.1 mmol scale and 76% yield on a 1.0

Table 4-2: Diamination of *N*-Allylguanidines



4-8a: R = H, P = CN
4-8b: R = H, P = Ts,
4-8c: R = Me, P = CN
4-8d: R = Me, P = Ts

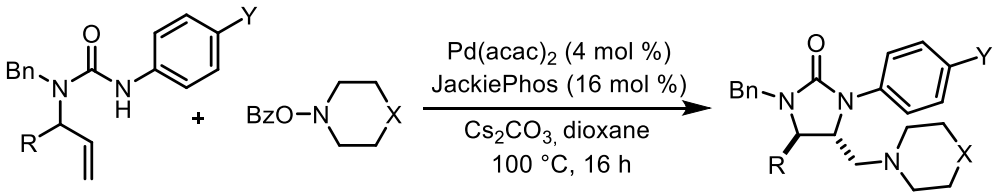
4-4a: X = O
4-4b: X = CH_2
4-4c: X = NBoc

entry	P	X	R	dr[b]	yield (%)[c,d]
1	CN	O	H		91 (**4-9a**)
2	CN	CH_2	H		92 (**4-9b**)
3	CN	NBoc	H		61 (**4-9c**)
4	Ts	O	H		86 (**4-9d**)
5	Ts	CH_2	H		77 (**4-9e**)
6	CN	O	Me	3:1 (4:1)	75 (**4-9f**)
7	CN	CH_2	Me	3:1	81 (**4-9g**)
8	Ts	O	Me	3:1	88 (**4-9h**)

[a]Conditions: 1.0 equiv **4-8**, 3.0 equiv **4-4**, 2 equiv Cs_2CO_3, 4 mol % $Pd(acac)_2$, 16 mol % JackiePhos, dioxane (0.1 M), 100 °C, 16 h. Reactions were conducted on a 0.1 mmol scale. [b]Diastereomeric ratios were determined by ^1H NMR analysis. Numbers shown in parentheses are dr values for the crude reaction mixture in cases where the crude and isolated dr differed. [c]Isolated yield (average of two or more experiments). [d]Experiments conducted by LJP.

mmol scale) and piperidine (83% yield). However, use of electrophile **4-3c** derived from *N*-boc piperazine led to a modest yield of the desired product. Although the presence of a methyl group at the allylic position was well tolerated in the reactions of guanidine nucleophiles **4-8c-d** (Table 4-2, entries 6–8), the coupling of analogous urea substrate **4-10b** proceeded in low yield (32%) to afford **4-11d** with 2:1 dr (Table 4-3, entry 4). Use of substrate **4-10c**, which contains an *N*-*p*-chlorophenyl group, led to lower yields than were observed in reactions of **4-10a** due to competing decomposition of the urea substrate to give *N*-allylbenzylamine and difficulties in isolation of the desired product.

Table 4-3: Diamination of *N*-Allylureas



4-10a: R = H, Y = NO_2 **4-3a-c** **4-11a-f**

4-10b: R = CH_3, Y = NO_2

4-10c[f]: R = H, Y = Cl

entry	Y	X	R	dr[b]	yield (%)[c]
1	NO_2	O	H		90 (**4-11a**)[e]
2	NO_2	CH_2	H		83 (**4-11b**)[e]
3	NO_2	NBoc	H		46 (**4-11c**)[e]
4	NO_2	O	Me	2:1	32 (**4-11d**)[e]
5[d]	Cl	O	H		45 (**4-11e**)
6[d]	Cl	CH_2	H		14 (**4-11f**)

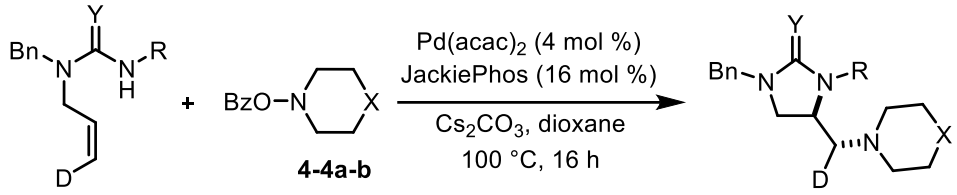
[a]Conditions: 1.0 equiv **4-10**, 3.0 equiv **4-4**, 2 equiv Cs_2CO_3, 4 mol % $Pd(acac)_2$, 16 mol % JackiePhos, dioxane (0.1 M), 100 °C, 16 h. Reactions were conducted on a 0.1 mmol scale. [b]Diastereomeric ratios were determined by ^1H NMR analysis. [c]Isolated yield (average of two or more experiments). [d]The reaction was conducted with 4 mol % $Pd(acac)_2$ and 6 mol % JackiePhos [e]Experiments conducted by LJP. [f]Compound **4-10c** was synthesized by EMH.

4.4 Stereospecific Reactions and Proposed Catalytic Cycle

In order to gain insight into the mechanism and stereospecificity of these new transformations, we examined the reactivity of deuterated substrates **4-*d*-8a-b** and **4-*d*-10a**. As shown in Table 4-4[22], the coupling of **4-*d*-8a** with **4-4a** afforded *anti*-addition product **4-*d*-9a** in 67% yield and 3:1 dr. The reactions of urea substrate **4-*d*-10a** and *N*-tosylguanidine **4-*d*-8b** with morpholino benzoate **4-4a** also proceeded via *anti*-addition to the alkene, but with higher diastereoselectivity (6:1 dr in both cases). The coupling of piperidin-1-yl benzoate **4-4b** with **4-*d*-8b** gave slightly higher diastereoselectivity (7:1 dr) than was obtained with morpholino benzoate. Thus, in contrast to the related copper-

catalyzed diamination reactions,[12] the Pd-catalyzed alkene diamination reactions are stereospecific, although the transfer of stereochemical information from substrate to product is thus far imperfect (but arguably synthetically useful).

Table 4-4: Alkene Addition Stereochemistry



4-*d*-8a: R = Bn, Y = N-CN
4-*d*-8b: R = Bn, Y = N-Ts
4-*d*-10a: R = C_6H_4-*p*-NO_2, Y = O

4-*d*-9a: R = Bn, Y = N-CN, X = O
4-*d*-9d: R = Bn, Y = N-Ts, X = O
4-*d*-9e: R = Bn, Y = N-Ts, X = CH_2
4-*d*-11a:R = C_6H_4-*p*-NO_2, Y = O, X = O

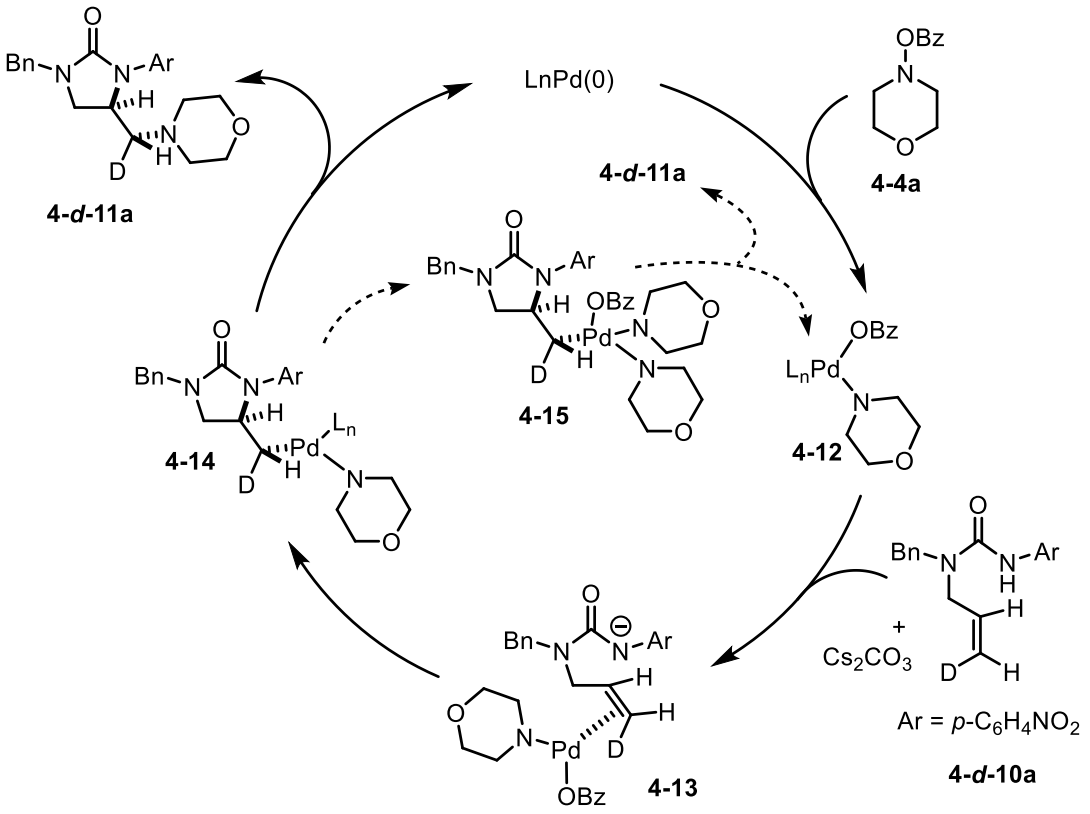
entry	Y	X	R	dr[b]	yield (%)[c,d]
1	N-CN	O	Bn	3:1	67 (**4-*d*-9a**)
2	O	O	C_6H_4-*p*-NO_2	6:1	75 (**4-*d*-11a**)
3	N-Ts	O	Bn	6:1	75 (**4-*d*-9d**)
4	N-Ts	CH_2	Bn	7:1	77 (**4-*d*-9e**)

[a]Conditions: 1.0 equiv **4-*d*-8**, or **4-*d*-10a**, 3.0 equiv **4-4a-b**, 2 equiv Cs_2CO_3, 4 mol % $Pd(acac)_2$, 16 mol % JackiePhos, dioxane (0.1 M), 100 °C, 16 h. Reactions were conducted on a 0.1 mmol scale. [b]Diastereomeric ratios were determined by ^{1}H NMR analysis. [c]Isolated yield (average of two or more experiments). [d]Experiments conducted by LJP.

Based on the alkene addition stereochemistry and our previous related chemistry, we initially proposed that these new Pd-catalyzed alkene diamination reactions proceed via the catalytic cycle shown in Scheme 4-1. Initial ligation and reduction of the $Pd(acac)_2$ pre-catalyst leads to formation of a Pd(0) complex, which then undergoes oxidative addition to the *O*-benzoyl hydroxylamine **4-4a** to afford intermediate **4-12**.[23] Coordination of the alkene to the Pd-complex followed by deprotonation and *anti*-aminopalladation of **4-13** then affords **4-14**, which undergoes C–N bond-forming reductive elimination to yield **4-*d*-11a** with concomitant regeneration of the Pd(0) catalyst. Given the considerable

nucleophilicity of guanidines and the use of the weak base Cs_2CO_3 in these reactions, it is also possible that deprotonation occurs after the aminopalladation event. Although we preferred the mechanism described, we also proposed an alternative pathway involving oxidation of **4-14** to Pd(IV) complex **4-15**, followed by reductive elimination to afford the product with formation of **4-12** to close the catalytic cycle. Subsequent studies, discussed in Chapter 5, revealed that neither of these two proposed pathways are operable in this system, and the transformation proceeds through a different mechanism.

Scheme 4-1: Initially Proposed Catalytic Cycle



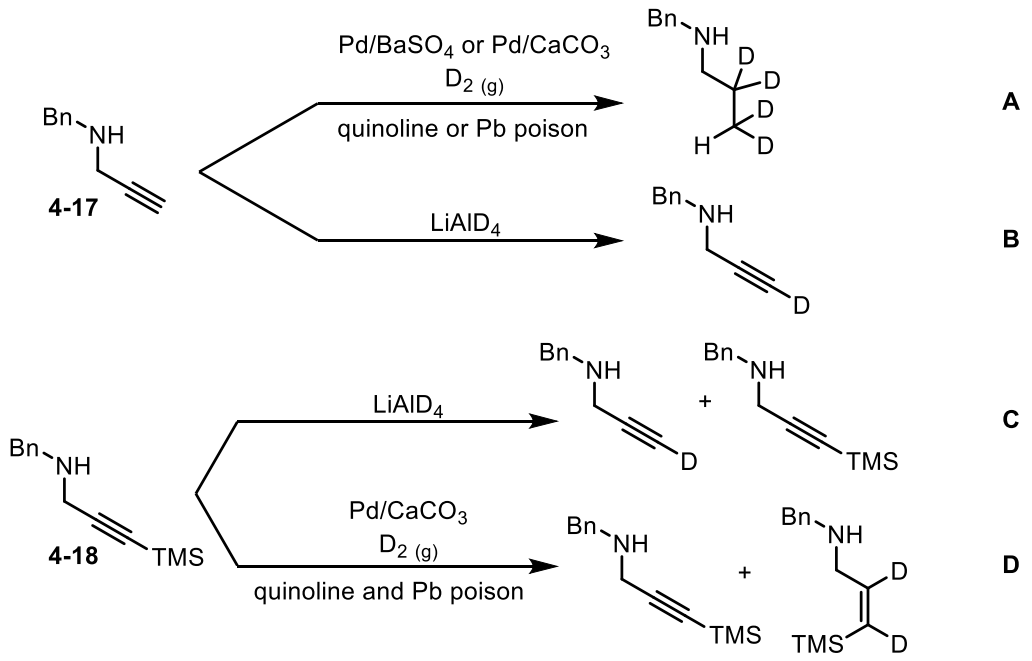
The minor stereoisomer observed in these reactions most likely originates via one of two pathways: (a) competing *syn*-aminopalladation via a palladium bis(amido) complex; or (b) erosion of the stereochemistry of intermediate **4-14** (or **4-15**, as the case may be) via β-hydride elimination/reinsertion to generate a tertiary β-amino palladium complex, which can undergo rotation around the C-CH_2D bond followed by a second β-hydride

elimination/reinsertion to invert the stereogenic center. To probe this question, we sought to slow the rate of potential β-hydride elimination from **4-14** by replacing the H-atom on the internal alkene carbon with a deuterium atom (R = D). β-hydride elimination reactions from Pd typically exhibit large primary kinetic isotope effects (over 5), so substitution of D for H in intermediate **4-14** should decrease the rate of β-hydride elimination without having much impact on the rate of reductive elimination. Therefore, if formation of the minor stereoisomer derives from β-hydride elimination from **4-14**, substitution of D for H should improve stereocontrol by slowing that process. We hoped that this substitution would either lead to higher stereocontrol, therefore suggesting that the minor stereoisomer originates from β-hydride elimination,[24] or would lead to no change in stereoselectivity, which would imply that the modest stereocontrol is due to competing *syn*- vs. *anti*-aminopalladation.[25]

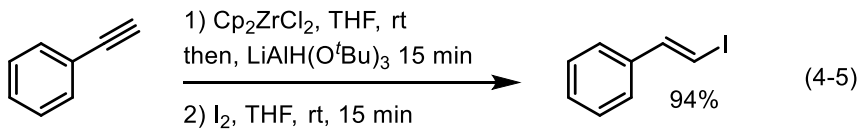
As such, we worked to synthesize doubly-deuterated alkene substrate **4-16**. We attempted several different methods to install the 1,2 di-deutero groups (Scheme 4-2). Traditional methods such as reduction with D_2 gas and $Pd/BaSO_4$ or $Pd/CaCO_3$ with catalyst poisons led to over reduction of N-benzylprop-2-yn-1-amine (**4-17**) to the alkane product (**A**). We could not replicate a literature reduction[26] of **4-17** with $LiAlD_4$ and D_2O. Instead, we only obtained deuteration of the terminal alkyne (**B**). We tried the reduction of a TMS protected alkyne (**4-18**) using either $LiAlD_4$ or under Lindlar conditions, but did not obtain the desired product in appreciable yields (**C, D**).

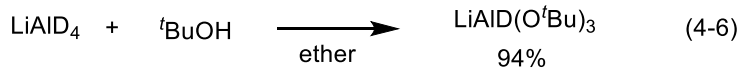
We then came upon a publication by Snieckus[27] in which they report an *in situ* prep of the Schwartz reagent ($Cp_2Zr(H)Cl$). The key to their synthesis is the use of $LiAlH(O^tBu)_3$ as the reductant to prevent the formation of over-reduced Cp_2ZrH_2 and other side

Scheme 4-2: Attempts to Synthesize Di-Deutero Alkene

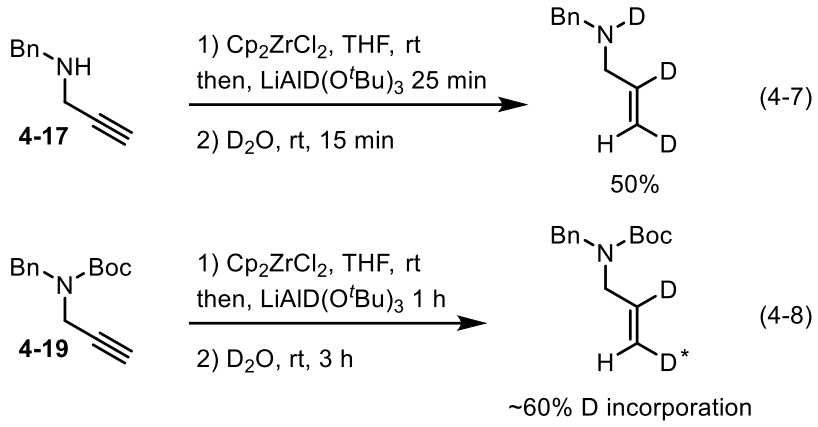


products. Most interesting to us was their report of the reduction of several alkynes to *E*-alkenes in high yields with their reduction process and quench with I_2 (eq 4-5). We began by preparing $LiAlD(O^tBu)_3$ from $LiAlD_4$ and freshly distilled *tert*-butyl alcohol (eq 4-6).[28]

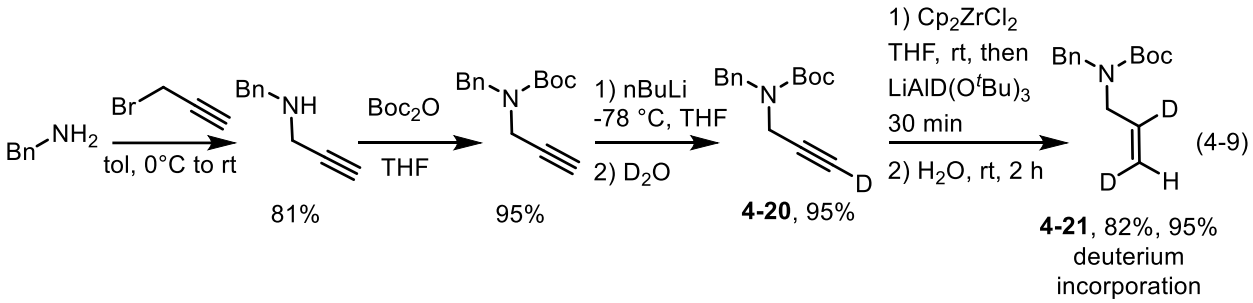




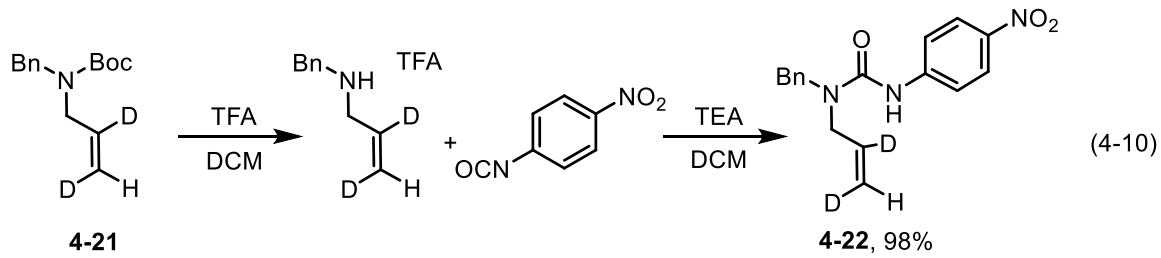
When we employed this modified Schwartz reduction to **4-17** with a D_2O quench, we only observed ~50% conversion even when accounting for the acidic N-H (eq 4-7). However, we were delighted to find that the reaction proceeded to ~70% conversion when using *N*-Boc protected amine **4-19**. With extended stir times we observed 95% conversion to the desired product. However, analysis of the deuterium incorporation showed that the



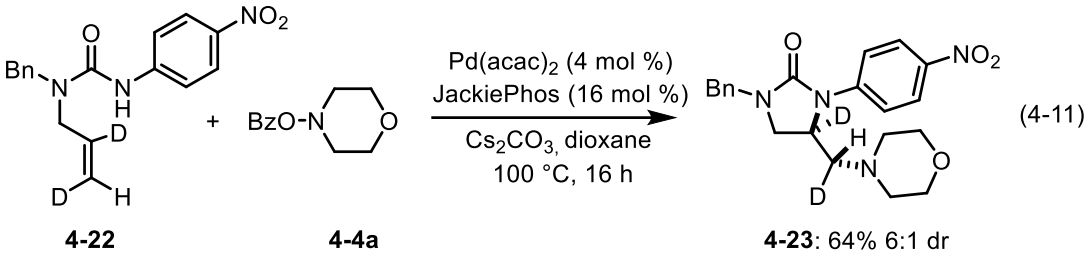
deuterium originating from the D_2O quench was only 70% incorporated (eq 4-8). Attempts to fix this by using a fresh ampule of D_2O and further extended stir times were unsuccessful. We changed strategy again and deuterated the terminal position of the Boc-protected amine (**4-20,** eq 4-9). We employed the modified Schwartz conditions, but this time with a H_2O quench and we obtained the desired product with 95% deuterium incorporation at each of the alkene positions (eq 4-9). With **4-21** in hand, we finished the



synthesis to **4-22** by TFA deprotection of the Boc group and then coupling with 4-nitrophenyl isocyanate (eq 4-10). As shown in eq 4-11, **4-22** was subjected to our standard reaction conditions and this transformation afforded **4-23** in 64% yield and 6:1 dr, which



is comparable to that obtained in the reaction of **4-*d*-10a**. Thus, the minor stereoisomer appears to result from competing *syn*-aminopalladation.



4-22 **4-4a** **4-23**: 64% 6:1 dr (4-11)

4.5 Considerations

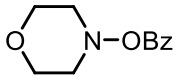
In this chapter, we discussed the development of a new class of Pd-catalyzed alkene diamination reactions that involve the coupling of *O*-benzoyl hydroxylamine derived electrophiles with *N*-allylguanidine or urea derivatives. The transformations proceed via stereospecific *anti*-addition of the two *N*-atoms to the alkene with up to 7:1 dr, which is in sharp contrast to previously reported Cu-catalyzed reactions.[12] These transformations appear to proceed via a rare sp^3C-sp^3N bond-forming reductive elimination. Chapter 5 will discuss new discoveries including the isolation of side products and control reactions which led to a new mechanistic hypothesis and discovered ligand effects on this diamination reaction.

The work described in this chapter was published in *Organic Letters*[29] and was adapted with permission from Peterson, L. J.; Kirsch, J. K.; Wolfe. J. P. Pd-Catalyzed Alkene Diamination Reactions of Nitrogen Electrophiles: Synthesis of Cyclic Guanidines and Ureas Bearing Dialkylaminomethyl Groups. *Org. Lett.*, **2018**, *20*, 3513.

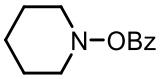
4.6 Experimental

General: All reactions were carried out under a nitrogen atmosphere in flame-dried glassware. All reagents, palladium precatalysts, and ligands were purchased from commercial sources and were used without purification unless otherwise noted. The substrates 1-allyl-1,3-dibenzyl-2-cyanoguanidine (**4-8a**),[30] 1,3-dibenzyl-1-(but-3-en-2-yl)-2-cyanoguanidine (**4-8c**),[30] *N*-{[allyl(benzyl)amino](benzylamino)methylene}-4-methylbenzenesulfonamide (**4-8b**),[30] *N*-{[benzyl(but-3-en-2-yl)amino](benzylamino)methylene}-4-methylbenzenesulfonamide (**4-8d**),[30] morpholino benzoate (**4-4a**),[31] piperidin-1-yl benzoate (**4-4b**),[31] and *tert*-Butyl 4-(benzoyloxy)piperazine-1-carboxylate (**4-4c**)[32] were prepared according to published procedures.[33] LiAlD(O*t*Bu)$_3$ was prepared according to a published procedure.[28] Bulk quantities of cesium carbonate were stored in nitrogen-filled glove box and small amounts were removed within a few days of use. Toluene, THF, dichloromethane and diethyl ether were purified using a GlassContour solvent purification system. Anhydrous dioxane was purchased from Sigma-Aldrich and was used without purification. Structural and stereochemical assignments were made on the basis of 2-D COSY and NOESY experiments. Ratios of diastereomers were determined by ^{1}H NMR analysis. Yields refer to isolated yields of compounds estimated to be ≥95% pure as determined by ^{1}H NMR analysis unless otherwise noted. The yields reported in the supporting information describe the result of a single experiment, whereas yields reported in Tables 4–2-4 are average yields of two or more experiments. Thus, the yields reported in the supporting information may differ from those shown in Tables 4–2-4.

Preparation and Characterization of Benzoate Electrophiles

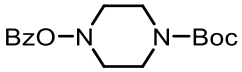


Morpholino benzoate (4-4a).[31,33] A flame dried flask was cooled under a stream of nitrogen and charged with morpholine (1.00 g, 11.48 mmol), THF (34 mL), and Na_2HPO_4 (8.149 g, 57.4 mmol). A solution of benzoyl peroxide (2.969 g, 12.26 mmol) in THF (12 mL) was then added slowly, and the reaction was heated to reflux with stirring overnight. The mixture was then cooled to rt, filtered through celite, and then concentrated *in vacuo*. The crude product was then purified via flash column chromatography on silica gel (EtOAc:Hexanes = 15:85) to yield 1.28 g (54%) of the product as a white solid, m.p. 81–83 °C (lit[34] m.p. 82–84 °C). Characterization data for this compound matched the data given in the literature.[34] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 7.6 Hz, 2 H), 7.56 (t, *J* = 7.2 Hz, 1 H), 7.43 (t, *J* = 7.6 Hz, 2 H), 3.95 (br s, 2 H), 3.89–3.82 (m, 2 H), 3.43 (d, *J* = 10 Hz, 2 H), 3.03 (br s, 2 H).



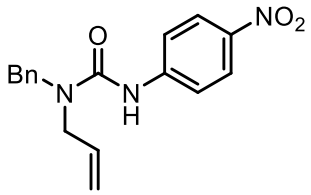
Piperidin-1-yl benzoate (4-4b).[31,33] The title compound was prepared from piperidine (1.25 g, 14.7 mmol), Na_2HPO_4 (9.39 g, 66.2 mmol), and benzoyl peroxide (3.91 g, 16.16 mmol) using a procedure analogous to that described above for the preparation of morpholino benzoate. The crude product was purified via flash column chromatography on silica gel (EtOAc:Hexanes = 15:85) to yield 2.06 g (68%) of the product as a white solid, m.p. 62–64 °C (lit[34] mp 55–59 °C). Characterization data for this compound matched the data given in the literature.[34] ^{1}H NMR (400 MHz, CDCl3) δ 7.99 (d, *J* = 6.8 Hz, 2 H),

7.54 (t, *J* = 7.2 Hz, 1 H), 7.43 (t, *J* = 8.0 Hz, 2 H), 3.48 (br s, 2 H), 2.78–2.70 (m, 2 H), 1.83–1.79 (m, 4 H), 1.67 (br s, 2 H).



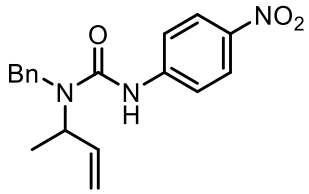
***tert*-Butyl 4-(benzoyloxy)piperazine-1-carboxylate (4-4c).**[32,33] The title compound was prepared from 1-Boc-piperizine (2.328 g, 12.5 mmol), Na_2HPO_4 (8.873 g, 62.5 mmol), and benzoyl peroxide (3.33 g, 13.75 mmol) using a procedure analogous to that described above for the preparation of morpholino benzoate. The crude product was then purified via flash column chromatography on silica gel (EtOAc:Hexanes = 15:85) to yield 2.50 g (65%) of the product as a white solid, m.p. 104–106 °C (lit[35] m.p. 103–105 °C). Characterization data for this compound matched the data given in the literature.[32] ^{1}H NMR (400 MHz, CDCl3) δ 7.98 (d, *J* = 7.2 Hz, 2 H), 7.56 (t, *J* = 7.2 Hz, 1 H), 7.43 (d, *J* = 7.6 Hz, 1 H), 4.02 (br s, 2 H), 3.44–3.25 (m, 4 H), 2.90 (br s, 2 H), 1.40 (s, 9 H).

Preparation and Characterization of Substrates

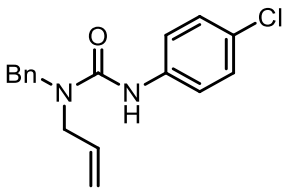


1-Allyl-1-benzyl-3-(4-nitrophenyl)urea (4-10a).[33] A flame-dried flask was cooled under a stream of nitrogen and charged with *p*-nitrophenyl isocyanate (0.500 g, 3.05 mmol) and dichloromethane (3 mL). *N*-benzylprop-2-en-1-ylamine (0.450 g, 3.05 mmol) was then added, and the reaction mixture was stirred at rt overnight. The reaction mixture was then concentrated *in vacuo*, and the crude product was purified via flash column chromatography on silica gel (10% ethyl acetate in hexanes) to afford 0.845 g (90%) of the title compound as a yellow solid, m.p. 108–110 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16–

8.13 (m, 2 H), 7.47–7.43 (m, 2 H), 7.41–7.37 (m, 2 H), 7.35–7.31 (m, 3 H), 6.79 (br s, 1 H), 5.93–5.84 (m, 1 H), 5.38–5.34 (m, 2 H), 4.61 (s, 2 H), 4.01 (d, *J* = 5 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.7, 145.3, 142.5, 136.8, 133.4, 129.0, 128.0, 127.5, 125.0, 118.3, 118.0, 50.8, 50.2; IR (film) 3332, 1654 cm^{-1}; HRMS (ESI^+) 312.1345 (312.1343 calcd for $C_{17}H_{17}N_3O_3$, M + H^+).



1-Benzyl-1-(but-3-en-2-yl)-3-(4-nitrophenyl)urea (4-10b).[33] The title compound was prepared from *p*-nitrophenyl isocyanate (0.356 g, 2.17 mmol) and *N*-benzylbut-3-en-2-ylamine (0.350 g, 2.17 mmol) using a procedure analogous to that described above for the synthesis of 1-allyl-1-benzyl-3-(4-nitrophenyl)urea. This procedure afforded 0.563 g (80%) of the title compound as a yellow solid, m.p. 90–92 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 7.2 Hz, 2 H), 7.42–7.28 (m, 7 H), 6.74 (br s, 1 H), 6.03–5.95 (m, 1 H), 5.32–5.27 (m, 2 H), 4.95 (br s, 1 H), 4.56 (d, *J* = 16.8 Hz, 1 H), 4.39 (d, *J* = 17.2 Hz, 1 H), 1.35 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.8, 145.2, 142.4, 138.7, 137.2, 127.3, 128.2, 126.8, 124.9, 118.2, 116.9, 52.8, 47.8, 16.5; IR (film) 3384, 1653; HRMS (ESI^+) 326.1502 (326.1499 calcd for $C_{18}H_{19}N_3O_3$, M + H^+).

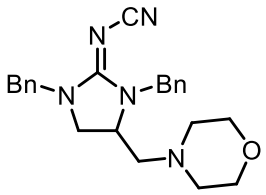


1-Allyl-1-benzyl-3-(4-chlorophenyl)urea (4-10c).[36] The title compound was prepared from *N*-benzylprop-2-en-1-amine (0.997 g, 6.6 mmol) and 4-chlorophenyl isocyanate

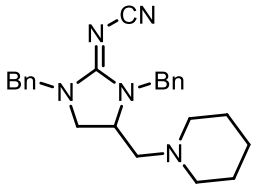
(1.44 g, 9.4 mmol) using a procedure analogous to that described above for the synthesis of 1-allyl-1-benzyl-3-(4-nitrophenyl)urea. This procedure afforded 1.68 g (85%) the title compound as a peach colored solid, m.p. 84–85 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.33 (m, 2 H), 7.37–7.27 (m, 3 H), 7.27–7.17 (m, 4 H), 6.45 (s, 1 H), 5.85 (ddt, J = 17.3, 10.5, 5.4 Hz, 1 H), 5.35–5.26 (m, 2 H), 4.58 (s, 2 H), 3.97 (dt, J = 5.6, 1.7 Hz, 2 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.5, 137.7, 137.4, 133.7, 128.9, 128.8, 127.9, 127.8, 127.5, 120.9, 117.6, 50.6, 50.0. IR (film) 3326, 1637, cm^{-1}. HRMS (ESI^+) 301.1114 (301.1102 calcd for $C_{17}H_{17}ClN_2O$ M + H^+).

Preparation and Characterization of Products

General Procedure for Pd-Catalyzed Diamination Reactions. A flame dried Schlenk tube equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with $Pd(acac)_2$ (4 mol%), JackiePhos (16 mol%), the *O*-benzoylhydroxylamine derived electrophile (3 equiv), and Cs_2CO_3 (2 equiv). The tube was purged with nitrogen and then a solution of the *N*-protected guanidine or urea substrate (1 equiv) in 1,4-dioxane (0.1 M) was added, and the solution was heated to 100 °C with stirring until the starting material had been consumed as judged by TLC or ^{1}H NMR analysis of the reaction mixture (ca 16 h). The mixture was then cooled to rt and diluted with diethyl ether (2 mL). The resulting mixture was then filtered through cotton, and this procedure was repeated once more. The solution was then concentrated *in vacuo*, and the crude product was purified via flash column chromatography on silica gel (methanol:dichloromethane = 1:99).

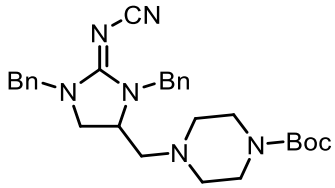


***N*-(1,3-Dibenzyl-4-(morpholinomethyl)imidazolidin-2-ylidene)cyanamide (4-9a)**.[33] The general procedure was followed for the coupling of 1-allyl-1,3-dibenzyl-2-cyanoguanidine **(4-8a)** (30.4 mg, 0.1 mmol) with morpholino benzoate **(4-4a)** (62.2 mg, 0.3 mmol). This procedure afforded 36 mg (92%) of the title compound as a tan, viscous oil. ^{1}H NMR (500 MHz, C_6D_6) δ 7.29–6.95 (m, 10 H), 5.24 (d, *J* = 15.5 Hz, 1 H), 4.56–4.46 (m, 2 H) 4.05 (d, *J* = 15.5 Hz, 1 H), 3.33–3.24 (m, 4 H), 3.01 (m, 1 H), 2.64 (app t, *J* = 9.5 Hz, 1 H), 2.52 (dd, *J* = 9.6, 7.1 Hz, 1 H), 1.87 (dd, *J* = 12.8, 5.6 Hz, 1 H), 1.77–1.66 (m, 4 H), 1.53 (dd, *J* = 12.8. 6.9 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.4, 135.9, 135.4, 128.9, 128.8, 128.2, 128.1, 128.0, 127.9, 116.5, 66.7, 61.0, 54.1, 51.9, 49.5, 49.3, 47.8; IR (film) 2919, 2171, 1596 cm^{-1}; HRMS (ESI^{+}) 390.2292 (390.2288 calcd for $C_{23}H_{27}N_5O$, M + H^{+}).

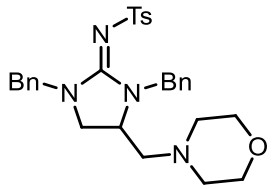


***N*-(1,3-Dibenzyl-4-(piperidin-1-ylmethyl)imidazolidin-2-ylidene)cyanamide (4-9b)**.[33] The general procedure was followed for the coupling of 1-allyl-1,3-dibenzyl-2-cyanoguanidine **(4-8a)** (30.4 mg, 0.1 mmol) with piperidin-1-yl benzoate **(4-4b)** (61.5 mg, 0.3 mmol). This procedure afforded 36 mg (93%) of the title compound as a tan, viscous oil. ^{1}H NMR (500 MHz, C_6D_6) δ 7.26 (d, *J* = 7.5 Hz, 2 H), 7.17–7.03 (m, 8 H), 5.31 (d, *J* = 16 Hz, 1 H), 4.51 (s, 2 H), 4.12 (d, *J* = 15.4 Hz, 1 H), 3.10 (dt, *J* = 13.1, 6.6 Hz, 1 H), 2.66

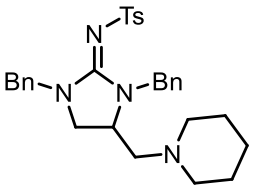
(t, *J* = 9.5 Hz, 1 H), 2.57 (dd, *J* = 9.6, 7.1 Hz, 1 H), 1.97 (dd, *J* = 12.7, 5.6 Hz, 1 H), 1.83 (br s, 4 H), 1.61 (dd, *J* = 12.8, 7.1 Hz, 1 H), 1.24 (h, *J* = 5.6 Hz, 4 H), 1.15 (q, *J* = 5.8 Hz, 2 H). ^{13}C NMR (100 MHz, C_6D_6) δ 158.3, 136.8, 136.0, 128.6, 128.5, 128.4, 128.3, 115.9, 61.2, 54.8, 51.9, 49.1, 47.4, 25.8, 24.0; IR (film) 2933, 2171, 1595 cm^{-1}; HRMS (ESI$^+$) 388.2496 (388.496 calcd for $C_{24}H_{29}N_5$, M + H$^+$).



***tert*-Butyl 4-{[1,3-dibenzyl-2-(cyanoimino)imidazolidin-4-yl]methyl}piperazine-1-carboxylate (4-9c)**.[33] The general procedure was followed for the coupling of 1-allyl-1,3-dibenzyl-2-cyanoguanidine **(4-8a)** (30.4 mg, 0.1 mmol) with *tert*-butyl 4-(benzoyloxy)piperazine-1-carboxylate **(4-4c)** (91.9 mg, 0.3 mmol). This procedure afforded 30 mg (61%) of the title compound as a pale yellow, viscous oil. One peak in the ^{13}C NMR spectrum is missing due to incidental equivalence. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.11 (m, 10 H), 5.28 (d, *J* = 15.6 Hz, 1 H), 4.83–4.61 (m, 2 H), 4.33 (d, *J* = 15.6 Hz, 1 H), 3.58 (dt, *J* = 12.4, 6.3 Hz, 1 H), 3.38 (t, *J* = 9.7 Hz, 1 H), 3.28 (br s, 4 H), 3.09 (dd, *J* = 9.8, 6.5 Hz, 1 H), 2.49 (dd, *J* = 12.9, 5.6 Hz, 1 H), 2.29–2.13 (m, 5 H), 1.42 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.3, 154.5, 135.8, 135., 128.8, 128.2, 128.0, 127.9, 127.8, 116.4, 79.7, 60.6, 53.4, 51.9, 49.4, 49.2, 47.7, 43.2, 28.3; IR (film) 2927, 2170, 1685, 1595 cm^{-1}; HRMS (ESI$^+$) 489.2970 (489.2973 calcd for $C_{28}H_{36}N_6O_2$, M + H$^+$).

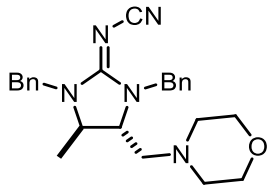


***N*-[1,3-Dibenzyl-4-(morpholinomethyl)imidazolidin-2-ylidene]-4-methylbenzenesulfonamide (4-9d)**.[33] The general procedure was followed for the coupling of *N*-{[allyl(benzyl)amino](benzylamino)methylene}-4-methylbenzenesulfonamide (**4-8b**) (43.3 mg, 0.1 mmol) with morpholino benzoate **(4-4a)** (62.2 mg, 0.3 mmol). This procedure afforded 42.5 mg (82%) of the title compound as a tan, viscous oil. ^{1}H NMR (500 MHz, C_6D_6) δ 8.27 (d, *J* = 8.1 Hz, 2 H), 7.29 (d, *J* = 7 Hz, 4 H), 7.19–7.09 (m, 4 H), 7.05 (td, *J* = 7.3, 4.8 Hz, 2 H), 6.82 (d, *J* = 7.9 Hz, 2 H), 5.48 (d, *J* = 15.3 Hz, 1 H), 4.84 (d, *J* = 15.0 Hz, 1 H), 4.68 (d, *J* = 15.0 Hz, 1 H), 4.15 (d, *J* = 15.3 Hz, 1 H), 3.37–3.30 (m, 4 H), 3.14–3.07 (m, 1 H), 2.76 (t, *J* = 9.7 Hz, 1 H), 2.67 (dd, *J* = 9.8, 6.4 Hz, 1 H), 1.91 (dd, *J* = 12.5, 5 Hz, 1 H), 1.89 (s, 3 H), 1.86–1.83 (m, 2 H), 1.79–1.74 (m, 2 H), 1.67 (dd, *J* = 12.8, 6.9 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.5, 142.9, 141.1, 136.2, 135.8, 129.0, 128.8, 128.7, 128.4, 128.1, 127.9, 127.8, 125.8, 66.7, 60.7, 54.1, 51.7, 50.8, 49.1, 48.7, 21.3; IR (film) 2921, 1559 cm^{-1}; HRMS (ESI^{+}) 519.2422 (519.2424 calcd for $C_{29}H_{34}N_4O_3S$, M + H^{+}).



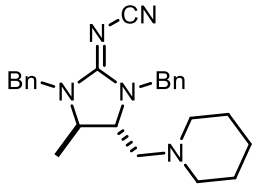
***N*-[1,3-Dibenzyl-4-(piperidin-1-ylmethyl)imidazolidin-2-ylidene]-4-methylbenzenesulfonamide (4-9e)**.[33] The general procedure was followed for the coupling of *N*-{[allyl(benzyl)amino](benzylamino)methylene}-4-

methylbenzenesulfonamide (**4-8b**) (43.3 mg, 0.1 mmol) with piperidin-1-yl benzoate **(4-4b)** (61.5 mg, 0.3 mmol). This procedure afforded 39 mg (76%) of the title compound as a tan, viscous oil. One signal in the ^{13}C NMR spectrum is missing due to incidental equivalence. ^{1}H NMR (400 MHz, C_6D_6) δ 8.26 (d, *J* = 8.0 Hz, 2 H), 7.34–7.27 (m, 4 H), 7.14–6.96 (m, 6 H), 6.81 (d, *J* = 8.0 Hz, 2 H), 5.46 (d, *J* = 15.2 Hz, 1 H), 4.82 (d, *J* = 15.0 Hz, 1 H), 4.70 (d, *J* = 15.0 Hz, 1 H), 4.22 (d, *J* = 15.3 Hz, 1 H), 3.22–3.14 (m, 1 H), 2.79 (t, *J* = 9.7 Hz, 1 H), 2.70 (dd, *J* = 9.8, 6.3 Hz, 1 H), 2.04 (dd, *J* = 12.8, 5.5 Hz, 1 H), 1.89 (s, 3 H), 1.88–1.83 (m, 4 H), 1.73 (dd, *J* = 12.8, 7.1 Hz, 1 H), 1.23 (br s, 4 H), 1.17–1.12 (m, 2 H); ^{13}C NMR (100 MHz, C_6D_6) δ 156.2, 144.3, 140.4, 137.1, 136.4, 128.8, 128.6, 128.5, 128.45, 128.41, 127.4 126.2, 61.1, 54.8, 51.7, 50.8, 48.8, 48.7, 25.8, 24.0, 20.7; IR (film) 2932, 1578 cm^{-1}; HRMS (ESI^+) 517.2633 (517.2632 calcd for $C_{30}H_{36}N_4O_2S$, M + H^+).



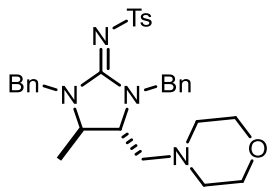
(4*R,5*R**)-*N*-[1,3-Dibenzyl-4-methyl-5-(morpholinomethyl)imidazolidin-2-ylidene]cyanamide (4-9f)**.[33] The general procedure was followed for the coupling of 1,3-dibenzyl-1-(but-3-en-2-yl)-2-cyanoguanidine **(4-8c)** (31.8 mg, 0.1 mmol) with morpholino benzoate **(4-4a)** (62.1 mg, 0.3 mmol). This procedure afforded 32.3 mg (80%) of the title compound as a tan, viscous oil. This compound was obtained as a 4:1 mixture of diastereomers as judged by ^{1}H NMR analysis of the crude reaction mixture. After purification the compound was isolated as a 3:1 mixture of diastereomers. ^{1}H NMR data are for the major diastereomer, ^{13}C NMR data are for the mixture. ^{1}H NMR (400 MHz,

C_6D_6) δ 7.22–7.17 (m, 5 H), 7.15–7.02 (m, 5 H), 5.42 (d, *J* = 15.5 Hz, 1 H), 5.35 (d, *J* = 15.5 Hz, 1 H), 4.07 (d, *J* = 16 Hz, 1 H), 3.85 (d, *J* = 16 Hz, 1 H), 3.33–3.27 (m, 4 H), 2.92 (p, *J* = 6.5 Hz, 1 H), 2.72 (q, *J* = 6.0 Hz, 1 H), 1.84 (dd, *J* = 13.0 Hz, 6.0 Hz, 1 H), 1.80–1.72 (m, 4 H), 1.50 (dd, *J* = 13.0, 6.5 Hz, 1 H), 0.57 (d, *J* = 5.2 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.0, 136.0, 135.8, 128.9, 128.8, 128.1, 128.0, 128.0, 127.9, 127.8, 127.7, 116.7, 66.8, 66.7, 60.7, 59.2, 56.7, 55.1, 54.3, 54.1, 54.0, 53.9, 47.8, 47.7, 56.8, 56.2, 18.6, 12.0; IR (film) 2925, 2170, 1591 cm^{-1}; HRMS (ESI^+) 404.2446 (404.2445 cacld for $C_{24}H_{29}N_5O$, M + H^+).

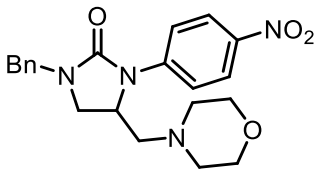


(4*R,5*R**)-*N*-[1,3-Dibenzyl-4-methyl-5-(piperidin-1-ylmethyl)imidazolidin-2-ylidene]cyanamide (4-9g)**.[33] The general procedure was followed for the coupling of 1,3-dibenzyl-1-(but-3-en-2-yl)-2-cyanoguanidine **(4-8c)** (31.8 mg, 0.1 mmol) with piperidin-1-yl benzoate **(4-4b)** (61.5 mg, 0.3 mmol). This procedure afforded 31 mg (76%) of the title compound as a tan, viscous oil. This compound was obtained as a 3:1 mixture of diastereomers as judged by ^{1}H NMR analysis; ^{1}H NMR data are for the major diastereomer, ^{13}C NMR data are for the mixture. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 6.8 Hz, 2 H), 7.15–7.00 (m, 8 H), 5.45 (d, *J* = 15.6 Hz, 1 H), 5.30 (d, *J* = 15.6 Hz, 1 H), 4.11 (d, *J* = 15.2 Hz, 1 H), 3.83 (d, *J* = 15.6 Hz, 1 H), 2.96–2.90 (m, 1 H), 2.79 (q, *J* = 6.0 Hz, 1 H), 1.91 (dd, *J* = 13.4, 4.8 Hz, 1 H), 1.83 (br s, 4 H), 1.55 (dd, *J* = 12.4 Hz, 6.4 Hz, 1 H), 1.20 (br s, 4 H), 1.18–1.12 (m, 2 H), 0.57 (d, *J* = 6 Hz, 3 H); ^{13}C NMR (125 MHz, C_6D_6) δ 158.1, 137.1 136.7, 136.5, 136.4, 128.6, 128.56, 128.51, 128.3, 128.2, 128.1,

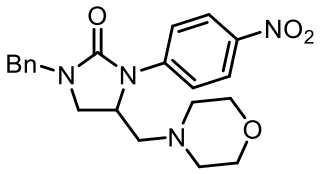
128.0, 127.8, 127.6, 116.0, 60.9, 59.3, 56.4, 55.3, 54.8, 54.6, 54.5, 53.6, 47.4, 47.2, 46.5, 45.9, 25.8, 25.7, 24.1, 24.0, 17.8, 11.3; IR (film) 2933, 2173, 1585 cm^{-1}; HRMS (ESI^+) 402.2650 (402.2652 calcd for $C_{25}H_{31}N_5$, M + H^+)



(4*R*,5*R*)-*N*-[1,3-Dibenzyl-4-methyl-5-(morpholinomethyl)imidazolidin-2-ylidene]-4-methylbenzenesulfonamide (4-9h).[33] The general procedure was followed for the coupling of *N*-{[benzyl(but-3-en-2-yl)amino](benzylamino)methylene}-4-methylbenzenesulfonamide **(4-8d)** (44.8 mg, 0.1 mmol) with morpholino benzoate **(4-4a)** (62.2 mg, 0.3 mmol). This procedure afforded 46 mg (86%) of the title compound as a tan, viscous oil. This compound was obtained as a 3:1 mixture of diastereomers as judged by ^{1}H NMR analysis; data are for the major diastereomer. Two peaks in the ^{13}C NMR spectrum are missing due to incidental equivalence. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.4 Hz, 2 H), 7.32–7.11 (m, 12 H), 5.34–5.22 (m, 2 H), 4.23 (d, *J* = 15.2 Hz, 1 H), 4.07 (d, *J* = 15.2 Hz, 1 H), 3.55–3.50 (m, 4 H), 3.31–3.27 (m, 1 H), 3.00 (q, *J* = 4.8 Hz, 1 H), 2.37–2.32 (m, 1 H), 2.23–2.13 (m, 4 H), 2.04 (dd, *J* = 12.8, 7.6 Hz, 1 H), 0.98 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (125 MHz, C_6D_6) δ 155.6, 144.2, 140.5, 136.9, 136.7, 128.8, 128.5, 128.48, 128.45, 128.3, 126.2, 66.4, 60.0, 58.8, 54.2, 54.0, 49.1, 48.0, 20.7, 18.2; IR (film) 2925, 1559 cm^{-1}; HRMS (ESI^+) 533.2580 (533.2581 calcd for $C_{30}H_{36}N_4O_3S$, M + H^+).

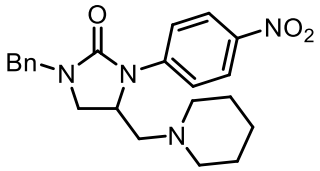


1-Benzyl-4-(morpholinomethyl)-3-(4-nitrophenyl)imidazolidin-2-one (4-11a).[33] The general procedure was followed for the coupling of 1-allyl-1-benzyl-3-(4-nitrophenyl)urea (**4-10a**) (31.1 mg, 0.1 mmol) with morpholino benzoate **(4-4a)** (62.2 mg, 0.3 mmol). This procedure afforded 46 mg (86%) of the title compound as a yellow solid, m.p. 108-110 °C. ^{1}H NMR (400 MHz, C_6D_6) δ 8.04 (d, *J* = 9.3 Hz, 2 H), 7.59 (d, *J* = 9.3 Hz, 2 H), 7.15–7.02 (m, 5 H), 4.30–4.19 m, 2 H), 3.44–3.34 (m, 4 H), 2.85 (dd, *J* = 8.9, 2.8 Hz, 1 H), 2.75 (t, *J* = 8.7 Hz, 1 H), 1.98 (dd, *J* = 13.0, 3.1 Hz, 1 H), 1.97–1.88 (m, 2 H), 1.83–1.75 (m, 2 H), 1.71 (dd, *J* = 13.0, 9.3 Hz, 1 H); ^{13}C NMR (125 MHz, C_6D_6) δ 155.8, 145.0, 142.0, 136.6, 128.6, 128.2, 127.9, 124.6, 116.8, 66.4, 58.7, 53.8, 50.0, 47.5, 45.3; IR (film) 2921, 1709 cm^{-1}; HRMS (ESI^{+}) 397.1868 (397.1870 calcd for $C_{21}H_{24}N_4O_4$, M + H^{+}).

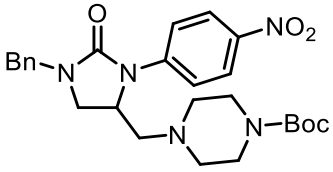


1-Benzyl-4-(morpholinomethyl)-3-(4-nitrophenyl)imidazolidin-2-one (4-11a).

The general procedure was followed for the coupling of 1-allyl-1-benzyl-3-(4-nitrophenyl)urea (**4-10a**) (0.3113 g, 1 mmol) with morpholino benzoate **(4-4a)** (0.6216 g, 3 mmol). This procedure afforded 0.3022 g (76%) of the title compound as a yellow solid. Spectroscopic data matched those reported above.

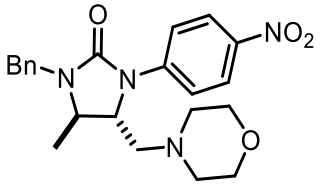


1-Benzyl-3-(4-nitrophenyl)-4-(piperidin-1-ylmethyl)imidazolidin-2-one (4-11b).[33] The general procedure was followed for the coupling of 1-allyl-1-benzyl-3-(4-nitrophenyl)urea (**4-10a**) (31.1 mg, 0.1 mmol) with piperidin-1-yl benzoate (**4-4b**) (61.5 mg, 0.3 mmol). This procedure afforded 32.2 mg (82%) of the title compound as a yellow solid, m.p. 92-95 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 9.3 Hz, 2 H), 7.75 (d, *J* = 9.3 Hz, 2 H), 7.41–7.26 (m, 5 H), 4.50–4.45 (m, 2 H), 4.30 (t, *J* = 8.8 Hz, 1 H), 3.46 (t, *J* = 8.8 Hz, 1 H), 3.33 (dd, *J* = 9.2, 2.8 Hz, 1 H), 2.54 (dd, *J* = 13.0, 3.2 Hz, 1 H), 2.43 (br s, 2 H), 2.37–2.20 (m, 3 H), 1.52–1.45 (m, 4 H), 1.40–1.35 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.5, 145.5, 141.8, 136.2, 128.8, 128.2, 127.7, 124.9, 117.1, 59.8, 55.3, 51.4, 47.8, 46.2, 25.9, 23.9; IR (film) 2932, 1710 cm^{-1}; HRMS (ESI$^+$) 395.2074 (395.2078 calcd for $C_{22}H_{26}N_4O_3$, M + H^+).

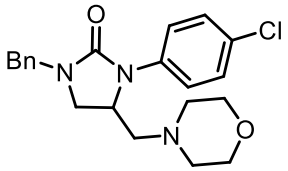


***tert*-Butyl 4-{[1-benzyl-3-(4-nitrophenyl)-2-oxoimidazolidin-4-yl]methyl}piperazine-1-carboxylate (4-11c)**.[33] The general procedure was followed for the coupling of 1-allyl-1-benzyl-3-(4-nitrophenyl)urea (**4-10a**) (31.1 mg, 0.1 mmol) with *tert*-butyl 4-(benzoyloxy)piperazine-1-carboxylate **(4-4c)** (91.9 mg, 0.3 mmol). This procedure afforded 21 mg (42%) of the title compound as a yellow solid, m.p. 98-102 °C. ^{1}H NMR (500 MHz, C_6D_6) δ 8.04 (d, *J* = 9.1 Hz, 2 H), 7.57 (d, *J* = 9.0 Hz, 2 H), 7.14–7.03 (m, 5 H),

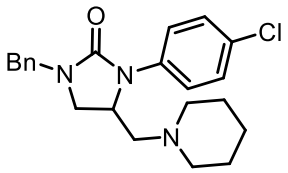
4.28–4.18 (m, 2 H), 3.41–3.35 (m, 1 H), 3.22 (br s, 4 H), 2.79 (dd, *J* = 8.9, 2.7 Hz, 1 H), 2.71 (t, *J* = 8.7 Hz, 1 H), 1.91–1.83 (m, 3 H), 1.81–1.72 (m, 2 H), 1.67 (dd, *J* = 13.1, 9.2 Hz, 1 H), 1.46 (s, 9 H); ^{13}C NMR (125 MHz, C_6D_6) δ 155.8, 154.0, 145.0, 142.0, 136.6, 128.6, 128.2, 127.9, 124.6, 116.7, 79.1, 58.2, 53.1, 50.2, 47.5, 45.2, 28.1, 28.0; IR (film) 2927, 1693 cm^{-1}; HRMS (ESI$^+$) 496.2548 (496.2554 calcd for $C_{26}H_{33}N_5O_5$, M + H$^+$).



(4*R,5*R**)-1-Benzyl-5-methyl-4-(morpholinomethyl)-3-(4-nitrophenyl)imidazolidin-2-one (4-11d)**.[33] The general procedure was followed for the coupling of 1-benzyl-1-(but-3-en-2-yl)-3-(4-nitrophenyl)urea (**4-10b**) (32.5 mg, 0.1 mmol) with morpholino benzoate **(4-4a)** (62.2 mg, 0.3 mmol). This procedure afforded 13 mg (34%) of the title compound as a viscous yellow oil. This compound was obtained as a 2:1 mixture of diastereomers as judged by ^{1}H NMR analysis; ^{1}H NMR data are for the major diastereomer; ^{13}C NMR data are for the mixture. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21–8.18 (m, 2 H), 7.75–7.68 (m, 2 H), 7.37–7.24 (m, 5 H), 4.93 (d, *J* = 15.2 Hz, 1 H), 4.06 (d, *J* = 15.2 Hz, 1 H), 3.89–3.86 (m, 1 H), 3.57–3.51 (m, 5 H), 2.55–2.36 (m, 4 H), 2.29–2.23 (m, 2 H), 1.25 (d, *J* = 6 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.1, 155.6, 145.5, 145.3, 142.3, 141.9, 136.7, 136.4, 128.8, 128.7, 128.2, 128.1, 127.8, 127.7, 125.0, 124.7, 118.9, 117.3, 66.9, 66.7, 58.8, 58.7, 55.5, 54.2, 54.0, 53.7, 51.9, 51.1, 45.1, 45.0, 18.9, 13.0; IR (film) 2923, 1708 cm^{-1}; HRMS (ESI$^+$) 411.2027 (411.2027 calcd for $C_{22}H_{26}N_4O_4$, M + H$^+$).



1-Benzyl-3-(4-chlorophenyl)-4-(morpholinomethyl)imidazolidin-2-one (4-11e). The general procedure was followed for the coupling of 1-allyl-1-benzyl-3-(4-chlorophenyl)urea (**4-10c**) (30.1 mg, 0.1 mmol) with morpholino benzoate **(4-4a)** (62.2 mg, 0.3 mmol). This procedure afforded 17.5 mg (45%) of the title compound as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.8 Hz, 2 H), 7.38–7.27 (m, 7 H), 4.46 (s, 2 H), 4.27 (tt, *J* = 8.6, 3.8 Hz, 1 H), 3.66–3.54 (m, 4 H), 3.45 (t, *J* = 8.9 Hz, 1 H), 3.29 (dd, *J* = 9.0, 4.1 Hz, 1 H), 2.55 (dd, *J* = 12.9, 3.3 Hz, 1 H), 2.50–2.23 (m, 5 H);^{13}C NMR (125 MHz, $CDCl_3$) δ 157.4, 137.7, 136.7, 128.9, 128.7, 128.3, 128.2, 127.6, 121.1, 66.8, 59.6, 54.2, 51.1, 47.9, 46.4; IR (film) 2917, 1700 cm^{-1}; HRMS (ESI^+) 386.1634 (386.1635 calcd for $C_{21}H_{24}ClN_3O_2$, M + H^+).

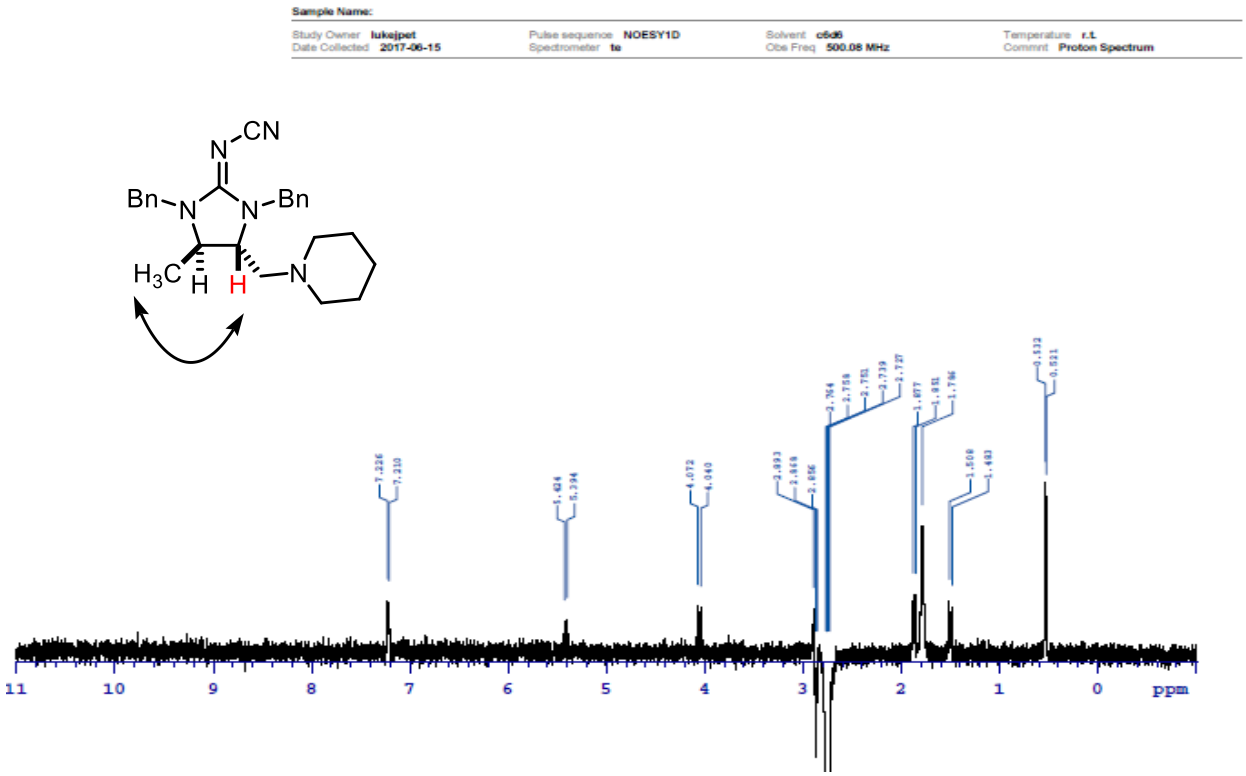


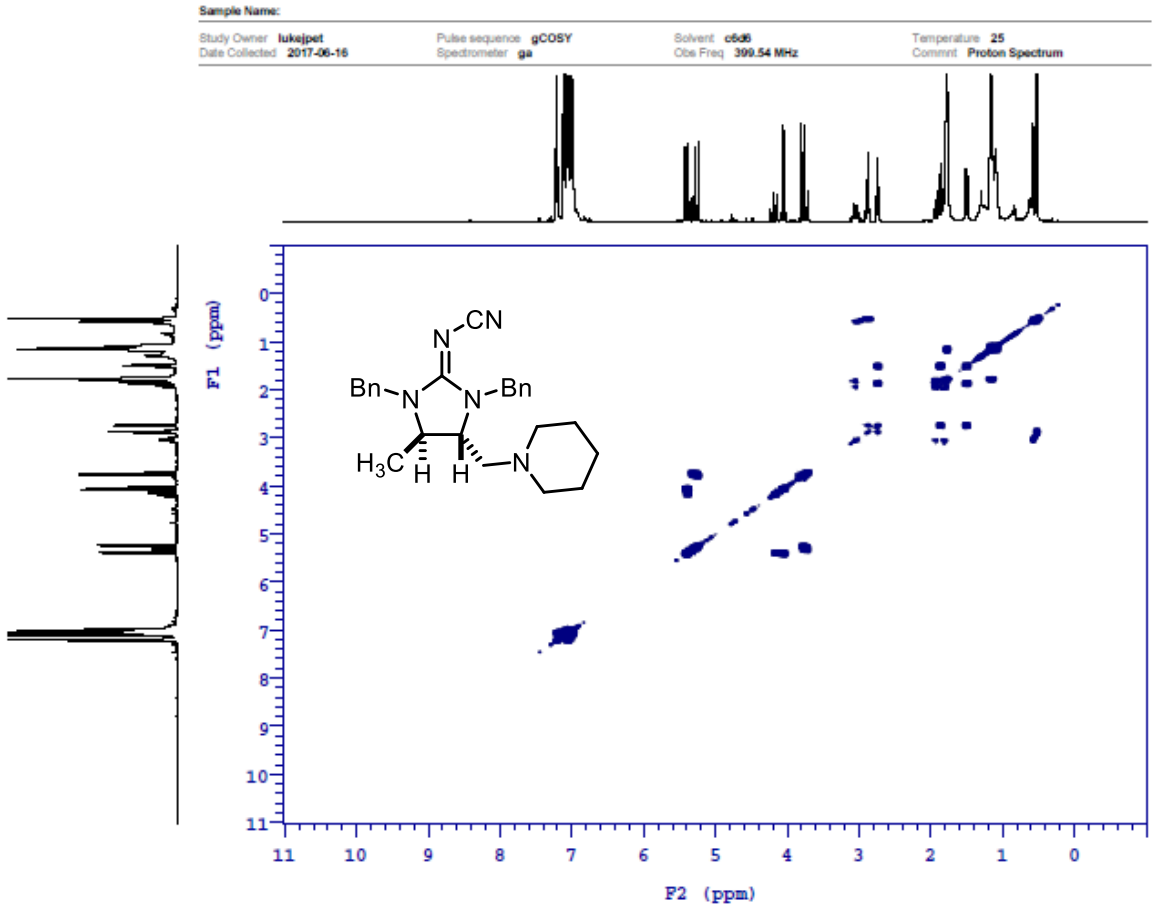
1-Benzyl-3-(4-chlorophenyl)-4-(piperidin-1-ylmethyl)imidazolidin-2-one (4-11f). The general procedure was followed for the coupling of 1-allyl-1-benzyl-3-(4-chlorophenyl)urea (**4-10c**) (30.1 mg, 0.1 mmol) with piperidin-1-yl benzoate **(4-4b)** (61.5 mg, 0.3 mmol). This procedure afforded 7.0 mg (18%) of the title compound as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.6 Hz, 2 H), 7.38–7.27 (m, 7 H), 4.55–4.37 (m, 2 H), 4.24 (td, *J* = 8.9, 4.5 Hz, 1 H), 3.44 (t, *J* = 8.8 Hz, 1 H), 3.28 (dd, *J* = 9.1, 4.0 Hz, 1 H), 2.51 (dd, *J* = 12.9, 3.1 Hz, 1 H), 2.42 (br m, 2 H), 2.35–2.20 (m, 3 H), 1.55–1.43 (m,

4 H), 1.37 (p, *J* = 6.2 Hz, 2 H);[13]C NMR (125 MHz, $CDCl_3$) δ 157.7, 138.0, 137.0, 129.0, 128.8, 128.4, 128.2, 127.7, 121.1, 60.3, 55.5, 51.6, 48.0, 46.9, 26.1, 24.2; IR (film) 2934, 1703 cm^{-1}; HRMS (ESI^+) 384.1847 (384.1837 calcd for $C_{22}H_{26}ClN_3O$, M + H^+).

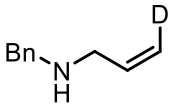
Assignment of relative stereochemistry for 4-9f-h and 4-11d.

The relative stereochemistry of **4-9g** was assigned using 2D COSY and 1D NOESY analysis, based on the low energy conformations described above. The key NMR signals are shown below. Structurally related products **4-9f**, **4-9h**, and **4-11d** were assigned based on analogy to **4-9g**



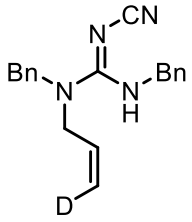


Synthesis of deuterated substrates and products



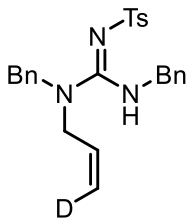
(Z)-*N*-Benzylprop-2-en-3-d-1-amine (4-S1).[33] A flame dried flask was cooled under a stream of nitrogen and charged with *N*-benzylprop-2-en-1-ylamine (1.00 g, 6.84 mmol) and diethyl ether (12 mL). The solution was cooled to -42 °C, and then *n*-butyllithium (8.2 mmol, 2.5 M in hexanes) was added slowly. After 30 min *tert*-butyl lithium (15 mmol, 1.7 M in pentane) was added slowly. After stirring at -42 °C for 30 min the reaction was transferred to an ice-water bath and allowed to stir for 1 hour. The reaction was then cooled to -78 °C, and deuterium oxide was added (2.5 mL, 136.8 mmol). After stirring

overnight the reaction was cooled on an ice-water bath, and then quenched with water (15 mL). The mixture was extracted with diethyl ether (2 x 20 mL) and separated. The combined organic layers were then dried, filtered, and evaporated. The crude product was purified via flash column chromatography on silica gel using 30% ethyl acetate in hexanes as the eluant to afford 0.568 g (56%) of the title compound as a pale yellow oil, with 84% deuterium incorporation as determined by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, J = 4.5 Hz, 4 H), 7.2–7.18 (m, 1 H), 6.03–5.79 (m, 1 H), 5.22–5.15 (m, 1 H), 5.12–5.06 (m, 1 H), 3.78 (s, 3 H), 3.27 (d, 6 Hz, 2 H).

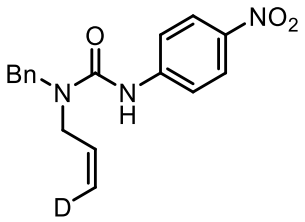


(*Z*)-1-[Allyl-3-*d*]-1,3-dibenzyl-2-cyanoguanidine (4-*d*-8a).[30,33] A round bottom flask was charged with methyl *N*-benzyl-*N*'-cyanocarbamimidothioate[30] (0.196 g, 0.96 mmol), ethanol (10 mL), and mercuric oxide (0.312 g, 1.44 mmol), then purged with nitrogen. Triethylamine (0.5 mL, 3.84 mmol) was added followed by (Z)-*N*-benzylprop-2-en-3-d-1-amine (**4-S1**) (0.170 g, 1.15 mmol). The reaction mixture was then stirred at rt for 72 h. The mixture was filtered through celite. The celite was rinsed with acetone, and the solution was concentrated *in vacuo*. The crude product was purified via flash column chromatography on silica gel (methanol:dichloromethane = 1:99) to yield 0.153 g (52%) of the title compound as a clear, viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.28 (m, 6 H), 7.24-7.18 (m, 4 H), 5.80–5.72 (m, 1 H), 5.23 (d, J = 10.4 Hz, 1 H), 5.15 (d, J = 17.2 Hz, 1 H), 4.98 (br, 1 H), 4.74 (d, J = 5.2 Hz, 2 H), 4.58 (s, 2 H), 3.95 (d, J = 5.2 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 137.1, 135.8, 129.0, 128.9, 128.0, 127.9, 127.7,

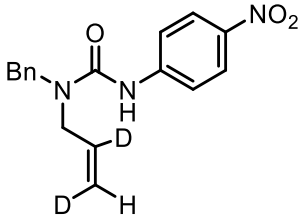
127.3, 118.2 (t, *J* = 23.5 Hz, 117.2, 52.2, 51.4, 47.5; IR (film) 3249, 2162, 1536 cm^{-1}; HRMS (ESI^+) 306.1827 (306.1823 calcd for $C_{19}H_{19}DN_4$, M + H^+).



(*Z*)-*N*-{[Allyl-3-d](benzyl)amino}-benzylaminomethylene-4-methylbenzenesulfonamide (4-*d*-8b). [30,33] A round bottom flask was charged with dimethyl tosylcarbonimidodithioate[30] (0.569 g, 1.70 mmol), ethanol (17 mL), and mercuric oxide (0.548 g, 2.53 mmol), then purged with nitrogen. Triethylamine (0.95 mL, 6.75 mmol) was added followed by (Z)-*N*-benzylprop-2-en-3-d-1-amine (**4-S1**) (0.300 g, 2.0 mmol). The reaction mixture was then stirred at rt for 72 h. The mixture was filtered through celite. The celite was rinsed with acetone, and the solution was concentrated *in vacuo*. The crude product was purified via flash column chromatography on silica gel (methanol:dichloromethane = 1:99) to yield 0.363 g (49%) of the title compound as a white solid, m.p. 79–81 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.4 Hz, 2 H), 7.33–7.20 (m, 6 H), 7.18–7.06 (m, 6 H), 6.96 (br s, 1 H), 5.75–5.67 (m, 1 H), 5.16 (d, *J* = 10.4 Hz, 1 H), 5.08 (d, *J* = 17.3 Hz, 1 H), 4.47 (s, 2 H), 4.37 (d, *J* = 5.9 Hz, 2 H), 2.37 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 141.7, 141.0, 136.9, 136.4, 132.3, 129.1, 128.9, 128.7, 128.0, 127.61, 127.6, 127.58, 127.4, 126.0, 118.6 (t, *J* = 25 Hz), 51.8, 51.75, 49.7; IR (film) 3322, 1564 cm^{-1}; HRMS (ESI^+) 435.1965 (435.1960 calcd for $C_{25}H_{26}DN_3O_2S$, M + H^+).



(*Z*)-1-(Allyl-3-d)-1-benzyl-3-(4-nitrophenyl)urea (4-*d*-10a).[33] The title compound was prepared from *p*-nitrophenyl isocyanate (0.244 g, 1.48 mmol) and (*Z*)-*N*-benzylprop-2-en-3-d-1-amine (**4-S1**) (0.220 mg, 1.48 mmol) using a procedure analogous to that described above for the synthesis of 1-allyl-1-benzyl-3-(4-nitrophenyl)urea. This procedure afforded 0.245 g (53%) of the title compound as a yellow solid, m.p. 108–110 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 9.2 Hz, 2 H), 7.12–7.04 (m, 7 H), 6.17 (s, 1 H), 5.37–5.30 (m, 1 H), 4.83–4.76 (m, 2 H), 4.17 (s, 2 H), 3.34 (d, *J* = 4.8 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.8, 145.3, 142.5, 136.9, 133.3, 129.1, 128.0, 127.5, 125.0, 118.3, 117.8 (t, *J* = 23.6 Hz), 50.9, 50.2; IR (film) 3346, 1652 cm^{-1}; HRMS (ESI^{+}) 313.1405 (313.1405 calcd for $C_{17}H_{16}N_3O_3$, M + H^{+}).



(*Z*)-1-(Allyl-2,3-*d*$_2$)-1-benzyl-3-(4-nitrophenyl)urea (4-22). A round-bottom flask equipped with a stirbar was charged with benzylamine (11.8 mL, 108 mmol) and cooled to 0 °C. Propargyl bromide (2 mL, 18 mmol, 80 wt% in toluene) was added dropwise and the mixture was warmed to rt and stirred overnight. The mixture was then concentrated *in* vacuo and the crude product was purified via flash column chromatography on silica gel (10% ethyl acetate in hexanes) to afford 2.11 g (81%) of N-benzylprop-2-yn-1-amine

as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.30 (m, 3 H), 7.28–7.26 (m, 2 H), 3.89 (s, 2 H), 3.44 (d, *J* = 2.4 Hz, 2 H), 2.26 (t, *J* = 2.4 Hz, 1 H), 1.50 (s, 1 H).

A round-bottom flask equipped with a stirbar was charged with di-*tert*-butyl dicarbonate (0.5786 g, 2.65 mmol) and THF (0.5 mL). The mixture was cooled to 0 °C and a solution of *N*-benzylprop-2-yn-1-amine (0.35 g, 2.41 mmol) in THF (0.7 mL) was added dropwise. The mixture was warmed to rt and stirred overnight, then THF (5 mL) and 1 M NaOH (5 mL) were added and the resulting mixture was stirred vigorously at rt for 24 h. The mixture was then diluted with ether and transferred to a separatory funnel. The layers were separated, the aqueous layer was extracted with ether (3 x 10 mL) and the combined organic layers were washed with satd. aq ammonium chloride (1 x 25 mL) and brine (1 x 25 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated *in vacuo* to afford *tert*-butyl benzyl(prop-2-yn-1-yl)carbamate as a clear oil (0.4743 g, 80%) that was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.30 (m, 2 H), 7.30–7.24 (m, 3 H), 4.55 (s, 2 H), 3.97 (d, *J* = 53.8 Hz, 2 H), 2.21 (s, 1 H), 1.49 (s, 9 H).

A flame dried flask was cooled under a stream of nitrogen and charged with THF (2 mL) and *n*-butyllithium (0.4 mL, 0.90 mmol, 1.1 equiv, 2.5 M in THF). The solution was cooled to –78 °C and a solution of *tert*-butyl benzyl(prop-2-yn-1-yl)carbamate (0.2 g, 0.815 mmol) in THF (2 mL) was added dropwise. The resulting mixture was stirred at –78 °C for 20 min, then warmed to 0 °C and quenched with D_2O (0.15 mL, 10 equiv). The mixture was diluted with ether and transferred to a separatory funnel. The layers were separated, the aqueous layer was extracted with ether (3 x 10 mL) and the combined organic layers were washed with brine (1 x 25 mL). The organic layer was dried over anhydrous sodium

sulfate and concentrated *in vacuo*, and the crude product was purified via flash column chromatography on silica gel (2% ethyl acetate in hexanes) to afford 0.1522 g (76%) of *tert*-butyl benzyl(prop-2-yn-1-yl-3-*d*)carbamate as a clear oil. This material was judged to have ca 95% deuterium incorporation at the terminal alkyne position, plus ca 25% deuterium incorporation at the benzylic position as judged by ^{1}H NMR analysis. The doubly deuterated material was not separated, and was carried forward through the synthesis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.30 (m, 2 H), 7.30–7.23 (m, 3 H), 4.54 (s, 2 H), 4.04 (s, br, 1 H), 3.90 (s, br, 1 H), 1.49 (s, 9 H).

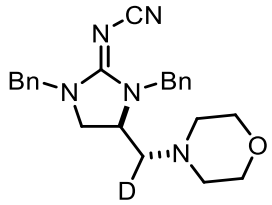
A flame dried flask was cooled under a stream of nitrogen and charged with zirconocene dichloride (0.3654 g, 1.25 mmol, 2.8 equiv) and THF (1.5 mL). The mixture was stirred vigorously, and then a solution of *tert*-butyl benzyl(prop-2-yn-1-yl-3-*d*)carbamate (0.110 g, 0.466 mmol) in THF (1 mL) was added. A solution of $LiAlD(O\textit{t}Bu)_3$ (0.32g, 2.8 equiv) in THF (0.5 mL) was added quickly, and the resulting mixture was stirred at rt for 30 min. Water (0.22 mL, 12 mmol, 26.8 equiv) was added dropwise, and the resulting mixture was stirred at rt for 2 h. The solution was then filtered through celite, rinsed with ethyl acetate and concentrated *in vacuo*. The crude product was purified via flash column chromatography on silica gel using 2% ethyl acetate in hexanes as the eluant to afford 0.0913 g (82%) of (*Z*)-*tert*-butyl-(allyl-2,3-d_2)(benzyl)carbamate as a clear oil. This material was judged to have ca 95% deuterium incorporation at both the internal alkene position and at the terminal alkene position, and was obtained as one stereoisomer (>20:1 dr) as judged by ^{1}H NMR analysis. This material also contained ca 25% d-incorporation at the benzylic position (carried through from the previous intermediate). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (t, J = 7.4 Hz, 2 H), 7.28–7.20 (m, 3 H),

5.12 (s, 1 H), 4.40 (s, 2 H), 3.84 (br s, 1 H), 3.72 (br s, 1 H), 1.47 (s, 9 H); ^{1}H NMR (500 MHz, C_6D_6) δ 7.28–7.03 (m, 5 H), 4.92 (s, 1 H), 4.43 (br s, 1 H), 4.24 (br s, 1 H), 3.83 (br s, 1 H), 3.56 (br s, 1 H), 1.44 (s, 9 H).

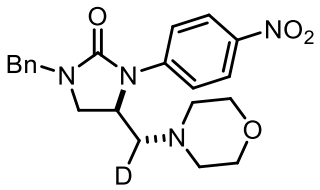
A 25 mL vial was charged with (*Z*)-*tert*-butyl-(allyl-2,3-d_2)(benzyl)carbamate (0.0913 g, 0.37 mmol) and dichloromethane (0.37 mL, 1 M) and the solution was cooled to 0 °C. Trifluoroacetic acid (0.37 mL, 1 M) was added dropwise and the solution was warmed to rt and stirred overnight. Toluene (2 mL) was added, and the resulting solution was concentrated *in vacuo*. Additional toluene (2 mL) was added, the mixture was concentrated again, and this process was repeated two additional times. This afforded the trifluoroacetate salt of (*Z*)-*N*-benzylprop-2-en-2,3-d_2-1-ylamine as a crude oil that was carried on to the next step without purification.

A round-bottom flask equipped with a stirbar was charged with dichloromethane (2 mL) and 4-nitrophenyl isocyanate (0.06 g, 0.37 mmol, 1 equiv). A solution of the crude (*Z*)-*N*-benzylprop-2-en-2,3-d_2-1-ylamine trifluroacetate salt (from the previous step) in dichloromethane (1.7 mL) was added, then triethylamine (0.2 mL, 0.44 mmol, 3.9 equiv) was added dropwise and the resulting solution was stirred at rt overnight. The mixture was then concentrated *in vacuo*, and the crude product was purified via flash column chromatography on silica gel using 10% ethyl acetate in hexanes as the eluant to afford 0.112 g (98%) of the title compound as a yellow solid, m.p. 105–107 °C. This material was determined to contain ca 95% deuterium incorporation at each of the alkene positions, along with ca 25% deuterium incorporation at the benzylic position (carried through from earlier intermediates) by ^{1}H NMR, ^{2}D NMR, and HRMS analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.9 Hz, 2 H), 7.45 (d, *J* = 8.8 Hz, 2 H), 7.39 (t, *J* = 7.5 Hz,

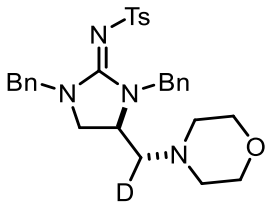
2 H), 7.34 (d, *J* = 7.1 Hz, 3 H), 6.79 (s, 1 H), 5.33 (s, 1 H), 4.61 (m, 2 H), 4.01 (s, 2 H); Note: the unusual multiplicity for the peak at δ 4.61 is due the ~25% deuterium incorporation at the benzylic position. ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.9, 145.4, 142.8, 137.0, 133.2 (t, *J* = 24.0 Hz), 129.2, 128.2, 127.7, 125.2, 118.5, 117.8 (t, *J* = 23.5 Hz), 51.0, 50.0; IR (film) 3347, 1657, 1610 cm^{-1}; HRMS (ESI$^+$) 314.1468 (314.1468 calcd for $C_{17}H_{15}D_2N_3O_3$, M + H$^+$).



(4*S,4'*R**)-*N*-(1,3-Dibenzyl-4-(morpholinomethyl-*d*)imidazolidin-2-ylidene)cyanamide (4-*d*-9a)**.[33] The general procedure was followed for the coupling of (*Z*)-1-[allyl-3-*d*]-1,3-dibenzyl-2-cyanoguanidine **(4-*d*-8a)** (30.5 mg, 0.1 mmol) with morpholino benzoate **(4-4a)** (62.2 mg, 0.3 mmol). This procedure afforded 26 mg (67%) of the title compound as a tan, viscous oil. This compound was obtained as a 3:1 mixture of diastereomers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (500 MHz, C_6D_6) δ 7.17–7.12 (m, 4 H), 7.11–6.98 (m, 6 H), 5.25 (d, *J* = 15.5 Hz, 1 H), 4.52 (q, *J* = 15.1 Hz, 2 H), 4.08–4.02 (m, 1 H), 3.29 (br s, 4 H), 3.01 (q, *J* = 7.4 Hz, 1 H), 2.65 (dd, *J* = 11.5, 7.3 Hz, 1 H), 2.54 (q, *J* = 8.2 Hz, 1 H), 1.89–1.84 (m, 1 H), 1.78–1.68 (m, 4 H), 1.58–1.51 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.4, 135.9, 135.4, 128.9, 128.8, 128.2, 128.1, 128.0, 127.9, 66.7, 60.5 (t, *J* = 21.9 Hz), 54.0, 51.8, 49.5, 49.3, 47.8; IR (film) 2924, 2169, 1583 cm^{-1}; HRMS (ESI$^+$) 391.2355 (391.2351 calcd for $C_{23}H_{26}DN_5O$, M + H$^+$).

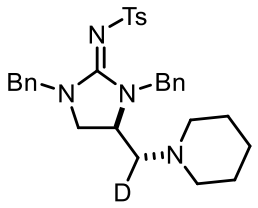


(4*S,4'*R**)-1-Benzyl-4-(morpholinomethyl-*d*)-3-(4-nitrophenyl)imidazolidin-2-one (4-*d*-11a).**[33] The general procedure was followed for the coupling of (*Z*)-1-(allyl-3-*d*)-1-benzyl-3-phenylurea **(4-*d*-10a)** (31.2 mg, 0.1 mmol) with morpholino benzoate (**4-4a**) (62.2 mg, 0.3 mmol). This procedure afforded 28 mg (70%) of the title compound as a yellow solid, m.p. 102-104 °C. This compound was obtained as a 6:1 mixture of diastereomers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (400 MHz, C_6D_6) δ 8.04 (d, *J* = 9.3 Hz, 2 H), 7.61 (d, *J* = 9.3 Hz, 2 H), 7.14–7.02 (m, 5 H), 4.31–4.19 (m, 2 H), 3.52–3.24 (m, 5 H), 2.85 (dd, *J* = 8.9, 2.8 Hz, 1 H), 2.75 (t, *J* = 8.7 Hz, 1 H), 1.95–1.88 (m, 3 H), 1.83–1.79 (m, 2 H), 1.72 (dd, *J* = 13.7, 9.3 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.4, 145.2, 142.0, 136.1, 128.8, 128.3, 127.9, 124.9, 117.4, 66.7, 58.9 (t, *J* = 19.0 Hz), 54.2, 50.8, 47.8, 45.9; IR (film) 2922, 1710 cm^{-1}; HRMS (ESI^{+}) 398.1929 (398.1933 calcd for $C_{21}H_{23}DN_4O_4$, M + H^{+}).



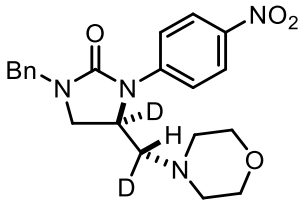
(4*S,4'*R**)-*N*-[1,3-dibenzyl-4-(morpholinomethyl-*d*)imidazolidin-2-ylidene]-4-methylbenzenesulfonamide (4-*d*-9d)**.[33] The general procedure was followed for the coupling of (*Z*)-*N*-{[allyl-3-*d*](benzyl)amino}benzylaminomethylene-4-methylbenzenesulfonamide **(4-*d*-8b)** (43.5 mg, 0.1 mmol) with morpholino benzoate **(4-4a)** (62.2 mg, 0.3 mmol). This procedure afforded 39 mg (75%) of the title compound as

a tan, viscous oil. This compound was obtained as a 6:1 mixture of diastereomers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (400 MHz, C_6D_6) δ 8.26 (d, *J* = 8.2 Hz, 2 H), 7.28 (d, *J* = 6.8 Hz, 4 H), 7.20–6.98 (m, 6 H), 6.81 (d, *J* = 8.1 Hz, 2 H), 5.47 (d, *J* = 15.4 Hz, 1 H), 4.83 (d, *J* = 15.0 Hz, 1 H), 4.66 (d, *J* = 14.9 Hz, 1 H), 4.12 (d, *J* = 15.3 Hz, 1 H), 3.33 (br s, 4 H), 3.15–3.05 (m, 1 H), 2.75 (t, *J* = 9.7 Hz, 1 H), 2.66 (d, *J* = 7.3 Hz, 1 H), 1.92–1.87 (m, 4 H), 1.84–1.70 (m, 4 H), 1.77–1.72 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.5, 142.9, 141.2, 136.1, 135.7, 129.9, 128.8, 128.7, 128.6, 128.4, 128.1, 127.9, 127.8, 125.8, 66.7, 60.2 (t, *J* = 19 Hz), 54.1, 51.6, 50.8, 49.0, 48.7, 21.4; IR (film) 2922, 1559 cm^{-1}; HRMS (ESI$^+$) 520.2482 (520.2487 cacld for $C_{29}H_{33}DN_4O_3S$, M + H^+).



(4*S,4'*R**)-*N*-[1,3-Dibenzyl-4-(-piperidin-1-ylmethyl-*d*)imidazolidin-2-ylidene]-4-methylbenzenesulfonamide (4-*d*-9e)**.[33] The general procedure was followed for the coupling of (*Z*)-*N*-{[allyl-3-d](benzyl)amino}-benzylaminomethylene-4-methylbenzenesulfonamide (**4-*d*-8b**) (43.5 mg, 0.1 mmol) with piperidin-1-yl benzoate (**4-4b**) (61.5 mg, 0.3 mmol). This procedure afforded 40 mg (77%) of the title compound as a tan, viscous oil. This compound was obtained as a 7:1 mixture of diastereomers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (500 MHz, C_6D_6) δ 8.26 (d, *J* = 8.0 Hz, 2 H), 7.33 (d, *J* = 7.5 Hz, 2 H), 7.28 (d, *J* = 7.5 Hz, 2 H), 7.15–7.07 (m, 4 H), 7.05–7.00 (m, 2 H), 6.82 (d, *J* = 8 Hz, 2 H), 5.46 (d, *J* = 15 Hz, 1 H), 4.82 (d, *J* = 14.5 Hz, 1 H), 4.65 (d, *J* = 15.5 Hz, 1 H), 4.22 (d, *J* = 15 Hz, 1 H), 3.19 (q, *J* = 9.5 Hz, 1 H), 2.80

(t, *J* = 9.5 Hz, 1 H), 2.72 (dd, *J* = 16.5 Hz, 6.5 Hz, 1 H), 2.05–2.00 (m, 1 H), 1.89 (s, 3 H), 1.86 (br s, 4 H), 1.76–1.71 (m, 1 H); ^{13}C NMR (125 MHz, C_6D_6) δ 156.2, 144.3, 140.4, 137.1, 136.5, 128.8, 128.6, 128.7, 128.6, 128.5, 128.4, 127.5, 126.2, 60.7 (t, *J* = 22 Hz), 54.8, 51.7, 50.8, 48.8, 48.7, 25.8, 24.1, 20.7; IR (film) 2931, 1559 cm^{-1}; HRMS (ESI$^+$) 518.2692 (518.2695 calcd for $C_{30}H_{35}DN_4O_2S$, M + H$^+$).

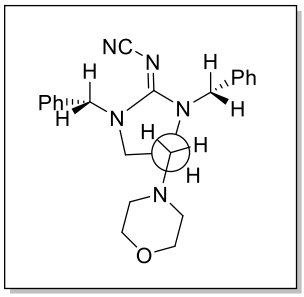


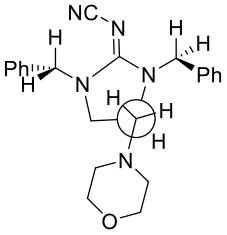
(4*S,4'*R**)-1-Benzyl-4-(morpholinomethyl-*d*)-3-(4-nitrophenyl)imidazolidin-2-one-4-*d* (4-23)**. A flame dried Schlenk tube was cooled under a stream of nitrogen and charged with (*Z*)-1-(allyl-2,3-d_2)-1-benzyl-3-(4-nitrophenyl)urea (**4-22**) (0.0313 g, 0.1 mmol), $Pd(acac)_2$ (0.0012g, 0.004 mmol), JackiePhos (0.0127 g, 0.016 mmol), morpholino benzoate (**4-4a**) (0.0622g, 0.3 mmol), Cs_2CO_3 (0.0652 g, 0.2mmol), and dioxane (1mL, 0.1 M). The solution was heated to 100 °C for 16 h, then was cooled to rt, filtered through cotton, rinsed with diethyl ether, and concentrated *in vacuo*. The crude product was purified via flash column chromatography on silica gel using 40% ethyl acetate in hexanes as the eluant to afford 25.4 mg (64%) of the title compound as a yellow solid, m.p. 105–106 °C. This material was obtained as a 6:1 mixture of diastereomers as judged by ^{1}H NMR analysis; data are for the major isomer. Note: this material also contains ca 25% deuterium incorporation at the benzylic position, which was carried over from the starting material, based on ^{1}H and ^{2}D NMR analysis. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22 (d, *J* = 9.4 Hz, 2 H), 7.75 (d, *J* = 8.8 Hz, 2 H), 7.40–7.29 (m, 5 H), 4.58–4.40 (m, 2 H), 3.62 (q, *J* = 9.4 Hz, 4 H), 3.49 (d, *J* = 9.1 Hz, 1 H), 3.36 (d, *J* = 9.3 Hz, 1 H), 2.59 (s, 1 H), 2.50 (d, *J*

= 8.0 Hz, 2 H), 2.37 (q, *J* = 9.7, 8.8 Hz, 2 H; ^{1}H NMR (500 MHz, C_6D_6) δ 8.05 (d, *J* = 9.3 Hz, 2 H), 7.60 (d, *J* = 9.2 Hz, 2 H), 7.21–7.02 (m, 5 H), 4.36–4.09 (m, 2 H), 3.35–3.49 (m, 4 H), 2.84 (d, *J* = 8.8 Hz, 1 H), 2.73 (d, *J* = 8.8 Hz, 1 H), 1.98–1.88 (m, 3 H), 1.81 (ddd, *J* = 10.5, 6.1, 3.1 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.5, 145.4, 142.2, 136.3, 129.0, 128.4, 128.0, 125.1, 117.5, 66.9, 59.0 (t, *J* = 20.3 Hz), 54.3, 50.7 (t, *J* = 20.9 Hz), 48.0, 45.9; IR (film) 2924, 2853, 1710 cm^{-1}; HRMS (ESI^+) 399.1995 (399.1996 calcd for $C_{21}H_{22}D_2N_4O_4$, $M + H^+$).

Computational Details – Energy minimization for assignment of stereochemistry of deuterated products by nOe.

All geometries were optimized using the spin-restricted B3LYP[37] density functional and the 6-31G* basis set. All density functional calculations were performed using Spartan'16.[38] The calculations are meant to be used for qualitative purposes only.





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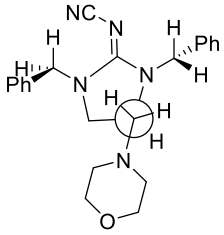
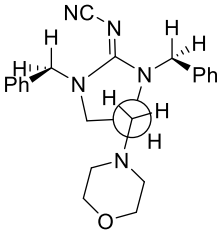
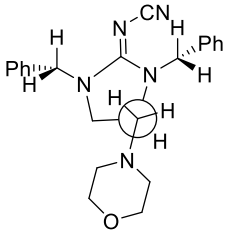


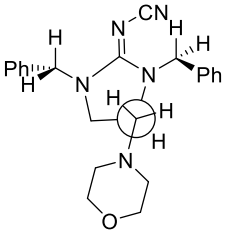
+0.3891 kcal/mol



+0.8810 kcal/mol



+0.5485 kcal/mol



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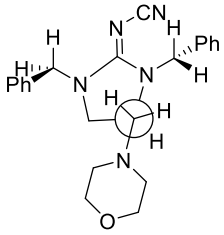
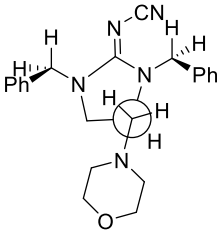
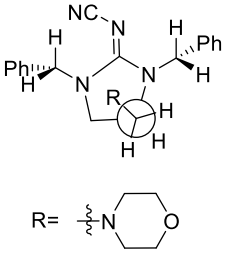


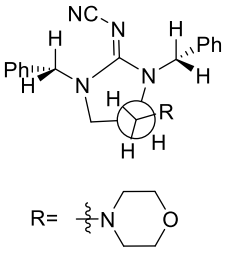
+0.6049 kcal/mol



+3.1426 kcal/mol



+2.4002 kcal/mol

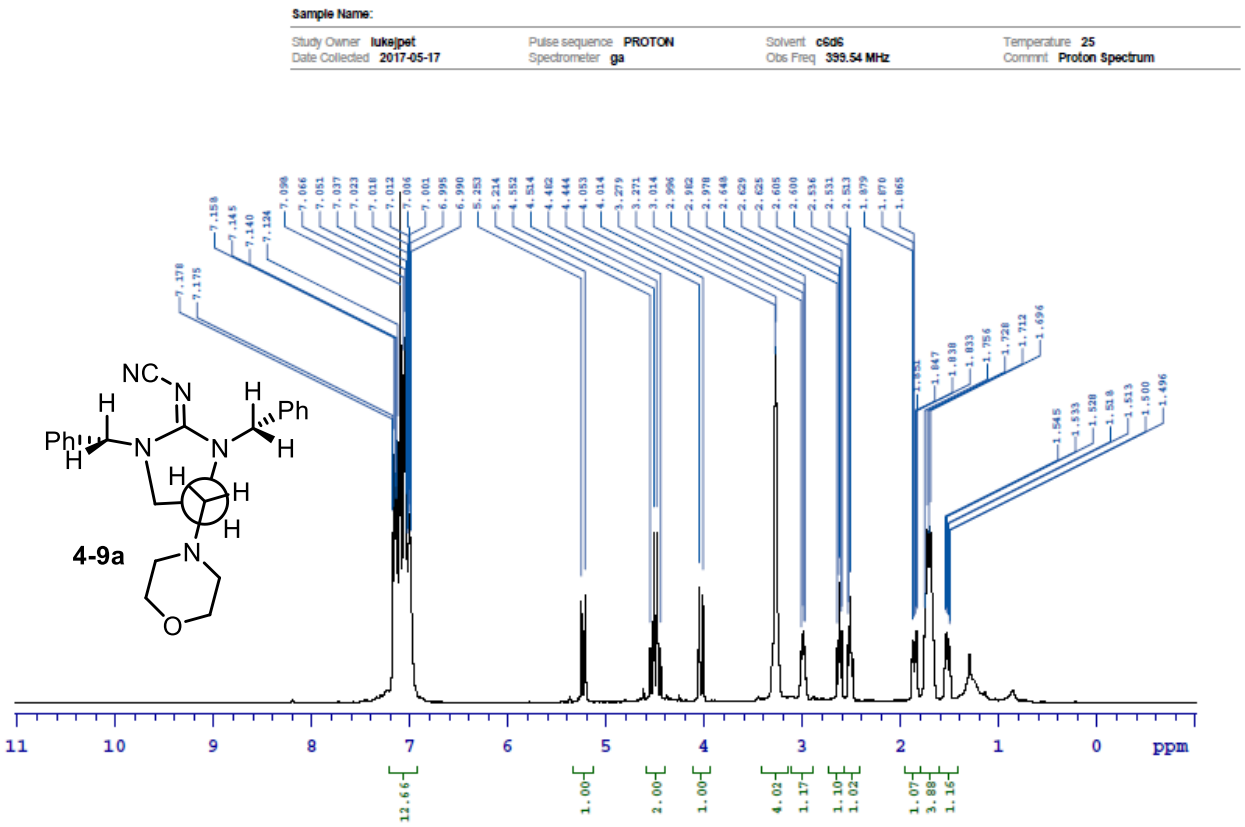


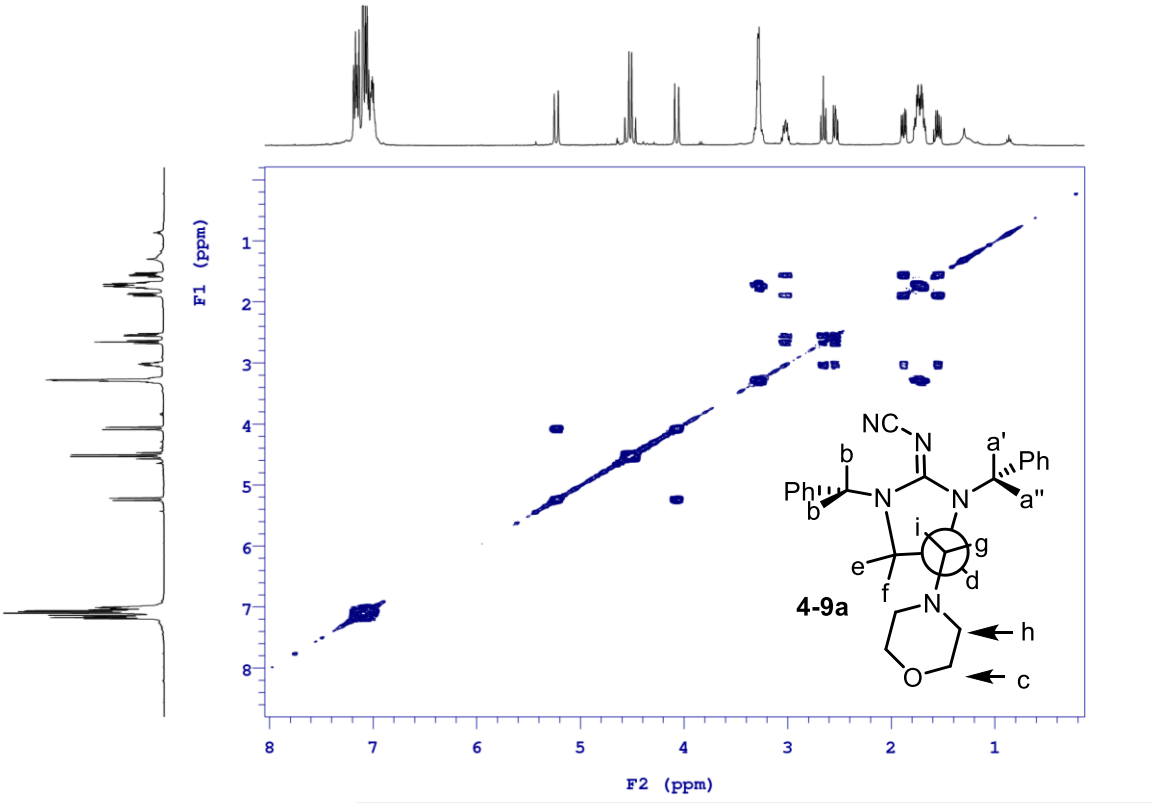
+0.5842 kcal/mol

Deuterium Labelling Studies – Assignment of product stereochemistry

In order to determine the relative stereochemical configuration of the deuterated products **4-*d*-9a**, **4-*d*-9d**, **4-*d*-9e**, and **4-*d*-11a**, the calculated ground state energy conformations[30] shown above were used in conjunction with 2D COSY and 1D ^{1}H nOe analysis of the all-proteo analogs of these compounds. The low energy conformation is shown in the box on the previous page, and is copied on the ^{1}H NMR, COSY, and 1D nOe spectra of **4-9a** shown on the following pages. Irradiation of the signal corresponding to H atom a'' led to

a strong nOe correlation to H g, and a weak correlation to H i (plus a strong correlation to the germinal H atom a'). In contrast, irradiation of H atom a' resulted only in nOe correlations to H d and H a''. The stereochemistry of the deuterated compounds was then assigned on the basis of which signal (H g vs. H i) was missing from the ^{1}H NMR spectra of the deuterated products.

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a'
Ph
b
Ph
b
N
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a''
i
g
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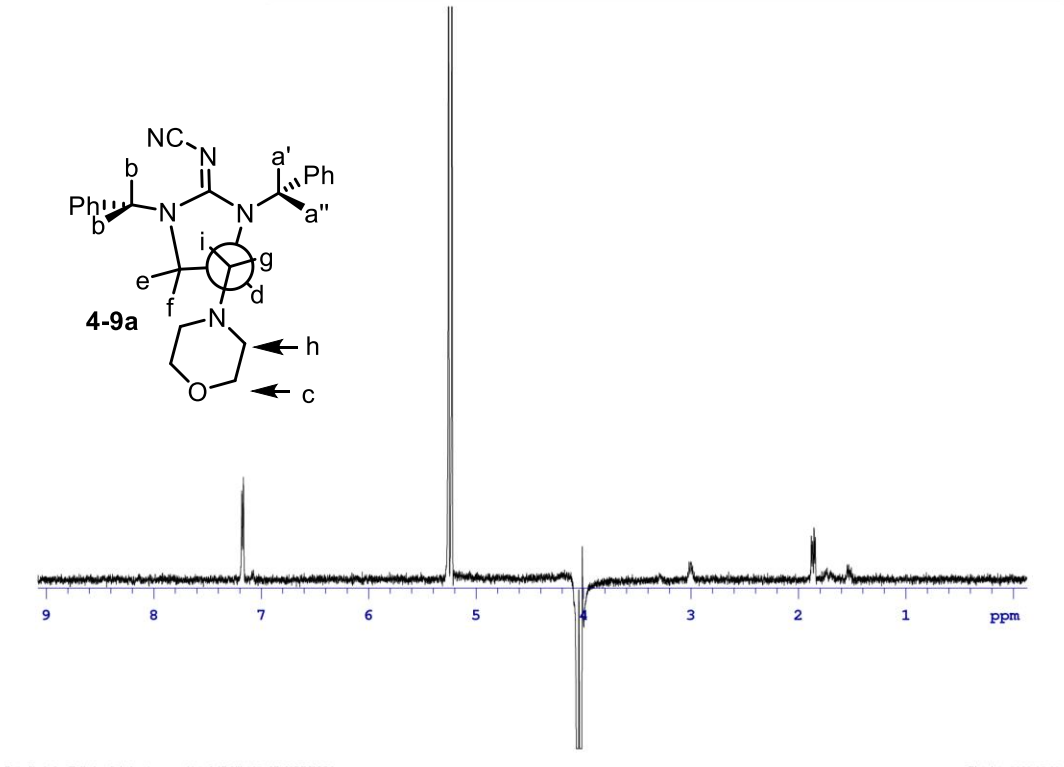
O
c
4-9a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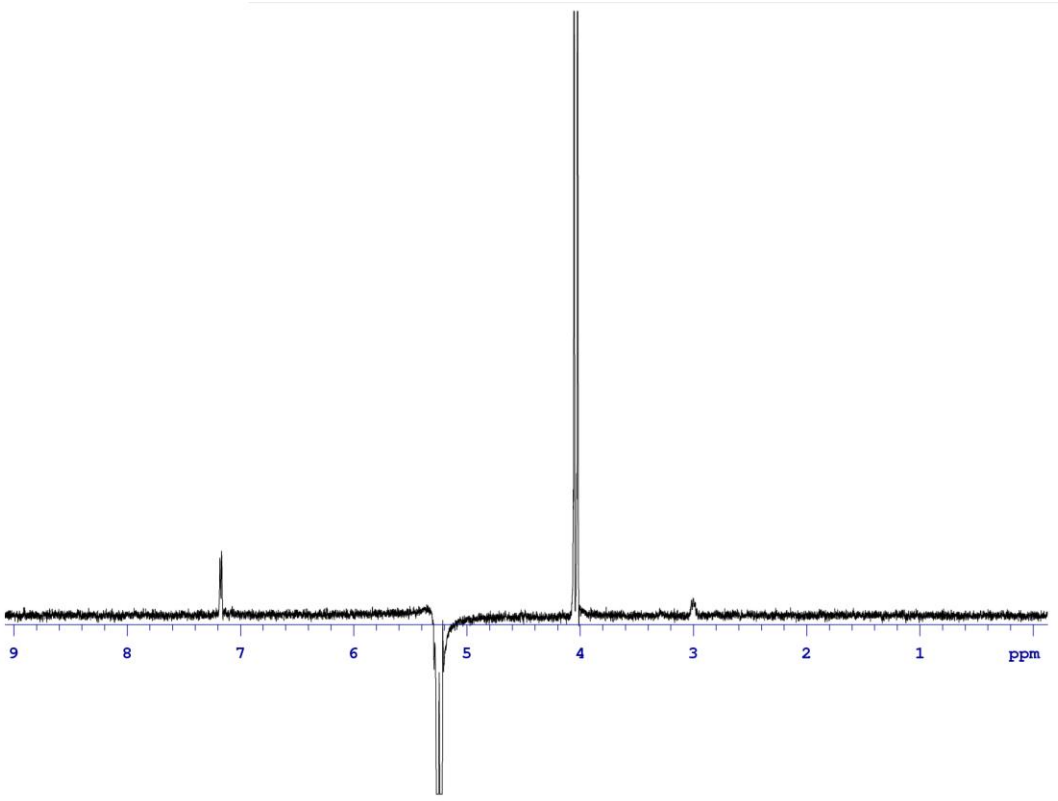
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References

(1) For recent reviews, see: (a) Schultz, D. M.; Wolfe, J. P. *Synthesis* **2012**, *44*, 351. (b) Wolfe, J. P. *Top. Heterocycl. Chem.* **2013**, *32*, 1. (c) Garlets, Z. J.; White, D. R.; Wolfe, J. P. *Asian J. Org. Chem.* **2017**, *6*, 636.

(2) For reactions between *N*-allylguanidines and aryl/alkenyl halides/triflates, see: (a) Peterson, L. J.; Luo, J.; Wolfe, J. P. *Org. Lett.* **2017**, *19*, 2817. (b) Zavesky, B. P.; Babij, N. R.; Fritz, J. A.; Wolfe, J. P. *Org. Lett.* **2013**, *15*, 5420. For reactions between *N*-allylureas and aryl/alkenyl halides/triflates, see: (c) Hopkins, B. A.; Wolfe, J. P. *Angew. Chem. Int. Ed.* **2012**, *51*, 9886. (d) Fritz, J. A.; Wolfe, J. P. *Tetrahedron*, **2008**, *64*, 6838. (e) Fritz, J. A.; Nakhla, J. S.; Wolfe, J. P. *Org. Lett.* **2006**, *8*, 2531.

(3) Sibbald, P. A.; Michael, F. E. *Org. Lett.*, **2009**, *11*, 1147.

(4) Sibbald, P. A.; Rosewall, C. F.; Swartz, R. D.; Michael, F. E. *J. Am. Chem. Soc.* **2009**, *131*, 15945.

(5) For a review, see: (a) Dong, X.; Liu, Q.; Dong, Y.; Liu, H. *Chem. Eur. J.* **2017**, *23*, 2481. For selected examples, see: (b) Berman, A. M.; Johnson, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 5680. (c) Yoo, E. J.; Ma, S.; Mei, T. -S.; Chan, K. S. L.; Yu, J. -Q. *J. Am. Chem. Soc.* **2011**, *133*, 7652. (d) Shi, H.; Babinski, D. J.; Ritter, T. *J. Am. Chem. Soc.* **2015**, *137*, 3775. (e) Dong, Z.; Dong, G. *J. Am. Chem. Soc.* **2013**, *135*, 18350.

(6) For examples of Cu-catalyzed diamination reactions in the presence of external oxidants, see: (a) Khoder, Z. M.; Wong, C. E.; Chemler, S. R. *ACS. Catal.* **2017**, *7*, 4775. (b) Chen, M.; Wang, L. -J.; Ren, P. -X.; Hou, X. -Y.; Fang, Z.; Han, M. -N.; Li, W. *Org. Lett.*

2018, 20, 510. (c) Chemler, S. R.; Copeland, D. A. *Top. Heterocycl. Chem.* **2013**, *32*, 39. (d) Sequeira, F. C.; Turnpenny, B. W.; Chemler, S. R. *Angew. Chem. Int. Ed.* **2010**, *49*, 6365. Thus far these reactions have not been demonstrated to be stereospecific.

(7) For examples of Pd-catalyzed alkene diamination reactions that involve strong oxidants and Pd(IV) intermediates, see: (a) Streuff, J. Hövelmann, C. H.; Nieger, M.; Muñiz, K. *J. Am. Chem. Soc.* **2005**, *127*, 14586. (b) Roben, C.; Souto, J. A.; Escudero-Adan, E. C.; Muñiz, K. *J. Org. Chem.* **2013**, *78*, 2168. (c) Muniz, K.; Hovelmann, C. H.; Streuff, J.; Campos-Gomez, E. *Pure Appl. Chem.* **2008**, *80*, 1089. (d) Ingalls, E. L.; Sibbald, P. A.; Kaminsky, W.; Michael, F. E. *J. Am. Chem. Soc.* **2013**, *135*, 8854. (f) Muniz, K.; Hovelmann, C. H.; Streuff, J. *J. Am. Chem. Soc.* **2008**, *130*, 763.

(8) For examples of Pd(II)-catalyzed alkene diamination reactions that involve allylpalladium intermediates, see: (a) Du, H.; Yuan, W.; Zhao, B.; Shi, Y. *J. Am. Chem. Soc.* **2007**, *129*, 7496. (b) Wu, Z.; Wen, K.; Zhang, J.; Zhang, W. *Org. Lett.* **2017**, *19*, 2813.

(9) (a) Chern, J. –W.; Tao, P. –L.; Wang, K. –C.; Gutcait, A.; Liu, S. -W.; Yen, M. –H.; Chien, S. –L.; Rong, J. –K. *J. Med. Chem.* **1998**, *41*, 3128. (b) Kondo, T.; Yagi, H.; Dan, A.; Masumoto, S.; Kinomura, N.; Koyama, K. PCT Int. Appl. WO2003053928A1, July 3, 2003, Scifinder Scholar 139:85334. (c) Galley, G.; Groebke Zbinden, K.; Norcross, R.; Stalder, H. PCT Int. Appl. WO2009003867A1, January 8, 2009, Scifinder Scholar 150:98327.

(10) For examples of transformations that involve sp^3C–N bond-forming reductive elimination from Pd(II) in systems that are not allylic or benzylic, see: (a) He, J.; Shigenari,

T.; Yu, J. –Q. *Angew. Chem. Int. Ed.* **2015**, *54*, 6545. (b) Brice, J. L.; Harang, J. E.; Timokhin, V. I.; Anastasi, N. R.; Stahl, S. S. *J. Am. Chem. Soc.* **2005**, *127*, 2868. (c) Hanley, P. S.; Marquard, S. L.; Cundari, T. R.; Hartwig, J. F. *J. Am. Chem. Soc.* **2012**, *134*, 15281. (d) Lautens, M.; Paquin, J. –F.; Piguel, S.; Dahlmann, M. *J. Org. Chem.* **2001**, *66*, 8127. (e) Pan, J.; Su, M.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2011**, *50*, 8647. (f) Catellani, M.; Del Rio, A. *Russ. Chem. Bull.* **1998**, *47*, 928.

(11) Gou, Q.; Liu, G.; Qin, J. *Chem. Eur. J.* **2015**, *21*, 15491.

(12) Shen, K.; Wang, Q. *Chem. Sci.* **2015**, *6*, 4279.

(13) For examples of related Cu-catalyzed alkene oxyamination reactions, see: (a) Hemric, B. N.; Shen, K.; Wang, Q. *J. Am. Chem. Soc.* **2016**, *138*, 5813. (b) Xie, J.; Wang, Y. –W.; Qi, L. –W.; Zhang, B. *Org. Lett.* **2017**, *19*, 1148.

(14) For related Cu-catalyze alkene aminoazidation reactions, see: Shen, K. Wang, Q. *J. Am. Chem. Soc.* **2017**, *139*, 13110.

(15) Entries 1-10 in Table 4-1 were conducted by LJP and entries 11-15 were conducted by JKK.

(16) *N*-allylguanidines (**4-8**) and *N*-allylureas (**4-10**) were synthesized in 2-3 steps according to procedures listed in section 4-6 or previously reported publications.

(17) Faulkner, A.; Scott, J. S.; Bower, J. F. *J. Am. Chem. Soc.* **2015**, *137*, 7224.

(18) Gioria, E.; del Pozo, J.; Martinez-Ilarduya, J. M.; Espinet, P. *Angew. Chem. Int. Ed.* **2016**, *55*, 13276.

(19) Hicks, J. D.; Hyde, A. M.; Cuezva, A. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 16720.

(20) The experiments detailed in Table 4-2 were conducted by LJP.

(21) Entries 1-4 in Table 4-3 were conducted by LJP and entries 5-6 were conducted by JKK. Compound **4-10c** was synthesized by Elsa M. Hinds.

(22) The experiments detailed in Table 4-4 were conducted by LJP.

(23) Tan, Y.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 3676.

(24) See: Mueller, J. A.; Goller, C. P.; Sigman, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 9724.

(25) For a related experiment in the context of guanidine carboamination, see reference 2a. In the present work, a deuterium atom was used instead of a methyl group at the internal alkene carbon because, thus far, substrates bearing substitution at this position have been unreactive in this system.

(26) Hu, S.; Wang, D.; Liu, J. Li, X. *Org. Biomol. Chem*. **2013**, *11*, 2761.

(27) Zhao, Y.; Snieckus, V. *Org. Lett.* **2014**, *16*, 390.

(28) Brown, H.; McFarlin, R. *J. Am. Chem. Soc.* **1958**, *80*, 5372.

(29) Peterson, L. J.; Kirsch, J. K.; Wolfe. J. P. *Org. Lett.*, **2018**, *20*, 3513.

(30) Peterson, L. J.; Luo, J.; Wolfe, J. P. *Org. Lett.* **2017,** *19,* 2817.

(31) Biloski, A. J.; Ganem, B. *Synthesis* **1983,** 537.

(32) Luo, B.; Gao, J. –M.; Lautens, M. *Org. Lett.* **2016**, *18*, 4166.

(33) Experiment conducted by LJP.

(34) Berman, A. M.; Johnson, J. S. *J. Org. Chem.* **2006**, *71*, 219.

(35) McDonald, S. L.; Hendrick, C. E.; Bitting, K. J.; Wang, Q. *Org. Synth.* **2015**, *92*, 356.

(36) Synthesized by EMH.

(37) (a) Becke, A. D. *J. Chem. Phys*. **1993**, *98*, 5648. (b) Lee, C.; Yang, W.; Parr, R.G. *Phys. Rev. B.* **1988**, *37*, 785. (c) Vosko, S. H.; Wilk, L.; Nusair, M. *Can. J. Phys*. **1980**, *58*, 1200. (d) Stephens, P. J.; Devlin, F. J.; Chabalowski, C. F.; Frisch, M. J. *J. Phys. Chem*. **1994**, *98*, 11623.

(38) Shao, Y.; Molnar, L. F.; Jung, Y.; Kussmann, J.; Ochsenfeld, C.; Brown, S. T.; Gilbert, A. T. B.; Slipchenko, L. V.; Levchenko, S. V.; O'Neill, D. P.; DiStasio Jr., R. A.; Lochan, R. C.; Wang, T.; Beran, G. J. O.; Besley, N. A.; Herbert, J. M.; Lin, C. Y.; Van Voorhis, T.; Chien, S. H.; Sodt, A.; Steele, R. P.; Rassolov, V. A.; Maslen, P. E.; Korambath, P. P.; Adamson, R. D.; Austin, B.; Baker, J.; Byrd, E. F. C.; Dachsel, H.; Doerksen, R. J.; Dreuw, A.; Dunietz, B. D.; Dutoi, A. D.; Furlani, T. R.; Gwaltney, S. R.; Heyden, A.; Hirata, S.; Hsu, C-P.; Kedziora, G.; Khalliulin, R. Z.; Klunzinger, P.; Lee, A. M.; Lee, M. S.; Liang, W. Z.; Lotan, I.; Nair, N.; Peters, B.; Proynov, E. I.; Pieniazek, P. A.; Rhee, Y. M.; Ritchie, J.; Rosta, E.; Sherrill, C. D.; Simmonett, A. C.; Subotnik, J. E.; Woodcock III, H. L.; Zhang, W.; Bell, A. T.; Chakraborty, A. K.; Chipman, D. M.; Keil, F. J.; Warshel, A.; Hehre, W. J.; Schaefer, H. F.; Kong, J.; Krylov, A. I.; Gill, P. M. W.; Head-Gordon, M. *Phys. Chem. Chem. Phys*. **2006**, *8*, 3172. Spartan'14; Wavefunction, Inc.: Irvine, CA, 2014.

Chapter 5

Palladium-Catalyzed Alkene Diamination of N-Allyureas, N-Allylguanidines, and Allylamides Utilizing Acac-Derived Ligands

5.1 Introduction

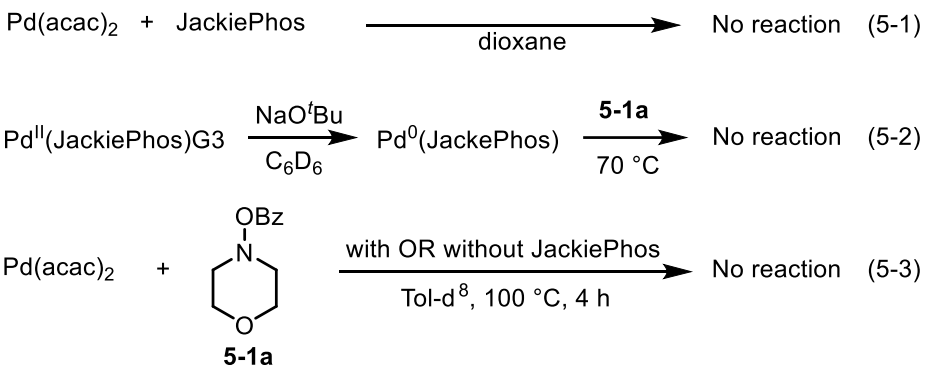
As previously discussed in Chapter 4, in 2018 we reported the Pd-catalyzed alkene diamination of guanidines and ureas bearing tethered alkenes with *O*-acylated hydroxylamine derivatives to provide cyclic guanidines or ureas bearing appended aminoalkyl groups in good to excellent chemical yield (Chapter 4, Tables 4-2-4).[1] In addition, reactions involving deuterated alkene substrates proceed with modest diastereoselectivity favoring products resulting from *anti*-addition of the two nitrogen atoms to the alkene.

We initially hypothesized that the mechanism of these reactions is similar to that of related alkene carboamination reactions, involving a typical Pd(0)/Pd(II) catalytic cycle (Chapter 4, Scheme 4-1).[1,2,3] In this chapter, we describe new experiments that have led us to revise our mechanistic hypothesis, along with the discovery that acac (2,4-pentanedione) and simple acac derivatives serve as highly effective ligands for this transformation.

5.2 Control Experiments and Precatalyst Effects

Following our preliminary studies, we set out to further examine this reaction and its mechanism. We elected to first explore the putative oxidative addition of the morpholino benzoate electrophile **5-1a** to either Pd(0) or Pd(II). However, in initial scouting

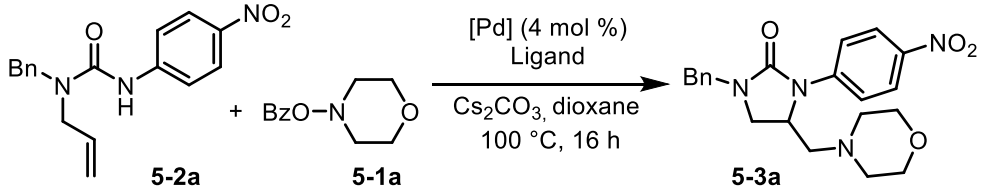
experiments we were surprised to find that the phosphine ligand JackiePhos did not bind to $Pd(acac)_2$ as judged by a lack of change of the ^{31}P NMR chemical shift of free JackiePhos vs the mixture of JackiePhos and $Pd(acac)_2$ (eq 5-1). In order to explore the possibility of oxidative addition to a Pd(0)/JackiePhos complex, we carried out NMR studies in which the Buchwald Pd(II)(JackiePhos) G3 precatalyst was reduced *in situ*, as judged by ^{31}P NMR analysis, and then treated with **5-1a** (eq 5-2). Surprisingly, we saw no evidence for oxidative addition of **5-1a** to this Pd(0) complex. In addition, we did not observe any evidence for oxidative addition of **5-1a** to the Pd(II) complex $Pd(acac)_2$ at 100 °C, either with or without JackiePhos present (eq 5-3). The results of these experiments immediately suggested two things: (i) since JackiePhos does not appear to bind to $Pd(acac)_2$, it may not be the actual ligand for palladium in these alkene diamination reactions; and (ii) our original mechanistic hypothesis is likely incorrect, as the proposed initial oxidative addition step does not appear to be viable with this catalyst system.



Given these results, we decided to revisit the influence of pre-catalyst and ligand on the outcome of the coupling reactions between **5-1a** and *N*-allylurea substrate **5-2a**. We had previously reported that the coupling of **5-1a** with **5-2a** and Cs_2CO_3 in the presence of $Pd(acac)_2$ and JackiePhos afforded a 90% isolated yield of the desired product **5-3a** (Table 5-1, entry 1). We first carried out the key control experiment in which JackiePhos

was omitted from these conditions and obtained the same result as when JackiePhos was included (entry 2). *This result suggests that the actual ligand for palladium is acac, not JackiePhos, and is further supported by the fact that Pd(TFA)$_2$ or other simple palladium pre-catalysts alone gave poor results (entries 3-4), but use of Pd(TFA)$_2$ and acac as additional ligand provided* ***5-3a*** *in >95% yield (entry 5).*

Table 5-1: Precatalyst Effects on Yield of **5-3a**



5-2a **5-1a** **5-3a**

entry	[Pd]	Ligand	Yield (%)[b]
1	$Pd(acac)_2$	JackiePhos[c]	90[d]
2	$Pd(acac)_2$	none	>95
3	$Pd(OAc)_2$	none	24
4	$Pd(TFA)_2$	none	35
5	$Pd(TFA)_2$	acac[e]	>95

[a]Conditions: 1.0 equiv of **5-2a**, 3.0 equiv of **5-1a**, 4 mol % of [Pd], 2 equiv of Cs_2CO_3, dioxane (0.1M), 100 °C, 16 h. [b]Yields were determined by ^{1}H NMR analysis using phenanthrene as an internal standard. [c]16 mol % of JackiePhos was used. [d]Isolated yield from *Org. Lett.*, **2018**, *20*, 3513. [e]8 mol % of acac was used.

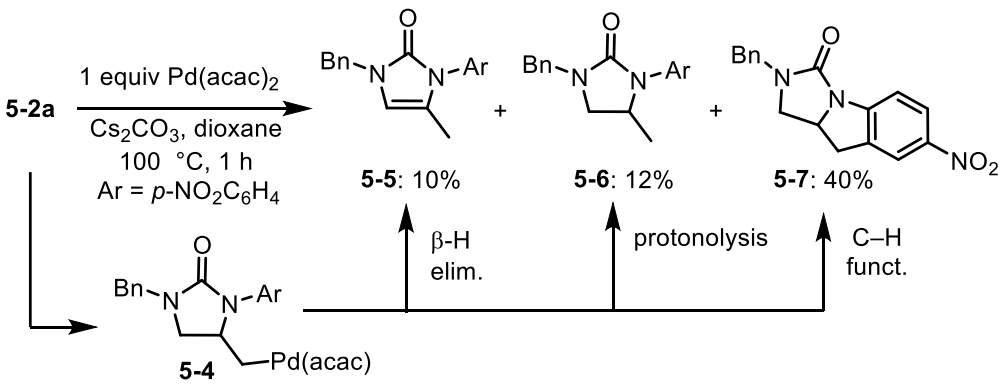
When we originally studied this transformation[1], we observed a clear trend where the yields steadily improved as we moved to bigger and more electron-deficient ligands. (Table 4-1). At the time, however, we neglected to perform a control reaction in which the phosphine ligand was absent and therefore misinterpreted the ligand trend. We now believe the trend simply reflects inhibition of the reaction by phosphine ligands. The ligands that do not bind to the metal as well – due to being bulky and electron-poor –

inhibit the reaction less than the more electron-rich ligands, leading to a higher observed yield.

5.3 Revised Mechanistic Hypothesis and Stereochemical Details

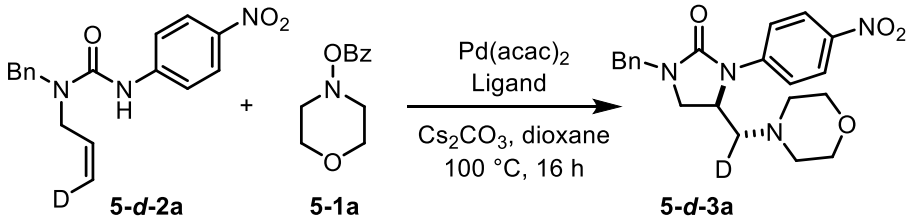
The experiments described in eq 5-1-3 & Table 5-1 suggest our initial Pd(0)/Pd(II) mechanistic hypothesis is incorrect; therefore, we sought to gain additional information about the mechanism of these transformations. In order to probe whether our reactions may proceed via a Pd(II)/Pd(IV) catalytic cycle that is similar to the catalytic cycle reported by Michael[4], we first sought to confirm that alkene aminopalladation could occur in the absence of the electrophile. As such, **5-2a** was treated with Cs_2CO_3 and a stoichiometric amount of $Pd(acac)_2$ (Scheme 5-1). These conditions afforded a roughly 1:1:4 mixture of products **5-5-7** in 62% combined yield. All three of these products likely arise from alkene aminopalladation (**5-2a** to **5-4)**, with **5-5** likely derived from β-hydride elimination of **5-4**, **5-6** potentially resulting from protonolysis of **5-4**, and **5-7** coming from aryl C–H functionalization of **5-4**. Therefore, we have evidence to suggest that (i) the electrophile is not necessary for aminopalladation to occur and (ii) the aminopalladation is viable with a Pd(II) precatalyst in the absence of an obvious metal oxidant.[3,5]

Scheme 5-1: Stoichiometric Reaction in the Absence of Electrophile



In our initial studies[1], we found that the $Pd(acac)_2$/JackiePhos -catalyzed coupling of **5-*d*-2a** with **5-1a** afforded **5-*d*-3d** in 60% yield and 6:1 dr[6] (Table 5-2, entry 1). A similar outcome was obtained when $Pd(acac)_2$ alone (no phosphine) was used as the catalyst for this reaction (entry 2). When we reduce the amount of **5-1a** to 1.5 equiv, we obtained similar isolated yields, but with much lower dr (entries 4-5). We proposed in our previous report[1] that competing *syn*-aminopalladation led to our observed moderate dr. The observation that the dr is also dependent on the amount of electrophile present suggests that the mechanistic step involving the electrophile (likely oxidative addition-see below) is slow. We believe having a higher concentration of the electrophile in the reaction helps promote this slow step.

Table 5-2: Ligand and Electrophile Effect on Stereoselectivity



5-*d*-2a **5-1a** **5-*d*-3a**

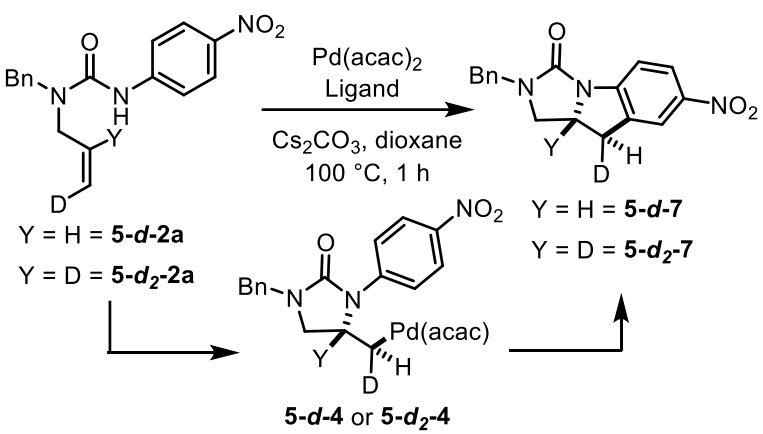
Entry	Equiv of **5-2a**	Ligand	dr	yield (%)[b]
1	3	JackiePhos	6:1	75[c]
2	3	None	6:1	74
3	1.5	JackiePhos	2.2:1	79
4	1.5	None	2.8:1	76

[a]Conditions: 1 equiv of **5-*d*-2a**, 1.5 or 3 equiv of **5-1a**, 4 mol % $Pd(acac)_2$, 8 mol % ligand, 2 equiv of Cs_2CO_3, 0.1M dioxane, 100 °C, 16 h. [b]Islated yields. [c]Result from *Org. Lett.*, **2018**, *20*, 3513

Since product **5-*d*-3a** results from net *anti*-addition to the alkene, we sought to gain additional information about the stereochemistry of alkene aminopalladation and reductive elimination. The overall *anti*-addition could result from either *anti*-

aminopalladation followed by reductive elimination with retention of configuration or may derive from *syn*-aminopalladation and subsequent reductive elimination with inversion of configuration. The related transformation reported by Michael has been demonstrated to proceed via *anti*-aminopalladation, followed by reductive elimination with inversion of configuration.[4c] In order to determine the alkene addition stereochemistry, we elected to take advantage of the relatively facile aminopalladation/C–H functionalization sequence described above in Scheme 5-1 (**5-2a** to **5-7**). As shown in Table 5-3, treatment of

Table 5-3: Stereochemistry of Alkene Aminopalladation



Entry	Y	Ligand	dr	Yield (%)
1	H	JackiePhos	1.7:1	37
2	H	none	1.5:1	20
3	D	none	1.6:1	38[b]

[a]Conditions: 1 equiv of **5-*d*-2a** or **5-*d*$_2$-2a**, 1 equiv of $Pd(acac)_2$, 2 equiv ligand, 2 equiv Cs_2CO_3, dioxane (0.1M), 100 °C, 1 h. [b]Crude ^1H NMR yield.

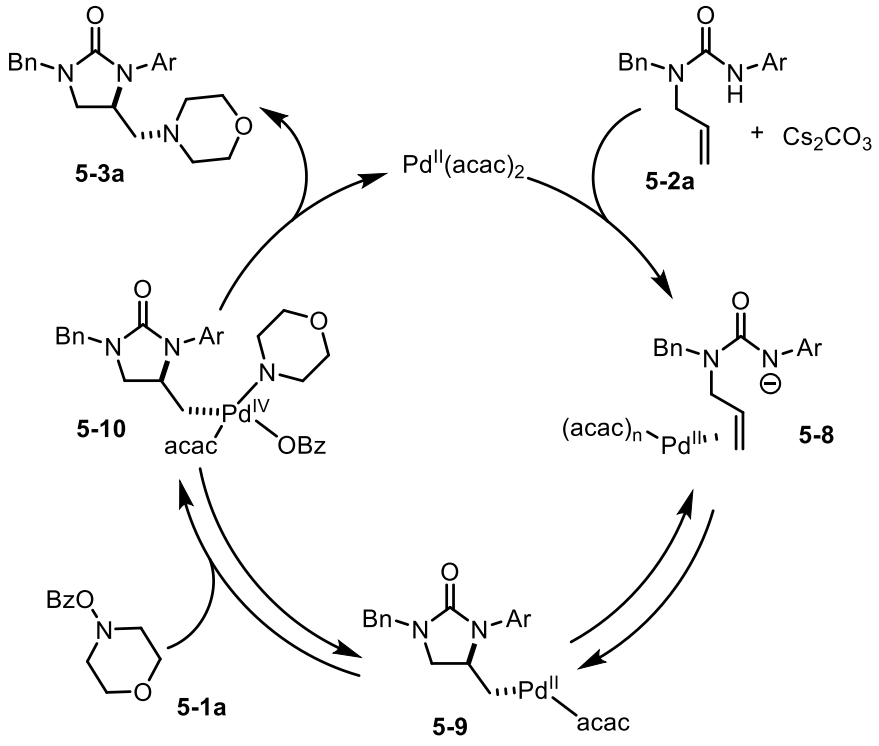
deuterated alkene substrate **5-*d*-2a** with $Pd(acac)_2$ and Cs_2CO_3 in the presence (entry 1) or absence of JackiePhos (entry 2) afforded **5-*d*-7** in modest yield (37 and 20%, respectively), with ca 1.5:1 diastereoselectivity favoring the product resulting from *anti*-aminopalladation.[7]

Given the low diastereoselectivity of the conversion of **5-*d*-2a** to **5-*d*-7** (1.5:1 dr, Table 5-3) relative to that for the conversion of **5-*d*-2a** to **5-*d*-3a** (6:1 dr, Table 5-2), it seemed possible that the aminopalladation stereoselectivity was being eroded by reversible β-hydride elimination from complex **5-*d*-4**.[8] However, the cyclization/C–H functionalization of di-deuterated substrate **5-*d*$_2$-2a**, which should undergo much slower β-deuterium

elimination from complex **5-*d*$_2$-4** than the rate for β-hydride elimination from complex **5-*d*-4**,[9] proceeded with comparable (1.6:1) diastereoselectivity (Table 5-3, entry 3). This suggests that the selectivity for *anti*- vs. *syn* aminopalladation is modest, and that since the overall conversion of **5-*d*-2a** to **5-*d*-7** (and **5-*d*$_2$-2a** to **5-*d*$_2$-7**) proceeds with net *anti*-addition, the C–N bond forming reductive elimination must occur with retention of configuration. Thus, although these transformations are mechanistically similar to the reactions previously described by Michael, the nature of the nitrogen nucleophile has an impact on the stereochemistry of reductive elimination, and transformations of the more electron-rich amine-derived electrophiles (this work) appear to involve stereoretentive, rather than stereoinvertive (Michael), reductive elimination.

Collectively, the results of the experiments shown in eq 5-1-3, Schemes 5-1, and Tables 5-1-3 suggest the mechanism of this transformation involves initial, and possibly reversible, *anti*-aminopalladation of the alkene to generate intermediate **5-9** (Scheme 5-

Scheme 5-2: Revised Mechanistic Hypothesis



2). Oxidative addition of the amine electrophile to **5-9** provides **5-10**, and then reductive elimination affords the observed product (**5-3a**) with regeneration of the Pd(II) catalyst.

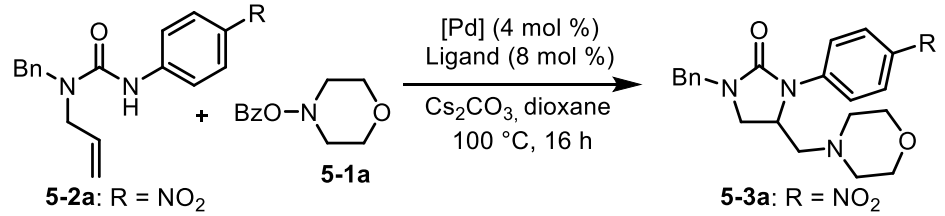
5.4 Influence of Acac Structure on Reactivity

The use of acac as a "standalone" (no added phosphine) ligand in Pd-catalyzed cross-coupling reactions is extremely rare, and the influence of acac ligand structure on reactivity in Pd-catalyzed reactions has not been thoroughly explored. In 2007, Guo reported phosphine-free conditions for Pd-catalyzed Mizoroki-Heck and Suzuki-Miyaura reactions in which they found acac (**5-12b**) and **5-12a** (see Table 5-4) can act as ligands for these transformations.[10] Later work has also found that the Fujiwara-Moritani reaction can also be promoted with acac as the ligand for palladium.[11] In order to determine whether acac analogs may be worth examining, we quickly screened the reactivity of $Pd(acac\text{-}F_6)_2$. Interestingly, this complex bearing an electron-deficient acac derivative gave very poor results (Table 5-4, entry 2, 10% yield of **5-3a**) in comparison to the results obtained with $Pd(acac)_2$ (entry 1, 90% yield). This result indicated the structure of the acac ligand does influence reactivity.

Accordingly, we explored the coupling of more challenging urea substrates **5-2b** and **5-2c** with several different acac-derived ligands. With our original catalyst system of $Pd(acac)_2$/JackiePhos, the coupling of **5-2b** with **5-1a** afforded **5-3b** in 90% crude yield and 45% isolated yield (Table 5-4, entry 3). The low isolated yield is due to difficulties in separating **5-3b** from side products formed in low amounts. By omitting JackiePhos and using a catalyst composed of $Pd(TFA)_2$/acac, we observed 74% crude yield (entry 4). Changing the ligand to **5-11** or **5-12a** (entries 5-6) resulted in significantly reduced yields. However, using acac derivatives **5-12c-e** gave a boost in yield to 83-88% (entries 7-9).

We saw the best crude yield when we employed the electron-rich derivative **5-12f** and obtained the isolated product in 84% yield (entry 10).

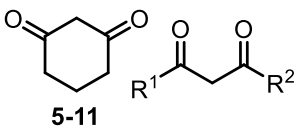
Table 5-4: Effect of Ligand Structure on Product Formation



5-2a: R = NO_2
5-2b: R = Cl
5-2c: R = OMe

5-1a

5-3a: R = NO_2
5-3b: R = Cl
5-3c: R = OMe



5-11

5-12a: R^1 = N(H)Ph, R^2 = CH_3
5-12b: R^1, R^2 = CH_3
5-12c: R^1, R^2 = ^{t}Bu
5-12d: R^1 = Ph, R^2 = Me
5-12e: R^1, R^2 = Ph
5-12f: R^1, R^2 = *p*-MeOPh

entry	R	[Pd]	Ligand	Yield (%)[b]
1	NO_2	$Pd(acac)_2$	none	>95, (69%)[c]
2	NO_2	$Pd(acac\text{-}F_6)_2$	none	11[d]
3	Cl	$Pd(acac)_2$	JackiePhos	90, (45)
4	Cl	$Pd(acac)_2$	none	74
5	Cl	$Pd(TFA)_2$	**5-11**	16[e]
6	Cl	$Pd(TFA)_2$	**5-12a**	24[e]
7	Cl	$Pd(TFA)_2$	**5-12c**	83[e]
8	Cl	$Pd(TFA)_2$	**5-12d**	86
9	Cl	$Pd(TFA)_2$	**5-12e**	88
10	Cl	$Pd(TFA)_2$	**5-12f**[f]	94, (84)
11	OMe	$Pd(acac)_2$	JackiePhos	<5
12	OMe	$Pd(acac)_2$	none	30[e]
13	OMe	$Pd(TFA)_2$	**5-12f**[f]	75[e], (42)[e]

[a]Conditions: 1.0 equiv of **5-2**, 1.5 equiv of **5-1a**, 4 mol % [Pd], 8 mol % ligand, 2.0 equiv of Cs_2CO_3, dioxane (0.1M), 100 °C, 16h. [b]Yields were determined by ^{1}H NMR analysis using phenanthrene as an internal standard. Yields in parentheses are isolated yields. [c]The reaction was conducted for 1 h.[d]The reaction was conducted with 3 equiv of **5-1a**. [e]Experiments conducted by MSF. [f]Ligand prepared by MRG.

We then turned our attention to the more electron-rich urea **5-2c**. We had previously observed <5% of product when using the $Pd(acac)_2$/JackiePhos catalyst system (entry 11). However, by only removing the JackiePhos, we observed 30% of **5-3c** (entry 12).

This is further increased to 75% when using ligand **5-12f** (entry13). However, issues with isolation resulted in only 42% isolated product. We were overall very pleased to learn that JackiePhos inhibits this reaction and the use of electron-rich acac-derived ligands can lead to improved results. We believe ligand **5-12f** allows for a more facile oxidation to Pd(IV) (Scheme 5-2, **5-9** to **5-10**) which leads to an increase in the desired product (**5-3c**) formation.

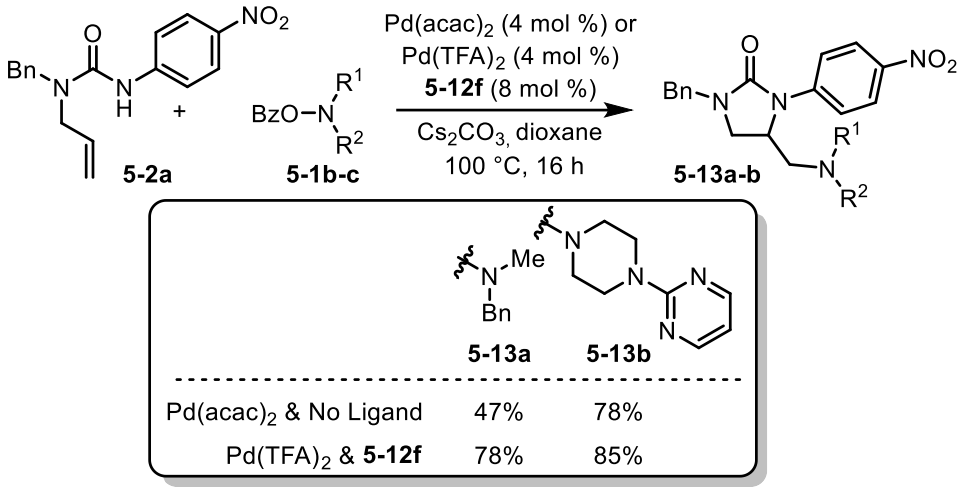
5.5 Further Exploration of the Substrate Scope

We learned through these studies that JackiePhos is not needed for the reaction to proceed and is even inhibitory in some cases. Additionally, we believe a Pd(II)/Pd(IV) mechanistic cycle is occurring for this transformation and that acac is the true ligand for palladium. Using more electron-rich acac-derivatives likely helps promote challenging reactions by potentially assisting with the difficult oxidation to Pd(IV).

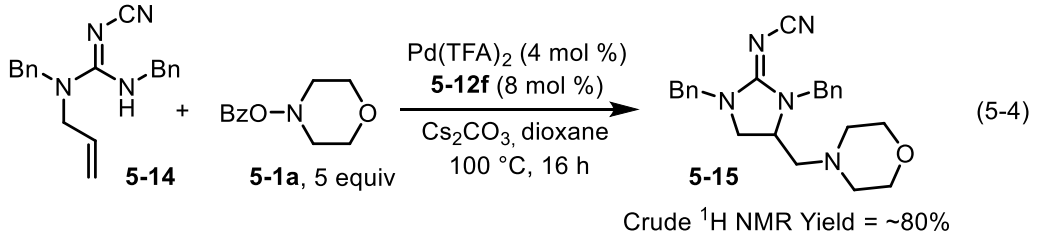
We next applied this information to study other reactions that we have found to be difficult with the previous conditions. Group member Gabriel A. Gonzalez, has been studying electrophiles beyond those reported in our previous publication.[1] When using electrophile **5-1b** with urea **5-2a** and $Pd(acac)_2$, he obtained a 47% isolated yield, but employing ligand **5-12f**, his yield increased to 78% (Scheme 5-3).[12] He observed a similar trend when using **5-1c**; the yield increased from 78 to 85%. We are very pleased that we have been able to increase the scope of this reaction to include acyclic, primary amines,

and amines containing additional functional groups. GAG is continuing to study this transformation and further increase the scope of the electrophile.

Scheme 5-3: Selected Examples of Electrophile Scope[12]

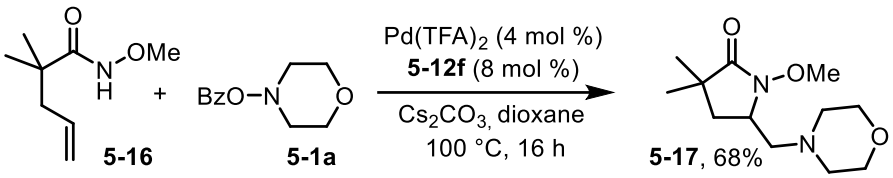


In addition to ureas, we previously studied the diamination transformation with *N*-allylguanidines and obtained the cyclic guanidine product in good yields.[1] We performed the analogous reaction in the absence of JackiePhos however, we only obtained ~80% crude yield when using our best ligand **5-12f** and 5 equiv of **5-1a** (eq 5-4). We are unsure why the yield has decreased in the absence of JackiePhos, although it may be due to different levels of experience working with the highly polar guanidine products. Future studies will be directed toward optimizing phosphine-free conditions with *N*-allylgaunidines.



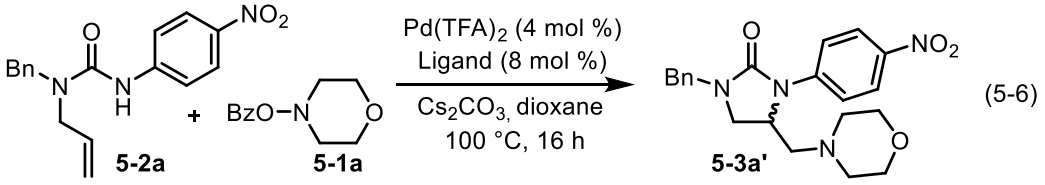
(5-4)

In addition to ureas and guanidines, we were interested in expanding the scope of the reaction to include other substrates. Mason S. Faculak began looking at amides with a tethered allyl group to form lactam products containing α-amino substitution. He found that **5-16** couples with **5-1a** and forms **5-17** in 68% isolated yield (eq 5-5).[13] At this point, the gem-dimethyl substitution is necessary for reactivity; future studies will be devoted to expanding the scope of the substrate and maintaining reactivity with the removal of gem-disubstitution.



(5-5)[13]

Inspired by a report by Michael,[4b] we were interested in applying chiral ligands to our system to induce enantioselectivity. Two ligands were screened for these preliminary results (eq 5-6). 2,6-Bis[(4S)-4-phenyl-2-oxazolinyl]pyridine[14] gave back starting material in addition to side products and other unidentified materials. (*R*)-Ph-Quinox was more promising, yielding about 30% by crude ^{1}H NMR, but other side products and decomposition of starting material was also observed. We attempted to isolate the product to measure the er by chiral HPLC, but the HPLC data was inconclusive.

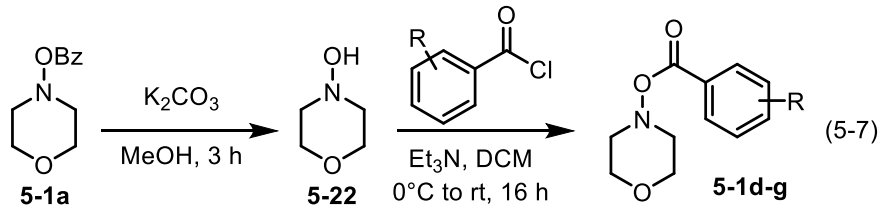


(5-6)

Ligand	Result
2,6-Bis[(4*S*)-4-phenyl-2-oxazolinyl]pyridine	= 0% **5-3a'**
(*R*)-Ph-Quinox	= 30% **5-3a'**, er not determined

5.6 Further Unpublished Work

Previous studies in the Wolfe lab have shown that the reaction conditions such as solvent, electrophile, and counterion of the base, can have significant impact on the ratio of products resulting from *syn*- or *anti*-aminopalladation pathways (Chapter 1, Scheme 1-3-4.[15] Conditions that stabilize a catanionic Pd promote the *anti*-aminopalladation pathway. When we discovered that competing *syn*-aminopalladation was resulting in moderate diastereoselectivities for our diamination reactions, (Chapter 4, Section 4.4) we looked to change our reaction conditions to help promote the *anti*-pathway. The previous study showed that less coordinating counterions, such as triflate, resulted in a more catanionic Pd. We were interested in varying the substitution on the phenyl ring of our benzoyl group to test whether substitution with electron withdrawing groups would result in a higher diastereomeric ratio. The synthesis of these substituted electrophiles required the synthesis of **5-1a**, then hydrolysis to form the hydroxylamine and then the desired products were formed via acyl transfer with the appropriate acid chloride (eq 5-7).

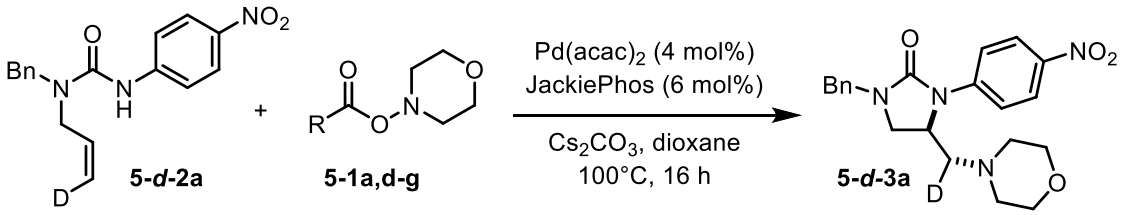


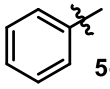
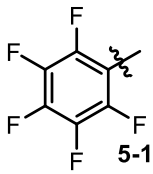
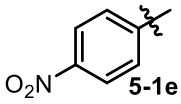
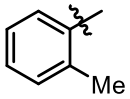
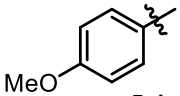
(5-7)

With the various substituted electrophiles **5-1d-g**, we subjected each to the reaction conditions including JackiePhos with **5-*d*-2a** (Table 5-5). At the time we conducted these reactions, we had not yet discovered that JackiePhos was not needed for the reaction to proceed. With the JackiePhos conditions, each of the substituted electrophiles showed yields lower than the original **5-1a** (entry 1), and the observed dr of each reaction was moderate (3:1-7:1) with the slightly higher drs observed with the electrophiles containing

electron donating groups (entry 4-5). It was noted that the more electron-poor electrophiles such as **5-1d**, decomposed rapidly after synthesis and purification. It is possible that the more electron-deficient electrophiles are more prone to hydrolysis therefore lowering the concentration in the reaction leading to lower observed yields and dr.

Table 5-5: Effect of Changing Phenyl Substitution of the Electrophile

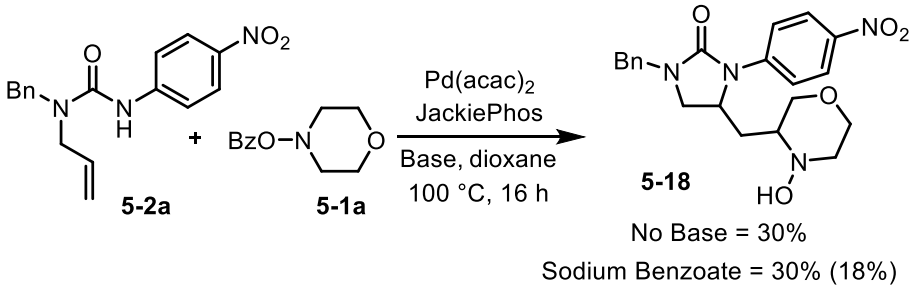


Entry	R	Yield	dr
1	 **5-1a**	74%	6.7:1
2	 **5-1d**	46%	4:1
3	 **5-1e**	31%	3:1
4	 **5-1f**	34%	7:1
5	 **5-1g**	56%	7:1

[a]Conditions: 1 equiv of **5-*d*-2a**, 3 equiv of **5-1**, 4 mol % $Pd(acac)_2$, 6 mol % JackiePhos, 2 equiv of Cs_2CO_3, dioxane (0.1M), 100 °C, 16 h. Isolated yields.

Another question we were interested in studying was if the benzoate anion that is formed upon oxidative addition of the electrophile was facilitating the deprotonation of the

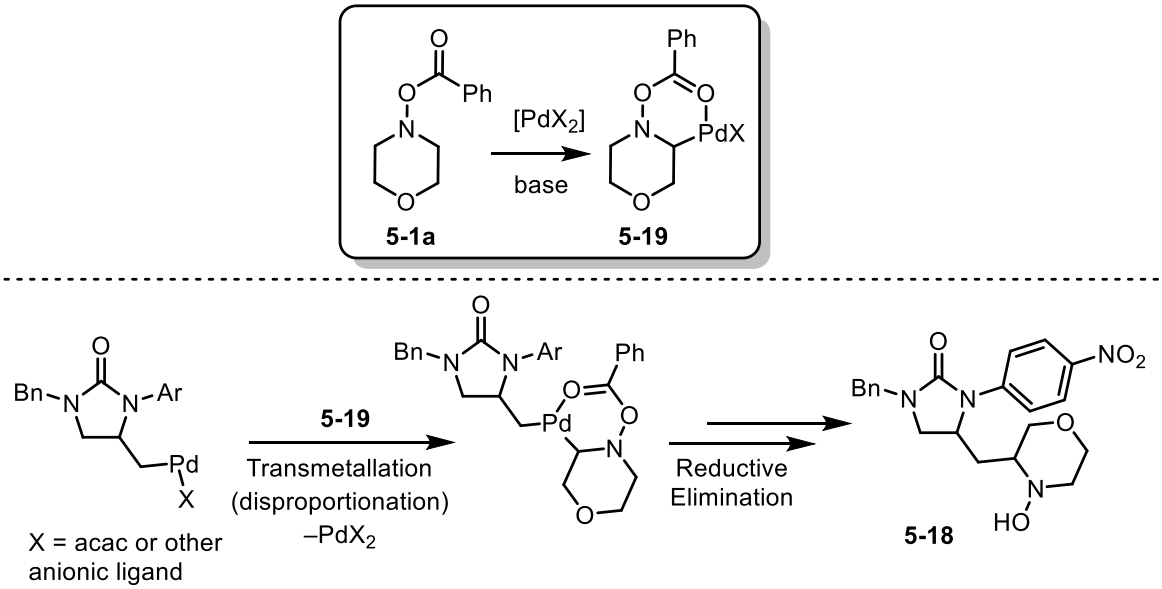
urea in the diamination reaction. We ran the reaction without Cs_2CO_3 and replacing Cs_2CO_3 with sodium benzoate (eq 5-8). In both cases we obtained about 30% of an



(5-8)

unexpected product. After extensive 2-D NMR studies and HRMS data, we have assigned this product to be **5-18**. We believe this product is forming via C-H activation that is directed by the carbonyl of the benzoyl group of **5-1a** to form **5-19**. **5-19** can undergo transmetallation with **5-9** and after reductive elimination form **5-18**. The benzoyl group is hydrolyzed at some point following the transformation (Scheme 5-4). The formation of **5-18** will be studied further in the future.

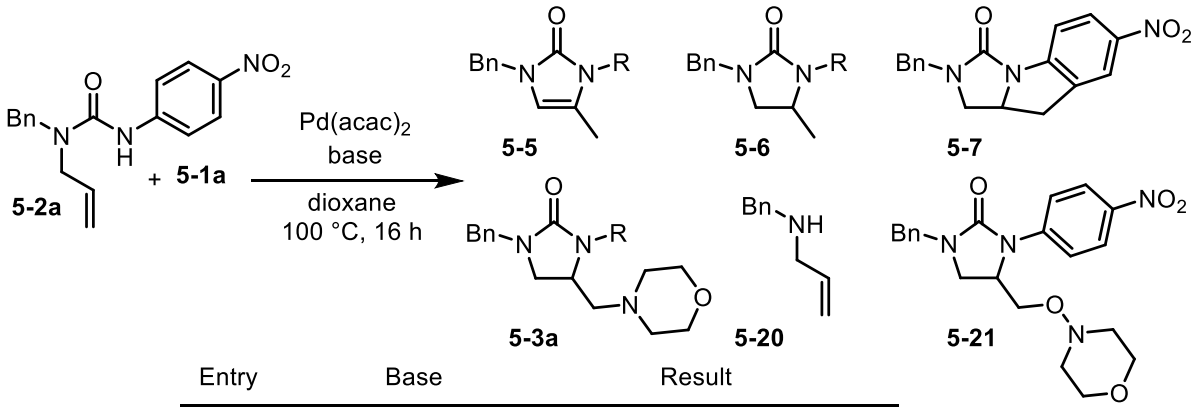
Scheme 5-4: Proposed Mechanism for the Formation of **5-18**



Around the time we had finished the studies shown in Table 5-5, eq 5-8, and Scheme 5-4, we discovered that JackiePhos was not the true ligand for palladium and we found evidence pointing to a Pd(II)/Pd(IV) catalytic cycle. In this new system, we still observed

only moderate dr when employing a single stereoisomer of our urea substrate (Table 5-2). We were interested in changing the base and counterion of the base to determine if these changes influenced the ratio of *anti* to *syn* addition products. We began our tests first with **5-2a**, to see if these bases were able to produce the desired product **5-3a**. We were surprised to find that the product was only obtained when Cs_2CO_3 and LiO^tBu were used (Table 5-6, entries 1-2). With each of the *tert*-butoxide bases and Li_2CO_3 varying amount of various side products were formed (entries 2-5). The formation of products **5-5-7** is discussed previously in this chapter in section **5.3**. **5-20** is formed from base-mediated decomposition of the urea. We were very intrigued by the formation of **5-21**

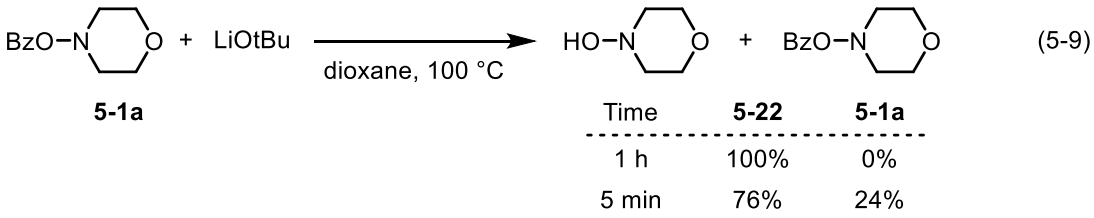
Table 5-6: Effect of Base on Product Distribution



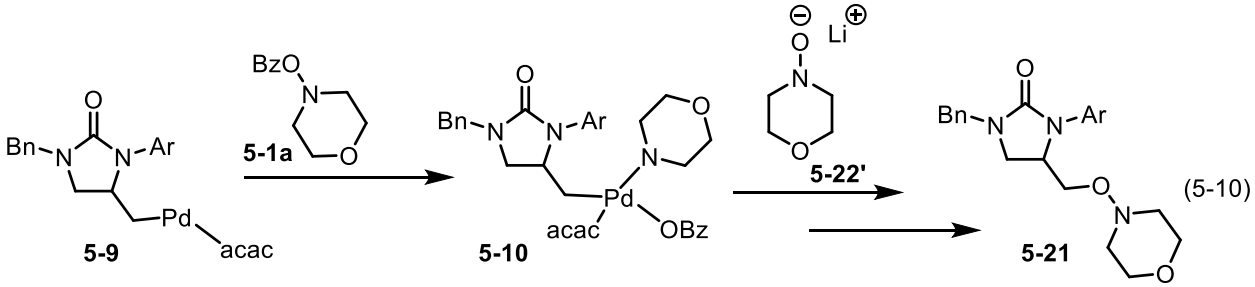
Entry	Base	Result			
1	Cs_2CO_3	**5-5** <5%	**5-6** <5%	**5-3a** 90%	
2	LiO^tBu	**5-5** <5%	**5-6** 16%	**5-3a** 35%	**5-21** 30%
3	NaO^tBu	**5-5** 5%	**5-6** 15%	**5-7** 15%	**5-20** 5%
4	KO^tBu	**5-6** 20%	**5-7** 20%	**5-20** 25%	
5	Li_2CO_3	**5-5** 18%	**5-6** 10%	**5-20** <5%	**5-2a** 15%

[a]Conditions: 1 equiv **5-2a**, 1.5 equiv **5-1a**, 4 mol % $Pd(acac)_2$, 2 equiv base, dioxane (0.1M), 100 °C, 16 h. Yields were determined by ^{1}H NMR analysis using phenanthrene as an internal standard.

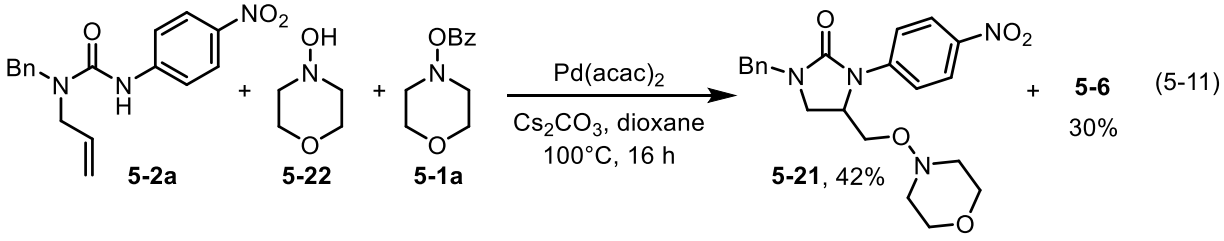
where a C-N and C-O bond had formed. We hypothesized that this product could be formed if the electrophile is becoming deacylated under the reaction conditions. When we mix **5-1a** with LiO^{t}Bu in dioxane for 1 hour, we observe complete deacylation to form **5-22** (eq 5-9).



Even after 5 minutes, the deacylation is 75% complete. From these observations, we propose that side product **5-21** is formed from substitution of the morpholino group in **5-10** with **5-22'** (or **5-22**), which is formed in the reaction mixture, followed by reductive elimination to form the C-O bond (**5-21**, eq 5-10). To test this hypothesis further, we

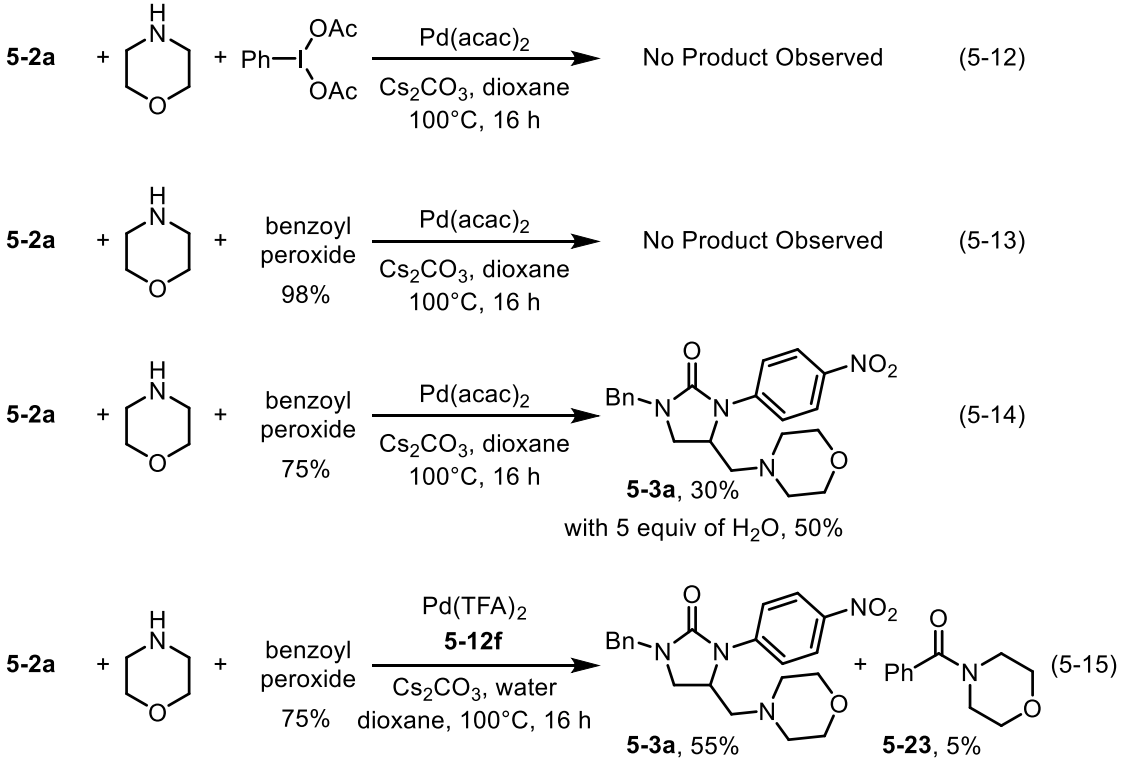


synthesized hydroxylamine **5-22** and subjected it to the optimized reaction conditions in a 1:1 ratio with **5-1a** (eq 5-11). In this preliminary reaction, we were pleased to obtain 42% of **5-21** by crude ^{1}H NMR. We plan to further optimize this transformation with hydroxylamine derivatives in addition to other nucleophiles in the future.



With further evidence that the electrophile **5-1a** may act as a sacrificial oxidant when a second nucleophile is present, we were interested to study whether this reaction would proceed if we replaced **5-1a** with an oxidant and morpholine. We believe that these reaction conditions may either allow for the *in situ* formation of **5-1a** or the oxidant might oxidize Pd(II) to Pd(IV) and morpholine would undergo reductive elimination with the alkyl-Pd intermediate to form the desired product. Either way, this would eliminate the need to synthesize and purify **5-1a**, which requires the use of DMF in the reaction and column chromatography purification.

We began our studies with (diacetoxyiodo)benzene as the oxidant. However, we did not observe the formation of **5-2a** either with or without a pre-stir with the oxidant and morpholine (eq 5-12) We then used benzoyl peroxide (98% peroxide, 2% water) in the reaction and again did not observe the desired product (eq 5-13). We were very surprised to find 30% product by crude ^{1}H NMR when we employed 75% benzoyl peroxide (25%



water) (eq 5-14). When we added an additional 5 equiv of water, we saw the crude yield increase to 50%. It is very apparent that water is important in this reaction, but the reason why is still unclear to us. However, this effect has also been described by Yamamoto and Banerjee, who recently reported a new procedure for the synthesis of O-benzoylhydroxylamines.[16] We looked at other oxidants such as H_2O_2 in water and mCPBA; H_2O_2 resulted in the formation of aminopalladation side products while the use of mCPBA result in an explosion of the reaction contents prior to heating. To further increase the yield of the reaction we used our $Pd(TFA)_2$/**5-12f** catalyst system and incorporated a pre-stir of the peroxide, morpholine, base, water, and dioxane for 30 min at rt prior to the addition of the Pd, ligand, and urea and heating. This resulted in 55% crude NMR yield however, a small amount of side product, that we believe to be **5-23**, resulted in difficulties in clean isolation (eq 5-15). Heating the contents of the pre-stir decreased the amount of desired product formed. Further studies need to be conducted to further optimize this reaction. However, we believe this has protocol will be very useful in the future because it will eliminate the need to synthesize and purify every electrophile that someone is interested in testing in their system. Additionally, we could potentially expand this protocol to include other exogenous nucleophiles beyond amines.

5.7 Conclusion

Through careful analysis of control reactions and characterization of isolated side products, we have determined that earlier hypotheses related to our Pd-catalyzed alkene diamination reaction were incorrect. We found evidence to support a Pd(II)/Pd(IV) catalytic cycle in which *anti*-aminopalladation occurs prior to oxidation of the metal by *O*-acylated hydroxylamines. Additionally, we discovered that acac, not JackiePhos, is the

true ligand for palladium in this transformation. These important discoveries led us to further optimize the acac ligand structure to facilitate challenging reactions, including those that had previously been unsuccessful. We are also using this as an opportunity to ask new questions and explore these new avenues. As such, this research will continue to be pursued in the Wolfe lab.

Portions of the work described in this chapter are in preparation for publication.

5.8 Experimental

General: All reactions were carried out under a nitrogen atmosphere using oven or flame-dried glassware. All palladium sources and reagents including **5-11** and **5-12a-e** were obtained from commercial sources and used without further purification unless otherwise noted. *N*-Allylurea and guanidines **5-2a-c**[1], 5-***d***-**2a**[1], **5-*d*$_2$-2a**[1], **5-14**[17], and **5-16**,[18] ligand **5-12f**,[1920] and electrophiles **5-1b**[21]**-c**[21,22] were prepared according to previously reported procedures. Dioxane was purified by distillation from Na metal and benzophenone. calcium hydride under a nitrogen atmosphere. All yields refer to isolated compounds that are estimated to be ≥95% pure as judged by ^{1}H NMR analysis unless otherwise noted. *The yields reported in the experimental section describe the result of a single experiment, whereas yields reported in Schemes 5-2 & 5-4 and equations 2-10–11 are average yields of two or more experiments. Thus, the yields reported in the experimental section may differ from those shown in Schemes 2-2 & 2-4 and equations 2-10–11.*

Procedures for eq 5-1-3

For eq 5-1: JackiePhos was added to an NMR tube and a ^{31}P NMR was taken. We observed two peaks, leading us to believe that the bottle contained both JackiePhos and JackiePhos-oxide. ^{31}P NMR (dioxane) δ 18.687, -19.401 ppm.

Triphenylphosphine oxide was added to an NMR tube and a ^{31}P NMR was taken. ^{31}P NMR (dioxane) δ 20.950.

JackiePhos and Triphenylphosphine oxide were added to an NMR tube and a ^{31}P NMR was taken. ^{31}P NMR (dioxane) δ 20.950, 18.546, -19.609

In an NMR tube, JackiePhos (104.5 mg, 0.13 mmol, 4 equiv), $Pd(acac)_2$ (10 mg, 0.033 mmol, 1 equiv), triphenylphosphine oxide (as a NMR reference std), and dioxane (2 mL) were shaken and a ^{31}P NMR was taken. ^{31}P NMR (dioxane) δ 20.950, 18.696, -19.429.

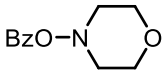
For eq 5-2: In an NMR tube, JakiePhosPdG3 (20 mg, 0.017 mmol, 1 equiv) and 1 mL of C_6D_6 were added and ^{31}P NMR and ^{1}H NMR were taken. NaO^{t}Bu (3 mg, 0.031 mmol, 1.8 equiv) was added and the NMR tube shaken and then ^{31}P NMR and ^{1}H NMR were taken. **5-1a** (3.6 mg, 0.017 mmol, 1 equiv) was added and the NMR tube shaken and then ^{31}P NMR and ^{1}H NMR were taken. The NMR tube was placed in an oil bath heated to 70 °C for 30 min and then ^{31}P NMR and ^{1}H NMR were taken. Evidence for oxidative addition was not observed.

For eq 5-3: $Pd(acac)_2$ (20 mg, 0.066 mmol, 1 equiv), **5-1a** (13.7 mg, 0.066 mmol, 1 equiv), and 1 mL of d8-toluene were added to an NMR tube. A ^{1}H NMR was taken of the mixture at rt, after 15 minutes of heating at 95 °C, and after an additional 30 minutes of heating

at 95 °C. Evidence of oxidative addition was not observed. A similar reaction was repeated by JPW and evidence of oxidative addition was not observed.

$Pd(acac)_2$ (5 mg, 0.0164 mmol, 1 equiv), JackiePhos (26.1 mg, 0.0328 mmol, 2 equiv), **5-1a** (3.4 mg, 0.0164 mmol, 1 equiv), triphenylphosphine oxide (as a NMR reference std) and 1 mL of dioxane were added to an NMR tube. A ^{31}P NMR was taken of the mixture at rt, and after 15 minutes of heating at 95 °C. Evidence of oxidative addition was not observed.

Synthesis and Characterization of Substrates and Ligands

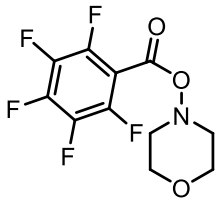


Morpholino benzoate (5-1a). Morpholine (1mL, 11.5 mmol, 1 equiv) was added to a stirring mixture of K_2HPO_4 (4.01 g, 23 mmol, 2 equiv), benzoyl peroxide (3.25 g, 13.4 mmol, 1.2 equiv) and DMF (58 mL, 0.2M). The reaction was stirred under Nitrogen atmosphere for 18 h. 50 mL of satd. $Na_2S_2O_3$ (aq) was added to the reaction and stirred for 20 minutes. 75 mL of EtOAc was added and the layers were separated. The aqueous layer was extracted with EtOAc 3x 75 mL. The combined organic layers were washed with water 3x 100 mL, 1M NaOH 1x 100 mL, and brine 1x 100 mL. The organic layer was dried with anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude mixture was purified by flash chromatography on silica gel (20% EtOAc in hexanes) to afford 1.38 g (58%) of the title compound as a white solid. The characterization data matched previously reported literature.[1,23]

General procedure for the Synthesis of 5-1d-g. (eq 5-7).

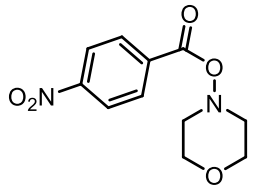
5-1a (1.18g, 5.7 mmol, 1 equiv), K_2CO_3 (1.58 g, 11.4 mmol, 2 equiv), and methanol (11.4 mL, 0.5M) were added to a flame-dried rbf. The solution was stirred under N_2 for 3 h after which the methanol was removed *in vacuo*. 15 mL of EtOAc and 15 mL of water were added to the resulting solid and the layers were separated. The aqueous layer was extracted with EtOAc 3x 20 mL. The combined organic layers were dried with anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude mixture containing **5-22** was carried over to the next step. An alternative synthesis of **5-22** is described below.

5-22, DCM (17 mL, 0.33M), and triethylamine (0.79 mL, 5.7 mmol, 1 equiv) were added to a rbf and cooled to 0°C with an ice-water bath. The appropriate acid chloride (5.7 mmol, 1 equiv) was added dropwise to the reaction mixture. The ice-water bath was removed, and the mixture stirred at rt for 16 h. 10 mL of water was added to the reaction and the layers were separated. The aqueous layer was extracted with DCM 3x 20 mL. The combined organic layers were dried with anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude mixture was purified by flash chromatography on silica gel.

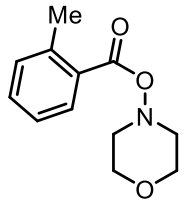


morpholino 2,3,4,5,6-pentafluorobenzoate (5-1d). The title compound was synthesized following the general procedure. The crude product was purified by flash chromatography on silica gel (20% EtOAc in hexanes) to afford 0.7084 g (42%) of the title compound as an orange oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.10 – 3.93 (m, 2H), 3.91 – 3.73

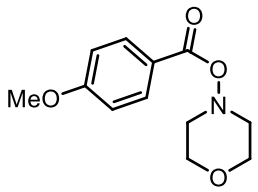
(m, 2H), 3.56 – 3.33 (m, 2H), 3.18 – 2.83 (m, 2H). IR (film) 2866, 1754, 1652, 1524, 1495 cm^{-1}; HRMS (ESI^+) 298.0499 (298.0497 calcd for $C_{11}H_9F_5NO_3$, M + H^+).



Morpholino 4-nitrobenzoate (5-1e). The title compound was synthesized following the general procedure. The crude product was purified by flash chromatography on silica gel (20% EtOAc in hexanes) to afford 0.3814 g (27%) of the title compound as an oil. ^1H NMR (500 MHz, $CDCl_3$) δ 8.30 (d, *J* = 8.6 Hz, 2H), 8.18 (d, *J* = 8.6 Hz, 2H), 4.11 – 3.93 (m, 2H), 3.92 – 3.81 (m, 2H), 3.57 – 3.41 (m, 2H), 3.13 – 3.00 (m, 2H).



Morpholino 2-methylbenzoate (5-1f). The title compound was synthesized following the general procedure except NaH (2 equiv) was used as the base instead of triethylamine and it allowed to stir with **5-24** and DCM for 10 min at rt prior to being cooled to 0°C and the addition of the acid chloride. The crude product was purified by flash chromatography on silica gel (1% methanol in DCM) to afford 0.2781 g (35%) of the title compound as an oil. ^1H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, *J* = 7.8 Hz, 1H), 7.41 (t, *J* = 7.7 Hz, 1H), 7.31 – 7.16 (m, 3H), 4.06 – 3.77 (m, 4H), 3.55 – 3.40 (m, 2H), 3.17 – 2.94 (m, 2H), 2.59 (s, 3H).

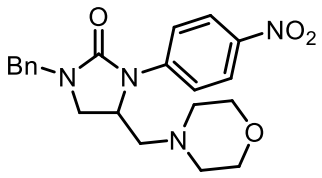


Morpholino 4-methoxybenzoate (5-1g). The title compound was synthesized following the general procedure except NaH (2 equiv) was used as the base instead of triethylamine and it allowed to stir with **5-24** and DCM for 10 min at rt prior to being cooled to 0°C and the addition of the acid chloride. The crude product was purified by flash chromatography on silica gel (1% methanol in DCM) to afford 0.1820 g (2j1%) of the title compound as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.9 Hz, 2H), 6.90 (d, *J* = 8.9 Hz, 2H), 3.99 – 3.90 (m, 2H), 3.89–3.80 (m, 2H), 3.84 (s, 3H),z 3.46 – 3.37 (m, 2H), 3.13 – 2.90 (m, 2H).

Preparation and Characterization of Products

General Procedure for Pd-Catalyzed Alkene Difunctionalization Reactions: Tables 5-1-6, Schemes 5-1, 5-3, and eq 5-4-6, 5-8, 5-11, 5-12-15

A flame-dried Schlenck tube equipped with a stirbar was cooled under a stream of N_2 and charged with the appropriate palladium source (4 mol %), the appropriate ligand (8-16 mol %), the appropriate urea, guanidine, or amide substrate (0.2 mmol, 1 equiv), the appropriate electrophile (0.3-0.6 mmol, 1.5-3.0 equiv) and cesium carbonate (0.4 mmol, 2 equiv). After purging the Schlenck tube with N_2, dioxane (2 mL, 0.1 M) was added and the reaction was headed to 100 ^{o}C for 16 h. The crude reaction mixture was filter through cotton with diethyl ether and concentrated *in* vacuo. The crude product was then purified by flash chromatography on silica gel.



1-Benzyl-4-(morpholinomethyl)-3-(4-nitrophenyl)imidazolidin-2-one (5-3a). For Table 5-4: The general procedure was used for the coupling of **5-2a** (62.3 mg, 0.2 mmol, 1 equiv) with morpholino benzoate (**5-1a**) (62.2 mg, 0.3 mmol, 1.5 equiv) using a catalyst composed of $Pd(acac)_2$ (2.4 mg, 0.008 mmol, 4 mol %) except the reaction was run for 1 h. The crude product was purified by flash chromatography on silica gel (10% 3:1 (ethyl acetate:ethanol) in hexanes) to afford 56.5 mg (71%) of the title compound as a yellow oil. The characterization data matched previously reported data.[1] The material was judged to have a 50:50 er by chiral HPLC analysis (ChiralCel ODH, 25 cm x 4.6 mm, 90% hexane + 0.1 % DEA 10% IPA, 1.5 mL/min, λ 333 nm, R_T = 20.657 min and 28.275 min)

For eq 5-12: The general procedure was used for the coupling of **5-2a** (62.3 mg, 0.2 mmol, 1 equiv) except with morpholine (26 µL, 0.3 mmol, 1.5 equiv) and (diacetoxyiodo)benzene (96.6 mg, 0.3 mmol, 1.5 equiv) using a catalyst composed of $Pd(acac)_2$ (2.4 mg, 0.008 mmol, 4 mol %). The crude reaction mixture was filter through cotton with diethyl ether and concentrated *in* vacuo. No desired product was observed.

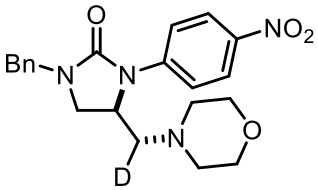
For eq 5-13: The general procedure was used for the coupling of **5-2a** (62.3 mg, 0.2 mmol, 1 equiv) except with morpholine (52 µL, 0.6 mmol, 3 equiv), and benzoyl peroxide (98%) (145.3 mg, 0.6 mmol, 3 equiv) using a catalyst composed of $Pd(acac)_2$ (2.4 mg, 0.008 mmol, 4 mol %) and 4 equiv of Cs_2CO_3 (260.6 mg, 0.8 mmol) was used instead of 2 equiv. At the completion of the reaction, aq NH_4Cl (satd.) (2 mL) and EtOAc (2 mL) was added to the reaction. The layers were separated, and the aqueous layer was extracted with

EtOAc 3x 2 mL. The combined organic layers were washed with brine 1x 5 mL and dried with anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. No desired product was observed.

For eq 5-14: The general procedure was used for the coupling of **5-2a** (31.1 mg, 0.1 mmol, 1 equiv) except with morpholine (26 µL, 0.3 mmol, 3 equiv), and benzoyl peroxide (75%) (72.7 mg, 0.3 mmol, 3 equiv) using a catalyst composed of $Pd(acac)_2$ (1.2 mg, 0.004 mmol, 4 mol %). 4 equiv of Cs_2CO_3 (130.3 mg, 0.4 mmol) was used instead of 2 equiv and the reaction was conducted at 0.1 mmol and 1 mL of dioxane was used. If appropriate water (9 µL, 0.5 mmol, 5 equiv) was added to the reaction. At the completion of the reaction, aq $NaHCO_3$ (satd.) (2 mL) and EtOAc (2 mL) was added to the reaction. The layers were separated, and the aqueous layer was extracted with EtOAc 3x 2 mL. The combined organic layers were washed with brine 1x 5 mL and dried with anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The desired product observed by ^1H NMR was not purified.

For eq 5-15: A flame-dried Schlenck tube equipped with a stirbar was cooled under a stream of N_2 and charged with benzoyl peroxide (75%) (145.3mg, 0.6 mmol, 3 equiv), Cs_2CO_3 (260.6 mg, 0.8 mmol, 4 equiv), morpholine (52 µL, 0.6 mmol, 3 equiv), water (18 µL, 1 mmol, 5 equiv), and 0.7 mL of dioxane. The solution was stirred at rt for 30 min after which **5-2a** (62.3 mg, 0.2 mmol, 1 equiv), $Pd(TFA)_2$ (2.7 mg, 0.008, 4 mol %), and **5-12f** (4.5 mg, 0.016 mmol, 8 mol %) were added as a solution in 0.3 mL of dioxane (0.2M total in reaction). The urea is difficult to dissolve at rt in dioxane so the addition was difficult. The reaction was headed to 100 ^oC for 16 h. The crude reaction mixture was filter through cotton with diethyl ether and concentrated *in* vacuo. The crude product was then purified

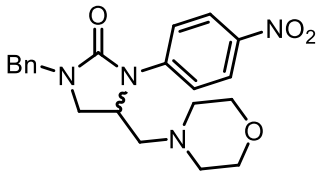
by flash chromatography on silica gel. At the completion of the reaction, aq $NaHCO_3$ (satd.) (2 mL) and EtOAc (2 mL) was added to the reaction. The layers were separated, and the aqueous layer was extracted with EtOAc 3x 2 mL. The combined organic layers were washed with brine 1x 5 mL and dried with anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (10% 3:1 (ethyl acetate:ethanol) in hexanes) to afford a mixture of **5-3a** and potentially **5-23**. The reaction mixture was not purified further.



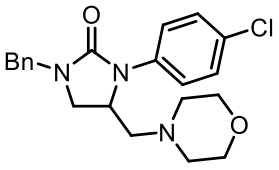
(4S*, 4'R*)-1-Benzyl-4-(morpholinomethyl-d)-3-(4-nitrophenyl)imidazolidin-2-one (5-*d*-3a). From Table 5-2: The general procedure was used for the coupling of **5-*d*-2a** (62.3 mg, 0.2 mmol, 1 equiv) with morpholino benzoate (**5-1a**) (62.2 mg, 0.3 mmol, 1.5 equiv or 124.3 mg, 0.6 mmol, 3 equiv) using a catalyst composed of $Pd(acac)_2$ (2.4 mg, 0.008 mmol, 4 mol %) and either no ligand or JackiePhos (12.7 mg, 0.016 mmol, 8 mol %) The crude product was purified by flash chromatography on silica gel (10% 3:1 (ethyl acetate:ethanol) in hexanes) to afford 58.6 mg (6:1 dr, 74%, entry 2), 62.8 mg (2.2:1 dr, 79%, entry 3), 60.3 mg (2.8:1 dr, 76%, entry 4), and 59.0 mg (6.7:1, 74%, ref 6) of the title compound as a yellow foam. This characterization data matched previously reported data.[1]

From Table 5-5: The general procedure was used for the coupling of **5-*d*-2a** (31.2 mg, 0.1 mmol, 1 equiv) with appropriate morpholino benzoate (**5-1a,** or **d-g**) (0.3 mmol, 3 equiv) using a catalyst composed of $Pd(acac)_2$ (1.2 mg, 0.004 mmol, 4 mol %) and

JackiePhos (4.8 mg, 0.006 mmol, 6 mol %) except it was conducted on a 0.1 mmol scale with 1 mL of dioxane. The crude product was purified by flash chromatography on silica gel (10% 3:1 (ethyl acetate:ethanol) in hexanes) to afford 18.3 mg (4:1 dr, 46%, entry 2), 12.4 mg (3:1 dr, 31%, entry 3), 13.4 mg (7:1 dr, 34%, entry 4), and 22.2 mg (7:1 dr, 56%, entry 5) of the title compound as a yellow foam. This characterization data matched previously reported data.[1]

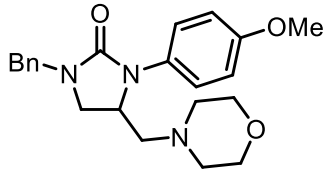


1-Benzyl-4-(morpholinomethyl)-3-(4-nitrophenyl)imidazolidin-2-one (5-3a'). The general procedure was used for the coupling of **5-2a** (31.1 mg, 0.1 mmol, 1 equiv) with morpholino benzoate (**5-1a**) (31.1 mg, 0.15 mmol, 1.5 equiv) using a catalyst composed of $Pd(TFA)_2$ (1.3 mg, 0.004 mmol, 4 mol %) and 1,3-bis(4-methoxyphenyl)propane-1,3-dione (**5-12f**) (4.5 mg, 0.016 mmol, 8 mol %) except the reaction was run at 0.1 mmol scale with 1 mL of dioxane. The crude product was purified by flash chromatography on silica gel (10% 3:1 (ethyl acetate:ethanol) in hexanes) to afford <5 mg of the title compound as a yellow oil.[1] We attempted to measure the er by chiral HPLC using the conditions listed for **5-3a**, but the data was inconclusive.

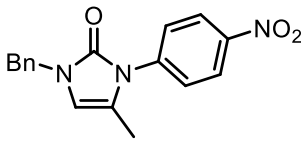


1-Benzyl-3-(4-chlorophenyl)-4-(morpholinomethyl)imidazolidin-2-one (5-3b). The general procedure was used for the coupling of **5-2b** (60.2 mg, 0.2 mmol, 1 equiv) with

morpholino benzoate (**5-1a**) (62.2 mg, 0.3 mmol, 1.5 equiv) using a catalyst composed of $Pd(TFA)_2$ (2.7 mg, 0.008 mmol, 4 mol %) and 1,3-bis(4-methoxyphenyl)propane-1,3-dione (**5-12f**) (4.5 mg, 0.016 mmol, 8 mol %). The crude product was purified by flash chromatography on silica gel (10% 3:1 (ethyl acetate:ethanol) in hexanes) to afford 65.4 mg (85%) of the title compound as a yellow oil. This characterization data matched previously reported data.[1]

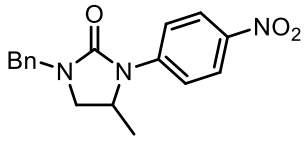


1-Benzyl-3-(4-methoxyphenyl)-4-(morpholinomethyl)imidazolidin-2-one (5-3c). The general procedure was used for the coupling of **5-2c** (59.3 mg, 0.2 mmol, 1 equiv) with morpholino benzoate (**5-1a**) (124.4 mg, 0.6 mmol, 3 equiv) using a catalyst composed of $Pd(TFA)_2$ (2.7 mg, 0.008 mmol, 4 mol %) and 1,3-bis(4-methoxyphenyl)propane-1,3-dione (**5-12f**) (4.5 mg, 0.016 mmol, 8 mol %). The crude product was purified by flash chromatography on silica gel (10% 3:1 (ethyl acetate:ethanol) in hexanes) to afford 34.5 mg (45%) of the title compound as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.27 (m, 7H), 6.93 – 6.83 (m, 2H), 4.56 – 4.36 (m, 2H), 4.23 (bs, 1H), 3.80 (s, 3H), 3.60 (bs, 4H), 3.45 (bs, 1H), 3.26 (bs, 1H), 2.54 (bs, 1H), 2.47 – 2.25 (m, 5H).^{13}C NMR (126 MHz, $CDCl_3$) at 50°C δ 158.5, 156.7, 137.4, 132.4, 128.8, 128.5, 127.7, 123.6, 114.6, 67.0, 60.5, 55.7, 54.4, 52.4, 48.4, 47.2. IR (film) 2915, 2852, 1693, 1512 cm^{-1}; HRMS (ESI$^+$) 382.2123 (382.2125 calcd for $C_{22}H_{28}N_3O_3$, M + H$^+$).



1-Benzyl-4-methyl-3-(4-nitrophenyl)-1,3-dihydro-2H-imidazol-2-one (5-5). The general procedure was used except **5-1a** was not included in the reaction. Instead **5-2a** (15.6 mg, 0.05 mmol, 1 equiv), $Pd(acac)_2$ (15.2 mg, 0.05 mmol, 1 equiv), Cs_2CO_3 (32.6 mg, 0.1 mmol, 2 equiv), and dioxane (0.5 mL, 0.1M) were heated to 100 °C for 16 h. The crude product was not isolated.

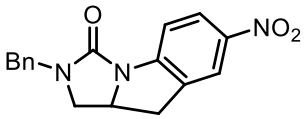
The general procedure was used except **5-1a** was not included in the reaction. Instead **5-2a** (31.1 mg, 0.1 mmol, 1 equiv), $Pd(acac)_2$ (30.5 mg, 0.1 mmol, 1 equiv), and NaO^tBu (19.2 mg, 0.2 mmol, 2 equiv), and dioxane (1 mL, 0.1M) were heated to 100 °C for 16 h. The crude product was purified by flash chromatography on silica gel (20% ethyl acetate in hexanes) and then further purified by prep TLC (40% EtOAc in hexanes) to afford 5.1 mg (17%) of the title compound as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.33 (d, J = 8.9 Hz, 2H), 7.56 (d, J = 8.9 Hz, 2H), 7.41 – 7.29 (m, 5H), 6.05 (s, 1H), 4.81 (s, 2H), 2.01 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.6, 146.3, 141.1, 136.7, 129.0, 128.3, 128.2, 127.2, 124.7, 118.2, 109.1, 47.3, 11.8. IR (film) 3116, 2926, 1690, 1641, 1594 cm^{-1}; HRMS (ESI^+) 310.1185 (310.1186 calcd for $C_{17}H_{16}N_3O_3$, M + H^+).



1-benzyl-4-methyl-3-(4-nitrophenyl)imidazolidin-2-one (5-6). The general procedure was used except **5-1a** was not included in the reaction. Instead **5-2a** (15.6 mg, 0.05 mmol, 1 equiv), $Pd(acac)_2$ (15.2 mg, 0.05 mmol, 1 equiv), Cs_2CO_3 (32.6 mg, 0.1 mmol, 2 equiv),

and dioxane (0.5 mL, 0.1M) were heated to 100 °C for 16 h. The crude product was not isolated.

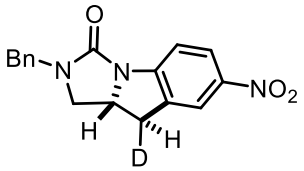
The general procedure was used except **5-1a** was not included in the reaction. Instead **5-2a** (31.1 mg, 0.1 mmol, 1 equiv), $Pd(acac)_2$ (30.5 mg, 0.1 mmol, 1 equiv), and NaO^tBu (19.2 mg, 0.2 mmol, 2 equiv), and dioxane (1 mL, 0.1M) were heated to 100 °C for 16 h. The crude product was purified by flash chromatography on silica gel (20% ethyl acetate in hexanes) to afford 4.9 mg (16%) of the title compound as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22 (d, *J* = 9.4 Hz, 2H), 7.73 (d, *J* = 9.3 Hz, 2H), 7.41 – 7.28 (m, 5H), 4.60 – 4.44 (m, 2H), 4.44 – 4.31 (m, 1H), 3.57 (app. t, *J* = 8.8 Hz, 1H), 3.00 (dd, *J* = 8.9, 3.8 Hz, 1H), 1.35 (d, *J* = 6.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.5, 145.2, 142.2 136.3, 129.0, 128.4, 128.0, 125.1, 118.0, 48.9, 48.1, 29.9, 19.2. IR (film) 2917, 2849, 1710, 1596 cm^{-1}; HRMS (ESI^+) 312.1342 (312.1343 calcd for $C_{17}H_{18}N_3O_3$, M + H^+).



2-Benzyl-7-nitro-1,2,9,9a-tetrahydro-3H-imidazo[1,5-a]indol-3-one (5-7). The general procedure was used except **5-1a** was not included in the reaction. Instead **5-2a** (15.6 mg, 0.05 mmol, 1 equiv), $Pd(acac)_2$ (15.2 mg, 0.05 mmol, 1 equiv), Cs_2CO_3 (32.6 mg, 0.1 mmol, 2 equiv), and dioxane (0.5 mL, 0.1M) were heated to 100 °C for 16 h. The crude product was not isolated.

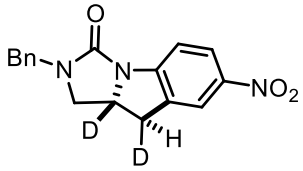
The general procedure was used except **5-1a** was not included in the reaction. Instead **5-2a** (31.1 mg, 0.1 mmol, 1 equiv), $Pd(acac)_2$ (30.5 mg, 0.1 mmol, 1 equiv), and NaO^tBu (19.2 mg, 0.2 mmol, 2 equiv), and dioxane (1 mL, 0.1M) were heated to 100 °C for 16 h. The crude product was purified by flash chromatography on silica gel (20% ethyl acetate

in hexanes) and then further purified by prep TLC (40% EtOAc in hexanes) to afford < 5 mg (~16%) of the title compound as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.7 Hz, 1H), 8.05 (s, 1H), 7.57 (d, *J* = 8.7 Hz, 1H), 7.40 – 7.27 (m, 5H), 4.71 (p, *J* = 9.1 Hz, 1H), 4.59 (d, *J* = 14.9 Hz, 1H), 4.32 (d, *J* = 15.0 Hz, 1H), 3.73 (t, *J* = 9.1 Hz, 1H), 3.38 (dd, *J* = 16.2, 9.4 Hz, 1H), 3.27 (t, *J* = 8.7 Hz, 1H), 3.01 (dd, *J* = 16.2, 9.2 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.3, 148.7, 144.0, 136.1, 133.2, 129.0, 128.4, 128.1, 125.3, 121.1, 114.4, 56.4, 51.2, 48.1, 36.0. IR (film) 2922, 1712, 1596 cm^{-1}; HRMS (ESI^+) 310.1195 (310.1186 calcd for $C_{17}H_{16}N_3O_3$, M + H^+).

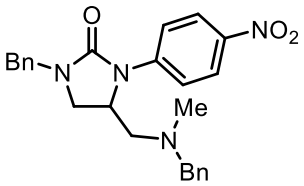


(9R*,9aR*)-2-benzyl-7-nitro-1,2,9,9a-tetrahydro-3H-imidazo[1,5-a]indol-3-one-9-d (5-*d*-7). From Table 5-3: The general procedure was used except **5-1a** was not included in the reaction. Instead **5-*d*-2a** (31.2 mg, 0.1 mmol, 1 equiv), $Pd(acac)_2$ (30.4 mg, 0.1 mmol, 1 equiv), JackiePhos , if appropriate, (159.3 mg, 0.2 mmol, 2 equiv), Cs_2CO_3 (65.2 mg, 0.2 mmol, 2 equiv), and dioxane (0.1 mL, 0.1M) were heated to 100 °C for 16 h. The crude product was via prep TLC (40% EtOAc in hexanes) to afford the title compound as a yellow oil 11.6 mg (entry 1, 1.7:1 dr, 37%) and 6.3 mg (entry 2, 1.5:1 dr, 20%) ^{1}H NMR for entry 1: (500 MHz, $CDCl_3$) δ 8.18 (dd, *J* = 8.7, 2.3 Hz, 1H), 8.08 – 7.99 (m, 1H), 7.57 (d, *J* = 8.7 Hz, 1H), 7.40 – 7.25 (m, 5H), 4.70 (q, *J* = 8.7 Hz, 1H), 4.59 (d, *J* = 14.9 Hz, 1H), 4.32 (d, *J* = 14.9 Hz, 1H), 3.73 (t, *J* = 9.1 Hz, 1H), 3.36 (d, *J* = 9.5 Hz, 0.40H), 3.27 (t, *J* = 9.3, 8.0 Hz, 1H), 2.99 (d, *J* = 9.2 Hz, 0.65H). ^{1}H NMR for entry 2: (500 MHz, $CDCl_3$) δ 8.18 (dd, *J* = 8.6, 2.3 Hz, 1H), 8.10 – 8.01 (m, 1H), 7.57 (d, *J* = 8.7 Hz, 1H), 7.40 – 7.25

(m, 5H), 4.71 (q, *J* = 8.7 Hz, 1H), 4.59 (d, *J* = 14.9 Hz, 1H), 4.32 (d, *J* = 14.9 Hz, 1H), 3.73 (t, *J* = 9.1 Hz, 1H), 3.36 (d, *J* = 9.4 Hz, 0.43H), 3.27 (t, *J* = 8.6 Hz, 1H), 2.99 (d, *J* = 9.3 Hz, 0.64H).

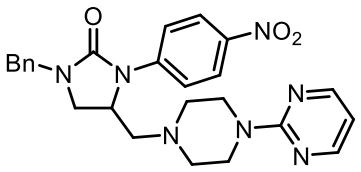


(9R*,9aR*)-2-benzyl-7-nitro-1,2,9,9a-tetrahydro-3H-imidazo[1,5-a]indol-3-one-9,9a-d2 (5-*d*$_2$-7). From Table 5-3: The general procedure was used except **5-1a** was not included in the reaction. Instead **5-*d*$_2$-2a** (15.9 mg, 0.05 mmol, 1 equiv), $Pd(acac)_2$ (15.3 mg, 0.05 mmol, 1 equiv), Cs_2CO_3 (32.6 mg, 0.1 mmol, 2 equiv), and dioxane (0.05 mL, 0.1M) were heated to 100 °C for 16 h. The crude product (1.6:1 dr, 38% crude ^{1}H NMR yield). was purified via a pipet column (2% methanol in DCM) followed by prep TLC (40% EtOAc in hexanes). The isolated yield was not written down in the lab notebook and due to Covid-19, the author was unable to determine the mass of the sample. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.4 Hz, 1H), 8.05 (s, 1H), 7.57 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.39 – 7.27 (m, 5H), 4.63 – 4.52 (m, 1H), 4.35 – 4.29 (m, 1H), 3.72 (d, *J* = 9.2 Hz, 1H), 3.36 (s, 0.45H), 3.26 (d, *J* = 9.3 Hz, 1H), 2.99 (s, 0.70H).



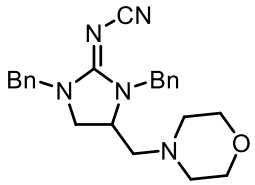
1-Benzyl-4-((benzyl(methyl)amino)methyl)-3-(4-nitrophenyl)imidazolidin-2-one (5-13a).[12] The general procedure was used for the coupling of **5-2a** (62.3 mg, 0.2 mmol, 1 equiv) with morpholino benzoate (**5-1b**) (97.0 mg, 0.4 mmol, 2 equiv) using a catalyst

composed of $Pd(TFA)_2$ (2.7 mg, 0.008 mmol, 4 mol %) and 1,3-bis(4-methoxyphenyl)propane-1,3-dione (**5-12f**) (4.5 mg, 0.016 mmol, 8 mol %) except the crude reaction mixture was filtered through Celite. The crude product was purified by flash chromatography on silica gel (30% 3:1 (ethyl acetate:ethanol) in hexanes) to afford 70.3 mg (82%) of the title compound as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (d, *J* = 9.3 Hz, 2H), 7.64 (d, *J* = 9.3 Hz, 2H), 7.38 – 7.25 (m, 8H), 7.21 (d, *J* = 6.6 Hz, 2H), 4.41 (q, *J* = 10.8 Hz, 2H), 4.21 (m, 1H), 3.52 (d, *J* = 12.9 Hz, 1H), 3.47 – 3.39 (m, 2H), 3.30 (dd, *J* = 9.1, 2.5 Hz, 1H), 2.60 (d, *J* = 2.7 Hz, 1H), 2.48 – 2.41 (m, 1H), 2.29 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.5, 145.5, 141.9, 138.5, 136.3, 129.2, 128.9, 128.6, 128.4, 128.0, 127.7, 125.1, 117.3, 63.5, 57.6, 52.0, 47.9, 45.8, 44.0. IR (film) 2921, 2850, 1712, 1595, 1503 cm^{-1}; HRMS (ESI^+) 431.2063 (431.2085 calcd for $C_{25}H_{27}N_4O_3$, M + H^+).

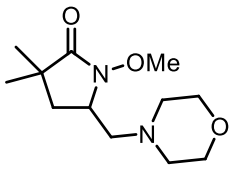


1-Benzyl-3-(4-nitrophenyl)-4-((4-(pyrimidin-2-yl)piperazin-1-yl)methyl)imidazolidin-2-one (5-13b).[12] The general procedure was used for the coupling of **5-2a** (62.3 mg, 0.2 mmol, 1 equiv) with morpholino benzoate (**5-1c**) (13.7 mg, 0.4 mmol, 2 equiv) using a catalyst composed of $Pd(TFA)_2$ (2.7 mg, 0.008 mmol, 4 mol %) and 1,3-bis(4-methoxyphenyl)propane-1,3-dione (**5-12f**) (4.5 mg, 0.016 mmol, 8 mol %) except the crude reaction mixture was filtered through Celite. The crude product was purified by flash chromatography on silica gel (30% 3:1 (ethyl acetate:ethanol) in hexanes) to afford 85.9 mg (91%) of the title compound as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (d, 2H), 8.21 (d, *J* = 9.3 Hz, 2H), 7.76 (d, *J* = 9.2 Hz, 2H), 7.40 – 7.29 (m, 5H), 6.49 (dd, *J* = 6.6,

2.9 Hz, 1H), 4.51 (q, *J* = 14.9 Hz, 2H), 4.40 (m, *J* = 8.6 Hz, 1H), 3.75 (m, 4H), 3.53 (t, *J* = 8.8 Hz, 1H), 3.41 (d, *J* = 9.2 Hz, 1H), 2.64 (d, *J* = 13.0 Hz, 1H), 2.59 – 2.53 (m, *J* = 10.0, 4.6 Hz, 2H), 2.49 – 2.35 (m, 3H). IR (film) 2925, 2851, 1709, 1585, 1548, 1501 cm^{-1}; HRMS (ESI^+) 474.2251 (474.2255 calcd for $C_{25}H_{28}N_7O_3$, M + H^+).

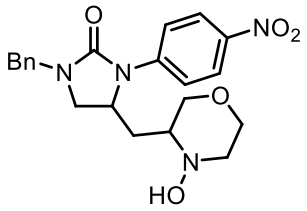


***N*-(1,3-Dibenzyl-4-(morpholinomethyl)imidazolidin-2-ylidene)cyanamide (5-15).** The general procedure was used for the coupling of **5-14** (30.4 mg, 0.1 mmol, 1 equiv) with morpholino benzoate (**5-1a**) (103.6 mg, 0.5 mmol, 5 equiv) using a catalyst composed of $Pd(TFA)_2$ (1.3 mg, 0.004 mmol, 4 mol %) and 1,3-bis(4-methoxyphenyl)propane-1,3-dione (**5-12f**) (2.3 mg, 0.008 mmol, 8 mol %) except the reaction was conducted on a 0.1 mmol scale with 1 mL of dioxane. The crude product was not purified and ~80% of the title compound was observed by ^1H NMR matching characterization data previously reported data.[1]



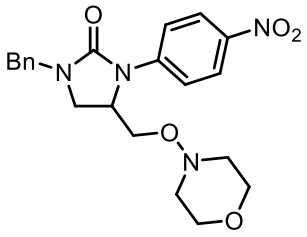
1-Methoxy-3,3-dimethyl-5-(morpholinomethyl)pyrrolidin-2-one (5-17).[13] The general procedure was used for the coupling of **5-15** (31.4 mg, 0.2 mmol, 1 equiv) with morpholino benzoate (**5-1a**) (124.4 mg, 0.6 mmol, 3 equiv) and a catalyst composed of $Pd(TFA)_2$ (2.7 mg, 0.008 mmol, 4 mol %) used ligand 1,3-bis(4-methoxyphenyl)propane-1,3-dione (**5-12f**) (4.5 mg, 0.016 mmol, 8 mol %). The crude product was purified by flash

chromatography on silica gel (20% 3:1 (ethyl acetate:ethanol) in hexanes) to afford 33.4 mg (69%) of the title compound as a pale-yellow oil. ^{1}H NMR (500 MHz, C_6D_6) δ 3.59 (s, 3H), 3.56 – 3.51 (m, 4H), 3.41 (m, 1H), 2.42 (dd, *J* = 12.5, 4.4 Hz, 1H), 2.21 – 2.07 (m, 4H), 2.03 (dd, *J* = 12.6, 7.3 Hz, 1H), 1.56 (dd, *J* = 12.7, 7.2 Hz, 1H), 1.31 (dd, *J* = 12.7, 7.9 Hz, 1H), 1.13 (s, 3H), 0.97 (s, 3H).^{13}C NMR (126 MHz, $CDCl_3$) δ 176.3, 66.7, 62.6, 61.5, 54.4, 52.7, 38.1, 37.5, 25.9, 25.2. IR (film) 2961, 2930, 2853, 2812, 1706 cm^{-1}; HRMS (ESI$^+$) 243.1707 (243.1703 calcd for $C_{12}H_{23}N_2O_3$, M + H$^+$).



1-Benzyl-4-((4-hydroxymorpholin-2-yl)methyl)-3-(4-nitrophenyl)imidazolidin-2-one (5-18). The general procedure was used for the coupling of **5-2a** (31.1 mg, 0.1 mmol, 1 equiv) with morpholino benzoate (**5-1a**) (62.2 mg, 0.3 mmol, 3 equiv) using a catalyst composed of $Pd(acac)_2$ (1.2 mg, 0.004 mmol, 4 mol %) and JackiePhos (4.8 mg, 0.006 mmol, 6 mol %) except the reaction was conducted with sodium benzoate (28.8 mg, 0.2 mmol, 2 equiv) as the base and was run on a 0.1 mmol scale with 1 mL of dioxane. The crude product was purified by flash chromatography on silica gel (1% methanol in DCM) followed by prep-TLC (5% methanol in DCM) to afford 7.2 mg (18%) of the title compound as a yellow oil. The reaction with no base followed the same procedure as above except no base was used. ^{1}H NMR (500 MHz, C_6D_6) δ 8.61 (s, 1H), 8.03 (d, *J* = 9.1 Hz, 2H), 7.61 (d, *J* = 8.7 Hz, 2H), 7.24 (d, *J* = 7.5 Hz, 2H), 7.18 – 7.16 (m, 2H), 7.10 (t, *J* = 7.4 Hz, 1H), 4.66 (d, *J* = 15.4 Hz, 1H), 4.28 (d, *J* = 15.4 Hz, 1H), 3.70 (br. s, 1H), 3.47 – 3.40 (m, 1H), 3.19 (dd, *J* = 12.0, 4.4 Hz, 1H), 3.16 – 3.09 (m, 2H), 2.95 – 2.86 (m, 1H), 2.83 (ddd, *J* =

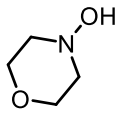
9.4, 7.3, 4.7 Hz, 1H), 2.77 (ddd, *J* = 13.2, 8.1, 3.6 Hz, 1H), 2.52 – 2.43 (m, 2H), 1.28 – 1.21 (m, 1H), 1.00 – 0.86 (m, 1H). ^{13}C NMR (126 MHz, C_6D_6) δ 156.0, 146.9, 142.5, 138.5, 128.9, 128.4 128.0, 125.3, 117.9, 75.0, 65.3, 62.6, 58.3, 50.9, 50.8, 49.6, 32.7. IR (film) 3312, 3086, 2920, 2858, 2247, 1672, 1597, 1550 cm^{-1}; HRMS (ESI^+) 413.1825 (413.1819 calcd for $C_{21}H_{25}N_4O_5$, M + H^+).



1-Benzyl-4-((morpholinooxy)methyl)-3-(4-nitrophenyl)imidazolidin-2-one (5-21). For Table 5-6: The general procedure was used for the coupling of **5-2a** (62.3 mg, 0.2 mmol, 1 equiv) with morpholino benzoate (**5-1a**) (62.2 mg, 0.3 mmol, 1.5 equiv) using a catalyst composed of $Pd(acac)_2$ (2.4 mg, 0.008 mmol, 4 mol %) except the reaction was run with LiO^tBu (32.0 mg, 0.4 mmol, 2 equiv) as the base. The crude product was purified by flash chromatography on silica gel (1% methanol in DCM) to afford 5.3 mg (6%) of the title compound as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22 (d, *J* = 9.3 Hz, 2H), 7.83 (d, *J* = 9.3 Hz, 2H), 7.42 – 7.28 (m, 5H), 4.57 (d, *J* = 14.9 Hz, 1H), 4.53 – 4.45 (m, 1H), 4.42 (d, *J* = 14.9 Hz, 1H), 3.95 – 3.82 (m, 3H), 3.67 (dd, *J* = 11.2, 7.6 Hz, 1H), 3.57 – 3.46 (m, 3H), 3.36 (dd, *J* = 9.2, 2.8 Hz, 1H), 3.06 – 2.96 (m, 2H), 2.59 (dtd, *J* = 18.6, 10.8, 3.4 Hz, 2H). ^{1}H NMR (500 MHz, C_6D_6) δ 8.03 (d, *J* = 9.3 Hz, 2H), 7.69 (d, *J* = 9.3 Hz, 2H), 7.16 – 7.03 (m, 5H), 4.29 (d, *J* = 14.8 Hz, 1H), 4.17 (d, *J* = 14.9 Hz, 1H), 3.67 – 3.59 (m, 1H), 3.53 (d, *J* = 11.7 Hz, 2H), 3.39 (dd, *J* = 11.3, 2.8 Hz, 1H), 3.26 – 3.12 (m, 3H), 2.83 (dd, *J* = 8.8, 2.7 Hz, 1H), 2.71 (t, *J* = 8.8 Hz, 1H), 2.58 – 2.46 (m, 2H), 2.36 (dtd, *J* = 21.3,

10.7, 3.3 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.6, 145.3, 142.2, 136.2, 129.0, 128.4, 128.1, 125.1, 117.6, 69.6, 66.3, 66.2, 56.8, 56.0, 51.6, 48.0, 45.3.^{13}C NMR (126 MHz, C_6D_6) δ 156.2, 145.4, 142.4, 137.0, 129.0, 128.6, 128.4, 125.0, 117.2, 69.3, 66.2, 66.0, 57.0, 56.1, 51.2, 47.9, 44.8. IR (film) 2924, 2854, 1711, 1595 cm^{-1}; HRMS (ESI^+) 413.1823 (413.1819 calcd for $C_{21}H_{25}N_4O_5$, M + H^+).

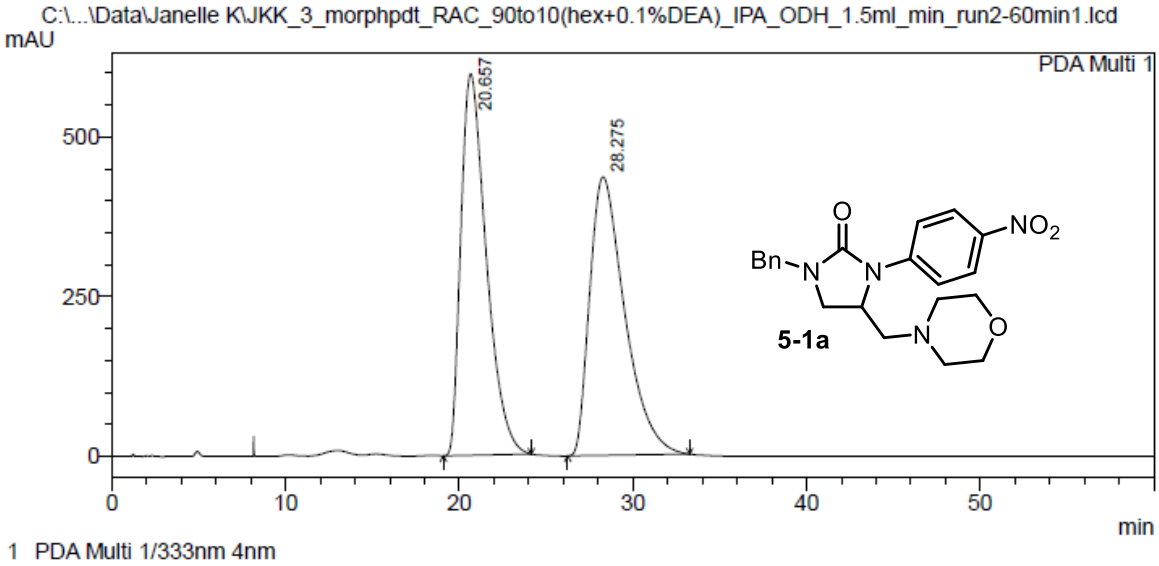
1-Benzyl-4-((morpholinooxy)methyl)-3-(4-nitrophenyl)imidazolidin-2-one (5-21). For eq 5-11: The general procedure was used for the coupling of **5-2a** (62.3 mg, 0.2 mmol, 1 equiv) with except with morpholino benzoate (**5-1a**) (78.7 mg, 0.38 mmol, 1.9 equiv) and **5-22** (38.8 mg, 0.38 mmol, 1.9 equiv) using a catalyst composed of $Pd(acac)_2$ (2.4 mg, 0.008 mmol, 4 mol %). The crude product was not purified.



Morpholin-4-ol (5-22). For eq 5-9: **5-1a** (31.1 mg, 0.15 mmol, 1 equiv), Li*O*^{t}Bu (16.0 mg, 0.2 mmol, 1.3 equiv) and dioxane (1 mL, 0.15 M) were stirred at 100 °C for 1 h. Water (1 mL) and EtOAc (1 mL) were added to the flask and the layers separated. The aqueous layer was extracted with EtOAc 3x 1 mL. The combined organic layers were dried with anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. 100% of the title compound was observed by ^{1}H NMR, but an isolated yield was not obtained. The following characterization data is from synthesizing **5-22** for eq 5-11. ^{1}H NMR (500 MHz, C_6D_6) δ 3.91 (d, *J* = 12.6, 2.2 Hz, 2H), 3.59 (t, *J* = 11.6, 2.2 Hz, 2H), 3.19 – 3.09 (m, 2H), 2.86 – 2.69 (m, 2H).

5.9 Unpublished Spectra

HPLC spectra for **5-1a**



1 PDA Multi 1/333nm 4nm

PeakTable

PDA Ch1 333nm 4nm

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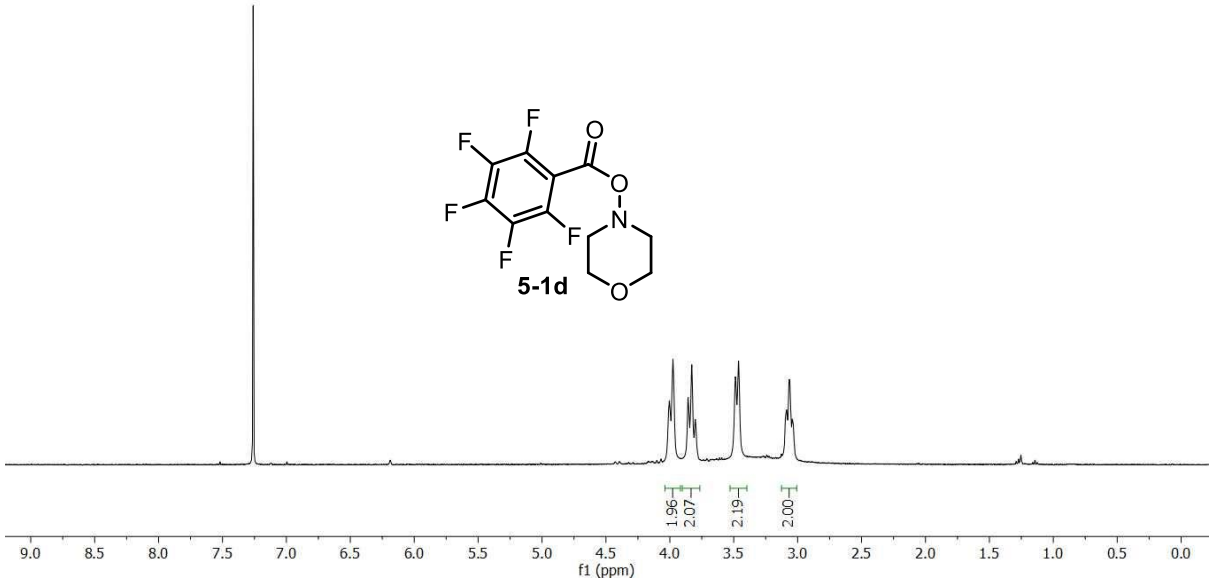

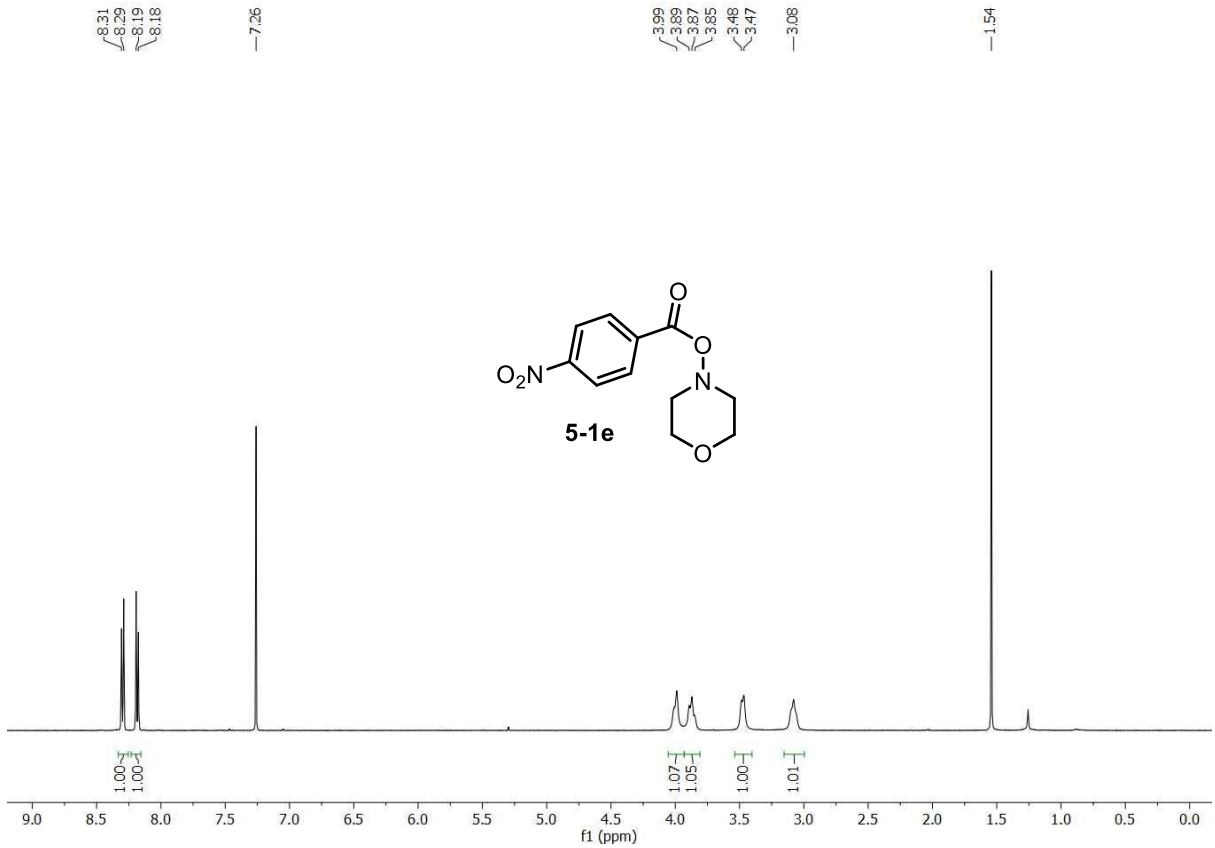
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8.18
7.26
3.99
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3.48
3.47
3.08
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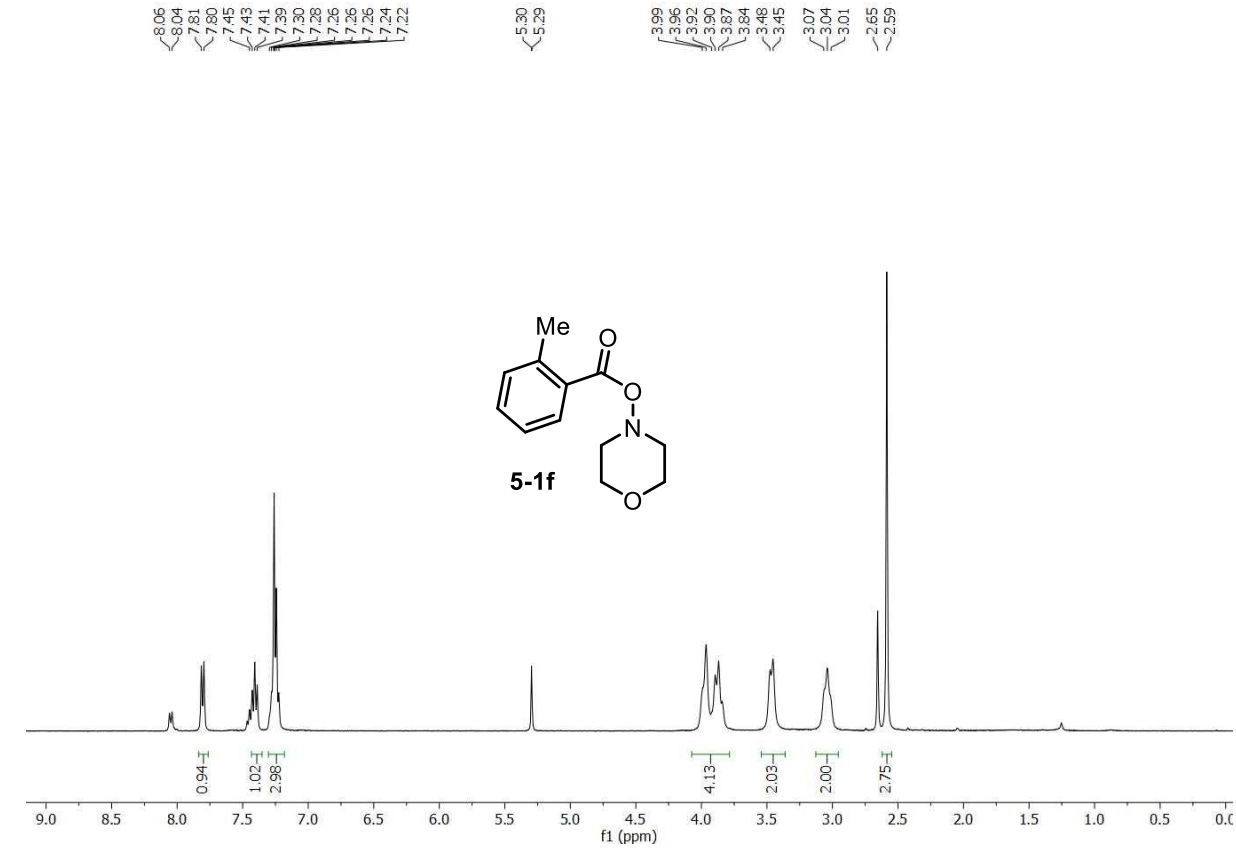
1.07
1.05
1.00
1.01
f1 (ppm)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7.24
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3.96
3.92
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3.84
3.48
3.45
3.07
3.04
3.01
2.65
2.59
Me
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O
N
O
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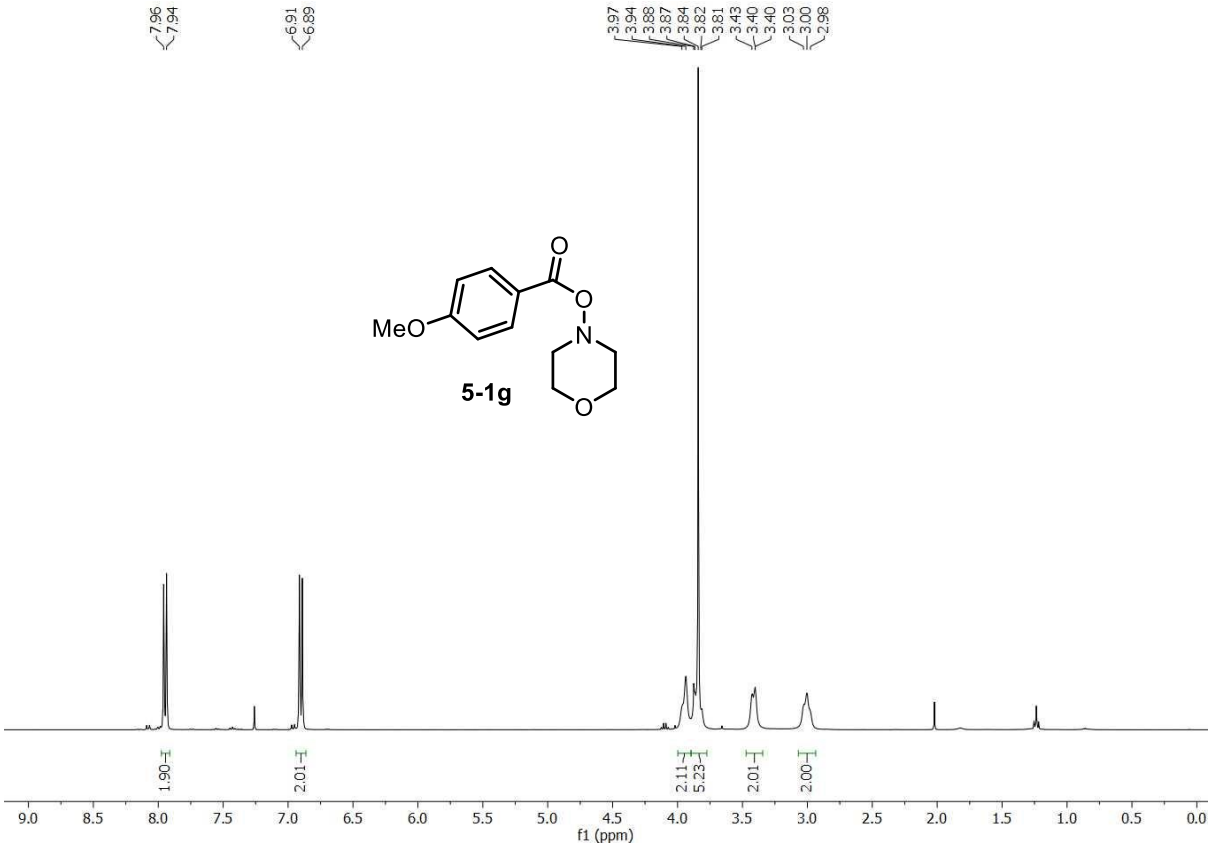
4.13
2.03
2.00
2.75
f1 (ppm)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3.40
3.03
3.00
2.98
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O
N
O
5-1g
1.90
2.01
2.11
5.23
2.01
2.00
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6.5
6.0
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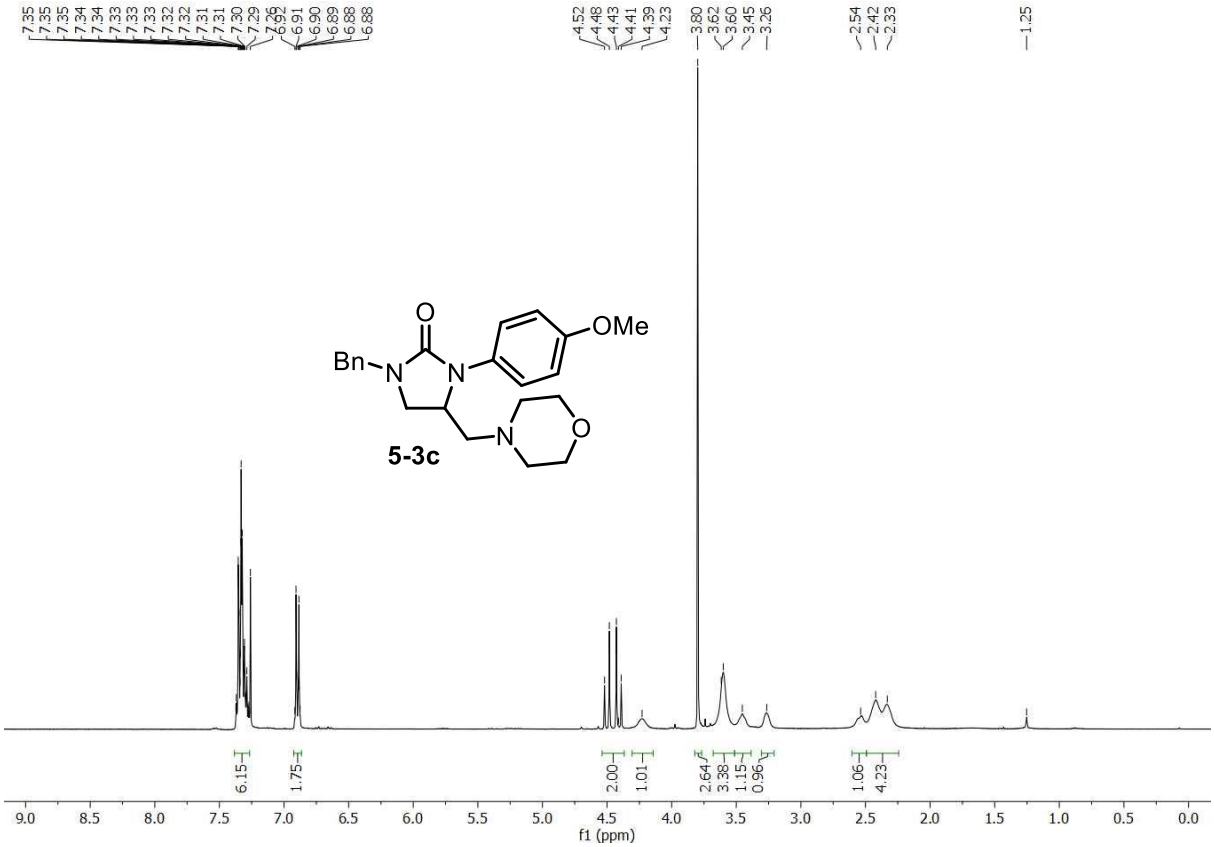
f1 (ppm)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3.62
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OMe
Bn
N
N
N
O
5-3c
6.15
1.75
2.00
1.01
2.64
3.38
1.15
0.96
1.06
4.23
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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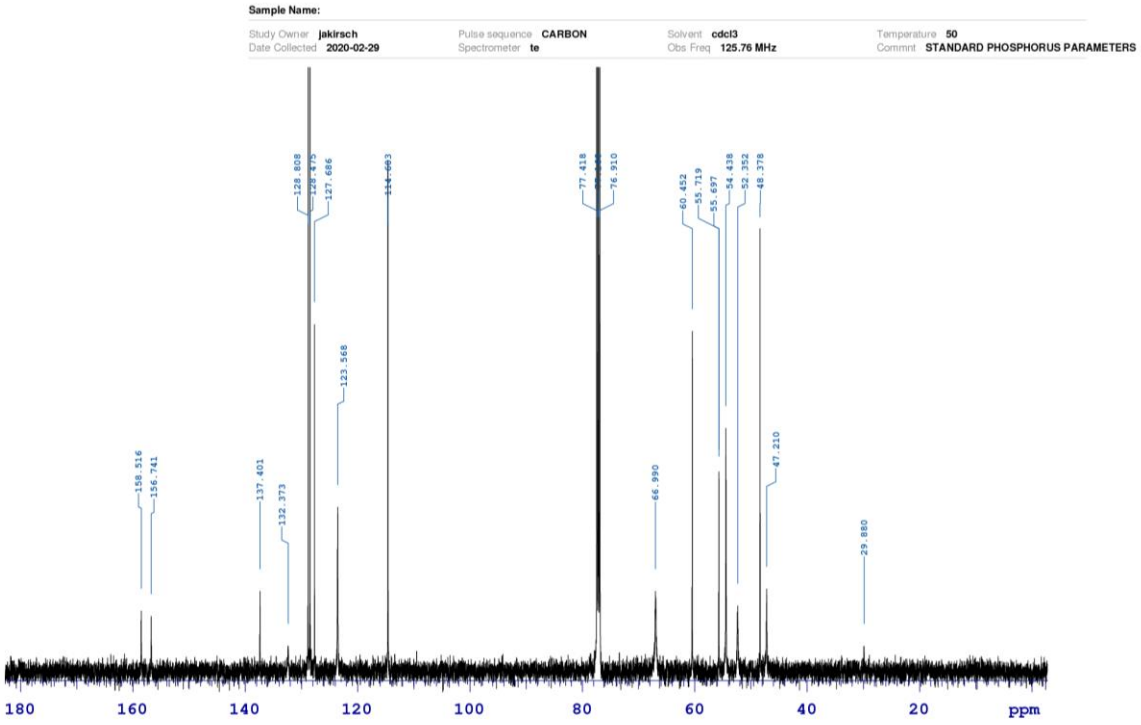
f1 (ppm)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Date Collected 2020-02-29
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Spectrometer te
Solvent cdcl3
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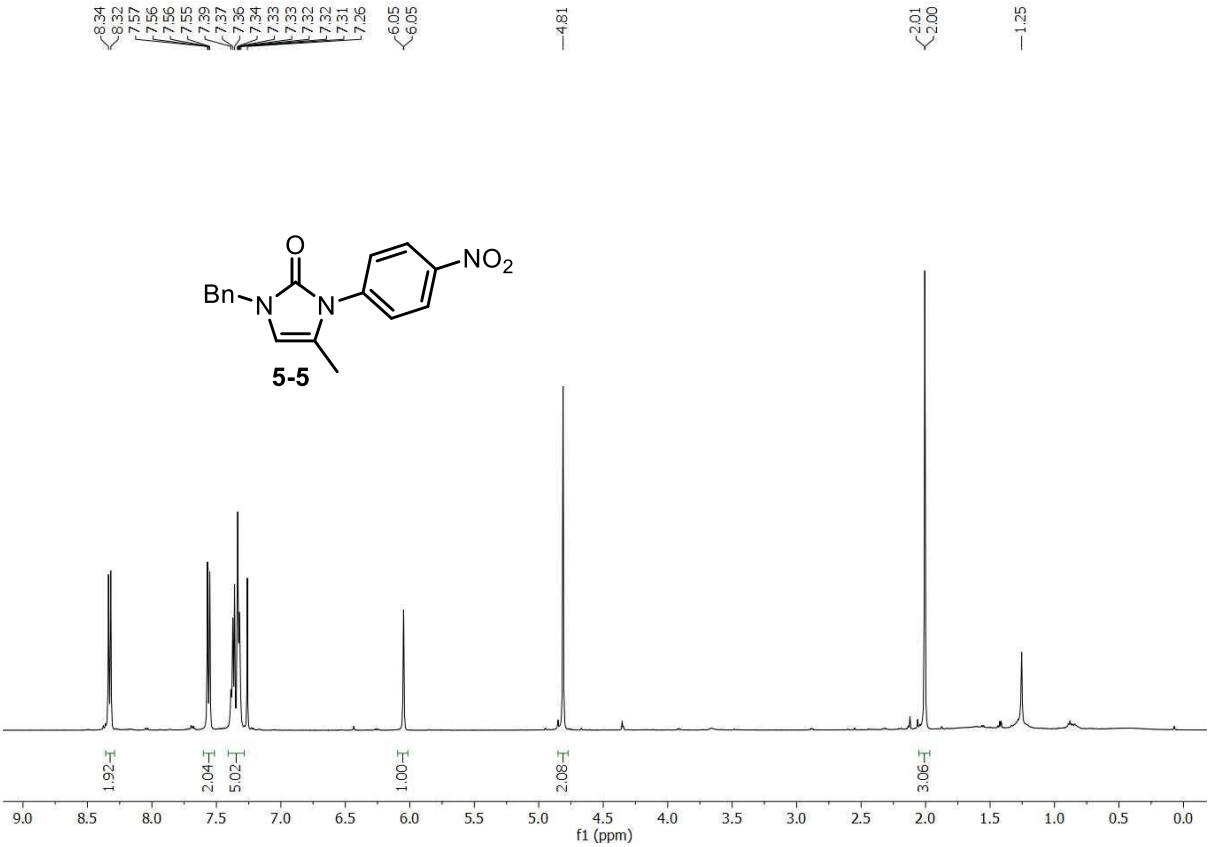
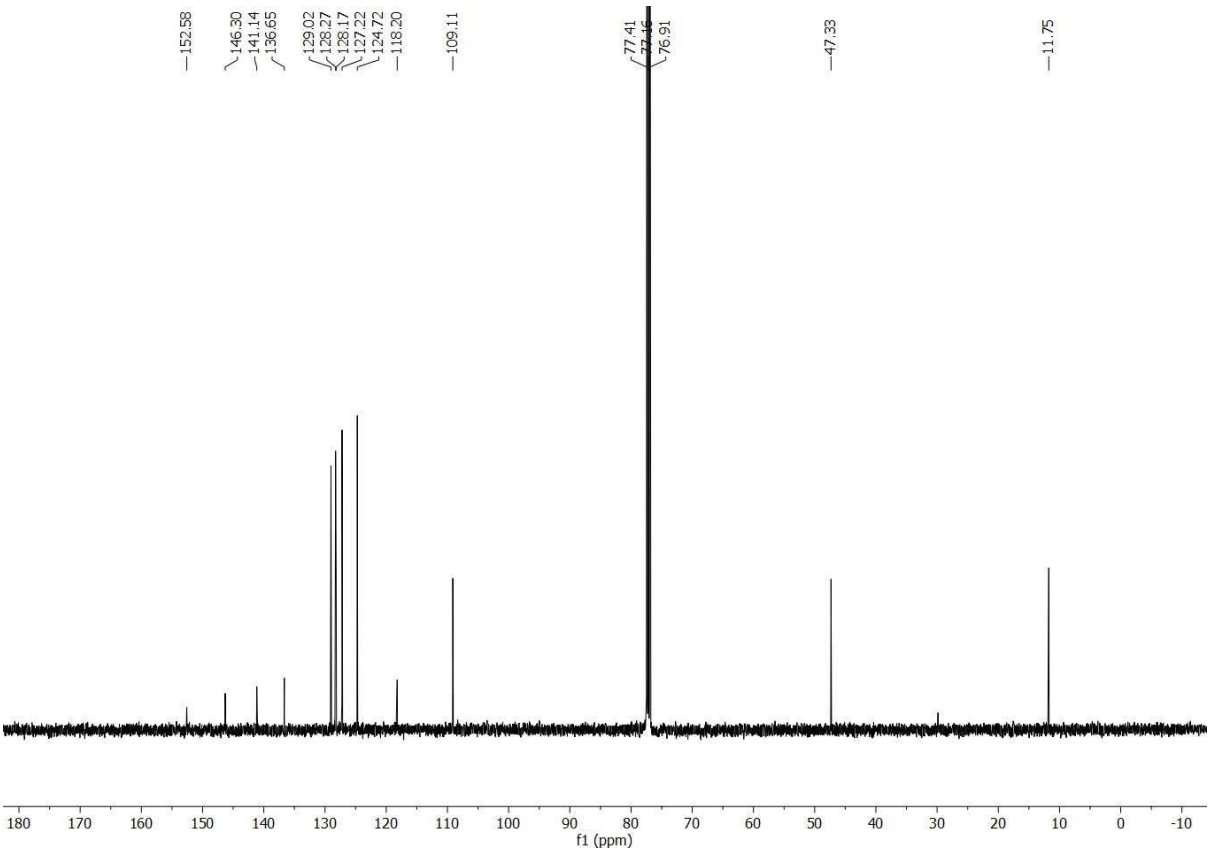
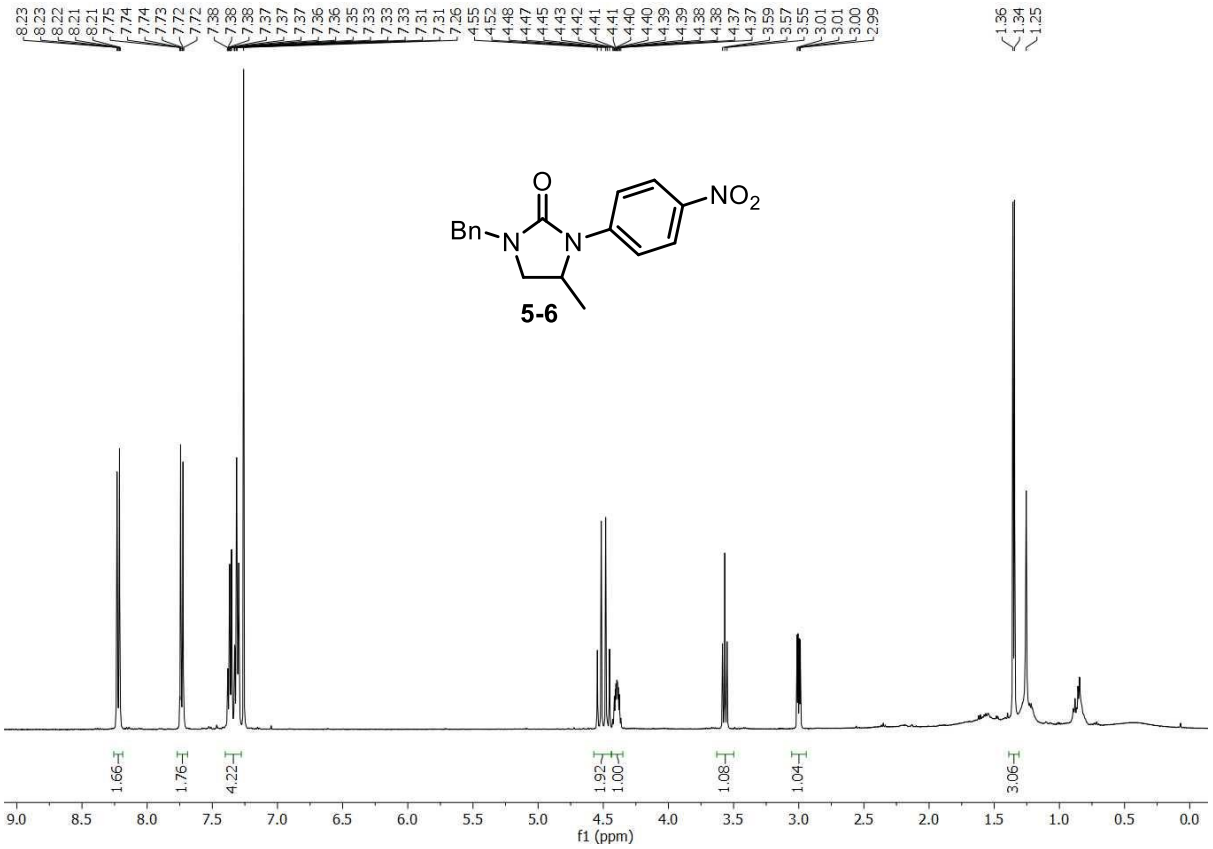
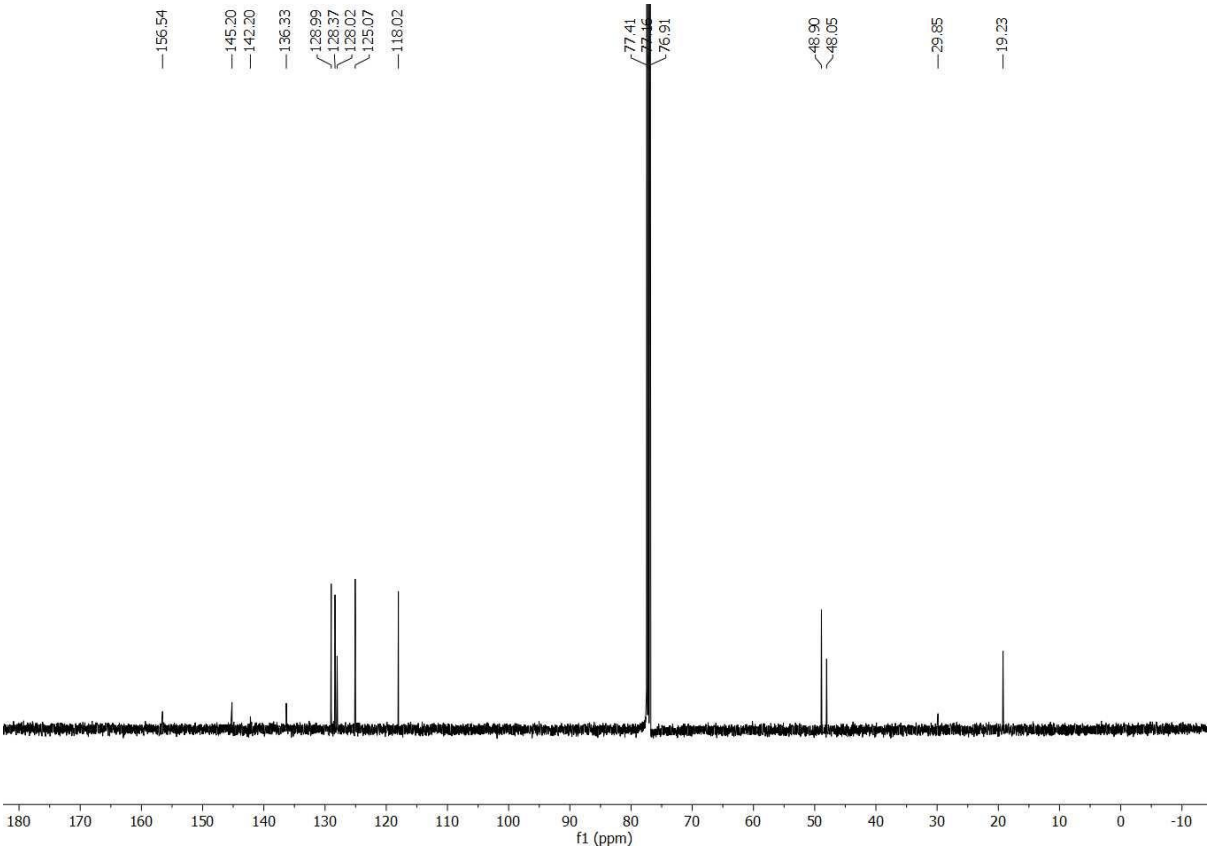
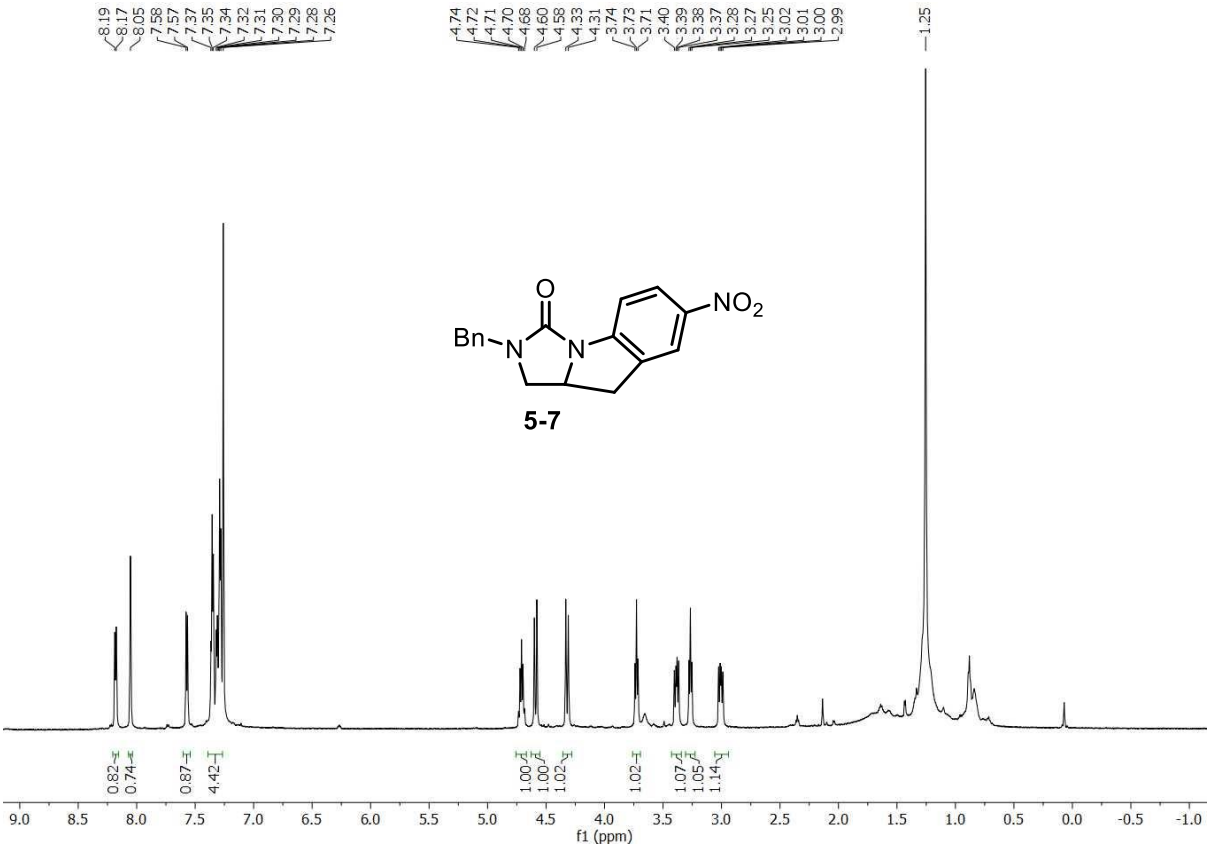
137.401
132.373
128.808
128.475
127.686
123.568
114.693
77.418
76.910
66.990
60.452
55.719
55.697
54.438
52.352
48.378
47.210
29.880
180
160
140
120
100
80
60
40
20
ppm

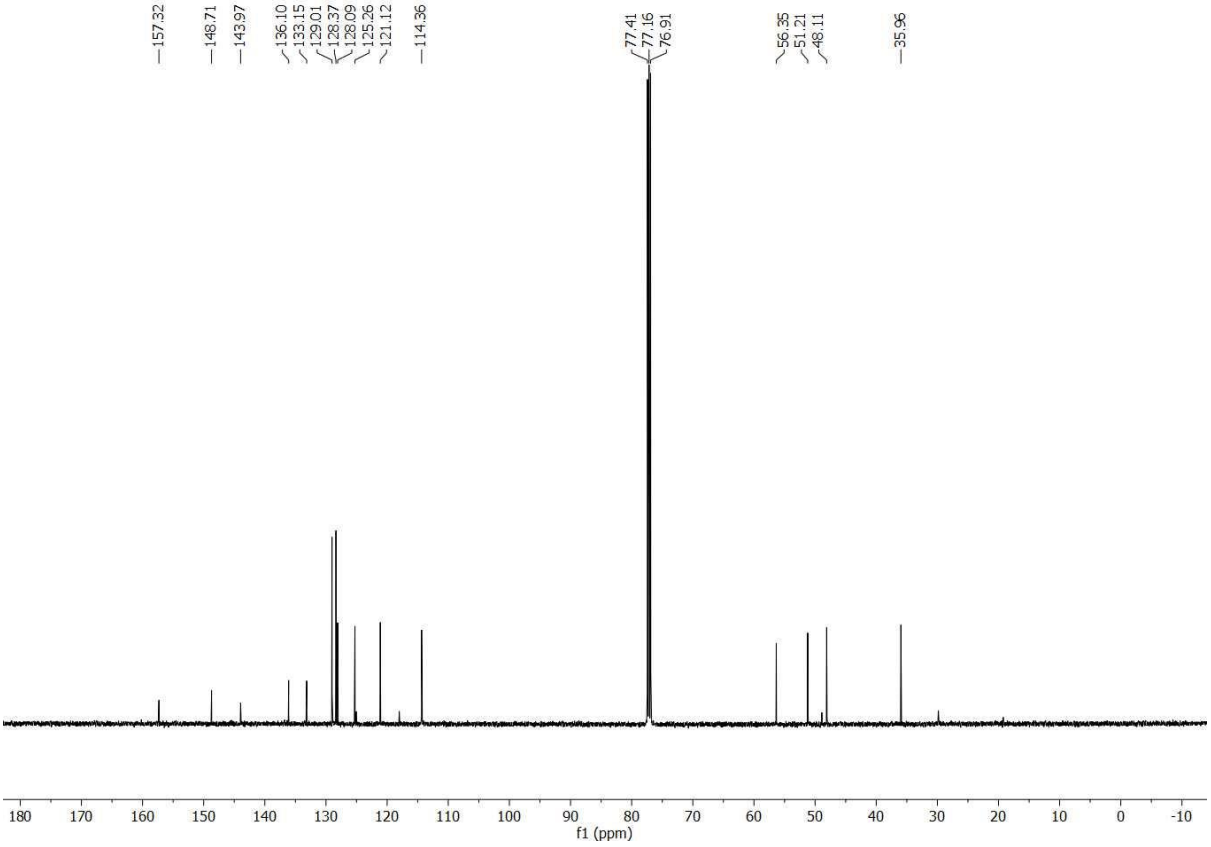

8.34
8.32
7.57
7.56
7.56
7.55
7.39
7.37
7.36
7.34
7.33
7.33
7.32
7.32
7.31
7.26
6.05
6.05
4.81
2.01
2.00
1.25
O
Bn
N
N
NO2
5-5
1.92
2.04
5.02
1.00
2.08
3.06
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

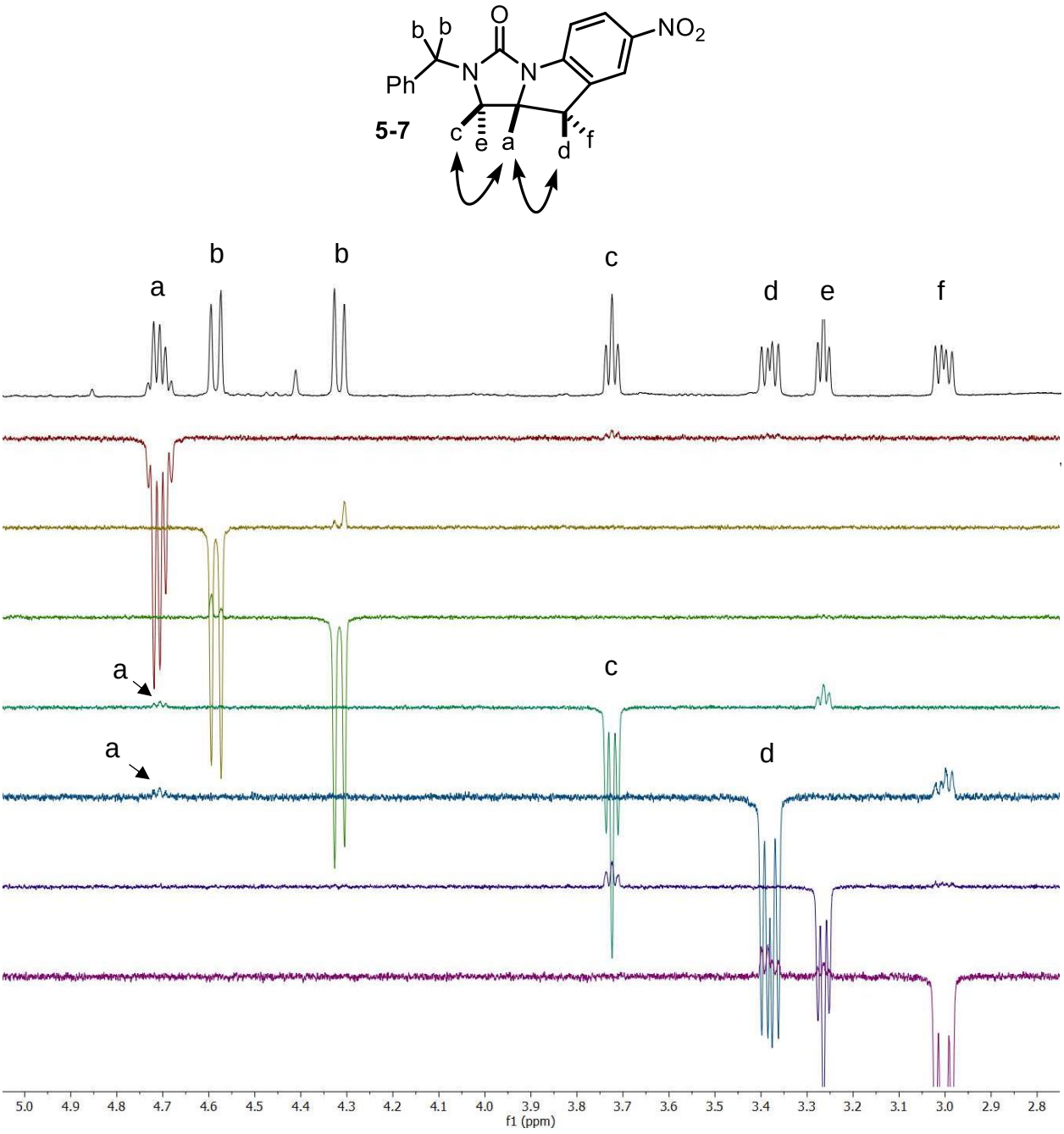

152.58
146.30
141.14
136.65
129.02
128.27
128.17
127.22
124.72
118.20
109.11
77.41
77.16
76.91
47.33
11.75
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

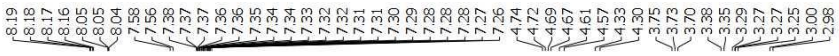

8.23
8.23
8.22
8.21
8.21
7.75
7.74
7.74
7.73
7.72
7.72
7.38
7.38
7.38
7.37
7.37
7.37
7.36
7.36
7.35
7.33
7.33
7.33
7.31
7.31
7.26
4.55
4.52
4.48
4.47
4.45
4.43
4.42
4.41
4.41
4.40
4.40
4.39
4.39
4.38
4.38
4.37
4.37
3.59
3.57
3.55
3.01
3.01
3.00
2.99
1.36
1.34
1.25
O
Bn
N
N
NO2
5-6
1.66
1.76
4.22
1.92
1.00
1.08
1.04
3.06
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

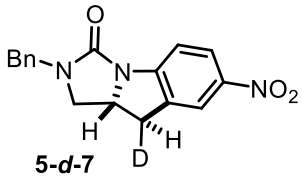

156.54
145.20
142.20
136.33
128.99
128.37
128.02
125.07
118.02
77.41
77.16
76.91
48.90
48.05
29.85
19.23
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


8.19
8.17
8.05
7.58
7.57
7.37
7.35
7.34
7.32
7.31
7.30
7.29
7.28
7.26
4.74
4.72
4.71
4.70
4.68
4.60
4.58
4.33
4.31
3.74
3.73
3.71
3.40
3.39
3.38
3.37
3.28
3.27
3.25
3.02
3.01
3.00
2.99
1.25
O
Bn
N
N
NO2
5-7
0.82
0.74
0.87
4.42
1.00
1.00
1.02
1.02
1.07
1.05
1.14
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)


157.32
148.71
143.97
136.10
133.15
129.01
128.37
128.09
125.26
121.12
114.36
77.41
77.16
76.91
56.35
51.21
48.11
35.96
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

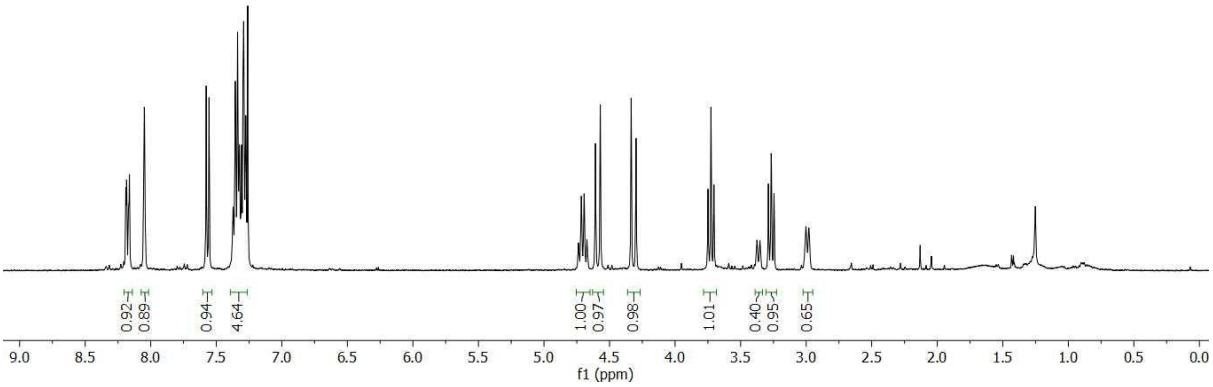

b b
O
NO2
Ph
N
N
5-7
c e a d f
a
b
b
c
d e f
a
a
c
d
5.0 4.9 4.8 4.7 4.6 4.5 4.4 4.3 4.2 4.1 4.0 3.9 3.8 3.7 3.6 3.5 3.4 3.3 3.2 3.1 3.0 2.9 2.8
f1 (ppm)

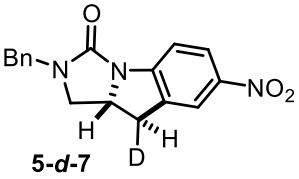




5-*d*-7

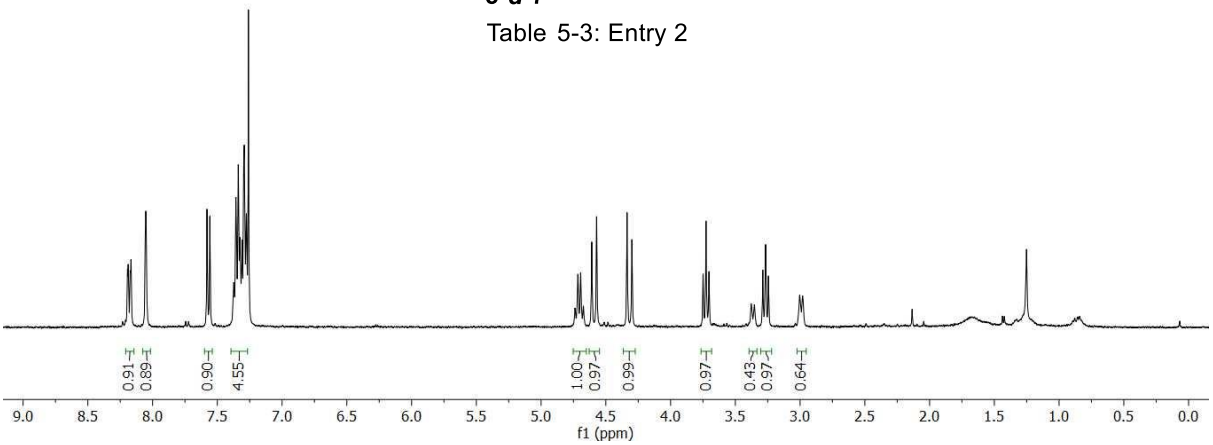
Table 5-3: Entry 1

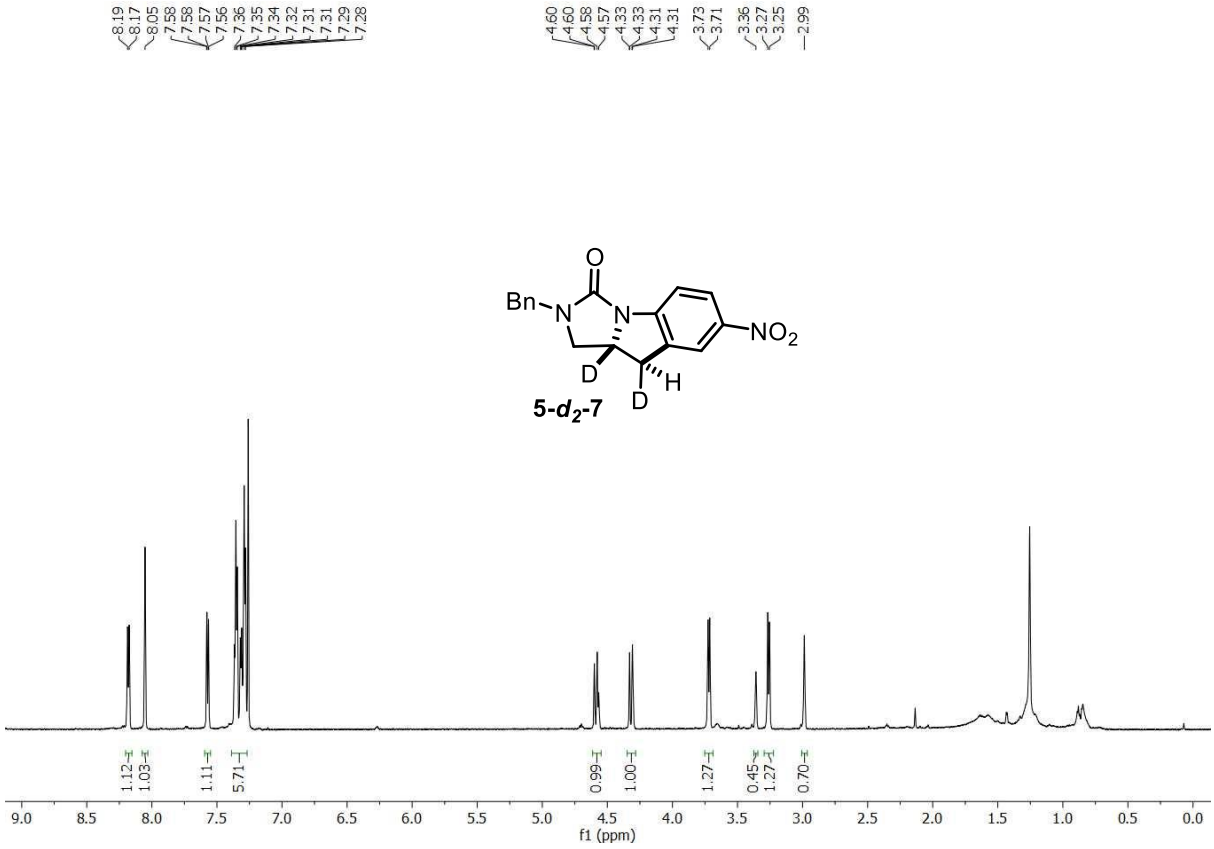


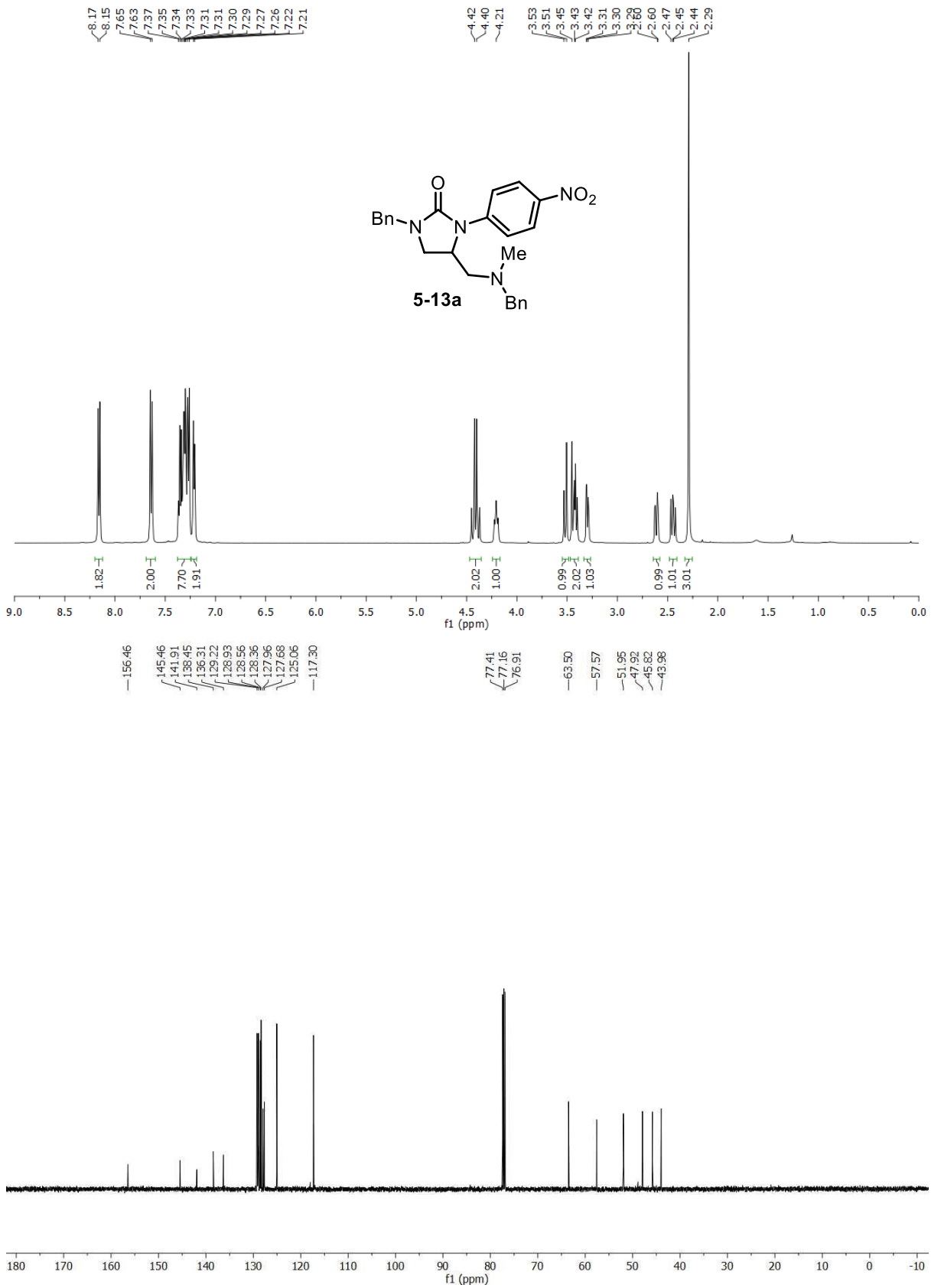


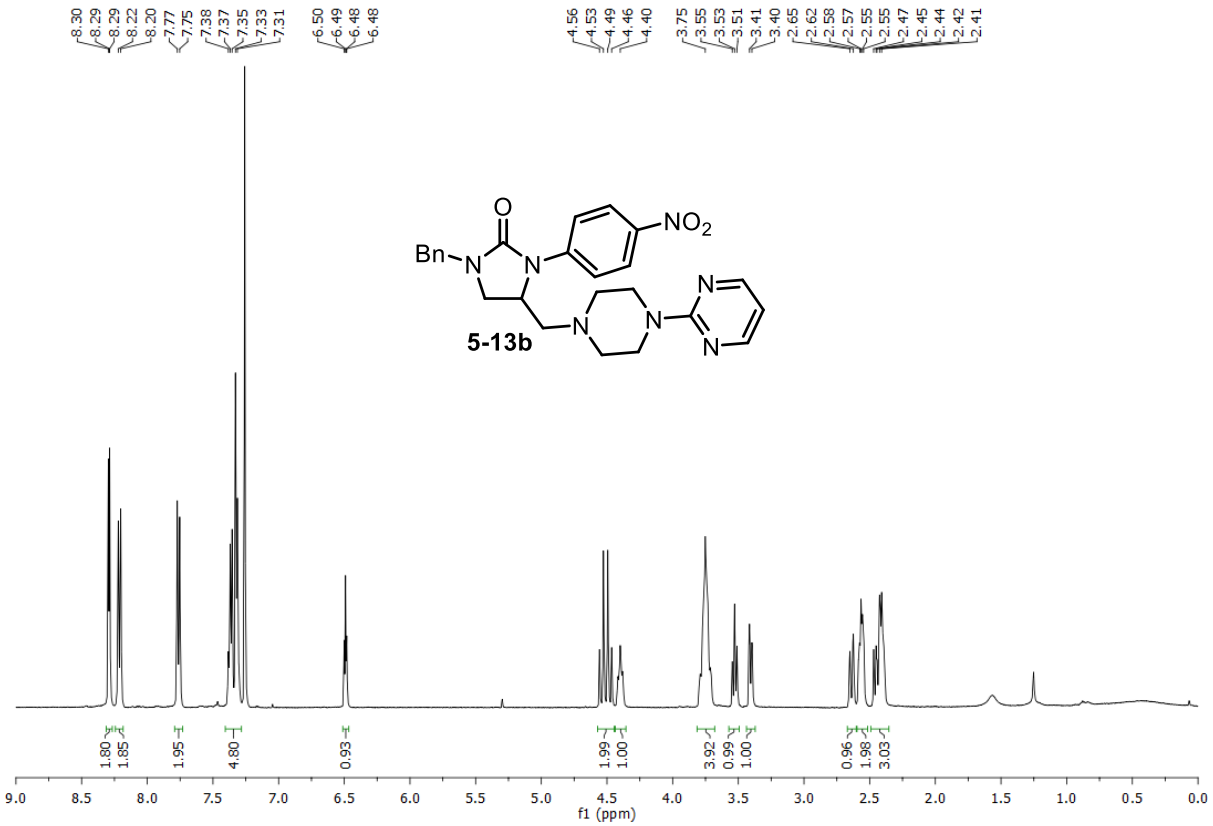
5-*d*-7

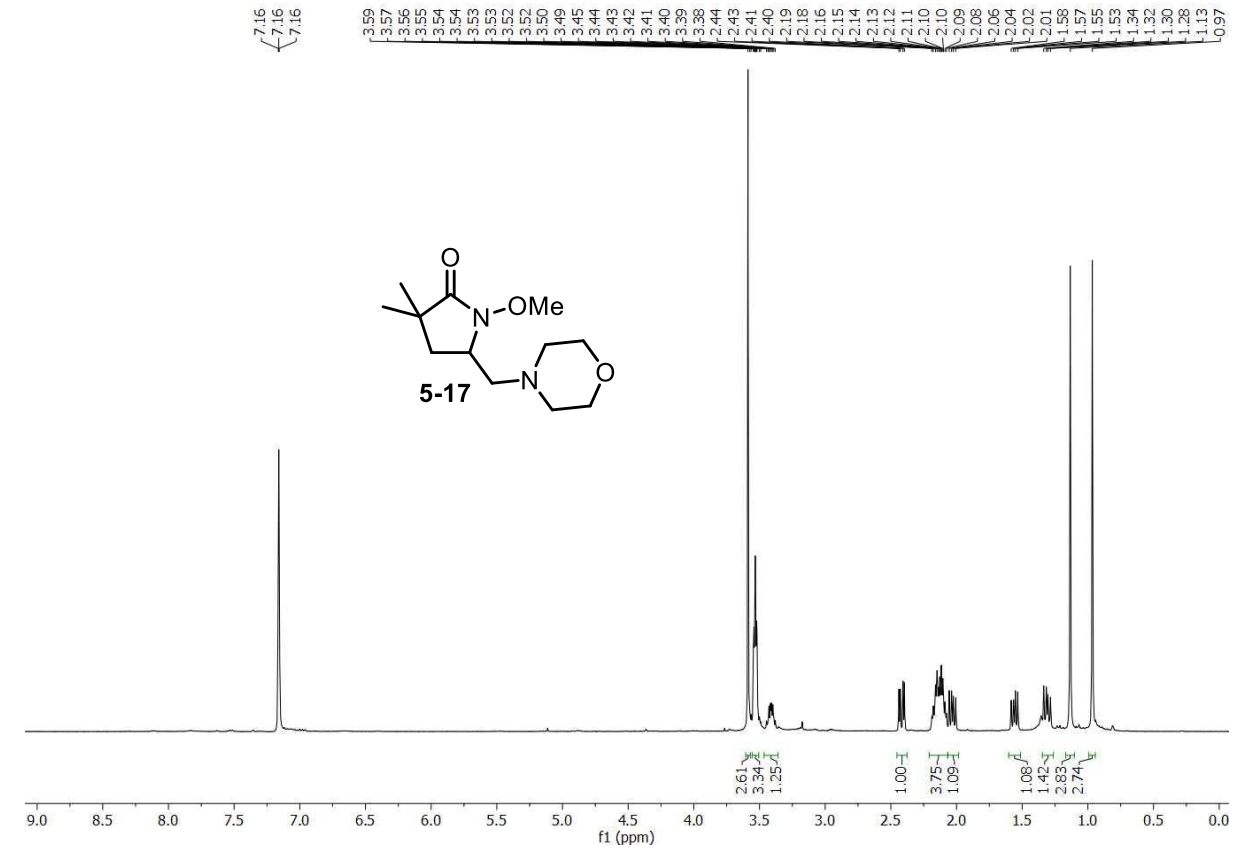
Table 5-3: Entry 2

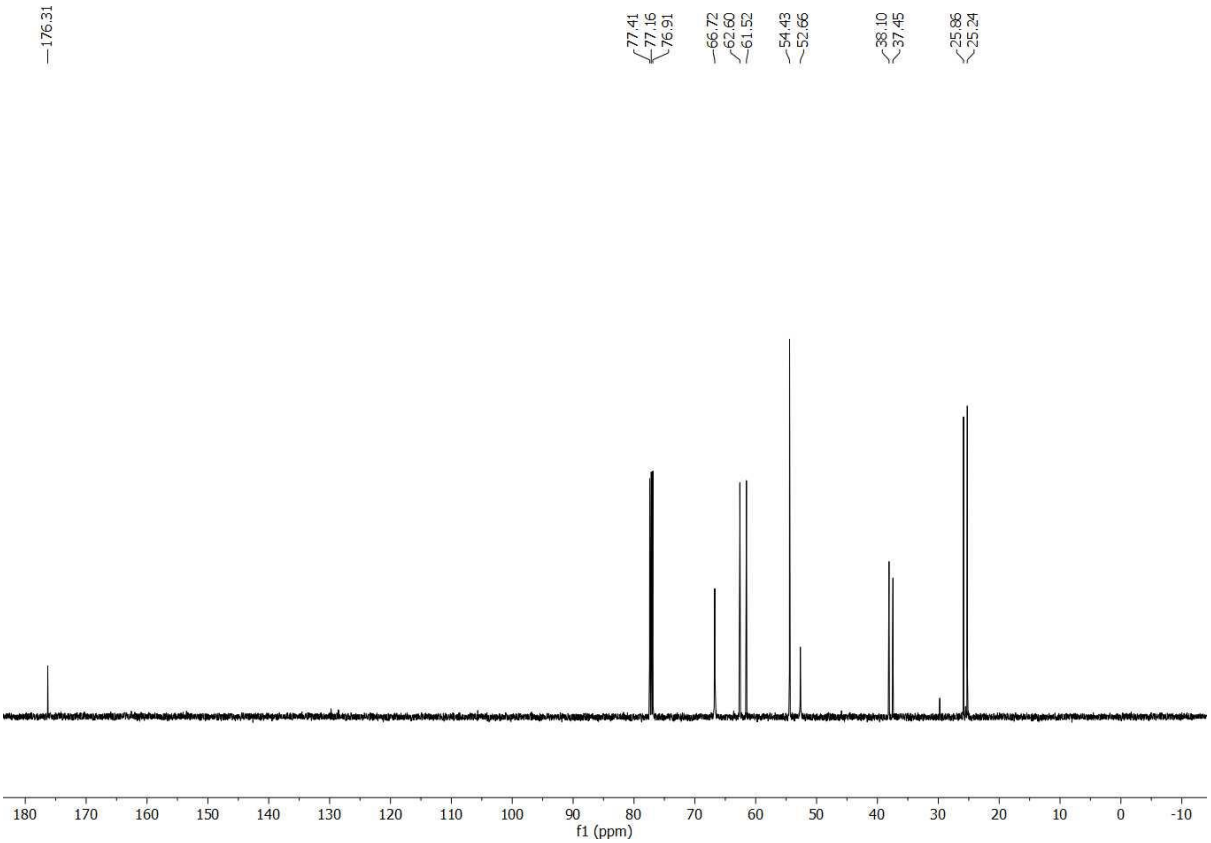


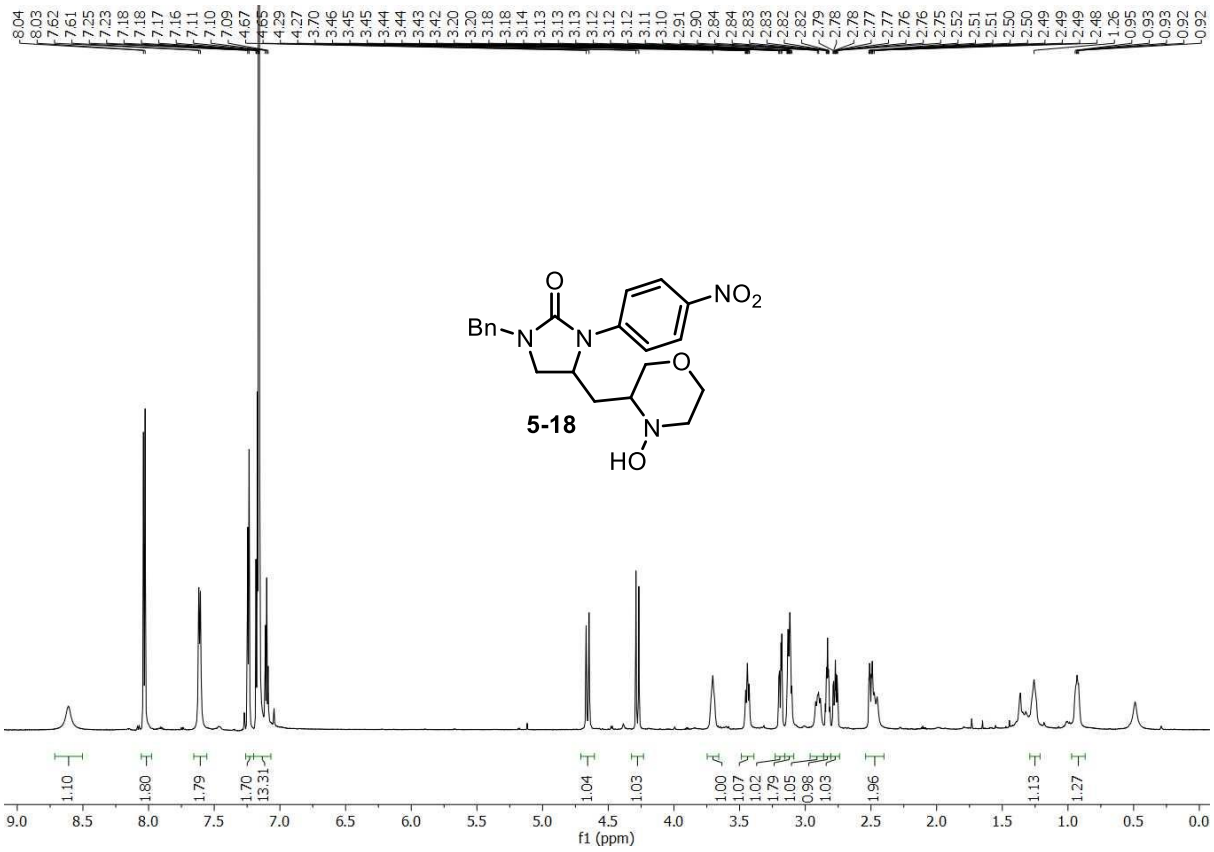

8.19
8.17
8.05
7.58
7.58
7.57
7.56
7.36
7.35
7.34
7.32
7.31
7.31
7.29
7.28
4.60
4.60
4.58
4.57
4.33
4.33
4.31
4.31
3.73
3.71
3.36
3.27
3.25
2.99
O
Bn
N
N
NO2
D
D
H
5-d2-7
1.12
1.03
1.11
5.71
0.99
1.00
1.27
0.45
1.27
0.70
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

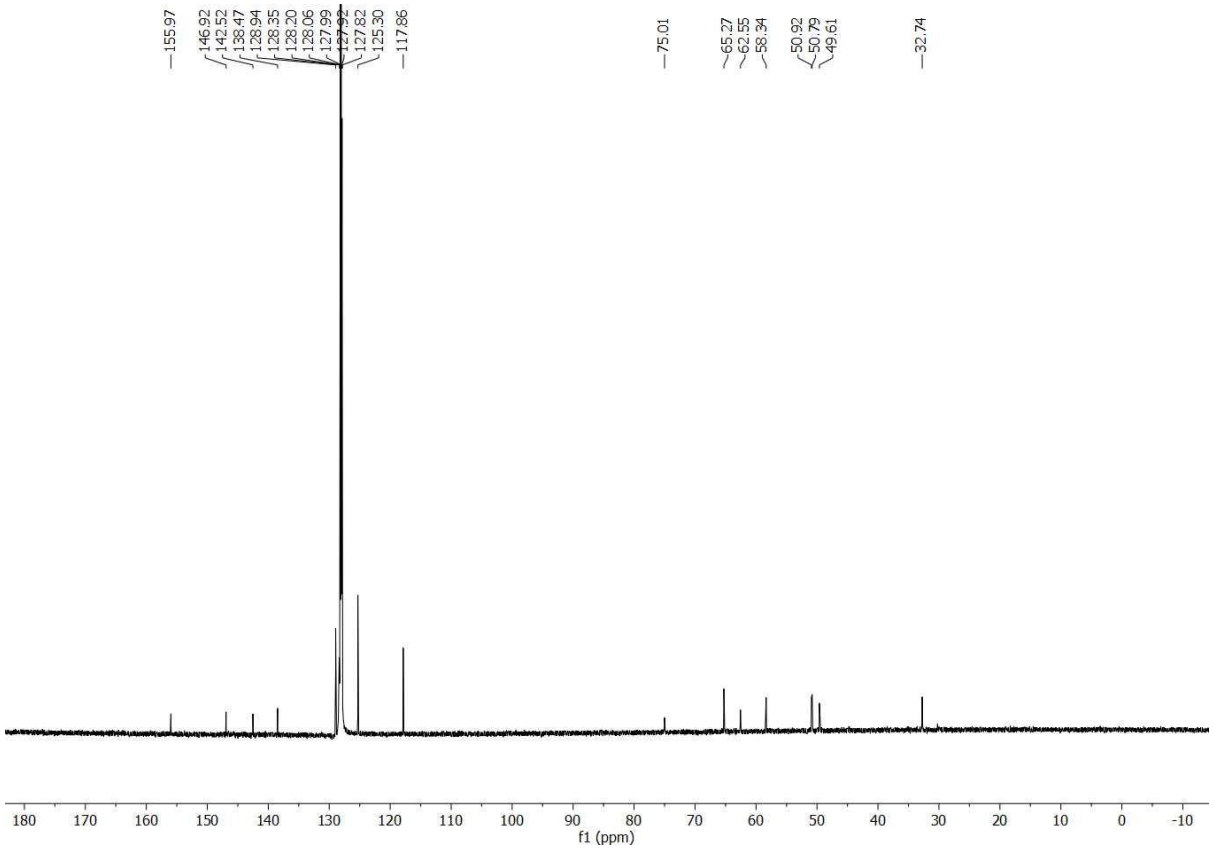

8.17
8.15
7.65
7.63
7.37
7.35
7.34
7.33
7.31
7.31
7.30
7.29
7.27
7.26
7.22
7.21
4.42
4.40
4.21
3.53
3.51
3.45
3.43
3.42
3.31
3.30
3.28
3.60
2.60
2.47
2.45
2.44
2.29
O
NO2
Bn
N
N
Me
N
Bn
5-13a
1.82
2.00
7.70
1.91
2.02
1.00
0.99
2.02
1.03
0.99
1.01
3.01
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)
156.46
145.46
141.91
138.45
136.31
129.22
128.93
128.56
128.36
127.96
127.68
125.06
117.30
77.41
77.16
76.91
63.50
57.57
51.95
47.92
45.82
43.98
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

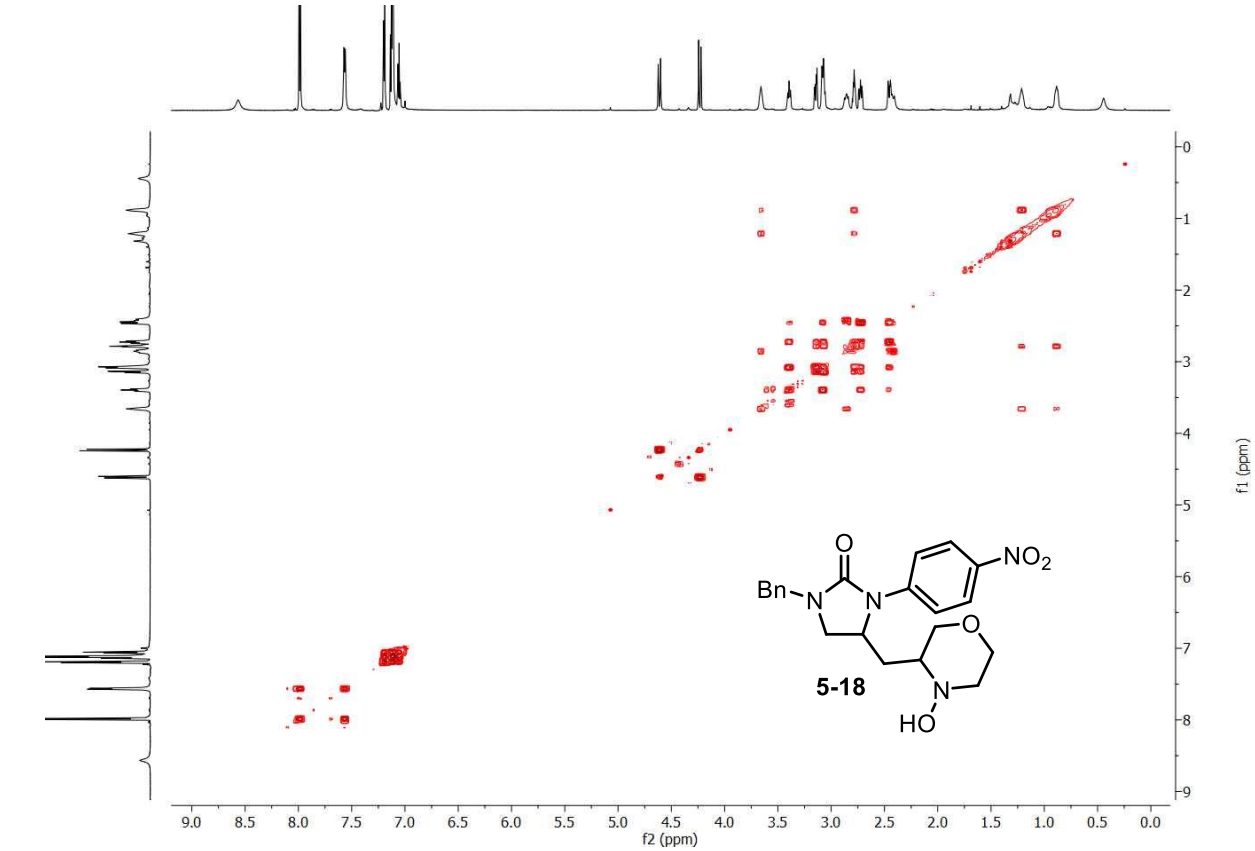

8.30
8.29
8.29
8.22
8.20
7.77
7.75
7.38
7.37
7.35
7.33
7.31
6.50
6.49
6.48
6.48
4.56
4.53
4.49
4.46
4.40
3.75
3.55
3.53
3.51
3.41
3.40
2.65
2.62
2.58
2.57
2.55
2.55
2.47
2.45
2.44
2.42
2.41
O
Bn
N
N
NO2
N
N
N
N
5-13b
1.80
1.85
1.95
4.80
0.93
1.99
1.00
3.92
0.99
1.00
0.96
1.98
3.03
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

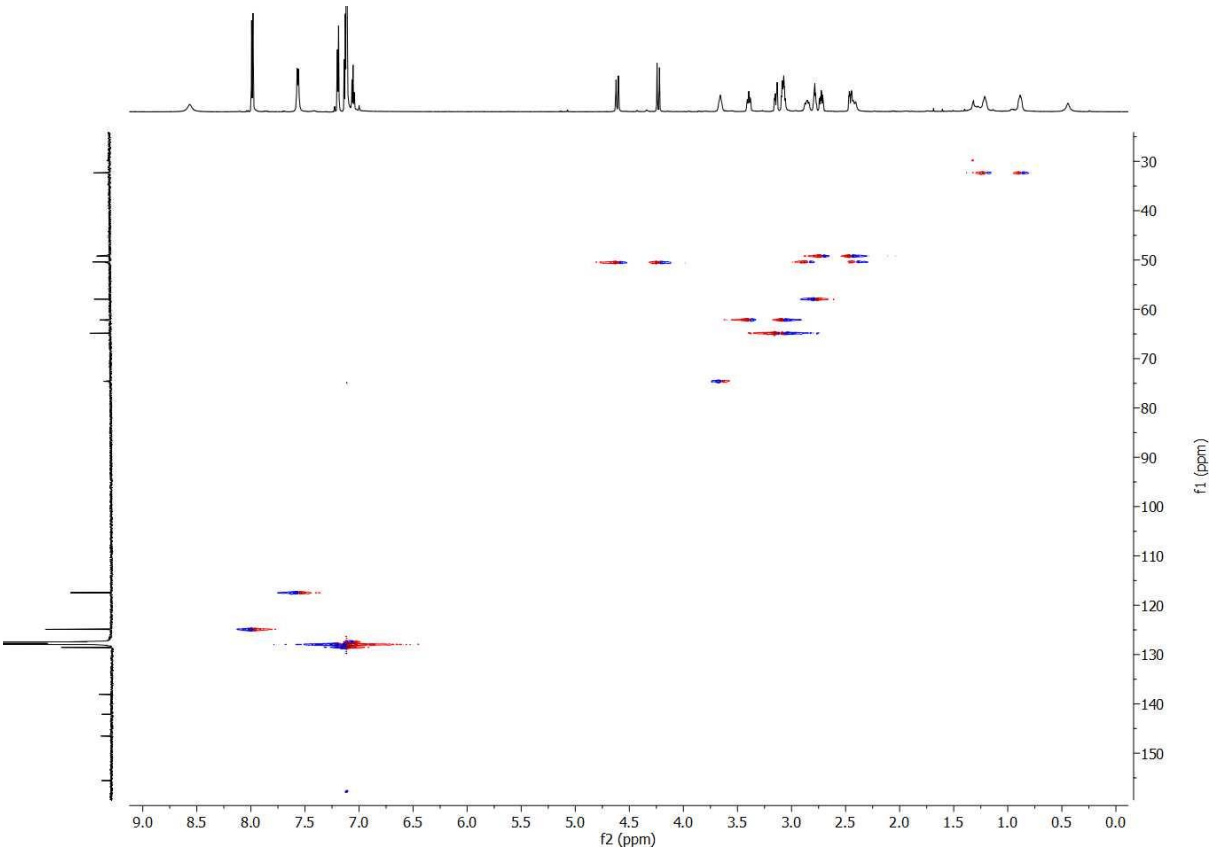

7.16
7.16
7.16
3.59
3.57
3.56
3.55
3.54
3.54
3.53
3.53
3.52
3.52
3.50
3.49
3.45
3.44
3.43
3.42
3.41
3.40
3.39
3.38
2.44
2.43
2.41
2.40
2.19
2.18
2.16
2.15
2.14
2.13
2.12
2.11
2.10
2.10
2.09
2.08
2.06
2.04
2.02
2.01
1.58
1.57
1.55
1.53
1.34
1.32
1.30
1.28
1.13
0.97
O
N
OMe
N
O
5-17
2.61
3.34
1.25
1.00
3.75
1.09
1.08
1.42
2.83
2.74
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

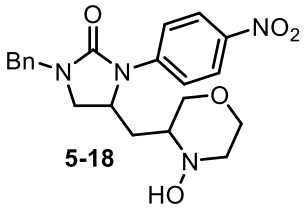

176.31
77.41
77.16
76.91
66.72
62.60
61.52
54.43
52.66
38.10
37.45
25.86
25.24
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


Bn
N
O
N
NO2
O
N
HO
5-18
f1 (ppm)

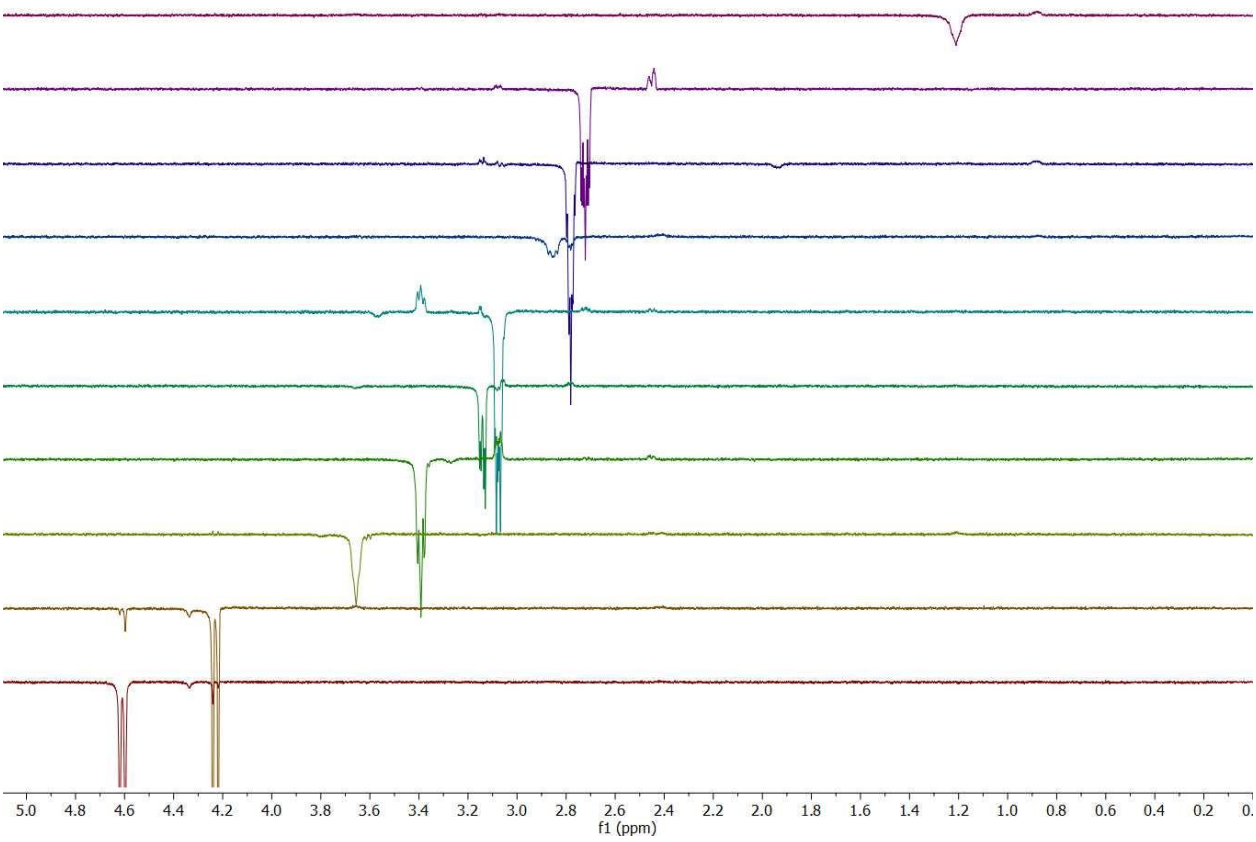

155.97
146.92
142.52
138.47
128.94
128.35
128.20
128.06
127.99
127.92
127.82
125.30
117.86
75.01
65.27
62.55
58.34
50.92
50.79
49.61
32.74
f1 (ppm)

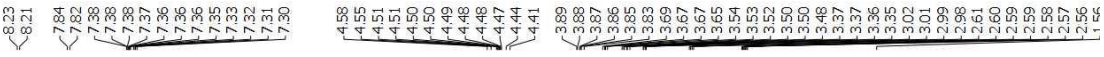

f2 (ppm)
f1 (ppm)
Bn
N
O
N
NO2
O
N
HO
5-18

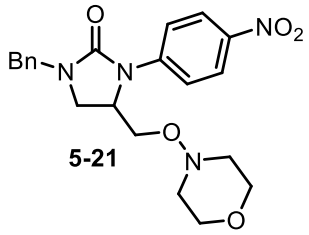

f2 (ppm)
f1 (ppm)


O
NO2
Bn
N
N
O
N
HO

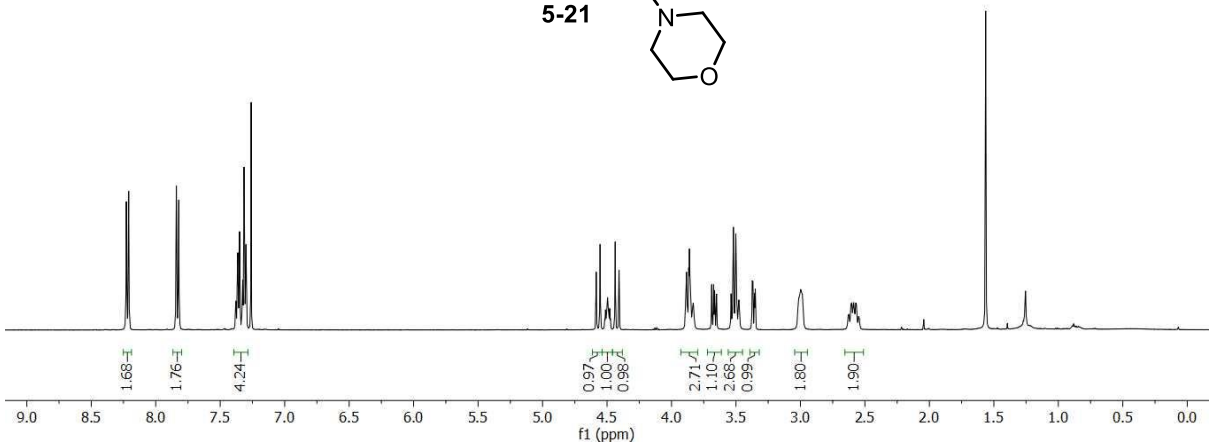
5-18

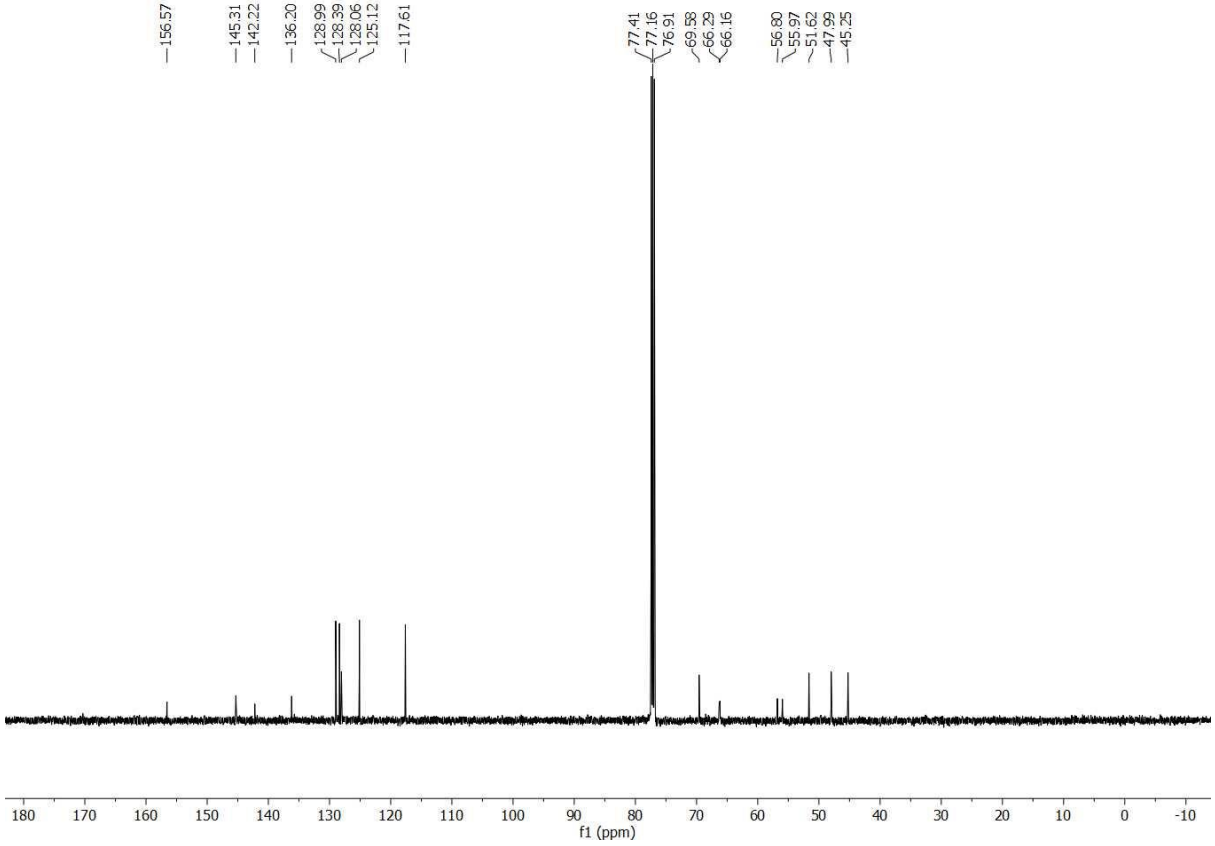

5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8 0.6 0.4 0.2
f1 (ppm)

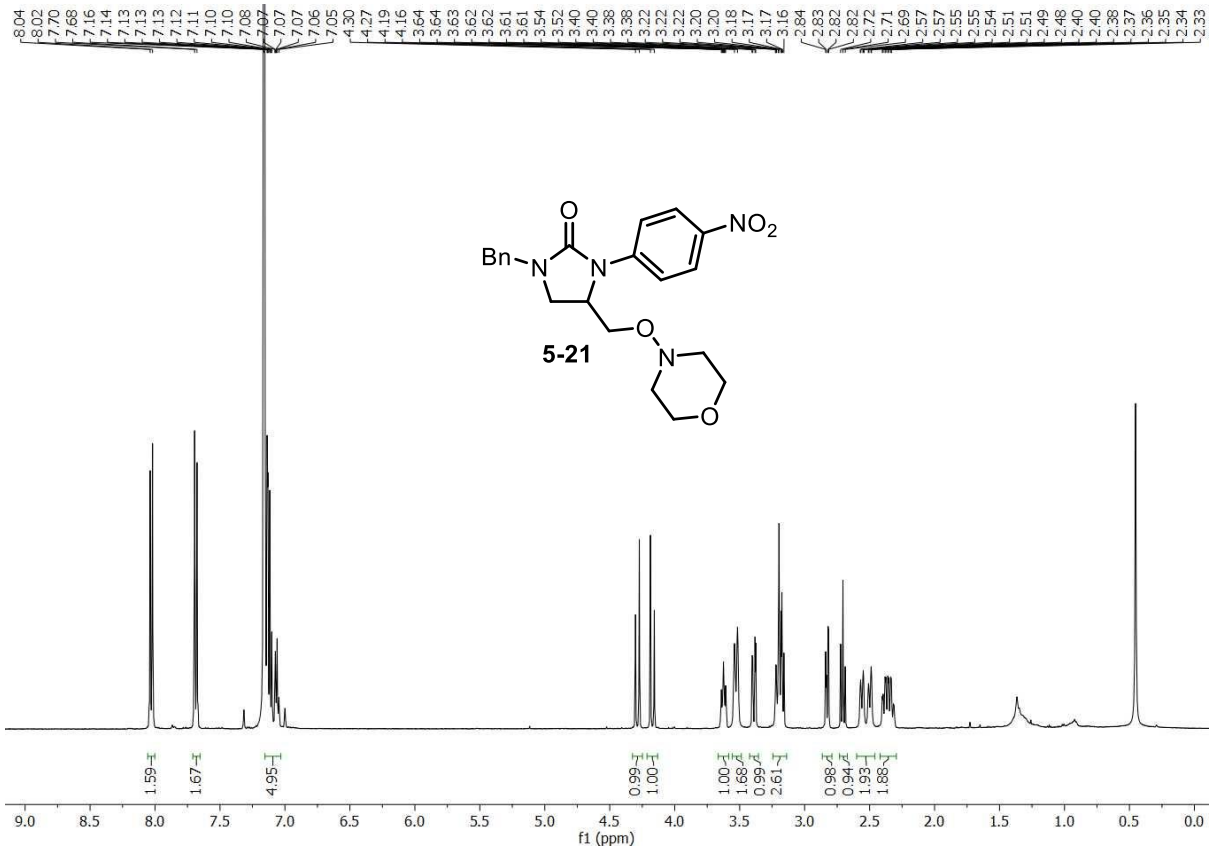


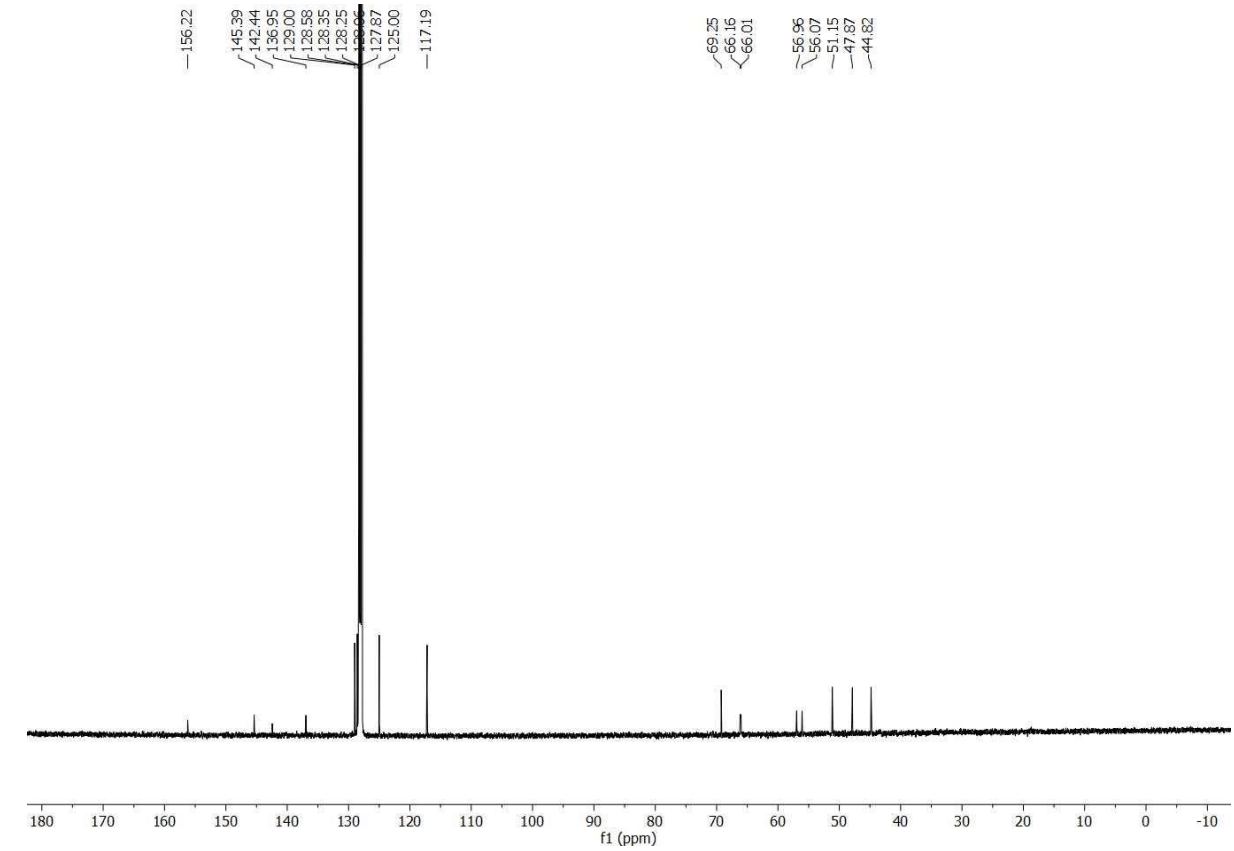

O
NO2
Bn
N
N
O
N
O

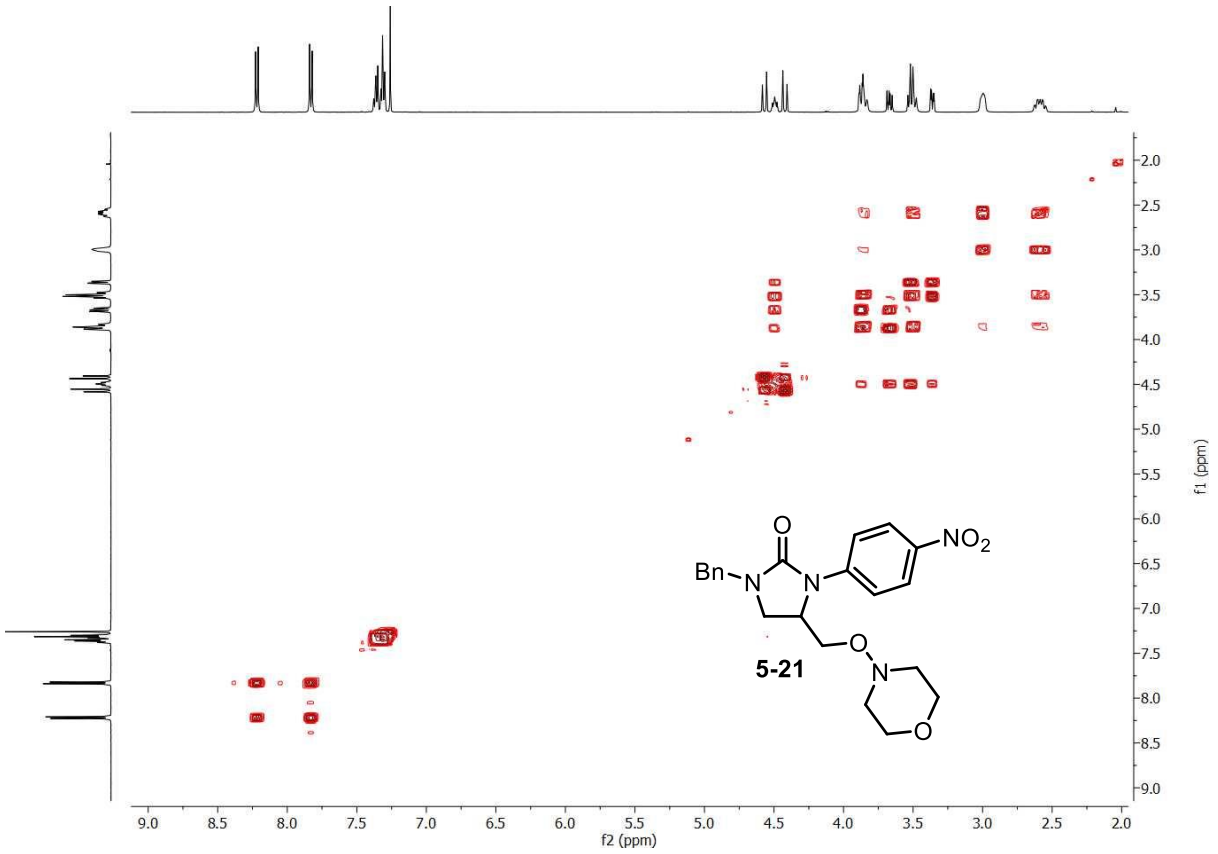
5-21

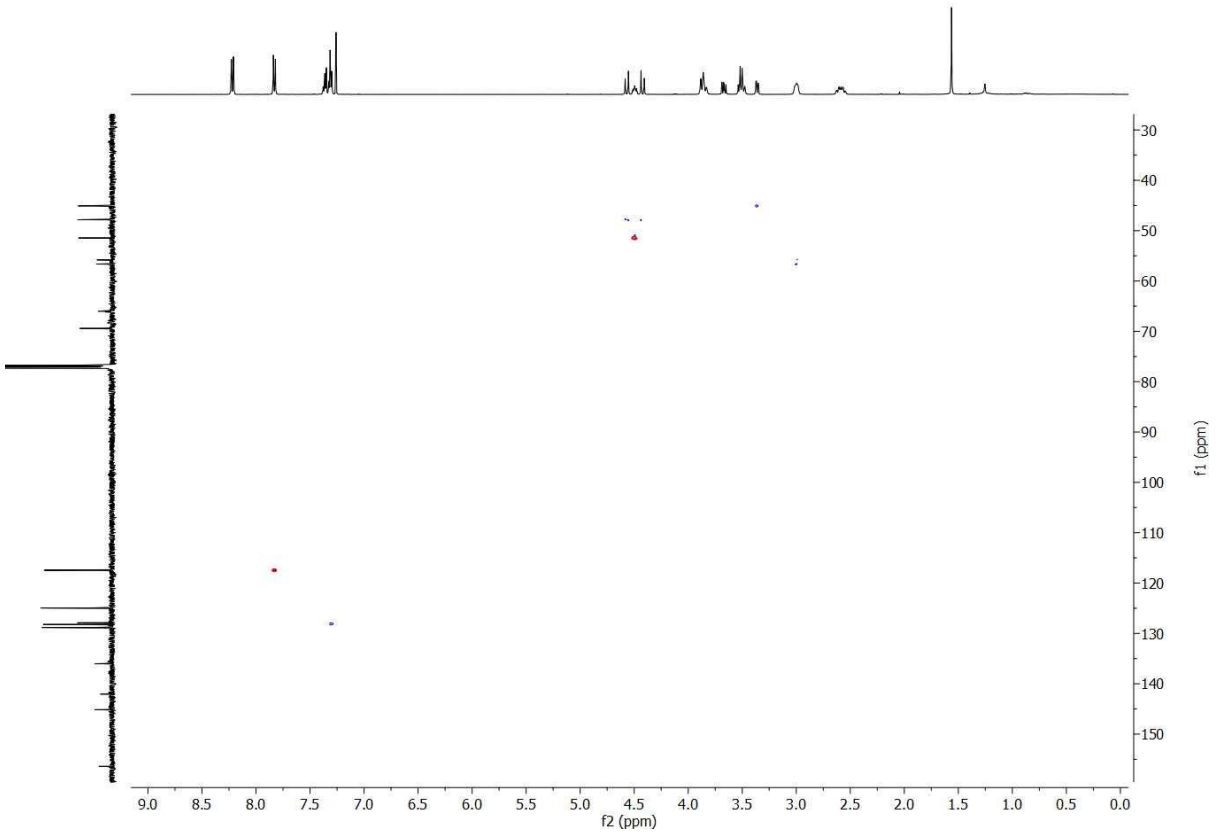

1.68
1.76
4.24
0.97
1.00
0.98
2.71
1.10
2.68
0.99
1.80
1.90
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

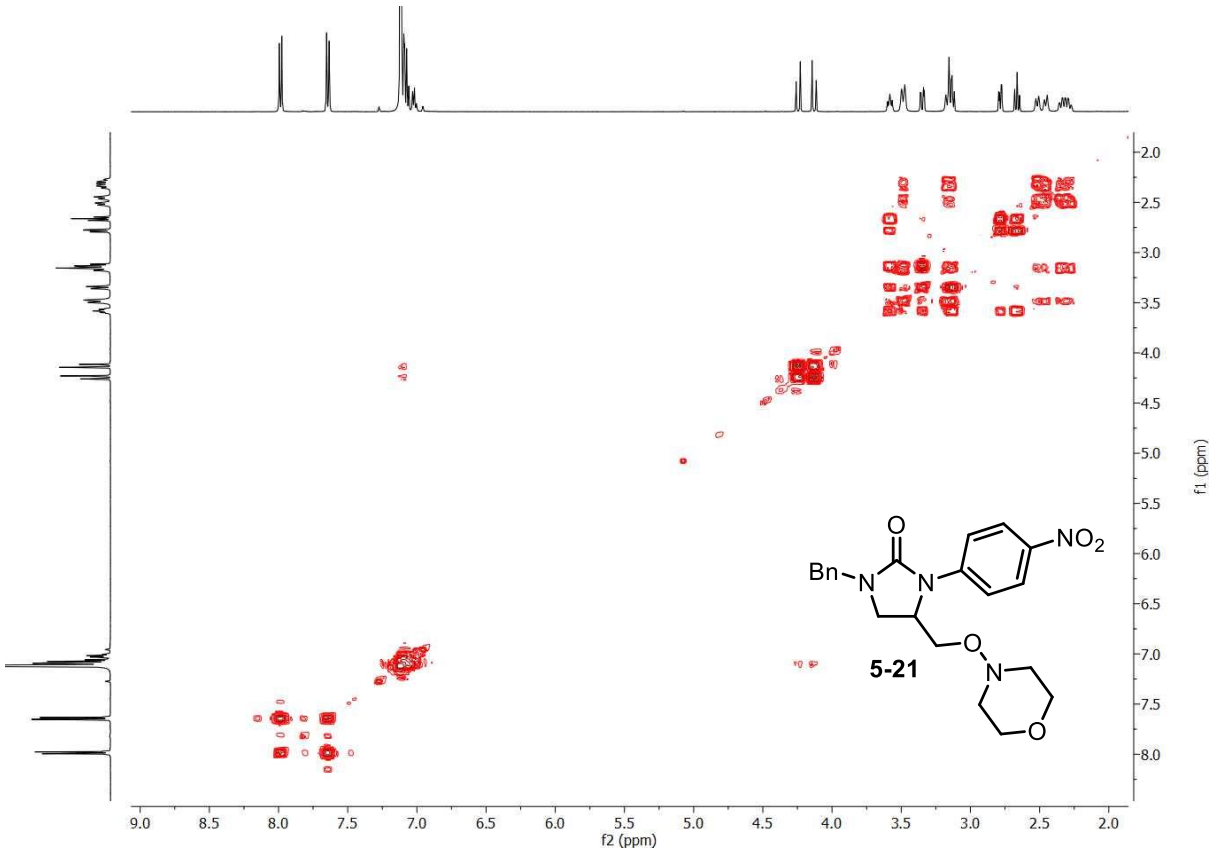

156.57
145.31
142.22
136.20
128.99
128.39
128.06
125.12
117.61
77.41
77.16
76.91
69.58
66.29
66.16
56.80
55.97
51.62
47.99
45.25
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

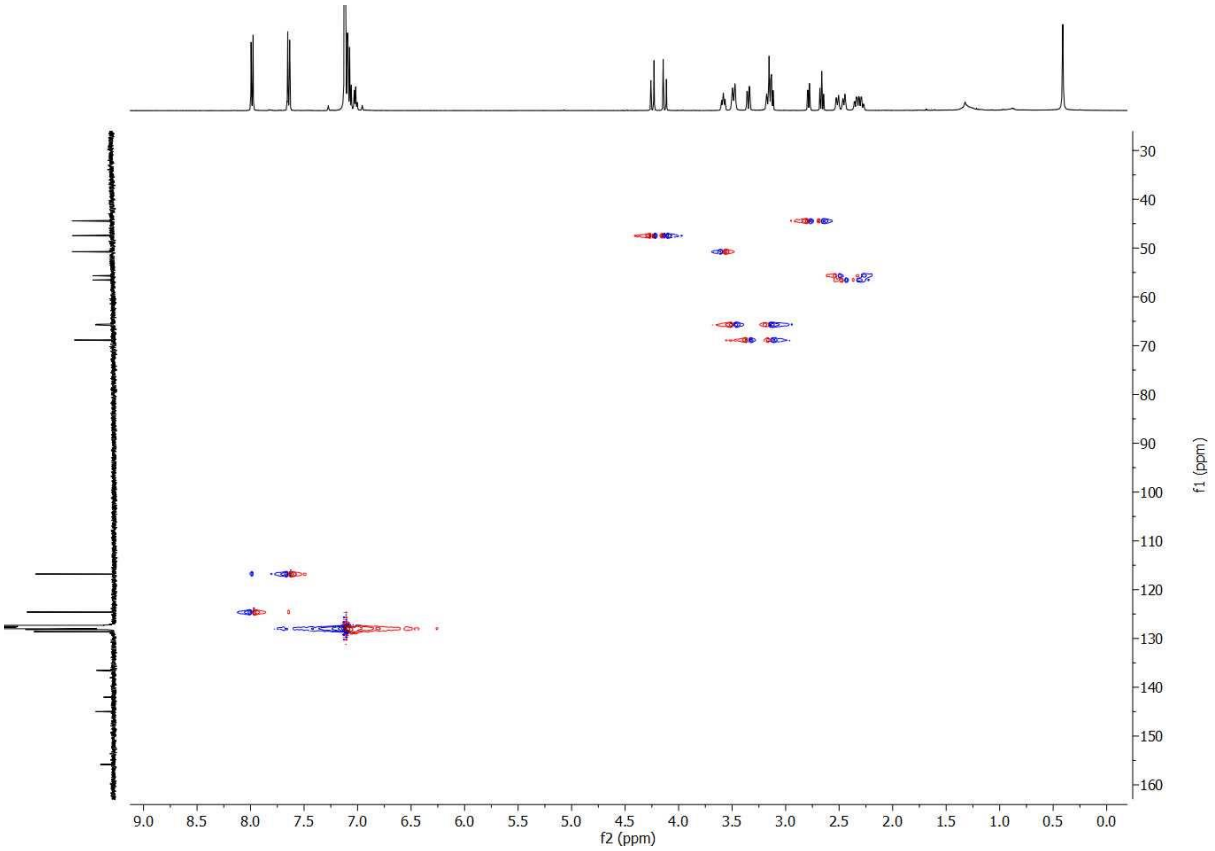

Bn
O
NO2
5-21
f1 (ppm)


f1 (ppm)

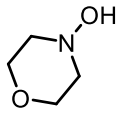

f2 (ppm)
f1 (ppm)
Bn
N
O
N
O
NO2
N
O
5-21


f2 (ppm)
f1 (ppm)

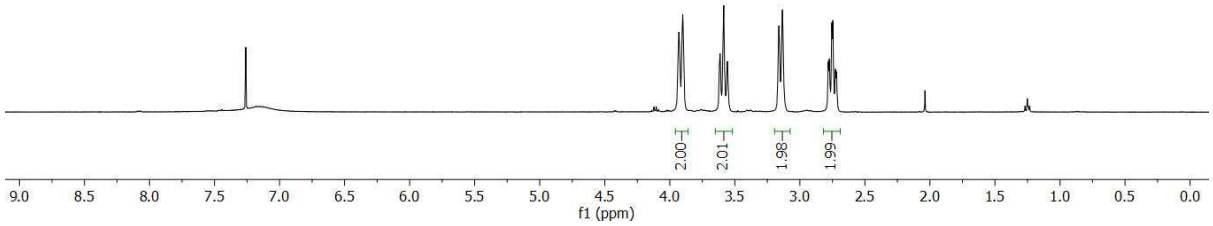

f2 (ppm)
f1 (ppm)
Bn
N
O
N
O
NO2
5-21
O
N
O


f2 (ppm)
f1 (ppm)


7.26
3.94
3.94
3.93
3.92
3.92
3.91
3.90
3.89
3.62
3.61
3.59
3.58
3.56
3.55
3.16
3.16
3.14
3.13
3.13
2.78
2.77
2.75
2.75
2.73
2.72


OH
N
O

5-22


2.00
2.01
1.98
1.99
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

References

(1) Peterson, L. J.; Kirsch, J. K.; Wolfe, J. P. *Org. Lett.* **2018**, *20*, 3513.

(2) Hartwig has previously demonstrated the oxidative addition of analogous *O*-acyl oximes to Pd(0). Tan, Y.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 3676.

(3) (a) Garlets, Z. J.; White, D. R.; Wolfe, J. P. *Asian J. Org. Chem.* **2017**, *6*, 636. (b) Wolfe, J. P. *Top. Heterocycl. Chem.* **2013**, *32*, 1. (c) Schultz, D. M.; Wolfe, J. P. *Synthesis* **2012**, *44*, 351. (d) Wolfe, J. P.; *Synlett* **2008**, 2913. (e) Wolfe, J. P. *Eur. J. Org. Chem.* **2007**, 571. (f) Kočovský, P.; Bäckvall, J. -E. *Chem. Eur. J.* **2015**, *21*, 36. (g) McDonald, R. I.; Liu, G.; Stahl, S. S. *Chem. Rev.* **2011**, *111*, 2981. (h) Jensen, K. H.; Sigman, M. S. *Org. Biomol. Chem*. **2008**, *6*, 4083. (i) Hanley, P. S.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2013**, *52*, 8510.

(4) (a) Sibbald, P. A.; Michael, F. E. *Org. Lett.*, **2009**, *11*, 1147. (b) Ingalls, E. L.; Sibbald, P. A.; Kaminsky, W.; Michael, F. E. *J. Am. Chem. Soc.* **2013**, *135*, 8854. (c) Sibbald, P. A.; Rosewall, C. F.; Swartz, R. D.; Michael, F. E. *J. Am. Chem. Soc.* **2009**, *131*, 15945.

(5) (a) Bäckvall, J.-E. *Tetrahedron Lett.* **1978**, *19*, 163. (b) Lorion, M. M.; Duarte, F. J. S.; Calhorda, M. J.; Oble, J.; Poli, G. *Org. Lett.* **2016**, *18*, 1020. (c) Liu, G.; Stahl, S. S. *J. Am. Chem. Soc.* **2007**, *129*, 6328. (d) Minatti, A.; Muñiz, K. *Chem. Soc. Rev.* **2007**, *36*, 1142.

(6) This reaction was repeated by JKK following the publication of the original work and isolated the product in 6.7:1 dr.

(7) Carbon-carbon bond-forming reductive elimination occurs with retention of configuration. See: Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 4981.

(8) Prior studies from our lab on the mechanism of Pd-catalyzed alkene carboalkoxylation reactions that afford THF products illustrated that stereoisomers can be generated from a single alkene heteropalladation intermediate. These stereoisomers arise from reversible β-hydride elimination/sigma bond rotation pathways. See: Hay, M. B.; Wolfe, J. P. *J. Am. Chem. Soc.* **2005**, *127*, 16468.

(9) β-Hydride elimination reactions from Pd exhibit large primary kinetic isotope effects (>5). See: Mueller, J. A.; Goller, C. P.; Sigman, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 9724.

(10) (a) Cui, X.; Li, J.; Liu, L.; Guo, Q. X. *Chin. Chem. Lett.* **2007**, *18*, 625. (b) For studies on the reactivity of Pd complexes that contain both an NHC ligand and an acac-derived ligand in Pd-catalyzed N-arylation reactions, see: Marion, N.; Navarro, O.; Stevens, E. D.; Ecarnot, E. C.; Bell, A.; Amoroso, D.; Nolan, S. P. *Chem. Asian. J.* **2010**, *5*, 841.

(11) (a) Jones, R. C. *Tetrahedron Lett.* **2020**, *61*, 151471. (b) Harada, S.; Yano, H.; Obora, Y. *ChemCatChem* **2013**, *5*, 121. For examples of acac or similar ligands in Pd(II) complexes for Suzuki-Miyaura , Mizoroki-Heck, or Sonogashira reactions see (c) Kim, M. J.; Jung, M. J.; Kim, Y. J.; Sung, H. K.; Lee, J. Y.; Ham, S. J.; Park, C. P. *Tetrahedron Letters* **2018**, *59*, 2989. (d) Saxena, P.; Muragavel, R. *Journal of Organometallic Chemistry* **2018,** *868*, 76. (e) Yuan, L.; Xu, Y.; Hu, X.; Yang, G.; Wu, Y. *Journal of Molecular Catalysis A: Chemical* **2015**, *396*, 55. (d) Hajipour, A. R.; Shirdashtzade, Z.; Azizi, G. *Appl. Organometal. Chem.* **2014**, *28*, 696.

(12) Reactions conducted by GAG.

(13) Reaction conducted by MSF.

(14) See List of Ligands (pg xxii) for the structure of ligands 2,6-Bis[(4S)-4-phenyl-2-oxazolinyl]pyridine and (*R*)-Ph-quinox.

(15) Fornwald, R. M.; Fritz, J. A.; Wolfe, J. P. *Chem. Eur. J.* **2014**, *20*, 8782.

(16) Banerjee, A.; Yamamoto, H. *Chem. Sci.* **2019**, *10*, 2124.

(17) Peterson, L. J.; Luo, J.; Wolfe, J. P. *Org. Lett.* **2017**, *19*, 2817.

(18) Shen, K.; Wang. Q. *Chem. Sci.* **2015**, *6*, 4279.

(19) Howard, J. L.; Sagatov, Y.; Repusseau, L.; Schotten, C.; Browne, D. L. *Green Chem.,* **2017**, *19*, 2798.

(20) Prepared by Michael R. Gatazka.

(21) Luo, B.; Gao, J.-M.; Lautens, M. *Org. Lett.* **2016**, *18*, 4166.

(22) Niljianskul, N.; Zhu, S.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2015**, *54*, 1638.

(23) Berman, A. M.; Johnson, J. S.; *J. Org. Chem.* **2006**, *71*, 219.