

THE DEVELOPMENT OF PALLADIUM CATALYZED REGIOSELECTIVE
REARRANGEMENTS AND CROSS-COUPPLINGS

by

Oliver Daniel Jackson

A dissertation submitted in partial fulfillment
of the requirements for the degree

of

Doctor of Philosophy

in

Chemistry

MONTANA STATE UNIVERSITY
Bozeman, Montana

May 2026

©COPYRIGHT

by

Oliver Daniel Jackson

2026

All Rights Reserved

DEDICATION

This dissertation is dedicated to my grandmother Renée Jackson

ACKNOWLEDGEMENTS

First and foremost, I would like to express my deepest gratitude to all the educators and staff that have supported and guided me on my academic journey thus far.

To Dr. Mark McLaughlin, your passion and enthusiasm towards teaching organic chemistry during my senior year undergraduate laboratory class and during my summer internship with you, inspired me to pursue a career in this field. I am forever grateful for the connection to your former PhD advisor Dr. Matthew Cook, paving the way towards my career in the United States.

To my former PhD advisor Matt, thank you for your patience and support during the first two years of my time at Montana State University. Your consistent effort to train and develop students in the lab molded me into the organometallic chemist that I am today. Whilst I will certainly not miss being grilled at the whiteboard from time to time, you are a brilliant organic chemist and can be described as an encyclopedia of named organic reactions.

To my current advisor Sharon Neufeldt, thank you for your willingness to take me into your laboratory following Matt's departure to sunny California. Over the past four years, I have grown so much both professionally and personally because of your dedication to mentorship and teaching. Looking back, I cannot believe the success we have had during our time together and if it was not for you, I would not be graduating with my PhD.

I am grateful to all my lab mates both past and present. Thank you for creating a positive and hard-working research environment, fostering growth and helping to develop leadership qualities. This in turn has enabled me to develop my own mentorship skills and it has been a true pleasure to witness my undergraduate students become the talented researchers that they are today.

I am very grateful to my committee members, Dr. Mary Cloninger, Dr. Michael Mock, Dr. David Fialho and Dr. Tom Livinghouse, for your commitment to teaching and your constant support. I would also like to thank Dr. Steven Holmgren for making my job as a teaching assistant so much easier and for the occasional (real) football banter. Dr. Christopher Lemon has also been a source of unwavering support and has always been willing to provide great ideas towards my research projects, thank you.

I am also grateful to the chemistry and biochemistry department staff, in particular Dr. Doreen Brown, for always having my back behind the scenes and making sure I completed departmental requirements in a timely manner. Additionally, my sincere thanks go to Dr. Brian Tripet for cleaning up my mess and his expertise in setting up complex 2D-NMR experiments.

Lastly, I would like to thank the people that have sacrificed for me to be in the position that I am in today. To my father Michael, thank you for showing me from an early age what it means to work extremely hard at your job. You always wanted better for me and your constant advice of sticking to my education eventually paid off. Thank you to my mum Heather, for always prioritizing my education and raising us to be caring and genuine. To my brothers Adam and Elliott, we endured so much growing up together in a working-class town in Greater Manchester and to see us all thriving today is a testament to hard work does pay off. Finally, to Grandma Renee, thank you for taking me out on trips when I was younger to experience the beautiful English countryside and to the Blackpool seaside. I think in many ways I can attribute my thought process in chemistry to most of our experiences together, driven by nature and curiosity.

TABLE OF CONTENTS

1. INTRODUCTION	1
Allylic Substitution Reactions	1
Controlling Selectivity in Allylic Substitution Reactions	2
Asymmetric Synthesis of All-Carbon Quaternary Stereocenters via Branched- Selective Tsuji-Trost Allylation Reactions.....	4
Cascade Reactions in Organic Synthesis	5
C—N and C—S Cross-Coupling	6
Catalyst Activation.....	7
Oxidative Addition at Pd(0)	9
Conventional Site-Selectivity of Di-Halogenated Heteroarenes	10
Isohyptic Catalysis.....	12
References	19
 2. HIGHLY DIASTEREO- AND BRANCHED SELECTIVE REARRANGEMENT OF SUBSTITUTED <i>N</i> -ALLOC- <i>N</i> -ALLYL YANMIDES	25
Contribution of Authors and Co-Authors	25
Manuscript Information	26
Abstract	27
Introduction.....	28
Results and Discussion	29
Optimization Studies.....	29
Substrate Scope	30
Reaction Stereospecificity and Synthetic Utility	32
Origin of Stereoselectivity	33
Conclusions.....	36
References.....	37
 3. C2-SELECTIVE PALLADIUM-CATALYZED C—S CROSS-COUPPLING OF 2,4- DIHALOPYRIMIDINES	40
Contribution of Authors and Co-Authors	40
Manuscript Information	41
Abstract	42
Introduction.....	43
Results and Discussion	44
Optimization Studies.....	44
Substrate Scope	47
Synthetic Utility	49
Mechanistic Studies	50
Conclusions.....	53

References	54
4. ISOHYPsic Pd-CATALYZED CROSS-COUPling ENABLES C2-SELECTIVE AMINATION OF 2,4-DICHLOROPYRIMIDINES	58
Contribution of Authors and Co-Authors	58
Manuscript Information	59
Abstract	60
Introduction	61
Results and Discussion	64
Optimization Studies	64
Substrate Scope	64
Mechanistic Proposal	67
Experimental Corroboration of Mechanism	69
Comparison to Catalyzed S _N Ar	72
Analysis of Other Catalysts	73
Conclusions	73
Acknowledgements	74
Funding	74
Author Contributions	74
References	75
5. TOWARD THE SYNTHESIS AND CHARACTERIZATION OF A LOW-VALENT, THERMALLY STABLE PALLADIUM(0) COMPLEX.....	81
Introduction	81
Results and Discussion	84
Synthesis of (Ph ₂ -COD) Ligand.....	84
Synthesis of Pd(Ph ₂ -COD) ₂ (Pathway 1).....	85
Assessment of Pd(Ph ₂ -COD) ₂ Stability	86
Synthesis of Pd(Ph ₂ -COD) ₂ (Pathway 2).....	87
Conclusions	88
References	89
6. CONCLUSIONS.....	91
Asymmetric Synthesis of All-Carbon Quaternary Stereocenters via Auto-Tandem Catalysis.....	91
C2-Selective Amination and Thiolation of 2,4-Dichloropyrimidine via Pd(II) Promoted Isohypsic Catalysis	92
Toward the Synthesis and Characterization of a Low-Valent Thermally Stable Pd(0) Complex.....	93
7. APPENDICES.....	94

TABLE OF CONTENTS CONTINUED

A. APPENDIX A: CHAPTER TWO SUPPORTING INFORMATION	94
B. APPENDIX B: CHAPTER THREE SUPPORTING INFORMATION	334
C. APPENDIX C: CHAPTER FOUR SUPPORTING INFORMATION.....	577
D. APPENDIX D: CHAPTER FIVE SUPPORTING INFORMATION	730

LIST OF TABLES

Table	Page
2.1 Selected Optimization Studies	30
3.1 Optimization of a C2-Selective Cross-Coupling of 2,4-Dichloropyrimidines	46

LIST OF FIGURES

Figure	Page
1.1 General Catalytic Cycle of the Pd-catalyzed Allylic Substitution Reaction.....	2
1.2 Formation of Pd η^3 -Allyl Intermediates Starting From a 1,3-Disubstituted Alkene.....	4
1.3 Chemical Structures of Cortisone and Morphine with the All-carbon Quaternary Stereocenter(s) Highlighted	5
1.4 General Catalytic Cycle of the Buchwald-Hartwig Amination Reaction	7
1.5 Selected Examples of Commercially Available Pd(II) Precatalysts Commonly Supported by Phosphine or N-heterocyclic Carbene Ligands	9
1.6 Calculated Bond Dissociation Energies (BDEs) in kcal/mol for Selected Dihalogenated Heteroarenes. The Highlighted Halide Corresponds to the Conventional Site of Reactivity	11
1.7 Pyrimidines in High-Value Pharmaceutical Drugs	12
1.8 Proposed Mechanism of the Cobalt(III)-Catalyzed Isohypsic Access to Isoquinolines...	14
1.9 Proposed Mechanism of the Pd(II)-Catalyzed Oxidative Heck Reaction Enabling the Formation of Substituted Benzoquinones.....	14
1.11 Proposed Mechanism of the Pd(II) Promoted Desymmetrization of Cyclohexenediones	15
1.12 (A) Tandem Heteroallylation-Buchwald-Hartwig Amination (B) Illustration of Isohypsic-Redox Tandem Catalysis	16
1.13 Catalytic Cycle of Metallaphotoredox C—N Coupling	17
3.1 Scope of C2-Selective Thiolation. Isolated Yields of the Indicated Regioisomer. Ratios Represent C2:C4-Functionalized Products Prior to Purification Based on ^1H NMR Analysis of the Crude Reaction. ^a Calculated Isolated Yield Adjusted to Account for ~96% Purity (Isolated Product is Contaminated by a Small Amount of C4-Functionalized Product). Variable Selectivity was Observed on Smaller Scale Trials with Certain Thiols: ^b Selectivity as low as 3:1 was Observed on a Smaller Scale. ^c Selectivity as low as 1:3 was Observed on a Smaller Scale. ^d The Catalyst-Free Control ($\text{S}_{\text{N}}\text{Ar}$) Favors the Same Regiosomer	48
3.2 (A) For heteroarenes 48 and 49 , $14e^-$ Pd Favors the Site with the Weaker C—Cl bond, while $12e^-$ Pd Favors the Site with the Larger LUMO coefficient. For Pyrimidine 1 , Both Factors Favor the Same Site (C4); (B) DFT Calculations Suggest that both	

12e ⁻ and 14e ⁻ Pd Should Favor Oxidative Addition at C4; (C) a Suzuki Coupling Under Conditions Analogous to the Thiolation Reaction Favors C4; (D) a C2-Functionalized Product is not Thermodynamically Favored Based on DFT Calculations; (E) C–S Coupling is not Reversible.	52
4.1 Relevance and Selectivity of Reactions of 2,4-dihalopyrimidines. (A) 4-Substituted-2-(arylamino)pyrimidines in Protein Kinase Inhibitors. (B) Conventional Selectivity of Cross-Coupling and S _N Ar. (C) Mechanism of Traditional Pd-Catalyzed Cross-Coupling Reactions. (D) Bond Strengths and LUMO Coefficients Favor Oxidative Addition at C4. (E) C2-Selective Amination Enabled by a Bulky C5 Substituent. (F) Chemoselective Approach to C2-Selective Amination.....	63
4.2 Pd-Catalyzed C2-Amination of Dihalopyrimidines. (A) Optimization. (B) Scope. (C) Diversity-Oriented Synthesis of Drug-Like Analogues. Conditions: (i) <i>o</i> -(POMe ₂)C ₆ H ₄ NH ₂ (1 equiv), HCl (excess), <i>i</i> PrOH, 70 °C, 24 h; (ii) <i>o</i> -(SO ₂ <i>i</i> Pr)C ₆ H ₄ NH ₂ (1 equiv), HCl (excess), <i>i</i> PrOH, 70 °C, 24 h; (iii) 3-Pyridylboronic acid (1 equiv), Pd(PPh ₃) ₄ (4.4 mol %), K ₂ CO ₃ (2 equiv), dioxane/H ₂ O (1:1), 90 °C, 72 h.	66
4.3 Mechanistic information. (A) A Suzuki-Miyaura Coupling Gives Conventional C4 Selectivity Under Conditions that Afford C2-Selective Amination (B) DFT Calculations Support a Redox-Neutral (Isohypsic) Mechanism for Amination; Calculated at the SMD(<i>p</i> -xylene)-MN15/def2-TZVPD//SMD(<i>p</i> -xylene)-MN15L/6-31G(d) (C, H)/6-31+G(d) (N, Cl, O)/LANL2DZ(Pd) Level of Theory; Free Energies in kcal/mol.....	69
4.4 Experimental Data are Consistent with Pd(II)-Catalyzed Mechanism. (A) Substrate 1 Coordinates to Pd ^{II} Through N1. (B) Pd ⁰ Sources Lead to Worse Selectivity. (C) C2-Selective Amination is Insensitive to Pure O ₂	71
4.5 Proposed Isohypsic Catalytic Cycle.....	72
5.1 Chemical Structures of Commercially Available Pd(0) Precatalysts	82
5.2 Structures of Metal Precatalysts Bearing Cyclooctadiene Derived Ligands with Documented Limitations.....	83
5.3 Synthesis of the (Ph ₂ -COD) Ligand (Pathway 2) and ¹ H-NMR of Product Mixture 4a and 4b Zoomed in on the Alkene Region	85
5.4 Synthesis Route 1 towards Pd(Ph ₂ -COD) ₂ and ¹ H-NMR of Complex 5 Zoomed in on the Alkene Region.....	86

LIST OF SCHEMES

Scheme	Page
1.1 General Example of an Allylic Substitution Reaction Leading to the Formation of Linear and Branched Products	3
1.2 General Mechanisms for Oxidative Addition Leading to Site-selective Cross-Coupling	9
1.3 Ziegler-Natta Polymerization of Olefins Involving a 1,2-Migratory Insertion Illustrated with a Metallocene Catalyst.....	13
1.4 Pd(II) Catalyzed [3,3] Sigmatropic Rearrangement of Allylic Esters	15
2.1 TOC Graphic for Manuscript in Chapter Two	27
2.2 Substrate Scope.....	32
2.3 Additional Allylic Substitution and Synthetic Utility Studies: (A) Alkene Stereospecificity, (B) Diaryl Allyl Substitution and (C) Spirocyclic Nitrile Formation....	33
2.4 Summary of DFT Analysis Examining the Diastereoselectivity in the Formation of 2a. ^a DFT Calculations Done At CPCM (Trifluorotoluene) M06L/BSII//ONIOM(M06L/BSI:PM6), Where BSI = 6-31+G(d) (C, H, P, O) /LANL2DZ (ECP Pd) and BSII = 6-311++G(2d,2p) (C, H, P, O)/LANL2DZ (ECP Pd); ^b Quasi-harmonic Solvent and Temperature (333.15 K) Corrected Gibbs Free Energies at 1 mol L ⁻¹ Standard State Are Reported; ^c For Optimised Structures, See Appendix A	35
3.1 TOC Graphic for Manuscript in Chapter Three.....	42
3.2 Derivatization of 2,4-Dichloropyrimidines.....	44
3.3 Divergent Synthesis of Analogues of a Reverse Transcriptase Inhibitor (PNU-142721). 49	
5.1 Attempted Synthesis Of (Ph ₂ -COD) via a Heck Cross-Coupling.....	84
5.2 Synthesis of [Ni(bpy)(COD)]	87
5.3 Synthesis Route 2 to Accessing Pd(Ph ₂ -COD) ₂	87

ABSTRACT

Palladium catalysts were used to control selectivity in two different classes of reaction. The first reaction, developed in the Cook lab, aims to tackle the limited methods available towards the asymmetric synthesis of all-carbon quaternary stereocenters, which are a common motif in natural products and high-value pharmaceuticals. We developed an auto-tandem, branched-selective rearrangement of substituted *N*-alloc-*N*-allyl ynamides that proceeds through two separate and distinct catalytic cycles using the same catalytic entity. This reaction provides ready access to complex quaternary nitrile products with vinylogous stereocenters in excellent diastereoselectivity (>20:1 d.r.), including contiguous all-carbon quaternary centers. The stereochemical outcome is determined via a Pd(0)-catalyzed dipolar ketenimine aza-Claisen rearrangement and computational studies exemplify the key role ligand geometry plays. The second reaction, developed in the Neufeldt lab, aims to disrupt the inherent reactivity trends of 2,4-dihalogenated pyrimidines. 2,4-Disubstituted pyrimidines appear frequently in bioactive small molecules; however, strategies to elaborate the pyrimidine core through divergent synthesis (e.g., to prepare a library) are limited because 2,4-dihalopyrimidines tend to react only at C4 in both cross-couplings and nucleophilic aromatic substitutions. Substrate-controlled approaches can enable C2-selective functionalization, but a catalyst-controlled strategy to invert the conventional selectivity of cross-coupling would be more step-economical and general. Here we report that Pd(II) precatalysts supported by bulky *N*-heterocyclic carbene ligands uniquely effect C2-selective cross-coupling of 2,4-dichloropyrimidines with thiols and amines. The unusual selectivity is proposed to arise from a novel isohypsic mechanism in which there is no oxidative addition step, enabling a new mode of Pd catalyzed cross-coupling. Additionally, we demonstrated the synthesis of a novel thermally stable Pd(0) complex, Pd(Ph₂-COD)₂ with the potential for future applications in cross-coupling reactions.

CHAPTER ONE

INTRODUCTION

Allylic Substitution Reactions

The palladium (Pd) catalyzed allylic substitution reaction is an indispensable tool in organic synthesis, commonly applied in the late-stage functionalization of high-value small molecules including pharmaceuticals, agrochemicals and organic materials.¹ These reactions employ a transition metal catalyst, a nucleophile and an alkene electrophile. The transformation is often applied in academic and industrial settings to access new sp^3 chemical bonds including C—C, C—N, C—S and C—O.²

The Pd catalyzed allylic substitution reaction proceeds through a catalytic cycle involving four elementary steps: alkene complexation, oxidative addition (ionization), nucleophilic addition and alkene decomplexation (Figure 1.1). Initial complexation takes place when a Pd(0) catalyst coordinates to an alkene in η^2 fashion. During oxidative addition, Pd inserts into the carbon—leaving group bond on the alkene electrophile. This generates a cationic η^3 Pd(II) π -allyl complex resulting in a partial positive charge located on both the Pd center and the allyl group, rendering both fragments susceptible to nucleophilic attack. The nucleophile may attack through two mechanistically distinct pathways. Soft nucleophiles, such as those derived from conjugate acids with a $pK_a < 25$ (e.g. malonates and β -dicarbonyl compounds), attack the least hindered carbon of the allyl moiety via an outer-sphere mechanism, whereas hard nucleophiles (e.g. alkyllithium and Grignard reagents) attack the metal center directly through an inner-sphere pathway (Figure 1.1.)³

In the latter case, reductive elimination follows nucleophilic attack to access the new C—Nu bond. The final step is decomplexation of the alkene completing the catalytic cycle and reforming Pd(0).

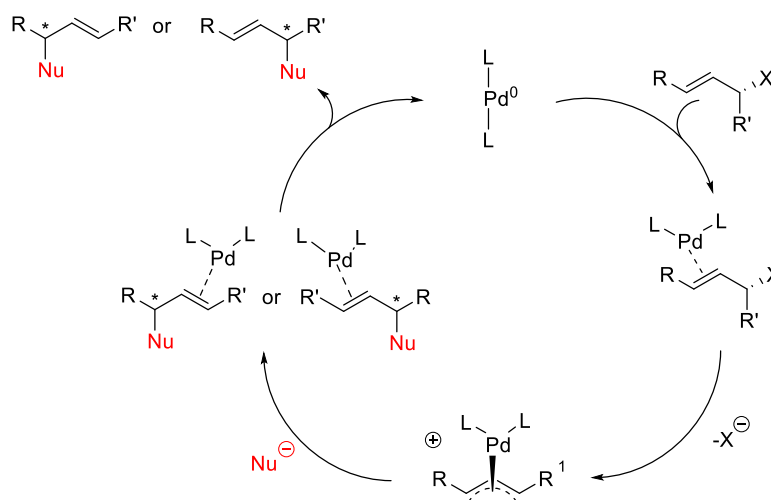


Figure 1.1 General Catalytic Cycle of the Pd-Catalyzed Allylic Substitution Reaction

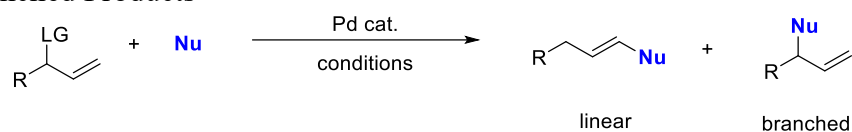
Transition metal catalyzed allylic substitution reactions were first pioneered by Jirō Tsuji in 1965 and later adapted by Barry Trost for the incorporation of phosphine ligand promoted Pd catalyzed approaches.^{4,5} The transformation later became known as the Tsuji-Trost reaction due to its high functional group tolerance, relatively mild reaction conditions and its overall contribution to the field of asymmetric catalysis. Prior to the development of this approach, synthetic chemists relied on alternative methodologies requiring high temperatures and strong base to construct new $\text{C}(\text{sp}^3)\text{—}(\text{C}(\text{sp}^3))$ and $\text{C}(\text{sp}^3)\text{—heteroatom}$ bonds.⁶

Controlling Selectivity in Allylic Substitution Reactions

The Tsuji-Trost reaction becomes more synthetically useful depending upon the nature of the substituents bound to the alkene. For 1,3-disubstituted alkenes, the steric bulk, electronic effects and the relative configuration of substituents bound to the alkene (cis/trans), all impact the regioselective outcome of the reaction. In theory there are two possible regioisomers: linear and

branched. The linear substituted product results from a nucleophilic attack at the least substituted carbon of the π -allyl Pd complex (Scheme 1.1) and is typically the major product as it is less sterically hindered and thermodynamically favored.⁷ The kinetically favored branched product results from nucleophilic attack at the more substituted carbon of the π -allyl Pd complex. The pathway leading to the branched product is significantly higher in energy when employing a Pd catalyst, due to fast π - σ - π isomerization between η^1 - η^3 haptomers.⁸

Scheme 1.1 General Example of an Allylic Substitution Reaction Leading to the Formation of Linear and Branched Products



Selectivity for the branched product has been achieved by employing bulky bi-dentate phosphine ligands, which prevent nucleophilic attack at the less substituted carbon of the η^3 π -allyl Pd complex.⁸ However, this approach has proven to be limited due to poor functional group tolerance. Alternative transition metals such as iridium and molybdenum provide more robust routes to access the branched isomer by slowing down the rate of π - σ - π isomerization between η^1 - η^3 haptomers.⁹ The stereochemical outcome of the reaction favoring the branched product may also be controlled by application of a chiral phosphine ligand.³

Prochiral electrophiles add an additional layer of complexity in attempts to control both the diastereoselective (when multiple stereocenters are present) and enantioselective outcome of the reaction. A single enantiomer can be accessed when both substituents on a 1,3-disubstituted alkene are an aryl or a bulky alkyl group. In these cases, the *syn/syn* isomers are energetically favored over the *syn/anti* and *anti/anti* isomers. (figure 1.2).²

Asymmetric Synthesis of All-Carbon Quaternary Stereocenters via Branched-Selective Tsuji-Trost Allylation Reactions

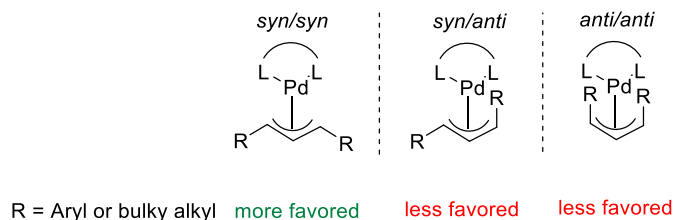


Figure 1.2 Formation of $\text{Pd } \eta^3\text{-allyl}$ Intermediates Starting from a 1,3-Disubstituted Alkene

One key synthetic application of the Tsuji-Trost reaction is the asymmetric construction of all-carbon quaternary stereocenters. Historically, achieving efficient construction of all-carbon quaternary centers remains a daunting challenge, primarily due to the steric congestion around each center.¹⁰ Increasing the number of contiguous quaternary centers inherently leads to more complex synthetic routes. Contiguous all-carbon quaternary centers are often found in natural products and active pharmaceutical ingredients (API's).¹¹ In fact, 20 of the 200 best-selling pharmaceuticals reported in 2018 contain at least one all-carbon quaternary stereocenter (examples in Figure 1.3).¹² However, the majority of these high-value intermediates cannot be synthesized in a laboratory and are sourced directly from nature.¹³ Therefore, the ability to access such motifs would provide a vital, strategically useful tool for the synthesis of currently inaccessible prodrugs and natural products with application towards medicinally relevant pharmaceuticals.

Prior methods to synthesize these all-carbon quaternary centers asymmetrically include the works of Stoltz who demonstrated an iridium-catalyzed asymmetric allylic alkylation of acyclic β -ketoesters.¹⁴ Limitations of allylic substitution reactions include the requirement of a strong base, which limits functional group tolerance. In addition, high temperatures are required to functionalize hindered tertiary centers.¹⁵

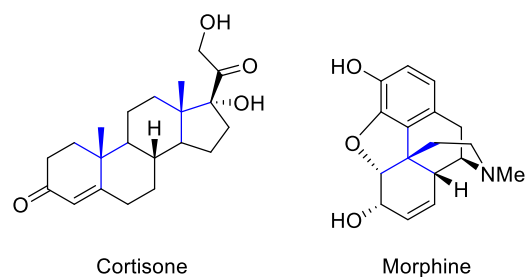


Figure 1.3 Chemical Structures of Cortisone and Morphine with the All-Carbon Quaternary Stereocenter(s) Highlighted.

Cascade Reactions in Organic Synthesis

Cascade organic reactions (or domino/tandem reactions) are powerful synthetic processes where multiple chemical bonds are formed in a single vessel without isolating intermediates. Cascade reactions allow chemists direct access to functionally complex molecules from simple achiral starting materials.¹⁶ These diverse synthetic pathways provide step- and atom-economical routes, in contrast to linear synthetic methodologies that require sequential purification in a multi-step pathway. Cascade reactions typically require mild conditions, which drive the reaction forward via highly reactive, short-lived intermediate.¹⁷ Cascade reactions are advantageous when designing pathways to natural products, as nature has adapted analogous strategies.¹⁸ Although controlling the stereochemical outcome of a short-lived intermediate remains ambitious, successful examples of stereoselective multi-component cascade reactions include the gold catalyzed synthesis of Waitziacuminone and the palladium-catalyzed cascade sequence towards quaternary nitriles.^{19,20} To date, cascade reactions have yet to be applied towards the synthesis of multiple, contiguous all-carbon quaternary stereocenters.

Chapter 2 of this dissertation will detail the development of a cascade reaction enabling access to contiguous all-carbon quaternary stereocenters, asymmetrically with high-branched regioselectivity using a palladium catalyst supported by a chiral phosphine ligand.

C—N and C—S Cross-Coupling

Pd catalyzed cross-coupling reactions are a mainstay in organic synthesis. This is in part due to the broad functional group tolerance and high reproducibility of these methods for forming C(sp²)—heteroatom bonds.²¹ These reactions enable access to a broad range of APIs and facilitate the rapid development of compound screening libraries for structure activity relationship studies (SAR).²¹ A commonly used cross-coupling method is the Buchwald-Hartwig amination reaction, enabling C(sp²)—N bond formation. The reaction is broadly defined as the Pd catalyzed cross-coupling of amines with heteroaryl(pseudo)halides, resulting in the formation of a new C—N bond. More traditional approaches for C—N bond formation such as nucleophilic aromatic substitution (S_NAr), reductive amination, and amide coupling have limited applicability due to the harsh conditions employed. In contrast, the Buchwald-Hartwig amination has proven to be a robust reaction with broad application across several different electrophiles.²² Pd-catalyzed C(sp²)—S cross-coupling has also been demonstrated to enable access to a range of pharmaceutical targets, due to the prevalence of thioethers in a range of bioactive compounds.^{23,24}

The mechanism of the Buchwald-Hartwig amination reaction involves a catalytic cycle with three key elementary steps: oxidative addition, amine coordination/deprotonation, and reductive elimination (Figure 1.4). During oxidative addition, Pd inserts into the carbon—leaving group bond present on the electrophile (Ar—X) and Pd(0) is oxidized to Pd(II). The amine then coordinates to Pd and undergoes deprotonation to form the Pd(II) amido complex. Finally, reductive elimination takes place to construct the new C—N bond, reforming Pd(0) and completing the catalytic cycle.

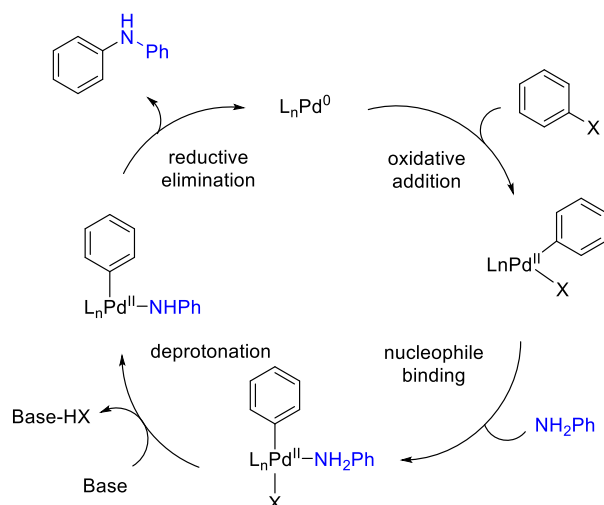


Figure 1.4 General Catalytic Cycle of the Buchwald-Hartwig Amination Reaction

Catalyst Activation

Within the context of transition metal catalyzed cross-coupling, generation of the active Pd(0) catalyst is an often-overlooked elementary step. Pd(II) precatalysts do not themselves participate in the catalytic cycle, and activation pathways are off-cycle. However, ignoring the activation mechanism can lead to complications when adapting reactions from lab-scale to the industrial scale, as differences in activation kinetics can cause high catalyst loading requirements, poor reproducibility, and unwanted side reactions (e.g., homocoupling).²⁵ There are several approaches to access the active Pd(0) catalyst that can enter the cross-coupling catalytic cycle. The first is to begin with a pre-formed Pd(II) pre-catalyst (e.g. Pd(OAc)₂) and combine this with the free ligand (Figure 1.4.). The anionic ligands also bound to palladium are displaced upon reduction to Pd(0) and are commonly described as “throwaway” ligands since they do not participate further in the catalytic cycle. An alternative approach is to begin from a Pd(0) precatalyst and combine this with the free ligand. In solution, the free ligand binds to Pd forming the active catalyst in-situ. In certain cases, the ancillary ligand is pre-bound to the Pd(0) complex (e.g. Pd(PPh₃)₄). From an industrial perspective, the Pd(II) precatalysts have greater utility since they are generally not prone

to oxidation and can often be stored and applied outside of an inert atmosphere glovebox. **Chapter 5** of this dissertation will discuss approaches towards the design, synthesis and isolation of a novel Pd(0) complex.

Studies have shown that the rate and mechanism of catalyst activation of Pd(II) to Pd(0) can impact the overall efficiency of cross-coupling reactions.²² Several research groups including those of Buchwald, Hazari, Organ, and Nolan, have dedicated years of research and development to commercializing bench stable Pd(II) precatalysts which work in a broad range of cross-coupling reactions (Figure 1.5).^{26,27,28} For example, the Hazari type pre-catalysts (bearing a tert-butyl indenyl ligand) are reported to be effective in preventing the formation of deleterious Pd(I) dimers.²⁶ The mechanism of activation for each class of named precatalyst has been investigated. There are several known pathways of activation for both of the Hazari and Nolan precatalysts however, these are generalized to outer-sphere nucleophilic attack of the η^3 -allyl moiety or initial dissociative ligand exchange/transmetallation, followed by reductive elimination.²⁹ The Buchwald palladacycle variants (generation 3 and 4) are activated by initial deprotonation of the Pd-amido complex followed by reductive elimination of the carbazole moiety.³⁰ Activation of Organ's Pd-PEPPSI-NHC complexes is promoted by initial ligand exchange/transmetallation followed by reductive elimination however, the preferred mechanism is highly dependent upon the nature of the nucleophile applied.³¹ Interestingly, the mechanism of activation of Pd-PEPPSI-NHC precatalysts with aniline remains unknown and is currently under investigation.³² Based on DFT calculations, Bao and co-workers proposed a redox-neutral sigma-bond metathesis pathway for the cross-coupling of chlorobenzene with aniline, whereby the Pd-PEPPSI-NHC precatalyst is not reduced to Pd(0); although this proposal has not been validated experimentally.³³ The proposed

mechanism is highly unlikely, due to application of potassium tert-butoxide as a base in this system, which is known to reduce Pd(II) to Pd(0).³⁴

Chapter 4 of this dissertation will discuss the role of Pd-PEPPSI-NHC complexes in redox neutral (isohypsic) catalysis.

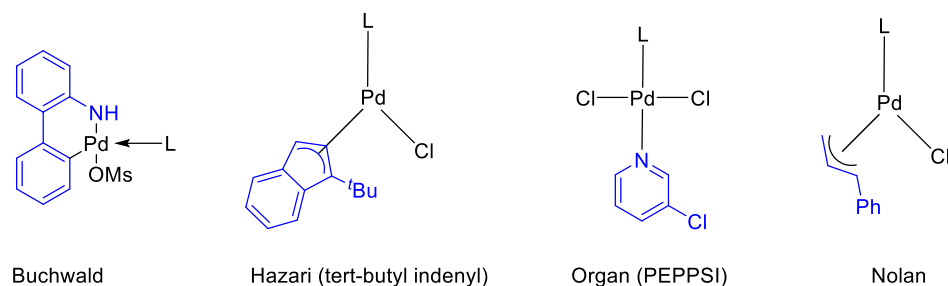
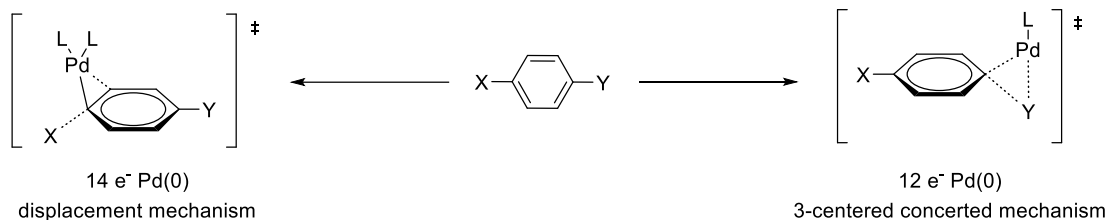


Figure 1.5 Selected Examples of Commercially Available Pd(II) Precatalysts Commonly Supported by Phosphine or *N*-heterocyclic Carbene Ligands

Oxidative Addition at Pd(0)



Scheme 1.2 General Mechanisms for Oxidative Addition Leading to Site-Selective Cross-Coupling

In the majority of Pd catalyzed cross-coupling reactions, oxidative addition is the selectivity determining step.³⁵ This becomes particularly important when considering an electrophile with multiple reactive sites present. In these cases, regioselectivity is dictated by which site (C—X or C—Y) oxidative addition takes place at most preferentially. (Scheme 1.2). There are two primary operative mechanisms for oxidative addition at Pd(0) of aryl halides (Scheme 1.2). First (left) is a nucleophilic displacement mechanism, which takes place at 14 e⁻ bisligated Pd(L)(L'). The second

(right) is a 3-centered concerted mechanism, taking place at 12 e⁻ monoligated Pd(L). The 3-centered concerted mechanism has also been reported to take place at 14 e⁻ bisligated Pd with a large L—Pd—L bite angle.³⁶ Therefore, the steric bulk of the ligand(s) applied to the cross-coupling reaction conditions, influences the ligation state of Pd and thus the mechanism of oxidative addition. Ultimately, this can enable ligand choice to influence the site at which cross-coupling takes place preferentially.³⁷ Ligand sterics enables the Buchwald-Hartwig amination to be effectively tuned towards the site and chemoselective functionalization of heteroarenes bearing multiple leaving groups, due to the extensive range of phosphine and *N*-heterocyclic carbene ligands that can be applied.

Conventional Site-Selectivity of Di-Halogenated Heteroarenes

Heteroarenes rank amongst the most prevalent classes of structural motifs in pharmaceutically relevant compounds. Therefore, their selective substitution when two (or more) halogens are present is of significant interest to the synthetic community.³⁸ Typically, aromatic ring substitution reactions are limited to C—H functionalization, electrophilic aromatic substitution, nucleophilic aromatic substitution, and cross-coupling. All of these reaction classes have established trends in reactivity and selectivity. In the context of cross-coupling of heteroaryl halides, bis-ligated Pd(L)(L') tends to preferentially undergo oxidative addition at sites adjacent to a heteroatom. This has been rationalized by Houk and Merlic to be related to C—X bond dissociation energy.³⁹ Hence, the most reactive site (typically the weaker bond) will react preferentially leading to the observed selectivity. For example, 2,4-dichloropyridine (Figure 1.6) (**1a**) conventionally reacts at the weaker C2—Cl position over the C4—Cl under cross-coupling conditions. The Neufeldt lab has used a ligand-based strategy to overcome the conventional C2 selectivity of **1a** by exploiting the larger LUMO coefficient at C4. Monoligated Pd(L)

preferentially undergoes oxidative addition at the site with the larger LUMO coefficient via the three-centered mechanism.⁴⁰ However, for 2,4-dichloropyrimidine (**1b**), both BDEs and LUMO coefficients favor reaction at C4, so there is no obvious substrate characteristic that can be exploited to achieve preferential reaction at C2. Hence, oxidative addition at Pd(0) always takes place at the C4 C—Cl bond regardless of the ligation state of Pd and the ligands applied.

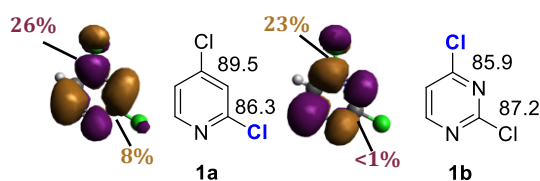


Figure 1.6 Calculated Bond Dissociation Energies (BDEs) in kcal/mol and LUMO coefficients for Selected Dihalogenated Heteroarenes. The Highlighted Halide Corresponds to the Conventional Site of Reactivity.^{37,40}

Developing a strategy to achieve C2-selective cross-coupling of 2,4-dihalopyrimidines would be valuable due to the prevalence of pyrimidine scaffolds in biologically active compounds (nucleic acids, alkaloids, folic acid, etc) in addition to synthetic analogs and pharmaceutical drugs (Figure 1.7).⁴¹

The pyrimidine core can be accessed via cyclocondensation between amidine, guanidine or thiourea derivatives with 1,3-diesters or 1,3-diketones.⁴² This strategy can enable the synthesis of pyrimidines substituted at both the 2 and 4 positions “from scratch”. However, a more modular method to functionalize both the 2 and 4 positions would be to proceed via pre-formed halogenated pyrimidines. Buchwald has demonstrated C2-selective amination of certain 2,4-dichloropyrimidines, however, a bulky C5 substituent is required in order to prevent reaction at C4.⁴³ Hence prior to the work described herein, there were no methods to achieve *catalyst-controlled* selective functionalization of 2,4-dihalopyrimidines.

Chapters 3 and 4 of this dissertation will detail the first demonstrations of a Pd catalyzed C2-selective thiolation and amination of 2,4-dichloropyrimidine.

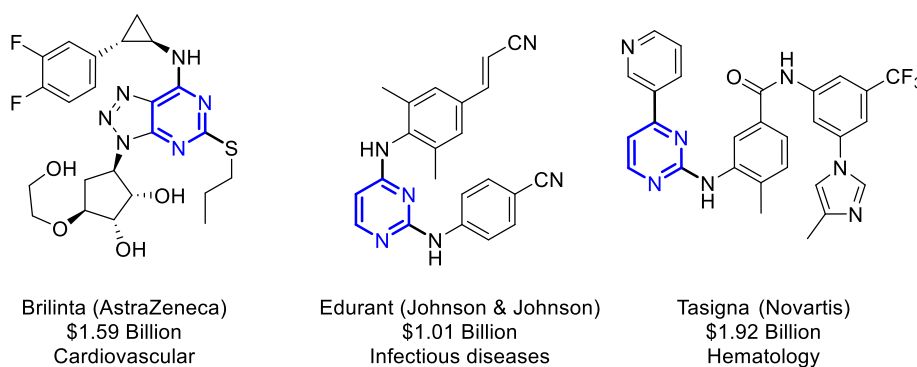


Figure 1.7 Pyrimidines in High-Value Pharmaceutical Drugs

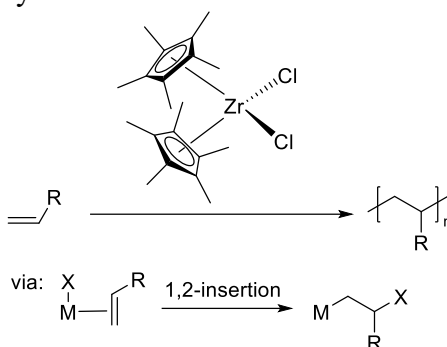
Isohypsic Catalysis

Transition metal mediated transformations usually proceed through catalytic cycles that involve oxidation and reduction of the metal. Less commonly, the oxidation state of the metal may remain unchanged throughout the entire catalytic cycle, referred to as isohypsic catalysis.⁴⁴ Lewis acid catalysis is technically a form of isohypsic catalysis, as a Lewis acid accepts an electron pair to activate a substrate without changing its own oxidation state throughout the catalytic cycle.⁴⁵ However, the term “Lewis acid catalysis” is generally used to describe processes for which the Lewis acid merely activates a substrate, and the mechanism otherwise takes place in the outer-sphere of the catalyst. In contrast, the term “isohypsic catalysis” is more useful when the catalyst mediates (or is a metal that might be expected to mediate) bond formation within its inner-sphere.⁴⁶

As an example, Ziegler-Natta catalysis is a powerful method used to polymerize α -olefins with high linearity and stereoselectivity.⁴⁷ The reaction is promoted by a transition metal catalyst (most commonly early d^0 transition metals including Ti, Zr, Hf) and an organoaluminum co-catalyst.⁴⁷ The transition metal catalyst does not behave as a traditional Lewis acid because the

primary mechanism of Ziegler-Natta catalysis involves an intramolecular 1,2-migratory insertion of an olefin (Scheme 1.3). The process can be described as isohypsic catalysis, because all of the mechanistic steps (olefin association and 1,2-migratory insertion) are redox-neutral. Indeed, isohypsic catalysis is perhaps most common for early transition metals (as opposed to late ones) because their reduction pathways are associated with high energy barriers and d^0 metals cannot be further oxidized.

Scheme 1.3. Ziegler-Natta Polymerization of Olefins Involving a 1,2-Migratory Insertion Illustrated with a Metallocene Catalyst⁴⁷



Isohypsic catalysis is also operative in certain reactions involving late transition metals, including the rhodium-catalyzed addition of organoboronates to unsaturated carbonyl compounds.⁴⁸ An isohypsic process catalyzed by Co(III) has also been used to synthesize a range of isoquinolines (Figure 1.8).⁴⁹ The mechanism of this reaction was proposed to proceed via reversible C—H activation through a concerted metalation-deprotonation pathway, followed by a 1,2-migratory insertion of an alkyne. C—N bond formation then takes place without change to cobalt's oxidation state due to cleavage of the N—O bond of the oxime ester, followed by facile acetate transfer in a concerted fashion affording the final isoquinoline product (Figure 1.8).

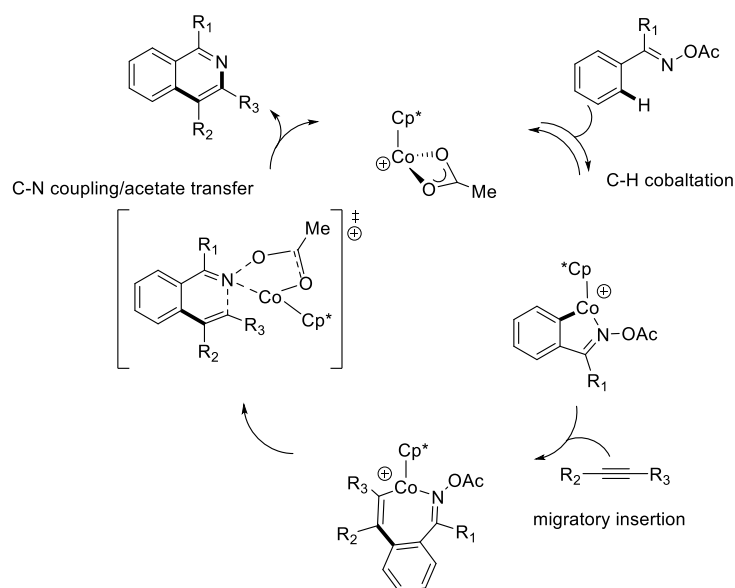


Figure 1.8 Proposed Mechanism of the Cobalt(III)-Catalyzed Isohypsic Access to Isoquinolines⁴⁹

With palladium in particular, certain classes of reactions also proceed through isohypsic mechanisms. These include the Pd(II)-catalyzed oxidative Heck reaction, used, for example, for the C—H functionalization of benzoquinone.⁵⁰

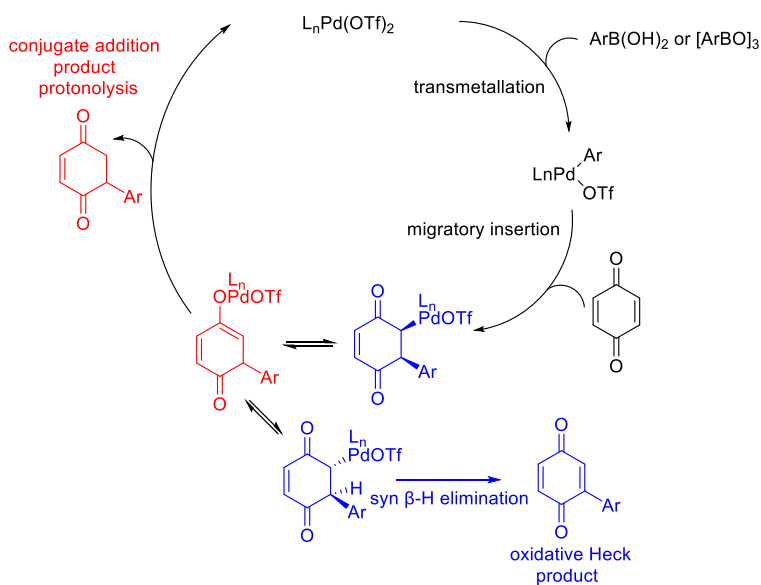


Figure 1.9 Proposed Mechanism of the Pd(II)-Catalyzed Oxidative Heck reaction Enabling Formation of Substituted Benzoquinones⁵⁰

The reaction also may proceed to provide the corresponding conjugate addition product. A Pd promoted desymmetrization of polycyclic cyclohexenediones was shown to provide access to five contiguous stereocenters with high diastereo and enantioselective control.⁵¹ The isohypsic mechanism proceeds via a Pd(II)-catalyzed conjugate addition desymmetrization reaction (Figure 1.11).

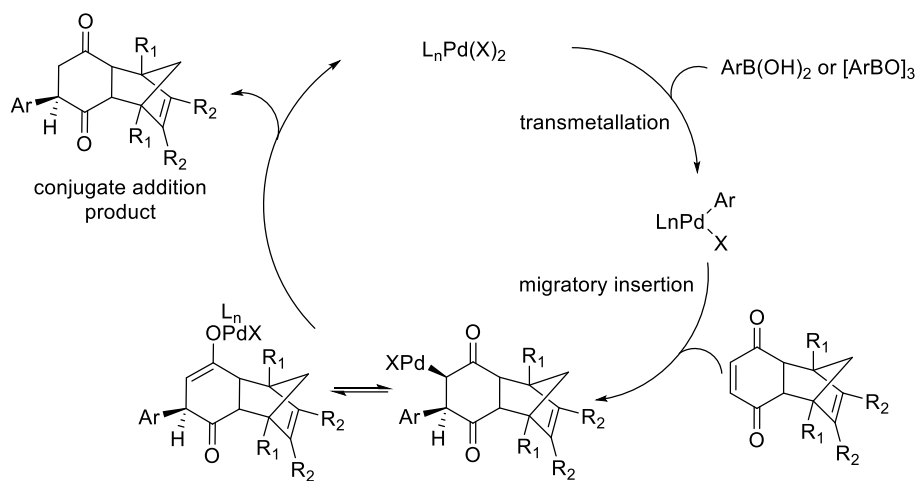
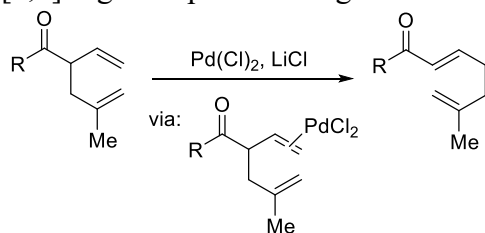


Figure 1.11 Proposed Mechanism of the Pd(II) Promoted Desymmetrization of Cyclohexenediones⁵¹

Pd(II) catalysts have also been shown to promote a wide range of [3,3]-sigmatropic rearrangements enabling new C—O, C—N, C—S and C—C bonds.⁵² Notably these transformations proceed through a π -Lewis acidic Pd(II) pathway (Scheme 1.4).

Scheme 1.4 Pd(II) Catalyzed [3,3] Sigmatropic Rearrangement of Allylic Esters



More recently, tandem isohypsic and redox active manifolds have been used to form multiple bonds in a single transformation.⁴⁴ This tandem sequence proceeds through the unification of Pd(II)-catalyzed isohypsic alkene heteroallylation (Figure 1.12A) with a redox active process such as a Suzuki-Miyaura coupling or a Buchwald-Hartwig amination (Figure 1.12B).

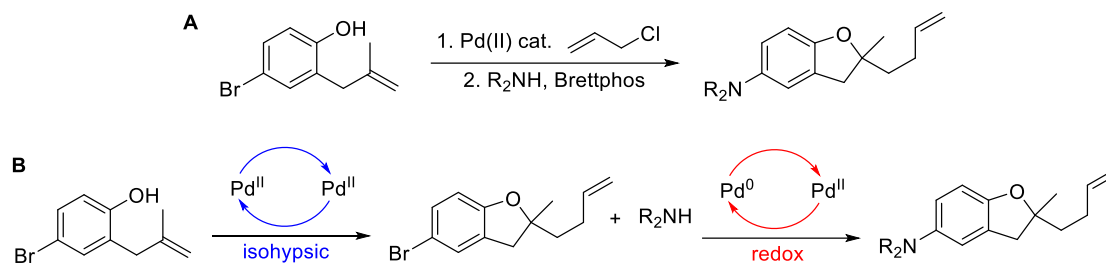


Figure 1.12 (A) Tandem Heteroallylation-Buchwald-Hartwig Amination Reaction and (B) Illustration of Isohypsic-Redox Tandem Catalysis

To date, however, all cross-coupling reactions catalyzed by transition metals are thought to proceed through traditional redox pathways (i.e., involving oxidative addition and reductive elimination). The traditional redox cycling is expected based on the reductive/oxidative roles of common reagents applied. For example, in a conventional Buchwald-Hartwig amination reaction, the organo(pseudo)halide serves as an oxidant for Pd(0), generating the organometallic oxidative addition adduct. The electron-rich amine nucleophile employed serves as a stoichiometric reductant of Pd(II) in the reductive elimination step. In many C—C bond-forming cross-couplings, organometallic reagents (e.g., arylboronic acids in a Suzuki-Miyaura coupling) serve as the stoichiometric reductants of Pd. In others, such as the Heck coupling, the base promotes on-cycle reduction step (e.g., deprotonation of a Pd-hydride).

Although the canonical cross-coupling reactions bring together an electrophilic and nucleophilic coupling partner via a Pd(0)/Pd(II) catalytic cycle, other cross-coupling variants use photo- or electrochemical control,^{53,54} couple two electrophiles together,⁵⁵ involve catalyst

oxidation states other than Pd(0)/Pd(II),⁵⁶ and/or use first-row metals like Ni or Co.^{57,58} Despite the variety of mechanistic manifolds through which cross-coupling can occur, even these more modern variants involve redox steps. For example, a Ni(I)/Ni(III) redox cycle is common for Ni-promoted metallaphotoredox catalysis.⁵⁹ These catalytic cycles generally proceed via initial generation of Ni(I) via single-electron transfer from a starting Ni(II) precatalyst. Oxidative addition then takes place most commonly at Ni(I) leading to a high-valent Ni(III) intermediate. A redox neutral radical addition of an organic radical then takes place followed by reductive elimination, regenerating the starting Ni(I) complex.⁵⁹ Finer details regarding the resting states of metallaphotoredox catalytic cycles and the roles of base in electron transfer quenching have been thoroughly investigated by MacMillan and co-workers (Figure 1.13).⁵⁹

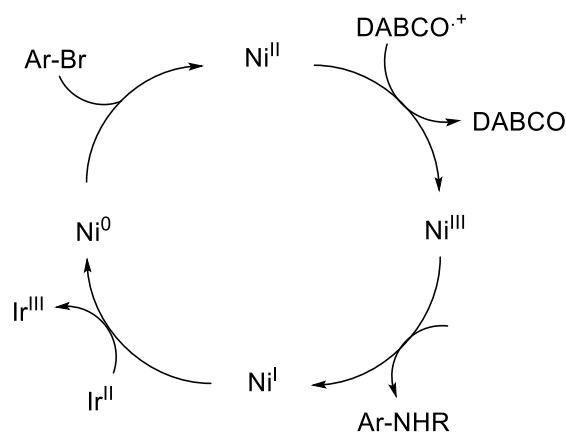


Figure 1.13. Catalytic Cycle of Metallaphotoredox C—N Coupling⁵⁹

Of relevance to **Chapter 4** of this dissertation, migratory insertion is an example of a “redox-neutral” elementary organometallic step for which the oxidation state of the metal center remains unchanged. This step involves an anionic ligand migrating to a *cis*-positioned neutral ligand creating a vacant coordination site at the metal center. This elementary step is critical to several multi-ton scale industrial processes including the Cativa and Monsanto Acetic Acid

processes.^{60,61} There are two types of migratory insertion reactions: a 1,1 and a 1,2-migratory insertion. A 1,1-migratory insertion involves a ligand migrating to the *same atom* of an unsaturated ligand also bound to the transition metal (like CO), essentially inserting the unsaturated ligand into the metal-X bond; while a 1,2-insertion involves a ligand migrating to the second atom of an unsaturated ligand (like an alkene or alkyne) as demonstrated in the Pd-catalyzed Mizoroki-Heck coupling reaction.⁶² The isohypsic mechanism described in **Chapter 4** of this dissertation includes a mechanistically distinct migratory insertion-like step (i.e., that is neither a 1,1- nor a 1,2-migratory insertion), where Pd(II) facilitates an intramolecular nucleophilic attack on C2 of 2,4-dichloropyrimidine by an amido ligand.

References

1. Yonehara, K.; Hashizume, T.; Mori, K.; Kouichi, O.; Uemura, S. Palladium-Catalyzed Asymmetric Allylic Substitution Reactions Using New Chiral Phosphinite-Oxazoline Ligands Derived from D-Glucosamine. *J. Org. Chem.* **1999**, *64*, 9374-9380
2. Pamies, O.; Margalef, S.; Canellas, S.; James, J.; Judge, E.; Guiry, P. J.; Moberg, C.; Backvall, J.; Pfaltz, A.; Pericas, M. A.; Dieguez, M. Recent Advances in Enantioselective Pd-Catalyzed Allylic Substitution: From Design to Applications, *Chem. Rev.* **2021**, *121*, 4373–4505
3. Trost, B. M.; Vranken, D. L. V. Asymmetric Transition Metal-Catalyzed Allylic Alkylations, *Chem. Rev.* **1996**, *96*, 395–422
4. Tsuji, J.; Takahashi, H.; Morikawa, M. Organic syntheses by means of noble metal compounds XVII. Reaction of π -allylpalladium chloride with nucleophiles, *Tetrahedron Letters*, **1965**, *49*, 4387-4388
5. Trost, B. M.; New synthetic reactions. Allylic alkylation, *J. Am. Chem. Soc.* **1973**, *95*, 292–294
6. Hardee, D. J.; Kovalchuke, L.; Lambert, T. H. Nucleophilic Acyl Substitution via Aromatic Cation Activation of Carboxylic Acids: Rapid Generation of Acid Chlorides under Mild Conditions, *J. Am. Chem. Soc.* **2010**, *132*, 5002–5003
7. Kim, B. S.; Hussain, M. M.; Norrby, P. O.; Walsh, P. J. Breaking Conjugation: Unusual Regioselectivity with 2-Substituted Allylic Substrates in the Tsuji-Trost Reaction, *Chem Sci.*, **2014**, *5*, 1241-1250
8. Bai, D. C.; Wang, W. Y.; Chen, D.; Li, H.; Liu, Q. R.; Ding, C. H.; Chen, B.; Hou, X. L. Palladium/N-heterocyclic carbene catalysed regio and diastereoselective reaction of ketones with allyl reagents via inner-sphere mechanism, *Nature Communications*, **2016**, *7*, 11806
9. Liu, J.; Cao, W. B.; You, S. L. Ligand-enabled Z-retentive Tsuji-Trost reaction, *Chem*, **2024**, *10*, 1295–1305
10. Xiong, Y. and Zhang, G., Enantioselective Synthesis of Quaternary Stereocenters via Chromium Catalysis, *Org. Lett.* **2016**, *18*, 5094–5097
11. Marek, I.; Minho, Y.; Pasco, M.; Mejuch, T.; Gilboa, N.; Chechik, H.; and Das, J.P, All-carbon quaternary stereogenic centers in acyclic systems through the creation of several C-C bonds per chemical step *J. Am. Chem. Soc.*, **2014**, *136*, 2682-2694

12. Fuentes, A. V.; Pineda, M.D. and Nagulapalli Venkata, K. C., Comprehension of Top 200 Prescribed Drugs in the US as a Resource for Pharmacy Teaching, Training and Practice *Pharmacy*, **2018**, *6*, 43
13. Trost, B.M.; Malhotra, S. and Chan W.H. Exercising regiocontrol in palladium-catalyzed asymmetric prenylations and geranylation: unifying strategy toward flustramines A and B *J.Am. Chem. Soc.*, **2011**, *133*, 7328-7331
14. Liu, W. B.; Reeves C. M.; Stoltz, B. M. Enantio-, Diastereo-, and Regioselective Iridium-Catalyzed Asymmetric Allylic Alkylation of Acyclic β -Ketoesters, *J. Am. Chem. Soc.* **2013**, *135*, 17298–17301
15. Eppe, G.; Diddier, D.; and Marek, I. Stereocontrolled Formation of Several Carbon–Carbon Bonds in Acyclic Systems. *Chem. Rev.*, **2015**, *115*, 9175-9206
16. Carpenter, N.E.; Kucera, D.J.; and Overman L.E., J. Palladium-catalyzed polyene cyclizations of trienyl triflates. *J. Org. Chem*, **1989**, *54*, 5846,
17. Trost, B.M.; Malhotra, S.; and Chan W.H. Natural Product Synthesis Enabled by Domino Processes Incorporating a 1,2-Rearrangement Step. *J.Am. Chem. Soc.*, **2021**, *133*, 7328-7331
18. Walsh, C.T. and Moore, B. S. Enzymatic Cascade Reactions in Biosynthesis, *Angew Chem Int Ed*, **2019**, *58*, 6846–6879
19. Tosatti, P.; Nelson, A. and Marsden, S. P. Recent advances and applications of iridium-catalysed asymmetric allylic substitution. *Org. Biomol. Chem.* **2012**, *10*, 3147–3163
20. Alexander, J. R.; Shchepetkina, V. I.; Stankevich, K. S.; Benedict, R. J.; Bernhard, S. P.; Dreiling, R. J.; Cook, M. J. Pd-Catalyzed Rearrangement of N-Alloc-N-allyl Ynamides via Auto-Tandem Catalysis: Evidence for Reversible C–N Activation and Pd(0)-Accelerated Ketenimine Aza-Claisen Rearrangement, *Org. Lett.* **2021**, *23*, 559–564
21. Buskes, M. J.; Blanco, M. J. Impact of Cross-Coupling Reactions in Drug Discovery and Development, *Molecules*, **2020**, *25*, 3493
22. Caron, S. Honoring 25 Years of the Buchwald–Hartwig Amination, *Org. Process Res. Dev.* **2019**, *23*, 1477
23. Bastug, G.; Nolan, S. P. Carbon–Sulfur Bond Formation Catalyzed by [Pd(IPr*OMe)(cin)Cl] (cin = cinnamyl) *J. Org. Chem*, **2013**, *78*, 9303-9308
24. Zhuang, J.; Ma, S. Recent Development of Pyrimidine-Containing Antimicrobial Agents *ChemMedChem*, **2020**, *15*, 1875-1886

25. Parmentier, M.; Wager, M.; Wickendick, R.; Baenziger, M.; Langlois, A.; Gallou, F. A General Kilogram Scale Protocol for Suzuki–Miyaura Cross-Coupling in Water with TPGS-750-M Surfactant *Org. Process Res. Dev.* **2020**, *24*, 1536–1542
26. Bruneau, A.; Roche, M.; Alami, M.; Messaoudi, S., 2-Aminobiphenyl Palladacycles: The “Most Powerful” Precatalysts in C–C and C–Heteroatom Cross-Couplings, *ACS Catal.* **2015**, *5*, 1386–1396
27. Melvin, P. R.; Nova, A.; Balcells, D.; Hazari, N.; Hruszkewycz, D. P.; Shah, H. P.; tudge, M. T. Design of a Versatile and Improved Precatalyst Scaffold for Palladium-Catalyzed Cross-Coupling: $(\eta^3\text{-1-tBu-indenyl})_2(\mu\text{-Cl})_2\text{Pd}_2$, *ACS Catal.* **2015**, *5*, 3680–3688
28. Semeniuchenko, V.; Sharif, S.; Rana, N.; Chandrasoma, N.; Braje, W. M.; Baker, R. T.; Manthorpe, J. M.; Pietro, W. J.; Organ, M. G. Experimental Evidence for Zerovalent Pd(NHC) as a Competent Catalyst in C–N Cross-Coupling (NHC = DiMeIHeptCl), *J. Am. Chem. Soc.* **2024**, *146*, 29224–29236
29. Melvin, P. R.; Balcells, D.; Hazari, N.; Nova, A. Understanding Precatalyst Activation in Cross-Coupling Reactions: Alcohol Facilitated Reduction from Pd(II) to Pd(0) in Precatalysts of the Type $(\eta^3\text{-allyl})\text{Pd(L)(Cl)}$ and $(\eta^3\text{-indenyl})\text{Pd(L)(Cl)}$, *ACS Catal.* **2015**, *5*, 5596–5606
30. Marion, N.; Nolan, S. P. Well-Defined N-Heterocyclic Carbenes–Palladium(II) Precatalysts for Cross-Coupling Reactions, *Acc. Chem. Res.* **2008**, *41*, 1440–1449
31. Wolesensky, R. M.; Colon, M. T. M.; Sanford, M. S., Initiation of Palladium Precatalysts: Efficiency and Product Selectivity as a Function of Ligand, Substrate, and Reaction Conditions, *ACS Catal.* **2025**, *15*, 18758–18768
32. Nasielski, J.; Hadei, N.; Achonduh, G.; Kantchev, E. A. B.; O’Brien, C. J.; Lough, A.; Organ, M. G. Structure–Activity Relationship Analysis of Pd–PEPPSI Complexes in Cross-Couplings: A Close Inspection of the Catalytic Cycle and the Precatalyst Activation Model, *Chem. Eur. J.* **2010**, *16*, 10844 – 1085
33. Wang, F.; Zhu, L.; Zhou, Y.; Bao, X.; Schaefer, H. F. Is Pd II-Promoted s-Bond Metathesis Mechanism Operative for the PdPEPPSI Complex-Catalyzed Amination of Chlorobenzene with Aniline? Experiment and Theory, *Chem. Eur. J.* **2015**, *21*, 4153 – 4161
34. E. C. Ashby, A. B. Goel, J. N. Argyropoulo, *Tetrahedron Lett.* **1982**, *23*, 2273 – 2276.
35. Larson, N. G.; Norman, J. P.; Neufeldt, S. R. Mechanistic Origin of Ligand Effects on Exhaustive Functionalization During Pd-Catalyzed Cross-Coupling of Dihaloarenes, *ACS Catal.* **2024**, *14*, 7127–7135

36. Kania, M. J.; Reyes, A.; Neufeldt, S. R. Oxidative Addition of (Hetero)aryl (Pseudo)halides at Palladium(0): Origin and Significance of Divergent Mechanisms, *J. Am. Chem. Soc.* **2024**, *146*, 19249–19260
37. Norman, J. P.; Larson, N. G.; Neufeldt, S. R. Different Oxidative Addition Mechanisms for 12- and 14-Electron Palladium(0) Explain Ligand-Controlled Divergent Site Selectivity, *ACS Catal.* **2022**, *12*, 8822–8828
38. Norman, J. P., Neufeldt, S. R., The Road Less Traveled: Unconventional Site Selectivity in Palladium-Catalyzed Cross-Couplings of Dihalogenated N-Heteroarenes *ACS Catal.* **2022**, *12*, 12014–12026
39. Legault C. Y.; Garcia Y.; Merlic, C. A.; Houk, K. N., Theoretical Bond Dissociation Energies of Halo-Heterocycles: Trends and Relationships to Regioselectivity in Palladium-Catalyzed Cross-Coupling Reactions *J. Am. Chem. Soc.* **2007**, *129*, 12664–12665
40. Norman, J. P, Larson, N. G, Entz, E. D, Neufeldt, S. R, Unconventional Site Selectivity in Palladium-Catalyzed Cross-Couplings of Dichloroheteroarenes under Ligand-Controlled and Ligand-Free Systems *J. Org. Chem.* **2022**, *87*, 7414–7421
41. Jackson, O. D.; Reyes, A.; Stein, C. D.; Larson, N. G.; Andrews, C. T.; Neufeldt, S. R. C2-Selective Palladium-Catalyzed C–S Cross-Coupling of 2,4-Dihalopyrimidines, *J. Am. Chem. Soc.* **2025**, *147*, 3017-3022
42. Lagoja, I.M. Pyrimidine as Constituent of Natural Biologically Active Compounds, *Chem. Biodivers.* **2005**, *2*, 1–50
43. Smith, S. M, Buchwald, S. L, Regioselective 2-Amination of Polychloropyrimidines, *Org. Lett.* **2016**, *18*, 2180–2183
44. Smith, C. D.; Phillips, D.; Tirla, A.; France, D. J. Catalytic Isohypsic-Redox Sequences for the Rapid Generation of Csp³-Containing Heterocycles, *Chem. Eur. J.* **2018**, *24*, 17201 – 17204
45. Prokopchuk, D. E.; Morris, R. H. Inner-Sphere Activation, Outer-Sphere Catalysis: Theoretical Study on the Mechanism of Transfer Hydrogenation of Ketones Using Iron(II) PNNP Eneamido Complexes, *Organometallics* **2012**, *31*, 7375–7385
46. Jackson, O. D.; Sandin, M. P.; Uter, C. T.; Lanske, D. Y.; Neufeldt, S. R. Isohypsic Pd(II)-Catalyzed Cross-Coupling Enables C2-Selective Amination of 2,4-Dihalopyrimidines, *Chemrxiv*, **2026**
47. Castonguay, L. A.; Rappe, A. K. Ziegler-Natta catalysis. A theoretical study of the isotactic polymerization of propylene, *J. Am. Chem. Soc.* **1992**, *114*, 5832–5842
48. Davies, H. M. L.; Manning J. R., *Nature* **2008**, *451*, 417 – 424

49. Wang, H.; Koeller, J.; Liu, W.; Ackermann, L. Cobalt(III)-Catalyzed C ϕ H/N ϕ O Functionalizations: Isohypsic Access to Isoquinolines, *Chem. Eur. J.* **2015**, *21*, 15525 – 15528
50. Walker, S. E.; Hore, J. A. J.; Johnson, D. G.; Macgregor, S. A.; Lee, A. L. Palladium-Catalyzed Direct C—H Functionalization of Benzoquinone, *Angew. Chem. Int. Ed.* **2014**, *53*, 13876 –13879
51. Lamb, C. J. C.; Vilela, F.; Lee, A. L. *Org. Lett.* **2019**, *21*, 8689–8694
52. Overman, L. E. Mercury(II)- and Palladium(II)-Catalyzed [3,3]-Sigmatropic Rearrangements, *Angew. Chem. Int. Ed.* **1984**, *23*, 579-586
53. Mu, B.; Zhang, Y.; Wang, X.; Jin, R.; Lu, W.; Selmi, N.; Liu, S.; Bhat, A.; Pahlen, S.; Bergonzini, G.; Duan, Z.; Song, Y.; Lu, X. Photochemical-Promoted Cross-Coupling Reaction of Alkyl Boronate Esters with DNA-Conjugated Aryl Bromides for DNA-Encoded Library Synthesis, *Bioconjugate Chem.* **2025**, *36*, 718–723
54. Sibille, S.; Ratovelomanana, V.; Nédélec, J. Y.; Périchon, J. An Efficient Route to Unsymmetrical Biaryls via the Electrochemical Preparation of Functionalized Aromatic Zinc Organometallics. *Synlett* **1993**, *1993*, 425–426.
55. Ehehalt, L. E.; Beleh, O. M.; Priest, I. C.; Mouat, J. M.; Olszewski, A. K.; Ahern, B. N.; Cruz, A. R.; Chi, B. K.; Castro, A. J.; Kang, K.; Wang, J.; Weix, D. J. Cross-Electrophile Coupling: Principles, Methods, and Applications in Synthesis, *Chem. Rev.* **2024**, *124*, 13397–13569
56. Kirsch, J. K.; Gonzalez, G. A.; Faculak, M. S.; Wolfe, J. P. Pd-Catalyzed Alkene Diamination Reactions with O-Benzoylhydroxylamine Electrophiles: Evidence Supporting a Pd(II/IV) Catalytic Cycle, the Role of 2,4-Pentanedione Derivatives as Ligands, and Expanded Substrate Scope, *J. Org. Chem.* **2021**, *86*, 11378–11387
57. Entz, E. D.; Russell, J. E. A.; Hooker, L. V.; Neufeldt, S. R. Small Phosphine Ligands Enable Selective Oxidative Addition of Ar—Cl Bonds at Nickel(0) *J. Am. Chem. Soc.* **2020**, *142*, 15454–15463
58. Mills, L. R.; Gygi, D.; Ludwig, J. R.; Simmons, E. M.; Wisniewski, S. R.; Kim, J.; Chirik, P. J. Cobalt-Catalyzed C(sp²)–C(sp³) Suzuki–Miyaura Cross-Coupling Enabled by Well-Defined Precatalysts with L,X-Type Ligands, *ACS Catal.* **2022**, *12*, 1905–1918

59. Till, N. A.; Tian, L.; Dong, Z.; Scholes, G. D.; MacMillan, D. W. C. Mechanistic Analysis of Metallaphotoredox C–N Coupling: Photocatalysis Initiates and Perpetuates Ni(I)/Ni(III) Coupling Activity, *J. Am. Chem. Soc.* **2020**, *142*, 15830–15841
60. Haynes, A.; Maitlis, P. M.; Morris, G. E.; Sunley, G. L.; Adams, H.; Badger, P. W.; Bowers, C. M.; Cook, D. B.; Elliott, P. I. P.; Ghaffar, T.; Green, H.; Griffin, T. R.; Payne, M.; Pearson, J. M.; Taylor, M. J.; Vickers, P. W.; Watt, R. J. Promotion of Iridium-Catalyzed Methanol Carbonylation: Mechanistic Studies of the Cativa Process, *J. Am. Chem. Soc.* **2004**, *126*, 2847–2861
61. Laasonen, K.; Kinnunen T.; The active catalytic species and its isomerization in the catalytic carbonylation of methanol — a density functional study, *Journal of Molecular Structure: THEOCHEM*, **2001**, *540*, 91-100
62. Watson, D. A. Legacy of Richard Heck, *Organometallics* **2016**, *35*, 1177–1178

CHAPTER TWO

HIGHLY DIASTREO- AND BRANCHED SELECTIVE
REARRANGEMENT OF SUBSTITUTED *N*-ALLOC-*N*-ALLYL
YNAMIDES

Contribution of Authors and Co-Authors

Manuscript in Chapter Two

Author: Oliver Jackson

Contributions: Conducted experimental work. Contributed to writing of the manuscript and supporting information (Appendix A).

Co-Author: Ksenia S. Stankevich

Contributions: Conducted computational experiments. Contributed to writing of the manuscript and supporting information (Appendix A).

Co-Author: Matthew J. Cook

Contributions: Provided insight and guidance for totality of the project. Participated in preparation and revision of the manuscript and supporting information (Appendix A).

Manuscript Information

Oliver D. Jackson, Ksenia S. Stankevich, Matthew J. Cook

Chemical Communications

Status of Manuscript:

☐ Prepared for submission to a peer-reviewed journal

☐ Officially submitted to a peer-reviewed journal

☐ Accepted by a peer-reviewed journal

☒ Published in a peer-reviewed journal

The Royal Society of Chemistry

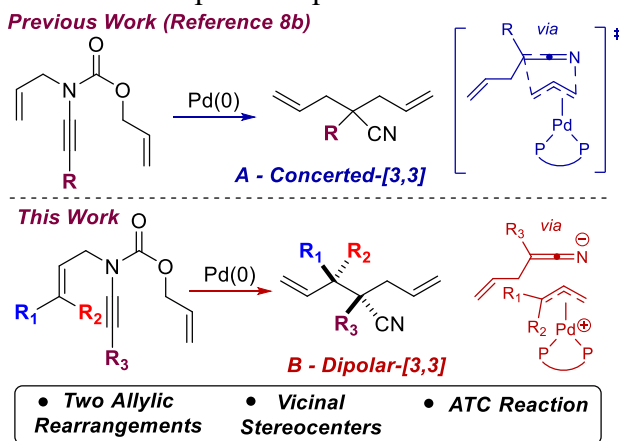
Chem. Commun., **2022**, 58, 11855-11858

DOI: 10.1039/d2cc03399b

Abstract

An auto-tandem catalytic, branched-selective rearrangement of substituted *N*-alloc-*N*-allyl ynamides was developed. This reaction provides ready access to complex quaternary nitrile products with vinylogous stereocenters in excellent diastereoselectivity, including the formation of contiguous all-carbon quaternary centers. The stereochemical outcome is determined *via* a Pd(0) catalyzed dipolar ketenimine aza-Claisen rearrangement inside a deep cleft on the catalyst. Computational studies exemplify the key role ligand geometry plays throughout the reaction coordinate in this previously unreported mechanism. This study provides new reaction pathways for both π -allyl and sigmatropic rearrangements.

Scheme 2.1 TOC Graphic for Manuscript in Chapter Two



Introduction

Using a single catalyst to perform multiple, mechanistically distinct reactions (auto-tandem catalysis [ATC])¹ can be a very powerful approach in synthesis.² ATC reactions are particularly impactful when multiple C–C bonds are formed,³ especially if stereogenic elements are generated during these processes. Of particular interest is the generation of all-carbon quaternary centers using ATC approaches, especially if additional vinylogous stereocenters are formed during the reaction, as these motifs can be problematic to access.⁴

The high reactivity and linear geometry of unstabilized nitrile anions have made them problematic in many catalytic reactions. Lewis basic additives (to form aggregated complexes),⁵ decarboxylative/deacylative approaches,⁶ and silyl ketenimines⁷ have all been utilized to circumvent these issues, however many challenges remain. Our contribution to the field was developing a palladium catalyzed rearrangement of *N*-alloc-*N*-allyl ynamides which formed quaternary diallyl nitriles (Scheme 2.1 A).^{8,9}

This ATC process performs two mechanistically distinct allylic rearrangements and avoids the formation of nitrile anion intermediates. Importantly, during this study we discovered a new mechanism for allylic rearrangements, whereby Pd(0) was acting as a nucleophilic catalyst, donating electron density into the $\sigma^*_{\text{C-N}}$ orbital triggering a concerted [3,3]-rearrangement (Scheme 2.1 A). In contrast, other palladium catalyzed aza-Claisen rearrangements proceed through an electrophilic Pd(II) pathway with the metal acting as a π -Lewis acid.¹⁰ We reasoned that substrates encompassing γ -substituted *N*-allyl groups would provide branched products containing two contiguous stereogenic centers in this reaction.

Moreover, if substrates include γ,γ -disubstitution, contiguous all-carbon quaternary stereocenters could be formed. Importantly, these are mechanistically distinct from previously

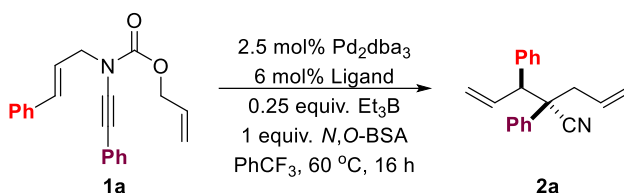
reported branched-selective allylations.¹¹ Herein, we report the development of a highly diastereoselective ATC reaction with complete branched selectivity under very mild conditions (Scheme 2.1 A). Of particular note is the dipolar allyl ketenimine-[3,3]-rearrangement which achieves high levels of diastereoselectivity, including the formation of vicinal all-carbon quaternary stereocenters (Scheme 2.1 B).

Results and Discussion

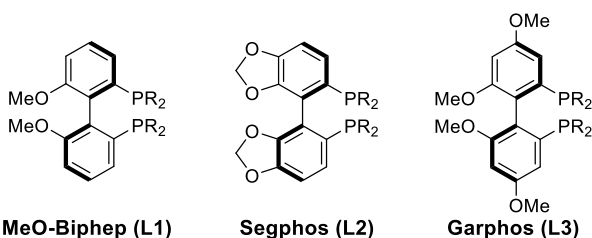
Optimization Studies

Optimization studies revealed that a variety of bidentate phosphine ligands provided complete branched selectivity (**2a**). Of note, were catalytic systems derived from Pd₂dba₃ and phosphine ligands (**L1–3**) due to the abundance of commercially available variants (Table 2.1). Unsubstituted phenyl, alkyl and furyl substituted ligands (**L1a–c**) gave poor reactivity and selectivity (entries 1–3). Ligands containing 3,5-disubstituted phenyl groups (**L1d–e**) led to improved selectivity (entries 4 and 5). The addition of electron donating groups at the 4-position (**L1f–h**), improved both yield and selectivity (entries 6–8), with DTBM MeOBiphep (**L1g**) proving optimal. Other DTBM substituted ligands (**L2g/3Lg**, entries 9 and 10) also provided selectivity, but with poor reactivity.

Table 2.1: Selected Optimization Studies



Entry	Ligand	Yield ^a	d.r. ^c
1	MeOBiphep (L1a)	11%	1.8:1
2	<i>i</i> -Pr-MeOBiphep (L1b)	5%	1:1.2
3	Fur-MeOBiphep (L1c)	35%	1:1.1
4	DM-MeOBiphep (L1d)	8%	3.6:1
5	DTB-MeOBiphep (L1e)	20%	5.4:1
6	DMM-MeOBiphep (L1f)	40%	9:1
7	DTBM-MeOBiphep (L1g)	70% (63%) ^b	13:1
8	<i>i</i> Pr-Me ₂ N-MeOBiphep (L1h)	57%	13:1
9	DTBM-Segphos (L2g)	15%	13:1
10	DTBM-Garphos (L3g)	25%	5:1



R = Ph (**a**); *i*-Pr (**b**); 2-Fur (**c**); 3,5-Me-Ph (**d**); 3,5-*t*-Bu-Ph (**e**); 3,5-Me-4-MeO-Ph (**f**); 3,5-*t*-Bu-4-MeO-Ph (**g**); 3,5-*i*-Pr-4-Me₂N-Ph (**h**)

^a Determined by ¹H NMR using mesitylene as internal standard; ^b Isolated yield; ^c Determined by ¹H NMR of crude reaction

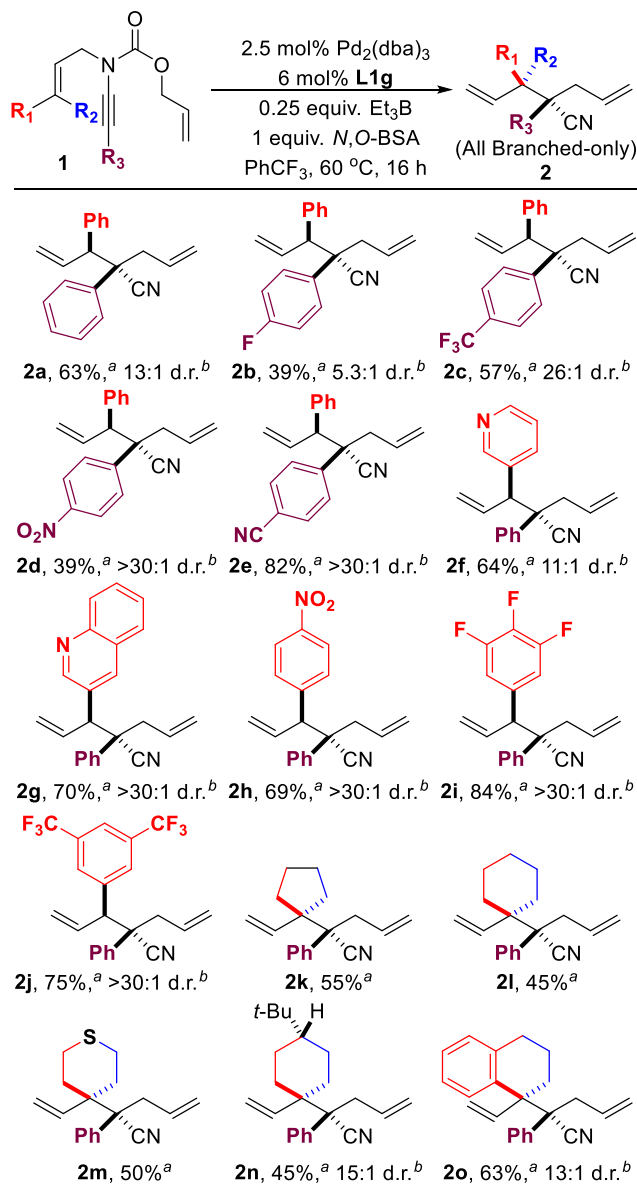
Substrate Scope

With the optimized conditions in hand (Table 2.1, Entry 8), we began examining the substrate scope (Scheme 2.2). Substitution on the ynamide phenyl group was investigated and the stereochemical outcome appears to be influenced by the mesomeric stabilization of an anion,¹² suggesting a dipolar mechanism (Scheme 2.1 B). Weakly π -donating groups, such as fluorine (**1b**, $\sigma=-0.03$), gave lower selectivity than **1a**, whereas strongly anion stabilizing groups including CF₃ (**1c**, $\sigma=0.65$), NO₂ (**1d**, $\sigma=1.27$), and CN (**1e**, $\sigma=1.00$) provided very high levels of stereoselectivity ($\geq 26:1$ d.r.). Next our attention turned to modulation of the γ -substituted *N*-allyl

group. Basic heterocycles could be tolerated in this reaction with pyridine (**1f**) and quinoline (**1g**) variants providing high yields and diastereocontrol. Other substitution could be tolerated on the migrating allylic group, with electron deficient groups providing excellent outcomes. 4-Nitro (**1h**), 3,4,5-trifluoro (**1i**), and 3,5-bis-(trifluoromethyl) (**1j**) substrates all gave high chemical yields with exquisite diastereoselectivity.

γ,γ -Disubstituted *N*-allyl groups were also examined, which upon rearrangement, produced highly congested vicinal all-carbon quaternary centers. Cycloalkyl and thiopyranyl substituted ynamides (**1k-m**) variants gave highly efficient routes to cyclic branched nitriles **2k-m**. We also investigated diastereoselectivity in the formation of contiguous all-carbon quaternary centers. Facial selectivity on the *N*-allyl group was probed by installing a 4-*tert*-butyl cyclohexyl group (**1n**), which provided the **2n** in 15:1 d.r. The formation of two contiguous all-carbon stereogenic centers could also be achieved, with tetralone derived ynamide **1o** providing nitrile **2o** in good yield and an impressive 13:1 d.r. This example (**1o** to **2o**) demonstrates the power of this approach in forming very congested C–C bonds as part of an auto-tandem catalytic sequence with high-levels of diastereoselectivity.

Scheme 2.2: Substrate Scope



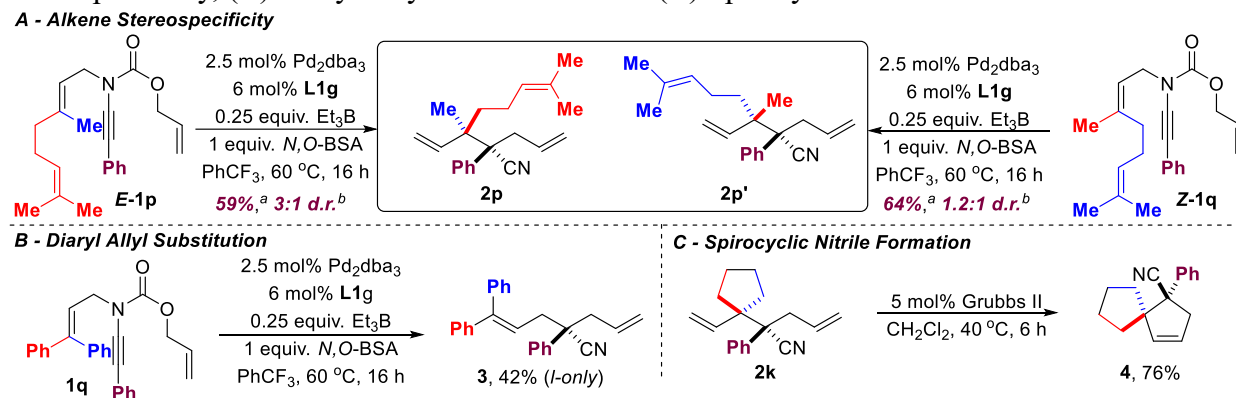
Substrate scope. ^a Isolated yield. ^b Determined by ^1H NMR. ^c **2l** produced in 16% ee.

Reaction Stereospecificity and Synthetic Utility

The stereospecificity of this reaction was further investigated by comparing the relative outcomes using *E* and *Z*-carbamates **E-1p** and **Z-1p** (Scheme 2.3 A). Both reactions proceeded with similar chemical efficiency, however **E-1p** provided a 3 : 1 mixture of diastereomers (**2p:2p'**), whereas the **Z-1p** resulted in a 1.2 : 1 ratio. These outcomes demonstrate stereospecificity, albeit

with a competing isomerization pathway. This π - σ - π pathway is a common source of low stereoselectivity with acyclic *Z*- π -allyl donors.¹³ Interestingly, γ,γ -diphenyl substituted allyl ynamide **1q** provided the only example where linear selectivity was achieved, affording nitrile **3** as a single isomer (Scheme 2.3 B). This alternative regiochemistry can be rationalized due to the increased conjugation of the linear isomer and the additional steric encumbrance in the branched product. Indeed, only one example of branched selectivity from a 1,1-diphenyl π -allyl metal species has been reported.¹⁴ The cyclic products could be converted into spirocycles using Grubb's 2nd generation catalyst to form [5,5]-spirocycle **4** in excellent yield (Scheme 2.3 C).¹⁵

Scheme 2.3: Additional Allylic Substitution and Synthetic Utility Studies: (A) Alkene Stereospecificity, (B) Diaryl Allyl Substitution and (C) Spirocyclic Nitrile Formation



^aIsolated yields; ^bDetermined by ¹H NMR and ratios refer to **2p**:**2p'** selectivity

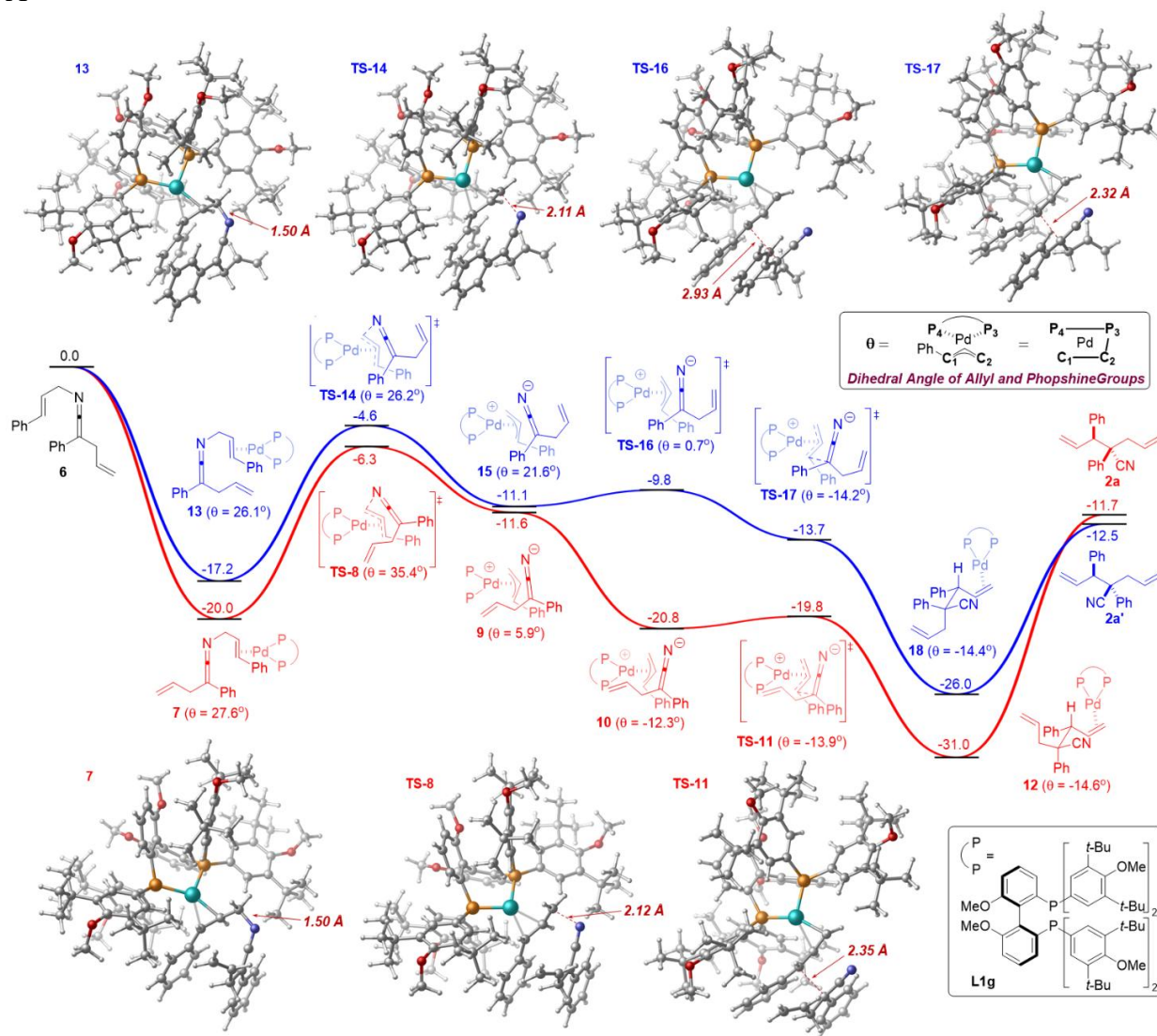
Origin of Stereoselectivity

To elucidate the origin of diastereoselectivity, we conducted a DFT study of the formation of **2a** at CPCM(Trifluorotoluene) M06L/BSII//ONIOM(M06L/BSI:PM6) level of theory (for BSI and BSII see Scheme 2.4 footnote). We found that the palladium bound ligand (**L1g**) forms a deep cleft in which reactivity occurs. This conformational restriction results in a dissociative formal process rather than a concerted [3,3]-rearrangement.^{8b} Although ketenimines are stereogenic, they

are highly epimerizable and exist as a dynamic mixture of isomers.¹⁶ Allyl ketenimine **6** coordinates deep within the binding pocket, forming diastereomeric complexes **7/13**. These interconvertible complexes (**7/13**) ionise through transition states **TS-8/TS-14**, determining the stereochemistry and forming ion pairs **9/15**. A possible explanation for this selectivity is the coplanarity of the phenyl groups leading to an offset π -stacking interaction (3.5 Å) in **TS-8** that is not present in **TS-14**.¹⁷ Indeed, an IGM 3D plot showed an isosurface consistent with a non-covalent stabilizing interaction between the two aromatic rings in **TS-8** (see Appendix A for full details).¹⁸

The possibility of competing concerted [3,3]-process was considered,^{8b} however, **7/13** do not have the necessary orbital overlap and no [3,3]-transition state could be located. The dihedral angle between the allylic termini and the phosphines can be used to highlight the conformational changes required between C–N bond breaking and C–C bond formation. Following ionisation, the two reaction pathways diverge for C–C bond formation. In the major pathway, ion-pair **9** (5.9°) undergoes a reorganisation of the ligand, rotating the π -allyl group within the cleft. Initially intermediate **10** (–12.3°) is formed, which is in reactive conformation for C–C formation *via* **TS-11** (–13.9°; +1.0 kcal mol^{–1} from **10**), to afford **12**. In contrast, ion pair **15** (21.61°) is much further from the reactive conformation for C–C bond formation, requiring rotation through **TS-16** (0.7°; +1.4 kcal mol^{–1} from **15**). This produces shallow intermediate **17** before proceeding directly into a C–C bond formation *via* **TS-18** (14.21, 0.1 kcal mol^{–1} from **17**), to form nitrile **19**. Despite the dipolar pathway, the ion pair does not fully dissociate or solvent separate, with the energetics suggesting a very rapid C–C bond formation following ionisation.

Scheme 2.4: Summary of DFT Analysis Examining the Diastereoselectivity in the Formation of **2a**. ^a DFT calculations done at CPCM(trifluorotoluene) M06L/BSII//ONIOM(M06L/BSI:PM6), where BSI = 6-31+G(d) (C, H, P, O)/LANL2DZ (ECP Pd) and BSII = 6-311++G(2d,2p) (C, H, P, O)/LANL2DZ (ECP Pd); ^b Quasi-Harmonic Solvent and Temperature (333.15 K) Corrected Gibbs Free Energies at 1 mol L⁻¹ Standard State are Reported; ^c For Optimised Structures, see Appendix A



Conclusions

In conclusion, a highly diastereoselective ATC method for the construction of stereochemically complex nitriles has been developed. This provides a highly attractive route to nitriles containing an all-carbon quaternary stereocentre and further vicinal substitution, including contiguous all-carbon quaternary stereocentres. In addition, we have developed a highly accurate computational model to deconvolution of the ketenimine rearrangement mechanism, including the discovery of a dipolar [3,3]-process which occurs in a deep cleft within the catalyst.

References

1. D. E. Fogg and E. N. dos Santos, Tandem catalysis: a taxonomy and illustrative review, *Coord. Chem. Rev.*, **2004**, *248*, 2365.
2. (a) J. E. Camp Auto-Tandem Catalysis: Activation of Multiple, Mechanistically Distinct Process by a Single Catalyst, *Eur. J. Org. Chem.*, 2017, 425. (b) N. T. Patil, V. S. Shinde and B. A. Gajula, One-Pot Catalysis: A Privileged Approach for Sustainable Polymers? *Org. Biomol. Chem.*, **2012**, *10*, 211. (c) A. R. O. Venning, M. R. Kwiatkowski, J. E. Roque Peña, B. C. Lainhart, A. A. Guruparan and E. J. Alexanian Palladium-Catalyzed Carbocyclizations of Unactivated Alkyl Bromides with Alkenes Involving Auto-tandem Catalysis, *J. Am. Chem. Soc.*, **2017**, *139*, 11595. (d) C. Zhou, J. Jiang and J. Wang Three-Component Synthesis of Isoquinoline Derivatives by a Relay Catalysis with a Single Rhodium(III) Catalysis, *Org. Lett.*, **2019**, *21*, 4971.
3. (a) P. Chen, Z.-C. Chen, Y. Li, Q. Ouyang, W. Du and Y.-C. Chen Auto-Tandem Cooperative Catalysis Using Phosphine/Palladium: Reaction of Morita–Baylis–Hillman Carbonates and Allylic Alcohols, *Angew. Chem., Int. Ed.*, **2019**, *58*, 4036. (b) J. Long, R. Yu, J. Gao and X. Fang Nickel-Catalyzed Migratory Hydrocyanation of Internal Alkenes: Unexpected Diastereomeric-Ligand-Controlled Regiodivergence, *Angew. Chem., Int. Ed.*, **2020**, *59*, 6785—6789. (c) M.-Z. Wang, C.-Y. Zhou and C.-M. A silver-promoted auto-tandem catalysis for the synthesis of multiply substituted tetrahydrocarbazoles Che, *Chem. Commun.*, **2011**, *47*, 1312.
4. (a) C. J. Douglas and L. E. Overman, Catalytic asymmetric synthesis of all-carbon quaternary stereocenters, *Proc. Natl. Acad. Sci. U. S. A.*, **2004**, *101*, 5363. (b) K. W. Quasdorf and L. E. Overman, Constructing Quaternary Stereogenic Centers Using Tertiary Organocuprates and Tertiary Radicals. Total Synthesis of trans-Clerodane Natural Products *Nature*, **2014**, *516*, 181. (c) J. P. Das and I. Marek, Enantioselective synthesis of all-carbon quaternary stereogenic centers in acyclic systems, *Chem. Commun.*, **2011**, *47*, 4593. (d) J. Feng, M. Holmes and M. J. Krische, Acyclic Quaternary Carbon Stereocenters via Enantioselective Transition Metal Catalysis, *Chem. Rev.*, **2017**, *117*, 12564—12580. (e) E. A. Peterson and L. E. Overman, Contiguous stereogenic quaternary carbons: A daunting challenge in natural products synthesis, *Proc. Natl. Acad. Sci. U. S. A.*, **2004**, *101*, 11943.
5. (a) Z. Jiao, K. W. Chee and J. S. Zhou, Asymmetric Iodonio-[3,3]-Sigmatropic Rearrangement to Access Chiral α -Aryl Carbonyl Compounds, *J. Am. Chem. Soc.*, 2016, **138**, *15*, 16240. (b) B. W. H. Turnbull and P. A. Evans, Enantioselective rhodium-catalyzed allylic substitution with a nitrile anion: construction of acyclic quaternary carbon stereogenic centers, *J. Am. Chem. Soc.*, **2015**, *137*, 6156.

6. (a) A. Recio and J. A. Tunge Regiospecific decarboxylative allylation of nitriles *Org. Lett.*, **2009**, *11*, 5630. (b) A. J. Grenning and J. A. Tunge, Deacylative Allylation: Allylic Alkylation via Retro-Claisen Activation *J. Am. Chem. Soc.*, **2011**, *133*, 14785.
7. S. E. Denmark and T. W. Wilson, Silyl Ketene Imines: Highly Versatile Nucleophiles for Catalytic, Asymmetric Synthesis *Angew. Chem., Int. Ed.*, **2012**, *51*, 9980.
8. (a) J. R. Alexander and M. J. Cook, Formation of Ketenimines via the Palladium-Catalyzed Decarboxylative π -Allylic Rearrangement of N-Alloc Ynamides *Org. Lett.*, **2017**, *19*, 5822. (b) J. R. Alexander, V. I. Shchepetkina, K. S. Stankevich, R. J. Benedict, S. P. Bernhard, R. J. Dreiling and M. J. Cook, Pd-Catalyzed Rearrangement of N-Alloc-N-allyl Ynamides via Auto-Tandem Catalysis: Evidence for Reversible C–N Activation and Pd(0)-Accelerated Ketenimine Aza-Claisen Rearrangement *Org. Lett.*, **2021**, *23*, 559.
9. (a) K. A. DeKorver, H. Li, A. G. Lohse, R. Hayashi, Z. Lu, Y. Zhang and R. P. Hsung, Ynamides: a modern functional group for the new millennium *Chem. Rev.*, **2010**, *110*, 5064. (b) G. Evano, A. Coste and K. Jouvin, Ynamides: Versatile Tools in Organic Synthesis, *Angew. Chem., Int. Ed.*, **2010**, *49*, 2840. (c) C. C. Lynch, A. Sripada and C. Wolf, Asymmetric synthesis with ynamides: unique reaction control, chemical diversity and applications, *Chem. Soc. Rev.*, **2020**, *49*, 8543.
10. (a) H. Bao and U. K. Tambar, Catalytic enantioselective allylic amination of unactivated terminal olefins via an ene reaction/[2,3]-rearrangement, *J. Am. Chem. Soc.*, **2012**, *134*, 18495. (b) J. S. Cannon and L. E. Overman, Palladium(II)-Catalyzed Enantioselective Reactions Using COP Catalysts, *Acc. Chem. Res.*, **2016**, *49*, 2220. (c) A. M. Danowitz, C. E. Taylor, T. M. Shrikian and A. K. Mapp, Synthesis and Reactivity of N-Allenyl Cyanamides, *Org. Lett.*, **2010**, *12*, 2574. (d) O. Gutierrez, C. E. Hendrick and M. C. Kozlowski, Divergent Reactivity in Pd-Catalyzed [3,3]-Sigmatropic Rearrangement of Allyloxy- and Propargyloxyindoles Revealed by Computation and Experiment, *Org. Lett.*, **2018**, *20*, 6539. (e) M. R. Siebert and D. J. Tantillo, Transition-State Complexation in Palladium-Promoted [3,3] Sigmatropic Shifts, *J. Am. Chem. Soc.*, **2007**, *129*, 8686.
11. (a) J.-M. Begouin, J. E. M. N. Klein, D. Weickmann and B. Plietker, First Direct A-Allylation of Carbonyl Compounds Using Ruthenium Catalysts, *Top. Organomet. Chem.*, **2012**, *38*, 280. (b) Y.-N. Wang, L.-Q. Lu and W.-J. Xiao, Non-Bonding Interactions Enable the Selective Formation of Branched Products in Palladium-Catalyzed Allylic Substitution Reactions, *Chem. – Asian J.*, **2018**, *13*, 2174. (c) Q. Cheng, H.-F. Tu, C. Zheng, J.-P. Qu, G. Helmchen and S.-L. You, Iridium-Catalyzed Asymmetric Allylic Substitution Reactions *Chem. Rev.*, **2019**, *119*, 1855. (d) S. L. Rössler, D. A. Petrone and E. M. Carreira, Iridium-Catalyzed Asymmetric Synthesis of Functionally Rich Molecules Enabled by (Phosphoramidite, Olefin) Ligands, *Acc. Chem. Res.*, **2019**, *52*, 2657.
12. C. Hansch, A. Leo and R. W. Taft, A survey of Hammett substituent constants and resonance and field parameters, *Chem. Rev.*, **1991**, *91*, 165.

13. (a) J. W. Faller, M. E. Thomsen and M. J. Mattina Palladium Catalyzed Kinetic and Dynamic Kinetic Asymmetric Transformations of γ -Acyloxybutenolides. Enantioselective Total Synthesis of (+)-Aflatoxin B1 and B2a, *J. Am. Chem. Soc.*, **1971**, 93, 2642. (b) G. Consiglio and R. M. Waymouth, Synthesis of cis-decalin derivative via π -allylpalladium intermediate and its transformation to usefully functionalized trans-decalin derivative *Chem. Rev.*, **1989**, 89, 257. (c) U. Kasmaier and F. L. Zumpe, Palladium-Catalyzed Allylic Alkylations without Isomerization-Dream or Reality?, *Angew. Chem., Int. Ed.*, **2000**, 39, 802.
14. S. Mizuno, H. Tsuji, Y. Uozumi and M. Kawatsura, Catalytic conversion of alkenes into allylic ethers and esters using diselenides having internal tertiary amines *Chem. Lett.*, **2020**, 49, 645.
15. (a) Y. Zheng, C. M. Tice and S. B. Singh, The use of spirocyclic scaffolds in drug discovery, *Bioorg. Med. Chem. Lett.*, **2014**, 24, 1673. (b) K. Hiesinger, D. Dar'in, E. Proschak and M. Krasavin, Spirocyclic Scaffolds in Medicinal Chemistry, *J. Med. Chem.*, **2021**, 64, 150
16. J. C. Jochims and F. A. Anet, Linear Ketenimines. Variable Structures of C,C-Dicyanoketenimines and C,C-Bis-sulfonylketenimines, *J. Am. Chem. Soc.*, **1970**, 92, 5524.
17. (a) C. Zheng, C.-X. Zhuo and S.-L. You, Catalytic Asymmetric Dearomatization by Transition-Metal Catalysis: A Method for Transformations of Aromatic Compounds, *J. Am. Chem. Soc.*, **2014**, 136, 16251. (b) J. A. Rossi-Ashton, A. K. Clarke, J. R. Donald, C. Zheng, R. J. K. Taylor, W. P. Unsworth and S.-L. You, Iridium-Catalyzed Enantioselective Intermolecular Indole C2-Allylation, *Angew. Chem., Int. Ed.*, **2020**, 59, 7598
18. Calculated using IGMPlot. <https://igmplot.univ-reims.fr>. See: C. Levfevre, H. Khartabil, J.-C. Boisson, J. Contreras-Garcia, J.-P. Piquemal and E. Hénon, *Chem. Phys. Chem.*, **2018**, 19, 724

CHAPTER THREE

C2-SELECTIVE PALLADIUM-CATALYZED C—S CROSS-
COUPLING OF 2,4-DIHALOPYRIMIDINESContribution of Authors and Co-Authors

Manuscript in Chapter Three

Author: Oliver D. Jackson

Contributions: Conducted experimental work. Contributed to writing of the manuscript and supporting information (Appendix B).

Co-Author: Albert Reyes

Contributions: Conducted experimental work. Contributed to writing of the manuscript and supporting information (Appendix B).

Co-Author: Collin D. Stein

Contributions: Conducted experimental work. Contributed to writing of the manuscript and supporting information (Appendix B).

Co-Author: Nathaniel G. Larson

Contributions: Conducted experimental work. Contributed to writing of the supporting information (Appendix B).

Co-Author: Calvin T. Andrews

Contributions: Conducted experimental work.

Co-Author: Sharon R. Neufeldt

Contributions: Provided insight and guidance for totality of the project. Conducted computational experiments. Participated in preparation and revision of the manuscript and supporting information (Appendix B).

Manuscript Information

Oliver D. Jackson, Albert Reyes, Collin D. Stein, Nathaniel G. Larson, Calvin T. Andrews,
Sharon R. Neufeldt

Journal of the American Chemical Society

Status of Manuscript:

- ☐ Prepared for submission to a peer-reviewed journal
- ☐ Officially submitted to a peer-reviewed journal
- ☐ Accepted by a peer-reviewed journal
- ☒ Published in a peer-reviewed journal

American Chemical Society

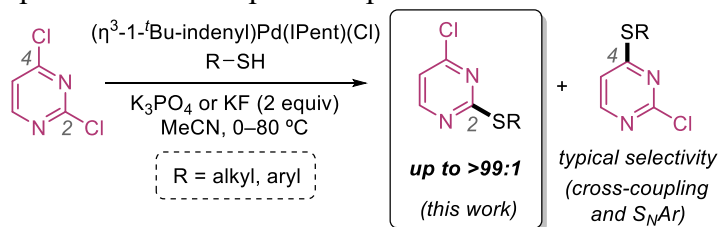
J. Am. Chem. Soc. **2025**, *147*, 4, 3017–3022

DOI: doi.org/10.1021/jacs.4c17020

Abstract

Under most conditions, 2,4-dihalopyrimidines undergo substitution reactions at C4. Here we report that Pd(II) precatalysts supported by bulky *N*-heterocyclic carbene ligands uniquely effect C2-selective cross-coupling of 2,4-dichloropyrimidine with thiols. The regioselectivity of this reaction stands in stark contrast to ~1500 previously reported Pd-catalyzed cross-couplings that favor C4 in the absence of other substituents on the pyrimidine ring. Selectivity in the catalytic system reported herein is extremely sensitive to the structure of the Pd(II) precatalyst, largely due to competing C4-selective nucleophilic aromatic substitution. C2-selectivity is high with most 1° thiols and thiophenols, and a range of substituted dichloropyrimidines can be used. The atypical selectivity of this transformation may facilitate diversity-oriented synthesis, as demonstrated for derivatives of an antiviral agent. Under these conditions, C2—Cl cleavage may not take place through a typical oxidative addition pathway.

Scheme 3.1 TOC Graphic for Manuscript in Chapter Three

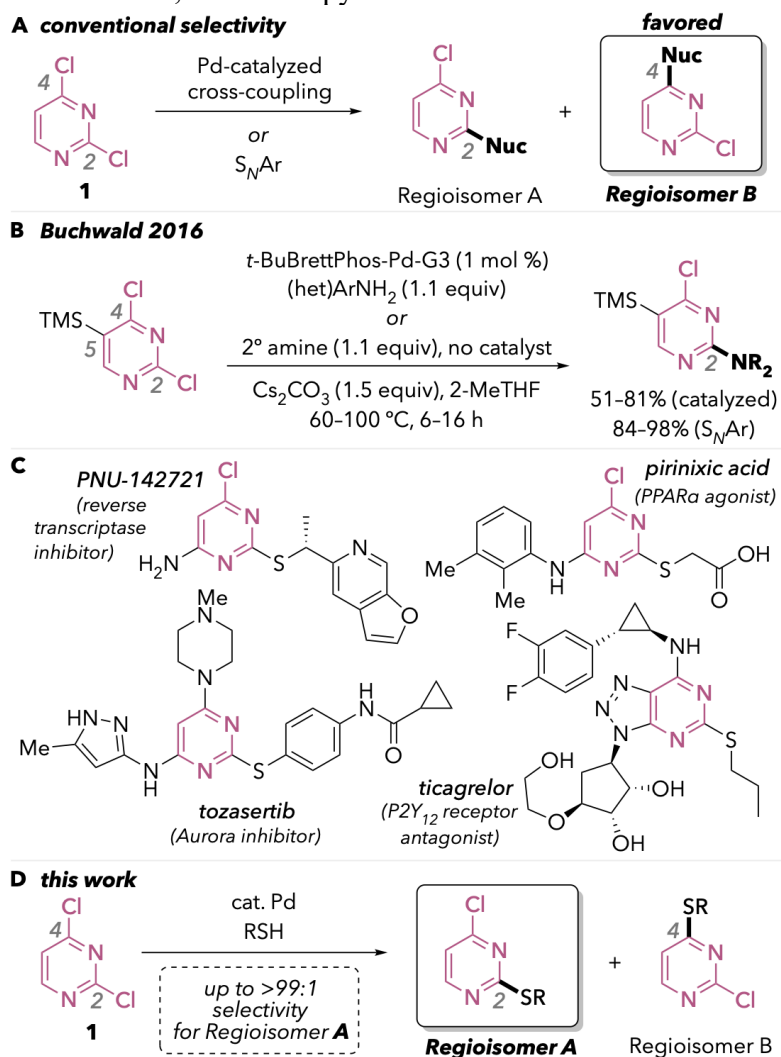


Introduction

Pyrimidines are common motifs in bioactive small molecules such as pharmaceutical drugs and agrichemicals, and are also of value for organic materials.^{1–5} The privileged role of pyrimidines in bioactive compounds can be understood by their ubiquity in nature. In particular, nucleobases (the building blocks of DNA) are pyrimidine derivatives. The majority of pyrimidine motifs in small molecule drugs are substituted at both the 2- and the 4-positions.⁶ As such, synthetic strategies to functionalize these sites are of high value. Readily available 2,4-dichloropyrimidines are logical precursors to 2,4-difunctionalized derivatives. These substrates typically undergo reaction at C4 to yield Regioisomer B (Scheme 3.2 A) in both cross-coupling and nucleophilic aromatic substitution (S_NAr) reactions.⁷ In fact, a survey of the literature indicates that, out of nearly 1500 reported examples, at least 99% of Pd- or Ni-catalyzed C–C, C–N, or C–S cross-couplings of **1** afford Regioisomer B as the major product.^{8,9} The handful of reported exceptions lack definitive structural characterization.¹⁰ Thus, obtaining Regioisomer A through the cross-coupling of unsubstituted **1** has not been feasible. Buchwald found that introducing bulky C5-substituents promotes formation of Regioisomer A in Pd-catalyzed and catalyst-free (S_NAr) aminations (Scheme 3.2 B).¹¹ A removable C5-substituent like TMS presents a useful workaround to the selectivity problem but also introduces additional synthetic steps.

The inability to directly cross-couple at the C2 position of 2,4-dihalopyrimidines without a bulky 5-substituent limits the chemical space that is likely to be targeted during diversity-oriented synthesis, for example, during the development of screening libraries. A catalyst-controlled approach to C2-functionalization would facilitate access to Regioisomer A and, therefore, broaden the landscape of readily accessible pyrimidine derivatives.

Scheme 3.2 Derivatization of 2,4-Dichloropyrimidines



Results and Discussion

Optimization Studies

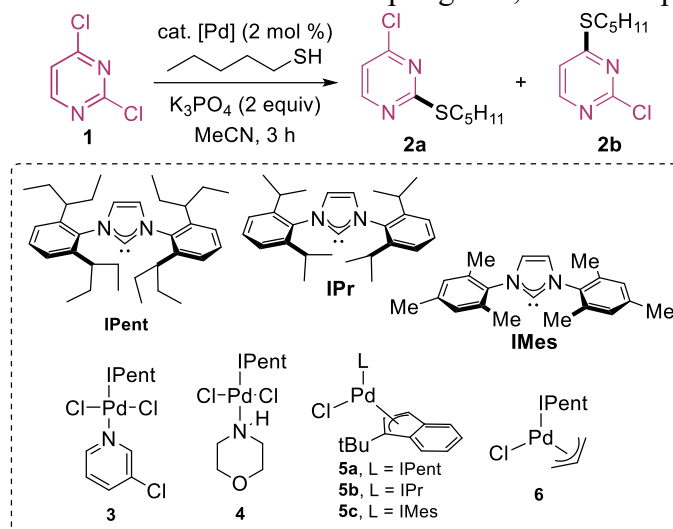
We began investigating cross-coupling with thiols, as thiopyrimidines represent a common substitution pattern in druglike compounds (Scheme 3.2 C). Although thiols are good nucleophiles, especially in the presence of base, the uncatalyzed S_NAr reactions of 2,4-dichloropyrimidines with thiols tend to afford C4-substituted products (for example, see ref ¹² as well as Table 3.1, entry 1).

Thus, we envisioned that a C2-selective catalytic process for C–S coupling would enable bond construction that was currently not possible to make in a single step. We were further inspired by reports of Pd-catalyzed C–S cross-coupling reactions of other substrates because these often benefit from the use of bulky monodentate ligands.^{13–17} We had recently found that bulky monodentate *N*-heterocyclic carbene (NHC) ligands are key to inversion of conventional site selectivity in cross-couplings of other dihalogenated heteroarenes.¹⁸

PEPPSI-Pd-IPent precatalyst **3** and its analogue **4** were selected for our initial studies (Table 3.1).¹⁷ Unfortunately, a preference for the conventional C4-functionalized product was observed with both precatalysts (entries 2 and 3). The C4-selectivity using **3** is even higher than that of the Pd-free control reaction (entry 1), suggesting that the selectivity observed with **3** may be due to Pd-catalysis and not to background S_NAr. Interestingly, morpholine complex **4** displayed a weaker preference for C4, leading to more C2 product (**2a**) than the Pd-free control (compare entries 1 and 3). Complex **4** is known to activate more quickly than **3** under C–S coupling conditions, which may be relevant to the difference in selectivity between these two precatalysts.

Remarkably, switching to precatalysts **5a** or **6**, supported by *t*-Bu-indenyl¹⁹ or allyl ligands,²⁰ led to a complete reversal of selectivity (entries 4–5). The contrast between **5a/6** and the other Pd-IPent precatalysts **3** and **4** is notable, considering that they are all expected to generate 12e[−] Pd⁰(IPent) as the active catalyst.²¹ The selectivity with commercial precatalyst **5a** was further improved by running the reaction at 0 °C, affording almost exclusive selectivity for C2-functionalized product **2a** (entry 6). This temperature effect may be partially due to suppression of background S_NAr, as the Pd-free control reaction is somewhat slower at 0 °C (compare entry 8 with 1).

Table 3.1 Optimization of a C2-Selective Cross-Coupling of 2,4-Dichloropyrimidine



entry	cat.	temp	2a + 2b (%)	2a : 2b
1	none	r.t.	82	1:7
2	3	r.t.	70	1:22
3	4	r.t.	71	1:2
4	5a	r.t.	62	14:1
5	6	r.t.	50	>99:1
6	5a	0 °C	90	>99:1
7	6	0 °C	73	77:1
8	none	0 °C	51	1:6
9	5b	0 °C	86	25:1
10	5c	0 °C	61	3:1

^a% Product yields and ratios determined by ¹H NMR spectroscopy of the crude reaction mixture using mesitylene as an internal standard

t-Bu-indenyl precatalysts bearing the smaller NHC ligands IPr and IMes (**5b** and **5c**) also promote unconventional selectivity at C2 (entries 9–10), but the preference is weaker and appears correlated with ligand sterics, where C2 selectivity follows the trend IPent > IPr > IMes. Product **2a** remains the major product in other polar solvents, but **2b** is favored in ethereal solvents (see Appendix B).

Substrate Scope

With **5a** identified as the optimal catalyst based on its selectivity and commercial availability, the scope of this reaction was examined (Figure 3.1). With other 1° thiols (**7a-23a**), high selectivity is maintained in most cases. Esters, amides, and alcohols are tolerated on the thiol reagent (**9a-11a**, **13a-15a**, and **23a**). These functional groups can be sensitive to POCl₃, a chlorinating reagent that would typically be used to install a chloride at the 4-position after constructing the thioether at C2.²² Synthetically useful, albeit much lower, C2-selectivity was also observed with 2° thiols (**24a-26a**), though selectivity was sometimes variable across reaction trials especially on small scales.²³ Notably, for these more hindered thiols, room temperature conditions tended to afford selectivities better than those at 0 °C. A tertiary thiol gave C4-selectivity (**42b**) in a ratio similar to the catalyst-free control, which could indicate that **42b** arises from S_NAr and not from catalysis.

Electron-rich, -neutral, and moderately electron-deficient thiophenols are also effective coupling partners (**27a-33a**). An aryl chloride and even an aryl bromide was tolerated on the thiol coupling partner (**32a** and **33a**). However, the reaction favors C4 coupling with a very electron-deficient thiophenol (**43b**). In this case, selectivity mirrors that of the catalyst-free reaction. The increased acidity of an electron-poor thiophenol would lead to a higher concentration of thiolate anion, which may allow S_NAr to outcompete catalysis. Interestingly, it was necessary to change

the base to KF and to increase the reaction temperature to 50–80 °C to get high conversion and C2-selectivity with thiophenol reagents (Table Appendix B.3).

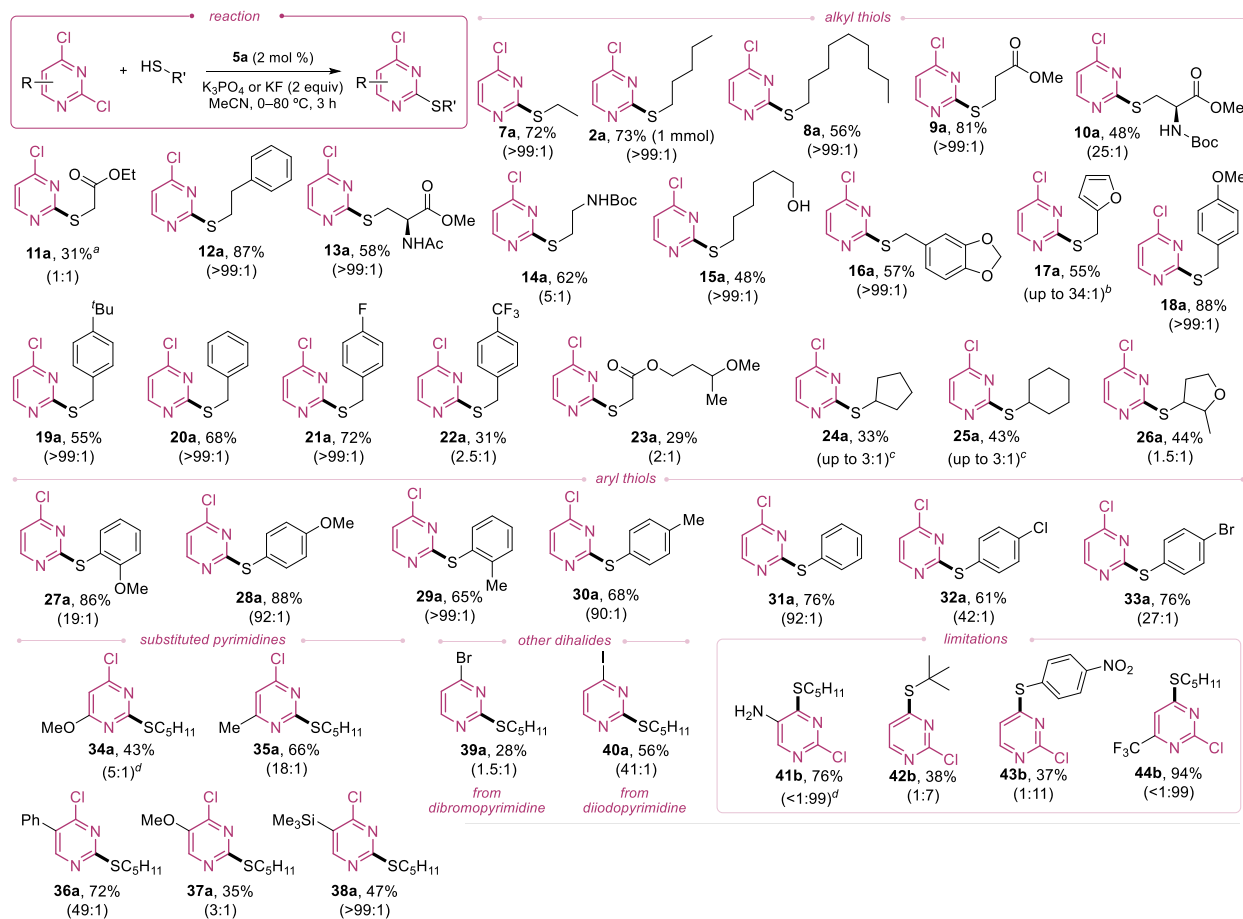


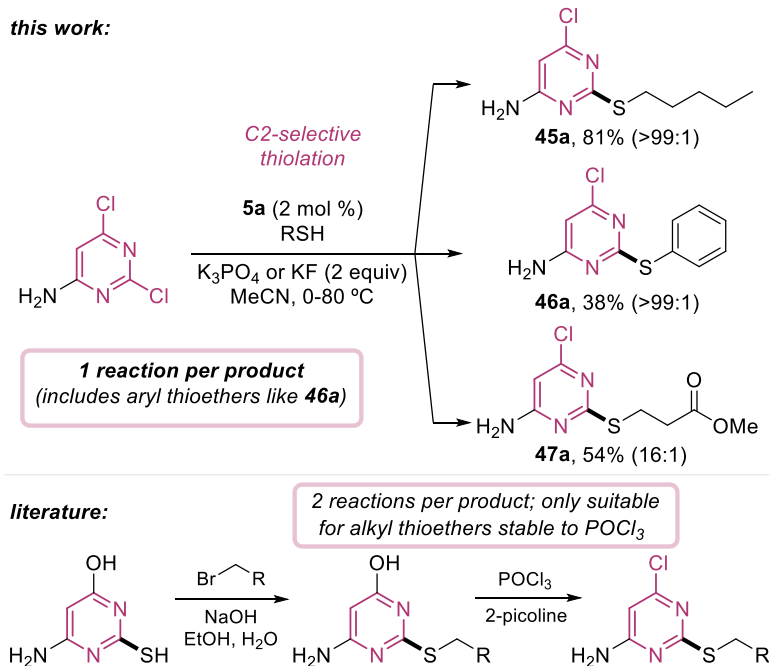
Figure 3.1 Scope of C2-Selective Thiolation. Isolated Yields of the Indicated Regioisomer. Ratios Represent C2:C4-Functionalized Products Prior to Purification Based on ¹H NMR Analysis of the Crude Reaction. ^aCalculated Isolated Yield Adjusted to Account for ~96% Purity (Isolated Product is Contaminated by a Small Amount of C4-Functionalized Product). Variable Selectivity was Observed on Smaller Scale Trials with Certain Thiols: ^bSelectivity as low as 3:1 was Observed on a Smaller Scale. ^cSelectivity as low as 1:3 was Observed on a Smaller Scale. ^dThe Catalyst-Free Control (S_NAr) Favors the Same Regioisomer.

Dibromo- and diiodopyrimidines also react preferentially at C2 (**39a**, **40a**). Unexpectedly, the dibromopyrimidine is less selective than either the dichloro or diiodo analog. Moderate to high C2-selectivity is upheld for a range of substituted 2,4-dichloropyrimidines (**34a–38a**). A substrate bearing a bulky C5-substituent¹¹ gives exclusive C2-selectivity (**38a**), even though the

corresponding catalyst-free S_NAr reaction slightly favors C4 (see p.23 Appendix B). However, the 5-amino analogue of **1** led to exclusive reaction at C4 (**41b**) under both catalytic and catalyst-free conditions. Furthermore, a very electron-deficient pyrimidine, which should be highly activated toward S_NAr , also gave exclusive C4-selectivity identical to that observed under catalyst-free conditions (**44b**).

Synthetic Utility

Scheme 3.3 Divergent Synthesis of Analogues of a Reverse Transcriptase Inhibitor (PNU-142721)



To demonstrate the utility of this C2-selective thiolation for divergent synthesis, the reaction was applied toward the preparation of analogues of PNU-142721, a reverse transcriptase inhibitor (Scheme 3.3).^{22,24} 6-Amino-2,4-dichloropyrimidine was compared to the previously reported synthetic methods; the C2-selective thiolation chemistry enables shorter divergent syntheses that avoid the use of $POCl_3$ and enable access to a broader scope of thioethers (Scheme 3.3).^{22,25}

Mechanistic Studies

The mechanistic origin of the unusual selectivity afforded by Pd/NHC precatalysts such as **5a** is unclear and is a topic of ongoing study in our lab. We have previously shown that bulky NHC ligands enable inversion of conventional site selectivity in C–C cross-couplings of dichloroheteroarenes **48** and **49** (Figure 3.2 A).¹⁸ The ligand-controlled divergent selectivity with those substrates apparently hinges on the complementary influences of bond strengths and frontier molecular orbital coefficients. With bulky NHC ligands, unconventional selectivity for reaction at the C–Cl bond distal to nitrogen in **48** and **49** is attributed to oxidative addition at monoligated $12e^-$ PdL. PdL is biased toward reaction at the site with the larger LUMO coefficient (distal to nitrogen for these substrates), due to its preferred oxidative addition mechanism (LUMO pictures in 3.2 A, bottom).^{18b,26,27} On the other hand, the site selectivity of bisligated $14e^-$ PdL₂ tends to trend with bond strength, and conventional selectivity for the weaker C–Cl bond proximal to nitrogen is seen when oxidative addition takes place at $14e^-$ PdL₂ (BDEs ²⁸ in Figure 3.2 A, top). However, 2,4-dichloropyrimidine **1** does not fit the pattern of **48** and **49**. For substrate **1**, C–Cl bond strengths and LUMO coefficients both favor reaction at the same site (C4), suggesting that both $14e^-$ and $12e^-$ Pd would favor the conventional C4 site.

Indeed, DFT calculations indicate that both PdL (L = IPr) and [Pd(L)(L')] (L = IPr, L' = SMe) should prefer to insert into C4–Cl (Figure 3.2 B, compare **TS50a** with **TS50b** and compare **TS51a** with **TS51b**). This prediction is inconsistent with our experimental results using precatalyst **5a**, although it is consistent with the large body of prior literature describing C4-selective cross-coupling. It appears that the thiol itself is significant to the unique C2 selectivity: a Suzuki cross-coupling using analogous conditions minus the thiol affords a C4-arylated product

(Figure 3.2 C). However, the addition of thiophenol to the Suzuki reaction in Figure 3.2 C does not alter the selectivity of arylation (see Appendix B).

We find no evidence to suggest that the reaction is under thermodynamic control, even under the high-temperature conditions optimized for coupling with aryl thiols. A C2 product is not predicted to be more stable than a C4-substituted regioisomer (Figure 3.2 D). Furthermore, resubjecting C4-coupled products such as **31b** to the catalytic reaction conditions did not result in any isomerization to C2-coupled product **31a**, even in the presence of a chloride source such as **1** (Figure 3.2 E); see also Appendix B).

Experimentally evaluating the reversibility of the individual C–Cl oxidative addition step is challenging, in part because Pd(II)(NHC)Ar complexes are generally not isolable.^{29,30} However, DFT calculations indicate that C–Cl oxidative addition through transition structures **TS50** or **TS51** should be highly exergonic and thus not reversible at 0 °C ($\Delta G^\ddagger$ for C–Cl reductive elimination >30 kcal/mol, see Figures S7 and S8 in appendix B). Thus, it appears that C2-selectivity in the C–S coupling may involve a nontraditional mechanism for C–Cl cleavage.

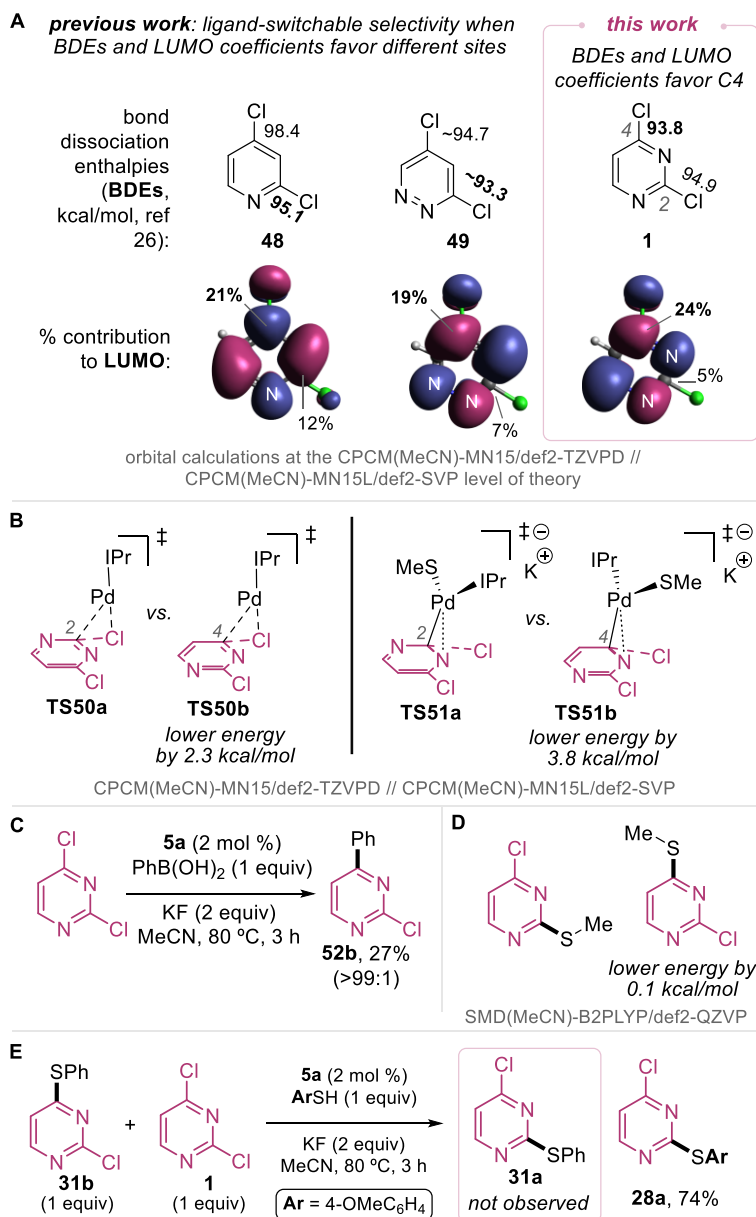


Figure 3.2. (A) For Heteroarenes **48** and **49**, 14e⁻ Pd Favors the Site with the Weaker C–Cl bond, while 12e⁻ Pd Favors the Site with the Larger LUMO coefficient. For pyrimidine **1**, both Factors Favor the Same site (C4); (B) DFT Calculations Suggest that both 12e⁻ and 14e⁻ Pd Should Favor Oxidative Addition at C4; (C) a Suzuki Coupling Under Conditions Analogous to the Thiolation Reaction Favors C4; (D) a C2-Functionalized Product is not Thermodynamically Favored on DFT Calculations; (E) C–S Coupling is not Reversible.

Conclusions

In summary, we report the first example of the C2-selective cross-coupling of 2,4-dichloropyrimidines that does not rely on substrate control. Palladium complexes containing the IPent ligand are optimal for promoting C2-selectivity, although the selectivity is highly dependent on the structure of the Pd^{II} precatalyst. The C2-selectivity is general for many thiols and substituted 2,4-dihalopyrimidines, but sterically hindered thiols and some substituted pyrimidines favor C4-coupling. In at least some of these cases, C4-selective S_NAr likely outcompetes the desired catalysis. Mechanistic investigation is ongoing, but preliminary studies indicate that the thiol coupling partner is an important element in C2-selectivity, and C–Cl cleavage under the catalytic thiolation conditions is unlikely to take place through a traditional oxidative addition mechanism.

References

1. Radi, M.; Schenone, S.; Botta, M. Recent highlights in the synthesis of highly functionalized pyrimidines. *Org. Biomol. Chem.* **2009**, *7*, 2841–2847.
2. Zhuang, J.; Ma, S. Recent Development of Pyrimidine-Containing Antimicrobial Agents. *ChemMedChem.* **2020**, *15*, 1875–1886.
3. Singh, S.; Dhanawat, M.; Gupta, S.; Kumar, D.; Kakkar, S.; Nair, A.; Verma, I.; Sharma, P. Naturally Inspired Pyrimidines Analogues for Alzheimer's Disease. *Curr. Neuropharmacol.* **2020**, *19*, 136–151.
4. Bharti, K. L.; Parmar, P. S.; Rathod, B. P.; Anjirwala, S. N.; Patel, S. K. Non-fused Pyrimidine Derivatives as Potential Pharmacological Entities: A Review. *Curr. Top. Med. Chem.* **2025**, *25*, 1032-1068
5. Selected examples of 2,4-disubstituted pyrimidines in molecules with interesting optical properties: (a) Itami, K.; Yamazaki, D.; Yoshida, J.-i. Pyrimidine-Core Extended π -Systems: General Synthesis and Interesting Fluorescent Properties. *J. Am. Chem. Soc.* **2004**, *126*, 15396–15397. (b) Hadad, C.; Achelle, S.; García-Martínez, J. C.; Rodríguez-López, J. 4-Arylvinyl-2,6-di(pyridin-2-yl)pyrimidines: Synthesis and Optical Properties. *J. Org. Chem.* **2011**, *76*, 3837–3845,
6. McGrath, N. A.; Brichacek, M.; Njardarson, J. T. A Graphical Journey of Innovative Organic Architectures That Have Improved Our Lives. *J. Chem. Educ.* **2010**, *87*, 1348–1349.
7. Lewis acids can influence the selectivity of S_NAr reactions. In one report, the use of stoichiometric or superstoichiometric $ZnCl_2$ promoted amination at the C2 position of some 2,4-dichloropyrimidines: Richter, D. T.; Kath, J. C.; Luzzio, M. J.; Keene, N.; Berliner, M. A.; Wessel, M. D. Selective addition of amines to 5-trifluoromethyl-2,4-dichloropyrimidine induced by Lewis acids. *Tetrahedron Lett.* **2013**, *54*, 4610–4612.
8. Substructure-based SciFinder searches were conducted on April 30, 2024 for transformations to convert **1** into either 2- or 4-chloropyrimidine bearing a C, N, or S substituent at either C4 or C2, respectively. Carbons 5 and 6 were “locked” to prevent substitution, and reaction mapping was used. Results were narrowed down to only include single-step reactions that include a Ni- or Pd-based catalyst. Results for C4-substitution: 83 hits for nitrogen, 1,371 hits for carbon, 1 hit for sulfur. Results for C2-substitution: 4 hits for nitrogen (all are patents), 18 hits for carbon (4 are journal articles, and in each the C2-substituted product is reported as the minor regioisomer), 0 hits for sulfur.

9. Norman, J. P.; Neufeldt, S. R. The Road Less Traveled: Unconventional Site Selectivity in Palladium-Catalyzed Cross-Couplings of Dihalogenated N-Heteroarenes. *ACS Catal.* **2022**, *12*, 12014–12026.
10. Reported exceptions occur in patents and are prophetic or otherwise lack characterization data. One example of C2-selective Suzuki coupling of 2,4-dibromo pyrimidine was reported in a journal article, but the regioselectivity of the product was not explicitly characterized; see Wellmar, U.; Hörnfeldt, A.-B.; Gronowitz, S. Syntheses of Various 5(Bromoaryl)substituted Uracils. *J. Heterocyclic Chem.* **1995**, *32*, 1159–1163.
11. Smith, S. M.; Buchwald, S. L. Regioselective 2-Amination of Polychloropyrimidines. *Org. Lett.* **2016**, *18*, 2180–2183.
12. Examples of C4-selective S_NAr of **1** using sulfur nucleophiles: (a) Liu, W.-M.; Zhu, Y.-Q.; Wang, Y.-F.; Liu, B.; Zou, X.-M.; Yang, H.-Z. Synthesis and Herbicidal Activity of 2-(3-(Trifluoromethyl)-5-(alkoxy)-1H-pyrazol-1-yl)-4-aryloxy pyrimidine Derivatives. *J. Heterocyclic Chem.* **2007**, *44*, 967–971. (b) Kamijo, S.; Kamijo, K.; Murafuji, T. Synthesis of Alkylated Pyrimidines via Photoinduced Coupling Using Benzophenone as a Mediator. *J. Org. Chem.* **2017**, *82*, 2664–2671. (c) Markovic, T.; Rocke, B. N.; Blakemore, D. C.; Mascitti, V.; Willis, M. C. Catalyst Selection Facilitates the Use of Heterocyclic Sulfonates as General Nucleophilic Coupling Partners in Palladium-Catalyzed Coupling Reactions. *Org. Lett.* **2017**, *19*, 6033–6035. (d) Bhujabal, Y. B.; Vadagaonkar, K. S.; Gholap, A.; Sanghvi, Y. S.; Dandela, R.; Kapdi, A. R. HFIP Promoted Low-Temperature S_NAr of Chloroheteroarenes Using Thiols and Amines. *J. Org. Chem.* **2019**, *84*, 15343–15354. (e) Liu, W.; Jin, X.; Ma, D. Nucleophilic Aromatic Substitution of Heteroaryl Halides with Thiols. *J. Org. Chem.* **2024**, *89*, 8745–8758.
13. Beletskaya, I. P.; Ananikov, V. P. Transition-Metal-Catalyzed C-S, C-Se, and C-Te Bond Formations via Cross-Coupling and Atom-Economic Addition Reactions. Achievements and Challenges. *Chem. Rev.* **2022**, *122*, 16110–16293.
14. Xu, J.; Liu, R. Y.; Yeung, C. S.; Buchwald, S. L. Monophosphine Ligands Promote Pd-Catalyzed C-S Cross-Coupling Reactions at Room Temperature with Soluble Bases. *ACS Catal.* **2019**, *9*, 6461–6466.
15. Scattolin, T.; Senol, E.; Yin, G.; Guo, Q.; Schoenebeck, F. Site-Selective C–S Bond Formation at C–Br over C–OTf and C–Cl Enabled by an Air-Stable, Easily Recoverable, and Recyclable Palladium(I) Catalyst. *Angew. Chem., Int. Ed.* **2018**, *57*, 12425–12429.
16. Bastug, G.; Nolan, S. P. Carbon-Sulfur Bond Formation Catalyzed by $[Pd(IPr^*OMe)(cin)Cl]$ (cin = cinnamyl). *J. Org. Chem.* **2013**, *78*, 9303–9308.

17. (a) Sayah, M.; Organ, M. G. Carbon-Sulfur Bond Formation of Challenging Substrates at Low Temperature by Using Pd-PEPPSI-IPent. *Chem.—EurJ.* **2011**, *17*, 11719– 11722, b) Sayah, M.; Organ, M. G. Potassium Isopropoxide: For Sulfination It is the Only Base You Need!. *Chem.—Eur. J.* **2013**, *19*, 16196– 16199. (c) Sayah, M.; Lough, A. J.; Organ, M. G. Sulfination by Using Pd-PEPPSI Complexes: Studies into Precatalyst Activation, Cationic and Solvent Effects and the Role of Butoxide Base. *Chem.—Eur. J.* **2013**, *19*, 2749– 2756, (d) Farmer, J. L.; Pompeo, M.; Lough, A. J.; Organ, M. G. [(IPent)PdCl₂(morpholine)]: a Readily Activated Precatalyst for Room-Temperature, Additive-Free Carbon-Sulfur Coupling. *Chem.—Eur.J.* **2014**, *20*, 15790– 15798.
18. (a) Norman, J. P.; Larson, N. G.; Entz, E. D.; Neufeldt, S. R. Unconventional Site-Selectivity in Palladium-Catalyzed Cross-Couplings of Dichloroheteroarenes under Ligand-Controlled and Ligand-Free Systems. *J. Org. Chem.* **2022**, *87*, 7414– 7421. (b) Norman, J. P.; Larson, N. G.; Neufeldt, S. R. Different Oxidative Addition Mechanisms for 12- and 14-Electron Palladium(0) Explain LigandControlled Divergent Site Selectivity. *ACSCatal.* **2022**, *12*, 8822– 8828.
19. Melvin, P. R.; Nova, A.; Balcells, D.; Dai, W.; Hazari, N.; Hruszkewycz, D. P.; Shah, H. P.; Tudge, M. T. Design of a Versatile and Improved Precatalyst Scaffold for Palladium-Catalyzed Cross-Coupling: (η^3 -1-^tBu-indenyl)₂(μ -Cl)₂Pd₂. *ACS Catal.* **2015**, *5*, 3680– 3688.
20. Marion, N.; Navarro, O.; Mei, J.; Stevens, E. D.; Scott, N. M.; Nolan, S. P. Modified (NHC)Pd(allyl)Cl (NHC = N-Heterocyclic Carbene) Complexes for Room-Temperature Suzuki-Miyaura and Buchwald-Hartwig Reactions. *J. Am. Chem. Soc.* **2006**, *128*, 4101– 4111.
21. Reviews: (a) DeAngelis, A.; Colacot, T. J. Prominent Ligand Types in Modern Cross-Coupling Reactions. *RSC Catal. Ser.* **2014**, *21*, 20– 90, (b) Chartoire, A.; Nolan, S. P. Advances in C–C and C–X Coupling Using Palladium–N-Heterocyclic Carbene (Pd–NHC) Complexes. *RSC Catal. Ser.* **2014**, *21*, 139– 227, c) Campeau, L.-C.; Hazari, N. Cross-Coupling and Related Reactions: Connecting Past Success to the Development of New Reactions for the Future. *Organometallics* **2019**, *38*, 3– 35, (d) Shaughnessy, K. H. Development of Palladium Precatalysts That Efficiently Generate LPd(0) Active Species. *Isr. J.Chem.* **2020**, *60*, 180– 194, (e) Firsan, S. J.; Sivakumar, V.; Colacot, T. J. Emerging Trends in Cross-Coupling: Twelve-Electron-Based L1Pd(0) Catalysts, Their Mechanism of Action, and Selected Applications. *Chem. Rev.* **2022**, *122*, 16983– 17027.
22. For example: Wishka, D. G.; Graber, D. R.; Seest, E. P.; Dolak, L. A.; Han, F.; Watt, W.; Morris, J. Stereoselective Synthesis of Furo[2,3-*c*]pyridine Pyrimidine Thioethers, A New Class of Potent HIV-1 Non-nucleoside Reverse Transcriptase Inhibitors. *J. Org. Chem.* **1998**, *63*, 7851– 7859.
23. Reproducibility challenges can be associated with radical chain reactions. However, the selectivity and yield in the reaction to form **2a** under the optimized conditions of [Table 1](#),

entry 6, is not affected by the addition of 1 equiv of the radical inhibitor γ -terpinene (NMR yield and selectivity = 85%, **2a:2b** > 99:1).

24. Wishka, D. G.; Graber, D. R.; Kopta, L. A.; Olmsted, R. A.; Friis, J. M.; Hosley, J. D.; Adams, W. J.; Seest, E. P.; Castle, T. M.; Dolak, L. A.; Keiser, B. J.; Yagi, Y.; Jeganathan, A.; Schlachter, S. T.; Murphy, M. J.; Cleek, G. J.; Nugent, R. A.; Poppe, S. M.; Swaney, S. M.; Han, F.; Watt, W.; White, W. L.; Poel, T. J.; Thomas, R. C.; Voorman, R. L.; Stefanski, K. J.; Stehle, R. G.; Tarpley, W. G.; Morris, J. (-)-6-Chloro-2-[(1-furo[2,3-c]pyridin-5-yl-ethyl)thio]-4-pyrimidinamine, PNU-142721, a New Broad Spectrum HIV-1 Non-Nucleoside Reverse Transcriptase Inhibitor. *J. Med. Chem.* **1998**, *41*, 1357–1360.
25. A multistep procedure has also been reported that avoids subjecting the alkyl thioether to POCl₃; see Nugent, R. A.; Schlachter, S. T.; Murphy, M. J.; Cleek, G. J.; Poel, T. J.; Wishka, D. G.; Graber, D. R.; Yagi, Y.; Keiser, B. J.; Olmsted, R. A.; Kopta, L. A.; Swaney, S. M.; Poppe, S. M.; Morris, J.; Tarpley, W. G.; Thomas, R. C. Pyrimidine Thioethers: A Novel Class of HIV-1 Reverse Transcriptase Inhibitors with Activity Against BHAP-Resistant HIV. *J. Med. Chem.* **1998**, *41*, 3793–3803.
26. Kania, M. J.; Reyes, A.; Neufeldt, S. R. Oxidative Addition of (Hetero)aryl (Pseudo)halides at Palladium(0): Origin and Significance of Divergent Mechanism. *J. Am. Chem. Soc.* **2024**, *146*, 19249–19260.
27. Lu, J.; Schley, N. D.; Paci, I.; Leitch, D. C. Mechanisms and Site Selectivity of (Het)Ar-X Oxidative Addition to Pd(0) Are Controlled by Frontier Molecular Orbital Symmetry. *Organometallics* **2024**, *43*, 3192–3203.
28. Computed BDEs (B3LYP) from Garcia, Y.; Schoenebeck, F.; Legault, C. Y.; Merlic, C. A.; Houk, K. N. Theoretical Bond Dissociation Energies of Halo-Heterocycles: Trends and Relationships to Regioselectivity in Palladium-Catalyzed Cross-Coupling Reactions. *J. Am. Chem. Soc.* **2009**, *131*, 6632–6639.
29. Gordeev, E. G.; Eremin, D. B.; Chernyshev, V. M.; Ananikov, V. P. Influence of R–NHC Coupling on the Outcome of R–X Oxidative Addition to Pd/NHC Complexes (R = Me, Ph, Vinyl, Ethynyl). *Organometallics* **2018**, *37*, 787–796.
30. Although [Pd(halide)(Ar)(NHC)] complexes typically undergo C–Ar reductive elimination, Organ et al. were able to isolate an oxidative addition complex of this structure when using an exceptionally bulky NHC ligand: Semeniuchenko, V.; Sharif, S.; Rana, N.; Chandrasoma, N.; Braje, W. M.; Baker, R. T.; Manthorpe, J. M.; Pietro, W. J.; Organ, M. G. Experimental Evidence for Zerovalent Pd(NHC) as a Competent Catalyst in C–N Cross-Coupling (NHC = DiMeIHept^{Cl}). *J. Am. Chem. Soc.* **2024**, *146*, 29224–29236.

CHAPTER FOUR

ISOHYPsic PD-CATALYZED CROSS-COUPling ENABLES
C2-SELECTIVE AMINATION OF 2,4-
DICHlorOPYRIMIDINESContribution of Authors and Co-Authors

Manuscript in Chapter Four

Author: Oliver D. Jackson

Contributions: Conducted experimental work. Contributed to writing of the manuscript and supporting information. Project supervision (Appendix C).

Co-Author: Matthew P. Sandin

Contributions: Conducted experimental work. Contributed to writing of the manuscript and supporting information (Appendix C).

Co-Author: Connor T. Uter

Contributions: Conducted experimental work.

Co-Author: Daniel Y. Lanske

Contributions: Conducted experimental work.

Co-Author: Sharon R. Neufeldt

Contributions: Provided insight and guidance for totality of the project. Conducted computational experiments. Participated in preparation and revision of the manuscript and supporting information (Appendix C).

Manuscript Information

Oliver D. Jackson, Matthew P. Sandin, Connor T. Uter, Daniel Y. Lanske, Sharon R. Neufeldt
Status of Manuscript:

- ☐ Prepared for submission to a peer-reviewed journal
- ☒ Officially submitted to a peer-reviewed journal
- ☐ Accepted by a peer-reviewed journal
- ☐ Published in a peer-reviewed journal

Abstract

4-Substituted-2-(arylamino)pyrimidines are a privileged motif found in protein kinase inhibitors, but synthetic routes to these compounds are limited by the reactivity of 2,4-dihalopyrimidine precursors. 2,4-Dihalopyrimidines typically react preferentially at C4 during Buchwald-Hartwig cross-couplings and nucleophilic aromatic substitutions, which is problematic when late-stage installation of the 4-substituent is desirable. In Pd-catalyzed cross-couplings, selectivity arises during oxidative addition, which is heavily biased toward the C4—Cl site. We report a Pd^{II}-catalyzed cross-coupling that enables the first C2-selective amination of 2,4-dichloropyrimidine. The unusual selectivity arises from a novel isohypsic mechanism in which there is no oxidative addition step. Diverse 4-chloro-2-(arylamino)pyrimidines can be synthesized by this method, and the work also reveals that redox steps do not have to be a part of cross-coupling catalytic cycles using Pd.

Introduction

Pyrimidine rings are common features of pharmaceutical drugs, appearing in around 20% of all small-molecule drugs approved by the FDA in the past decade.^{1,2} These heteroarenes are especially well-represented among protein kinase inhibitors, a rapidly growing class of therapeutic agents used primarily to treat cancer and inflammatory diseases.^{3,4} Of the 95 FDA-approved small molecule protein kinase inhibitors, 49 (~52%) contain pyrimidine cores.¹⁻⁵ Pyrimidines also appear in other drug classes such as antivirals,⁶ antibiotics,^{7,8} and cardiovascular agents,⁹ as well as in organic electronic materials.¹⁰ Among small molecule drugs, 2-(arylamino)pyrimidines bearing an additional substituent at C4 are particularly privileged, appearing in fifteen protein kinase inhibitors currently on the market as well as others in clinical 10 trials (examples in Fig. 4.1A).^{5,11}

Despite the importance of 4-substituted-2-(arylamino)pyrimidines, synthetic routes to make these molecules are limited. The most modular and cost-effective strategies typically begin with 2,4-dichloropyrimidines. These substrates can be elaborated through cross-coupling or nucleophilic aromatic substitution (S_NAr). However, in the absence of certain substituents at C5, both types of reactions occur with preferential cleavage of the C4—Cl bond (Fig. 4.1B). Consequently, synthetic routes to 4-substituted-2-(arylamino)pyrimidines usually require that the 4-substituent is installed prior to the 2-(arylamino) substituent. This requirement is problematic for discovery chemistry, where structure-activity relationship studies demand highly modular routes for which the order of synthetic steps can be manipulated. Furthermore, during synthesis of compounds on a large scale, the early-stage installation of a 4-substituent is undesirable if that portion of the molecule is complex and more costly to prepare than the group at C2 (e.g., fostamatinib). Thus, the ability to selectively aminate 2,4-dichloropyrimidines at the 2-position could benefit drug discovery and production.

Excluding our recent work, over 98% of >1600 reported Pd-catalyzed C—C and C—N cross-coupling reactions of 2,4-dichloropyrimidine (**1**)—and all examples for which regiochemistry is unambiguously established—favor the C4-functionalized product.^{12,13} Although C2-selective amination of certain substituted 2,4-dichloropyrimidines is possible, these transformations require bulky (Fig. 4.1E) or strongly electron-withdrawing substituents at C5, limiting their generality.¹⁴⁻¹⁵ C2-selective amination of 4-chloro-2-(methylsulfonyl)pyrimidine (**2**) can be achieved by exploiting the greater reactivity of a sulfonyl leaving group over a chloride toward S_NAr (Fig. 4.1F), but **2** is considerably more costly than **1**, and the scope of the reaction is limited by strongly basic conditions and the requirement for activating the arylamine nucleophile by first converting it to a formamide.¹⁶

The site-selectivity of cross-coupling reactions typically arises during oxidative addition (Fig. 4.1C and 1D).¹⁷⁻²⁰ This step is generally assumed to be conserved across cross-coupling reactions catalyzed by transition metals and can take place through a polar or radical mechanism.²¹⁻²³ During oxidative addition of aryl halides (ArX) at palladium, low-valent Pd (usually Pd(0)) behaves like a nucleophile, formally donating two electrons as it cleaves an Ar—X bond.²⁴ With 2,4-dichloropyrimidine, Pd(0) reacts preferentially at C4 because the C4—Cl bond is weaker and C4 has a larger LUMO coefficient than C2, which lies on a node (Figure 4.1D).^{25,26} Two distinct mechanisms have been established for Ar—X oxidative addition at Pd(0) (Fig. 4.1D), and we and others have shown that ligand choice can influence the operative mechanism.²⁷⁻²⁹ For some dihalogenated substrates, the two mechanisms favor different reaction sites, and selectivity can be manipulated through ligand choice.^{27,28} These cases seem to require that the site with the larger LUMO coefficient is not also the one with the weaker C—X bond. With 2,4-dichloropyrimidine, for which both LUMO coefficients and bond strengths favor the C4 site, both mechanisms for

oxidative addition are faster at C4.²⁶ Nevertheless, here we describe a Pd-catalyzed amination of 2,4-dichloropyrimidine that is highly selective for the C2 position. We report evidence that the observed inversion of selectivity arises from a novel redox-neutral (isohypsic) mechanism: a Pd(II)-catalyzed cross-coupling cycle for which there is no oxidative addition step.^{30,31}

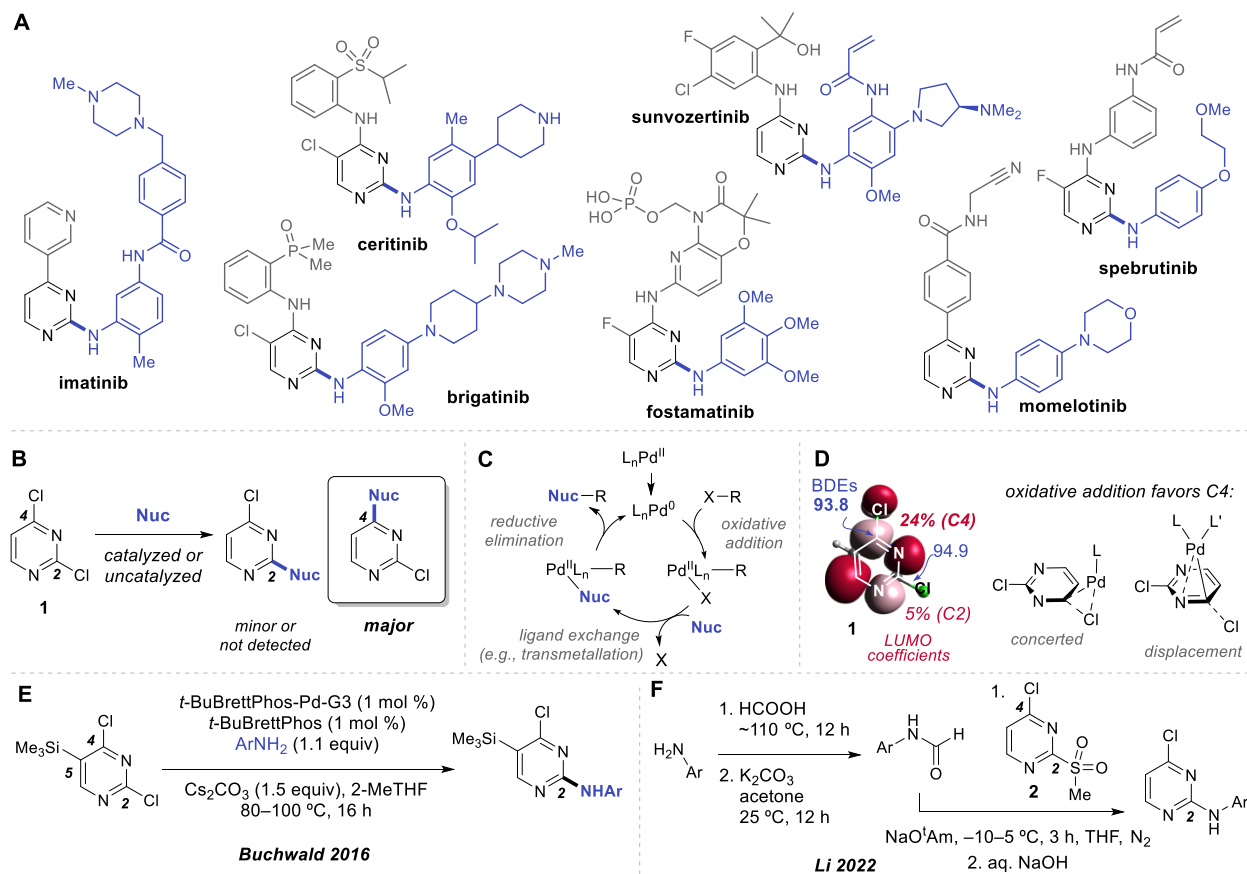


Figure 4.1 Relevance and Selectivity of Reactions of 2,4-Dihalopyrimidines. (A) 4-Substituted-2-(arylamino)pyrimidines in Protein Kinase Inhibitors. (B) Conventional Selectivity of Cross-Coupling and S_NAr . (C) Mechanism of Traditional Pd-Catalyzed Cross-Coupling Reactions. (D) Bond Strengths and LUMO Coefficients Favor Oxidative Addition at C4. (E) C2-Selective Amination Enabled by a Bulky C5 Substituent (F) Chemoselective Approach to C2-Selective Amination.

Results and Discussion

Optimization Studies

During initial efforts to study the selectivity of a Pd-catalyzed amination of **1** with aniline, the use of conditions similar to those we had developed for C—S coupling, using the precatalyst (η^3 -*t*-butylindenyl)Pd(IPent)Cl in acetonitrile, resulted in poor yield and exclusive reaction at the undesired C4 site (Fig. 4.2A, entry 1).²⁶ A Pd-free control reaction suggested that the uncatalyzed S_NAr reaction is competitive under these conditions (entry 2). To suppress S_NAr, we turned to less polar solvents that would destabilize anions. Gratifyingly, aromatic solvents in combination with a more soluble inorganic base (Cs₂CO₃) enabled high yields of cross-coupled product (entry 3). Although the major product still resulted from reaction at C4 (**3b**), a significant quantity of the desired regioisomer **3a** was also formed. No aminated products are detected in the absence of Pd under these conditions (entry 4), indicating that **3a** and **3b** result from Pd catalysis and not from background S_NAr. Remarkably, changing the precatalyst to Pd-PEPPSI-IPent, another Pd(II) source supported by the same ancillary ligand IPent, resulted in exclusive formation of the desired C2-coupled product **3a** (entry 5). Pd-PEPPSI-IPr afforded similar results (entry 6), but a smaller *N*-heterocyclic carbene (NHC) ligand IMes provided a substantial improvement in yield (entry 7). The related dichloride dimer gives similarly high yield with identical exclusive C2-selectivity (entry 8).

Substrate Scope

Thus, the optimal reaction conditions use Pd-PEPPSI-NHC or [(NHC)PdCl₂]₂, where NHC is usually IMes, although slightly better results were obtained with [(IPr)PdCl₂]₂ for a few

anilines.^{32,33} Under the optimized conditions, simple primary anilines bearing electron-donating (**4a–6a**), -neutral (**3a**), and -withdrawing (**7a–10a**) groups can be coupled to **1** (Fig. 4.2B). Mono-ortho substitution (**4a** and **5a**) and a terminal alkene are tolerated (**11a**), with no evidence for occurrence of Heck coupling in the latter reaction. Remarkably, the reaction tolerates halogen substituents on the aniline (**12a–14a**), including ortho-iodo (**14a**). This result is notable because aryl iodides typically react rapidly with Pd(0).²⁵ The optimized conditions also enable installation of arylamino substituents at C2 reminiscent of the structures of several known protein kinase inhibitors (**15a–19a**). C2-selective amination of some 5- and 6-substituted 2,4-dichloropyrimidines also occurs under these conditions (**20a–24a**). 2,4-Dibromo and 2,4-diiodopyrimidine also give exclusively the C2-aminated regioisomers (**25a** and **26a**), with conversions similar to those obtained with **1**.³⁰ Finally, three analogues of momelotinib (**27–29**) were prepared through derivatization of the common intermediate **16a**, which was synthesized by the C2-selective amination protocol. These analogues contain pharmacophores at C4 that are found in other protein kinase inhibitors, and two of these analogues are novel (**28** and **29**).

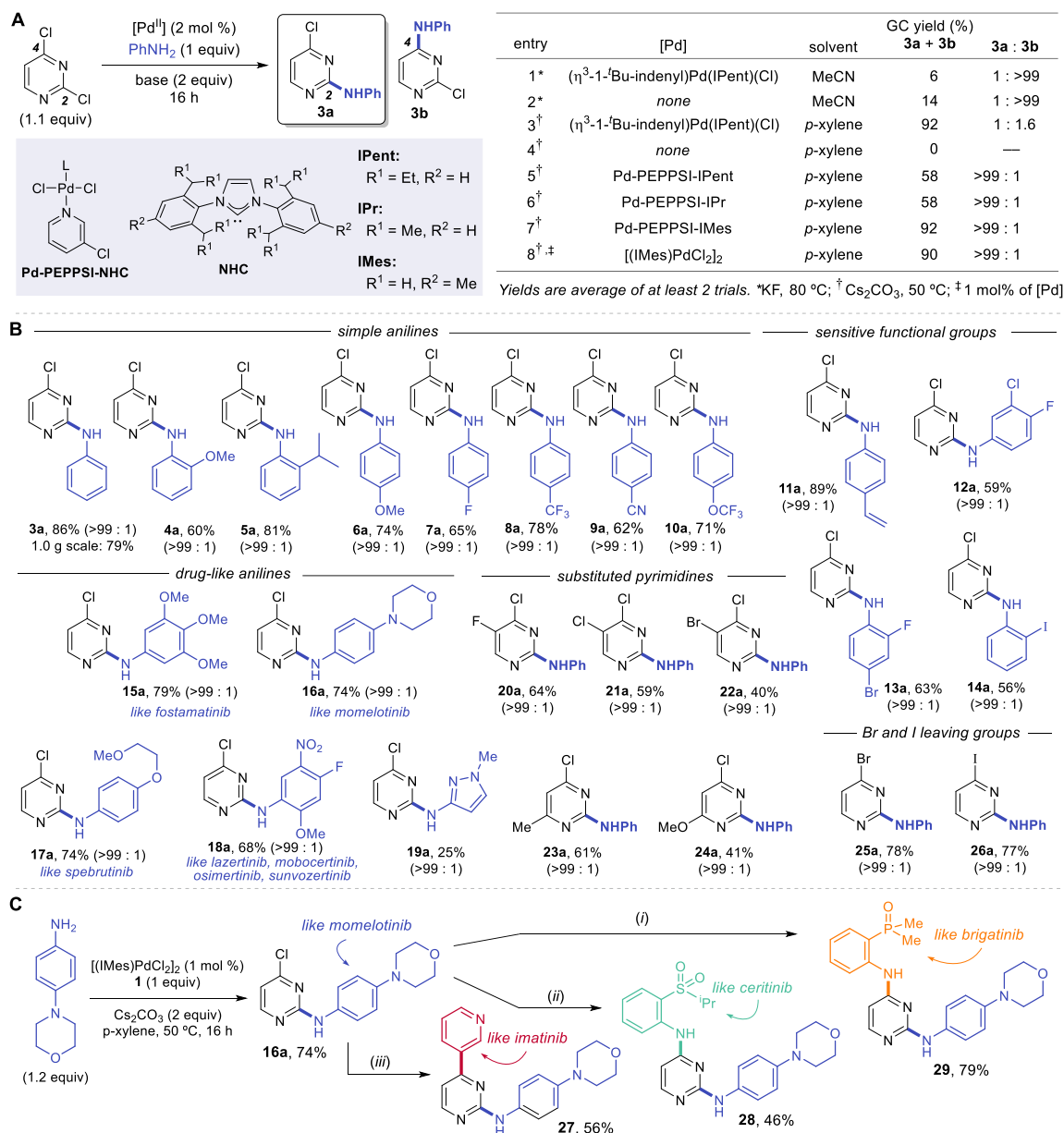


Figure 4.2 Pd-Catalyzed C2-Amination of Dihalopyrimidines. (A) Optimization. (B) Scope. (C) Diversity-Oriented Synthesis of Drug-Like Analogues. Conditions: (i) *o*-(POMe)₂C₆H₄NH₂ (1 equiv), HCl (excess), iPrOH, 70 °C, 24 h; (ii) *o*-(SO₂iPr)C₆H₄NH₂ (1 equiv), HCl (excess), iPrOH, 70 °C, 24 h; (iii) 3-pyridylboronic acid (1 equiv), Pd(PPh₃)₄ (4.4 mol %), K₂CO₃ (2 equiv), dioxane/H₂O (1:1), 90 °C, 72 h.

Mechanistic Proposal

We next turned to understanding the mechanistic origin of the unique C2-selectivity in this catalytic amination. All evidence to date indicates that oxidative addition at Pd(0) should favor reaction of the C4—Cl bond, which contradicts the observed C2-selectivity in this case. In contrast to the C2-selective amination, a Suzuki-Miyaura coupling under the conditions optimized for amination leads to exclusive arylation at the conventional C4-position (**30b**, Fig. 4.3A). When aniline is included in the Suzuki-Miyaura reaction (to better imitate the optimized conditions), amination is observed exclusively at C2, but arylation still takes place only at the C4 site. The observed selectivity in the Suzuki-Miyaura coupling corroborates DFT calculations, which indicate that oxidative addition should be faster at C4—Cl regardless of whether it takes place at mono- or bisligated Pd(0) and whether it occurs through a 3-centered concerted or a nucleophilic displacement mechanism. Oxidative addition involving PdI /PdI dimers has been described as an alternate mechanism for Ar—X cleavage, but literature precedent suggests that a mechanism involving a PdI /PdI dimer would also favor the conventional C4 site of **1**.³⁴ DFT calculations do not support reversible oxidative addition which precludes a Curtin-Hammett scenario in which a later step could be selectivity-determining. The reaction conditions are not typical for catalysis by Pd nanoparticles (i.e., no tetralkylammonium salts, no polar solvents), and the reaction mixtures do not turn brown or black (Figure Appendix C1). Thus, catalysis by nanoparticles or heterogeneous Pd is unlikely.

Ultimately, the observed catalyst trends pointed us toward considering a redox-neutral mechanism. In particular, the optimal precatalysts (Pd^{II}-PEPPSI-NHC or [(NHC)Pd^{II}Cl₂]₂) do not have an obvious low-energy path for reduction to Pd⁰. Although such catalysts are known to effect other Buchwald-Hartwig couplings using aniline, presumably proceeding through Pd⁰, those

couplings require significantly higher temperatures (80-110 °C) and/or addition of alkoxide activators.^{33, 37-43} In contrast, the optimized conditions for C2-amination of **1** involve a weaker carbonate base and a temperature of 50 °C; in fact, the reaction proceeds to >50% conversion even at room temperature (Table Appendix C1, entries 45-46). As such, we considered whether the C2-selective amination could be catalyzed by Pd^{II} rather than Pd⁰.

Remarkably, DFT calculations support the feasibility of a redox-neutral catalytic cycle in which Pd^{II} facilitates an intramolecular nucleophilic attack on C2 by an amido ligand (Fig. 4.3B). The computed mechanism begins with coordination of aniline to break up the dimer, followed by deprotonation to generate Pd^{II}-amido complex **33**. These steps are predicted to be exergonic, although it should be noted that DFT is not expected to provide very accurate relative energies of ionic compounds (Cs₂CO₃, CsHCO₃, and KCl) due to difficulty in accounting for solvent effects and salt speciation. Complex **33** can coordinate to N1 of **1** to give **34a**, placing the amido ligand in close proximity to C2, but far away from C4. The calculations then predict a facile migratory insertion-like step **TS35a** to transfer the amido ligand onto C2, displacing chloride ($\Delta G^\ddagger_{30} = 14.3$ kcal/mol measured from **34a**). An intrinsic reaction coordinate calculation in the forward direction starting from **TS35a** appears to lead to an ion pair involving hydrogen bonding between chloride and NH (Figure Appendix C6), although calculations attempting to optimize this putative ion pair intermediate did not converge. Intermediate **36a**, representing the collapse of the ion pair, then undergoes ligand exchange to regenerate complex **32** and release aminated product **3a**. Importantly, formation of the experimentally disfavored C4 regioisomer through an analogous mechanism would require substrate **1** to coordinate to Pd through N3 (**34b**). N3-coordination is predicted to be less favorable than N1 coordination, which is consistent with the expected weaker Lewis basicity of N3 due to both electronics and sterics. The higher energy associated with N3-

coordination persists in the transition state for migratory insertion (**TS35b**). Overall, reaction at C2 through **TS35a** is predicted to be favored by 2.4 kcal/mol. Other DFT methods predict a similar preference for reaction at C2, with $\Delta G^\ddagger$ **TS35b**–**TS35a** values ranging from 2.2–4.4 kcal/mol (Table Appendix C6).

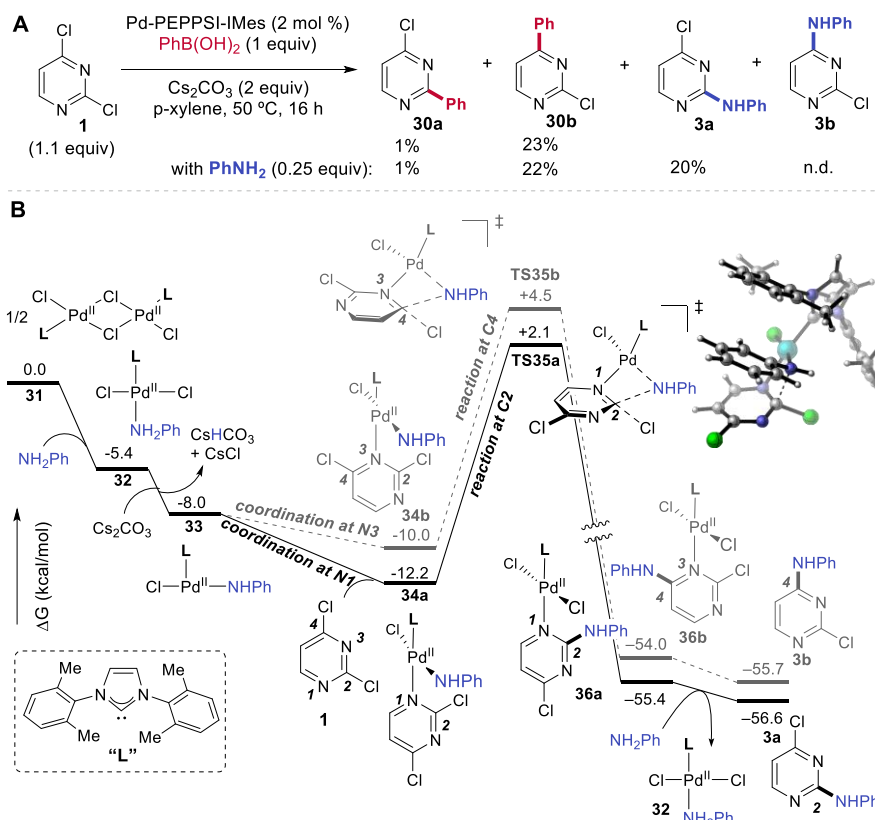


Figure 4.3 Mechanistic Information. (A) A Suzuki-Miyaura Coupling Gives Conventional C4 Selectivity Under Conditions that Afford C2-Selective Amination (B) DFT Calculations Support a Redox-Neutral (Isohyspic) Mechanism for Amination; Calculated at the SMD(p-xylene)-MN15/def2-TZVPD//SMD(p-xylene)-MN15L/6-31G(d) (C, H)/6-31+G(d) (N, Cl, O)/LANL2DZ(Pd) Level of Theory; Free Energies in kcal/mol.

Experimental Corroboration of Mechanism

The isohypsic Pd^{II} -catalyzed mechanism suggested by DFT leads to several predictions that are experimentally testable. First, complex **37** was prepared by the reaction of $[(\text{IMes})\text{PdCl}_2]_2$ with

1. As confirmed by X-ray diffraction, the pyrimidine ligand indeed coordinates to Pd^{II} through N1 (Fig. 4.4A). Second, if the greater Lewis basicity of N1 is key to selectivity, and if Pd⁰ is not operative, then C2 selectivity might still be expected even for substrate **38**, which is extraordinarily biased toward reaction at C4 through an oxidative addition mechanism. However, amination was observed exclusively through cleavage of the C2—Cl bond to give **26a**, despite the presence of an iodide at C4 (Fig. 4.4B). This result supports the conclusion that oxidative addition is not part of the operative catalytic cycle.

Next, we evaluated the effect of Pd⁰ precatalysts in the amination reaction. If the C2-selective transformation is catalyzed by Pd^{II}, then Pd⁰ complexes might be expected to give worse selectivity, as they can engage in C4-selective oxidative addition. Under the optimized conditions with Pd^{II}-PEPPSI-IMes, the overall ratio of reaction at C2:C4 is >99:1 (Figure 4.4C, entry 1). This ratio takes into account a minor side product **39a**, corresponding to aniline diarylation via reaction at the C2 positions of two equivalents of **1**. Only a trace amount of the diarylated regioisomer **39b** (involving reaction at C4) is observed, and none of **39c** is detected. Similar results are obtained with the combination of Pd^{II}Cl₂ and IMes•HCl (entry 2). However, the use of Pd⁰ sources together with IMes•HCl leads to a large increase in the amount of products resulting from reaction at the C4 position (**39b** and **39c**, entries 3–5). These results are consistent with the hypothesis that Pd^{II} reacts selectively at C2 through a redox-neutral pathway, while oxidative addition at Pd⁰ prefers the C4 site. It is interesting that reaction at C2 occurs to a substantial extent even when starting with Pd⁰ sources. The exclusive C4-selectivity observed in the Suzuki-Miyaura coupling (Figure 3a) and DFT calculations suggest that Pd⁰ is highly selective for C4 functionalization, so the C2-aminated products in all of the reactions in Fig. 4.4D likely result from Pd^{II}-catalysis. This suggests

that there is a pathway for Pd^0 to become converted to catalytically active Pd^{II} (e.g., oxidative addition and ligand exchange).

Finally, the effect of O_2 on the C2-selective reaction was examined. If the catalytic cycle involves only Pd^{II} , and not Pd^0 , the reaction should not be oxygen-sensitive. To test this, the reaction mixture was first sparged with pure O_2 and then allowed to stir overnight under a balloon of oxygen (~ 1 atm). Remarkably, the reaction is equally efficient under O_2 compared to an inert atmosphere (Fig. 4.4C). This result is unusual because Pd-catalyzed cross-couplings typically require an inert atmosphere and Pd^0 tends to react rapidly with O_2 .⁴⁴⁻⁴⁷ Although some rare examples of Pd-catalyzed cross-couplings using NHC ligands have been described under air, the use of pure O_2 (1 atm) has been reported to shut down catalysis.⁴⁸ The lack of oxygen sensitivity of the C2-selective amination of **1** is thus inconsistent with a mechanism involving Pd^0 .

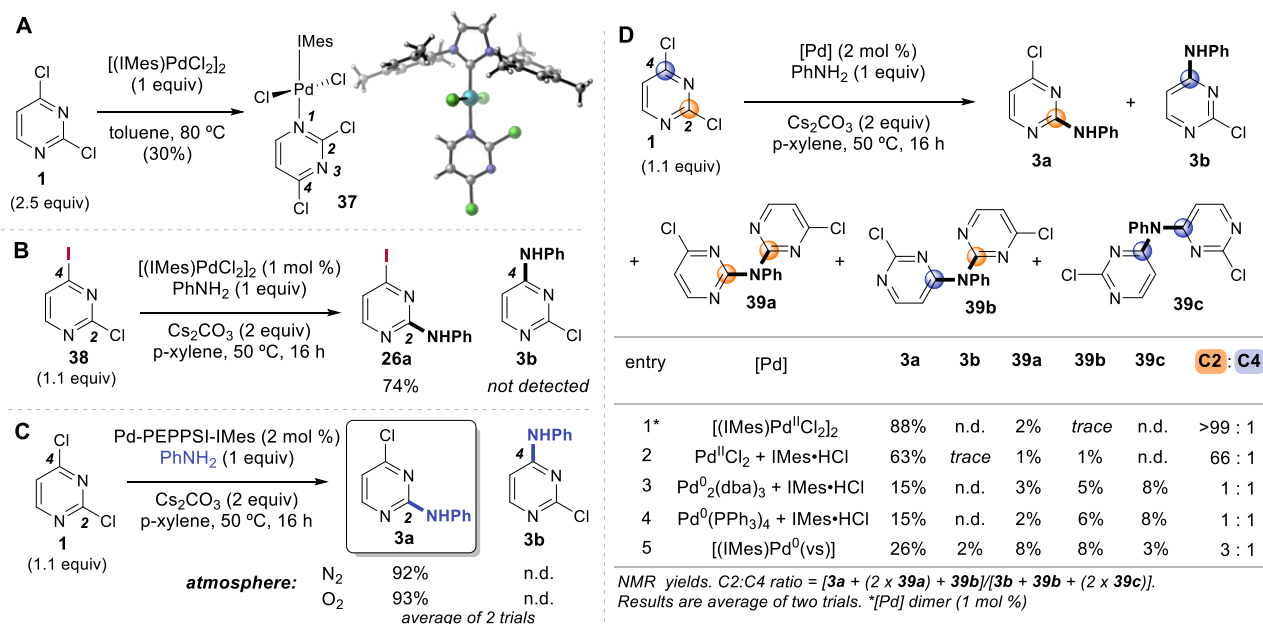


Figure 4.4 Experimental Data are Consistent with Pd(II)-Catalyzed Mechanism. (A) Substrate 1 Coordinates to Pd(II) through N1. (B) Pd(0) Sources Lead to Worse Selectivity. (C) C2-Selective Amination is Insensitive to Pure O_2 .

Comparison to Catalyzed S_NAr

The proposed Pd^{II} -catalyzed amination of dihalopyrimidines (Fig. 4.5) might be described as either a cross-coupling or a catalytic S_NAr reaction. However, its mechanism (Fig. 4.5) differs from other S_NAr reactions catalyzed by electrophilic transition metals (Ru^{II} or Rh^{III}) because nucleophilic attack takes place within palladium's inner sphere in a migratory insertion-like step. In contrast, Ru^{II} and Rh^{III} -catalyzed S_NAr reactions are proposed to involve π -coordination of the metal to one face of an aryl halide substrate and outer-sphere attack of the nucleophile to the opposite face.⁴⁹⁻⁵¹ DFT predicts that such a π -coordination mechanism for the reaction of **1** with Pd^{II} and aniline would be prohibitively high in energy. Furthermore, outer-sphere attack on a σ -coordinated intermediate like **34a** would be a high-energy pathway with neutral aniline and would result in the wrong (C4) selectivity with anilide. Instead, the inner-sphere mechanism that we propose more resembles a stoichiometric “internal S_NAr ” reaction reported by Goddard, III and Gunnoe, wherein a Rh^{III} complex was observed to transfer a carboxylate group onto a fluoroarene fragment of a diquinoline ligand.⁵²

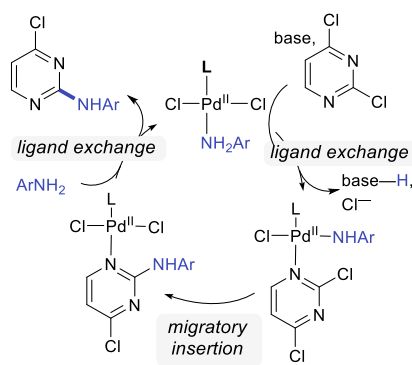


Figure 4.5 Proposed Isohyspic Catalytic Cycle

Analysis of Other Catalysts

Main group and d^{10} Lewis acidic metals, including Mg^{2+} , Zn^{2+} , and Cu^{+1} have been reported to direct S_NAr ortho to Lewis basic functional groups preferentially over more distal sites.⁵³⁻⁵⁷ Notably, Zn^{2+} salts enable C2-selective S_NAr of activated 2,4-dichloropyrimidines that are substituted by a strong electron-withdrawing group at C5.¹⁴ However, under our conditions, no or very little reaction is observed when replacing catalytic Pd^{II} with traditional Lewis acids (Table Appendix C5). Some Lewis acids in stoichiometric quantities lead to higher conversions, but give selectivity $\sim 1:1$ or favoring the C4 product. Trials using catalytic Ni^{II} or Cu^I NHC complexes led to low yields and selectivity, while a Au^I NHC complex affords relatively high yield of the conventional C4 product (Table Appendix C5). Some Pd/phosphine precatalysts also promote C2-selectivity, but yields are low (Table Appendix C1). Thus, at present, Pd^{II}/NHC precatalysts offer uniquely high C2-selectivity and yield.

Conclusions

Because of the medicinal relevance of 2-aminopyrimidines and the absence of alternative general methods for selective amination at the 2-position of 2,4-dihalopyrimidines, the reported transformation is expected to be useful for the synthesis of pharmaceutical drugs, including protein kinase inhibitors. Furthermore, a vast body of work has established that oxidative addition is a fundamental step of cross-coupling cycles catalyzed by transition metals. However, the C2-selective amination of 2,4-dichloropyrimidines described herein demonstrates that redox steps are not always a part of these cycles. It is possible that the isohypsic mechanistic manifold for Pd-catalyzed cross-couplings may prove relevant to other cross-couplings that were assumed to be

catalyzed by Pd⁰, and the isohypsic mechanism also presents a new strategy for improving or developing new cross-couplings.

Acknowledgements

We thank Dr. Daniel Decato for collection of X-ray crystallographic data and Dr. Nathaniel Larson for helpful mechanistic discussions. We are grateful to Umicore for gifts of some palladium complexes.

Funding

National Institutes of Health grant R35GM137971 (ODJ, MPS, CTU, DYL, SRN)
MSU PhD Completion Award (ODJ)
National Science Foundation NMR Instrumentation CHE-2018388
National Science Foundation NMR Instrumentation DBI-1532078
Murdock Charitable Trust Foundation NMR Instrumentation 2015066:MNL
National Institutes of Health MS Instrumentation P20GM103474
National Institutes of Health MS Instrumentation S10OD28650
National Institutes of Health Crystallography P30GM140963
National Science Foundation Crystallography CHE-1337908
ACCESS computational allocation CHE240059

Author Contributions

Conceptualization: SRN
Methodology: ODJ, SRN
Investigation: ODJ, MPS, CTU, DYL, SRN
Visualization: SRN
Funding acquisition: SRN
Project administration: SRN
Supervision: SRN, ODJ
Validation: MPS, CTU, DYL
Writing – original draft: SRN
Writing – review & editing: ODJ, MPS, SRN

References

1. FDA. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations <https://www.fda.gov/drugs/drug-approvals-and-databases/approved-drug-products-therapeutic-equivalence-evaluations-orange-book> (accessed 2nd September 2025).
2. Y. Zhang, X. Liu, C. Zhang, Y. Li, G. Zhang, Z. Du, FDA-Approved Pyrimidine-Containing Drugs: Synthesis and Clinical Application. *Med. Res. Rev.* **2025**, 1–36.
3. M. M. Attwood, D. Fabbro, A. V. Sokolov, S. Knapp, H. B. Schiöth, Trends in kinase drug discovery: targets, indications, and inhibitor design. *Nat. Rev. Drug Discov.* **2021**, 20, 839–861.
4. R. Lorenz, J. Wu, F. W. Herberg, S. S. Taylor, R. A. Engh, Drugging the Undruggable: How Isoquinolines and PKA Initiated the Era of Designed Protein Kinase Inhibitor Therapeutics. *Biochemistry* **2021**, 60, 3470–3484.
5. R. Roskoski, Properties of FDA-approved small molecule protein kinase inhibitors: A2026 update. *Pharm. Res.* **2026**, 224, 108107.
6. T. A. Farghaly, M. F. Harras, A. M. R. Alsaedi, H. A. Thakir, H. K. Mahmoud, D. F. Katowah, Antiviral Activity of Pyrimidine Containing Compounds: Patent Review. *Mini Reviews in Medicinal Chemistry* **2023**, 23, 821–851.
7. J. Zhuang, S. Ma, Recent Development of Pyrimidine-Containing Antimicrobial Agents. *ChemMedChem*, **2020**, 15, 1875–1886.
8. V. Alagarsamy, B. Narendhar, M. Thasthagir Sulthana, G. Sabarees, V. R. Solomon, Pyrimidine Based Scaffolds: Emerging Frontiers in Antimicrobial Drug Discovery. *ChemistrySelect*, **2025**, 10, e00907.
9. S. Benkirane, A. Ez-Zoubi, H. Misbahi, Pyridine and pyrimidine derivatives, potent pharmacophore with various biological activities and significant therapeutic properties: Recent advances. *J. Mol. Struct.* **2026**, 1350, 144031.
10. S. Achelle, J. Rodríguez-López, F. Robin-le Guen, The arylvinylpyrimidine scaffold: a tunable platform for luminescent and optical materials. *Org. Biomol. Chem.* **2023**, 21, 39–52.
11. P. H. Schafer, A. J. Kivitz, J. Ma, S. Korish, D. Sutherland, L. Li, A. Azaryan, J. Kosek, M. Adams L. Capone, E. M. Hur, D. R. Hough, G. E. Ringheim, Spebrutinib (CC-292) Affects

Markers of B Cell Activation, Chemotaxis, and Osteoclasts in Patients with Rheumatoid Arthritis: Results from a Mechanistic Study. *Rheumatol. Ther.* **2020**, 7, 101–119.

12. Substructure-based SciFinder searches were conducted on February 3, 2026 for transformations convert 1 into either 2- or 4-chloropyrimidine bearing a C or N substituent at either C4 or C2, respectively. Carbons 5 and 6 were “locked” to prevent substitution and reaction mapping was used. Results were limited to single-step reactions that include a Pd catalyst. Results for C4-substitution: 90 hits for nitrogen, 1508 hits for carbon. Results for C2-substitution: 5 hits for nitrogen, 19 hits for carbon.
13. S. M. Smith, S. L. Buchwald, Regioselective 2-Amination of Polychloropyrimidines. *Org. Lett.* **2016**, 18, 2180–2183.
14. D. T. Richter, J. C. Kath, M. J. Luzzio, N. Keene, M. A. Berliner, M. D. Wessel, Selectiaddition of amines to 5-trifluoromethyl-2,4-dichloropyrimidine induced by Lewis acids. *Tetrahedron Lett.* **2013**, 54, 4610–4612.
15. M. Lee, T. Rucil, D. Hesek, A. G. Oliver, J. F. Fisher, S. Mobashery, Regioselective Control of the S_NAr Amination of 5-Substituted-2,4-Dichloropyrimidines Using Tertiary Amine Nucleophiles. *J. Org. Chem.* **2015**, 80, 7757–7763.
16. C. Li, F. Haeffner, S. Wang, C. Yuan, D. Shang, X. Shi, B. Ma, B. T. Hopkins, E. M. O’Brien, Sulfone Displacement Approach for Large-Scale Synthesis of 4-Chloro-N-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-amine. *Org. Process Res. Dev.* **2022**, 26, 137–143.
17. J. Almond-Thynne, D. C. Blakemore, D. C. Pryde, A. C. Spivey, Site-selective Suzuki Miyaura coupling of heteroaryl halides– understanding the trends for pharmaceutically important classes. *Chem. Sci.* **2017**, 8, 40–62.
18. E. K. Reeves, E. D. Entz, S. R. Neufeldt, Chemodivergence between Electrophiles in Cross-Coupling Reactions. *Chem. Eur. J.* **2021**, 27, 6161–6177.
19. V. Palani, M. A. Perea, R. Sarpong, R. Site-Selective Cross-Coupling of Polyhalogenated Arenes and Heteroarenes with Identical Halogen Groups. *Chem. Rev.* **2022**, 122, 10126–10169.
20. J. P. Norman, S. R. Neufeldt, The Road Less Traveled: Unconventional Site Selectivity in Palladium-Catalyzed Cross-Couplings of Dihalogenated N-Heteroarenes. *ACS Catal.* **2022**, 12, 12014–12026.
21. C. C. C. Johansson Seechurn, M. O. Kitching, T. J. Colacot, V. Snieckus, Palladium Catalyzed Cross-Coupling: A Historical Contextual Perspective to the 2010 Nobel Prize. *Angew. Chem. Int. Ed.*, **2012**, 51, 5062–5085.

22. L. C. Campeau, N. Hazari, Cross-Coupling and Related Reactions: Connecting Past Success to the Development of New Reactions for the Future. *Organometallics*, **2019**, *38*, 3–35
23. S. J. Firsan, V. Sivakumar, T. J. Colacot, Emerging Trends in Cross-Coupling Twelve-Electron-Based L1Pd(0) Catalysts, Their Mechanism of Action, and Selected Applications. *Chem. Rev.* **2022**, *122*, 16983–17027.
24. J. A. Labinger, Tutorial on Oxidative Addition. *Organometallics* **2015**, *34*, 4784–4795.
25. Y. Garcia, F. Schoenebeck, C. Y. Legault, C. A. Merlic, K. N. Houk, Theoretical Bond Dissociation Energies of Halo-Heterocycles: Trends and Relationships to Regioselectivity in Palladium-Catalyzed Cross-Coupling Reactions. *J. Am. Chem. Soc.* **2009**, *131*, 6632–6639.
26. O. D. Jackson, A. Reyes, C. D. Stein, N. G. Larson, C. T. Andrews, S. R. Neufeldt, C2 Selective Palladium-Catalyzed C—S Cross-Coupling of 2,4-Dihalopyrimidines. *J. Am. Chem. Soc.* **2025**, *147*, 3017–3022.
27. J. P. Norman, N. G. Larson, S. R. Neufeldt, Different Oxidative Addition Mechanisms for 12 and 14-Electron Palladium, *ACS Catal.* **2022**, *12*, 8822–8828.
28. M. J. Kania, A. Reyes, S. R. Neufeldt, Oxidative Addition of (Hetero)aryl (Pseudo)halides at Palladium(0): Origin and Significance of Divergent Mechanism. *J. Am. Chem. Soc.* **2024**, *146*, 19249–19260.
29. M. Besora, F. Maseras, The diverse mechanisms for the oxidative addition of C—Br bonds to Pd(PR₃) and Pd(PR₃)₂ complexes. *Dalton Trans.* **2019**, *48*, 16242–16248.
30. C. D. Smith, D. Phillips, A. Tirla, D. J. France. Catalytic Isohysic-Redox Sequences for the Rapid Generation of Csp³-Containing Heterocycles. *Chem. Eur. J.* **2018**, *24*, 17201–17204.
31. M. Magre, J. Cornella, Redox-Neutral Organometallic Elementary Steps at Bismuth: Catalytic Synthesis of Aryl Sulfonyl Fluorides. *J. Am. Chem. Soc.* **2021**, *143*, 21497–21502.
32. C. J. O'Brien, E. A. B. Kantchev, C. Valente, N. Hadei, G. A. Chass, A. Lough, A. C. Hopkinson, M. G. Organ, Easily Prepared Air- and Moisture-Stable Pd–NHC (NHC=N Heterocyclic Carbene) Complexes: A Reliable, User-Friendly, Highly Active Palladium Precatalyst for the Suzuki–Miyaura Reaction. *Chem. Eur. J.* **2006**, *12*, 4743–4748.
33. M. S. Viciu, R. M. Kissling, E. D. Stevens, S. P. Nolan, An Air-Stable Palladium/NHeterocyclic Carbene Complex and Its Reactivity in Aryl Amination. *Org. Lett.* **2002**, *4*, 2229–2231.

34. F. Proutiere, M. Aufiero, F. Schoenebeck, Reactivity and Stability of Dinuclear Pd(I) Complexes: Studies on the Active Catalytic Species, Insights into Precatalyst Activation and Deactivation, and Application in Highly Selective Cross-Coupling Reactions. *J. Am. Chem. Soc.* **2012**, *134*, 606–612.
35. N. W. J. Scott, M. J. Ford, N. Jeddi, A. Eyles, L. Simon, A. C. Whitwood, T. Tanner, C. E. Willans, I. J. S. Fairlamb. A Dichotomy in Cross-Coupling Site Selectivity in a Dihalogenated Heteroarene: Influence of Mononuclear Pd, Pd Clusters, and Pd Nanoparticles—the Case for Exploiting Pd Catalyst Speciation. *J. Am. Chem. Soc.* **2021**, *143*, 9682–9693.
36. J. P. Norman, N. G. Larson, E. D. Entz, S. R. Neufeldt, Unconventional Site Selectivity in Palladium-Catalyzed Cross-Couplings of Dichloroheteroarenes under Ligand Controlled and Ligand-Free Systems. *J. Org. Chem.* **2022**, *87*, 7414–7421.
37. T. Tu, W. Fang, J. Jiang, A highly efficient precatalyst for amination of aryl chlorides: synthesis, structure and application of a robust acenaphthoimidazolydene palladium complex. *Chem. Commun.* **2011**, *47*, 12358–12360.
38. A. Chartoire, X. Frogneux, A. Boreux, A. M. Z. Slawin, S. P. Nolan, S. P. [Pd(IPr*)(3-C pyridinyl)Cl₂]: A Novel and Efficient PEPPSI Precatalyst. *Organometallics* **2012**, *31*, 6947–6951.
39. K. H. Hoi, S. Calimsiz, R. D. J. Froese, A. C. Hopkinson, M. G. Organ, Amination with Pd-NHC Complexes: Rate and Computational Studies Involving Substituted Aniline Substrates. *Chem. Eur. J.* **2012**, *18*, 145–151.
40. K. H. Hoi, J. A. Coggan, M. G. Organ, Pd-PEPPSI-IPentCl: An Effective Catalyst for the Preparation of Triarylamines. *Chem. Eur. J.* **2013**, *19*, 843–845.
41. M. Pompeo, J. L. Farmer, R. D. J. Froese, M. G. Organ, Room-Temperature Amination of Deactivated Aniline and Aryl Halide Partners with Carbonate Base Using a PdPEPPSI-IPentCl-o-Picoline Catalyst, *Angew. Chem. Int. Ed.* **2016**, *53*, 3223–3226.
42. D.-H. Li, X.-B. Lan, A.-X. Song, M. M. Rahman, C. Xu., F.-D. Huang, R. Szostak, M., F.-S. Liu, Buchwald-Hartwig Amination of Coordinating Heterocycles Enabled by Large-but-Flexible Pd-BIAN-NHC Catalysts. *Chem. Eur. J.* **2022**, *28*, e202103341.
43. X.-F. Deng, Y.-J. Chen, L.-Y. Yi, J. Huang, New NHC–Pd complexes bearing bulky steric hindrance: Synthesis and catalytic activity in the Heteroaryl–Heteroaryl Buchwald–Hartwig amination reaction. *Tetrahedron*, **2025**, *177*, 134567.

44. M. M. Konnick, I. A. Guzei, S. S. Stahl, Characterization of Peroxo and Hydroperoxo Intermediates in the Aerobic Oxidation of N-Heterocyclic-Carbene-Coordinated Palladium(0). *J. Am. Chem. Soc.* **2024**, *126*, 10212–10213.
45. M. Yamashita, K. Goto, T. Kawashima, Fixation of Both O₂ and CO₂ from Air by a Crystalline Palladium Complex Bearing N-Heterocyclic Carbene Ligands. *J. Am. Chem. Soc.* **2005**, *127*, 7294–7295.
46. C. Adamo, C. Amatore, I. Ciofini, A. Jutand, H. Lakmini, Mechanism of the Palladium-Catalyzed Homocoupling of Arylboronic Acids: Key Involvement of a Palladium Peroxo Complex. *J. Am. Chem. Soc.* **2006**, *128*, 6829–6836.
47. S. Fantasia, S. P. Nolan, A General Synthetic Route to Mixed NHC–Phosphane Palladium(0) Complexes (NHC= N-Heterocyclic Carbene). *Chem. Eur. J.* **2008**, *14*, 6987–6993.
48. X. B. Lan, F.-M. Chen, B.-B. Ma, D.-S. Shen, F.-S. Liu, Pd-PEPPSI Complexes Bearing Bulky [(1,2-Di-(tert-butyl)acenaphthyl] (DtBu-An) on N-Heterocarbene Backbones: Highly Efficient for Suzuki–Miyaura Cross-Coupling under Aerobic Conditions. *Organometallics*, **2016**, *35*, 3852–3860.
49. M. Otsuka, K. Endo, T. Shibata, Catalytic S_NAr reaction of non-activated fluoroarenes with amines via Ru h₆-arene complexes. *Chem. Commun* **2010**, *46*, 336–338.
50. Q. K. Kang, Y. Lin, Y. Li, L. Xu, K. Li, H. Shi, Catalytic S_NAr Hydroxylation and Alkoxylation of Aryl Fluorides. *Angew. Chem. Int. Ed.* **2021**, *60*, 20391–20399.
51. K. Chen, Y. Ma, Y. Lin, J.-Y. Li, H. Shi, Ruthenium/ η^5 -Phenoxo-Catalyzed Amination of Phenols with Amines. *J. Am. Chem. Soc.* **2024**, *146*, 15833–15842.
52. M. E. O'Reilly, S. I. Johnson, R. J. Nielson, W. A. Goddard, III, T. B. Gunnoe, Transition-Metal-Mediated Nucleophilic Aromatic Substitution with Acids. *Organometallics* **2026**, *35*, 2053–2056.
53. R. E. Banks, W. J. Jondi, A. E. Tipping, Reaction of pentafluoropyridine with lithiumhydrazonides; competing monosubstitution at the 2- and 4-positions. *J. Fluor. Chem.* **1996**, *99*, 87–92.
54. R. E. Banks, W. J. Jondi, A. E. Tipping, Reaction of octafluorotoluene, 3,5-dichlorotrifluoropyridine, 3-chlorotetrafluoropyridine and tetrafluoropyrimidine with alkali-metal oximates. *J. Fluor. Chem.* **1996**, *80*, 109–116.

55. S. G. Ruggeri, B. C. Vanderplas, B. G. Anderson, R. Breitenbach, F. J. Urban, A. M. Stewart, III, G. R. Young, Regioselective Addition of Mesityl to a 2,4-Dichloropyridine. *Org. Process Res. Dev.* **2008**, *12*, 411–413.
56. M. D. Wendt, A. R. Kunzer, Ortho-selectivity in S_NAr substitutions of 2,4-dihaloaromatic compounds. Reactions with anionic nucleophiles. *Tetrahedron Lett.* **2020**, *51*, 3041–3044.
57. L. C. Campeau, S. J. Dolman, D. Gauvreau, E. Corley, J. Liu, E. N. Guidry, S. G. Ouellet, D. Steinhuebel, M. Weisel, P. D. O'Shea, Convergent Kilo-Scale Synthesis of a Potent Renin Inhibitor for the Treatment of Hypertension. *Org. Process Res. Dev.* **2011**, *15*, 1138–1148.

CHAPTER FIVE

TOWARD THE SYNTHESIS AND CHARACTERIZATION OF
A LOW-VALENT, THERMALLY STABLE PALLADIUM(0)
COMPLEXIntroduction

Pd catalyzed cross-coupling is one of the most-widely used methodologies in modern synthetic organic chemistry with broad applicability in process chemistry, total synthesis, agrochemistry, and materials synthesis, among others.¹ Whilst ligand identity is critical in tuning the reaction yield, selectivity, and generality of these systems, recent attention has also turned to focusing on the nature of the precatalyst scaffold.² Screening of reaction conditions with a single-component Pd(II) precatalyst can be advantageous in certain systems however, a more general strategy would be to combine a free ligand with a Pd(0) source, generating the active catalyst *in situ*. A possible advantage of using the latter approach is not requiring a formal reduction step in activating the catalyst which can lead to the formation of inactive palladium (I) dimers and nanoparticles.³

Pd₂dba₃ and Pd(PPh₃)₄ effectively the only available commercial Pd(0) precursors for general use in catalyst screening, albeit with having significant limitations.^{4,5} Pd₂dba₃ and its various solvates suffer from poor solubility, batch to batch inconsistency in catalytic performance, and are prone to decomposition whether in the solid state or in solution.⁶ In contrast, Pd(PPh₃)₄ alleviates the prior inconsistencies in catalytic performance, but is limited in application since PPh₃ is a common ligand applied in several areas of transition metal catalysis and due to its noninnocence may outcompete other ligands applied *in situ*.⁷

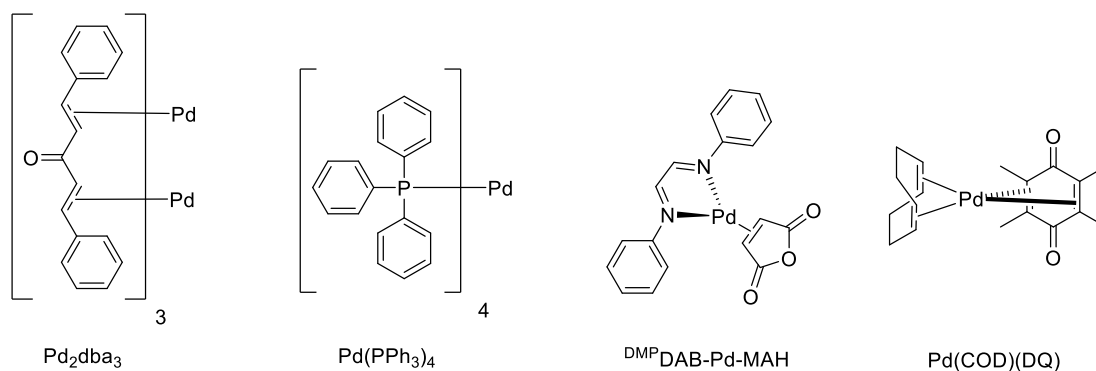


Figure 5.1 Chemical Structures of Commercially Available Pd(0) Precatalysts

In 2021, Leitch and co-workers reported an alternative Pd(0) precursor DMP-Pd-MAH stabilized by the *N,N'*-diaryldiazabutadiene (DAB) and maleic anhydride (MAH) ligands (Figure 5.1).⁸ The complex demonstrates good solubility in a range of organic solvents, high solid state and solution stability when open to air, and can be applied towards the synthesis of alternative [phosphine]-Pd-MAH precatalysts. DMPDAB-Pd-MAH was also demonstrated to have high catalytic performance at low Pd loading (0.25-5 mol %) in a range of C—C, C—N and C—O cross-couplings. Whilst this presents a significant breakthrough to the field of Pd catalyzed cross-couplings, DMPDAB-Pd-MAH is synthesized from $\text{Pd}_2(\text{dba})_3$ and has low solution state stability in several frequently used solvents e.g (acetone, CHCl_3). Additionally, maleic anhydride is a relatively strong π -acceptor ligand, which may limit application in stoichiometric studies, for example in isolating oxidative addition adducts.

Engle and co-workers also reported the synthesis of $\text{Pd}(\text{COD})(\text{DQ})$ (COD = 1,5-cyclooctadiene, DQ = duroquinone), demonstrating similar properties to DMPDAB-Pd-MAH in terms of stability and applicability towards a range of organic transformations, with the added benefit of the relatively inert duroquinone ligand instead of maleic anhydride.⁹ Similar to DMPDAB-Pd-MAH , $\text{Pd}(\text{COD})(\text{DQ})$ also exhibits low solution stability in certain reaction solvents

commonly used in cross-coupling reactions such as benzene, toluene, and THF.⁹ Duroquinone also has similar properties to maleic anhydride with potential limitations for use stoichiometrically.

Therefore, the synthesis of a Pd(0) precatalyst bearing weakly π -accepting properties should permit a more general precatalyst scaffold for Pd-catalyzed cross-couplings, with the potential for applications in stoichiometric studies (e.g. facile synthesis of oxidative addition adducts). For instance, Ni(cod)₂ is the most widely used precatalyst in Ni cross-coupling despite its high sensitivity to oxidation and thermal decomposition, due to the lack of sensitive functionality on cyclooctadiene (COD) that does *not* impede catalysis upon ligand dissociation. COD is a bidentate chelating ligand with relatively weak π -accepting properties. This enables facile ligand exchange with strong π -acceptor ligands such as phosphines.¹⁰ Interestingly, the synthesis of the analogous Pd(COD)₂ complex has been reported by Görls and co-workers, however this complex decomposes above cryogenic temperatures (Figure 5.2).¹¹ Alternative derivatives of COD have shown promising applications as ligands in catalysis including Dibenzo[a,e]cyclooctatetraene in iridium catalyzed allylic substitution and 1,5-diphenyl-1,5-cyclooctadiene in rhodium catalyzed 1,4-addition reactions.^{12,13}

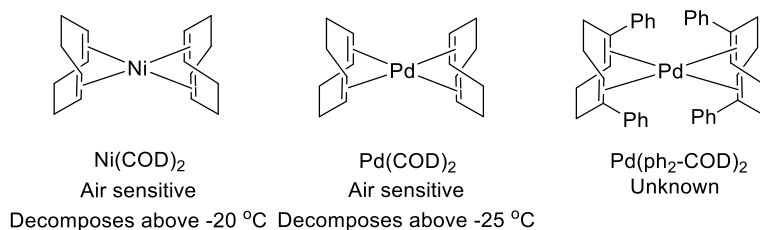


Figure 5.2 Structures of Metal Precatalysts Bearing Cyclooctadiene Derived Ligands With Documented Limitations

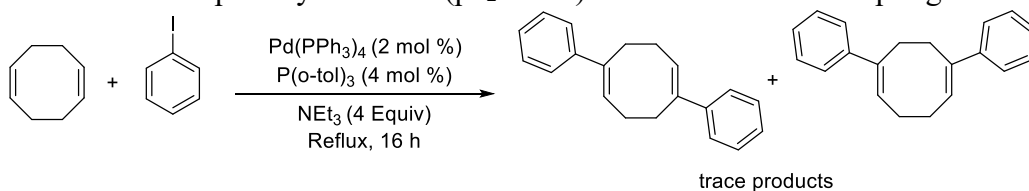
We selected 1,5-diphenyl-1,5-cyclooctadiene as our ancillary ligand towards the synthesis of a more stable Pd(0) complex bearing an innocent throwaway ligand, leveraging the well-established ability of COD to coordinate with late transition metals and form stable chelate complexes.¹⁴ The increased π -acidity and steric hindrance of the phenyl substituents should stabilize the proposed complex over Pd(COD)₂ (Figure 5.2).

Results and Discussion

Synthesis of (Ph₂-COD) Ligand

Initially, we conducted a series of experiments in attempt to directly access the (Ph₂-COD) ligand via a Pd catalyzed Heck coupling of COD and iodobenzene. To our surprise, application of standardized conditions towards the Heck coupling reaction yielded only trace amounts of the desired product.¹⁵

Scheme 5.1 Attempted Synthesis of (ph₂-COD) via a Heck Cross-Coupling



We then proceeded to synthesize 1,5-dibromo-1,5-cyclooctadiene which can be accessed from COD by bromination with Br₂ followed by dehydrobromination with potassium tert-butoxide.¹⁶ However, instead of selectively forming 1,5-dibromo-1,5-cyclooctadiene **3b**, we observed the formation of a near 1 : 1 mixture of **3b** and 1,6-dibromo-1,5-cyclooctadiene **3a** (regioselectivity was confirmed by comparison to the reported 1,5-dibromo-1,5-cyclooctadiene isomer) (Figure 5.3).¹⁷ Separation of the respective isomers was unsuccessful by normal or reverse

phase chromatography. As a result, both **4a** and **4b** were obtained by the palladium catalyzed Kumada cross-coupling between phenyl-magnesium bromide and the mixture of **3a** and **3b** in excellent yield (Figure 5.3).¹⁴ Separation of isomers **4a** and **4b** also proved unsuccessful by chromatography or distillation methods.

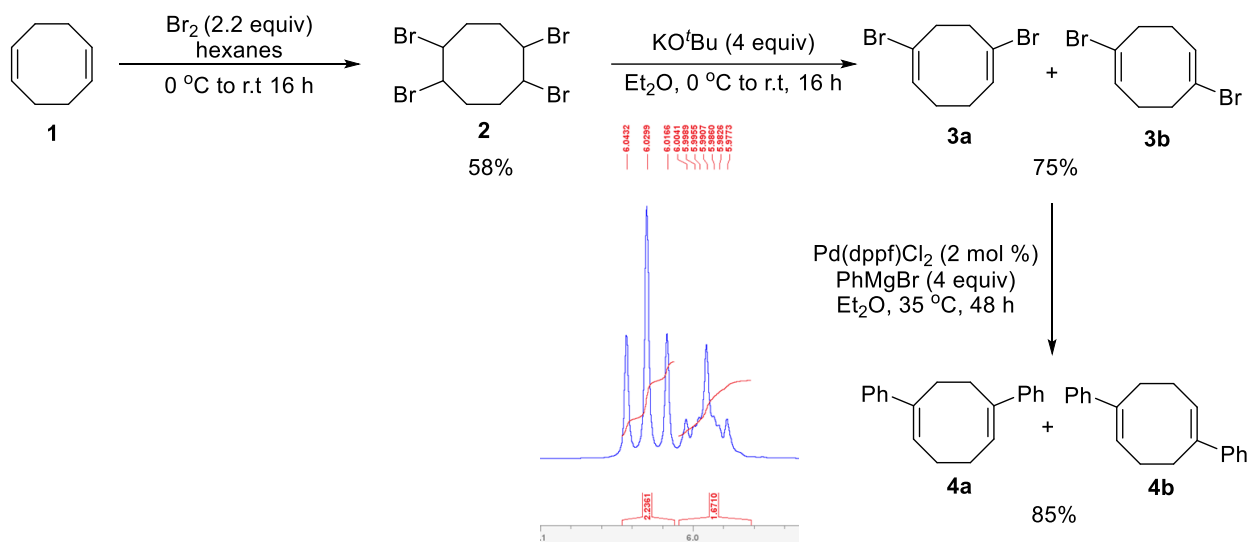


Figure 5.3 Synthesis of the (Ph₂-COD) Ligand (Pathway 2) and ¹H-NMR Spectrum of Product Mixture **4a** and **4b**, Zoomed in on the Alkene Region

Synthesis of Pd(Ph₂-COD)₂ (Pathway 1)

The first synthetic pathway explored to metalate Ph₂-COD to Pd required the careful choice of a Pd(II) precursor, enabling access to Pd(0) whilst avoiding the formation of inactive nanoparticles. (COD)Pd(CH₂TMS)₂ is commonly employed for studying reaction mechanisms due to its ability to readily form Pd(0) in-situ. The trimethylsilylmethylene groups undergo reductive elimination at ambient temperatures, as demonstrated by Skrydstrup towards the synthesis of [phosphine]-Pd-COD complexes.¹⁸ Therefore, we first synthesized complex **5** by analogy to a procedure as described by Ruiz et al (Figure 5.4).¹⁶ Interestingly only one alkene signal was observed by ¹H-NMR spectroscopic analysis of **5**, suggesting that a single isomer of the (Ph₂-

COD)PdCl₂ complex was formed in this reaction. Complex **6** was obtained by stirring **5** with (trimethylsilyl)methylmagnesium bromide in diethyl ether. Notably, **6** demonstrates unique stability in the solid state at room temperature under an inert atmosphere, following a period of 24 h. This is in stark contrast to the unsubstituted COD analog reported by Skrydstrup which rapidly decomposes at room temperature.¹⁸ An excess of the Ph₂-COD ligand was then applied to complex **6**, yielding target complex **7** as light-yellow crystals (Figure 5.4).

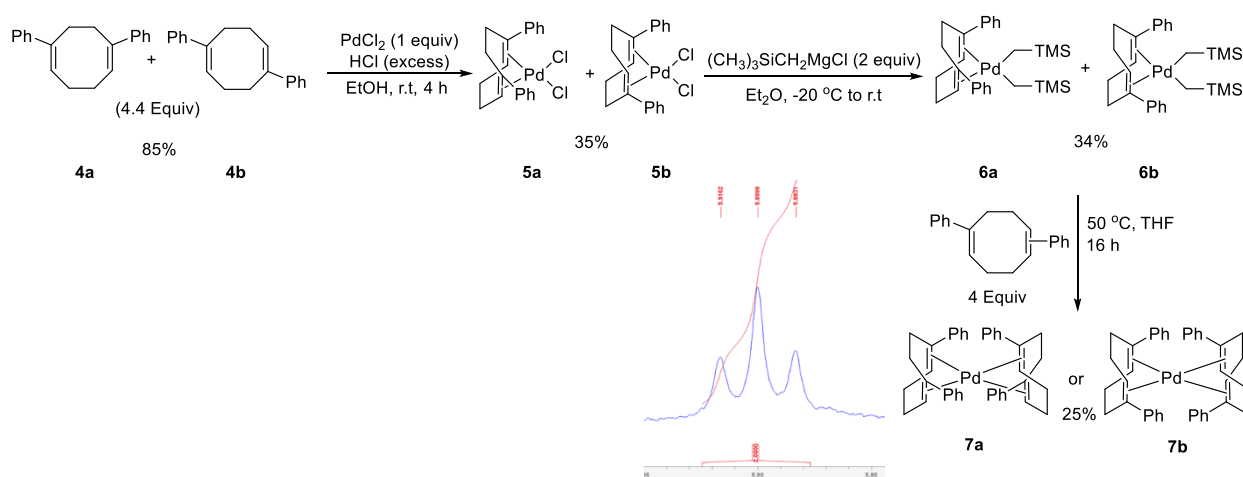


Figure 5.4 Synthesis Route 1 towards Pd(Ph₂-COD)₂ and ¹H-NMR of Complex **5** Zoomed in on the Alkene Region

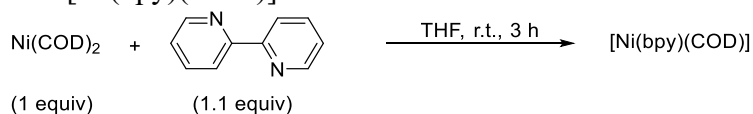
Assessment of Pd(Ph₂-COD)₂ Stability

We began running diagnostics on complex **7** by assessing its stability under ambient conditions. To our delight, Pd(Ph₂-COD)₂ showed no evidence of decomposition in the solid state by ¹H-NMR analysis following 14 days storage at room temperature in a nitrogen atmosphere glovebox. Complex **7** was then stored open to air at room temperature. The color of the solid did not change until 5 days after exposure to oxygen. Following this time, the bright yellow crystals of Pd(Ph₂-COD)₂ turned to an off-white color. Indeed, in the solid state, the complex would need to be stored under inert atmosphere.

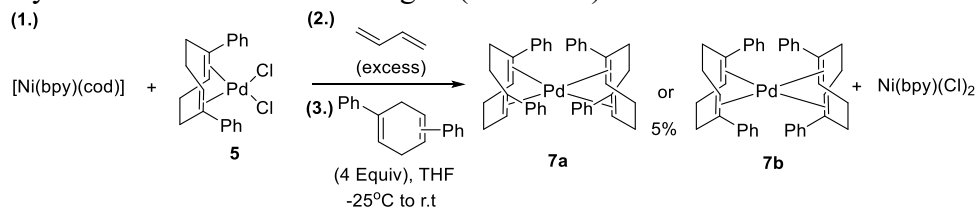
Synthesis of Pd(Ph₂-COD)₂ (Pathway 2)

The aim of synthesizing an alternative thermally stable Pd(0) complex was achieved, albeit over six synthetic steps with a low overall yield. Therefore, we were interested to assess if an approach used by Görls and co-workers towards the synthesis of Pd(COD)₂ would streamline the synthesis of Pd(Ph₂-COD)₂.¹¹ Their approach involves the use of a nickel(0) complex Ni(bpy)(COD) as a mild reducing agent of Pd(COD)Cl₂ in the presence of 1,3-butadiene. Butadiene was also key in stabilizing the Pd(butadiene)_n(COD) intermediate from dimerization to (Pd(COD)Cl)₂. The Ni(bpy)(COD) complex was synthesized as a stock solution in THF by a ligand substitution reaction of Ni(COD)₂ with bipyridine. (Scheme 5.2). The stock solution of [Ni(bpy)(COD)] was then combined with complex **5**, followed by 1,3-butadiene, and finally the Ph₂-COD ligand in one-pot fashion. This resulted in the formation of complex **7** at a 5% isolated yield (Scheme 5.3). Synthesis pathway 1 is therefore preferred due to the low yield observed in pathway 2, even with an additional synthetic step required.

Scheme 5.2 Synthesis of [Ni(bpy)(COD)]



Scheme 5.3 Synthesis Route 2 to Accessing Pd(Ph₂-COD)₂



Conclusions

The synthesis of a novel thermally stable Pd(0) complex Pd(Ph₂-COD)₂ was achieved using two separate synthetic strategies. Studies to investigate the stability of the complex demonstrated high thermal stability in contrast to Pd(COD)₂ and improved resistance to oxidation relative to alternative commercially available precatalysts. Due to the innocence of the Ph₂-COD ligand, this complex may be compatible with a broad range of organic transformations than Pd₂dba₃ and/or ^{DMP}DAB-Pd-MAH. Future work is required to definitively confirm the complex structure and its regioselectivity by X-ray diffraction analysis and to evaluate the competency of the catalyst in cross-coupling reactions and related Pd-catalyzed transformations.

References

1. Almond-Thynne, J.; Blakemore, D. C.; Pryde, D. C.; Spivey, A. C. Site-Selective Suzuki-Miyaura Coupling of Heteroaryl Halides – Understanding the Trends for Pharmaceutically Important Classes. *Chem. Sci.* **2017**, *8*, 40-62.
2. Withbroe, G. J.; Singer, R. A.; Sieser, J. E. Streamlined Synthesis of the Bippyphos Family of Ligands and Cross-Coupling Applications. *Org. Process Res. Dev.* **2008**, *12*, 480–489
3. Hruszkewycz, D. P.; Balcells, D.; Guard, L. M.; Hazari, N.; Tilset, M. Insight into the Efficiency of Cinnamyl-Supported Precatalysts for the Suzuki–Miyaura Reaction: Observation of Pd(I) Dimers with Bridging Allyl Ligands During Catalysis. *J. Am. Chem. Soc.* **2014**, *136*, 7300–7316.
4. Ito, T.; Takahashi, Y.; Ishii, Y. Convenient Preparation of Novel Palladium– π -Olefin Complexes from Bis(Dibenzylideneacetone) Palladium(0). *Chem. Commun.* **1972**, 629a.
5. D. R. Coulson, Tetrakis(triphenylphosphine)palladium(0), *Inorg. Synth.*, **1972**, *13*, 121
6. Zalesskiy, S. S.; Ananikov, V. P. Pd₂(dba)₃ as a Precursor of Soluble Metal Complexes and Nanoparticles: Determination of Palladium Active Species for Catalysis and Synthesis. *Organometallics* **2012**, *31*, 2302–2309.
7. Yu, H.; Liu, Y.; Zhang, L.; Gao, S.; Song, C.; Huang, K. Confined synthesis of homogeneous Tetrakis(triphenyl phosphine) palladium within hollow porous polymeric nanospheres for catalysis application, *Microporous and Mesoporous Materials*, **2021**, *322*, 111155
8. Huang, J.; Isaac, M.; Watt, R.; Becica, J.; Dennis, E.; Saidaminov, M. I.; Sabbers, W. A.; Leitch, D. C. DMPDAB–Pd–MAH: A Versatile Pd(0) Source for Precatalyst Formation, Reaction Screening, and Preparative-Scale Synthesis, *ACSCatal.* **2021**, *11*, 5636–5646
9. He, W. J.; Qin, W. Z.; Yang, S.; Ma, D.; Kim, N.; Schultz, J. E.; Palkowitz, M. D.; He, C.; Ma, A.; Schmidt, M. A.; Gembicky, M.; Wisniewski, S. R.; Engle, K. M. *Chemrxiv*, **2024**, sj081
10. Boit, T. B.; Spence, K. A.; Garg, N. K. From glovebox to benchtop, *Nat Catal* **2020**, *3*, 2–3
11. Schwalbe, M. S.; Walther, D.; Schreier, H.; Langer, J.; Gorls, H. A new synthesis for thermolabile low-valent palladium complexes by electron transfer reactions from nickel(0) to palladium(II) compounds, *Journal of Organometallic Chemistry*, **2006**, *691*, 4868-4873
12. Lang, F.; Breher, F.; Stein, D.; Gruntzmacher, H. Chiral Olefins as Steering Ligands: Syntheses of C1-Symmetric Dibenzo[a,e]cyclooctenes (^Rdbcot), *Organometallics*, **2005**, *24*, 2997-3007

13. Kina, A.; Ueyama, K.; Hayashi, T. Enantiomerically Pure Rhodium Complexes Bearing 1,5-Diphenyl-1,5-cyclooctadiene as a Chiral Diene Ligand. Their Use as Catalysts for Asymmetric 1,4-Addition of Phenylzinc Chloride Asato Kina, Kazuhito Ueyama, and Tamio Haya, *Org. Lett.* **2005**, 7, 5889-5892
14. Detert, H.; Rose, B.; Mayer, W.; Meier, H. Herstellung von 1,5-Cyclooctadiin und 1,3,5,7-Cyclooctatetraen aus 1,5-Cyclooctadien, *Chem. Ber.* **1994**, 127, 1529
15. Wang, Z.; Feng, X.; Fang, W.; Tu, T. Efficient Aqueous-Phase Heck Reaction Catalyzed by a Robust Hydrophilic Pyridine-Bridged Bisbenzimidazolylidene-Palladium Pincer Complex, *Synlett*, **2011**, 7, 951-954
16. Hossain, A. M. S.; Balbin, A.; Erami, R. S.; Prashar, S.; Fajardo, M.; Gomez-Ruiz, S. Synthesis and study of the catalytic applications in C–C coupling reactions of hybrid nanosystems based on alumina and palladium nanoparticles, *Inorganica Chimica Acta*, **2017**, 455, 645-652
17. Detert, H.; Rose, B.; Mayer, W.; Meier, H. Herstellung von 1,5-Cyclooctadiin und 1,3,5,7-Cyclooctatetraen aus 1,5-Cyclooctadien, *Chem. Ber.* **1994**, 127, 1529
18. Anderson, T. L.; Kramer, S.; Overgaard, S.; Skrydstrup, T. Evidence for Single-Electron Pathways in the Reaction between Palladium(II) Dialkyl Complexes and Alkyl Bromides under Thermal and Photoinduced Conditions, *Organometallics* **2017**, 36, 2058–2066

CHAPTER SIX

CONCLUSIONS

Asymmetric Synthesis of All-Carbon Quaternary Stereocenters via Auto-Tandem Catalysis

Chapter 2 of this dissertation detailed the development of a Pd-catalyzed cascade reaction enabling access to all-carbon quaternary stereocenters with high diastereoselectivity and branched selectivity (over linear). The reaction was demonstrated with 17 examples including access to vicinal all-carbon quaternary stereocenters. The mechanism of this reaction initially proceeds through a decarboxylative Pd- π allyl rearrangement to access the *N*-allyl ketenimine intermediate. This intermediate then undergoes a separate distinct Pd catalyzed dipolar [3,3] rearrangement. The origin of diastereoselectivity in this reaction is rationalized by the allyl ketenimine coordinating deep within the binding pocket of the active catalyst, undergoing ionization to the η^3 π -allyl complex, with the favored diastereomeric complex stabilized by a π -stacking interaction between the two aromatic substituents on the allyl ketenimine.

Whilst the optimal conditions provide a high degree of diastereocontrol over the transformation, the resulting 16% enantiomeric excess imparted by the DTBM-MeOBIPHEP ligand, limits the application of the reaction in asymmetric synthesis. A broader ligand screen should be evaluated to improve the enantioselective outcome. Additionally, utility of this reaction could be expanded towards the synthesis of three contiguous all-carbon quaternary stereocenters, mediated by substitution across the *N*-allyl and *N*-alloc alkenes.

C2-Selective Amination and Thiolation of 2,4-Dichloropyrimidine via Pd(II) Promoted Isohypsic Catalysis

Chapters 3 and 4 of this dissertation discuss the discovery of a catalyst-controlled approach to C2-selective functionalization of 2,4-dihalopyrimidines. The reaction was optimized to furnish exclusive selectivity for the 2-position with both primary alkyl thiols, thiophenol derivatives and later aryl amines. Profoundly, competing reactions including nucleophilic aromatic substitution and conventional cross-coupling do not arise under the reaction conditions for C2-selective amination that would lead to substitution at the C4 position. This suggests that the unique selectivity afforded in both the C2-selective amination and thiolation proceeds through a non-conventional catalytic cycle.

Critically, it was found that the C2-selective amination reaction proceeds through a redox-neutral isohypsic pathway whereby palladium is not reduced to Pd(0) at any stage during catalysis. The key selectivity determining step involves a migratory insertion like mechanism, where the C2—carbon of pyrimidine migrates over to the Pd—N—(aryl) bond as a result of palladium's preference to coordinate to the more Lewis basic nitrogen 1 of pyrimidine. This demonstrates a new mode of cross-coupling in Pd catalysis, whereby a highly electrophilic substrate such as 2,4-dichloropyrimidine does not undergo oxidative addition or nucleophilic aromatic substitution.

Future work is required to provide experimental confirmation of the selectivity determining migratory insertion step, especially for the C—S coupling. In theory, the rate-limiting step of the transformation is also migratory insertion, so the reaction may be first order with respect to 2,4-dichloropyrimidine and aniline. Kinetic studies should be performed and later validated by advanced techniques such as a ^{13}C kinetic isotope effect for migratory insertion. Whilst it is likely that the origins of C2-selective thiolation also arise from the same mechanism, this needs to be validated using a similar strategy, which would enable a mechanistic guided approach to

developing a C2-selective C—O cross-coupling of 2,4-dichloropyrimidine and other related transformations.

Toward the Synthesis and Characterization of a Low-Valent
Thermally Stable Pd(0) Complex

Chapter 5 of this dissertation demonstrated progress toward the synthesis of a novel thermally stable Pd(0) complex $\text{Pd}(\text{Ph}_2\text{-COD})_2$. The complex has potential for use as a precatalyst in reaction screening due to the possible relative innocence of the 1,5-diphenyl-1,5-cyclooctadiene “throwaway” ligand in contrast to alternative Pd(0) sources. Stability studies demonstrated relatively slow oxidation of the complex when exposed to air, and resistance to decomposition at room temperature, which could render this an alternative user-friendly palladium source. Future work should evaluate the competency of the catalyst in a range of cross-coupling reactions and related Pd-catalyzed transformations.