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Enantioselectivity Data as a Tool for Mechanistic Investigations of Ni-Catalyzed
Cross-Coupling Reactions

A Dissertation submitted in partial satisfaction
of the requirements for the degree of

Doctor of Philosophy

in

Chemistry

by

Brennan Donahue McManus

September 2026

Dissertation Committee:

Dr. Michael C. Pirrung, Chairperson

Dr. Ana Bahamonde, Advisor

Dr. Timothy Su

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2026

The Dissertation of Brennan Donahue McManus is approved:

Committee Chairperson

University of California, Riverside

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LIST OF PUBLICATIONS

The text of this dissertation is in part a reprint of the material as they appear in the following publications:

Chapter 2:

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ABSTRACT OF THE DISSERTATION

Enantioselectivity Data as a Tool for Mechanistic Investigations of Ni-Catalyzed Cross-Coupling Reactions

by

Brennan Donahue McManus

Doctor of Philosophy, Graduate Program in Chemistry
University of California, Riverside, September 2026
Dr. Michael C. Pirrung, Chairperson

The versatility of Ni-catalyzed reactions enables a wide range of bond-forming methods but also complicates mechanistic understanding, as numerous pathways can lead to product formation. This thesis describes mechanistic investigations of two distinct Ni-catalyzed systems: photochemical Ni-catalyzed THF arylation and Ni-catalyzed cross-electrophile coupling of aryl iodides with benzyl chlorides. The approaches used to interrogate these systems rely on leveraging enantioselectivity data to determine the operative pathways under standard catalytic conditions. This work focuses on identifying the enantioselectivity-determining steps in these reactions to elucidate key catalytic intermediates. This strategy is broadly applicable across a variety of catalytic systems and reaction conditions, providing a general

framework for gaining deeper mechanistic insight into transition metal-catalyzed reactions.

The first approach involves conducting time-point experiments throughout a reaction and monitoring trends in product enantioselectivity over time. The second approach involves performing stoichiometric experiments with Ni species proposed to participate in the enantioselectivity-determining step, followed by comparison of the product ee obtained under stoichiometric conditions with that observed under catalytic conditions.

To perform stoichiometric experiments that generate enantioenriched products, the Ni-complex must contain a chiral ligand. Despite the utility of chiral ligand scaffolds in asymmetric catalysis, examples of well-defined Ni-complexes bearing these ligands remain comparatively limited relative to their achiral counterparts. To address this gap, a general procedure was developed for the synthesis of Ni-complexes bearing bisoxazoline (BOX) and bioxazoline (BiOX) ligands that accommodates the structural diversity of these scaffolds. Our hope is that applying these studies to two different, difficult-to-investigate scenarios may serve as a roadmap for others investigating complex mechanistic scenarios.

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Chapter 1: Using Enantioselectivity Data to Elucidate the Complexities of Ni-Catalyzed Reactions.

Section 1.1: Abstract

This chapter will cover the fundamental properties of nickel (Ni) and how its access to one- and two-electron steps makes it a versatile catalyst for C–C bond construction. The field of Ni-catalysis has developed far beyond the use of Ni as a Pd surrogate. The current focus is on exploring the unique properties of Ni-catalysts. A better understanding of these properties enables more diverse applications and, therefore, more ways to construct bonds. As with all transition metals, the properties of Ni-catalysts are heavily influenced by the ligand, which determines the propensity for one-electron, two-electron, or both types of reactivity. This ultimately complicates mechanistic scenarios, making these systems difficult to interrogate. By using a chiral ligand to construct enantioenriched compounds, we can identify enantioselectivity-determining steps within these complex systems, which can then be proposed beyond asymmetric systems.

Section 1.2: Ni vs. Pd

The impact transition metals have had on the field of organic chemistry cannot be overstated.¹⁻⁶ Early examples of C–N and C–C bond formation, such as the Ullmann coupling⁷ and reductive biaryl synthesis,⁸⁻¹¹ were powerful pioneering advances in bond construction. However, the drawbacks of these reactions included the need for stoichiometric amounts of metal, raising sustainability concerns.¹²

Developing reaction conditions for the same bond constructions using catalytic amounts of transition metals has drastically improved efficiency, scalability, and cost-effectiveness.^{12, 13} Traditionally, Pd is considered the standard for catalytic cross-coupling due to its robust nature and predictable reactivity.¹⁴ Examples such as the Pd-catalyzed Buchwald-Hartwig coupling^{15, 16} and Pd-catalyzed Suzuki-Miyaura cross-coupling^{17, 18} have been revolutionary in the pharmaceutical industry, both enabling C–N and C–C bond formation that had previously required stoichiometric amounts of Cu or Ni.¹⁹⁻²⁴ However, the rising cost of Pd raises sustainability concerns. This has led to a search for more commercially available alternatives as Pd becomes scarcer.

Ni catalysts were originally considered a favorable alternative due to Ni's position in the periodic table as a group 10 transition metal.²⁵⁻³² Additionally, as of April 2026, the cost of Ni is \$8.67 per pound, while Pd is \$1484 per ounce.³³ If the metals behaved identically, Pd catalysts would be obsolete in favor of Ni catalysts.

However, despite both being group 10 metals, the reactivity profile of Ni differs markedly from that of Pd. Switching from a Pd catalyst to a Ni catalyst in a system optimized for Pd-catalyzed cross-coupling typically results in lower yields or complete reaction failure. This fact alone does not mean Ni catalysts are incapable of achieving similar bond construction as Pd catalysts.³⁴ Rather, we need to deepen our understanding of Ni-catalyzed systems and develop conditions that play to nickel's strengths and achieve the same overall bond construction, rather than pigeonholing Ni catalysts as a direct surrogate for conditions optimized for Pd catalysts.

Size and Electronegativity

	Ni	Pd
Van Der Waals radius	1.92 Å	2.05 Å
Electronegativity	1.91	2.20
HSAB	Hard	Soft

Redox Potentials

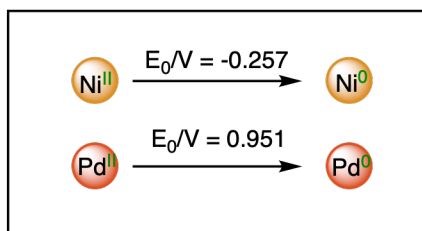


Figure 1.1: Comparison between Ni and Pd size, electronegativity, and oxidation/reduction potentials.

The best starting point for developing conditions for each metal is to identify the similarities and differences. To start, the metals have different electronegativities,

first ionization energies, atomic radii, and oxidation/reduction potentials for two-electron processes (**Figure 1.1**). This can be simplified to say that Ni is more readily oxidized than Pd, leading to different challenging steps in their respective catalytic cycles. This underscores the importance of ligand design (which will be discussed further in the next section), as it is optimal to choose ligands that facilitate reductive elimination in Ni-catalysis and ligands that promote oxidative addition in Pd-catalysis.³⁵⁻³⁷ This is also reflected in the instability and air-sensitivity of Ni(0) pre-catalysts (such as Ni(COD)₂).³⁸ To access low-valent Ni-species such as Ni(I) or Ni(0), there is a need to add exogenous reductants,³⁹ electrochemically induced current,⁴⁰ photocatalysts,⁴¹ or UV-light to Ni(II) pre-catalysts.⁴¹ Comparatively, Pd's ability to be readily reduced from Pd(II) to Pd(0) *in situ* occurs under mild reaction conditions.⁴² These properties affect the ability of Pd(II) species to readily undergo reductive elimination, whereas Ni catalysts must undergo oxidation to Ni(III) or undergo energy transfer at Ni(II) to facilitate reductive elimination.^{43,44}

Another difference between the two metals is their atomic radii, which affect the relative strength of M–H agostic interactions. Pd, being larger, readily engages in β -hydride elimination to afford alkenes, whereas Ni(II) alkyl species face a much higher energy barrier to generate an alkene (**Figure 1.2**).⁴⁵

β -Hydride Elimination

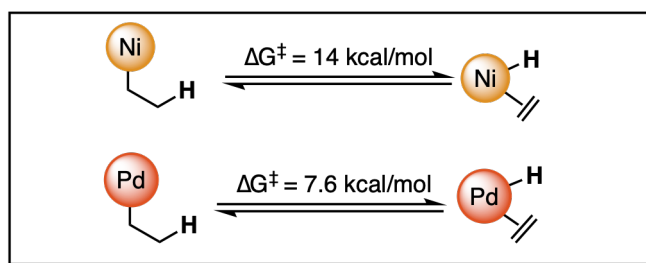
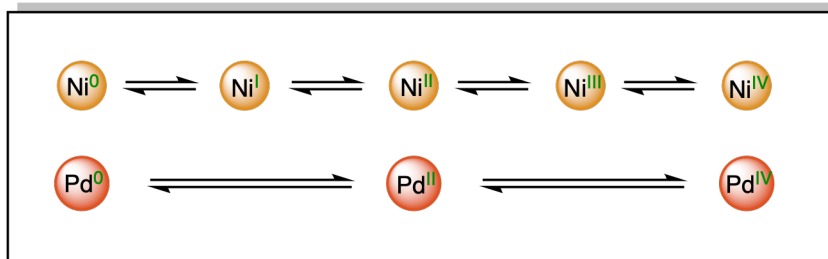


Figure 1.2: Comparing ease of β -hydride elimination.

The key difference (in the context of this thesis) between the two metals is their ability to access different oxidation states. Ni chemistry readily affords oxidation states 0, I, II, and III (and the rare IV), whereas Pd traditionally undergoes exclusively two-electron pathways, limiting oxidation states to 0 and II (**Figure 1.3**). Recent studies have found that photoactive Pd complexes can access Pd(I) and Pd(III) species, but this is more the exception than the rule.^{46, 47} Ni can access open-shell species Ni(I) and Ni(III) more readily than Pd because Ni has a higher electron pairing energy, leading to relatively more “stable” (or more stable than 4d and 5d counterparts) open-shell configurations (**Figure 1.4**).⁴⁸⁻⁵¹ As a result, Ni has access

to the two-electron pathways akin to those in Pd-catalyzed reactions, as well as single-electron oxidation/reduction processes.

Access to Varying Oxidation States



Single and Two Electron Pathways

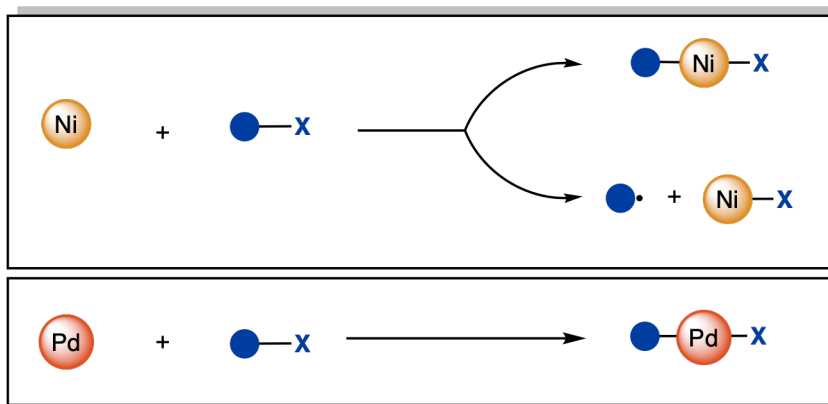


Figure 1.3: Access to oxidation states and the resulting one- and two-electron pathways.

The complexity of Ni-catalyzed mechanisms lies in the accessibility of both pathways. The favorability of each pathway can be influenced by the ligand, but using different scaffolds does not guarantee that every step will follow a one- or two-electron pathway. Instead, Ni-catalytic cycles often involve a mixture of both options, leading to unpredictable changes in oxidation state and, consequently, reactivity. Unsurprisingly, this access to multiple-electron pathways can complicate mechanistic scenarios, making it increasingly challenging to develop new systems or improve existing ones without a detailed understanding of their operation. While

computational studies are useful for ruling out high-barrier pathways for individual elementary steps, mechanistic investigations across various systems can support or refute possible pathways.

Pairing Energy

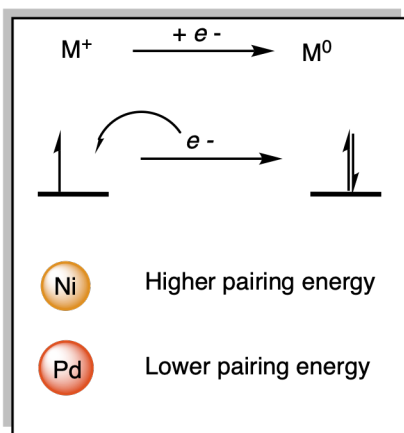


Figure 1.4: *Relative pairing energies. Ni, with a higher value, allows access to odd-electron states because there's a higher energy penalty for filling the orbital.*

Section 1.3: The Importance of Ligand Scaffold in Ni-Catalyzed Reactions

Access to open-shell Ni intermediates is essential for Ni-catalyzed reactions. High-valent open-shell Ni(III) readily undergoes reductive elimination, while Ni(II) reductive elimination is much more energetically demanding.⁵² There are exceptions to this, such as light-promoted reductive elimination from Ni(II),^{53, 54} but ground-state reductive elimination from this species remains more challenging than from Pd(II) counterparts. Equally important is considering the product of reductive elimination from Ni(III). Low-valent open-shell Ni(I) can undergo oxidative addition, yielding intermediates distinct from those formed by oxidative addition into Ni(0).⁵⁵ If Ni(I) intermediates were incapable of undergoing oxidative addition or single-electron steps, Ni-catalysts would not be catalysts at all, as each Ni would be good for only one turnover. Harnessing the power of Ni(I) and making it reactive through ligand choice enables catalytic cycles to continue even after reductive elimination from Ni(III) (**Figure 1.5**). While Ni(0) oxidative addition remains a commonly invoked pathway, Ni(I) oxidative addition is a critical, catalytically relevant step that enables many transformations.^{44, 56} This is because the products of each oxidative addition generate different species that can inadvertently affect the mechanism.⁴⁴

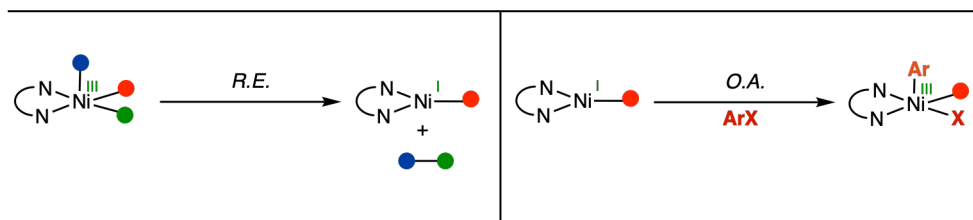


Figure 1.5: Two-Electron Reactions of Open-Shell Ni-species.

The utility of Ni in undergoing two-electron steps, such as oxidative addition or reductive elimination, from open-shell intermediates (such as Ni(I) or Ni(III)) is one reason the catalyst is so versatile. However, Ni can also undergo single-electron reactions as a closed-shell species. Examples include Ni–X or Ni–C bond photolysis at Ni(II), resulting in a net reduction to Ni(I),^{41, 57} or Ni(II) trapping a carbon-centered radical,^{44, 53, 58} resulting in a net oxidation to Ni(III). Arguably, the most important kind of single-electron oxidation of Ni is the capture of a carbon-centered radical, which acts as the partner in cross-coupled reactions (**Figure 1.6**). The accessibility of odd-electron states enables many Ni-catalyzed reactions and is the distinguishing factor that extends Ni chemistry beyond its role as a Pd surrogate.

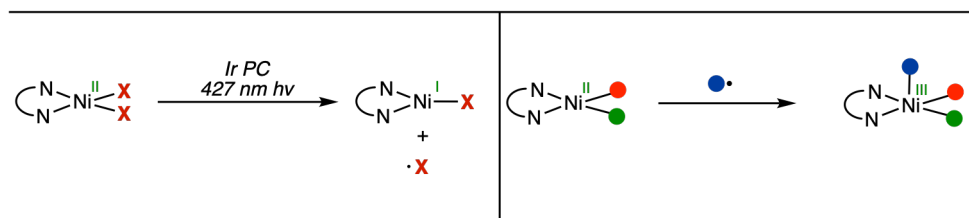


Figure 1.6: Single-electron reactions from closed-shell Ni-species.

Access to different Ni intermediates can be influenced by the ligand of choice. When conducting a reaction that aims to facilitate two-electron steps, traditional strong σ -donor ligands, such as NHC and phosphine ligands, help confine Ni-

catalyzed systems to Ni(0)/Ni(II) cycles and two-electron steps. This is in part due to the large field splitting of these σ -donor ligands, which destabilizes open-shell Ni species.⁵¹ However, when there is a desire to exploit both single- and two-electron pathways, Ni-catalyzed cross-coupling reactions will use *N*, *N*-bidentate and *N*, *N*, *N*-tridentate ligands.^{59, 60} These ligands facilitate Ni(I)/Ni(III) cycles and single-electron steps.⁶¹

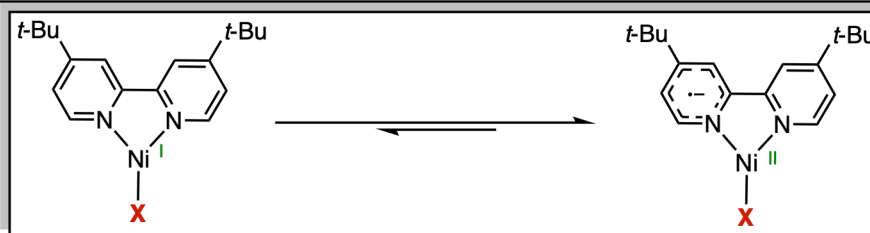
Popular examples of this are the bipyridine and phenanthroline ligands. Due to their strong π -back bonding capabilities, single-electron oxidation or reduction events can be stabilized by the ligand scaffold.⁶¹⁻⁶³ Examples such as bipyridine-ligated Ni(II) dihalide complexes can be formally reduced to Ni(I) and subsequently undergo metal-ligand charge transfer (MLCT), stabilizing the resulting Ni(I) species by storing an electron in the bipyridine scaffold and formally yielding Ni(II) ligated to a radical anionic ligand.^{54, 64} This is possible for ligands whose LUMO is the π^* orbital and are therefore considered “redox-active ligands”. Whether the unpaired electron is delocalized within the ligand scaffold or centered on the metal can be determined by electron paramagnetic resonance (EPR) studies, thereby helping assess whether a ligand is redox-active.⁶⁵

More recently, designer ligands capable of intra-ligand charge transfer (ILCT) have further facilitated the generation of open-shell Ni species.^{56, 66} Non-redox-active ligands (such as TMEDA) do not have a π^* orbital as their LUMO (**Figure 1.7**).^{67,68} However, Ni(I)/(III) cycles are not strictly limited to only redox-active ligands, as our

lab and others have demonstrated the presence of these intermediates in various C–heteroatom cross-coupling reactions.⁶⁹

While not necessary for accessing open-shell species, the choice of ligand scaffold can completely alter reactivity by changing the relative stability and lifetime of these open-shell intermediates. This has multiple implications for the formation of intermediates in Ni-catalyzed systems. Redox-active ligands that better stabilize odd-electron Ni-intermediates affect the relative rates within a system, influence the oxidation state of the metal, and influence the redox properties of the complex. Whether these effects are beneficial or harmful depends on the system of interest and is one reason why ligand choice can completely halt reactivity in some cases while being the perfect fit in others.

a) Redox Active Ligand Stabilization of Ni(I)



b) Redox Inactive Ligand Localized Electron onto Ni(I)

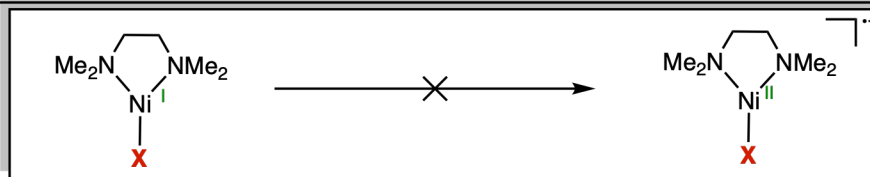


Figure 1.7: Comparison of redox-active and non-redox-active *N, N*-bidentate ligands. Redox activity of the ligand does not preclude access to open-shell intermediates, but it does affect the relative rates of the reaction.

One final class of ligands important for accessing these odd-electron Ni species is the class of monodentate ligands. Indeed, seminal reports detailing the oxidative addition of Ni(0) and bi-aryl synthesis proposed the presence of open-shell intermediates, possibly due to ligand displacement.^{70 71} While useful, these strategies require higher ligand loadings in catalytic reactions because some ligand is consumed to form the open-shell intermediate. This can lead to deleterious side reactions and is less atom-economical for cross-coupling.

Section 1.4: Probing Complex Mechanistic Scenario Using Enantioselectivity Data

As discussed, the versatility of Ni-catalyzed reactions enables a multitude of methods for bond construction but complicates mechanistic understanding due to the sheer number of possible pathways to product formation. Understanding these systems should not be limited to identifying the main operative pathway; it should also include identifying other possible pathways that can generate product, as well as side reactions. We have found that a powerful tool for doing this is to examine asymmetric systems, as the product ee is a direct readout of the $\Delta\Delta G^\ddagger$.

Asymmetric catalysis is invaluable for generating enantioenriched compounds.^{72, 73} But beyond that, using product ee data for mechanistic studies can also be a powerful tool for validating proposed enantioselectivity-determining steps and, often, product-determining steps in a reaction. This is because the step at which the product's enantioselectivity is set usually coincides with the product-determining step. The drawback is that the steps preceding the enantioselectivity-determining step cannot be effectively interrogated by this strategy. However, successfully identifying the enantioselectivity-determining intermediate provides better insight into how key intermediates may be generated. This essentially enables a retrosynthetic approach to proposing a catalytic cycle and helps identify which studies should be conducted to elucidate the earlier steps in a catalytic reaction.

When investigating these systems, the choice of ligand is crucial. In Ni-catalyzed cross-coupling, *N, N*-bidentate ligands are a popular and optimal choice for a wide range of reactions.⁵⁸ A drawback of scaffolds such as bipyridine or phenanthroline is that most of these ligands are achiral, with few exceptions.⁷⁴ To investigate systems that leverage enantioselectivity data, it is necessary to select a chiral ligand scaffold. A common assumption when extrapolating data from these studies is that switching the ligand scaffold (e.g., from bipyridine to PyOX) will not affect mechanistic steps.

In recent years, studies have demonstrated that the scaffold can change redox properties either minimally or drastically.⁶⁵ This, in turn, can affect the relative lifetimes of open-shell Ni species, making subsequent steps easier or harder depending on their relative concentrations. Even if a reaction is high-yielding when switching to a chiral scaffold, there is no guarantee that you are interrogating the exact same system as the racemic variant. To overcome this, we need to confidently identify the similarities and differences among Ni intermediates bearing different scaffolds and, with that information, determine where in a reaction sequence the mechanism could be affected. This effort has largely been spearheaded by the Diao group,^{65, 75} however, part of my research has also focused on developing chiral Ni complexes.⁷⁶

The study of these complexes is not limited to understanding their properties relative to achiral ligand scaffolds; they are also extremely useful in stoichiometric experiments. This class of experiment is used to probe the enantioselectivity-determining step of the reaction. This has been demonstrated in multiple studies, including our own.⁴⁴ The goal of these experiments is to compare the product's enantioselectivity with that of the product obtained under catalytic conditions. If the enantioselectivities match, this affirms that the Ni species used in the study is the predominant species involved in product formation under catalytic conditions. However, if the enantioselectivities do not match, this is also valuable information, as it indicates that the proposed step is possible for product formation but is likely a minor pathway when the reaction is run catalytically.

Another example of an experiment that leverages ee data is taking reaction time points under different conditions. This class of experiment provides direct insight into the mechanistic pathway and into how different reaction components can affect the enantioselectivity-determining step. This information is conveyed by the observed trends in product ee. If the product ee is consistent throughout the reaction's runtime, we conclude that only one pathway is operative under those conditions across multiple catalyst turnovers. However, if ee increases or decreases over time, we can infer a change in the enantioselectivity-determining step as the reaction progresses, and, with it, a change in mechanism.

When observing changes in product ee, it becomes easier to rationalize which species may be in solution by critically examining the reaction conditions and comparing them to the standard reaction conditions. These experiments can help inform decisions about which future experiments to pursue to determine which species are present (such as EPR or kinetic analysis).

These two classes of experiments are extremely useful for examining enantioselectivity-determining steps in Ni-catalyzed reactions, but they are not limited to Ni-catalyzed systems. Our hope is that applying these studies to two different, challenging, and difficult-to-investigate scenarios may serve as a useful guide for others when investigating complex mechanistic scenarios. The systems of interest to be discussed are photochemical C–H activation (described in **Chapter 3**) and cross-electrophile coupling (XEC) (described in **Chapter 4**).

Section 1.5: Outlook and Thesis Overview

My PhD has focused primarily on chiral Ni complexes bearing bisoxazoline (BOX) and bioxazoline (BiOX) ligands. I have developed procedures for synthesizing a series of these (L)Ni(II) aryl halide and (L)Ni(II) dihalide complexes, with various examples of these scaffolds (described in **Chapter 2**). We hope these will be useful for both stoichiometric reactions and for improving our understanding of how changes in the ligand scaffold influence catalyst properties. I subsequently used these complexes to study the photochemical Ni-catalyzed THF-arylation (described in **Chapter 3**) and the Ni-catalyzed XEC of aryl iodides and benzyl chlorides (described in **Chapter 4**). This work has helped advance understanding of Ni-catalyzed reactions and enabled the identification and synthesis of catalytically relevant intermediates.

Section 1.6: References

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Chapter 2: Synthesis of (BOX)Ni(II) aryl halide complex and (BiOX)Ni(II) aryl halide complexes

Section 2.1: Abstract

This chapter will detail the procedures for synthesizing and characterizing bisoxazoline (BOX)Ni(II) aryl halide complexes, as reported in Organometallics.¹ Slight modifications to the general procedures presented in that paper resulted in successful adaptation to bioxazoline (BiOX)Ni(II) aryl halide complexes, an equally challenging-to-access class of Ni-complex that is underdeveloped and under-characterized. My hope is that the development of the (BiOX)Ni(II) aryl halide complexes can be submitted as a communication very similar in style to the (BOX)Ni(II) aryl halide manuscript. I performed all the synthesis and characterization described in this chapter. The only work not conducted by me was the X-ray analysis (by Philip Farias and Veronica Carta) and the calculations (by Olivia Taylor and N. Coddington).

As a point of clarification, ligands and complexes are all prefaced with “2” to indicate they are relevant to **Chapter 2**.

Section 2.2: Background

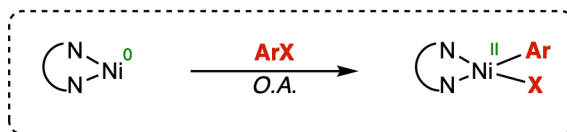
The use of bidentate *N, N*-chiral ligands in Ni-catalyzed cross-coupling methodologies has emerged as a powerful strategy for generating enantioenriched molecules. This is possible due to the diverse reactivity profile of Ni catalysts and their ability to undergo single- and two-electron pathways when ligated to these ligand classes (for more details, see **Chapter 1**).²⁻¹⁵ Synthesis of *N, N*-bidentate chiral ligands and *N, N, N*-tridentate chiral ligands traditionally begins with amino alcohols, yielding a diverse chemical space derived from natural and designer amino alcohols that are readily available in enantiopure form.¹⁶⁻²³

Despite the growing number of reports that use these chiral ligands in asymmetric transformations, there remains a stark lack of characterization of Ni(II) complexes bearing these ligands compared with achiral *N, N*-bidentate Ni(II) complexes.²⁴⁻²⁷ Given how common (*N, N*)Ni(II) aryl halide species are proposed to be catalytic resting states or key intermediates in the enantioselectivity-determining step of various reactions, we envisioned that developing a reliable synthesis to access these complexes and validate such claims would be valuable.²⁸ Characterization of these Ni species is key to elucidating complex mechanisms, specifically to identify on- or off-cycle intermediates. Moreover, these intermediates are proposed to be accessible via oxidative addition into Ni(0) or Ni(I) species,

meaning their synthesis is useful for understanding a wide assortment of Ni-reactions (**Figure 2.1**).^{13, 29-31}

Access to these complexes is useful not only for identifying reaction intermediates and conducting kinetic studies but also for stoichiometric experiments. Specifically, stoichiometric experiments using chiral Ni complexes can probe enantioselectivity-determining steps. The ee observed in stoichiometric studies can be compared with that obtained under catalytic conditions to confirm or dispute key steps in catalytic cycles. Practical applications and examples of this will be covered in **Chapters 3** and **4**. A common strategy used by other labs has been to attempt to characterize a system that uses a BOX or BiOX ligand by switching to a bipyridine or another, easier-to-handle chiral ligand scaffold. However, such a change inadvertently reveals information about another system. At best, it changes only the ligand. At worst, it can completely change the mechanism due to differences in redox properties. Therefore, I embarked on a project to synthesize the commonly proposed, but rarely accessed, Ni(II) aryl halide complexes bearing both BOX and BiOX ligands.

a) Route to Ni(II) aryl halide via Ni(0)



b) Route to Ni(II) aryl halide via Ni(I)

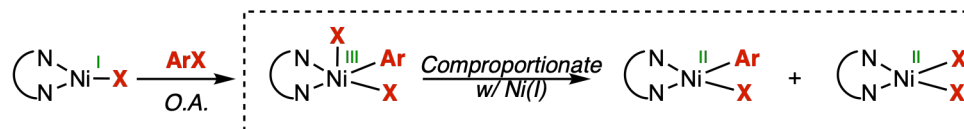


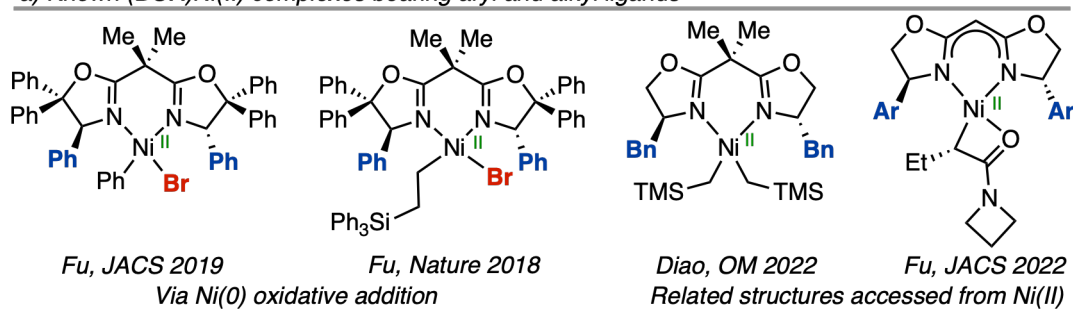
Figure 2.1: Routes to (BOX)Ni(II) aryl halide complexes via oxidative addition.

Prior to this work, there were very few examples of Ni(II) complexes containing BOX ligands (**Figure 2.2a**). The first example shown in **Figure 2.2a** is a (BOX)Ni(II) bromobenzene complex synthesized by the Fu group.³² The BOX ligand used in the synthesis of this complex was chosen for its steric bulk, which would cause the complex to precipitate from a pentane solution. The second complex in **Figure 2.2a** is a (BOX)Ni(II) alkyl bromide complex. Similarly, a bulky BOX ligand had to be used, making the procedure niche to this specific system.¹⁵ The last two examples in **Figure 2.2a** are a (BOX)Ni(II) dialkyl complex synthesized by the Diao group³³ and a (BOX)Ni(II) enolate complex synthesized by the Fu group.¹⁶ While impressive, these complexes are not relevant to the study of asymmetric systems using aryl halides as cross-coupling partners.

To address the lack of guidance for synthesizing chiral Ni(II) complexes,^{15, 16, 27, 34, 35} I developed a general route and alternatives for the successful synthesis of (BOX)Ni(II) aryl halide complexes (**Figure 2.2b**). This work would not be possible without the pioneering work of the Fu lab, which published the first example of this

class of complex.³² During this study, I found that slight changes in either the ligand or the aryl halide could drastically affect the reaction outcome. As a result, I wanted to account for possible ways the reaction could fail, whether the failure lay in ligand coordination or in oxidative addition. I aimed to provide alternatives to the general method I developed, recognizing that a single synthetic route is insufficient to synthesize every ligand and aryl halide combination.

a) Known (BOX)Ni(II) complexes bearing aryl and alkyl ligands



b) This work, diverse scaffolds, via Ni(0) oxidative addition

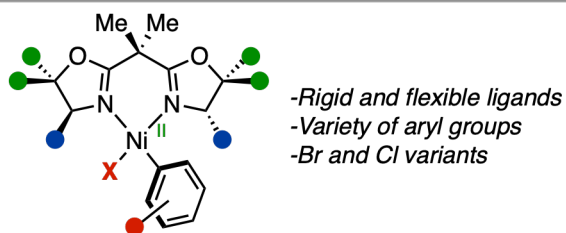


Figure 2.2: (BOX)Ni(II) oxidative addition complexes and related structures.

Section 2.3: Discussion of Route Optimization

The BOX ligands **L2.1**, **L2.2**, **L2.3**, and **L2.4** were a good set for developing conditions because they spanned a range of steric bulk and rigidity and were all commercially available from Ambeed (**Figure 2.3**). I opted to use **L2.1** in the reaction development for a few reasons. First, **L2.1** afforded good yield and selectivity in our THF-arylation study,²⁸ which required the use of these complexes (described in **Chapter 3**). Second, the ligand represented a good midpoint in rigidity, having more rotational freedom than **L2.3** but not as greasy as **L2.4**. Finally, **L2.1** is a solid, making it easier to handle than BOX ligands that are oils or near-liquids, such as **L2.4**.

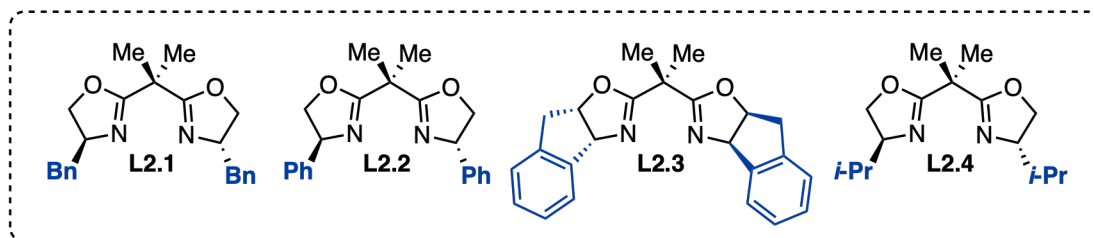
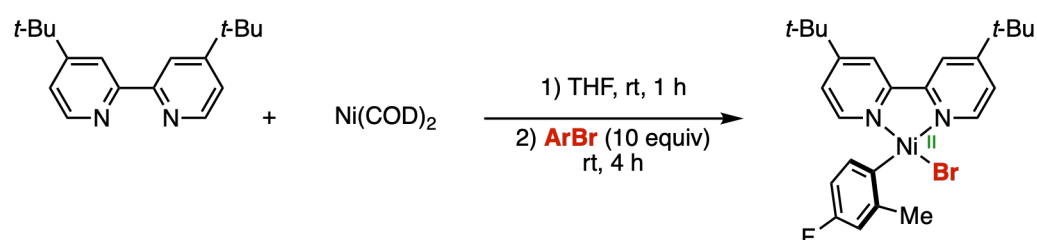


Figure 2.3: Scope of BOX ligands used in the Organometallics report.¹

When attempting to synthesize a (BOX)Ni(II) aryl halide complex using **L2.1**, the first procedure I tried was the same as that used to synthesize the analogous bipyridyl Ni complex (**Figure 2.4a**).³⁶ This led to decomposition prior to the addition of the aryl halide. I speculated that this is due to a difference in binding constants. In reports detailing the ligand-field strength of each nitrogen in PyOX ligands, it is accepted that mesomeric effects make oxazolines stronger-field ligands than pyridines.^{37, 38} However, these claims are based on the bond lengths of Pd complexes, not Ni complexes. I believe the difference between Pd being a “soft” metal and Ni

being a “hard” metal may reverse the relative coordination strength of these two azacycles, with pyridines acting as stronger ligands for nickel. More research is needed to make a definitive claim; this hypothesis is based on observations of bipyridine ligands coordinating to Ni(COD)_2 in polar solvents, whereas BOX ligand ligation in polar solvents results in a black precipitate.

a) Successful with dtbbpy



b) Unsuccessful with **L2.1**

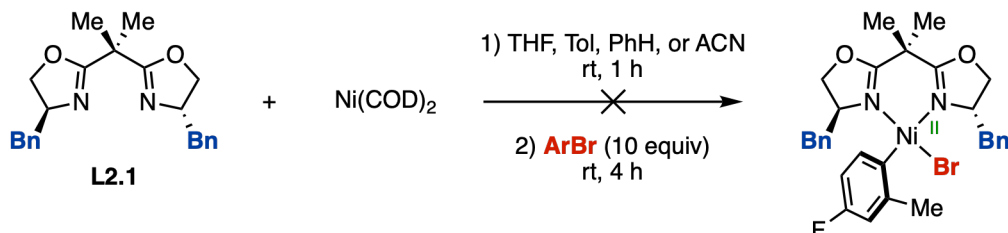


Figure 2.4: Attempted coordination of **L2.1** in THF.

My theory for why this reaction fails is that, when attempting to coordinate the ligand in THF in solvent quantities, the BOX coordinates more slowly than the solvent. THF, while not by any means a strong-field ligand, is present in sufficient quantities to out-compete the bidentate BOX ligand and coordinate to the Ni(COD)_2 , resulting in the formation of a black precipitate. Attempting to perform the coordination step in various solvents (such as benzene, toluene, DCM, DMF, and ACN) also resulted in the

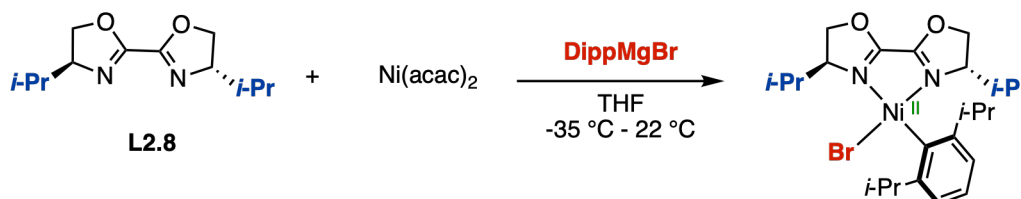
formation of a black precipitate. Given the difficulty with this initial ligand displacement, I looked for similar reports that did not use bipyridine ligands.

The Diao group prepared a very similar complex with a BiOX ligand scaffold starting from $\text{Ni}(\text{acac})_2$. This approach addresses the difficulty of coordinating to $\text{Ni}(0)$ by using a Lewis acidic $\text{Ni}(\text{II})$ center instead (**Figure 2.5a**).^{33, 34} The Diao procedure relied on a double transmetallation with a Grignard reagent to afford the desired $(\text{BiOX})\text{Ni}(\text{II})$ aryl halide complex. The driving force of this reaction is presumably the formation of the $\text{Mg}(\text{acac})_2$ salt, which can then be separated from the $(\text{BiOX})\text{Ni}(\text{II})$ complex.

I was unsuccessful in using this procedure to synthesize analogous $(\text{BOX})\text{Ni}(\text{II})$ aryl halide complexes. I believe the reasons are 1) the overall solubility of $(\text{BOX})\text{Ni}(\text{II})$ aryl halide complexes in Et_2O or THF varies drastically with the scaffold, leading to inseparable Ni and Mg salts; 2) the double transmetallation onto $(\text{BOX})\text{Ni}(\text{II})(\text{acac})_2$ is extremely difficult and requires precise stoichiometry of the Grignard reagent and temperature control to prevent decomposition; 3) trace water in THF, Et_2O , or $\text{Ni}(\text{acac})_2$ will quench the Grignard reagent, leading to irreproducible results and a mixture of products. The reaction proved unsuccessful when screening other $\text{Ni}(\text{II})$ sources (such as $\text{NiBr}_2\cdot\text{glyme}$ or $\text{NiCl}_2\cdot\text{glyme}$) to avoid double transmetallation (**Figure 2.5b**). Unfortunately for our purposes, the Diao procedure proved too sensitive. Additionally, the need to purchase or synthesize each Grignard reagent

individually (or to try other organometallic nucleophiles) for complex synthesis led us to avoid the transmetallation approach.

a) Diazo synthesis using BiOX ligands



b) Our attempts using BOX ligands

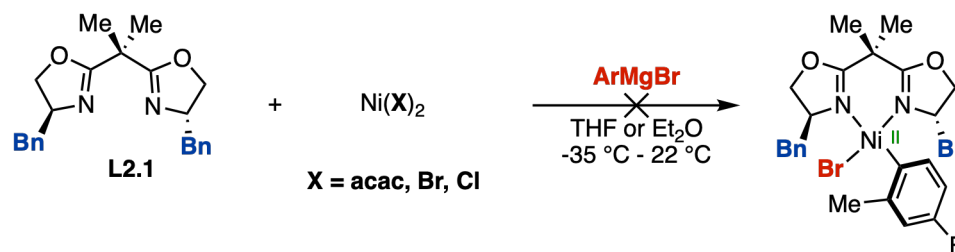


Figure 2.5: Attempted synthesis using Ni(II) and Grignard reagent.

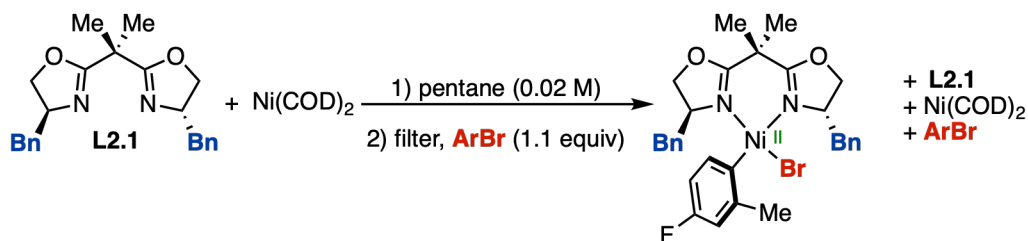
Upon reevaluating synthetic routes, the Fu group developed conditions for synthesizing their own (BOX)Ni(II) aryl halide complex via Ni(0) oxidative addition.³² They additionally showed the difficulties in synthesizing the (BOX)Ni(II) aryl halide complex via a transmetallation route. To overcome the challenges of competitive solvent coordination and Ni degradation, the Fu group stirred the BOX ligand with $\text{Ni}(\text{COD})_2$ in pentane. The solution was then passed through a syringe filter, after which bromobenzene was added. Interestingly, switching the solvent to toluene and leaving the reaction undisturbed would afford (BOX)Ni(II) bromide and the biphenyl. Under these conditions, the desired (BOX)Ni(II) aryl halide complex is transiently formed and undergoes self-transmetallation to afford (BOX)Ni(II) bromide and

biphenyl. The product is isolable when the reaction is run in pentane, but not in toluene, because the complex is insoluble in pentane. Once oxidative addition occurs, the (BOX)Ni(II) aryl halide complex precipitates from a pentane solution but not from a toluene solution (**Figure 2.6a**). Reaction success depends on precipitation; otherwise, the complex will continue to react. To prevent this in our studies, we used aryl halides bearing an ortho substituent to reduce the likelihood of *in situ* transmetallation.

I applied these conditions to test whether they were applicable to other ligand-aryl halide combinations (**Figure 2.6b**). My initial attempts using **L2.1** were unsuccessful, as the pentane solution turned gray, then black, and a black precipitate formed. This was due to trace amounts of volatile solvents from column chromatography purification, despite leaving the ligand under reduced pressure for 12 h. At the time, we switched to purchasing **L2.1**, but since then, I have learned an invaluable trick for removing trace solvents and water from the ligands. A simple benzene azeotrope, followed by azeotroping with a 1:1 v/v pentane/benzene mixture, completely removes trace solvents and water. When using commercially available **L2.1**, the reaction did not immediately turn gray; instead, it formed a pale-yellow pentane solution. The solution was then passed through a syringe filter, changing from cloudy pale yellow to clear yellow. After adding the aryl halide, no visible change was observed, and the mixture was stirred for 4 h.

Within 4 h, I observed an orange precipitate suspended in the pentane solution, which I assumed to be a complex. I attempted to characterize this material using ^1H and ^{19}F NMR spectroscopy, but analysis proved difficult because the Fu group did not report any ^1H NMR spectra for comparison. The best comparison I had was a ^{19}F peak at -57.3 ppm, which closely matched that of the dtbbpy analog at -58.2 ppm upon switching the aryl halide to 2-bromobenzotrifluoride. This was a minor product compared with the abundant aryl bromide. The ^1H NMR showed remaining starting materials (such as aryl halide, **L2.1**, $\text{Ni}(\text{COD})_2$, and some free COD) and signal broadening. At this point, the formation of the product was tentatively assigned by ^{19}F NMR.

a) *Fu, JACS 2019 approach leading to impure complex*



b) *Modified procedure*

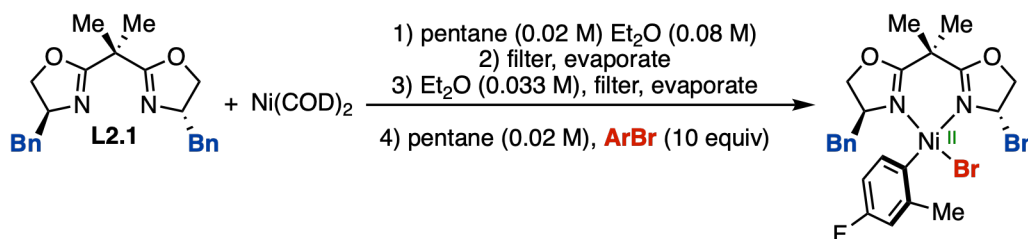


Figure 2.6: *Fu procedure and modifications.*

To reduce impurities in the ^1H NMR spectrum, I made a few adjustments to the groundwork laid by the Fu group. After filtering the pentane mixture, I evaporated the solution to afford (**L2.1**) $\text{Ni}(\text{COD})$ as a sticky yellow/brown solid. I redissolved this solid

in diethyl ether because unreactive Ni(COD)_2 is insoluble in this solvent. Indeed, this step consistently led to the observation of a few grains of yellow Ni(COD)_2 floating in the solution. I attribute this to the difficulty of the coordination step, which leaves some unreacted starting material (which, in this case, can be filtered away and is inconsequential). I then passed the ether solution through another syringe filter to remove residual Ni(COD)_2 and obtain clean **(L2.1)Ni(0)** as a starting material. Aryl halide could then be added directly to the ether solution, or the solution could be evaporated, and the residual **(L2.1)Ni(0)** could be redissolved in pentane, followed by the addition of aryl halide. I found that both methods worked exceedingly well for aryl bromides and electron-poor aryl chlorides. If oxidative addition is performed in pentane, the complex precipitates out of solution.

When run in Et_2O , the complex sometimes precipitates from solution (depending on the ligand and aryl halide choice), or adding pentane can precipitate the desired complex. The only further purification required was washing with pentane through a frit to remove any residual aryl halide (**Figure 2.6b**). The synthesized complexes are listed below (**Figure 2.7**). Details of their individual syntheses are provided in **Section 2.6.3**, with the highest-yielding procedure listed, even though these complexes can be prepared by multiple methods.

Quantitative NMR (qNMR) was used to assess the purity of the **(BOX)Ni(II)** aryl halide complexes.³⁹ The experiment is carried out by dissolving an internal standard

(1,3,5-trimethoxybenzene) and the compound whose purity is being assessed ((BOX)Ni(II) aryl halide) in a deuterated solvent. It is paramount that the accurate weights of both the standard and the complex be recorded and that both be fully soluble. A standard ^1H NMR experiment is then performed on the mixture of the internal standard and the complex. The purity is assessed by calculating the weight percent (wt%) of the compound relative to the internal standard. The calculated wt% is an indicator of complex purity, with higher wt% indicating higher purity and lower wt% indicating the presence of impurities. This is done by comparing the integration of a peak in the standard to that of a peak in the complex to calculate the molar ratio. It is also paramount that the reference peak of the internal standard be separate and distinct from the signals in the complex being analyzed. While qNMR is also possible by comparing peak integrations of a fluorine-bearing internal standard and a fluorine-bearing complex via ^{19}F NMR, we opted to perform these experiments with ^1H NMR, as it yielded consistent results across multiple runs. Further details and equations used to calculate wt% for purity assessment are described in **Section 2.7.3**.

Additional purity tests were performed on complexes **2.1b** and **2.1c** to assess air sensitivity and *in situ* decomposition. For the *in situ* studies, ^1H NMR spectra of aliquots of a d_6 -benzene solution containing 1,3,5-trimethoxybenzene and **2.1b** or **2.1c** were acquired hourly to assess wt% variation over time by comparing peak integrations between the standard and the complex. Both complexes were found to have a decrease in wt% over time. The complexes were found to degrade in wt% in

other solvents as well. To assess complex stability in air, complexes **2.1b** and **2.1c** were left open to air for 12 h, then prepared with 1,3,5-trimethoxybenzene for qNMR experiments by acquiring a ^1H NMR spectrum. Analysis of the ^1H NMR afforded lower wt%’s compared to freshly prepared samples in the glovebox, indicating these complexes will degrade when exposed to air for prolonged periods as solids.

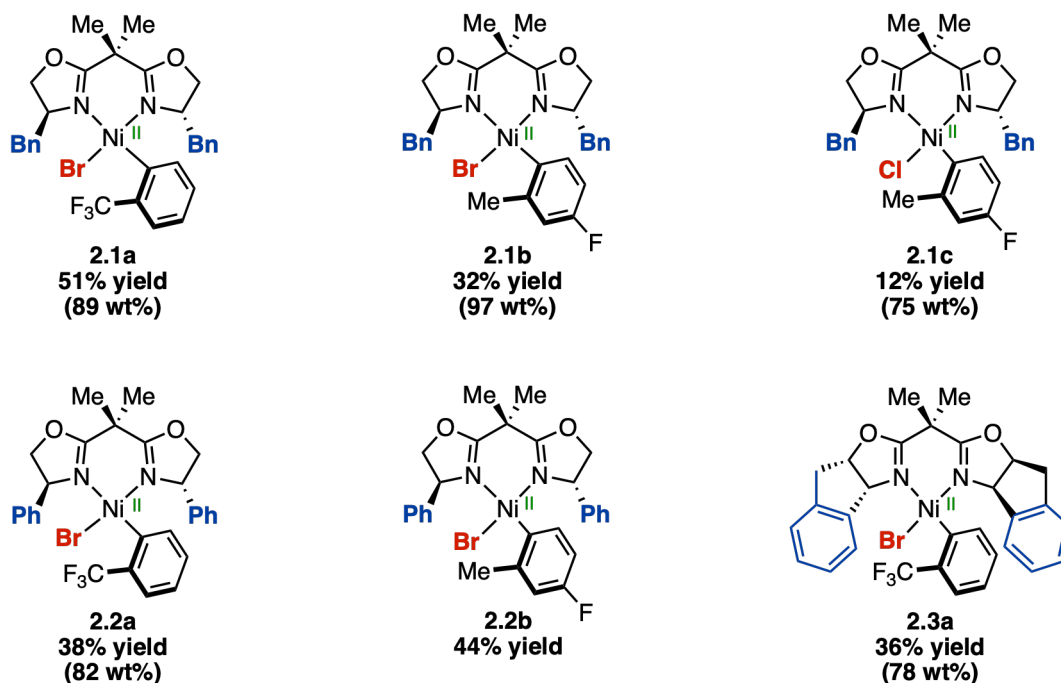


Figure 2.7: Scope of complexes. Complex 2.2b does not have a calculated wt% due to poor solubility in d_6 -benzene.

Additional information I’ve found is that the reaction can be light-sensitive. All the syntheses I completed were performed with the glovebox lights off. Performing the oxidative addition in pentane with the lights on did not precipitate the desired oxidative addition complex. Additionally, I found that performing the initial coordination step of the BOX ligand with $\text{Ni}(\text{COD})_2$ in diethyl ether did not lead to decomposition, but the resulting complex always contained very large $\text{Ni}(\text{COD})_2$

peaks in addition to the desired Ni(II) complex. Thus, all procedures start with the initial coordination in pentane, with the addition of Et₂O as a cosolvent only if the ligand (such as **L2.3**) is insoluble in pentane.

Finally, synthesis of (BOX)Ni(II) aryl halide complexes is possible when using **L2.4** (which bears *i*-Pr groups), but unfortunately, the complexes themselves are soluble in pentane, making them impossible to separate from aryl halide and free ligand.

Section 2.4: Interpretation of Spectra and Characterization

Despite the removal of impurities, interpreting the ^1H NMR spectrum remained challenging due to extensive peak broadening. We believed the simplest explanation for this broadening was the presence of paramagnetic impurities, which can create strong local magnetic fields that affect the sample's relaxation.^{40, 41} To ensure the broadening did not arise from paramagnetic Ni(I) impurities, I performed EPR spectroscopy on complexes **2.1b** and **2.1c**, which showed no characteristic peaks of an open-shell Ni species. I also acquired a ^1H NMR spectrum of independently synthesized (**L2.1**)Ni(II) bromide.⁴² The spectrum of this compound shows a characteristic peak at ~ 20 ppm, which was not observed in any of the spectra of the isolated complexes.

The geometry and connectivity of two complexes in the solid state were unambiguously assigned by single-crystal X-ray diffraction. I grew single crystals of complexes **2.1a** and **2.3a** by slowly evaporating solutions of the complexes in Et_2O /pentane. Subsequently, Veronica Carta and Philip Farias determined the structures. By measuring the bond angles in these X-ray structures, I calculated geometry indices to assess whether the crystal structures were perfectly square planar, which would imply that the Ni(II) complexes are diamagnetic and have zero unpaired electrons. A non-square planar or a distorted square planar geometry would imply that the complexes could exhibit some degree of paramagnetism despite being

EPR-silent. Geometry indices are useful descriptors for quantifying the geometry of a coordination center. For four-coordinate Ni complexes, the calculated geometry indices indicate whether the structure is square planar or tetrahedral, or the degree of distortion from perfect square planar or tetrahedral. When the geometry index values τ_4 and $\tau'_4 = 0$, the complex is square planar and, therefore, diamagnetic. When the geometry index values τ_4 and $\tau'_4 = 1$, the complex is tetrahedral and, therefore, paramagnetic. This is useful in cases where there is an isolated X-ray structure, but it does not describe the behavior of complexes *in situ* and thus cannot fully rationalize the peak broadening. The measured angles were used to calculate the geometry indices (**Table 2.1**), which supported a distorted square planar geometry since the τ_4 and τ'_4 values were both close to zero. For comparison, I also calculated the geometry index of (**L2.1**)NiBr₂, which possesses a tetrahedral geometry.⁴² Details on these calculations can be found in **Section 2.7.3**. While helpful, these results still did not address the peak broadening observed in the ¹H NMR spectra. However, we believed that the slight distortion could be correlated to a slight degree of paramagnetism in the complexes, which merited further investigation.⁴³

Entry	Complex	τ_4	τ'_4
1	2.1a	0.098	0.085
2	2.3a	0.11	0.099
3	bpyanalogue of 2.1b	0.046	0.041
4	(L2.1)NiBr ₂	0.869	0.849

Table 2.1: Geometry indices were calculated for complexes that afforded a crystal structure.

To determine the number of unpaired electrons and assess the paramagnetism of complex **2.1b** *in situ*, I applied the Evans method. The Evans method uses the chemical shift difference between protonated and deuterated solvents (the residual protonated solvent found in deuterated solvents) in a proton NMR spectrum to measure magnetic susceptibility, which quantifies a compound's attraction to a magnetic field. The concept behind this experiment is that if the complex is paramagnetic and contains unpaired electrons, a large magnetic susceptibility will be observed, as diamagnetic and paramagnetic compounds interact differently with the magnetic fields generated by NMR. Paramagnetic complexes have a slight attraction to a magnetic field, whereas diamagnetic complexes have a slight repulsion from magnetic fields. Depending on the number of unpaired electrons a paramagnetic complex has, its response to an induced magnetic field will vary, whereas diamagnetic compounds have little to no response. More unpaired electrons mean a greater attraction to the induced magnetic field. Measuring the magnetic susceptibility can then be related to the number of unpaired

electrons in a compound by calculating the corresponding effective magnetic moment.

Our rationale for doing this is that if the number of unpaired electrons is zero, we could conclude the complexes are diamagnetic and that the peak broadening is not caused by paramagnetic species. A nonzero number could indicate two distinct scenarios: the complex has a diamagnetic square-planar ground state but is in equilibrium with a paramagnetic tetrahedral conformer, or the presence of paramagnetic impurities in the sample.

This experiment was performed using capillaries containing a mixture of d_8 -toluene and toluene. A capillary was placed in an NMR tube, followed by the addition of a d_8 -toluene solution of **2.1b**. A ^1H NMR spectrum was acquired at room temperature, followed by analyzing the difference in chemical shift between the deuterated toluene and the protonated toluene. The difference in chemical shift was used to calculate the magnetic susceptibility. Details on these calculations are listed in **Section 2.7.8**.

A magnetic susceptibility (X_m) of $2.78 \times 10^{-9} \text{ m}^3 \text{ mol}^{-1}$ was calculated, which equates to an effective magnetic moment (μ_{eff}) of $0.72 \mu\text{B}$ and less than 1 unpaired spin.⁴⁴ This nonzero, small magnetic moment is consistent with a ground-state square planar diamagnetic complex that is in equilibrium with a high-spin tetrahedral complex, hence the peak broadening.⁴⁵⁻⁴⁹

Finally, UV-vis spectra of **2.1a**, **2.1b**, **2.1c**, and **2.2b** were recorded (**Figure 2.8**). The largest effects were observed when switching the X-type ligands (halide or aryl) rather than the BOX ligand. Switching the halogen from Br to Cl produced a red shift in λ_{max} , with **2.1c** λ_{max} = 460 nm compared with the bromide analog **2.1b** λ_{max} = 420 nm. A smaller but significant shift was also observed upon changing the aryl moiety, with λ_{max} = 420 nm for **2.1b** and λ_{max} = 430 nm for **2.1a**.

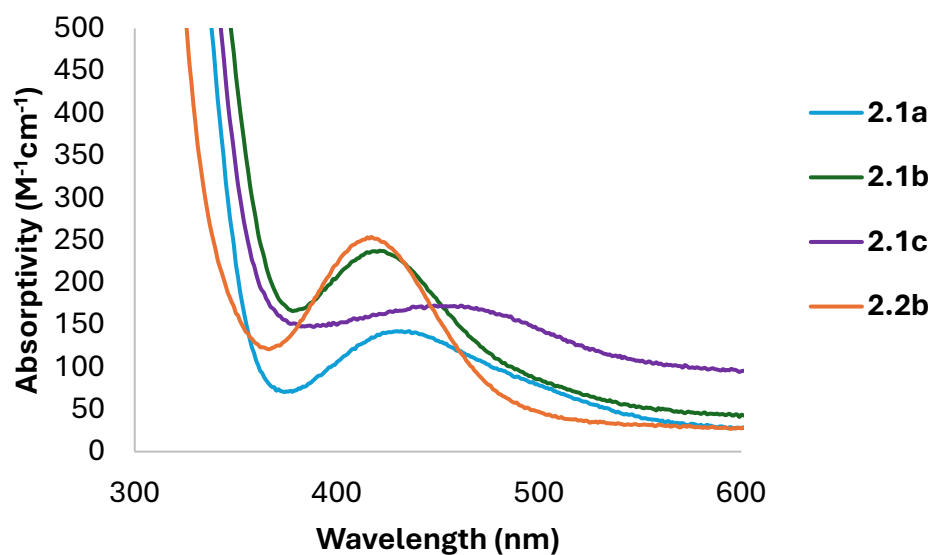


Figure 2.8: *UV-vis spectra of complexes.*

Section 2.5: Synthesis of BiOXNi(II) Aryl Halide Complexes via Oxidative Addition

After the successful publication on the synthesis of (BOX)Ni(II) aryl halide complexes, I ventured into synthesizing (BiOX)Ni(II) aryl halide complexes using a slightly modified procedure. Their synthesis will be covered in **Section 2.7.2**, and their application will be discussed in **Chapter 4**. My hope is that the procedure for their synthesis will be published as a communication similar to the (BOX)Ni(II) aryl halide report.¹

There are multiple examples in the literature in which switching the ligand scaffold from BiOX to BOX completely halts reactivity.⁵⁰ Thus, it is important to have a general method for synthesizing this class of compounds as well, since switching the ligand scaffold is not always an option when investigating a mechanism. Despite the Diao group's successful synthesis of this class of compounds, I wanted to leverage our findings to synthesize these complexes via oxidative addition rather than worry about the transmetallation route's sensitivity. At the very least, having multiple options for synthesizing a class of complexes is useful, especially when different Ni sources are used. I chose to investigate BiOX ligands with varying degrees of rigidity and to develop a generalized procedure (**Figure 2.9**). Like the BOX ligands, they are commercially available and easy to synthesize and purify.⁵¹ I opted to use **L2.5** in screening conditions, as it is the highest-performing ligand in both yield and

selectivity for the work we are currently conducting on a cross-electrophile coupling (details of this study will be in **Chapter 4**).⁵¹

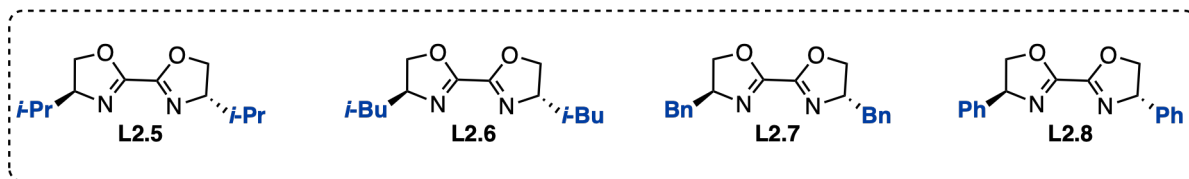
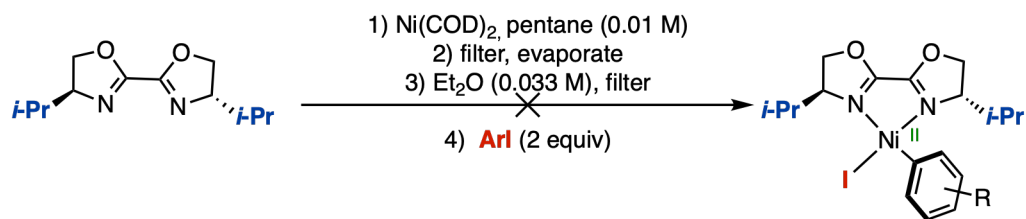


Figure 2.9: Scope of BiOX ligands.

My initial attempts to prepare a (BiOX)Ni(II) aryl halide complex followed the optimized procedure in **Section 2.2**, using **L2.5**. Early on, I found that BiOX ligands are much less soluble in pentane than BOX analogs. For example, a mixture of **L2.1** (BOX R = Bn) and Ni(COD)₂ is fully soluble as a 0.01 M pentane solution. However, a mixture of **L2.7** (BiOX, R = Bn) and Ni(COD)₂ is insoluble as a 0.005 M pentane solution. Some BiOX ligands, such as **L2.5** and **L2.6**, are fully soluble as 0.01 M pentane solutions, likely because of the greasy nature of the alkyl R groups. Therefore, in cases where BiOX ligands contain aromatic R groups such as **L2.7** or **L2.8**, the key to solubilizing is the addition of Et₂O, as in synthesizing complexes using **L2.3**. The exact amount will vary with the ligand's rigidity, but I've found that a 0.005 M 1:1 (v/v) Et₂O/pentane solution is sufficient to dissolve **L2.5** and Ni(COD)₂. The other change observed in this step was that, instead of the solution turning opaque yellow upon coordination, as with BOX ligands, coordination with BiOX scaffolds produced a midnight-blue solution.

a) Procedure for synthesizing **L2.1**Ni(II) aryl halide complexes unsuccessful for BiOX scaffold



b) Slightly modified procedure

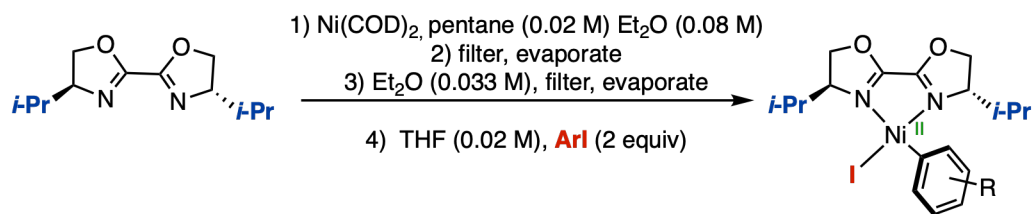


Figure 2.10: Synthesis of (BiOX)Ni(II) aryl halide complexes.

I then passed the pentane solution through a syringe filter, followed by evaporation of the pentane and re-dissolving the solid in Et₂O to remove any unreacted Ni(COD)₂. I then attempted to add the aryl iodide directly to the Et₂O solution, which immediately resulted in a black precipitate (**Figure 2.10a**). Subsequently, I tried evaporating the Et₂O, re-dissolving the (**L2.5**)Ni(0)COD in pentane, and then adding the aryl iodide. This also resulted in immediate decomposition and formation of a black precipitate. My speculation was that the issue with the synthesis was not the coordination, but oxidative addition itself.

My next idea was to dissolve the (**L2.5**)Ni(0)COD in THF. Up to this point, I had avoided using THF because I've found it very difficult to remove trace amounts from Ni(II) complexes, which often appear in the ¹H NMR despite keeping it under reduced pressure for hours at a time. Despite this, I figured it was at least worth an attempt. I initially tried a 0.067 M THF solution before adding the aryl iodide. After the addition

of aryl iodide, the solution immediately turned deep red, which I attribute to the successful formation of a Ni(II) aryl halide complex. I let this stir for another 10 min to ensure complete conversion of the starting material, but the solution turned grey and was suspended with a black precipitate. I repeated the experiment using a 0.025 M THF solution and found that the reaction still turned deep red after the aryl iodide addition. After stirring for 20 min, the solution remained deep red, at which point I assumed full conversion of Ni(0).

To isolate the complex, I began slowly evaporating the excess THF. I feared this would lead to decomposition, as the more concentrated solution had originally turned black after sitting too long, but to my surprise, I was able to evaporate THF to dryness without any visible discoloration of the complex. I believe that once the oxidative addition reaches full conversion, solubility is no longer an issue. I then redissolved the sticky red solid in 1.5 mL of THF and added pentane, immediately affording a red powder, almost identical in color to (BOX)Ni(II) aryl halide complexes. I poured the solution over a fine frit and washed the solid with pentane to afford the desired (**L2.8**)Ni(II) aryl iodide complex. I found concentrating the mother liquor, redissolving in THF, and adding additional pentane could precipitate more of the complex.

I've found that these complexes (compared to the (BOX)Ni(II) aryl halide complexes) are poorly soluble in *d*₆-benzene and *d*₈-toluene, leading to rapid

decomposition during NMR experiments. The spectra I have obtained and those Hai Ly has obtained from his own syntheses resemble the BOX complexes, as they also exhibit substantial peak broadening. Further analyses, such as qNMR and the Evans method, will be performed to provide more comprehensive characterization. We have not observed characteristic peaks of independently synthesized (**L2.5**)Ni(II) bromide, indicating a lack of transmetallation despite the lack of an ortho substituent on the aryl halide. I find this trend is consistent with (BOX)Ni(II) aryl halide complexes, with rates of transmetallation (detected by biaryl in ^1H NMR) being fastest for ArCl, then ArBr, and slowest for ArI. More comprehensive studies must be performed to determine stability in solution and in air, but I would expect a similar trend to that of the (BOX)Ni(II) aryl halide complexes.

Section 2.6: Conclusion

Syntheses and characterization of two classes of chiral nickel complexes using BOX and BiOX ligands are described in this chapter. I believe this will have a positive impact on the field of asymmetric Ni-catalyzed reactions, as readily available syntheses of commonly proposed intermediates can facilitate mechanistic elucidation. Specifically, these complexes are useful for stoichiometric experiments as well as crossover experiments that will help distinguish between Ni(0) and Ni(I)-mediated processes. Our mechanistic investigation of photochemical Ni-catalyzed THF-arylation is one example of the application of these complexes (discussed in **Chapter 3**), and we are currently using them to investigate a Ni-catalyzed cross-electrophile coupling (XEC) reaction (discussed in **Chapter 4**). I believe that as mechanistic studies of Ni-catalyzed systems progress and the systems become more complex, the synthesis of these complexes, which enables us to leverage ee data, can be an invaluable tool for mechanistic elucidation.

Chapter 2.7: Procedures and Characterization

Section 2.7.1: General Information

All reagents were purchased from commercial suppliers and used without further purification. Ni(COD)_2 : 2 g bottles of bis (1,5-cyclooctadiene)nickel (0), 98+% were purchased from STREM and used without any further purification (catalog number 18-0010). The Ni(COD)_2 was immediately cycled into the glovebox and stored in the freezer at -30 °C. Between uses, the bottle cap was sealed with electrical tape.

Pentane: 1 L bottles of *n*-pentane, anhydrous, 99.5+%, over molecular sieves, packaged under argon in resealable ChemSeal™ bottles were purchased from Thermo Fisher Scientific (catalog number 047115.K2). The pentane, while still sealed, was cycled into the glovebox and used without any further purification.

Diethyl ether: A 2.5 L bottle of diethyl ether, 99.5%, extra dry, stabilized with BHT, AcroSeal® was purchased from Thermo Fisher Scientific (currently unavailable). The bottle, while still sealed, was cycled into the glovebox and used without any further purification.

Deuterated benzene: Bottles of d_6 -benzene >99% were purchased from Oakwood Chemical (catalog number 099808) in 10 mL and 25 mL quantities. While still sealed, the bottles were cycled into the glovebox overnight upon arrival and then used as NMR solvents without further purification. Between uses, the bottle was sealed with

electrical tape, and the glovebox was freshly purged before opening every time to prevent solvent vapor contamination.

Stir bar: Avantor magnetic stirring bars (1/2 x 5/16") (catalog number 58949-036) were oven-dried at 130 °C for at least 1 h before being cycled into the glovebox and used for all stirring. After each use, the stir bars were cleaned in water and acetone, then stirred in an aqua regia solution overnight, followed by a sodium bicarbonate wash to remove any excess acid.

All syringe filters used were purchased from VWR (catalog number 76479-016). These have a 33 mm diameter and a 0.22 µm pore-size PES membrane.

Aryl halides: All aryl halides used in this study (2-bromobenzotrifluoride, 2-bromo-5-fluorotoluene, and 2-chloro-5-fluorotoluene) were all purchased from TCI chemicals in 25 g quantities. Each bottle, while still sealed, was cycled into the glovebox and used without further purification.

Bisoxazoline (BOX) ligands: All BOX ligands used in this study were purchased in 1 g amounts from Ambeed. Each bottle, while still sealed, was cycled into the glovebox and stored in the freezer at -30 °C between uses.

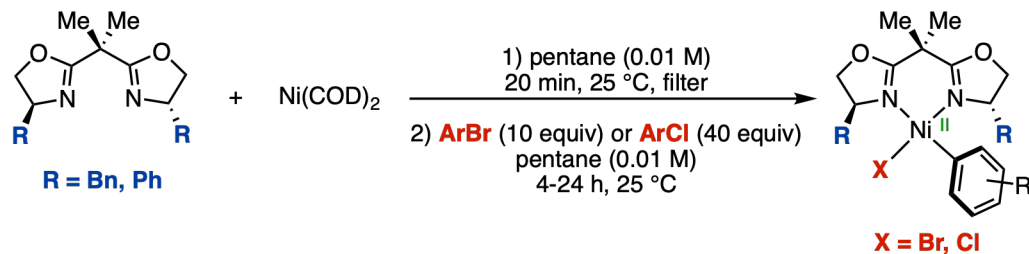
¹H NMR spectra were obtained in C₆D₆ or C₇D₈ (*d*₈-toluene) at 400 MHz or 600 MHz using Bruker instruments. Chemical shifts are reported in ppm and referenced to the residual C₆H₆ singlet (δ = 7.16 ppm) or the C₇D₈ singlet (δ = 2.08 ppm). ¹³C NMR spectra were obtained in C₆D₆ at 101 MHz or 151 MHz and referenced to the center

peak of the C_6D_6 triplet ($\delta = 128.39$). ^{19}F NMR spectra were obtained in C_6D_6 at 376 MHz or 564 MHz and referenced to the $\text{C}_6\text{H}_5\text{CF}_3$ singlet ($\delta = -63.72$ ppm) in C_6D_6 . The abbreviations s, d, t, m, and bs stand for the resonance multiplicities singlet, doublet, triplet, multiplet, and broad singlet, respectively. Single-crystal X-ray diffraction spectra were acquired using a Bruker D8 Venture diffractometer. UV-vis spectra were acquired using an Agilent Cary 60 UV/Vis spectrophotometer. NMR, X-ray diffraction, and UV-Vis were all performed at the Analytical Chemistry Instrumentation Facility at the University of California, Riverside.

Section 2.7.2: Synthesis of (BOX)Ni(II) Aryl Halide Complexes

All bisoxazoline (BOX) and bioxazoline (BiOX) complexes were synthesized in a nitrogen-filled glovebox using oven-dried glassware, with the glovebox lights off to avoid potential light sensitivity of the Ni complexes. Diminished yields were observed when the glovebox lights were left on during synthesis. This observation aligns with studies of analogous Ni(II) complexes, which have been shown to be light-sensitive in solution.⁵² No effect of ambient light on the reaction yields was observed. The final (BOX)Ni(II) complexes in the solid state are insensitive to glove box or ambient light. The (BOX)Ni(II) and (BiOX)Ni(II) oxidative addition complexes were prepared from commercially available **L2.1** ((4S,4'S)-2,2'-(propane-2,2-diyl)bis(4-benzyl-4,5-dihydrooxazole)), **L2.2** ((4S,4'S)-2,2'-(propane-2,2-diyl)bis(4-phenyl-4,5-dihydrooxazole)), **L2.3** ((3aR,3a'R,8aS,8a'S)-2,2'-(propane-2,2-diyl)bis(3a,8a-dihydro-8H-indeno[1,2-d]oxazole)), and **L2.8** ((4S,4'S)-4,4'-diisopropyl-4,4',5,5'-tetrahydro-2,2'-bioxazole) and Ni(COD)₂ without further purification. The (BOX)Ni(II) complexes reported are moisture-sensitive and will gradually decompose if left open to air. They are also prone to decomposition in solution (see **Section 2.7.6** for more details).

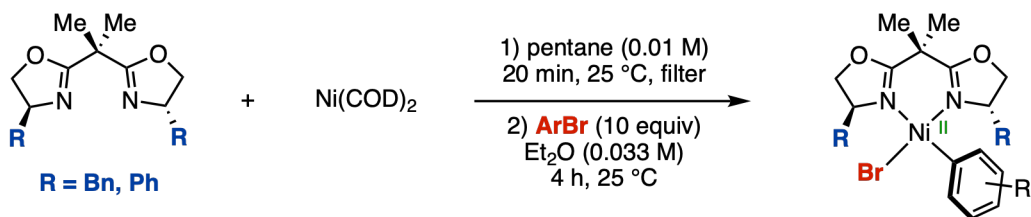
General Procedure 2A



Ligands **L2.1** or **L2.2** (0.2 mmol, 1 equiv) and Ni(COD)₂ (0.2 mmol, 1 equiv, 55.0 mg) were added to a 20 mL scintillation vial, followed by anhydrous pentane (0.01 M, 20 mL).³² The mixture was vigorously stirred (1400 RPM) for 20 min. The time required for full dissolution of the ligand and Ni(COD)₂ depends on the BOX ligand used; more rigid ligands generally take longer, often more than 40 min. The initial suspension gradually turned from opaque yellow to clear yellow, with free COD and some BOX clouding the side of the vial as the Ni(COD)₂ and the ligand dissolved. Once no granular Ni(COD)₂ remained suspended in solution and no solid ligand remained, the solution was filtered through a syringe filter (PES, 30 mm, 0.22 μm) into a 50 mL filtering flask, yielding a clear yellow solution. Immediately after, the filtering flask was capped, and the pentane was removed *in vacuo* at room temperature by slowly introducing the vacuum. Once all the pentane was evaporated, the filtering flask was kept under vacuum for an additional 15 min. The resulting solid was dissolved in diethyl ether (0.03 M, 6 mL) and filtered through a second syringe filter into another 20 mL scintillation vial to remove excess Ni(COD)₂. The diethyl ether was then quickly removed *in vacuo* by slowly applying vacuum until a sticky yellow solid remained in

the scintillation vial. This yellow solid was then redissolved in fresh anhydrous pentane and stirred rapidly until fully dissolved. Aryl bromide (10 equiv) or aryl chloride (20 equiv) was then added in one portion to the pentane solution and stirred for 4 h (for aryl bromides) to 24 h (for aryl chloride) until a precipitate formed (precipitate color depends on the aryl halide). The solution containing the precipitate was poured over a fine-porosity frit. Washing with 3 × 4 mL of pentane and drying the solid in vacuo afforded the desired (BOX)Ni(II) aryl halide complexes.

General Procedure 2B²⁸

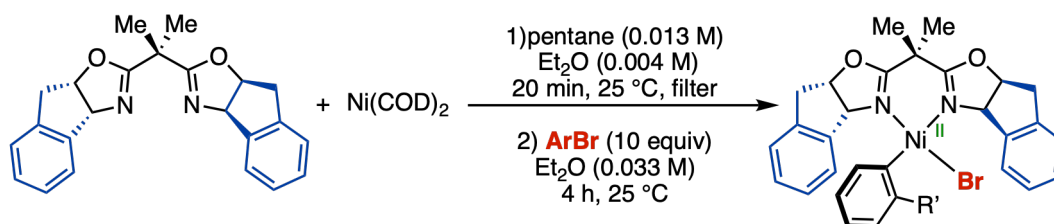


Ligands **L2.1** or **L2.2** (0.2 mmol, 1 equiv) and $\text{Ni}(\text{COD})_2$ (0.2 mmol, 1 equiv, 55.0 mg) were added to a 20 mL scintillation vial, followed by anhydrous pentane (0.01 M, 20 mL).³² The mixture was vigorously stirred at 1400 RPM for ~20 min. The time required for full dissolution of the ligand and $\text{Ni}(\text{COD})_2$ depends on the BOX ligand used; more rigid ligands generally take longer, often more than 40 min. The initial suspension gradually turned from opaque yellow to clear yellow, with free COD and some BOX clouding the vial's side as $\text{Ni}(\text{COD})_2$ and the ligand dissolved. Once no granular $\text{Ni}(\text{COD})_2$ remained suspended in solution and no solid ligand remained, the solution was filtered through a syringe filter (PES, 30 mm, 0.22 μm) into a 50 mL filtering flask, yielding a clear yellow solution. Immediately after, the filtering flask was capped, and the pentane was removed *in vacuo* at room temperature by slowly introducing a vacuum. Once all the pentane was evaporated, the filtering flask was kept under vacuum for an additional 15 min. The resulting solid was dissolved in diethyl ether (0.03 M, 6 mL) and filtered through a second syringe filter into another 20 mL scintillation vial to remove excess $\text{Ni}(\text{COD})_2$.

In contrast with the previous procedure, the diethyl ether was not removed. Instead, the aryl bromide (10 equiv) was added to the diethyl ether solution and

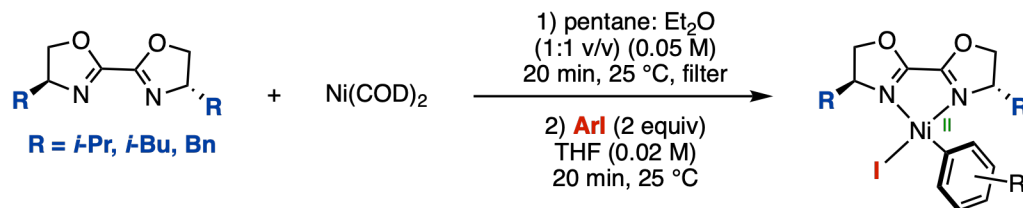
stirred for 4 h under constant monitoring until the solution turned deep red. The solution was then filtered through a Celite® plug into a fresh 20 mL scintillation vial. Then, ~4 mL of diethyl ether was removed *in vacuo*, affording a concentrated solution. This solution was slowly added to 15 mL of pre-cooled anhydrous pentane in a scintillation vial at - 40 °C using a cold well equipped with a mixture of acetonitrile and dry ice in a dewar outside the glovebox. The scintillation vial was capped and stirred for 2 min, resulting in the desired nickel complex precipitating from the solution. The contents of this scintillation vial were poured over a fine porosity frit. Washing with 3 x 4 mL of pentane afforded the desired (BOX)Ni(II) aryl bromide complex.

General Procedure 2C



Ligand **L2.3** (0.2 mmol, 1 equiv, 71.7 mg) and $\text{Ni}(\text{COD})_2$ (0.2 mmol, 1 equiv, 55.0 mg) were added to a 20 mL scintillation vial, followed by pentane (0.005 M, 10 mL) and diethyl ether (0.005 M, 10 mL). The mixture was vigorously stirred (1400 RPM) for 45 min until no **L2.3** remained suspended in solution. The initial suspension gradually turned opaque yellow as $\text{Ni}(\text{COD})_2$ and the ligand dissolved. Once no granular $\text{Ni}(\text{COD})_2$ or **L2.3** remained suspended in solution, the solution was filtered through a syringe filter (PES, 30 mm, 0.22 μm) into a 50 mL filtering flask, yielding a clear yellow solution. The solvent was then removed *in vacuo* at room temperature by slowly introducing the vacuum. Once all the pentane and ether were evaporated, the filtering flask was kept under vacuum for an additional 15 min. The resulting solid was dissolved in diethyl ether (6 mL) and filtered through a second syringe filter into another 20 mL scintillation vial to remove excess $\text{Ni}(\text{COD})_2$. Aryl bromide (10 equiv) was immediately added to the diethyl ether solution and allowed to stir under constant monitoring. After ~4 h, the solution turned deep red, and the desired complex precipitated. The precipitate was immediately poured over a fine porosity frit. The solid was washed over a fine frit with 3 x 4 mL of pentane to afford the desired (BOX)Ni(II) aryl bromide complex.

General Procedure 2D



BiOX **L2.5** (0.2 mmol, 1 equiv, 44.9 mg) and Ni(COD)_2 (0.2 mmol, 1 equiv, 55.0 mg) were added to a 20 mL scintillation vial, followed by anhydrous pentane (0.01 M, 20 mL). The mixture was vigorously stirred (1400 RPM) for ~20 min. The time required for full dissolution of the ligand and Ni(COD)_2 depends on the BiOX ligand used; bulkier ligands take longer, often >40 min, and require a diethyl ether cosolvent. The initial suspension gradually turned light green, then light blue, and finally dark midnight blue, with free COD and some BiOX clouding the vial's side. The midnight blue color indicates successful coordination, and the solution was stirred for another 5 min. The solution was filtered through a syringe filter (PES, 30 mm, 0.22 μm) into a 50 mL filtering flask, yielding a dark blue solution. Immediately after, the filtering flask was capped, and the pentane was removed *in vacuo* at room temperature by slowly introducing the vacuum. Once all the pentane was evaporated, the filtering flask was kept under vacuum for an additional 15 min. The resulting blue/brown solid was dissolved in diethyl ether (0.03 M, 6 mL) and filtered through a second syringe filter into another 20 mL scintillation vial to remove excess Ni(COD)_2 . The diethyl ether was then quickly removed *in vacuo* by slowly introducing the vacuum until a sticky yellow solid remained in the scintillation vial.

This solid (either blue or yellow/brown, depending on how long it was left under vacuum) was then redissolved in fresh THF and stirred until the midnight-blue color was restored. Aryl iodide (0.4 mmol, 2 equiv, 98.4 mg) was then added in one portion to the THF solution, immediately turning from dark blue to deep red. The mixture was stirred for an additional 20 min.

The THF was removed *in vacuo* by slowly introducing vacuum until a sticky red solid remained in the scintillation vial. This solid was then redissolved in 1 mL of THF, followed by the addition of 19 mL of pentane while stirring at 1000 RPM to precipitate the (BiOX)Ni(II) aryl iodide complex. The precipitate was immediately poured over a fine porosity frit. Washing with 3 × 4 mL of pentane and drying the solid *in vacuo* afforded the desired (BiOX)Ni(II) aryl halide complex. This procedure is amenable to aryl bromides and electron-poor aryl chlorides.

Section 2.7.3: Quantitative NMR Experiments

General Procedure 2E: qNMR Experiments

In a nitrogen-filled glovebox, 10-15 mg of 1,3,5-trimethoxybenzene was weighed into a 20 mL scintillation vial, and the exact mass was recorded. The scale was then tared, and 10-15 mg of the (BOX)Ni(II) aryl halide complex was added, with the exact amount recorded. Next, 2-3 mL of d_6 -benzene was added, and the mixture was gently stirred until both solids were fully dissolved. Finally, 0.6 mL of the solution was transferred to an NMR tube and sealed with a septa cap. The sample was removed from the glovebox, and a ^1H NMR spectrum was acquired (delay time: 5 s, number of scans: 30). The spectrum was analyzed by comparing the integration of the 1,3,5-trimethoxybenzene aromatic singlet to the integration of an aromatic signal of each complex (varies). These integration values were then used in the equations below to calculate the wt% and assess complex purity. The calculated wt% is a measure of each complex's purity, indicating how much of the isolated yield is the desired complex.

$$\text{Molar ratio} = \frac{\left[\frac{I_{cpd}}{nH_{cpd}}\right]}{\left[\frac{I_{std}}{nH_{std}}\right]}$$

Eq 2.1: Molar ratio calculation.

$$\text{wt}\% = \frac{(mg_{std})(MW_{cpd})(\text{molar ratio})(P_{std})}{(mg_{cpd})}$$

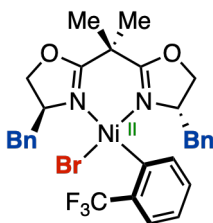
Eq 2.2: Calculation for wt% to assess complex purity.

Where,

- $\text{wt}\%$ = purity of the Ni complex
- I_{cpd} = proton integral area of a known peak on the complex
- nH_{cpd} = number of hydrogens associated with the complex NMR peak
- I_{std} = proton integral area of a known peak of 1,3,5-trimethoxybenzene
- nH_{std} = number of hydrogens associated with the 1,3,5-trimethoxybenzene NMR peak
- mg_{std} = amount in milligrams of the 1,3,5-trimethoxybenzene weighed for analysis
- mg_{cpd} = amount in milligrams of the complex being analyzed
- MW_{std} = molecular weight of 1,3,5-trimethoxybenzene
- MW_{cpd} = molecular weight of the complex being analyzed
- P_{std} = wt% purity of the 1,3,5-trimethoxybenzene expressed as a decimal value. For the purposes of this calculation, a value of 1.00 may be assumed.

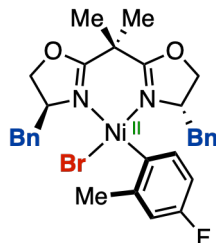
Section 2.7.4: Complex Characterization

Nickel(II) (2-(trifluoromethyl)phenyl) (bromide) (4*S*,4'*S*)-2,2'-(propane-2,2-diyl)bis(4-benzyl-4,5-dihydrooxazole) (**2.1a**)



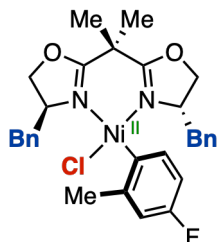
(BOX)Ni(II) aryl bromide complex **2.1a** was prepared according to *General Procedure 2A* using **L2.1** (0.2 mmol, 1 equiv, 72.5 mg) and 2-bromobenzotrifluoride (2.0 mmol, 10 equiv, 0.27 mL). In total, 74.2 mg of light pink solid was isolated. Quantitative NMR experiments using 1,3,5-trimethoxybenzene as an internal standard revealed a purity of 89%. Therefore, the adjusted yield for this resulting (BOX)Ni(II) was 51% (66.0 mg). **¹H NMR** (600 MHz, C₆D₆) δ 8.91 (bs, 1H), 7.81 – 6.32 (m, 13H), 4.84 (bs, 1H), 4.59 – 3.37 (m, 4H), 3.08 (bs, 2H), 2.76-2.15 (m, 3H), 1.27-0.87 (m, 6H). **¹³C NMR** (151 MHz, C₆D₆) δ 172.4, 169.6, 154.2, 143.5, 138.8, 136.6, 136.4, 130.6, 130.2, 129.0, 128.7, 127.4, 125.6, 122.7, 72.4, 67.9, 42.1, 40.0, 38.8, 25.9, 22.5. The remaining signal overlaps with the peaks from deuterated benzene, confirmed by HSQC correlations. **¹⁹F NMR** (564 MHz, C₆D₆) δ -57.31

Nickel(II) (4-fluoro-2-methylphenyl) (bromide) (4*S*,4'*S*)-2,2'-(propane-2,2-diyl)bis(4-benzyl-4,5- dihydrooxazole) (3.1b)



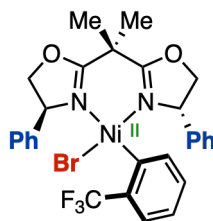
(BOX)Ni(II) aryl bromide complex **2.1b** was originally reported in our previous article²⁸ and labeled as **3.II-Br1** in the context of **Chapter 3** in this thesis. Herein, we report an updated approach to its synthesis, following *General Procedure 2C* using **L2.1** (0.2 mmol, 1 equiv, 72.5 mg) and 2-bromo-5-fluorotoluene (2.0 mmol, 10 equiv, 0.25 mL). In total, 39.8 mg of light orange solid was isolated. Quantitative NMR experiments using 1,3,5-trimethoxybenzene as an internal standard revealed a purity of 97%. Therefore, the adjusted yield for this resulting (BOX)Ni(II) was 32% (38.6 mg). **¹H NMR** (400 MHz, C₆D₆) δ 8.12 (t, J = 7.5 Hz, 1H), 7.57-7.22 (m, 2H), 7.02 (dt, J = 16.2, 7.5 Hz, 7H), 6.87 (ddd, J = 13.5, 9.3, 4.2 Hz, 3H), 5.00 (bs, 2H), 3.59 (bs, 2H), 3.58 (s, 3H), 3.04 (bs, 3H), 2.79 – 2.16 (m, 3H), 1.00 (s, 6H). **¹³C NMR** (101 MHz, C₆D₆) 163.8, 161.4, 145.1, 139.5, 136.9, 130.6, 129.0, 127.4, 114.6, 114.4, 111.0, 110.9, 72.0, 67.1, 40.0, 38.7, 27.2, 24.4. The remaining signals overlap with the peaks from deuterated benzene, as confirmed by HSQC correlations. **¹⁹F NMR** (376 MHz, C₆D₆) δ -127.24.

Nickel(II) (4-fluoro-2-methylphenyl) (chloride) (4*S*,4'*S*)-2,2'-(propane-2,2-diyl)bis(4-benzyl-4,5- dihydrooxazole) (2.1c)



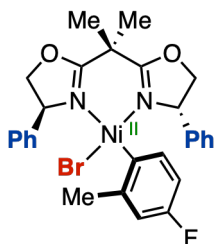
(BOX)Ni(II) aryl chloride complex **2.1c** was originally reported in our previous article and was labeled as **3.II-Cl1** in **Chapter 3** of this thesis. Herein, we report an updated approach to its synthesis, following *General Procedure 2A* using **L2.1** (0.2 mmol, 1 equiv, 72.5 mg) and 2-chloro-5-fluorotoluene (4.0 mmol, 20 equiv, 0.54 mL). In total, 18.8 mg of light grey/orange solid was isolated. Quantitative NMR experiments using 1,3,5-trimethoxybenzene as an internal standard revealed a purity of 75%. Therefore, the adjusted yield for this resulting (BOX)Ni(II) was 12% (14.1 mg). **¹H NMR** (400 MHz, C₆D₆) δ 8.01 (t, *J* = 7.2 Hz, 1H), 7.62 -7.30 (m, 2H), 7.11-6.53 (m, 10H), 4.86 (bs, 2H), 3.83-3.63 (m, 2H), 3.58 (s, 3H), 3.22-2.83 (m, 3H), 2.78-1.95 (m, 3H), 0.97 (s, 6H). **¹³C NMR** (101 MHz, C₆D₆) δ 163.8, 161.4, 144.3, 138.8, 138.3, 130.6, 130.2, 129.0, 127.4, 114.1, 113.9, 110.5, 110.3, 72.4, 67.9, 42.1, 38.7, 26.2, 24.3. The remaining signals overlap with the peaks from deuterated benzene. **¹⁹F NMR** (376 MHz, C₆D₆) δ -126.99.

Nickel(II) (2-(trifluoromethyl)phenyl) (bromide) (4*S*,4'*S*)-2,2'-(propane-2,2-diyl)bis(4-phenyl-4,5- dihydrooxazole) (2.2a)



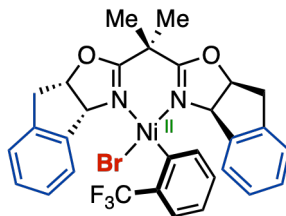
(BOX)Ni(II) aryl bromide complex **2.2a** was prepared according to *General Procedure 2A* using **L2.2** (0.2 mmol, 1 equiv, 66.9 mg) and 2-bromobenzotrifluoride (2.0 mmol, 10 equiv, 0.27 mL). In total, 57.4 mg of dark purple solid was isolated. Quantitative NMR experiments using 1,3,5-trimethoxybenzene as an internal standard revealed a purity of 82%. Therefore, the adjusted yield for this resulting (BOX)Ni(II) was 38% (47.1 mg). **¹H NMR** (400 MHz, C₆D₆) δ 8.26 (bs, 1H), 7.36-6.87 (m, 13H), 6.56 (bs, 2H), 3.48 (m, 4H), 1.46 (bs, 6H). The remaining peaks overlap with trace benzene in the NMR solvent. **¹³C NMR** (101 MHz, C₆D₆) δ 173.9, 170.6, 143.8, 141.4, 137.0, 132.1, 129.2, 127.9, 127.4, 126.8, 125.8, 125.6, 122.1, 76.9, 75.7, 70.3, 69.9, 39.5, 25.2, 25.1. The remaining signals overlap with the peaks from deuterated benzene. **¹⁹F NMR** (376 MHz, C₆D₆) δ -57.15.

Nickel(II) (4-fluoro-2-methylphenyl) (bromide) (4*S*,4'*S*)-2,2'-(propane-2,2-diyl)bis(4-phenyl-4,5- dihydrooxazole) (2.2b)



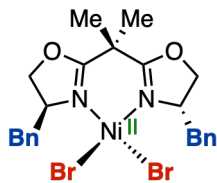
(BOX)Ni(II) aryl bromide complex **2.2b** was prepared according to **General Procedure 2A** using **L2.2** (0.2 mmol, 1 equiv, 66.9 mg) and 2-bromo-5-fluorotoluene (2.0 mmol, 10 equiv, 0.25 mL). The resulting (BOX)Ni(II) complex was isolated as a pale-yellow solid in 44% yield (50.7 mg). Quantitative NMR experiments were not possible due to the complex's poor solubility in solvents in which it does not readily decompose. **¹H NMR** (400 MHz, C₆D₆) δ 7.61-6.77 (m, 13H), 6.45-6.35 (m, 2H), 3.60-3.17 (m, 4H), 3.03 (bs, 3H), 1.68-1.25 (m, 6H). The remaining peaks overlap with trace benzene in the NMR solvent. Due to the poor solubility of **2.2b** in C₆D₆, we were unable to obtain a **¹³C NMR** spectrum. **¹⁹F NMR** (376 MHz, C₆D₆) δ -128.54.

Nickel(II) (2-(trifluoromethyl)phenyl) (bromide) (3a*R*,3a'*R*,8a*S*,8a'*S*)-2,2'-(propane-2,2-diyl)bis(3a,8a-dihydro-8*H*-indeno[1,2-*d*]oxazole) (2.3a)



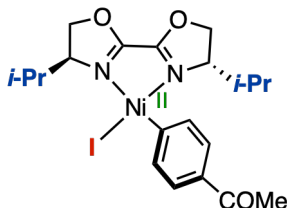
(BOX)Ni(II) aryl bromide complex **2.3a** was prepared according to *General Procedure 2C* using 2-bromobenzotrifluoride (2.0 mmol, 10 equiv, 0.27 mL). In total, 58.8 mg of light purple solid was isolated. Quantitative NMR experiments using 1,3,5-trimethoxybenzene as an internal standard revealed a purity of 78%. Therefore, the adjusted yield for this resulting (BOX)Ni(II) was 36% (45.9 mg). **¹H NMR** (400 MHz, C₆D₆) δ 10.15 (bs, 1H), 9.54 (bs, 2H), 7.87 (bs, 1H), 7.31-7.20 (m, 3H), 7.09 (bs, 2H), 6.87-6.80 (m, 3H), 6.11-4.18 (m, 2H), 3.99 (bs, 2H), 2.70 (d, *J* = 17.9 Hz, 2H), 2.26 (bs, 2H), 0.89 (bs, 6H). **¹³C NMR** (101 MHz, C₆D₆) δ 174.7, 169.3, 145.0, 140.7, 139.0, 132.6, 129.6, 128.9, 124.9, 122.7, 87.7, 83.5, 77.5, 76.2, 66.3, 40.2, 38.8, 37.3, 24.7. The remaining signals overlap with the peaks from deuterated benzene. **¹⁹F NMR** (376 MHz, C₆D₆) δ -55.61. A small amount of remaining unreacted 2-bromobenzotrifluoride can be observed at -63.43 in the ¹⁹F NMR spectrum.

Nickel(II) bis(bromide) (4*S*,4'*S*)-2,2'-(propane-2,2-diyl)bis(4-benzyl-4,5-dihydrooxazole) ((L2.1**)NiBr₂)**



Complex (**L2.1**)NiBr₂ was prepared according to a previously reported procedure⁵³ and isolated as a dark purple solid in quantitative yield. This complex was used as a reference for the appearance of paramagnetic peaks. ¹H NMR (600 MHz, C₆D₆) δ 20.44 (s, 2H), 8.31 (s, 6H), 7.44 (s, 10H), 3.71 (s, 2H), 0.40 (s, 6H).

Nickel(II) (4-acetylphenyl) (iodide) (4*S*,4'*S*)-4,4'-diisopropyl-4,4',5,5'-tetrahydro-2,2'-bioxazole



(BiOX)Ni(II) aryl bromide complex **2.5d** was prepared according to **General Procedure 2D** using 1-(4-iodophenyl)ethan-1-one (0.4 mmol, 2 equiv, 98.4 mg). In total, 64.2 mg of dark-orange solid was isolated (41% yield). Quantitative NMR experiments using 1,3,5-trimethoxybenzene as an internal standard were not possible in d_6 -benzene due to extremely poor solubility. **^1H NMR** (600 MHz, C_6D_6) δ 7.84 (d, J = 7.6 Hz, 2H), 7.30 (d, J = 9.3 Hz, 2H), 3.58 (s, 1H), 2.51 (s, 1H), 2.15 (s, 3H), 1.63 – 1.11 (m, 18H).

Section 2.7.5: UV-vis Absorption Spectra

General Procedure 2F: UV-vis Experiments

In a nitrogen-filled glovebox, the desired complex was weighed out in a 4 mL vial and dissolved in acetonitrile to afford ~2 mL of 0.005 M (5mM) solution. Approximately 0.5 mL of each solution was then added to a 1-mm-path quartz cuvette, and another 1-mm quartz cuvette was filled with ~0.5 mL of acetonitrile to obtain a blank. **Figures 2.10 to 2.14** display the absorption spectra measured for these solutions.

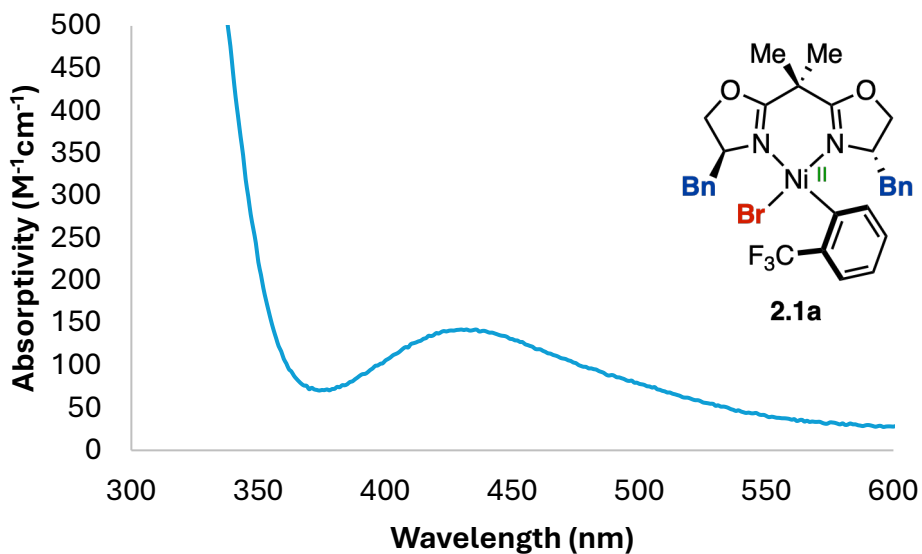


Figure 2.11: UV-Vis absorption spectrum of complex 2.1a (5 mM in ACN, 1 mm path cuvette)

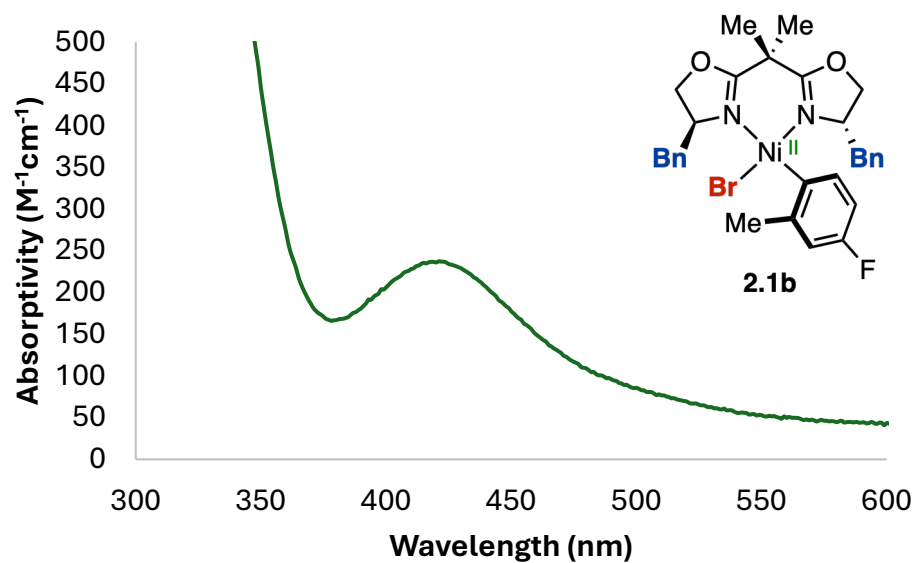


Figure 2.12: UV-Vis absorption spectrum of complex **2.1b** (5 mM in ACN, 1 mm path cuvette).

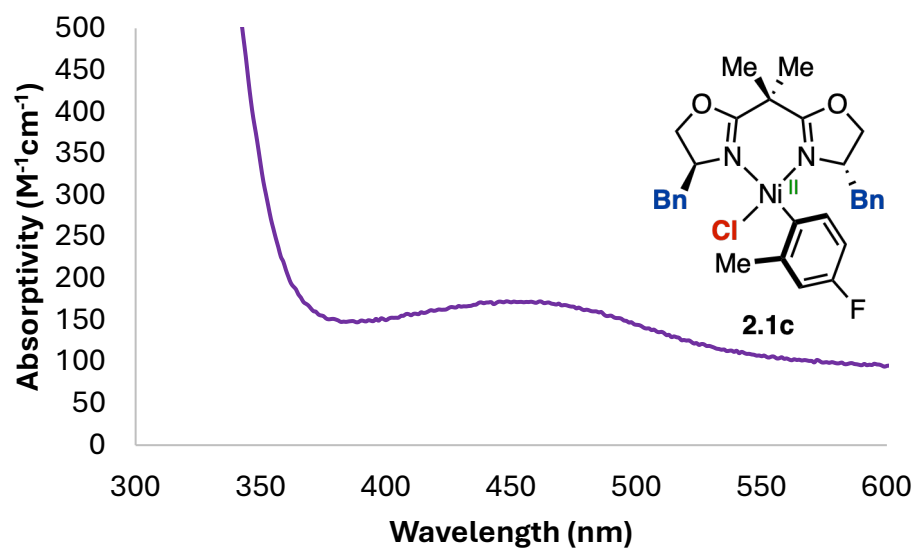


Figure 2.13: UV-Vis absorption spectrum of complex **2.1c** (5 mM in ACN, 1 mm path cuvette)

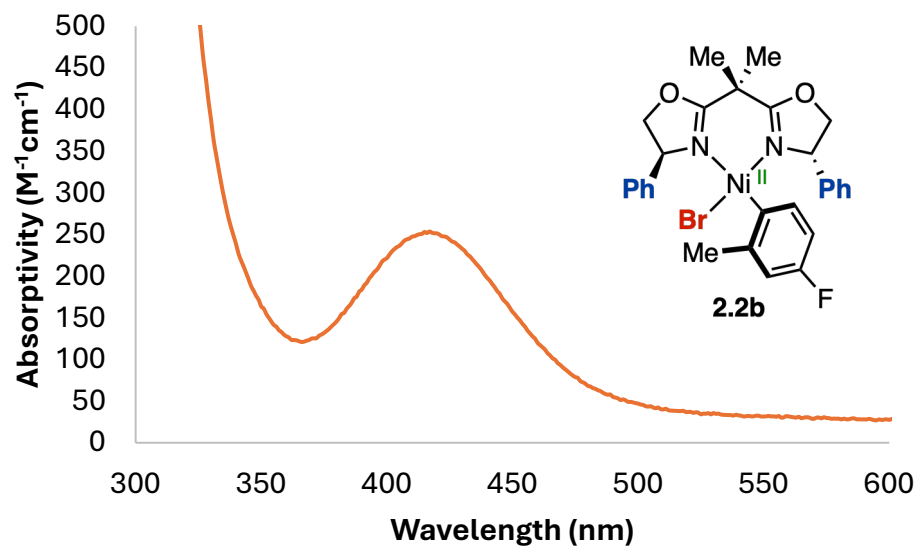


Figure 2.14: UV-Vis absorption spectrum of complex **2.2b** (5 mM in ACN, 1 mm path cuvette).

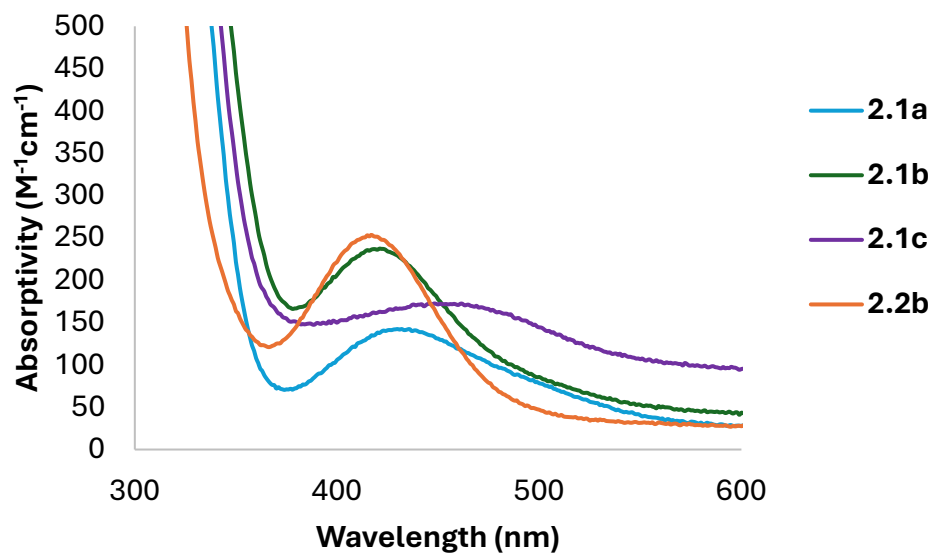


Figure 2.15: UV-Vis spectra overlay.

Section 2.7.6: Complex Stability Studies

Stability in solution

In a nitrogen-filled glovebox, complexes **2.1b** (0.036 mmol, 22.2 mg) and **2.1c** (0.036 mmol, 20.4 mg) were independently dissolved in 1 mL of C_6D_6 (0.036 M) with an added internal standard (1,3,5-trimethoxybenzene). The solutions were kept under nitrogen and analyzed by ^1H NMR at 1-h intervals to quantify the stability of the Ni-complexes in solution. The results are shown in **Figure 2.15**, where both complexes present a similar decay profile, with significant decomposition beginning within the first h.

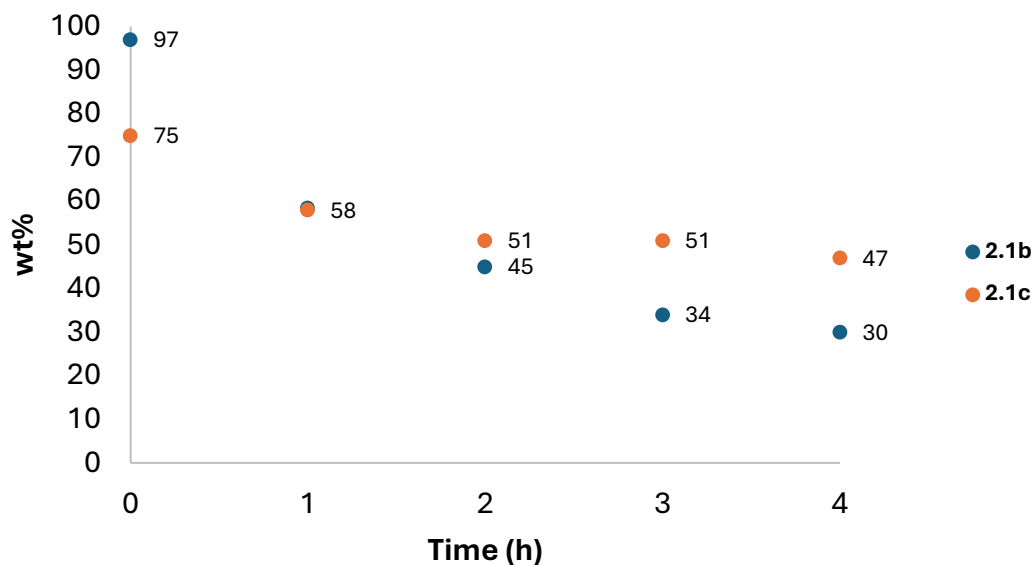


Figure 2.16: *Decomposition studies of 2.1b and 2.1c in C_6D_6 solution.*

Solid state stability

The complexes can be stored in a nitrogen-filled glovebox without appreciable decomposition for multiple weeks. Additionally, the stability of solid samples of complexes **2.1b** and **2.1c** in air was tested. Both complexes (~10 mg) were removed from the glovebox and exposed to open air at room temperature in the fume hood for 12 h. After this time, the purity of the samples was measured by ^1H NMR using C_6D_6 as the solvent and 1,3,5-trimethoxybenzene as the internal standard. The measurements revealed that the wt% of complex **2.1b** decreased from 97% to 70%, and complex **2.1c** decomposed much faster, with its purity decreasing from 75% to 25%.

Section 2.7.7: Geometry Indices Calculation

Geometry index values^{54, 55} (τ_4 and τ'_4) were calculated using the following equations, where α and β are the two greatest dihedral angles in the complex and is $\alpha < \beta$:

$$\theta = \cos^{-1}(-1/3) \approx 109.5^\circ$$

Eq. 2.3

$$\tau_4 = \frac{360 - (\alpha + \beta)}{141}$$

Eq. 2.4

$$\tau'_4 = \frac{\beta - \alpha}{250.5} + \frac{180 - \beta}{70.5}$$

Eq 2.5

Complexes **2.1a** and **2.3a** were determined to have distorted square planar geometries with τ_4 and τ'_4 values close to 0. For comparison, the indices calculated from other previously reported complexes are displayed in **Table 2.1**

Section 2.7.8: Evans Method Calculations

General Procedure 2G: Evans Method Experiment

In a nitrogen-filled glovebox, complex **2.1b** (0.015 mmol, 9.4 mg) was weighed out into a fresh 20 mL scintillation vial. In a separate 20 mL scintillation vial, ~0.80 mL (754.1 mg) of d_8 -toluene and ~0.06 mL (49.5 mg) of toluene were weighed out and mixed. Complex **2.1b** was then dissolved in this mixture and added to an NMR tube. Finally, a sealed glass ampule containing 35 μ L d_8 -toluene and 5 μ L toluene was added to the NMR tube. The ^1H NMR experiment was then conducted using a Bruker Neo 400 MHz instrument at 24 °C. The resulting spectrum was then used to calculate molar magnetic susceptibility (X_m) (Eq. 2.6) by comparing the chemical shift of the benzylic peak of toluene to the benzylic peak of the residual toluene peak in d_8 -toluene. Subsequently, the magnetic susceptibility was used to calculate the effective magnetic moment (μ_{eff}) (Eq. 2.7). Finally, the effective magnetic moment was used to calculate the number of unpaired electrons (n) (Eq. 2.8) using the following equations.^{56, 57}

$$X_m = \frac{6}{1000} \cdot \frac{1}{c} \cdot \frac{\Delta f}{f}$$

Eq. 2.6: Calculation for molar magnetic susceptibility.

$$\mu_{eff} = 798\sqrt{X_m T}$$

Eq. 2.7: Equation for effective magnetic moment.

$$\mu_{eff} = \sqrt{n(n+2)}$$

Eq. 2.8: Equation for number of unpaired electrons.

Concentration (M)	Temperature (°K)	Δf (Hz)	X_m (m ³ mol ⁻¹)	μ_{eff} (μ _B)	n
0.01798	297.15	3.33	2.78E-09	0.725	0.235

Table 2.2: Values derived from the Evans method.

This non-zero magnetic susceptibility is consistent with:

a) The complex has a diamagnetic square planar ground state but is in equilibrium with a paramagnetic tetrahedral conformer.

b) The presence of paramagnetic impurities in the sample. However, it is hypothesized that these are not the cause of these values, as the presence of the most likely paramagnetic impurity (**L2.1**)NiBr₂ was discarded based on the NMR data.

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Chapter 3: Mechanistic Interrogation of Photochemical Nickel-Catalyzed Tetrahydrofuran Arylation Leveraging Enantioselectivity Data

Section 3.1: Abstract

Mechanistic studies of Ni/Ir dual photoredox and photochemical systems lag behind the rapid development of these methodologies. The complexity of these reactions often stems from Ni catalysts' redox promiscuity, leading to deleterious side reactivity via comproportionation, disproportionation, and photolysis events. To better understand these systems, the early years of my PhD focused on investigating a photochemical Ni-catalyzed cross-coupling reaction between aryl halides and THF, mediated by hydrogen atom transfer (HAT). Our aim was to identify the main operative pathway by leveraging product ee data, specifically by examining the step that determines enantioselectivity.¹⁻³ The conclusions were based on the results of stoichiometric experiments, multivariate linear regression (MLR) modeling, time-point experiments, and EPR studies. My role in the success of this project included the synthesis of select bisoxazoline (BOX) ligands, the development of (BOX)Ni(II) aryl halide complexes (described in **Chapter 2**), and the execution of the subsequent stoichiometric experiments and time point reactions.

Ligand synthesis was assisted by Lang Cheng (Oscar) Hung, who also performed detailed characterization of all novel ligands. Oscar also helped with this project through extensive screening (bases, temperatures, light wavelength, Ni sources, additives), substrate scope, and time point reactions (described in **Section**

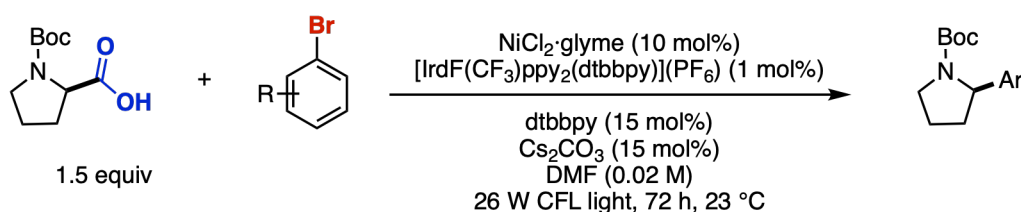
3.6). MLR modeling was completed by Olivia Taylor, who also assisted with the time point reactions. The crystal structures of (BOX)Ni(II) aryl halide complexes were determined by Veronica Carta and Philip Farias. Other authors contributed to ligand synthesis and screening. The manuscript described in this chapter was written predominantly by Ana Bahamonde, with additional edits and contributions from me, Oscar, and Olivia. The following information in **Chapter 3** provides an overview of this manuscript and was written by me.¹

As a point of clarification, Ni-intermediates are numbered with Roman numerals while starting materials, products, and ligands are all prefaced with “3” to indicate they are relevant to **Chapter 3**.

Section 3.2: Irradiation of Ni Species and Subsequent Reactivity

Ni/Ir dual photoredox-catalyzed cross-coupling reactions have evolved significantly since the seminal reports in 2014 by the Macmillan/Doyle and Molander labs.^{4,5} In these initial reports, each group used an aryl halide as one coupling partner and alkyl radical precursors as the other, thereby furnishing C–C bonds. The Molander group used trifluoroborate salts as radical precursors, whereas the Doyle/MacMillan labs used carboxylic acids. Both examples required an excited-state photocatalyst (PC) as a single-electron oxidant to generate carbon-centered radicals, which could then be trapped by Ni species, followed by reductive elimination to afford cross-coupling (**Figure 3.1**).

a) Doyle/MacMillan (2016)



b) Molander Proposal (2016)

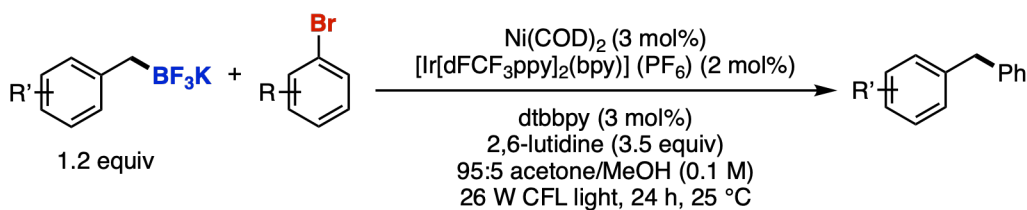


Figure 3.1: Seminal Ni/Ir dual photoredox-catalyzed cross-coupling reactions.

Nickel is a suitable transition-metal catalyst for these systems for several reasons. As discussed in **Chapter 1**, the proclivity of Ni catalysts (with the right ligand choice) to undergo single-electron pathways makes them ideal candidates for

capturing carbon-centered radicals (resulting in a net +1 oxidation). As opposed to traditional C–C cross-coupling methodologies, which require transmetallation from an organometallic nucleophile, radical capture at a Ni center places the coupling partner on the Ni center and raises the oxidation state by +1, making for easier reductive elimination. The field has expanded dramatically because of the many combinations of standard coupling partners (aryl, acyl, alkenyl halides) with alkyl radical precursors (carboxylic acids, trifluoroborate salts, alkyl halides) that are compatible with photochemical conditions, and because of the utility of having a catalytic oxidant/reductant available in the reaction.⁶ Additionally, photoredox strategies are not the only means of generating alkyl radicals for these cross-couplings.

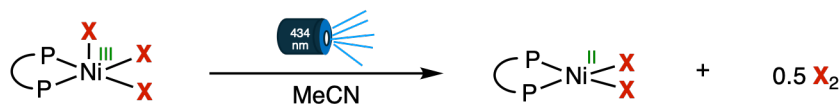
Despite the power of this strategy as an alternative to traditional cross-coupling methods, elucidating the mechanism of Ni/Ir dual photoredox systems remains notoriously difficult. These reactions are traditionally run under continuous irradiation to generate an excited-state photocatalyst, which then serves as either a photoreductant, photooxidant, or energy-transfer species. However, the selectivity of a desired intermediate reacting with light or a photocatalyst is extremely low and difficult to predict, as each newly generated intermediate can react with light or a photocatalyst instead of continuing along the product-forming pathway. Because of this, side reactions that can occur in these systems are numerous and unpredictable.

Elucidating these mechanisms is dependent on a few factors: first, understanding what can react in solution. As the catalytic cycle progresses and different Ni species are generated, these species may react with light or the photocatalyst rather than follow the desired product-forming pathway. Knowledge of such deleterious reactivity is crucial for optimizing a system. Second is understanding what (at any given point of the reaction) is the Ni resting state, thus presenting the highest concentration and being more likely to engage in productive catalysis.⁷ Despite Ni's ability to access odd-electron configurations (Ni(I) or Ni(III)), it is very unlikely at any given point in the reaction that they are in high concentration, due to their high reactivity. This means that when determining what can react within these systems, it is equally important to consider what is most likely to be present in the highest concentration. These are the principles that guided our mechanistic investigation and will be discussed in this chapter.

Before critically examining any Ni/Ir system, it is useful to understand the possible reactivities of different catalytically relevant intermediates under light, either alone or in the presence of a photocatalyst. This ultimately provides context for why certain mechanistic steps are proposed. I will cover this section in three parts: how Ni-intermediates can react with blue light, how Ni-intermediates can react with blue light in the presence of an Ir PC, and how Ni-intermediates can react with UV light.

It is a misconception that the presence of blue or UV light in these reactions affects only the Ir PC and not any Ni species. Given that the reactions are under constant irradiation, it is useful to know how likely it is for intermediates to undergo photochemical steps independently of the photocatalyst. Reports from the Nocera group indicate that Ni(III) trihalide species ($X = \text{Cl}, \text{Br}$) can liberate a halogen radical upon blue-light irradiation, causing a net reduction (-1) of Ni.^{8,9} Subsequent reports by the Mirica group showed this was also possible with cationic Ni(III) dihalide species (**Figure 3.2**).¹⁰ These findings were essential to initial mechanistic hypotheses and explained how highly reactive Ni(III) species could react. However, in the context of catalytic systems, it is unlikely that Ni(III) or cationic Ni(III) are persistent enough to react preferentially over Ni-species that are in higher concentration.

a) Nocera (2015)



b) Mirica (2021)

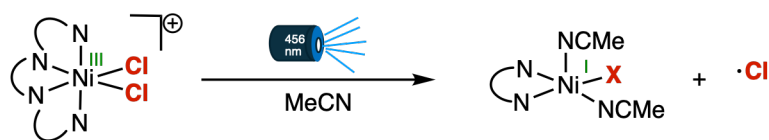
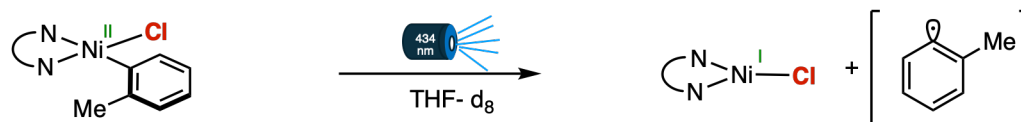


Figure 3.2: Studies by the Nocera and Mirica groups detailing the reactions of Ni(III) complexes in the presence of light.

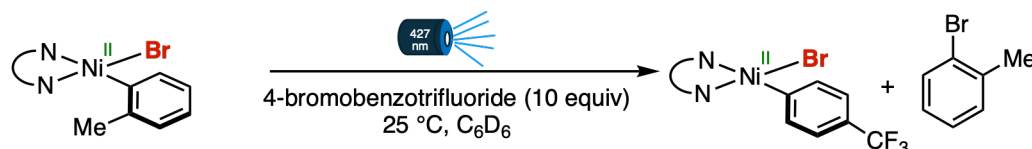
The Ni species that are likely to be in the highest concentration in Ni-catalyzed reactions are traditionally Ni(II) species. In particular, Ni(II) pre-catalysts such as Ni(II)

bromide or chloride and Ni(II) aryl halides are proposed as common catalytic resting states. At any given time, the light or photocatalyst is likely to engage these species because they are the most abundant *in situ*. In a 2020 study conducted by the Doyle lab, it was found that a Ni(II) aryl chloride would undergo homolysis of the C(sp²)–Ni bond upon blue-light irradiation, generating an aryl radical (**Figure 3.3a**).¹¹ In a subsequent study conducted in 2024, the Doyle lab found that Ni(II) aryl bromide complexes could undergo aryl halide exchange (in the presence of excess exogenous aryl bromide) upon irradiation at 427 nm, with or without a photocatalyst (**Figure 3.3b**).¹² This means that under photochemical conditions, the oxidative addition of aryl halides is fast and reversible.^{13, 14} Finally, a recent report by the Reid group showed that photoactivation of Ni(II) chloride with 360 nm UV light triggers photolysis, generating Ni(I) chloride and a chlorine radical (**Figure 3.3c**).¹⁵ One final experiment conducted by the Doyle lab showed that a Ni(II) aryl alkyl species can undergo the otherwise challenging reductive elimination in the presence of light at room temperature (**Figure 3.3c**).¹²

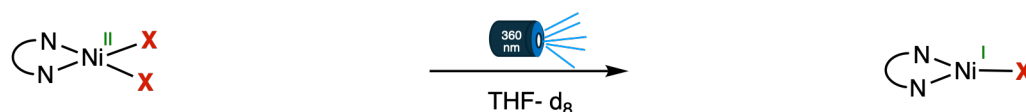
a) Doyle 2020: Aryl radical generation



b) Doyle 2024: Reversibility of oxidative addition under photochemical conditions



c) Reid 2025: Photolysis of halide ligand forming Ni(I) and halide radical



d) Doyle (2024): Photochemically induced reductive elimination

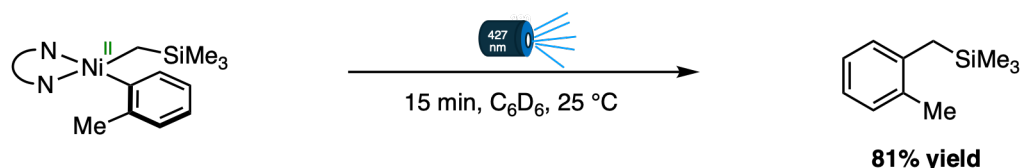


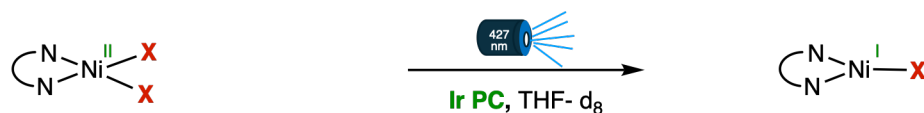
Figure 3.3: Reactivity of Ni(II) species in the presence of blue light and UV light.

As discussed in **Chapter 1**, Ni(II) species have considerably higher barriers to reductive elimination than Pd(II) counterparts, meaning external forces (such as oxidizing to Ni(III) or excitation) are necessary. The Doyle group found that when a Ni(II) aryl-alkyl complex was kept in the dark, only a trace amount of cross-coupling product was observed, whereas under 390 nm or 427 nm light, the cross-coupling product formed within 5 min, with almost full conversion by 15 min (**Figure 3.3d**). This establishes the relevance of this Ni species as a possible intermediate in cross-

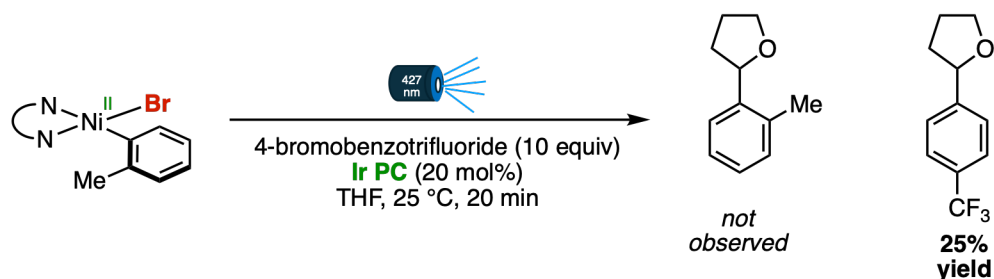
coupling processes, especially given that reductive elimination from this complex can be a product-determining step in $C(sp^3)-C(sp^2)$ cross-coupling reactions.

The Ir photocatalysts in these systems serve two purposes: substrate activation (as in the initial reports)^{4, 5} to generate carbon-centered radicals, and reaction with Ni intermediates. Extensive studies have been conducted to determine whether Ir photocatalysts engage Ni species via a triplet-triplet energy transfer (EnT) mechanism or a photoinduced electron transfer (PET) mechanism. My work in the Bahamonde lab has not concerned the direct elucidation of EnT or PET, but a series of recent reports have shown evidence for energy transfer from the excited state photocatalyst to Ni-intermediates.¹⁶⁻²⁰ A common method to uncover these mechanisms is to use shorter-wavelength light (UV light) without an Ir photocatalyst and assess whether similar results can be achieved under reaction conditions with blue light (427 nm) in the presence of a photocatalyst. The idea behind these experiments is that lower-wavelength light can directly excite Ni. If subsequent reactivity mimics conditions that invoke blue light and a photocatalyst, this is evidence that electron-transfer steps are not required for the observed reactivity. An example of this is a report from the Reid group demonstrating Ni–Cl bond photolysis upon blue-light irradiation of a Ni(II) dihalide pre-catalyst in the presence of an Ir photocatalyst. This is the same reactivity observed when irradiating a Ni(II) dihalide pre-catalyst at 360 nm (**Figure 3.4a**).¹⁵

a) Reid 2024



b) Doyle 2024



c) Doyle 2024

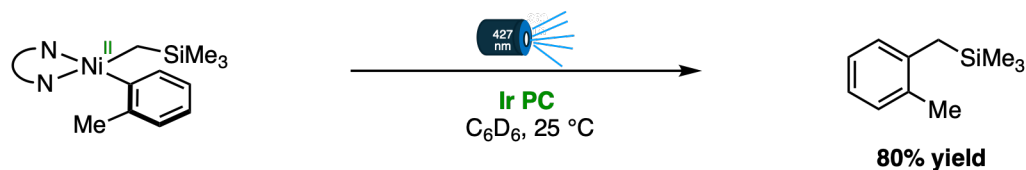


Figure 3.4: Reactivity of Ni(II) complexes in the presence of blue light and photocatalyst.

Further demonstrating the predominance of EnT pathways, the Doyle lab showed the reversibility of oxidative addition via crossover experiments (**Figure 3.4b**) and the reductive elimination of the Ni(II) aryl-alkyl species in the presence of the photocatalyst (**Figure 3.4c**).¹² These results are consistent with those shown in **Figures 3.3b** and **3.3d**, indicating that the photocatalyst is likely undergoing energy transfer to the Ni complex. The question may arise: why do we even need to use a photocatalyst (which is incredibly expensive) if simple irradiation with blue or UV light will give comparable reactivity in many cases? A specific example of this instance will be discussed in later sections.

Section 3.3: Further Development of Ni/Ir Dual Photoredox Systems

The most appealing aspect of Ni/Ir dual photoredox strategies is their versatility for bond formation. As discussed, pairing a traditional coupling partner, such as an aryl halide, with a coupling partner bearing a redox-active leaving group as a radical precursor is an excellent method for forming C–C bonds. The importance of the redox-active leaving group, however, is not the identity of the group itself but rather its function as a radical precursor. Therefore, reaction development has shifted toward limiting the need for redox-active leaving groups as radical precursors and instead generating radicals from starting materials that do not require pre-functionalization.

In 2016, the MacMillan lab leveraged the low bond dissociation energy (BDE) of C(*sp*³)–H bonds in *N*-Boc pyrrolidine to afford α -*N*-arylation cross-coupled products.²¹ The success of this method depended on the presence of an exogenous hydrogen-atom transfer (HAT) agent to generate the carbon-centered radical used in cross-coupling (**Figure 3.5**). This method did not require a redox-active leaving group to generate the alkyl radical; instead, it used a HAT agent, 3-acetoxyquinuclidine, to generate it. Their mechanistic proposal details the excited-state Ir photocatalyst oxidizing the 3-acetoxyquinuclidine to form the subsequent radical cation (highlighted in the red square). Subsequently, the nitrogen radical cation performs the HAT as the resulting N–H bond has a higher BDE than the *N*-Boc pyrrolidine's α -*N*

C(sp³)-H bond. This carbon-centered radical is then captured by a Ni-intermediate to furnish the cross-coupling product.

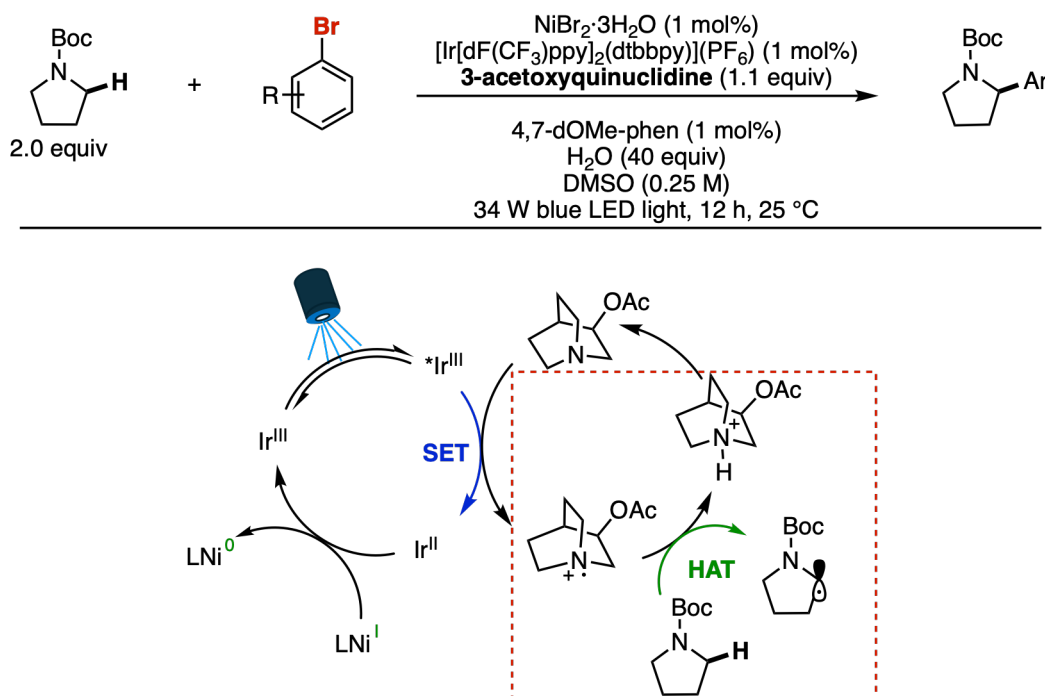


Figure 3.5: Ni/Ir dual photoredox catalyzed cross-coupling using exogenous HAT agent (3-acetoxy quinuclidine).

While inspiring, this report still has the Ir PC acting in multiple roles. The photocatalyst is used to oxidize the HAT agent and reduce Ni species, thereby serving multiple roles. Overall, this makes the Ni/Ir systems more difficult to investigate, as the photocatalyst can be reacting with either the substrate or Ni species at any given time. The next logical step, then, would be to remove a HAT agent that the Ir PC needed to oxidize and instead relegate the Ir PC exclusively to reacting with the Ni.

A simpler system emerged shortly after, based on independent reports from the Doyle and Molander labs. Each report detailed a THF-arylation facilitated by a

halogen radical formed *in situ*, which functioned as a HAT agent.^{2, 3} These reports used different Ni pre-catalysts and proposed different mechanistic pathways. The Doyle report, which utilized Ni(COD)₂ as the pre-catalyst, proposes oxidative addition into Ni(0) (**I**) to form Ni(II) aryl halide complex (**II**). Subsequently, they propose that **II** is oxidized by the excited-state Ir PC via PET to afford the cationic Ni(III) aryl halide complex **IIIa** and a reduced photocatalyst. Based on the work of the Nocera⁸ and Mirica¹⁰ groups, who independently showed photoelimination of halide radicals from Ni(III) species (refer to **Figure 3.2**), the Doyle group proposed that intermediate **IIIa** would undergo reductive photolysis to afford cationic Ni(II) aryl (**IVa**). Subsequently, the liberated chlorine radical performs HAT to generate the carbon-centered radical, the coupling partner in this reaction. This radical is then trapped by **Va** to afford cationic Ni(III) aryl alkyl species (**VIa**), which rapidly reductively eliminate to afford the cross-coupled product and cationic Ni(I) (**VIIa**). The catalytic cycle is closed by the reduction of **VIIa** with the reduced photocatalyst, regenerating **I** and simultaneously closing the Ni and Ir catalytic cycles.

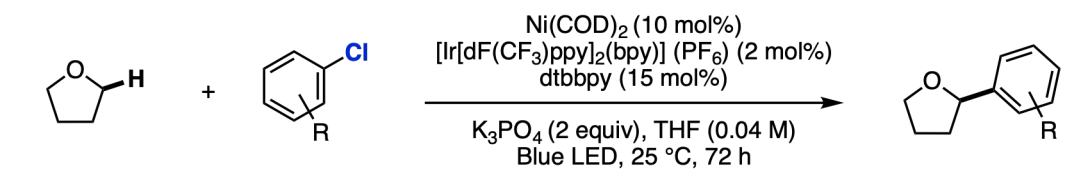
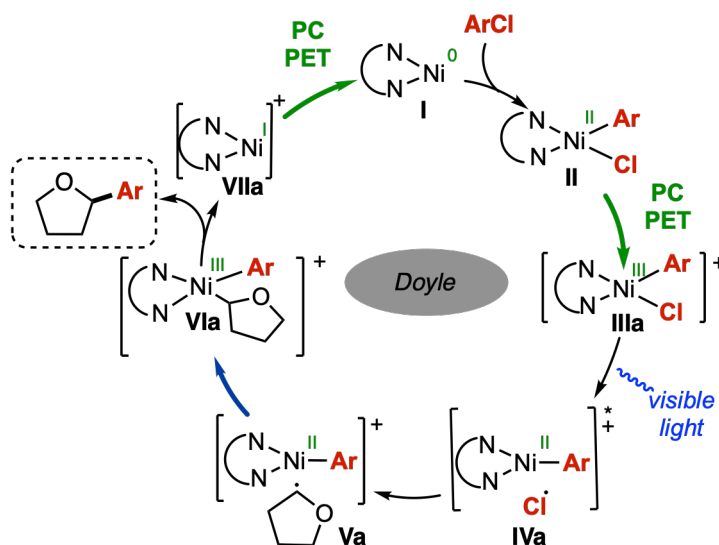


Figure 3.6: Doyle 2016 report describing THF-arylation via HAT agent generated *in situ*.

Mechanistic understanding has progressed considerably since this proposal, with further studies on photochemically induced reductive elimination and the role of Ir photocatalysts in these systems. However, in 2016, this mechanism was considered cutting-edge given the state of the field at the time, only two years after the seminal reports. The main drawback of this mechanistic proposal is the transience of the Ni species proposed to capture the THF carbon-centered radical. The presence of a cationic Ni(II) species (**IVa** or **Va**) at any given time in solution is likely a much lower concentration than Ni(II) aryl halide complex (**II**). The proposed step that **II** is oxidized is feasible given its relative concentration *in situ*, but the

subsequent radical capture at **Va** is unlikely, given the instability of this species, which is proposed to capture a comparatively unstable radical. Similarly, the restoration of Ni(0) (**I**) through a reduced photocatalyst is also unlikely, given the instability of **VIIa**, as well as it being easier for the reduced photocatalyst to reduce any other proposed Ni species (aside from **I**), as they are all in a higher oxidation state.

A more complex issue to investigate (which was eventually tackled in the Doyle lab's 2024 report)¹² is the role of the photocatalyst in these reactions. The Doyle lab's 2016 proposal invoked a PET to generate **IIIa**, which was needed to generate the *in situ* HAT agent. While this mechanism involves only the Ir photocatalyst interacting with Ni, it is difficult to ascertain, without further experiments, whether the chlorine radical is generated this way or by other means.

The other 2016 paper from the Molander lab employed a Ni(II) pre-catalyst and assigned the Ir PC an EnT role, since the photocatalyst was not strongly oxidizing (**Figure 3.7**). The first proposed step in this mechanism is oxidative addition into Ni(0) (**I**) to form Ni(II) aryl bromide complex (**II**). It is then proposed that excited-state Ir PC undergoes EnT with **II**, forming excited-state Ni(II) aryl halide (**II***). This triggers Ni–Br bond homolysis to afford Ni(I) aryl intermediate (**IV**) and bromine radical. It is then proposed that the bromine radical will perform HAT on THF, generating a carbon-centered radical that will then recombine with **IV**. The resulting Ni(II) aryl THF species (**V**) will then undergo reductive elimination to afford the cross-coupled product and **I**.

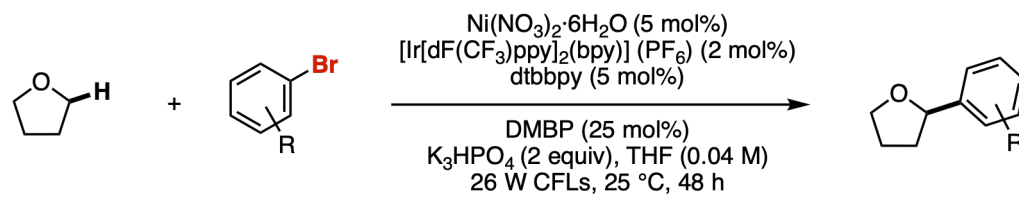
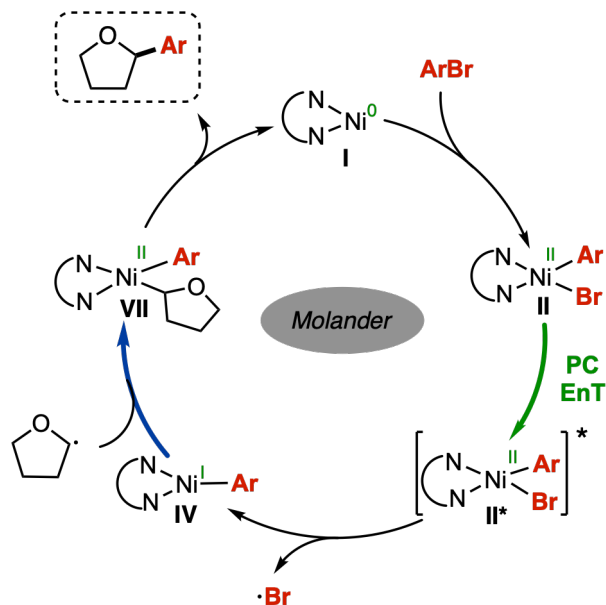


Figure 3.7: Molander proposal.

Like the 2016 Doyle proposal, this one has multiple shortcomings. First is the question of how Ni(0) (I) is accessed, considering a Ni(II) pre-catalyst is used. This would mean that two subsequent reductions would need to occur in the absence of reductants *in situ*; the photocatalyst is proposed to participate only in EnT. To give the Molander proposal its due, it was only years later that studies showed that EnT with Ni(II) pre-catalysts could generate Ni(I) species (see **Figure 3.4a**).¹⁵ Additionally, it was only years later that the viability of oxidative addition into Ni(I) species was shown.²²⁻²⁴ Still, the explanation for how low-valent Ni is generated is absent from this

proposal. The second issue is that the trapping of the THF radical by **IV** is unlikely due to the transient nature of Ni(I) species and the transient nature of radicals. For successful radical trapping to occur, we envision the radical must be captured by 1) a Ni-species that is in high concentration and 2) a Ni-species that is stable enough under photochemical conditions to persist in solution.

Section 3.4: Initial Mechanistic Hypotheses

What we found particularly interesting about both Doyle's and Molander's proposals was the *in situ* generation of the HAT agent. In both proposals, the Ir PC reacts only with Ni to generate the HAT agent. This somewhat simplifies the mechanistic picture by limiting side reactions between Ir and other reagents. However, identifying which Ni intermediates are involved and the mechanism of Ni/Ir interaction (PET or EnT) remained a challenge. It is also interesting to note that both proposals involve the Ni(II) aryl halide species interacting with the excited state photocatalyst, undergoing EnT in the Molander lab's proposal or PET in the Doyle lab's proposal. This behavior was shown to be relevant in the Doyle lab's subsequent 2024 report and was previously discussed in **Section 3.2**. The findings that Ni(II) aryl halide species, under photochemical conditions, react with the Ir PC to trigger Ni–C bond homolysis, generating an aryl radical, or to induce reductive elimination (**Figure 3.3a** and **Figure 3.3b**) are incredibly helpful for crafting mechanistic proposals, yet this was unknown at the time we started our work. At the outset of our research, we thought that the photocatalyst reacting with this Ni(II) species is not unlikely *per se*, but it is not part of the predominant product-forming pathway in this reaction.

Alternatively, we envisioned that the Ni(II) aryl halide species (**II**) captured the THF radical, furnishing the desired cross-coupled product (**Figure 3.8**). We hypothesized that active Ni(I) catalyst (**III**) is generated from the NiCl₂·glyme pre-

catalyst either via EnT followed by homolysis of the Ni–Cl bond or via direct reduction by the excited-state photocatalyst. Ni(I) (**III**) then undergoes oxidative addition to form Ni(III) (**IX**). Taking inspiration from the Nocera group's work, in which a halide radical was generated from a Ni(III) species,⁸ we initially envisioned that energy transfer at **IX** would generate the excited-state Ni(III) species (**IX***). This highly reactive, excited Ni would then undergo reductive photolysis of one of the halogen ligands to form a halide radical and Ni(II) aryl halide species **II**. The halide radical would then perform HAT on THF, which would be captured by **II**, forming Ni(III) (**X**). Reductive elimination would occur rapidly, restoring Ni(I) to Ni(III), thereby perpetuating the catalytic cycle.

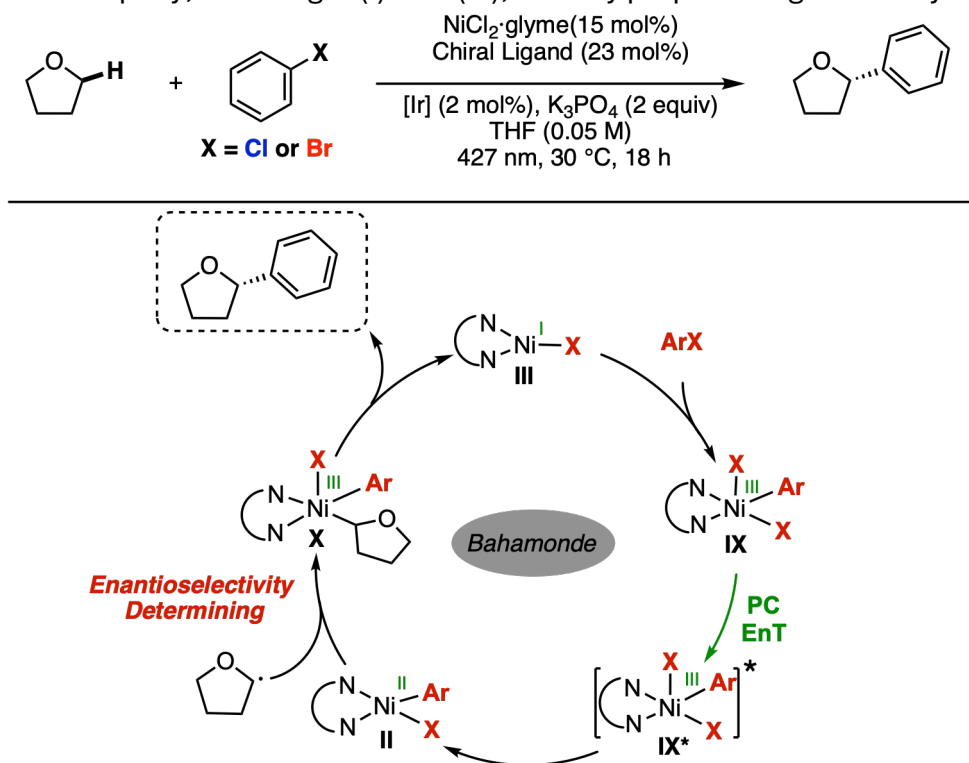


Figure 3.8: Initial mechanistic hypothesis.

While the original proposals focused on Ni(II) aryl halide (**II**) interacting with the excited state photocatalyst, our initial thought was that this was the Ni species responsible for radical capture. We envisioned a simple way to test this by running stoichiometric experiments with complex **II** to determine whether it could capture a carbon-centered radical and undergo reductive elimination to afford the cross-coupled product (**II**→**X**). Had we chosen to investigate the reaction using the ligand reported in the initial reports, di-*tert*-butyl bipyridine (dtbppy), it would not have been possible to state whether product formation resulted from **II** capturing the radical and subsequent reductive elimination, or from another pathway. Product formation alone is not definitive confirmation that our predicted path is the one we are following.

Considering how to ensure that this was the pathway through which radical capture was occurring, we noted that the product-determining step (**II**→**X**) would also be the enantioselectivity-determining step of the reaction. Therefore, we opted to use chiral ligands to compare the product ee obtained under stoichiometric and catalytic conditions. This was to be a direct probe of the product-determining step of the reaction while also giving insight into product formation through minor pathways. We believed that if the ee matched, this was the predominant step for product formation. If there was a discrepancy in ee, this Ni species was not responsible for THF radical capture as the main operative pathway.

As described in **Chapter 2**, developing conditions for synthesizing **II** in high purity proved challenging. Another challenge we faced was developing conditions to generate a THF radical without using Ir PC, to prevent the photocatalyst from reacting with the complex. Finally, identifying and ruling out other competitive pathways was necessary to fully support our proposed mechanism. This was made possible by leveraging enantioselectivity data and is complementary to the Doyle report, published at a similar time, as we each took different approaches to probe the mechanism.^{1, 12}

Section 3.5: Enantioselective THF-Arylation w/ HAT Agent Generated *in situ*

Our model reaction screening began with methyl 4-chlorobenzoate (**3.1a**) as the coupling partner to THF (**Figure 3.9**). The initial screening evaluated multiple chiral ligand scaffolds (such as PyOX, BiOX, PyBOX, BiIM, and BOX). When comparing the results of the initial screening (all of which were synthesized from *L*-valinol), the BOX scaffold afforded the highest yield and ee. We then decided to proceed with the BOX ligand as our scaffold of choice. The synthesis and screening effort was assisted by Lang Cheng (Oscar) Hung and two undergraduate students, Alfredo Cedeño and Paul Nguyen, approximately one year into the project. To expedite the ligand screening, MLR was used to analyze results from ligands screened in the reaction and to guide subsequent ligand synthesis.²⁵⁻²⁸ This work was conducted by Olivia Taylor. This was an iterative process in which the experimental data informed the model, which then predicted ligands that would afford high ee. Oscar and I would then synthesize these ligands, screen them, and obtain the ee of the resulting product **3.2a**. These results, especially if they disagreed with the predictive model, were then used to revise the model and improve its predictive capabilities.

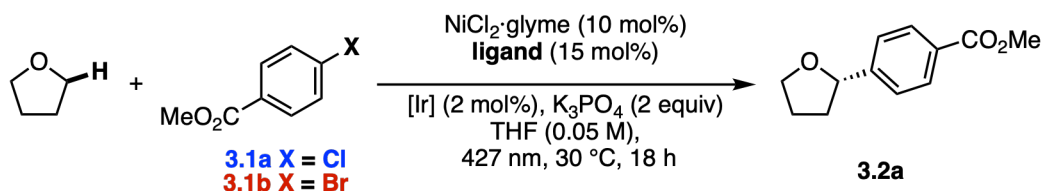
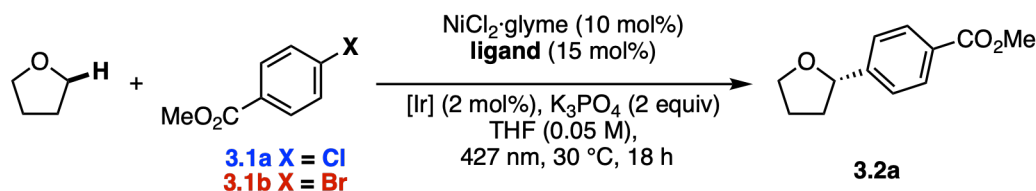
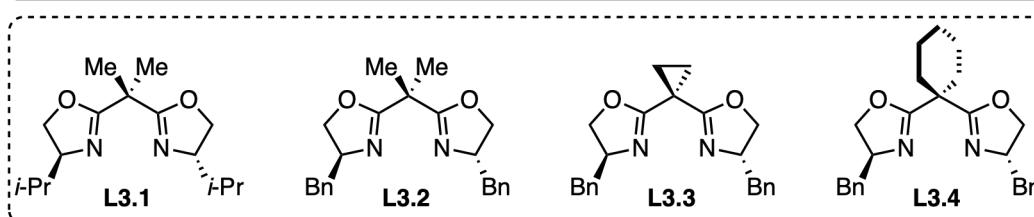


Figure 3.9: Initial reaction screening.

During screening, we opted to try the analogous aryl bromide **3.1b** to see whether aryl bromides would afford higher yields (**Table 3.1**). Surprisingly, across all screened chiral ligands, we observed a difference in **3.2a** enantioselectivity depending on whether **3.1a** or **3.1b** was used. We conducted time-course studies to rule out a decrease in product ee over the course of the reaction, due either to ligand degradation or to product racemization (described further in **Section 3.8.7**). Additional experiments included subjecting enantioenriched product **3.2a** to the reaction conditions with exogenous aryl bromide and running the reaction in the presence of KBr (described in further detail in **Section 3.8.7**). These reactions confirmed the product's instability under prolonged reaction conditions, but we did not observe any degradation of ee, indicating that the lower ee observed when using **3.1b** was not due to ligand degradation or product racemization.



entry	ligand	other variations	ArCl	ArBr
1	L3.1	none	30%, 50% ee	25%, 22% ee
2	L3.2	none	40%, 64% ee	30%, 24% ee
3	L3.3	none	33%, 60% ee	25%, 30% ee
4	L3.4	none	40%, 64% ee	20%, 14% ee
5	L3.4	No light, PC, or Ni	n.d.	n.d.
6	L3.4	No PC, 390 nm light	n.d.	32%, 52% ee
7	L3.4	10 °C	63%, 78% ee	33%, 58% ee
8	L3.2	NiBr ₂ ·glyme	23%, 42% ee	30%, 16% ee

Table 3.1: Initial reaction screening shows a discrepancy in ee when employing **3.1a** compared to **3.1b** as the aryl halide starting material.

One result we were particularly interested in was **Entry 6**, where we used 390 nm UV light instead of 427 nm blue light and omitted the photocatalyst. Interestingly, the reaction worked for **3.2b** but not **3.2a**. As previously discussed, experiments like this can help elucidate the role of the photocatalyst in a system (EnT or PET). Presumably, under these conditions, the Ni(II) pre-catalyst can be reduced even without a photocatalyst. The Reid group subsequently provided evidence that Ni(II) dihalide pre-catalysts form Ni(I) species either under 390 nm light or under 427 nm light with an Ir PC.¹⁵ These results are rationalized as an EnT pathway. If Ni(I) formation is consistent in both reactions using **3.1a** and **3.1b**, there must be a reason the reaction with aryl chloride does not work. A possible hypothesis is that Ni(I)

oxidative addition into aryl chlorides is slower than into aryl bromides.^{22, 24} Additionally, the 52% ee of this reaction is much higher than that of the same reaction run with 427 nm light and the photocatalyst. This is another example in which changing the conditions alters the product's enantioselectivity.

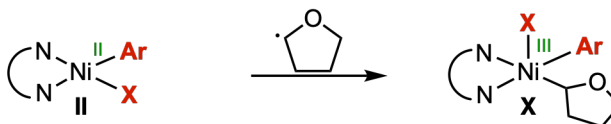
When analyzing the data in **Table 3.1**, we focused on why changing the aryl halide (and the nickel source, as explained later) affected the product ee. We did not extensively examine why changing the light source in this case affected the ee. I propose that this is likely the result of a different enantioselectivity-determining step. Using UV light and maintaining constant irradiation would excite more Ni-intermediate species than using blue light and an Ir PC, which is limited by the catalytic amount of photocatalyst. In other words, using blue light and photocatalysts, rather than strictly UV light, to promote reactivity can alter the mechanism, which should be evaluated in the context of each individual system. In the case of THF-arylation, using blue light and a photocatalyst gave us the widest scope (across both aryl bromides and aryl chlorides), which is why we examined the system under these conditions rather than using UV light.

To rationalize the discrepancy of product enantioselectivity when switching from **3.1a** to **3.1b**, we considered two mechanistic hypotheses: 1) changing the aryl halide changed the mechanism, or 2) both conditions follow analogous mechanisms, and the halogen of the aryl halide is involved in the enantioselectivity-determining

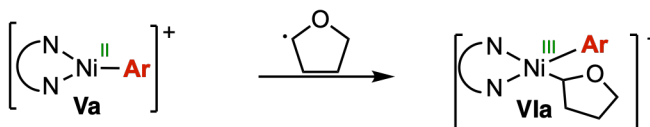
step of the reaction. When considering hypothesis 2, Ni(II) aryl halide (**II**) was the Ni species we initially predicted would capture the radical. We opted to test the second hypothesis by synthesizing (BOX)Ni(II) aryl halide complexes (**II**) bearing bromide or chloride halogen ligands (**Figure 3.10a**). The idea was that by varying the halogen in these complexes, we could directly observe any change in ee.

The synthesis of these complexes (**II**) has been described in **Chapter 2** of this thesis. By independently synthesizing **II** and developing conditions to generate a THF radical *in situ*, we proposed that **II** could trap the radical and subsequently undergo reductive elimination to afford the product. This would allow us to test if the halide on the Ni was having a drastic effect on the ee. We could then compare the ee of **3.2a** generated via the stoichiometric experiments with that of the catalytic reaction. If the ee obtained under the stoichiometric conditions is in accordance with that measured under the catalytic conditions, this would strongly suggest that this is the Ni complex that traps the radical species.

a) Bahamonde Proposal (2024)



b) Doyle Proposal (2016)



c) Molander Proposal (2016)

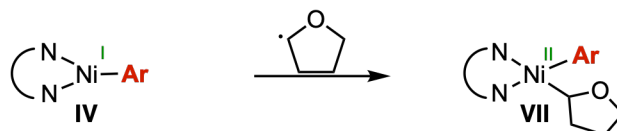


Figure 3.10: Summary of THF radical trapping steps.

As previously mentioned, the Doyle and Molander mechanisms' (**Figure 3.10b** and **Figure 3.10c**) main drawback is radical capture via transient Ni-species. Additionally, the previously proposed mechanisms did not include a halogen in the step that determines enantioselectivity. In contrast, our initial screening with multiple chiral ligands showed a change in product ee when using **3.1a** or **3.1b**, indicating that the aryl halide halogen is key to the enantioselectivity-determining step. Trapping at **Va** or **IV** does not explain why changing the aryl halide affects the ee. Our proposal addresses both shortcomings: first, by making the halogen a key component of **II**, and second, by noting that this Ni-intermediate is likely present at a higher concentration in solution than **Va** or **IV**. As previously mentioned, shortly before this research was published, the Doyle lab conducted their own mechanistic investigation of this system, revising their 2016 work to propose **II** as the predominant Ni species that captured the radical to afford the cross-coupled product.¹² The Doyle

lab's approach was complementary to ours, taking different approaches to the same system, ultimately leading to similar conclusions.

To rationalize how the halide on **II** affects product ee, additional statistical modeling was performed by Olivia Taylor to compare the properties of **II** when bearing either a bromide or a chloride. I will not cover this work in detail, but I want to highlight the distinguishing parameter between bromide and chloride complexes. The average angle among the carbons of the aromatic system varied with halogen identity, possibly due to non-covalent interactions that occur only when bromide is present (**Figure 3.11**). This phenyl ring distortion (labeled γ) showed the strongest correlation with the observed ee, while other possible descriptors had a much smaller effect.

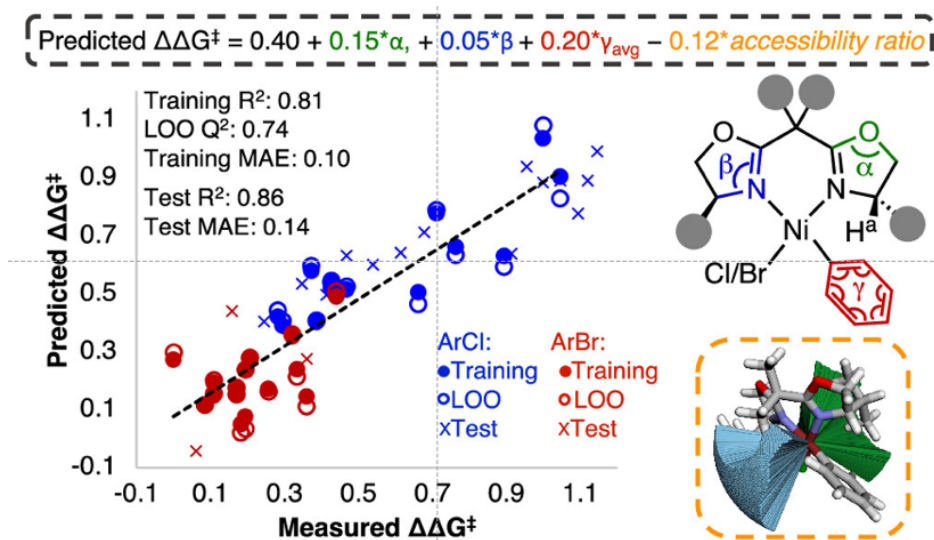
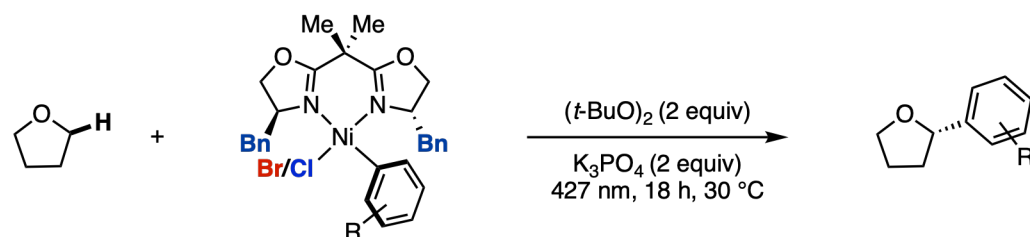


Figure 3.11: Multivariate linear regression (MLR) model.

Section 3.6: Mechanistic Investigation

To probe the mechanistic step described in **Figure 3.10a**, I synthesized a series of (BOX)Ni(II) aryl halide complexes (**II**) (BOX = **L3.2**) (**Table 3.2**). A detailed procedure for the synthesis of these complexes is described in **Chapter 2** and in our other published work.²⁹ I synthesized four complexes, two of which bore a bromide ligand and the other two bore a chloride ligand. An important feature when deciding which targets to synthesize was choosing aryl halides that were competent coupling partners in the catalytic reaction. After obtaining the product ee from the catalytic reaction, I ran the corresponding stoichiometric experiment for each complex and compared the results (**Table 3.2**). Conditions for generating the THF radical were adapted from a report using di-*tert*-butyl peroxide (*t*-BuO₂) under thermal conditions.³⁰ To our delight, the products generated in the stoichiometric experiments afforded near identical ees to the products formed under catalytic conditions, thus strongly suggesting that **II** is the Ni species that traps the THF carbon-centered radical, and the halide strongly influences the resulting ee (**Table 3.2 Entries 2 and 4**).



entry	aryl halide	catalytic data	stoichiometric data
1		24% ee 30% yield	25% ee 47% yield
2		29% ee 16% yield	28% ee 60% yield
3		68% ee 21% yield	68% ee 56% yield
4		61% ee 4% yield	63% ee 17% yield

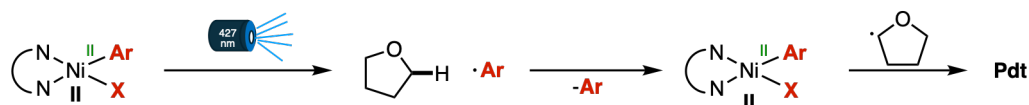
Table 3.2: Results from stoichiometric experiments.

While optimizing the procedure for the stoichiometric experiments, I ran initial experiments using (dtbbpy)Ni(II)o-tol bromide. Interestingly, when screening the light source, product formation was still observed at 390 nm or 427 nm in the absence of peroxide. This is consistent with the Molander report, which observed product formation upon irradiating Ni(II) aryl halide (**II**) dissolved in THF.³ However, product formation in these examples is only possible through degradation of the complex itself. The mechanistic scenario where this can occur is described below (**Figure 3.11a**). Upon irradiation, **II** will cleave the Ni–C bond, forming an aryl radical. This quickly performs HAT, generating the THF radical. This can either be trapped by a separate molecule **II** or alternatively be trapped by the previously formed Ni(I) halide

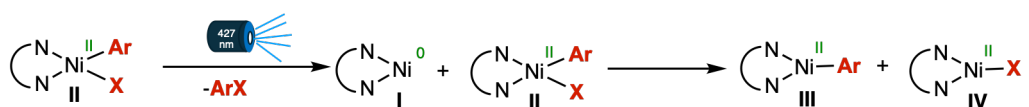
(IV). Additionally, the newly formed Ni(I) halide could undergo comproportionation/disproportionation reactions, thereby accelerating degradation of **II** and hampering product formation. Given that we still see the formation of product under these conditions, it is likely that the THF radical is captured by residual unreacted **II**. However, we do not believe this is the primary operative pathway in our stoichiometric experiments with peroxide. If this scenario were true, the maximum yield would be 50%. For every THF radical generated, one molecule of the complex would have to be sacrificed as an aryl radical precursor.

In two examples (**Entries 2** and **3**), the product yield is above 50%, leading us to believe that the oxygen-centered radical from the cleaved peroxide acts as the HAT agent, as shown in **Figure 3.11c**. The lower yields in the other stoichiometric experiments (**Entries 1** and **4**) can be rationalized by the competitive pathway described above, which reduces the availability of **II**. However, the similar ees obtained in these reactions, compared with those in their catalytic reactions, suggest that radical trapping and subsequent reductive elimination still occur at **II**. If another product-forming pathway were occurring under the stoichiometric reaction conditions, the ee would change.

a) Sacrificial complex for Aryl Radical Formation to Perform HAT



b) Photochemically Induced Reductive Elimination



c) Productive Product Forming Pathway

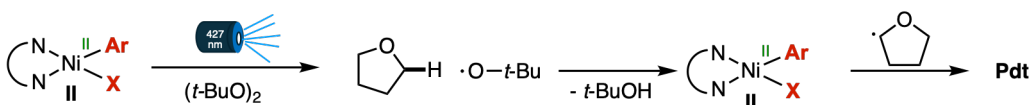


Figure 3.11: Possible pathways of complex **II** under irradiation.

A final deleterious pathway that can occur is light-induced reductive elimination of **II**, forming Ni(0) **I** (**Figure 3.11b**). This Ni(0) has two possible pathways: oxidative addition into the re-formed aryl halide or comproportionation with residual **II**. This results in two Ni(I) species, **III** and **IV**. Product formation can still occur from either of these Ni species (as will be discussed later), but we do not believe it is the predominant pathway. This is because the enantioselectivity would change if a different Ni species captured the THF radical. This is why using a chiral ligand can be useful in these systems, as using an achiral ligand will always afford a racemic product, no matter the product-determining step.

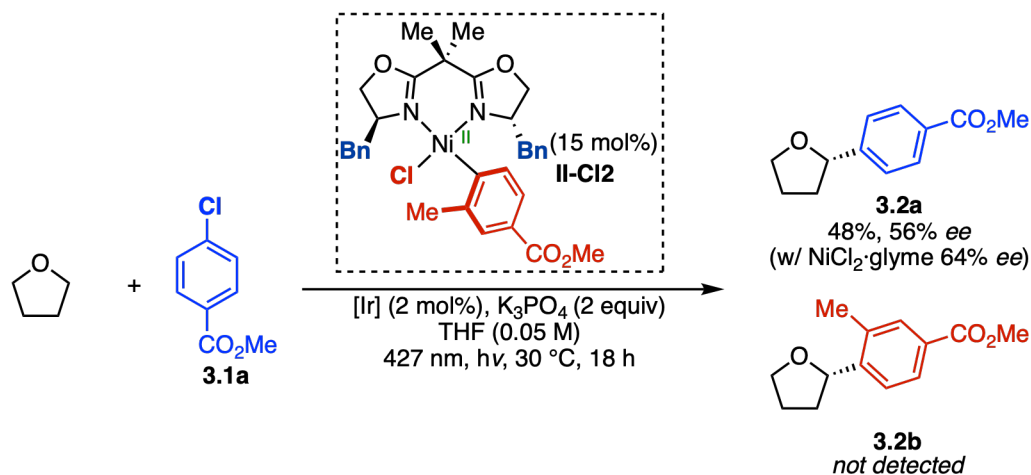
At this point in our study, we had successfully confirmed the relevance of **II** in trapping the THF carbon-centered radical. However, we wanted to have an enantioselectivity handle for both initial and subsequent catalytic turnovers. Therefore, we conducted crossover experiments using **II** and exogenous aryl halides

to determine whether initiating the reaction at a high concentration of **II** would affect the catalytic cycle. Going into these experiments, our hope was that the THF radical could be generated via **Figure 3.11a**, that a small amount of cross-coupled product with the aryl group already on **II** would be obtained, and that the catalyst would then react with the exogenous aryl halide (**Figure 3.12**).

The two crossover experiments in which the aryl group of **II** bore an *ortho* substituent (**II-Cl2** and **II-Br1**) were unsuccessful in generating the cross-coupled products **3.2b** or **3.2c**, with only compound **3.2a** observed (**Figures 3.12a** and **3.12b**). Upon examining the ¹H and ¹⁹F NMR spectra, we did not observe any dehalogenated arene, indicating that irradiation did not generate an aryl radical from **II**. However, **II** must somehow have been reduced to react with the exogenous aryl halide. In line with the Doyle report, we proposed that a photochemically induced reductive elimination via EnT from the excited-state photocatalyst was taking place, thereby reducing **II-Br2** and forming Ni(0). In the context of this reaction, it would make sense that the excited-state photocatalyst would directly engage **II**, as it is the highest in concentration (since it is the pre-catalyst) and relatively stable because it bears an *ortho*-substituent. We propose reductive elimination and subsequent oxidative addition into the electron-deficient aryl halides **3.1a** or **3.1b**, which were in excess (refer to **Figure 3.3b**).¹² This would mean the oxidative addition step occurs at a Ni(0) species rather than our proposed Ni(I) species. Interestingly, there was a slight

change in the ees of **3.2a** under these conditions compared to using $\text{NiCl}_2\cdot\text{glyme}$ as a pre-catalyst, where we believe oxidative addition happens at Ni(I) .

a) Crossover Experiment 1 w/ ortho-substituted II



b) Crossover Experiment 2 w/ ortho-substituted II

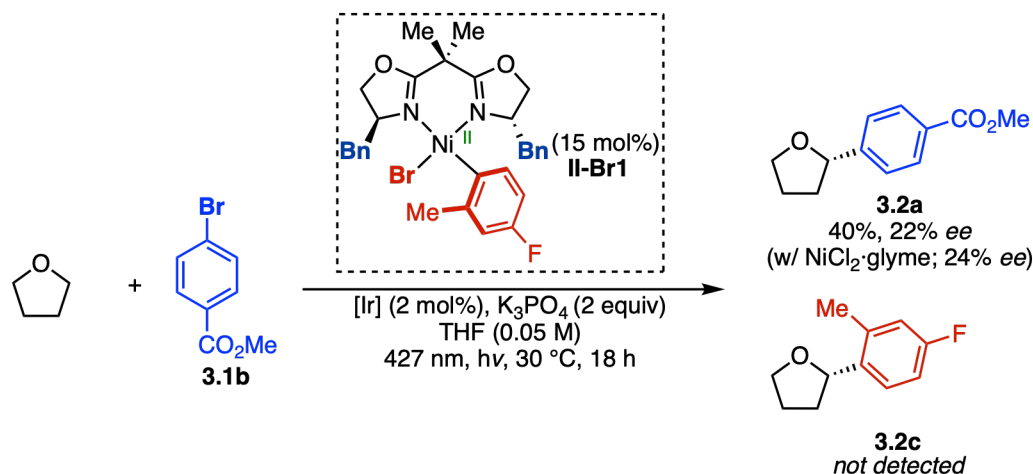


Figure 3.12: Crossover experiments using complexes (II) bearing ortho-substituents.

When using **II-Br2** as a pre-catalyst, both cross-coupled products are observed (**Figure 3.13**), but, as in the previous two examples, the ee differs from that obtained with $\text{NiCl}_2\cdot\text{glyme}$ (refer to **Figure 3.3c**). We believe both products were

formed in this case because **II-Br2** lacks an ortho substituent, thereby allowing faster subsequent reactions.

We shifted our attention to understanding how the presence Ni(0) could affect the reaction. The three possible pathways we settled on were: 1) Ni(0) oxidative addition into the exogenous aryl halide, followed by radical capture and product formation (akin to the enantioselectivity determining step shown in **Figure 3.10a**), 2) Ni(0) oxidative addition into the exogenous aryl halide, followed by photo-induced reductive elimination, regenerating starting materials, or 3) Ni(0) undergoes comproportionation or disproportionation reactions with other Ni species. These hypotheses will be explored and explained in a later section. Based on the different product ee we observed when using **II** as a pre-catalyst (which likely undergoes photoinduced reductive elimination to afford Ni(0)), we believed that the generation of Ni(0) species could alter the mechanistic pathway, as reflected in the changing ee.

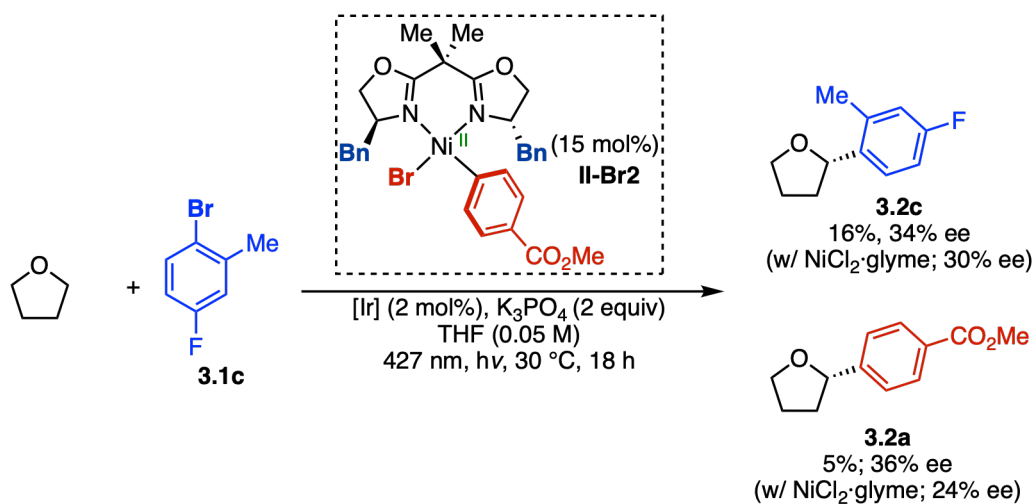
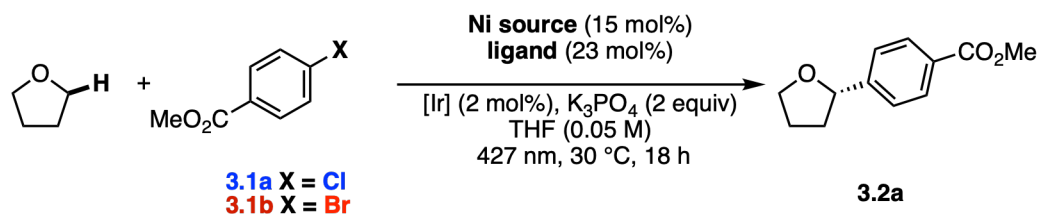


Figure 3.13: Crossover experiment using complexes (**II**) bearing no ortho-substituents.

We then ventured to using $\text{Ni}(\text{COD})_2$ as a pre-catalyst to see if we could obtain product under these conditions and subsequently compare enantioselectivities. Unfortunately, using $\text{Ni}(\text{COD})_2$ and an added ligand would not afford any cross-coupled product. However, when using $(\text{BOX})\text{Ni}(0)(\text{COD})$ ($\text{BOX} = \text{L3.2}$ or L3.4) (**I**) as pre-catalysts in the reaction, we were delighted to observe product formation (**Table 3.3**). When comparing the enantioselectivity of the product across the pre-catalysts, we observed a slight change in two examples (**Entries 1** and **3**), but a much larger difference in others (**Entries 2** and **4**). We postulated that the discrepancy is due to differences in enantioselectivity-determining steps that depend on the pre-catalyst, as reflected in the crossover experiments. To interrogate this difference further, we took time points of $\text{Ni}(0)$ and $\text{Ni}(\text{II})$ initiated reactions. Our prediction was that a consistent product ee throughout the reaction run time would suggest only one operative pathway, whereas a change in product ee over time would suggest a change in mechanism.



entry	Aryl halide, ligand	NiCl ₂ ·glyme + BOX	(BOX)Ni(COD)
1	3.1a , L3.2	40%, 64% ee	55%, 60% ee
2	3.1a , L3.4	40%, 72% ee	3%, 62% ee
3	3.1b , L3.2	30%, 24% ee	31%, 28% ee
4	3.1b , L3.4	20%, 14% ee	10%, 34% ee

Table 3.3: Screening of Ni(II) versus Ni(0) and observing changes in ee with pre-catalyst.

Having determined that halide identity is important in the enantioselectivity-determining step of the catalytic cycle under standard conditions (with NiCl₂·glyme as pre-catalyst), we took time points under conditions that mitigated potential halide scrambling. Additional experiments performed by Oscar showed that the product's enantioselectivity could also be affected by salt additives, so we took extra precautions to mitigate halide scrambling. In **Figure 3.14**, the first entry (blue open circle) uses **3.1a** and NiCl₂·glyme. We observed a consistent ee from the initial formation of **3.2a** through reaction completion (64% ee), indicating that only a single pathway is operative over multiple turnovers. Similarly, using **3.1b** and NiBr₂·glyme (red open circle), the observed ee of product **3.2a** remained relatively consistent throughout the reaction run time (16% ee). The most interesting results we observed came from using (L3.2)Ni(0)(COD) (**I**) with **3.1a** (blue filled circle) or **3.1b** (red filled circle). Initial formation of **3.2a** for both reactions afforded products with a much smaller ee gap compared to using Ni(II) pre-catalysts (**VIII**). However, **I** with **3.1a** led

to a gradual increase in ee (from 38% ee at 15 min to 60% ee at the end), while **I** with **3.1b** led to a gradual decrease in ee (from 32% ee at 15 min to 24% ee at the end). Our explanation for these results is that the Ni(0) reaction follows a distinct pathway during initial turnovers, in which halide identity is not part of the step that determines enantioselectivity (38% ee for **3.1a** and 32% ee for **3.1b** at the start of the reaction). As the concentration of Ni(0) (**I**) decreases over time (due to comproportionation and disproportionation reactions), the mechanism will converge toward the Ni(II) pre-catalyst pathways, as indicated by the growing disparity in ee, resembling conditions using Ni(II) dihalide species (**VIII**).

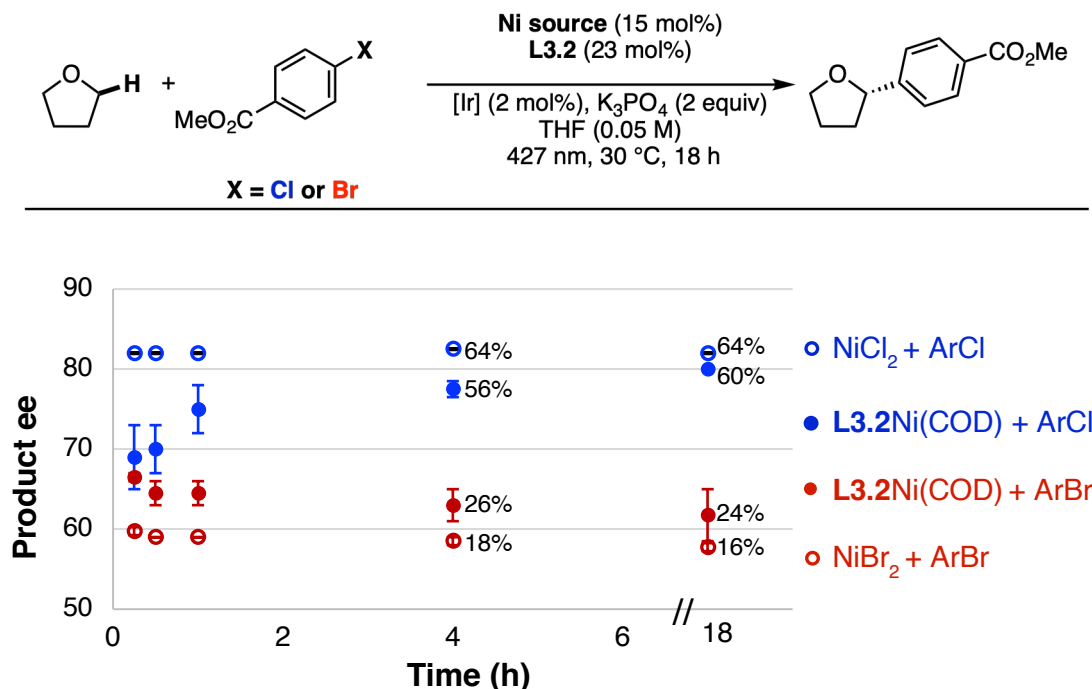


Figure 3.14: Time point reactions with Ni(II) (VIII) and Ni(0) (I) as pre-catalysts.

We next aimed to identify distinct routes to product formation. As previously described, one of our key speculations about the Doyle and Molander mechanisms was that transient Ni species trap the THF radical. We therefore considered Ni(II) a plausible radical-trapping species because it is comparatively more stable and a commonly proposed resting state in Ni-catalyzed reactions. Proposing an open-shell species for radical trapping without adequate support disregards the progress made in this field. We began to think that, under these conditions, we needed to provide evidence that open-shell Ni species are more abundant at early time points when Ni(0) is used, and therefore capable of a distinct product-forming pathway. Equally important, this separate product-determining step would need to incorporate the data we had gathered from the time point reactions, noting that at early Ni(0) time

points, halide identity is agnostic to the enantioselectivity of the product. To determine the possible Ni-intermediates formed *in situ* when using Ni(0) (**I**) as a pre-catalyst, Olivia Taylor conducted EPR studies (**Figure 3.15**). Our goal was to observe the well-precedented comproportionation and disproportionation events that low-valent Ni can undergo.^{11, 22-24, 31-34} We used an analogous ligand (dtbbpy) to enable a more straightforward comparison with literature values.³⁵ Additionally, I found that using THF as a solvent to mix Ni(COD)₂ with BOX ligands resulted in decomposition (described in more detail in **Chapter 2**), making EPR analysis with BOX ligands far more difficult.

The EPR analysis consisted of two types of experiments. In the first experiment, a THF solution of the ligand and Ni(COD)₂ was mixed with a solution of either an aryl chloride or an aryl bromide and then flash-frozen with liquid nitrogen after 10 s. A characteristic Ni(I) EPR signal was observed in four examples (two aryl bromides and two aryl chlorides) (**Figure 3.15a**). In the second variation, solutions of the ligand, Ni(COD)₂, and Ni(II) dihalide (**VIII**) were mixed, flash-frozen, and analyzed by EPR, with characteristic peaks observed in both cases (**Figure 3.14b**). Both experiments afforded characteristic Ni(I) peaks. We presumed that, in our system with the BOX ligand, similar phenomena occur, but further studies on these scaffolds are needed to determine whether switching the ligand affects these comproportionation events by altering the rate of metal-ligand charge transfer (MLCT).

a) EPR w/ Ni(0) and aryl halides



b) EPR w/ Ni(0) and Ni(II)

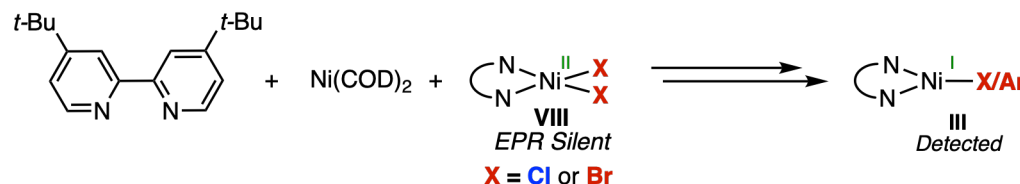


Figure 3.15: EPR Studies.

We believe the appearance of Ni(I) EPR signals for the experiments shown in **Figure 3.15** is evidence of successful oxidative addition to form (dtbbpy)Ni(II) aryl halide complex (**II**), which is diamagnetic and EPR silent, followed by comproportionation with residual Ni(0) (**I**) starting material. This event forms Ni(I) species **III** and **IV**, which, unlike the other two complexes, are EPR active. The mixing experiments demonstrate the presence of all four possible Ni species upon oxidative addition to **I** ($\text{I} + \text{II} \rightarrow \text{III} + \text{IV}$). Additionally, Ni species **I** and **III** are accessible when using **II** as a pre-catalyst under photochemical conditions (whether that's by reductive elimination or Ni–C homolysis), further supporting the hypothesis that there can be a different operative pathway when using **I** as a pre-catalyst.^{12, 36-38}

Therefore, we considered possible pathways of product formation that could arise under these conditions and are distinct from the pathway we found when using **VIII** as a pre-catalyst. Additionally, the proposed alternative pathways would be constructed based on the results of the time point reactions (**Figure 3.16**).

In **Pathway A**, Ni(0) complex **I** traps a THF radical, forming Ni(I) (**XI**), followed by oxidative addition into either **3.1a** or **3.1b**. The resulting Ni(III) species would rapidly undergo reductive elimination to afford the cross-coupled product.³⁹ Alternatively, **Pathway B** shows product formation via photoinduced reductive elimination from Ni(II) species **VII**.^{12, 16, 40, 41} This intermediate (**VII**) can be accessed through either THF radical trapping by Ni(I) aryl (**IV**), or disproportionation of two distinct Ni(I) species (**XI** and **IV**), which also would make **I**. Another possible pathway is the trapping of a THF radical by **III**, but we believe product formation from this path is unlikely. For product formation to occur, the resulting Ni(II) alkyl halide would need to funnel back through **Pathway A** or **B**. Finally, product formation from **II** is evidenced by stoichiometric experiments, which yield different ee values for aryl bromides and chlorides.

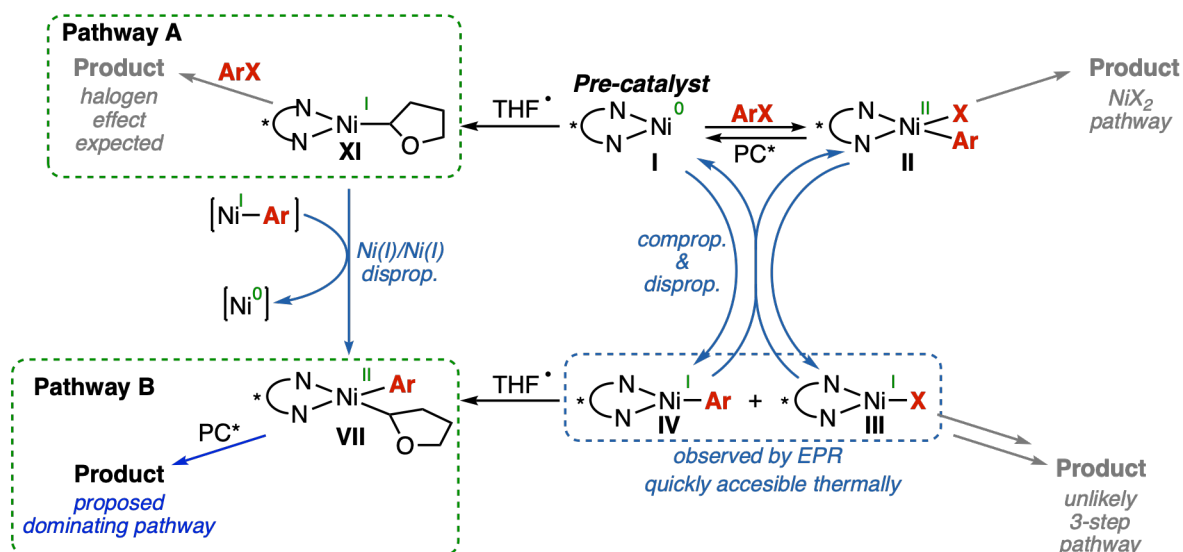


Figure 3.16: Possible pathways to product formation when using Ni(0) as a pre-catalyst.

Both **Pathways A** and **B** share the mechanism for THF radical formation. Based on the presence of Ni(II) complex (**II**) but not Ni(II) dihalide (**VIII**), we proposed that the photolysis of the aryl group within **II** would generate an aryl radical, which then performs HAT to generate the THF radical.¹¹ The homolysis of the Ni-C bond is preceded both via a direct light-promoted event and via EnT with the excited-state photocatalyst.^{11, 42}

There are a few shortcomings with **Pathway A**. First, the oxidative addition into **XI** would have to outcompete disproportionation pathways (with either **III** or **IV**). Second, recent studies on the rates of oxidative addition to Ni(I) species show sluggish reactivity toward aryl chlorides, suggesting that disproportionation may be faster.^{7, 24, 43, 44} Third, the enantioselectivity-determining step in this pathway, the reductive elimination, would bear the halide that **XI** had just added into, contradicting the results that halide is agnostic to the enantioselectivity in the Ni(0) pre-catalyst pathway during initial turnovers.

In **Pathway B**, there are two routes to the product-forming step. In the first scenario, we propose comproportionation between **I** and **II** to generate the two different Ni(I) intermediates (**III**) and (**IV**), as evidenced by the previously discussed EPR data. If Ni(I) aryl (**IV**) traps a THF radical, subsequent photo-induced reductive elimination can occur at Ni(II) aryl THF species (**VII**).^{12, 16, 40}³ This is not the only accessible route to **VII**. In the event Ni(0) (**I**) captures the THF radical to form **XI**, unlike

in **Pathway A**, where **XI** would undergo oxidative addition, **XI** instead will undergo disproportionation with **IV** to generate **VII**.^{22, 23, 31, 32}

Notably, the reductive elimination occurring from intermediate **VII** was also proposed in the original Molander report.³ Additionally, reductive elimination from this species is consistent with our time point results, indicating that halide identity is not a determinant of enantioselectivity in early turnovers of Ni(0) reactions.

Our support for aryl ligand cleavage (forming an aryl radical HAT agent) when using Ni(0) (**I**) as a pre-catalyst with either aryl bromide or aryl chloride was observing trace dehalogenation as a side product.¹² However, we do not believe Ni–C bond homolysis occurs when using Ni(II) dihalide (**VIII**) as a pre-catalyst, as we consistently did not observe any dehalogenated product under these reaction conditions. When using Ni(II) dihalide as a pre-catalyst, the HAT agent can be generated by Ir PC EnT with **VIII** to form a halogen radical and **III**.⁴⁵ Additionally, the pre-catalyst is in the highest concentration at the start of these reactions, making it most likely that the excited state photocatalyst will react with **VIII** as opposed to waiting for another intermediate to be generated.

We also do not suspect that Ni–C bond homolysis is the main operative pathway for product formation in our stoichiometric experiments. As stated previously, if this were occurring, it would mean that for every cross-coupled product formed, two equivalents of **II** would be needed: one for radical capture and one as a

sacrificial aryl radical precursor. The maximum yield in this scenario would be 50%, which contradicts our maximum yields, and in the cases where the yield is less than 50%, the ee obtained matches that of the catalytic reactions.

To summarize, we believe this pathway is more common in the Ni(0) (**I**) pre-catalyst pathway as we observe dehalogenated product under those conditions, but not when using **VIII** as a pre-catalyst. The other side product observed when using **I** as a pre-catalyst is a biaryl, likely due to the faster buildup of **II** in solution, thereby promoting transmetallation.

Based on the collected data, we propose mechanisms consistent with the unique results observed for each pre-catalyst (**Figure 3.17**). Our proposal, when using Ni(II) dihalide pre-catalyst (**VIII**), begins with **VIII** undergoing energy transfer with the excited-state photocatalyst to afford Ni(I) (**III**) and a halogen radical, which performs HAT on THF, generating the THF radical.⁴⁵ Subsequently, oxidative addition of Ni(I) (**III**) with aryl halide generates Ni(III) (**IX**). The pathway from Ni(III) (**IX**) to Ni(II) aryl halide complex (**II**) could be envisioned to occur via direct photolysis, as it is thermodynamically feasible.³ However, the reduced photon availability and rapid comproportionation in the presence of unreacted Ni(I) (**III**) make this pathway (**III** + **IX** → **II** + **VIII**) the favorable alternative.^{22-24, 32} This step simultaneously regenerates the Ni(II) dihalide pre-catalyst (**VIII**), which acts as a reservoir of the HAT agent and an active catalyst precursor, and Ni(II) aryl halide complex (**II**), which is primed to

capture the THF radical. As supported by stoichiometric experiments, the halide that is on **II** (bromide or chloride) has an immense effect on the enantioselectivity of the cross-coupled product. Once captured, the transiently formed Ni(III) species (**X**) is primed for reductive elimination to afford the cross-coupled product and regenerate Ni(I) halide (**III**), thereby continuing the catalytic cycle.

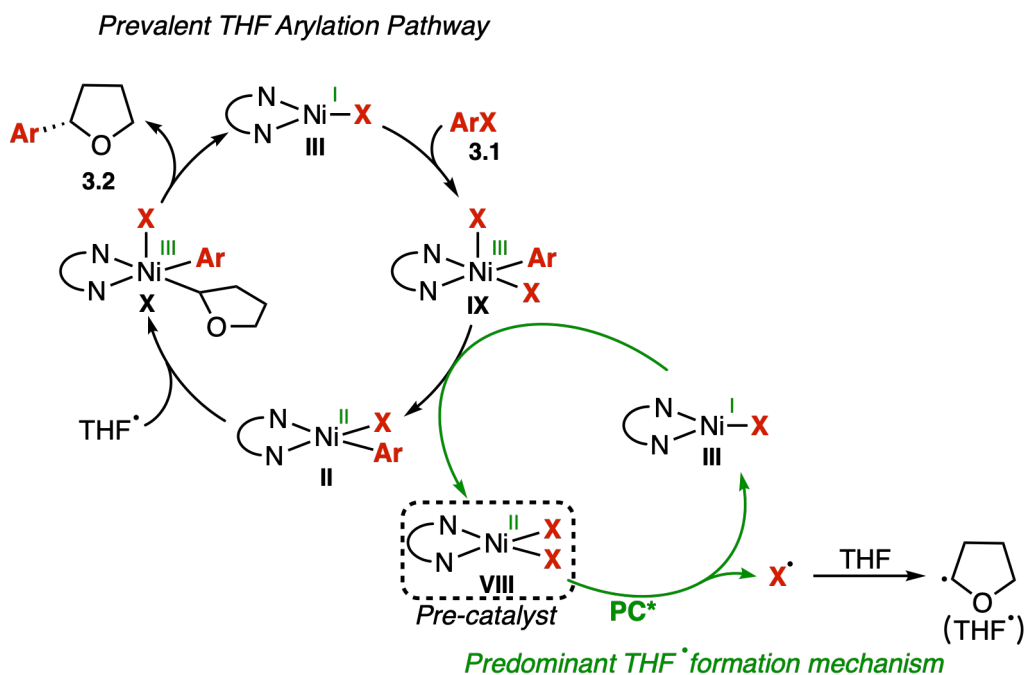


Figure 3.17: Proposed catalytic cycle when using Ni(II) **VIII** as pre-catalyst.

When considering our mechanism, we account for possible halide scrambling that could affect the ee. Upon using NiCl₂·glyme as a pre-catalyst with aryl bromide **3.1b**, the enantioselectivities we observed at early time points were slightly higher, followed by a slight decrease, then remained stagnant throughout the remainder of the reaction (data in **Section 3.8.6**). We do not attribute this to a change in mechanism, but to the presence of chloride on **II** during the initial turnovers. During the key comproportionation step (**III** + **IX** → **II** + **VIII**) in this specific scenario, the first

turnovers will have the unique Ni(III) species **IX** bearing both a chloride (coming from the pre-catalyst) and bromide (coming from the oxidative addition). If comproportionation with Ni(I) chloride (**III**) generates Ni(II) **II** with a chloride instead of a bromide and Ni(II) dihalide (**VIII**) as Ni(II) monochloride monobromide, the enantioselectivity at this first turnover would be higher due to the presence of a chloride on **II**. However, as the reaction proceeds, the ratio of bromide to chloride ions will quickly increase (due to the higher concentration of **3.1b**), and reactivity will become dominated by **II** bearing a bromide ligand. For this exact reason, when running the time point reactions in **Figure 3.14**, we opted to avoid halide scrambling by using all-chloride or all-bromide systems.

As previously discussed, the Ni(0) pre-catalyst has its own pathway when the *in situ* Ni(0) concentration is high (**Figure 3.18**). First, oxidative addition into aryl halide forms **II**. Complex **II**, under these conditions, is extremely reactive and can a) undergo photoinduced reductive elimination,¹² b) comproportionate,²² or c) undergo Ni–C bond homolysis.¹¹ It is likely that a mixture of all three of these steps is occurring, but we know that for any cross-coupling to be possible, there must be a HAT agent to form the THF radical. Therefore, we propose that **II** undergoes Ni–C bond homolysis, generating an aryl radical (which performs HAT, forming a THF radical) and Ni(I) halide (**III**). Once **III** is generated, it will either engage in disproportionation reactions (right cycle) or start forming product in accordance with the Ni(II) pre-catalyst (left cycle). If the enantioselectivity of the Ni(0) pathways remained

consistent over time, I would argue that the disproportionation route is favorable. However, the evolution of ee over time suggests that Ni(I) (**III**) will engage in the catalytic cycle on the left.

To complete the catalytic cycle on the right, we presume the successful formation of the THF radical. The route to **VII** can be achieved through two routes, as previously discussed. If comproportionation occurs between **II** and **I**, the resulting Ni(I) aryl (**IV**) can capture the THF radical, forming **VII**, which can then undergo light-induced reductive elimination. Alternatively, Ni(0) (**I**) can capture the THF radical forming **V**, which can then disproportionate with Ni(I) aryl (**IV**) to get to Ni(II) aryl THF (**VII**) and regenerate Ni(0) **I**. The specific route by which **VII** is accessed warrants further study, but we are confident that this species is responsible for the enantioselectivity-determining step when Ni(0) is used as the pre-catalyst.

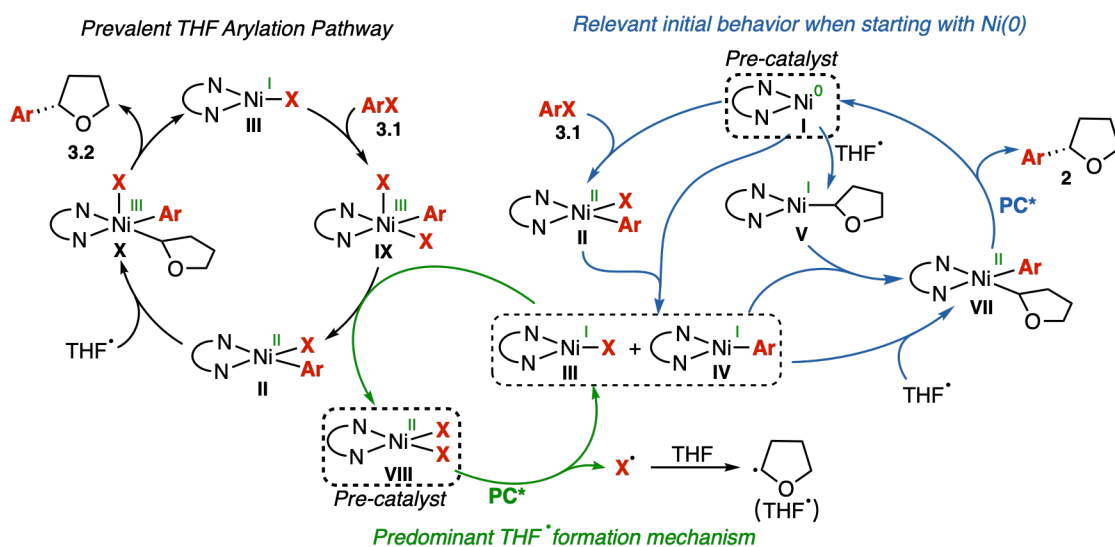


Figure 3.18: Overall mechanistic proposal considering both pre-catalysts.

Section 3.7: Conclusion

The work I performed for this paper greatly influenced the approach we are using to understand the mechanism of cross-electrophile coupling reactions (explained in **Chapter 4**). The change in ee for both the pre-catalyst and the aryl halide was studied extensively to propose the mechanism shown in **Figure 3.18**. Our main conclusion is that the dominant mechanism is operative from the outset with $\text{NiCl}_2\cdot\text{glyme}$ (**VIII**) and becomes prevalent after the initial turnovers with $(\text{BOX})\text{Ni}(\text{COD})$ (**I**) as the pre-catalyst. This work highlights the utility of leveraging enantioselectivity data to propose different mechanistic scenarios. We believe that the complexities of this Ni-catalyzed mechanism are not unique to Ni-photoredox systems, which is why we are now exploring XEC reactions.

Section 3.8: Procedures and Characterization

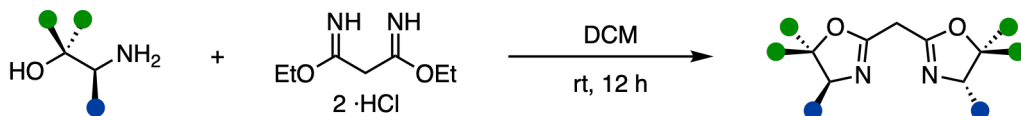
Section 3.8.1: General Information

This section details the compounds I helped synthesize and characterize. For the full supporting information of this work, please see our published manuscript.¹ All reagents were purchased from commercial suppliers and used without further purification except for **L3.3** – **L3.4**,⁴⁶ **L3.9** – **L3.11**,⁴⁶ **L3.12**,⁴⁷ **L3.13**,⁴⁸ **L3.14**,⁴⁹ **L3.15**,⁵⁰ and **L3.16**,⁵¹, which were synthesized according to reported procedures, and **L3.17**–**L3.30**, whose syntheses were adapted from existing literature.⁵² NiBr₂·glyme was purchased from Strem™, stored in a glovebox, and handled only under a dry, inert atmosphere to avoid reproducibility issues due to the compound's extreme hygroscopicity. ¹H NMR spectra were obtained in CDCl₃ or C₆D₆ at 400 MHz, 500 MHz, or 600 MHz. Chemical shifts are reported in ppm and referenced to the CHCl₃ singlet at 7.26 ppm or the C₆H₆ singlet at 7.16 ppm. ¹³C NMR spectra were obtained in CDCl₃ or C₆D₆ at 101 MHz or 151 MHz and referenced to the center peak of the CDCl₃ triplet at 77.16 ppm or the center peak of the C₆D₆ triplet at 128.39. ¹⁹F NMR spectra were obtained in CDCl₃ or C₆D₆ at 376 MHz or 564 MHz and referenced to the C₆H₅CF₃ singlet at -63.72 ppm in CDCl₃. The abbreviations s, d, t, q, quint, sept, dd, ddd, dt, dq, dqint, td, tdd, quintd, m, and bs stand for the resonance multiplicities singlet, doublet, triplet, quartet, quintet, septet, doublet of doublets, doublet of doublet of doublets, doublet of triplets, doublet of quartets, doublet of quintets, triplet of

doublets, triplet of doublets of doublets, quintet of doublets, multiplet, and broad singlet, respectively. Either a Kessil® PR160L-390 nm lamp or a Kessil® PR160L-427 nm lamp was used in the photochemical reactions. Thin-layer chromatography was performed with EMD silica gel 60 F254 plates eluting with the solvents indicated, visualized by a 254 nm UV lamp or with potassium permanganate or phosphomolybdic acid stains. Flash chromatography was performed using EM reagent silica 60 (230-400 mesh). Enantiomeric excess ratios were determined with an ACQUITY UPC² System using chiral stationary phase columns (Trefoil™ AMY1 or CEL1) by comparing the samples with the corresponding racemic samples. Optical rotation was measured using a Rudolph AutoPol IV polarimeter at 24 °C in a 100 mm sample cell. High-resolution, accurate mass spectral data were obtained on an Agilent 6545 LC/SFC Hybrid Q-TOF instrument. NMR, EPR, X-ray diffraction, and mass spectra were all obtained using the Analytical Chemistry Instrumentation Facility at the University of California, Riverside.

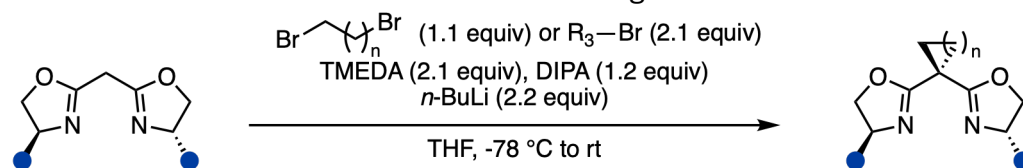
Section 3.8.2: Ligand Synthesis and Screening Results

General Procedure 3A: Synthesis of BOX Ligands



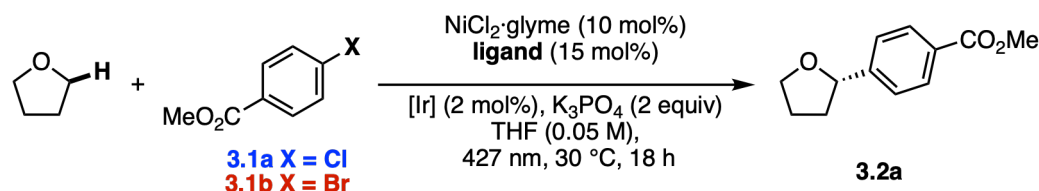
Bisoxazoline (BOX) ligands were synthesized following a previously reported procedure.^{52, 53} A flame-dried two-necked round-bottom flask equipped with a magnetic stir bar was purged and backfilled with N₂ three times. The amino alcohol (10 mmol, 1 equiv), diethyl malonimidate dihydrochloride (5 mmol, 0.5 equiv), and dichloromethane (DCM) were added to the round-bottom flask. The reaction was stirred at room temperature overnight. The reaction mixture was quenched with deionized water and extracted with DCM three times. The organic layer was washed with brine. The resulting organic layer was dried over Na₂SO₄ and concentrated under reduced pressure to an oil. The oil was purified by column chromatography to obtain the product.

General Procedure 3B: Functionalization of BOX Ligands

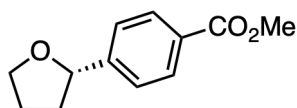


Bisoxazoline (BOX) ligands were synthesized following a previously reported procedure.^{52, 53} A flame-dried two-necked round-bottom flask equipped with a magnetic stir bar was purged and backfilled with N_2 three times. A THF (0.055 M, 27 mL) solution of “methylene BOX” ligand (1.5 mmol, 1 equiv) was added to the round-bottom flask. Subsequently, tetramethylethylenediamine (TMEDA, 3.15 mmol, 2.1 equiv, 0.47 mL) and diisopropylamine (DIPA, 1.8 mmol, 1.2 equiv, 0.252 mL) were added to the round-bottom flask. The solution was cooled to $-78\text{ }^\circ\text{C}$ in a dry ice/acetone bath. $n\text{-BuLi}$ (2.5 M, 1.4 mL) was added dropwise to the cold solution, and the resulting mixture was stirred for 30 min at $-78\text{ }^\circ\text{C}$. The alkyl halide (3.155 mmol or 1.65 mmol, 2.1 equiv or 1.1 equiv) was added to the reaction at $-78\text{ }^\circ\text{C}$. The mixture was allowed to warm to room temperature and stirred overnight. The reaction progress was monitored by TLC and ^1H NMR. Upon completion, the reaction was quenched with a saturated NH_4Cl solution and extracted with EtOAc three times. The organic layer was washed with brine. The resulting organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography to obtain the desired product.

General Procedure C: Conditions for Screening BOX ligands in reaction



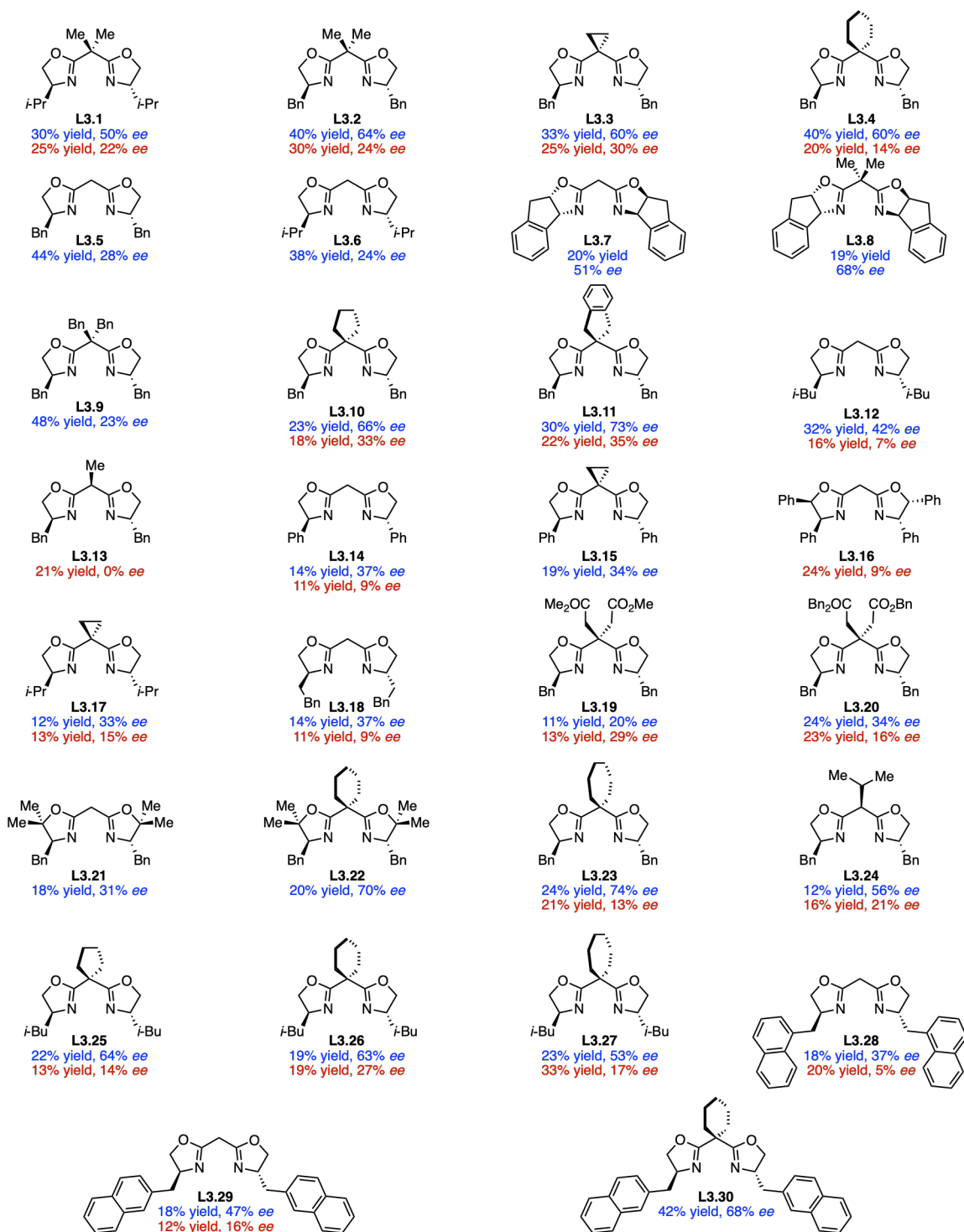
An oven-dried 10 mL Schlenk tube was equipped with a stir bar and allowed to cool to room temperature. Either methyl 4-chlorobenzoate **3.1a** (0.1 mmol, 1 equiv, 17.1 mg) or methyl-4-bromobenzoate **3.1b** (0.1 mmol, 1 equiv, 21.4 mg) was then added to the vial, followed by K_3PO_4 (0.2 mmol, 2 equiv, 42.5 mg), $\text{NiCl}_2 \cdot \text{glyme}$ (0.01 mmol, 10 mol%, 2.2 mg) and $\text{Ir}[\text{dF}(\text{CF}_3)\text{ppy}]_2(\text{dtbbpy})\text{PF}_6$ (0.002 mmol, 2 mol%, 2.2 mg). The Schlenk tube was then connected to a Schlenk line and purged three times to remove trace air. Finally, a solution of bisoxazoline (BOX) ligand in THF (0.0075 M, 2 mL) was added to the Schlenk tube. The reaction mixture was stirred and irradiated with a single 427 nm lamp at 30 °C in a temperature-controlled water bath.



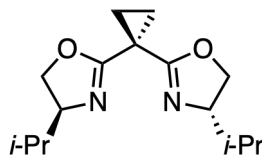
Compound **2a** was prepared according to **General Procedure 2C**. Characterization of this compound matches previously published examples.⁵⁴ The crude material was purified by silica gel column chromatography (Hexane/EtOAc = 97/3 to 95/5, R_f = 0.3 in 95/5 Hexanes/EtOAc) to obtain **3.2a** as colorless oil ^1H NMR (600 MHz, CDCl_3) δ 8.00 (d, J = 7.8 Hz, 2H), 7.39 (d, J = 7.8 Hz, 2H), 4.94 (t, J = 7.2 Hz, 1H), 4.10 (q, J = 7.2 Hz, 1H), 3.95 (q, J = 7.2 Hz, 1H), 3.90 (s, 3H), 2.36 (dq, J = 13.6, 7.2 Hz, 1H), 2.00 (quint,

$J = 7.2$ Hz, 2H), 1.82 – 1.72 (m, 1H). **^{13}C NMR** (151 MHz, CDCl_3) δ 167.0, 149.0, 129.7, 128.9, 125.5, 80.2, 68.9, 52.1, 34.7, 26.0. **HRMS** (ESI- TOF) m/z calculated for $\text{C}_{12}\text{H}_{14}\text{O}_3$ ($\text{M}+\text{H}$) $^+$: 207.1016, found 207.1016. The enantiomeric ratio was measured by UPC² analysis using a chiral column: TrefoilTM AMY1, 2.5 μm 3.0 x 150 mm column, 40 °C, $\text{CO}_2/\text{ACN} = 97.5/2.5$ as eluent, 234 nm, 1.25 mL/min. $t_{\text{R}} = 8.5$ min (major), 10.1 min (minor). **Optical Rotation:** $[\alpha]_{\text{D}}^{24-35} \pm 3$ (c 0.5, CH_3CN) for 78% ee

Section 3.8.3: Ligand Screening Results

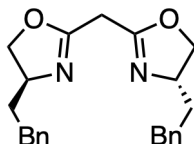


(4*S*,4'*S*)-2,2'-(cyclopropane-1,1-diyl)bis(4-isopropyl-4,5-dihydrooxazole) (**L3.17**)



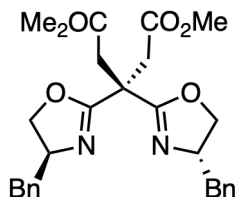
L3.17 was prepared according to **General Procedure 2B**, using **L3.6** (1.5 mmol, 1 equiv, 357.5 mg), TMEDA (3.15 mmol, 2.1 equiv, 0.47 mL), DIPA (1.8 mmol, 1.2 equiv, 0.252 mL) in THF (0.055 M, 27 mL). The reaction mixture was cooled to -78 °C, and *n*-BuLi (2.5 M, 1.6 mL) was added dropwise. The reaction was stirred for 30 min before 1,2-dibromoethane (1.65 mmol, 1.1 equiv, 0.14 mL) was added. The reaction mixture was purified by column chromatography on silica gel (DCM/EtOAc from 80/20 to 50/50, R_f = 0.5) to obtain **L3.17** as a yellow oil. **¹H NMR** (600 MHz, CDCl₃) δ 4.22 (t, *J* = 7.8 Hz, 2H), 3.98 (t, *J* = 7.8 Hz, 2H), 3.88 (q, *J* = 7.8 Hz, 2H), 1.72 (dq, *J* = 14.9, 7.8 Hz, 2H), 1.42 (d, *J* = 5.6 Hz, 2H), 1.31 (d, *J* = 5.6 Hz, 2H), 0.89 (d, *J* = 7.8 Hz, 6H), 0.82 (d, *J* = 7.8 Hz, 6H). **¹³C NMR** (151 MHz, CDCl₃) δ 165.4, 71.7, 70.3, 32.5, 18.7, 18.2, 17.7, 15.3. **HRMS** (ESI-TOF) *m/z* calculated for C₁₅H₂₄N₂O₂ (*M*+*H*)⁺: 265.1920, found 265.1911. Optical Rotation: [α]_D²⁴ -98.66 ± 0.04 (c 0.5, CH₃CN).

bis((S)-4-phenethyl-4,5-dihydrooxazol-2-yl)methane (**L3.18**)



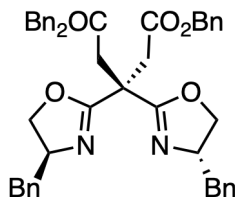
L3.18 was prepared according to **General Procedure 2A**, using (S)-2-amino-4-phenylbutan-1-ol (2 mmol, 1 equiv, 330 mg), which was synthesized by the literature procedure,⁵⁵ diethyl malonimidate dihydrochloride (1 mmol, 0.5 equiv, 230 mg), and DCM (0.55 M, 3.6 mL), stirred under RT overnight. The reaction mixture was purified by column chromatography on silica gel (EtOAc, R_f = 0.3) to obtain **L3.18** as a yellow oil. **¹H NMR** (600 MHz, CDCl₃) δ 7.30 (t, J = 7.0 Hz, 4H), 7.22 (d, J = 7.0 Hz, 6H), 4.37 (t, J = 8.8 Hz, 2H), 4.17 (dq, J = 14.9, 8.8 Hz, 2H), 3.95 (t, J = 8.8 Hz, 2H), 3.40 (s, 2H), 2.79 (dt, J = 14.9, 8.8 Hz, 2H), 2.72 (dt, J = 14.9, 8.8 Hz, 2H), 1.99 (dq, J = 14.9, 8.8 Hz, 2H), 1.85 (dq, J = 14.9, 8.8 Hz, 2H). **¹³C NMR** (151 MHz, CDCl₃) δ 161.8, 141.6, 128.4, 128.3, 126.0, 72.9, 65.9, 37.5, 32.1, 28.5. **HRMS** (ESI-TOF) m/z calculated for C₂₃H₂₆N₂O₂ (M+H)⁺: 363.2085, found 363.2010. **Optical Rotation**: $[\alpha]_D^{24}$ -95.79 $\pm$ 0.07 (c 0.5, CH₃CN).

dimethyl 3,3-bis((S)-4-benzyl-4,5-dihydrooxazol-2-yl)pentanedioate (**L3.19**)



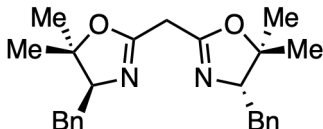
L3.19 was prepared according to **General Procedure 2B**, using **L5** (1.5 mmol, 1 equiv, 501.6 mg), TMEDA (3.15 mmol, 2.1 equiv, 0.47 mL), DIPA (1.8 mmol, 1.2 equiv, 0.252 mL) in THF (0.055 M, 27 mL). The reaction mixture was cooled to -78 °C, and *n*-BuLi (2.5 M, 1.6 mL) was added dropwise. The reaction was stirred for 30 min before methyl bromoacetate (3.15 mmol, 2.1 equiv, 0.30 mL) was added. The reaction mixture was purified by column chromatography on silica gel (Hexane/Et₂O = 50/50, **R_f** = 0.4) to obtain **L3.19** as a yellow oil. **¹H NMR** (400 MHz, CDCl₃) δ 7.36 – 7.15 (m, 10H), 4.47 – 4.36 (m, 2H), 4.21 (t, *J* = 8.8 Hz, 2H), 4.07 – 3.98 (m, 2H), 3.69 (s, 6H), 3.33 (s, 4H), 3.10 (dd, *J* = 13.7, 5.5 Hz, 2H), 2.63 (dd, *J* = 13.7, 5.5 Hz, 2H). **¹³C NMR** (101 MHz, CDCl₃) δ 170.8, 165.8, 137.9, 129.3, 128.5, 126.4, 72.6, 67.4, 51.7, 42.0, 41.3, 37.3. **HRMS** (ESI-TOF) *m/z* calculated for C₂₇H₃₀N₂O₆ (*M*+H)⁺:479.2199, found 479.2178. **Optical Rotation:** [α]_D²⁴ -72.38 (c 1.0, CH₃CN).

dibenzyl 3,3-bis((S)-4-benzyl-4,5-dihydrooxazol-2-yl)pentanedioate (**L3.20**)



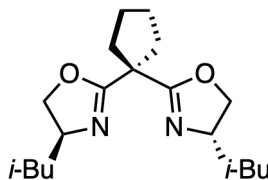
L3.20 was prepared according to **General Procedure 2B**, using **L5** (501.6 mg, 1.5 mmol, 1 equiv), TMEDA (3.15 mmol, 2.1 equiv, 0.47 mL), DIPA (1.8 mmol, 1.2 equiv, 0.252 mL) in THF (0.055 M, 27 mL). The reaction mixture was cooled to -78 °C and *n*-BuLi (2.5 M, 1.6 mL) was added dropwise. The reaction was stirred for 30 min before benzyl bromoacetate (3.15 mmol, 2.1 equiv, 0.50 mL) was added into the reaction. The reaction mixture was purified by silica gel column chromatography (Hexane/Et₂O 50:50, *R_f* = 0.4) to obtain **L3.20** as yellow oil. **¹H NMR** (400 MHz, CDCl₃) δ 7.52 – 7.31 (m, 14H), 7.31 – 7.19 (m, 6H), 5.20 (s, 4H), 4.40 (ddd, *J* = 15.1, 9.0, 6.2 Hz, 2H), 4.17 (t, *J* = 9.0 Hz, 2H), 4.06 – 3.95 (m, 2H), 3.52 (s, 4H), 3.12 (dd, *J* = 13.6, 8.4 Hz, 2H), 2.63 (dd, *J* = 13.6, 8.4 Hz, 2H). **¹³C NMR** (101 MHz, CDCl₃) δ 170.2, 165.7, 138.1, 136.0, 129.4, 128.6, 128.6, 128.2, 128.2, 126.5, 72.7, 67.5, 66.3, 42.2, 41.4, 37.8. **HRMS** (ESI-TOF) *m/z* calculated for C₃₉H₃₈N₂O₆ (*M*+H)⁺:631.2822, found 631.2838. **Optical Rotation**: [α]_D²⁴ -54.48 (c 1.0, CH₃CN).

bis((S)-4-benzyl-5,5-dimethyl-4,5-dihydrooxazol-2-yl)methane (**L3.21**)



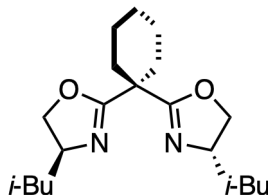
L3.21 was prepared according to **General Procedure 2A**, using (S)-3-amino-2-methyl-4-phenylbutan-2-ol (3.62 mmol, 1 equiv, 642 mg) that was synthesized according to the literature procedure,⁵⁶ and added with diethyl malonimidate dihydrochloride (1.81 mmol, 0.5 equiv, 419 mg) and DCM (0.4 M, 9 mL) to a round-bottom flask. The reaction mixture was stirred at room temperature for 72 h. The crude material was purified by silica gel column chromatography (EtOAc, R_f = 0.1) to obtain **L3.21** as yellow oil. **¹H NMR** (600 MHz, CDCl₃) δ 7.36 – 7.30 (m, 7H), 7.27 – 7.18 (m, 3H), 4.06 – 3.99 (m, 2H), 3.29 (s, 2H), 2.96 (dd, J = 13.4, 8.8 Hz, 2H), 2.76 (dd, J = 13.4, 8.8 Hz, 2H), 1.35 (s, 6H), 1.31 (s, 6H). **¹³C NMR** (151 MHz, CDCl₃) δ 160.8, 139.2, 129.1, 128.4, 126.2, 86.9, 74.9, 37.4, 29.5, 28.4, 21.9. **HRMS** (ESI-TOF) m/z calculated for C₂₅H₃₀N₂O₂ (M+H)⁺: 391.2394, found 391.2380. **Optical Rotation**: $[\alpha]_D^{24}$ -47.15 $\pm$ 0.03 (c 1.0, CH₃CN).

(4*S*,4'*S*)-2,2'-(cyclopentane-1,1-diyl)bis(4-isobutyl-4,5-dihydrooxazole) (**L3.25**)



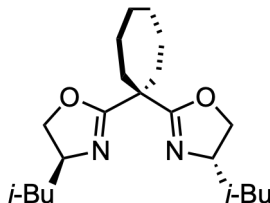
L3.25 was prepared according to **General Procedure 2B**, using **L3.12** (1.5 mmol, 1 equiv, 399.5 mg), TMEDA (3.15 mmol, 2.1 equiv, 0.47 mL), DIPA (1.8 mmol, 1.2 equiv, 0.252 mL) in THF (0.055 M, 27 mL). The reaction mixture was cooled to -78 °C, and *n*-BuLi (2.5 M, 1.6 mL) was added dropwise. The reaction was stirred for 30 min before 1,4-dibromobutane (1.65 mmol, 1.1 equiv, 0.20 mL) was added. The reaction mixture was purified by column chromatography on silica gel (DCM/EtOAc = 80/20; **R_f** = 0.5) to obtain **L3.25** as a yellow oil. **¹H NMR** (600 MHz, CDCl₃) δ 4.16 (dd, *J* = 9.1, 7.2 Hz, 2H), 3.97 (m, 2H), 3.69 (dd, *J* = 8.9, 5.2 Hz, 2H), 2.12 (dd, *J* = 11.4, 6.6 Hz, 2H), 2.01 (dd, *J* = 11.4, 6.6 Hz, 2H), 1.56 (dq, *J* = 13.1, 6.2 Hz, 6H), 1.43 (dt, *J* = 13.1, 6.2 Hz, 2H), 1.12 (dt, *J* = 13.1, 6.2 Hz, 2H), 0.77 (t, *J* = 6.6 Hz, 12H). **¹³C NMR** (151 MHz, CDCl₃) δ 167.9, 73.3, 64.4, 48.9, 45.2, 35.3, 25.2, 24.8, 23.0, 22.4. **HRMS** (ESI-TOF) *m/z* calculated for C₁₉H₃₂N₂O₂ (M+H)⁺: 321.2550, found 321.2531. **Optical Rotation**: [α]_D²⁴ -90.61 (c 1.0, CH₃CN).

(4S,4'S)-2,2'-(cyclohexane-1,1-diyl)bis(4-isobutyl-4,5-dihydrooxazole) (**L3.26**)



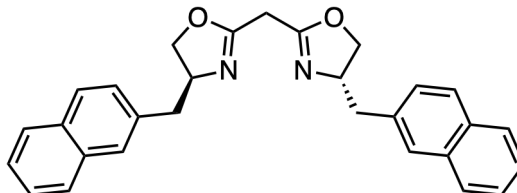
L3.26 was prepared according to **General Procedure 2B**, using **L3.12** (1.5 mmol, 1 equiv, 399.5 mg), TMEDA (3.15 mmol, 2.1 equiv, 0.47 mL), DIPA (1.8 mmol, 1.2 equiv, 0.252 mL) in THF (0.055 M, 27 mL). The reaction mixture was cooled to -78 °C and *n*-BuLi (2.5 M, 1.6 mL) was added dropwise. The reaction was stirred for 30 min before 1,5-dibromopentane (1.65 mmol, 1.1 equiv, 0.22 mL) was added into the reaction. The reaction mixture was purified by column chromatography on silica gel (DCM/EtOAc = 75/25, **R_f** = 0.2) to obtain **L3.26** as a yellow oil. **¹H NMR** (600 MHz, CDCl₃) δ 4.28 (t, *J* = 7.2 Hz, 2H), 4.15 (quint, *J* = 7.2 Hz, 2H), 3.84 (t, *J* = 7.2 Hz, 2H), 2.11 – 2.01 (m, 2H), 2.01 – 1.89 (m, 2H), 1.70 (dq, *J* = 13.3, 6.7 Hz, 2H), 1.64 – 1.57 (m, 4H), 1.53 – 1.38 (m, 4H), 1.27 (dt, *J* = 13.3, 6.7 Hz, 2H), 0.99 – 0.86 (m, 12H). **¹³C NMR** (151 MHz, CDCl₃) δ 167.4, 72.9, 64.6, 45.5, 42.9, 32.6, 25.4, 25.3, 23.2, 22.6, 22.5. **HRMS** (ESI-TOF) *m/z* calculated for C₂₀H₃₄N₂O₂ (M+H)⁺: 335.2708, found 335.2695. **Optical Rotation**: [α]_D²⁴ -83.76 (c 1.0, CH₃CN).

(4*S*,4'*S*)-2,2'-(cycloheptane-1,1-diyl)bis(4-isobutyl-4,5-dihydrooxazole) (**L3.27**)



L3.27 was prepared according to **General Procedure 2B**, using **L3.12** (1.5 mmol, 1 equiv, 399.6 mg), TMEDA (3.15 mmol, 2.1 equiv, 0.47 mL), DIPA (1.8 mmol, 1.2 equiv, 0.252 mL) in THF (0.055 M, 27 mL). The reaction mixture was cooled to -78 °C, and *n*-BuLi (2.5 M, 1.6 mL) was added dropwise. The reaction was stirred for 30 min before 1,5-dibromopentane (1.65 mmol, 1.1 equiv, 0.22 mL) was added. The reaction mixture was purified by column chromatography on silica gel (DCM/EtOAc = 75/25, R_f = 0.3) to obtain **L3.27** as a yellow oil. **¹H NMR** (600 MHz, CDCl₃) δ 4.27 (t, *J* = 7.4 Hz, 2H), 4.13 (quint, *J* = 7.4 Hz, 2H), 3.83 (t, *J* = 7.4 Hz, 2H), 2.23 (dd, *J* = 14.3, 7.8 Hz, 2H), 2.08 (dd, *J* = 14.3, 7.8 Hz, 2H), 1.68 (dq, *J* = 13.1, 6.6 Hz, 2H), 1.64 – 1.46 (m, 10H), 1.26 (dt, *J* = 13.8, 6.6 Hz, 2H), 0.96 – 0.88 (m, 12H). **¹³C NMR** (151 MHz, CDCl₃) δ 168.5, 73.1, 64.5, 46.0, 45.4, 34.6, 29.9, 25.4, 23.2, 23.2, 22.5. **HRMS** (ESI-TOF) *m/z* calculated for C₂₁H₃₆N₂O₂ (*M*+H)⁺: 349.2863, found 349.2852. **Optical Rotation**: [α]_D²⁴ -63.83 (c 0.5, CH₃CN).

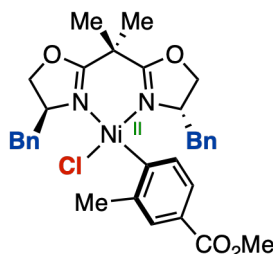
bis((S)-4-(naphthalen-2-ylmethyl)-4,5-dihydrooxazol-2-yl)methane (**L3.29**)



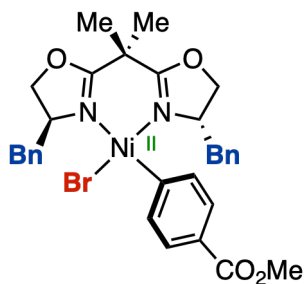
L3.29 was prepared according to **General Procedure 2A**. (S)-2-amino-3-(naphthalen-2-yl)propan-1-ol (1.41 mmol, 1 equiv, 283 mg) was synthesized according to the literature procedure,⁵⁷ and added with diethyl malonimidate dihydrochloride (0.70 mmol, 0.5 equiv, 162 mg) and DCM (0.1 M, 7 mL) to a round-bottom flask. This was stirred at room temperature overnight. The reaction mixture was purified by silica gel column chromatography (EtOAc, R_f = 0.2) to obtain **L3.28** as yellow oil. **¹H NMR** (600 MHz, CDCl₃) δ 7.84 – 7.76 (m, 6H), 7.64 (s, 2H), 7.46 (sept, J = 7.8 Hz, 4H), 7.35 (d, J = 7.8 Hz, 2H), 4.54 (quint, J = 8.2 Hz, 2H), 4.22 (t, J = 8.2 Hz, 2H), 4.05 (t, J = 8.2 Hz, 2H), 3.34 (s, 2H), 3.32 – 3.22 (m, 2H), 2.85 (dd, J = 12.6, 9.1 Hz, 2H). **¹³C NMR** (151 MHz, CDCl₃) δ 162.2, 135.3, 133.6, 132.3, 128.2, 127.8, 127.7, 127.7, 127.6, 126.1, 125.6, 72.3, 67.4, 41.6, 28.5. **HRMS** (ESI-TOF) m/z calculated for C₂₉H₂₆N₂O₂ (M+H)⁺: 435.2085, found 435.2068. **Optical Rotation**: $[\alpha]_D^{24}$ -41.96 $\pm$ 0.03 (c 1.0, CH₃CN).

Section 3.8.4: Ni-Complex Characterization

Full details on Ni-complex synthesis of **II** are described in **Chapter 2**. To avoid redundancy, only complexes unique to this report (**II-Cl-2** and **II-Br-1**) will be covered in this section. All detailed procedures are listed in **Chapter 2** and are used to synthesize these complexes.



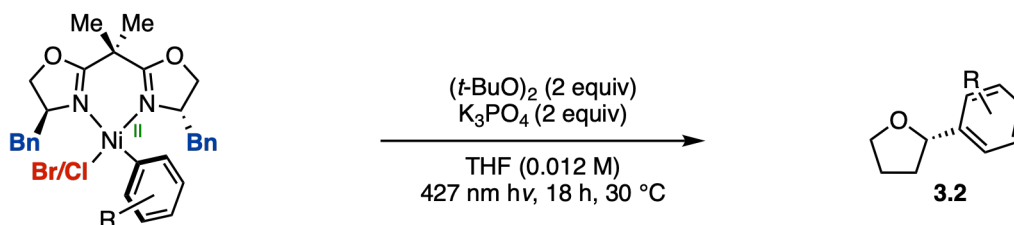
Aryl chloride oxidative addition complex **II-Cl2** was prepared according to **Chapter 2 General Procedure 2A** using methyl 4-chloro-3-methylbenzoate (8.0 mmol, 40 equiv, 1.2 mL). The resulting (**L3.2**)Ni(II) aryl halide complex was collected as a light-yellow powder in a 31% yield (37.6 mg). ¹H NMR (400 MHz, C₆D₆) δ 8.34 (d, *J* = 7.8 Hz, 1H), 8.04 – 7.84 (m, 2H), 7.46 (bs, 4H), 7.01-6.81 (m, 6H), 3.91-3.37 (m, 8H), 3.10-2.29 (m, 4H), 1.05 – 0.77 (m, 10 H). ¹³C NMR (101 MHz, C₆D₆) δ 168.4, 132.4, 130.4, 130.1, 129.4, 128.3, 128.1, 127.8, 126.9, 126.2, 125.7, 123.5, 51.2, 38.4, 26.1, 19.8, 17.9. Remaining signals overlap with the peaks from deuterated benzene.



Aryl bromide oxidative addition complex **II-Br1** was prepared according to **Chapter 2 General Procedure 2A** using methyl-4-bromobenzoate (8.0 mmol, 40 equiv, 1702.4 mg). The resulting (**L3.2**)Ni(II) aryl bromide complex was collected as a dark orange solid and afforded a 36% yield (45.8 mg). **¹H NMR** (400 MHz, C₆D₆) δ 8.62 (bs, 2H), 8.10 (bs, 2H), 7.11-6.93 (m, 10H), 3.59 (bs, 6H), 3.07 (bs, 3H), 2.92-2.46 (m, 4H), 0.95 (bs, 6H). **¹³C NMR** could not be obtained due to rapid transmetallation and reductive elimination of the complex to afford dimethyl [1,1'-biphenyl]-4,4'-dicarboxylate and the decomposed complex.

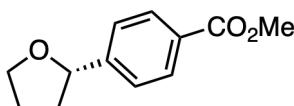
Section 3.8.5: Stoichiometric Experiments

General Procedure 3D: Stoichiometric Experiments



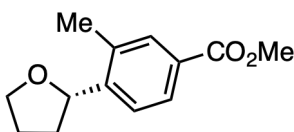
In a nitrogen-filled glovebox, (**L3.2**)Ni(II) aryl halide complex (0.05 mmol, 1.0 equiv) and K_3PO_4 (0.1 mmol, 2.0 equiv) were weighed out into a 10 mL Schlenk tube and dissolved in THF (0.012 M, 4.2 mL). The Schlenk tube was removed from the glovebox and immediately placed under nitrogen on a Schlenk line. Under constant efflux of N_2 , di-*tert*-butyl peroxide (0.1 mmol, 2.0 equiv, 26 μL) was added to the solution via Hamilton syringe. The Schlenk tube was then sealed with electrical tape, placed in a temperature-controlled water bath at 30 °C, irradiated with a single 427 nm lamp, and stirred for 18 h. The solution was then filtered through a Celite™ plug, and the excess THF was removed by evaporation. The crude material was then purified via column chromatography.

methyl (S)-4-(tetrahydrofuran-2-yl)benzoate (**3.2a**)



Compound **3.2a** was prepared according to **General Procedure 3D** using **II-Br1** (0.05 mmol, 1.0 equiv, 31.8 mg), K_3PO_4 (0.1 mmol, 2.0 equiv, 21.2 mg), di-*tert*-butyl peroxide (0.1 mmol, 2.0 equiv, 18.3 μ L), and anhydrous THF (0.012 M, 4.2 mL). The crude material was purified by column chromatography on silica gel (Hexane/EtOAc from 97/3 to 95/5) to obtain **2a** as a colorless oil (4.9 mg, 47% isolated yield, 25% ee). Characterization of this compound matches previously published examples.⁵⁴

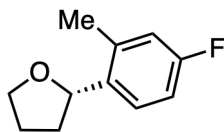
methyl (S)-3-methyl-4-(tetrahydrofuran-2-yl)benzoate (**3.2b**)



Compound **3.2b** was prepared according to **General Procedure 2D** using **II-Cl2** (0.05 mmol, 1.0 equiv, 28.3 mg), K_3PO_4 (0.1 mmol, 2.0 equiv, 21.2 mg), di-*tert*-butyl peroxide (0.1 mmol, 2.0 equiv, 18.3 μ L), and anhydrous THF (0.012 M, 4.2 mL). The crude material was purified by column chromatography on silica gel (Hexane/EtOAc from 97/3 to 95/5) to obtain **2b** as a colorless oil (6.2 mg, 56% isolated yield, 68% ee). **¹H NMR** (400 MHz, $CDCl_3$) δ 7.85 (d, J = 8.0 Hz, 1H), 7.80 (s, 1H), 7.52 (d, J = 8.0 Hz,

1H), 5.07 (t, $J = 6.7$ Hz, 1H), 4.15 (quint, $J = 6.7$ Hz, 1H), 3.94 (q, $J = 6.7$ Hz, 1H), 3.89 (s, 3H), 2.46 – 2.36 (m, 1H), 2.35 – 2.28 (m, 3H), 2.00 (dt, $J = 14.2, 6.7$ Hz, 2H), 1.67 – 1.58 (m, 1H). **^{13}C NMR** (101 MHz, CDCl_3) δ 167.2, 147.4, 134.2, 131.3, 128.5, 127.4, 124.6, 77.8, 68.8, 52.0, 33.1, 26.0, 19.2. **HRMS** (ESI-TOF) m/z calculated for $\text{C}_{12}\text{H}_{16}\text{O}_3(\text{M}+\text{H})^+$: 221.1173, found. 221.1172. The enantiomeric excess ratio was measured by UPC² analysis using a chiral column: Trefoil™ AMY1, 2.5 μm 3.0 x 150 mm column, 40 °C, $\text{CO}_2/\text{ACN} = 97.5/2.5$ as eluent, 234 nm, 1.5 mL/min. $t_R = 5.2$ min (major), 8.3 min (minor). Characterization of this compound matches previously published examples.⁵⁸

(S)-2-(4-fluoro-2-methylphenyl)tetrahydrofuran (**3.2c**)



Compound **3.2c** was prepared according to **General Procedure 2D** using **II-Cl1** (0.05 mmol, 1.0 equiv, 28.2 mg) or **II-Br2** (0.05 mmol, 1.0 equiv, 30.5 mg), K_3PO_4 (0.1 mmol, 2.0 equiv, 21.2 mg), di-*tert*-butyl peroxide (0.1 mmol, 2.0 equiv, 18.3 μL), and anhydrous THF (0.012 M, 4.2 mL). The crude material was purified by silica gel column chromatography (Hexane/EtOAc = 99/1 to 96/4) to obtain **2c** as a colorless oil (stoichiometric experiment with **II-Cl1**: 1.5 mg, 17% isolated yield, 63% ee; stoichiometric experiment with **II-Br2**: 5.4 mg, 60% isolated yield, 27% ee). **^1H NMR**

(600 MHz, CDCl₃) δ 7.39 (t, J = 7.5 Hz, 1H), 6.87 (t, J = 7.5 Hz, 1H), 6.83 (d, J = 9.6 Hz, 1H), 5.00 (t, J = 7.1 Hz, 1H), 4.13 (q, J = 7.1 Hz, 1H), 3.92 (q, J = 7.1 Hz, 1H), 2.37 – 2.27 (m, 4H), 2.01 (quint, J = 7.1 Hz, 2H), 1.64 (dq, J = 15.6, 7.1 Hz, 1H). **¹³C NMR** (151 MHz, CDCl₃) δ 161.6 (d, $^1J_{C-F}$ = 241.6 Hz), 137.4 (d, $^4J_{C-F}$ = 2.3 Hz), 136.5 (d, $^3J_{C-F}$ = 8.0 Hz), 126.3 (d, $^3J_{C-F}$ = 8.3 Hz), 116.7 (d, $^2J_{C-F}$ = 21.1 Hz), 112.5 (d, $^2J_{C-F}$ = 20.8 Hz), 77.6, 68.6, 33.2, 26.0, 19.2. **¹⁹F NMR** (564 MHz, CDCl₃) δ -118.22. **HRMS** (ESI-TOF) m/z calculated for C₁₁H₁₃FO (M+H)⁺: 181.1028, found. 181.1023. The enantiomeric ratio was measured by UPC² analysis using a chiral column: Trefoil™ AMY1, 2.5 μ m 3.0 x 150 mm column, 40 °C, CO₂/ACN = 99.5/0.5 as eluent, 234 nm, 1.0 mL/min. t_R = 2.9 min (major), 3.1 min (minor). Characterization of this compound matches previously published examples.¹²

Section 3.8.6: Time Point Reactions

All ee data were determined by UPC² with a chiral column and are the average of experiments run in duplicate. Yields of product, remaining starting material, and byproducts were determined by ¹H NMR with internal standard (1,3,5-trimethoxybenzene).

General Procedure 3E: Utilizing Ni(0) Pre-Catalysts

In the glovebox, methyl-4-chlorobenzoate (0.2 mmol, 1 equiv, 35 mg) or methyl-4-bromobenzoate (0.2 mmol, 1 equiv) and K₃PO₄ (0.4 mmol, 2 equiv, 84.9 mg) were added to a 10 mL Schlenk tube equipped with a magnetic stir bar. (L3.2)Ni(COD) solution (0.0075 M, 4 mL) was added to the Schlenk tube and brought out from the glove box. Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ (0.004 mmol, 2 mol%, 4.4 mg) was added under constant efflux of N₂. The reaction mixture was stirred and irradiated with a single 427 nm lamp at 30 °C in a temperature-controlled water bath. Aliquots of the reaction were taken according to the times shown in the following tables.

General Procedure 3F: Utilizing Ni(II) Pre-Catalysts

In the glovebox methyl 4-chlorobenzoate (0.2 mmol, 1 equiv, 35 mg) or 4-bromobenzoate (0.2 mmol, 1 equiv), K_3PO_4 (0.4 mmol, 2 equiv, 84.9 mg), **L3.2** (0.045 mmol, 22.5 mol%, 16.3 mg) and $NiCl_2 \cdot glyme$ (0.03 mmol, 15 mol%, 6.6 mg) or $NiBr_2 \cdot glyme$ (0.015 mmol, 7.5 mol%, 4.3 mg) were added to a 10 mL Schlenk tube equipped with a magnetic stir bar. The reaction mixture was brought out from the glove box $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (0.004 mmol, 2 mol%, 4.4 mg) was added into the Schlenk tube while the Schlenk tube was flushed with N_2 . The reaction mixture was stirred and irradiated with one 427 nm lamp at 30 °C in a temperature-controlled water bath. Aliquots of the reaction were taken according to the times shown in the following tables.

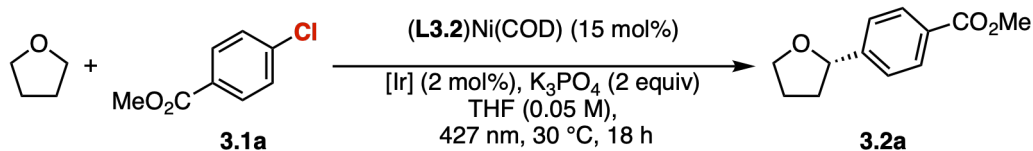
General Procedure 3G: Utilizing Ni(II) Pre-Catalysts with aryl chloride with COD additive

In the glovebox, methyl 4-chlorobenzoate (0.2 mmol, 1 equiv, 35 mg), K_3PO_4 (0.4 mmol, 2 equiv, 84.9 mg), **L3.2** (0.045 mmol, 22.5 mol%, 16.3 mg), and $NiCl_2 \cdot glyme$ (0.03 mmol, 15 mol%, 6.6 mg) were added to a 10 mL Schlenk tube equipped with a magnetic stir bar. The reaction mixture was removed from the glovebox. $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (0.004 mmol, 2 mol%, 4.4 mg) and 1,5-Cyclooctadiene (0.03 mmol, 15 mol%, 4 μ L) were added to the Schlenk tube while the Schlenk tube was flushed with N_2 . The reaction mixture was stirred and irradiated with one 427 nm lamp at 30 °C in a temperature-controlled water bath. Aliquots of the reaction were taken according to the times shown in the following tables.

General procedure 3H - for Ni(0) and $NiX_2 \cdot glyme$ with ArX ⁵⁹

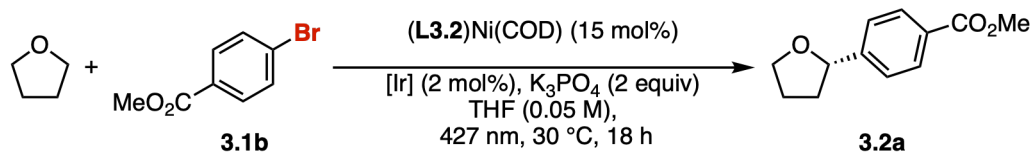
In the glovebox methyl-4-chlorobenzoate (0.2 mmol, 1 equiv, 35 mg) or methyl-4-bromobenzoate (0.2 mmol, 1 equiv, 43 mg), K_3PO_4 (0.4 mmol, 2 equiv, 84.9 mg), **L3.2** (0.0225 mmol, 0.01125 equiv, 8.2 mg), and $NiCl_2 \cdot glyme$ (0.015 mmol, 7.5 mol%, 3.3 mg) or $NiBr_2 \cdot glyme$ (0.015 mmol, 7.5 mol%, 4.3 mg) were added to a 10 mL Schlenk tube equipped with a magnetic stir bar. THF (2 mL) and (**L3.2**)Ni(COD) solution (0.0075 M, 2 mL) was added to the Schlenk tube and brought out from the glove box. $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (0.004 mmol, 2 mol%, 4.4 mg) was added while the Schlenk tube was flushed with N_2 . The reaction mixture was stirred and irradiated

with one 427 nm lamp in a 30 °C water bath. The aliquots were taken at the times shown in the table.



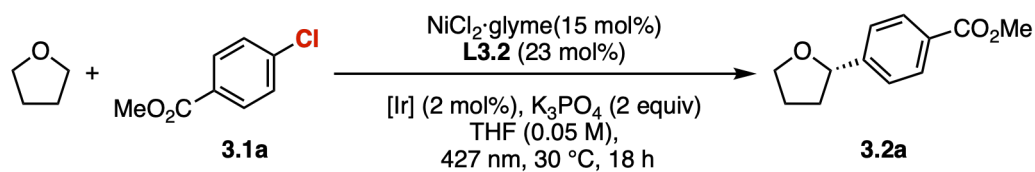
Entry	Time (h)	Ar-X	Ar-THF	Ar-H	Ar-Ar	ee (%)
1	0.25	76%	18%	1%	5%	38%
2	0.5	70%	19%	1%	10%	40%
3	1	69%	20%	1%	10%	50%
4	4	53%	35%	2%	10%	56%
5	18	28%	55%	6%	11%	60%

Table 3.4: Enantiomeric ratio through time with (L3.2)Ni(COD) catalyst and ArCl.



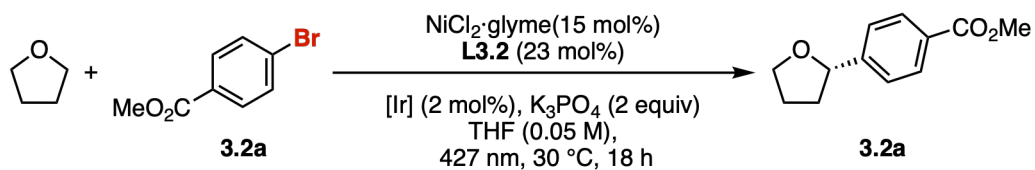
Entry	Time (h)	Ar-X	Ar-THF	Ar-H	Ar-Ar	ee (%)
1	0.25	70%	5%	0%	25%	32%
2	0.5	63%	10%	0%	27%	30%
3	1	15%	40%	0%	36%	28%
4	4	0%	45%	12%	33%	26%
5	18	0%	50%	10%	35%	24%

Table 3.5: Enantiomeric ratio through time with (L3.2)Ni(COD) catalyst and ArBr.



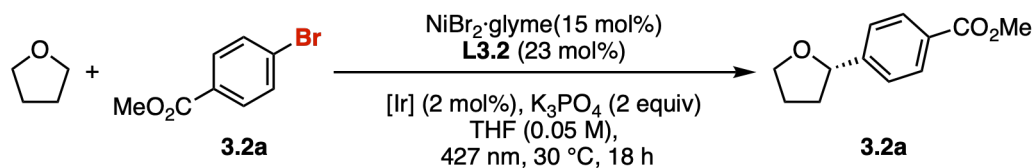
Entry	Time (h)	Ar-X	Ar-THF	Ar-H	Ar-Ar	ee (%)
1	0.25	95%	5%	0%	0%	64%
2	0.5	95%	5%	0%	0%	64%
3	1	83%	17%	0%	0%	64%
4	4	18%	19%	0%	0%	66%
5	18	60%	40%	0%	0%	64%

Table 3.6: Enantiomeric ratio through time for ArCl with NiCl₂·glyme + **L3.2**.



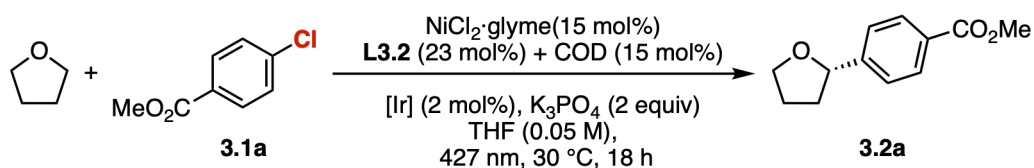
Entry	Time (h)	Ar-X	Ar-THF	Ar-H	Ar-Ar	ee (%)
1	0.25	86%	5%	1%	0%	54%
2	0.5	60%	14%	7%	1%	38%
3	1	37%	27%	10%	1%	30%
4	4	2%	54%	10%	2%	24%
5	18	1%	30%	15%	2%	24%

Table 3.7: Enantiomeric ratio through time for ArBr with NiCl₂·glyme + **L3.2**.



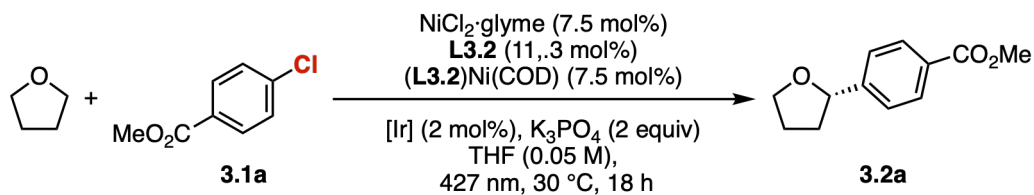
Entry	Time (h)	Ar-X	Ar-THF	Ar-H	Ar-Ar	ee (%)
1	0.25	74%	22%	0%	4%	20%
2	0.5	60%	32%	6%	2%	18%
3	1	52%	34%	10%	4%	18%
4	4	46%	32%	19%	3%	17%
5	18	12%	30%	56%	2%	16%

Table 3.8: Enantiomeric ratio through time for ArBr with NiBr₂·glyme + **L3.2**



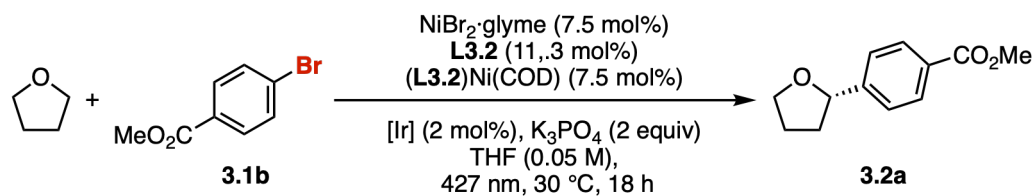
Entry	Time (h)	Ar-X	Ar-THF	Ar-H	Ar-Ar	ee (%)
1	0.25	92%	6%	2%	0%	66%
2	0.5	90%	8%	2%	0%	66%
3	1	87%	12%	1%	0%	66%
4	4	79%	20%	1%	0%	66%
5	18	59%	39%	2%	0%	66%

Table 3.9: Enantiomeric ratio through time for ArCl with NiCl₂·glyme + **L3.2** with COD additive.



Entry	Time (h)	Ar-X	Ar-THF	Ar-H	Ar-Ar	ee (%)
1	0.25	81%	14%	0%	5%	38%
2	0.5	67%	25%	3%	5%	40%
3	1	21%	58%	10%	11%	50%
4	4	2%	80%	10%	8%	56%
5	18	0%	88%	5%	7%	60%

Table 3.10: Enantiomeric ratio through time for ArCl with NiCl₂·glyme + **L3.2** and (**L3.2**)Ni(COD) mixture.

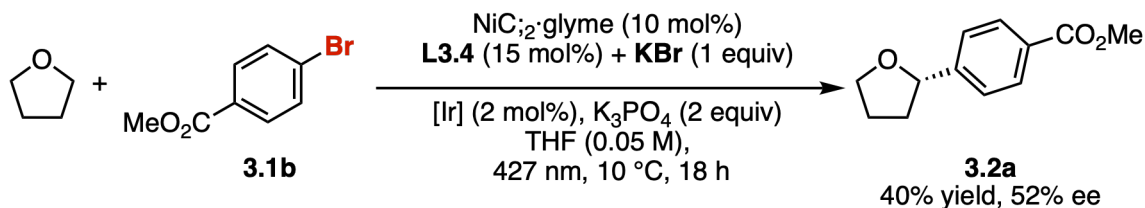


Entry	Time (h)	Ar-X	Ar-THF	Ar-H	Ar-Ar	ee (%)
1	0.25	79%	3%	0%	18%	34%
2	0.5	76%	6%	0%	18%	30%
3	1	76%	7%	0%	17%	30%
4	4	16%	63%	0%	21%	26%
5	18	0%	74%	0%	26%	24%

Table 3.11: Enantiomeric ratio through time for ArBr with NiBr₂·glyme + **L3.2** and (**L3.2**)Ni(COD) mixture.

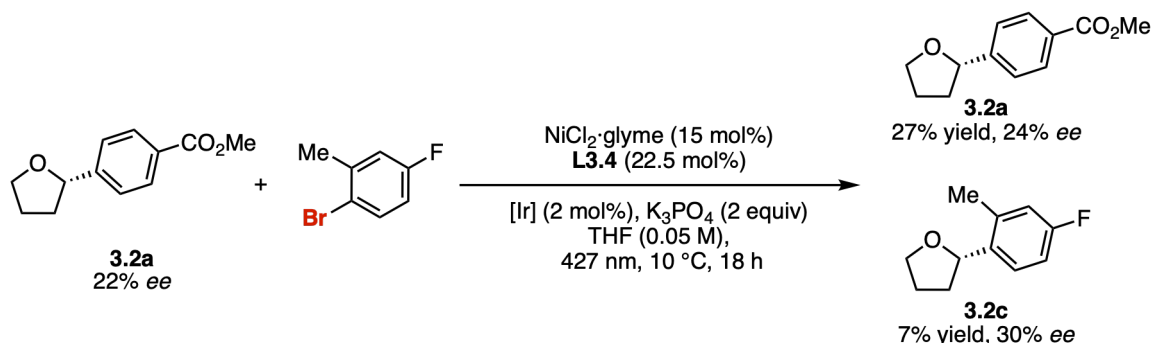
Section 3.8.7: Testing for Possible Product Racemization

a. Addition of an exogenous bromide source



An oven-dried Schlenk tube equipped with a magnetic stir bar was charged with methyl 4-bromobenzoate **3.1b** (0.2 mmol, 1 equiv, 43.0 mg), $\text{NiCl}_2 \cdot \text{glyme}$ (0.02 mmol, 10 mol%, 4.4 mg), and $\text{Ir}[\text{dF}(\text{CF}_3)\text{ppy}]_2(\text{dtbbpy})\text{PF}_6$ (0.004 mmol, 2 mol%, 4.5 mg), **KBr** (0.2 mmol, 1 eq, 23.8 mg) and K_3PO_4 (0.4 mmol, 2 eq, 84.9 mg). The flask was purged and backfilled with N_2 three times, then **L3.4** in THF (0.0075 M, 4 mL) was added. The reaction mixture was stirred and irradiated with one 427 nm lamp at 10 °C for 18 h. The product was isolated by column chromatography according to the procedure outlined for substrate **2a**. The yield was determined by ^1H NMR with internal standard (1,3,5-trimethoxybenzene). The enantiomeric ratios were measured by chiral SFC from the isolated products.

b. Addition of enantioenriched product



An oven-dried Schlenk tube equipped with a magnetic stir bar was charged with 1-bromo-4-fluoro-2-methylbenzene (0.1 mmol, 1 equiv, 13 μL), $\text{NiCl}_2 \cdot \text{glyme}$ (0.015 mmol, 15 mol%, 3.3 mg), $\text{Ir}[\text{dF}(\text{CF}_3)\text{ppy}]_2(\text{dtbbpy})\text{PF}_6$ (0.002 mmol, 2 mol%, 2.2 mg), **L3.4** (0.225 mmol, 22.5 mol%, 8.2 mg) and K_3PO_4 (0.2 mmol, 2 equiv, 42.3 mg). The flask was purged and backfilled with N_2 three times, then **3.2a** in THF (0.05 M, 2 mL) was added. The reaction mixture was stirred and irradiated with one 427 nm lamp at 10 °C for 18 h. The product was isolated by column chromatography according to the procedure outlined for substrate **3.2c**. The yield was determined by ^1H NMR with internal standard (1,3,5-trimethoxybenzene). The enantiomeric ratios were measured by chiral SFC from the isolated products.

Section 3.9: References

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Chapter 4: Mechanistic Investigation of Ni-catalyzed Cross-Electrophile Coupling (XEC) of Aryl Iodides with Benzyl Chlorides

Section 4.1: Abstract

Enantioconvergent catalysis is a powerful strategy to transform racemic starting materials into enantioenriched products.¹ This chapter discusses our ongoing mechanistic investigation of an enantioconvergent cross-electrophile coupling (XEC) reaction initially disclosed by the Reisman group in 2017.² Our aim in this investigation is to propose a mechanism that explains how the product ee changes as the reductant used in this reaction is varied. We are currently carrying out a series of time point experiments varying the pre-catalyst to help differentiate between on and off-cycle pathways. Additionally, we are leveraging my experience with synthesizing bisoxazoline (BOX)Ni(II) aryl halide complexes to synthesize bioxazoline (BiOX)Ni(II) aryl halide complexes (details in **Chapter 2**).^{3,4} Our goal is to use these complexes in stoichiometric experiments to probe the capture of radicals by a Ni(II) aryl halide species. This is the common step among radical-chain XEC proposals.⁵⁻⁷ The results disclosed in this chapter are a combination of my own results and those of Hai Ly, who has assisted with this work and will continue the project in my absence. Hai's contributions in this work were the screening of Lewis acids and salt additives, which are discussed in **Section 4.5**.

Naming conventions are consistent with those in the other chapters. Ni-intermediates are denoted by Roman numerals, while starting materials, products, and ligands are prefaced with “4” to indicate their relevance to **Chapter 4**.

Section 4.2: Exploration of C(sp³)-C(sp²) XEC reactions

Modern-day metal-catalyzed C-C cross-coupling can be categorized into three classes: classical,^{8,9} C-H functionalization,¹⁰ and cross-electrophile coupling (XEC).¹¹ Traditional cross-coupling methodologies (Suzuki-Miyaura,¹² Negishi,¹³ and Kumada)¹⁴ utilize a metal/metalloid-carbon nucleophile and a carbon-halogen or pseudo-halogen (C-X) coupling partner. While reliable, these traditional methods of cross-coupling have the inconvenience of requiring metal-carbon nucleophiles (organozinc,¹⁵ organolithium,¹⁶⁻¹⁸ organoboron,¹⁹ and Grignard reagents²⁰), which often require a separate synthesis for immediate use. C-H functionalization leverages low bond dissociation energy (BDE) or steric accessibility of some C-H bonds to afford site-selective cross-coupling.²¹ As a result, these methods are often limited in site selectivity to substrates bearing low BDE C(sp³)-H bonds (α -heteroatoms,²²⁻²⁴ α -carbonyl,²⁵ aldehyde C-H,²⁶ allylic,²⁷ propargylic,²⁸⁻³⁰ or benzylic³¹⁻³³ positions). XEC couples two distinct electrophiles by leveraging differences in activation pathways and their relative rates, thus avoiding those limitations.¹¹ However, this field comes with its own benefits and drawbacks, detailed below.

The recent surge in XEC methodologies has been driven by the widespread commercial availability of C-X electrophiles. The disparity of commercial availability when compared to organometallic nucleophiles is so large that even organic iodides, the least common amongst the C-X electrophiles, are more available than

organoboron reagents, the most commercially available and stable metal-carbon nucleophilic coupling partner.¹¹ Furthermore, synthesis of organolithium, organozinc, Grignard, and organoboron reagents typically requires a C–X precursor. Thus, using XEC saves an entire synthetic step for achieving the same overall bond construction. In addition to saving steps in precursor synthesis, making complex molecules with exploitable C–X bonds can alleviate the strict site selectivity observed in C–H functionalization. Using XEC methodologies in this context can lead to more direct routes in the synthesis of natural products^{34–40} and complex targets.⁴¹

XEC reactions provide a robust platform for accessing a wide variety of C–C cross-coupled products, such as C(*sp*)–C(*sp*³), C(*sp*²)–C(*sp*²), C(*sp*²)–C(*sp*³), C(*sp*³)–C(*sp*³), and di-functionalization of alkenes and alkynes.¹¹ This is made possible by using 3d transition metals rather than the 4d transition metals used in seminal cross-coupling reports. This is due to Ni's ability to undergo both single- and two-electron redox pathways, allowing access to a multitude of oxidation states (0, I, II, III) much less commonly seen in reactions with 4d transition metal catalysts (discussed in **Chapter 1**). This means Ni catalysts can engage electrophiles via a traditional two-electron pathway (as with Pd) or via one-electron pathways. Both options, working in concert, allow two electrophiles to be cross-coupled.

While the redox promiscuity of Ni catalysts enables diverse synthetic transformations, it can also be detrimental given the mechanistic complexity that

can arise. Other drawbacks in XEC methodologies lie mainly in the environmental impact upon scale-up. Large quantities of amide solvents (DMA or DMF) and the generation of multiple equivalents of metal salt byproducts are environmentally hazardous.⁴²⁻⁴⁴ Alternative non-metal reductants, such as tetrakis(dimethylamino)ethylene (TDAE) and similar derivatives, are tedious to synthesize and arguably more prone to decomposition than the metal-carbon nucleophiles that XEC aims to avoid. Additionally, XEC mechanisms will always face competing pathways that favor deleterious homocoupling over the desired cross-coupling, thereby decreasing efficiency.

In this context, mechanistic investigation can be vital to lessening the overall drawbacks of using XEC methods and expediting the optimization campaign for emerging methods. Having knowledge of metal-reductant effects on reactivity may enable the development of XEC reactions that avoid them altogether, such as those involving the growing use of electrochemical cells or photoredox-catalyzed XEC.¹¹ Understanding the mechanism also informs the development of reactions to broaden the range of potential coupling partners and eventually move away from harmful reaction conditions while still achieving the same overall transformation. Finally, it is important to gain better insights into the relationship between the dominant cross-coupling pathway and possible homocoupling pathways, which will help guide future reaction optimization.

In this chapter, I will focus on XEC methodologies that enable C(sp^2)-C(sp^3) cross-coupling.¹¹ Examples include coupling aryl, vinyl, and acyl electrophiles with a variety of unactivated and activated alkyl electrophiles. The von Wangelin group's initial reports used an Fe catalyst to couple aryl and alkyl electrophiles, with Mg acting as a shuttle for the electrophiles between two iron centers.⁴⁵ Following reports by the Gosmini group, a similar XEC reaction was described using a Co catalyst, with Mn serving as the reductant.⁴⁶ The trend of using first-row transition-metal catalysts continued with the Durandetti group, who employed a Ni catalyst to couple aryl halides and α -chloroesters, using Mn as a reductant.⁴⁷ The rise in Ni-catalyzed XEC reactions was further fueled when the Weix group soon after reported their own Ni-catalyzed XEC to couple aryl bromides and electron-poor aryl chlorides with primary alkyl bromides.⁴⁸

An interesting finding from the Weix report was that both Mn and Zn were competent reductants, but using Zn afforded a higher yield.⁴⁷ However, TDAE or electrochemical conditions are commonly used conditions to achieve XEC reactions, suggesting reaction success is determined by having a reductant and not the generation of *in situ* organometal nucleophiles.

A larger literature survey shows that these inconsistencies in yield across the different reductants are ubiquitous.¹¹ Furthermore, our lab became interested in this phenomenon when we noticed that several reports indicate that the identity of the

reductant influences the ee of the product. Observing this trend of changing yield with varying the reductant, we postulated that a resulting change in ee would validate that each reductant could be acting differently within the context of XEC reactions, or alternatively, that it is operating in the enantioselectivity-determining step. I then conducted a thorough literature search to find enantioconvergent XEC systems that afford products across multiple reductants.

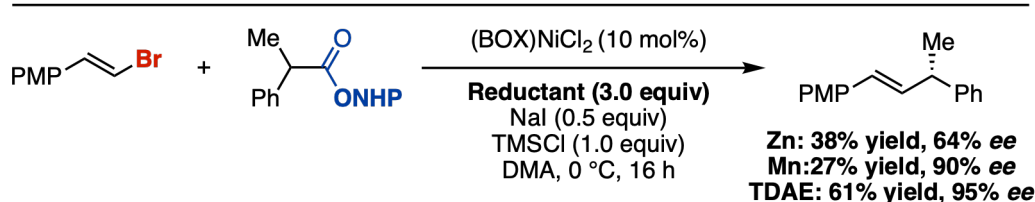
Section 4.3: Enantioconvergent XEC Strategies

Despite the popularity of C(sp^3)–C(sp^2) bond construction in XEC, there are relatively few examples of enantioconvergent XECs.⁴⁹ This can be attributed to the limited scope of prochiral “activated” C(sp^3) electrophiles that can be employed in this cross-coupling, which will generate a chiral center, and the difficulty in trapping sterically encumbered alkyl radicals in an enantioselective fashion. Common examples of alkyl coupling partners include secondary benzyl chlorides,² α -chloroesters,⁵⁰ α -chlorosulfones,⁵¹ α -chloronitriles,⁵² secondary benzylic NHP-esters,⁵³ chlorobenzyl silanes,⁵⁴ and 1-chloro-1-alkanol esters.⁵⁵ All enantioselective XEC methodologies utilize secondary electrophiles, with no asymmetric reports of tertiary electrophiles. This can be attributed to the challenges of capturing a more sterically encumbered tertiary radical. On the other hand, the C(sp^2) electrophile scope is generally limited to alkenyl halides, aryl halides, or acyl chlorides.⁵⁶

When examining the literature to identify the ideal system to analyze, I reviewed multiple reports that screened Mn, Zn, and TDAE as reductants in the reactions and compared yields and ee. In 2017, the Reisman group reported the enantioselective XEC of NHP esters with vinyl bromides, observing a stark change in product yield and enantioselectivity (**Figure 4.1a**).⁵³ One possible explanation for the change in yield is that the reductants reduce nickel at different rates. However, the product's selectivity also appears to depend on the identity of the reductant

employed, which would be consistent with a competing mechanism for accessing the product. This stark difference in product ee depending on the reductant used also appears in other XEC reports (**Figure 4.1b**), such as the XEC of heteroaryl iodides with α -chloronitriles.⁵² Considering the non-negligible change in the product ee in these cases, we postulated two possible explanations: 1) the reductant is a part of the enantioselectivity-determining step, or 2) changing the reductant completely changes the mechanism.

a) Reisman (2017)



b) Reisman (2015)

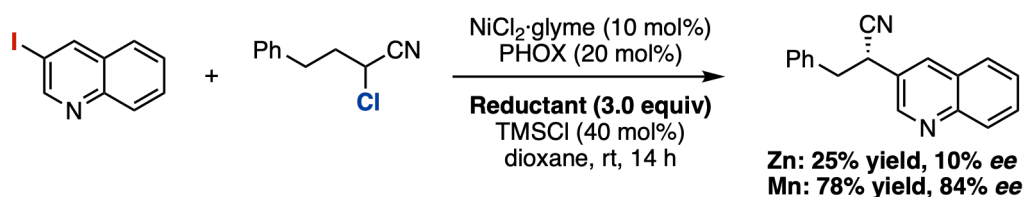
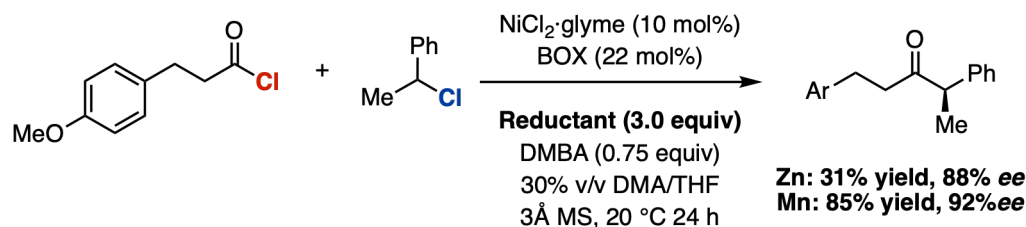


Figure 4.1: XEC reactions where changing the reductant has a large impact on product ee.

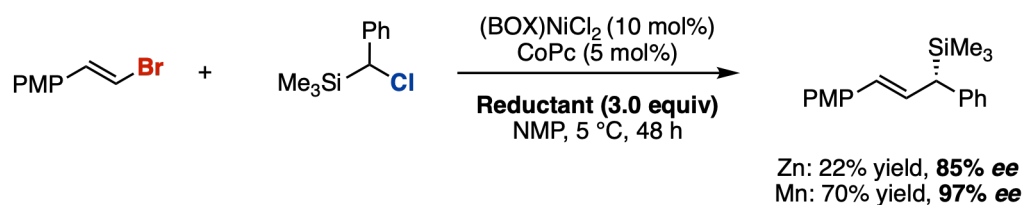
However, this is not the case for all XEC reactions; sometimes the difference in enantioselectivity can be minor or non-existent when the reductant is changed. The reactions in **Figure 4.2** are examples of such cases.^{54, 56-58} This suggests that the field of XEC may not have a “one mechanism fits all” approach. However, there is currently no rationale for why ee sometimes changes and sometimes remains unchanged in these reactions. Additionally, there is no clear trend to predict how

large a gap in ee will be between different reductants, or whether there will be any gap at all. Finally, there is no correlation among electrophile types that would yield a substantial gap.

a) Reisman (2013)



b) Reisman (2018)



c) Gong (2025)

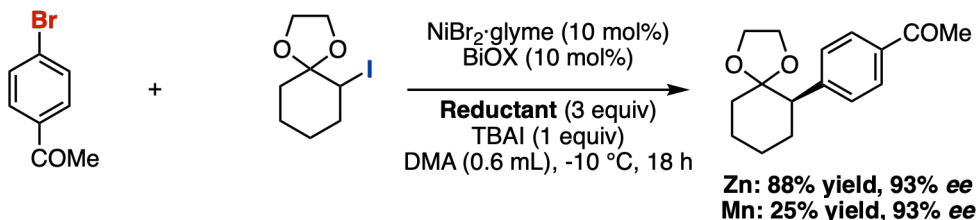


Figure 4.2: XEC reactions where changing the reductant does not cause a large difference in ee.

This raises the question: are reductants serving simply to reduce Ni, with the change in yield attributed to superior rate matching, or does changing the reductant completely change the reaction mechanism? One simple way to assess this is to observe changes in product ee as the reductant is varied. If the reductant is serving the same role in every reaction, which is typically a distinct step from the

enantioselectivity-determining step, the enantioselectivity of the product should remain the same (or at least within a small margin of error).

Our aim is to investigate a reaction with a substantial difference in ee between reductants to determine how the reductant is involved in the enantioselectivity-determining step, or whether changing the reductant completely changes the mechanism. The initial study detailed in this chapter is not meant to generalize to all XEC reactions, but rather to provide insight into why, in this specific case, we are observing the ee gap.

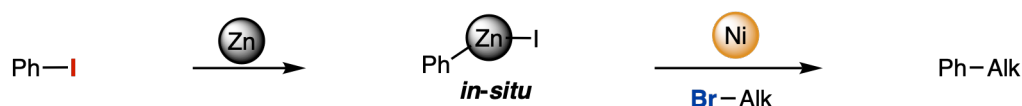
Section 4.4: Current Mechanistic Understanding

The understanding of XEC mechanisms is continually evolving due to the numerous routes that can afford the product and the influence of each electrophile and ligand on the prevalent pathways. An excellent early mechanistic investigation was conducted by the Weix lab, which investigated the XEC of aryl and alkyl halides using the di-*tert*-butyl bipyridine (dtbbpy) ligand (**Figure 4.3**).⁵ The Weix group covered the four classes of mechanistic proposals that were commonly proposed and systematically eliminated unlikely scenarios through Ni-loading and stoichiometric experiments.

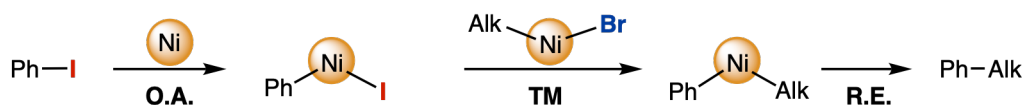
Figure 4.3a shows the in situ formation of a carbon nucleophile with either Zn or Mn, followed by a traditional mechanism seen in Kumada or Negishi-type cross-coupling. The Weix group ruled out the possibility of this pathway operating in this system by screening TDAE, an organic reductant, and observing the formation of the cross-coupled product. The second proposal discussed was individual activation of each electrophile by two distinct Ni-species, followed by a final transmetallation step between two Ni(II) species (Ni(II) alkyl halide and Ni(II) aryl halide), and subsequent reductive elimination to afford the desired cross-coupled product (**Figure 4.3b**). This process was ruled out by increasing the Ni loading, which revealed a higher cross-coupled product/dimer ratio at the lowest catalyst loadings. If this were the operative pathway, Ni loading should have no bearing on cross-selectivity, and the cross-

coupled product/dimer ratio should remain consistent regardless of catalyst loading. A third option proposed a sequential oxidative addition mechanism from a single nickel center, resulting in a high-valent nickel species that could readily undergo reductive elimination to afford the product (**Figure 4.3c**). This proposal was subsequently ruled out through increasing catalyst loading and analyzing the product distribution of radical clock experiments. Finally, the fourth proposal invoked a radical chain mechanism via the buildup of a Ni(II) aryl halide complex that traps a carbon-centered radical (**Figure 4.3d**).

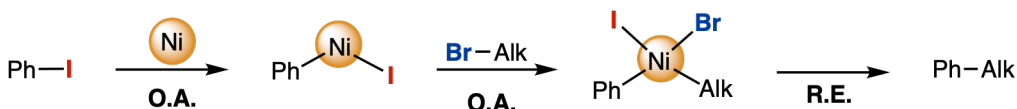
a) Pre-formation of metal-carbon nucleophile



b) Transmetalation between Ni species



c) Sequential OA at single Ni center



d) Radical chain reaction

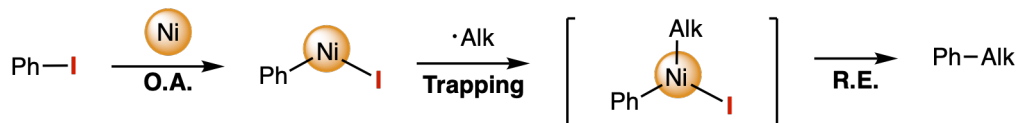


Figure 4.3: Commonly proposed pathways of Ni-catalyzed XEC reactions.

The radical chain mechanism that Weix lab proposed (**Figure 4.4**) began with initial reduction to Ni(0) (**I**) followed by oxidative addition into aryl halide to form Ni(II) aryl halide complex (**II**). This complex then traps a C(*sp*³) radical to form the transient Ni(III) (**III**), which undergoes reductive elimination to form the desired cross-coupled product. The resulting Ni(I) (**IV**) then continues the radical chain via halogen atom transfer (XAT) from the alkyl halide to reform Ni(II) dihalide (**V**). This species is then reduced to Ni(0) (**I**), thereby continuing the catalytic cycle.

This proposal is supported by a series of kinetic and stoichiometric experiments that highlight the faster oxidative addition of aryl iodide before Ni reacts with alkyl halides (via halogen atom transfer (XAT) or oxidative addition). Hence, **II** is proposed to trap an alkyl radical rather than a Ni(II) alkyl halide trapping an aryl radical. This also rules out the possibility of sequential oxidative addition of the alkyl halide followed by the aryl iodide.^{5, 59}

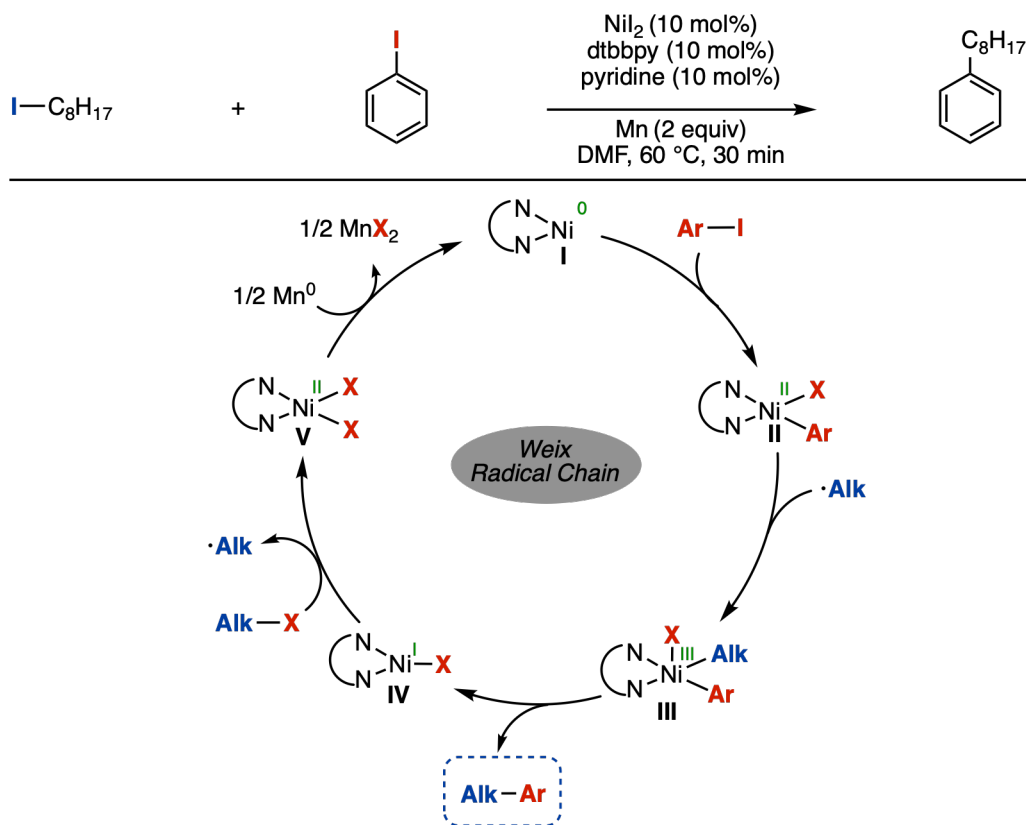


Figure 4.4: Weix radical chain proposed mechanism.

The success of the reaction is dependent on having high concentrations of Ni(II) aryl halide **II** in solution that can trap the alkyl radical. However, some proposals suggest that a Ni(II) alkyl intermediate can react directly with an aryl iodide to afford the product.⁶⁰⁻⁶² This pathway is less commonly proposed due to the high reactivity of alkyl nickel complexes, the demonstrated faster reactivity of low-valent Ni species with aryl halides over alkyl halides, and their potential to undergo β -hydride elimination as a deleterious side reaction. Nevertheless, this remains a possibility that warrants consideration as we explore potential mechanisms.

Subsequent alternative radical chain mechanisms have emerged in the literature as understanding of Ni-catalysis has further developed, with additional methodologies and mechanistic investigations. In 2021, the Diao group investigated the behavior of bioxazoline (BiOX) ligated Ni species and their relative reactivities towards the reduction of Ni(II) species, oxidative addition, and reductive elimination.^{6, 63} These studies aimed to clarify the mechanism of the asymmetric XEC reaction developed by the Reisman group in 2017 (**Figure 4.5**).² Compared to other *N,N*-bidentate ligands (such as bpy, phen, biim, and pyBOX) the BiOX complexes had a noticeable lack of redox activity (in CV and EPR experiments). Other ligands typically undergo MLCT upon reduction, generating a radical-ion pair (a radical-anion ligand and a cationic Ni), thereby enabling more facile reduction. The Weix group has often proposed that (dtbbpy)Ni(II) dihalides can be reduced to Ni(0) *in situ* due to the redox activity of these complexes.^{64, 65} However, in contrast, the Diao group found the reductions of the (BiOX)Ni(II) aryl halide ($E_{1/2}[\text{Ni(II)/(I)}]$ (V vs Fc^+/Fc) = -2.12 V) and (BiOX)Ni(II) dibromide ($E_{1/2}[\text{Ni(II)/(I)}]$ (V vs Fc^+/Fc) = -1.55 V) with Mn (-1.55 V) or Zn (-1.31 V) would be difficult due to extremely negative reduction potentials of these complexes.⁶⁶ This was the case for both single-electron reduction to Ni(I) and two-electron reduction to Ni(0).

It should be noted that the reduction of (BiOX)Ni(II) dibromide to Ni(I) was successful with Rieke's Mn and Zn. The mechanistic implication of this result is that, when using (BiOX)Ni catalysts, access to Ni(0) becomes much more difficult, if not

impossible. This is due to Rieke's Mn or Zn performing an inner-sphere reduction as opposed to an outer-sphere reduction.⁶⁷ This alternative reduction manifold may therefore play a role in the mechanism of these reactions, as the accessibility of (BiOX)Ni(I) from (BiOX)Ni(II) dihalide differs from that of (dtbbpy)Ni(II) to (dtbbpy)Ni(0).

As we had previously observed in our THF arylation, proposing oxidative addition from Ni(I) vs Ni(0) greatly changes the reaction profile and affects the accessible paths to the different Ni-intermediates.³ Therefore, to probe the competency of Ni(I), the Diao group synthesized (BiOX)Ni(I) bromide and (BiOX)Ni(I) aryl species and determined how they could engage electrophiles through a series of stoichiometric experiments.⁶ This led to their own distinct mechanistic proposal based on these results.

The Diao mechanism (**Figure 4.5**) takes a unique approach that accounts for the difficulty of reducing (BiOX)Ni(II) complexes. Since they claim that (BiOX)Ni(II) bromide cannot be reduced using Zn or Mn, the reaction must be initiated in a different way. Reaction initiation occurs via the generation of a benzylic radical. Despite the popularity of Ni(I) performing XAT, the Diao group proposes that Ni(II) pre-catalyst (**V**) acts as a Lewis acid to promote benzylic radical generation in the presence of Mn and TMSCl (**V** to **VI** in the left cycle).⁶⁸ This generates a benzylic radical, which is trapped by the pre-catalyst (**V**), yielding a highly reactive Ni(III) (**VI**).

This species is either reduced by the Mn or undergoes reductive elimination to generate Ni(I) halide (**IV**) and benzyl halide. Upon generation of low-valent Ni(I) (**IV**), the productive catalytic cycle shown on the right can start.

The Diao group proposes two potential pathways from here: either a potential bimolecular oxidative addition to generate **II** as well as regenerate pre-catalyst **V** (left and right cycles following **IV**),⁶⁹ or mononuclear oxidative addition forming Ni(III) aryl dihalide **VII**, followed by reduction with Mn to afford **IV** (right cycle). This step was proposed based on the results of a stoichiometric experiment in which (BiOX)Ni(I) bromide reacted with iodomesitylene to afford both nickel species: (BiOX)Ni(II) aryl halide (**II**) and (BiOX)Ni(II) dihalide (**V**). At this stage, the Ni(II) species **II** then is proposed to act as a Lewis acid to form an additional benzyl radical in the presence of Mn, benzyl chloride, and TMSCl (**II** to **III** in the right cycle, similar to what was also proposed in the left cycle, **V** to **VI**). This benzylic radical is readily trapped by **II** to form transient Ni(III) (**III**), which undergoes reductive elimination to form the desired cross-coupled product while regenerating **IV**.

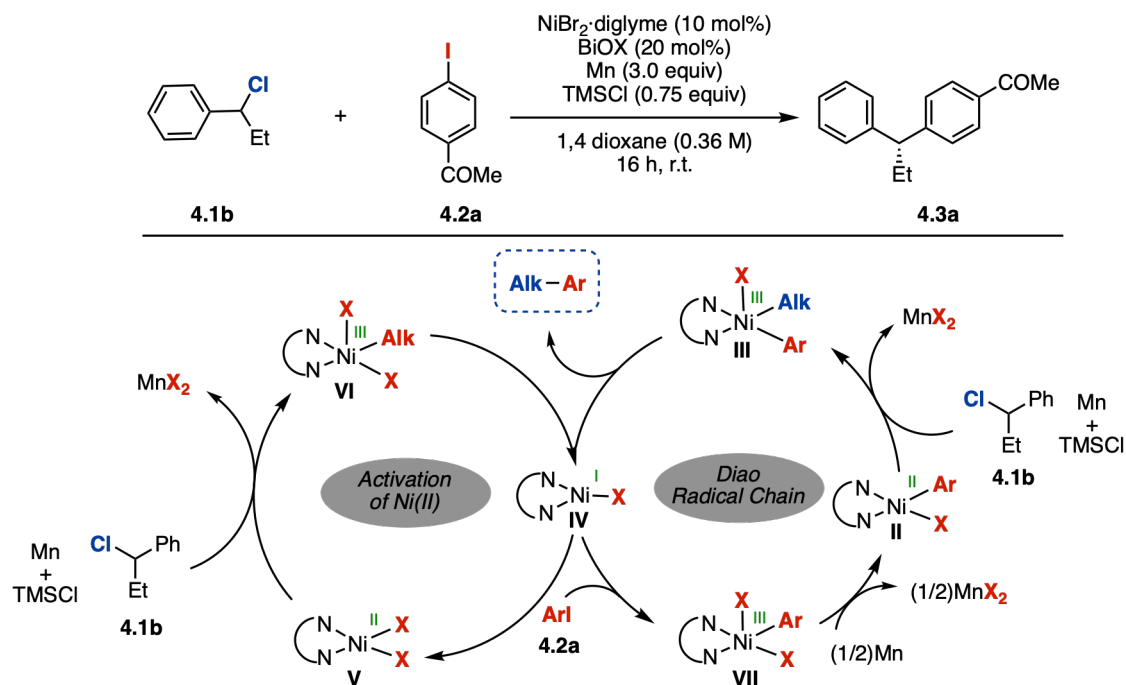


Figure 4.5: Diao radical chain proposed mechanism.

This specific mechanistic scenario was only possible to propose due to the diligence of the Diao group, which investigated the reactivity of (BiOX) Ni complexes. However, the reaction's ability to still produce product with other non-BiOX ligands (such as dtbbpy) raises the question: does the reaction switch mechanism when the ligand is changed? Additionally, within the Reisman report iodomesitylene was not included in the substrate scope, likely due to its steric bulk and electron-rich nature.² This was the aryl iodide used in all of the Diao group's stoichiometric studies, raising the question of the catalytic relevance of these results. Stoichiometric reactions performed with non-catalytically active substrates or ligands can yield misleading information about Ni-catalyzed systems, as they are not a direct comparison to the system of interest. Regardless, the important takeaway from this study is the ability

of Mn to engage the benzyl chloride to generate the alkyl radical, the proposal of Ni(I) doing the oxidative addition instead of Ni(0), and contextualizing the difficulty of reducing (BiOX)Ni(II) complexes to Ni(I) or Ni(0) species.

One additional mechanistic study by the Reisman group on the Ni-catalyzed XEC of alkenyl bromides with benzyl chlorides and alkyl NHP esters was recently reported.^{7, 70} This work also investigated the Ni-catalyzed XEC of alkenyl bromides with alkyl NHP-esters.^{7, 53} The two systems were chosen for their similar coupling partners and use of a bisoxazoline (BOX) ligand. Within this work, the Reisman group conducted a series of cyclic voltammetry experiments to deduce whether their (BOX)Ni(II) dihalide was able to be reduced to Ni(0), finding that this two-electron reduction happened out of the solvent window of DMA and a Ni(I) species was stabilized with a coordinating DMA molecule.⁷¹ This difficult reduction is comparable to the results reported by the Diao group for (BiOX)Ni(II) complexes.⁶ This information, along with EPR studies, was used when proposing yet another radical chain mechanism for these transformations.

The Reisman proposal (**Figure 4.6**) differs from the Weix proposal primarily in the role of Ni(I). In this mechanism, the initial pre-catalyst (**V**) is reduced with Zn to Ni(I) (**IV**). Despite the difficulty of the reduction, the Reisman group claims that using DMA as a solvent facilitates it. From here, Ni(I) (**IV**) will oxidatively add to the alkenyl bromide to form Ni(III) (**VII**), which is then reduced by Zn to form Ni(II) alkenyl bromide

(II). Alternatively, **IV** will perform XAT to generate a benzylic radical, regenerating Ni(II) dihalide (**V**) and perpetuating the radical chain. Through CV studies, the Reisman group demonstrated that **IV** will preferentially react with an alkenyl bromide rather than benzyl chloride when present in equimolar amounts. This will lead to a buildup of **II**, which is then proposed to trap the benzylic radical. The resulting Ni(III) (**III**) rapidly undergoes reductive elimination to afford the desired cross-coupled product.

While conducting their studies, the Reisman group observed a slight induction period. They propose this is due to the buildup of **II** (which leads to the consumption of alkenyl bromide), as their CV studies showed that lowering the concentration of alkenyl bromide is necessary for XAT with **IV** to occur. Additionally, Ni(I) was found to be suitable for direct engagement with benzyl chloride, as they observed the formation of a dimer when reacting benzyl chloride with Ni(II) dihalide and Mn exclusively. This is thought to arise from the build-up of benzyl radical *in situ*, which then leads to the formation of the resulting dimer.

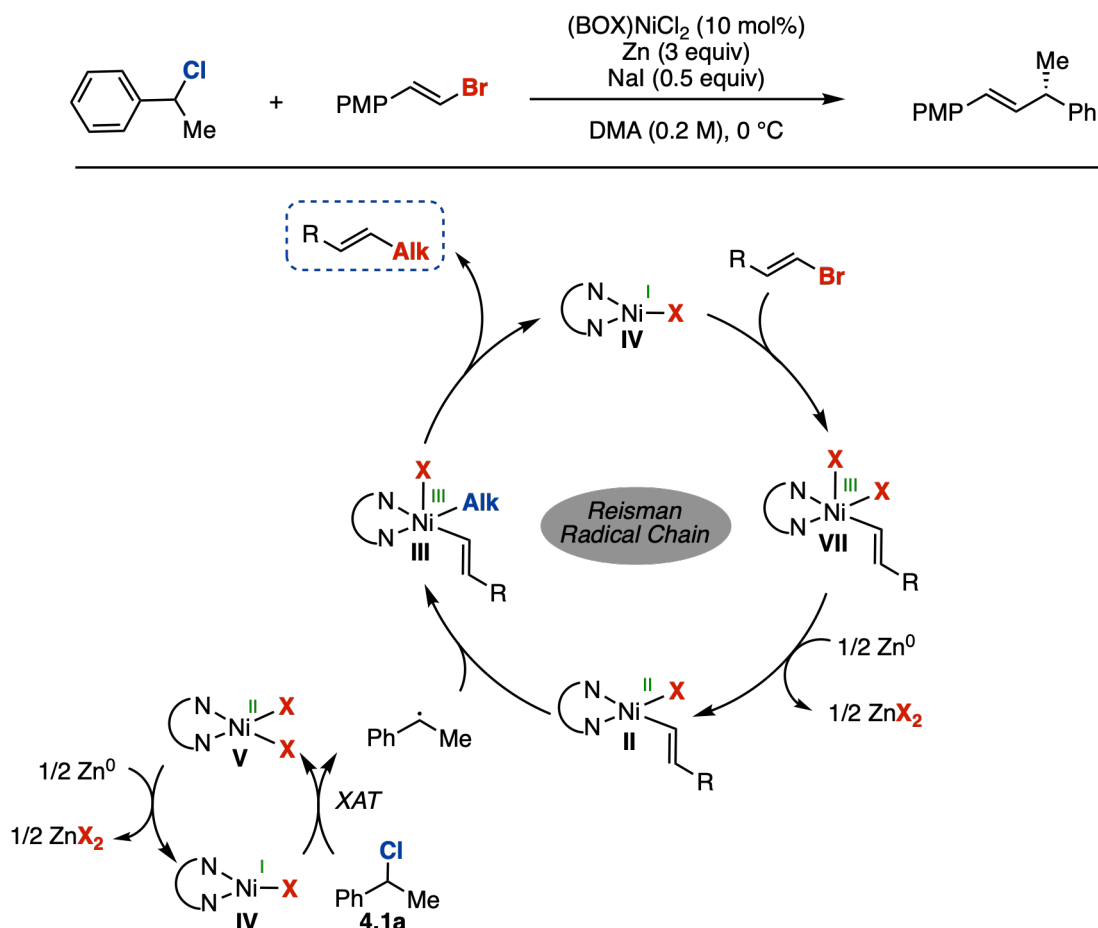


Figure 4.6: *Reisman radical chain proposal.*

This is in opposition to the Diao proposal, which posits that, during the formation of benzylic radicals, a Ni(II) complex acts as a Lewis acid. Here, the Reisman group proposes that **IV** acts as an XAT agent. This divergence could be attributed to a difference in the ligand scaffold, but the Diao group has also demonstrated that the redox inactivity of (BOX)Ni(II) complexes is comparable to that of (BiOX)Ni(II) complexes.⁶³ Another possibility is that the observed different results in the reduction could be due to solvent effects. The Reisman group emphasized the role of DMA in stabilizing Ni(I) species, which they used for CV studies, whereas the

Diao group did not use amide solvents. Nevertheless, the similarities in the conditions studied in both reports and the discrepancies in the proposed mechanism highlight the need for further mechanistic understanding of these systems.

When comparing the Weix,⁵ Diao,⁶ and Reisman⁷ proposals, there are substantial differences in the activation of the pre-catalyst, activation pathway of the alkyl electrophile, and the valency of the Ni throughout the mechanism. Most importantly, none of the proposed mechanisms account for differences in product enantioselectivity that can arise when switching reductants, because the reductant is not involved in the step that determines enantioselectivity. Indeed, all three mechanisms share the same proposed enantioselectivity-determining step: capture of a C(*sp*³) radical via a (L)Ni(II) C(*sp*²) halide complex (**II**). This step is identical to the one we hypothesized and tested as the enantioselectivity-determining step in the HAT-mediated THF-arylation reaction (**Figure 4.7**).³ Therefore, we chose the XEC of aryl iodides and benzyl chlorides as our system of interest, since I have already optimized the procedure for making **II** with BOX ligands (described in **Chapter 2**).²

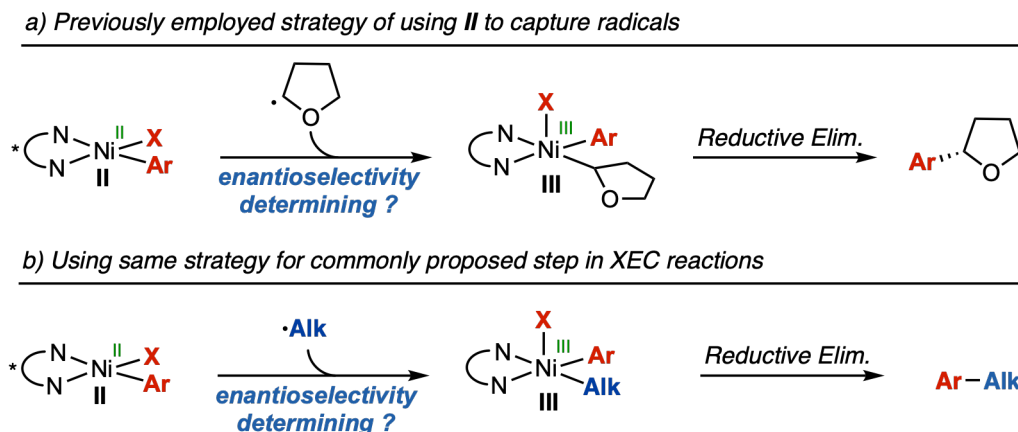


Figure 4.7: Strategy for interrogating commonly proposed mechanistic steps in XEC reactions.

The use of **II** in stoichiometric experiments will provide key insights. If the ee matches the ee obtained under catalytic conditions, this would validate the feasibility of the enantioselectivity-determining step. If the ee were different, it would open the possibility of considering alternative pathways. In this context, we wanted to clarify some of the divergences among the proposed mechanisms by focusing on the one step they all share (**Figure 4.7b**). Additionally, this system appears to exhibit drastic differences in product enantioselectivity depending on the reductant (**Figure 4.8**), making it an ideal system to investigate compared with systems that show similar ee across reductants.⁷ Finally, this system contains no additives that increase mechanistic complexity (such as NaI) and is a rare example of an XEC run in a non-amide solvent. All these factors made this system ideal for our mechanistic investigation.

While our focus is on the product and the enantioselectivity-determining step, there are still other questions of interest for this reaction. For instance, do Ni-

catalyzed XEC reactions using BiOX and BOX ligands have completely different mechanisms than other methodologies using *N, N*-bidentate ligands due to their lower redox activity? If so, how does (BOX)Ni(II) and (BiOX)Ni(II) reduction occur? Do amide solvents play a critical role in stabilizing reduced Ni-species as proposed by the Reisman and Hadt groups? ⁷¹ Is the direct reduction of these complexes limited only to amide solvents? These questions all play an important role in elucidating the mechanisms of XEC reactions. Our focus in this work, however, is strictly on the enantioselectivity-determining step and on elucidating the role the reductant plays in it. Our hope is that with these initial studies, the field can further develop to answer more of these pressing questions.

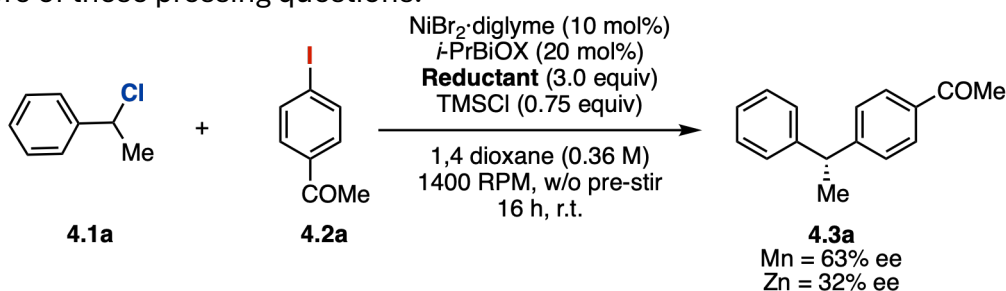


Figure 4.8: Reaction system of interest.

Section 4.5: Current Progress and Screening Results

Our work began with a screening of BiOX ligands (**Table 4.1**). The optimized ligand in the initial report was ((4*R*,4'*R*)-4,4'-diheptan-4-yl)-4,4',5,5'-tetrahydro-2,2'-bioxazole, which requires a multistep synthesis of an amino alcohol starting material.² For the purposes of our investigation, we opted against the timely synthesis of this ligand in favor of BiOX ligands that could be synthesized from commercially available amino alcohols and still afforded adequate yield and ee. Other changes made to the Reisman system were the reaction vessel and the stir bar. In the initial report, all reactions were conducted on a 0.2 mmol scale under an inert atmosphere in a 20 mL scintillation vial with a cross-shaped stir bar. We opted to use a 10 mL Schlenk tube to keep the reaction under nitrogen while taking aliquots. Given the shape of the Schlenk tube, we also switched to a pill-shaped stir bar to ensure uniform vigorous stirring of the heterogeneous mixture. This was shown to be key for attaining reproducible yield and ee. Switching from a Schlenk tube to a 20 mL scintillation vial or 2 mL dram vial slightly altered the yield and enantioselectivity of the product, likely due to the buildup of local concentration gradients from uneven stirring.⁷² Finally, the (1-chloropropyl)benzene (**4.1b**) used in the initial report was replaced with (1-chloroethyl)benzene (**4.1a**) due to its commercial availability.

I synthesized three BiOX ligands and performed the initial screening results with 1-(4-iodophenyl)ethan-1-one (**4.2a**) (**Table 4.1**). This reaction gave comparable

yields across all three screened ligands, but a substantially higher product ee when using ligand **L4.1**. Notably, the optimal ligand (**L4.1**) is structurally similar to the 4-*n*-heptyl bioxazoline ligand used in the initial report and can be readily synthesized from commercially available *L*-valinol.²

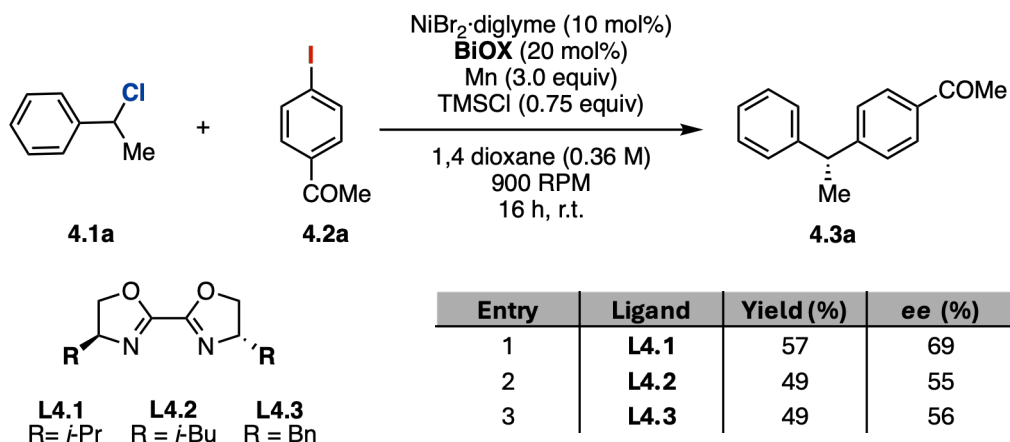


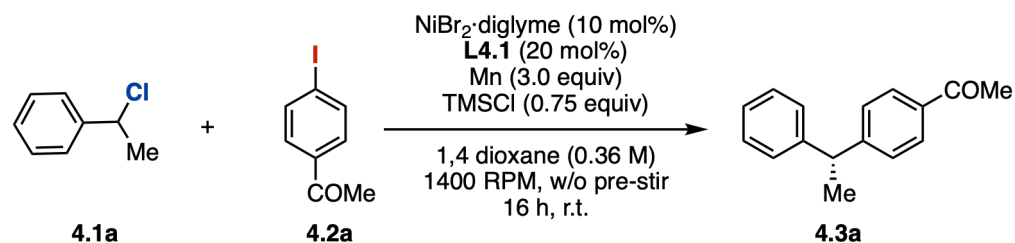
Table 4.1: Initial ligand screening.

To potentially increase the yield and reaction rate, the stirring rate was increased to the maximum value of 1400 RPM, which increased the yield from 57% to 85% but slightly decreased the ee to 63% (**Table 4.2, Entry 1**).⁷² The change in yield is expected, but the drop in ee was surprising. I will further address this phenomenon in a later section.

Another change we made during screening was to remove the initial pre-stir of the ligand, Ni, **4.2a**, and Mn in dioxane before adding **4.1a** and TMSCl. This pre-stir was a part of the Reisman group's procedure and was utilized in their optimization campaign in their initial report. The purposes of this pre-stir will be further explained

in detail in a later section, but we found that the overall yield and selectivity were comparable with or without the pre-stir (**Table 4.2 Entry 2**).

When screening reductants, TDAE afforded no cross-coupled product (**Table 4.2 Entry 3**). Although the product was obtained in low yield when using Zn, we were able to measure the enantioselectivity and found it had decreased drastically to 32% ee (**Table 4.2, Entry 4**). This was an encouraging result for investigating differences in ee values across different reductants. Finally, lowering the stir rate further to 600 RPM reduced the yield to 51% but increased the ee to 70% (**Table 4.2, Entry 5**). As previously mentioned, this stirring effect on ee will be discussed in detail in a later section.



Entry	Deviation	Yield (%)	ee (%)
1	none	83	63
2	with pre-stir	85	63
3	TDAE instead of Mn	N.D	N.D.
4	Zn instead of Mn	8	32
5	stir at 600 rpm	51	70

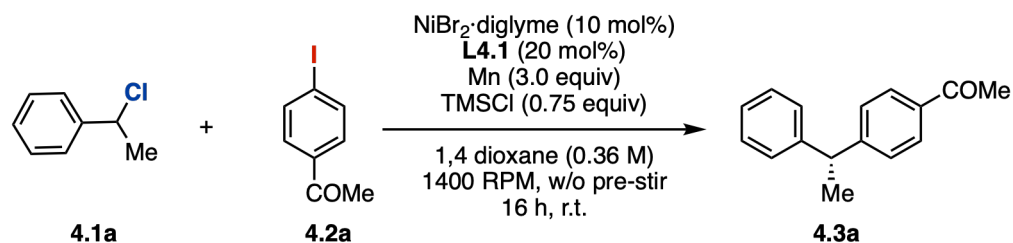
Table 4.2: Reductant and stirring screening results. Unless otherwise noted, all reactions were performed at 1400 RPM without the pre-stir of Ni, aryl halide, ligand, and Mn in 1,4- dioxane. Yield and ee were both calculated using an Acquity UPC² system with benzophenone as the internal standard.

We next studied the effect of changing the halides present in the reaction. We started by screening the bromide analog of **4.2a** to assess whether enantioselectivity would change with the starting material, as observed in the THF arylation report.³ Despite a low yield of 13%, we were able to assess the product enantioselectivity, which was consistent with the standard reaction conditions (**Table 4.3 Entry 1**). This contrasted with our THF-arylation findings, surprising us with the lack of change in ee.³

Subsequently, we tested the effect of adding various halide salt additives to determine whether the enantioselectivity would change (**Table 4.3, Entries 2-4**). In our THF-arylation report, we found that adding chloride salts as an exogenous chloride source increased the product enantioselectivity, even with an aryl bromide starting material.³ In the context of this reaction, there was a slight change in yield,

but the ee remained within a narrow window of the standard reaction. As of now, our results indicate that halogen identity on the Ni(II) aryl halide species (**II**) is not a key factor in the enantioselectivity-determining step of the reaction. We are working to confirm this through stoichiometric experiments, such as the ones performed in our THF-arylation report (see **Figure 4.7**). More details on the stoichiometric experiments will be discussed in **Section 4.8**, as initial attempts have given us inconclusive results.

Although aryl halide and salt additives showed no effect on the ee, we wanted to investigate every source of halide and its potential effect on the product ee. When changing the Lewis acid to TMSBr, the reaction yield decreased to 60%, and the ee decreased to 54% (**Table 4.3 Entry 5**). An even larger decrease was observed with TMSI, affording a 35% yield and 47% ee (**Table 4.3, Entry 6**). Finally, the absence of a Lewis acid afforded no conversion of the starting material, indicating its essential role in the reaction (**Table 4.4, Entry 7**).



Entry	Deviation	Yield (%)	ee (%)
1	ArBr instead of ArI	13	63
2	NaCl (2 equiv)	6	70
3	NaBr (2 equiv)	76	67
4	NaI (2 equiv)	87	70
5	TMSBr instead of TMSCl	60	54
6	TMSI instead of TMSCl	35	47
7	No TMSCl	N.D.	N.D.

Table 4.4: Screening of halide sources.

The role of the Lewis acid in these reaction systems is typically associated with the removal of the manganese oxide or zinc oxide layers that can build up on the surfaces of the reductants.^{52, 73} This agrees with our control reaction, which shows no product formation and full recovery of the aryl iodide in the absence of the Lewis acid (**Table 4.3, Entry 7**). This is due to either Mn containing a layer of manganese oxide preventing reduction of the Ni, Mn containing a layer of manganese oxide preventing generation of the benzylic radical, or the Lewis acid being necessary to generate the benzylic radical.^{6, 7}

Further involvement of silane in mechanistic proposals is traditionally observed only when studying systems involving NHP esters. The role of the silane in those reactions is to raise the NHP ester's reduction potential and prohibit decomposition into a carboxylic acid byproduct.^{7, 74} However, reexamining the Diazo proposal (which does not involve an NHP ester coupling partner), the Lewis acid is

invoked to help activate the benzyl chloride and promote the formation of the benzyl radical.⁶

To differentiate among these scenarios, the Rousseaux group performed an experiment in an XEC reaction of aryl iodides with NHP esters, pre-treating their Zn with TMSCl and subsequently removing the excess Lewis acid.⁷⁴ They then carried out the XEC reaction without adding a Lewis acid. This was to determine whether TMSCl served only to remove zinc oxide particles or was necessary for radical formation. We intend to repeat the same experiment to determine whether TMSCl directly participates in generating the benzyl radical from **4.1a**. It will be particularly relevant to us, given the unexpected observation of changes in *ee* upon changing Lewis acids.

The final halide source we are interested in screening is the bromide and chloride analogs of **4.1a**. We are currently finding these results to be difficult to reproduce, especially for the benzyl iodide reaction. In both cases, though, we are observing a slight change in product enantioselectivity. We find it interesting that in the cases of Lewis acid and alkyl halide, the *ee* changed, whereas with aryl halide, it did not. We plan on incorporating this information into our mechanistic proposal.

Section 4.6: Effect of Different Ni-Sources on System Reactivity

After successfully screening multiple reaction components, we began to question why we were observing a slight change in ee when running the reaction at lower stirring rates. The step we suspected was impacting the ee was the one that invoked Mn or Zn, whether by reducing Ni or generating the benzyl radical. Reduction using Mn or Zn powder occurs in two steps: first, mass transfer as Ni is adsorbed onto the surface, and second, electron transfer from the reductant to Ni. The reduction depends on several factors: the convective transfer rate, the electron transfer rate, and the available surface area.⁷⁵ It has been observed in XEC reactions using metal reductants that the stirring rate can affect the reaction rate and overall yield. However, the effect of ee on stir rate, even in a small way, is a less-explored concept.

One simple explanation for the results could be product racemization at the higher stir rate. Given that the stir rate directly affects the reaction rate in these systems, it's possible that as more product is generated in a shorter time, the catalyst will begin racemizing the product. When there is a higher concentration of **4.3a** *in situ*, HAT may occur at the product benzylic position (the HAT agent could be a benzylic radical generated from **4.1a** during the catalytic cycle), thereby slowly racemizing the product. We believed this was possible in our THF-arylation system as well and ruled it out by subjecting the cross-coupled product to standard reaction conditions to see whether the product ee decreased over time.³ To rule out this

possibility in this system, I began running time point reactions. If, at each stirring rate, the enantioselectivity remains constant throughout the reaction run, this supports the conclusion that the change in ee arises from changes in stirring, not from product racemization.

To monitor both yield and enantioselectivity, we used our ACQUITY UPC² system with benzophenone as an internal standard. Before any time point reactions were conducted, we ensured that benzophenone did not affect yield or ee by running two experiments in parallel and comparing isolated yields and ee, which were nearly identical for both reactions.

We started the time point studies with the exact procedure used by the Reisman lab. All the solids were added to the Schlenk (Mn, Ni, ligand, **4.2a**), then the 1,4-dioxane was added. This mixture was stirred for 20 min, after which **4.1a** and TMSCl were added, and the reaction was sealed (**Figure 4.9**). The initial results showed a steady increase in yield, with minor fluctuations in ee. The product was detected as early as the 15-min time point.

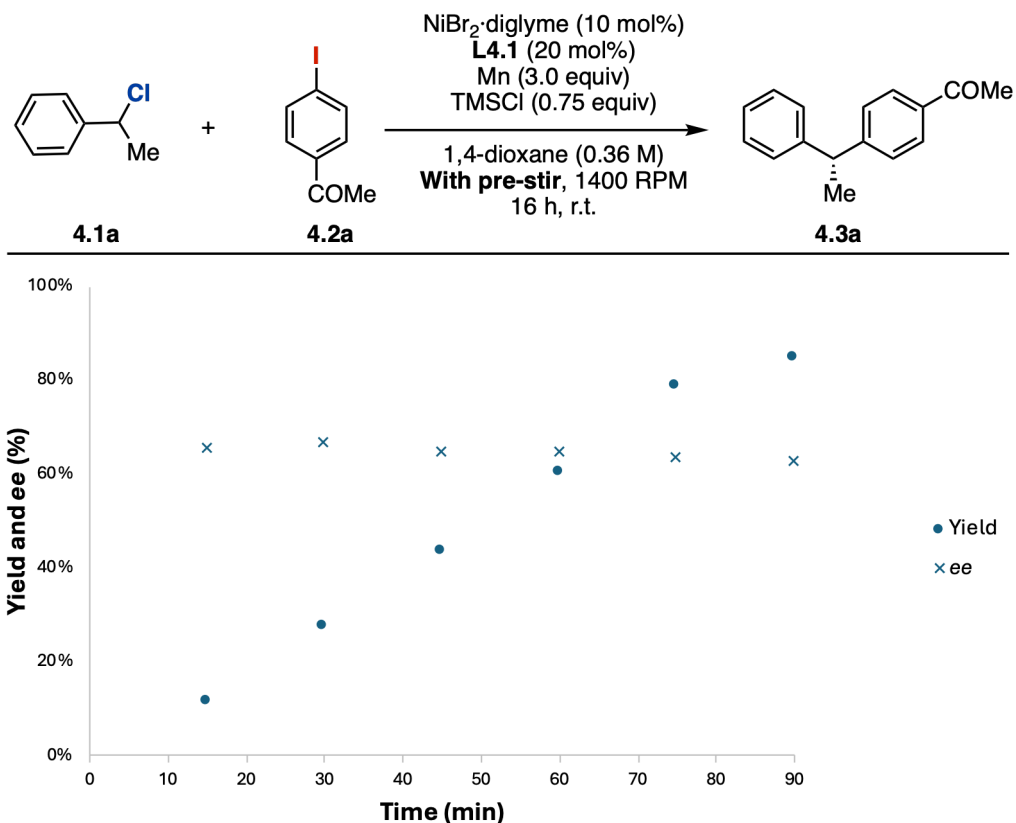


Figure 4.9: Time points run under Reisman conditions (with pre-stir).

We wondered how the observed induction period was affected by pre-stirring the reaction components during setup. One can envision that pre-stirring is necessary for ligand substitution of **L4.1** onto $\text{NiBr}_2 \cdot \text{diglyme}$ before the addition of **4.1a**, or for generating catalytically relevant intermediates. We then compared a reaction carried out without pre-stirring before the addition of **4.1a** and TMSCl with another in which the remaining reaction components were pre-stirred as previously described (**Figure 4.10**).

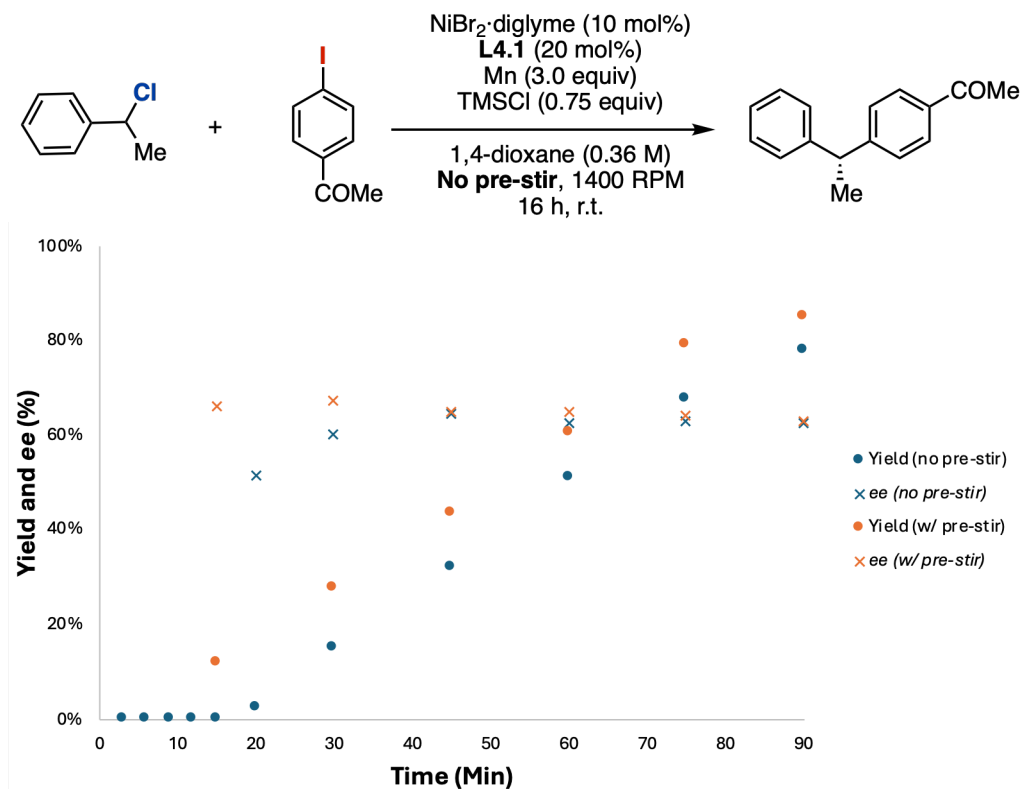


Figure 4.10: Time point reactions of standard conditions with pre-stir.

The reaction without any pre-stir showed an induction period up to the 20-min mark, a slightly diminished yield, but a consistent ee under standard conditions at 1400 RPM (63% ee). This induction period is likely attributed to our previously stated hypotheses: either Ni ligation or generation of the active catalyst. Our main takeaway from these experiments, however, was a consistent ee in the product as the reaction progressed, implying that the active catalyst is not racemizing the product and that there is no competition from different enantioselectivity-determining steps at early time points.

While this was helpful information to us, it left us more confused on why there was a discrepancy in ee data with stir rate since we could rule out the racemization hypothesis. One final test I performed was to compare reactions run at different stirring rates. (**Figure 4.11**).

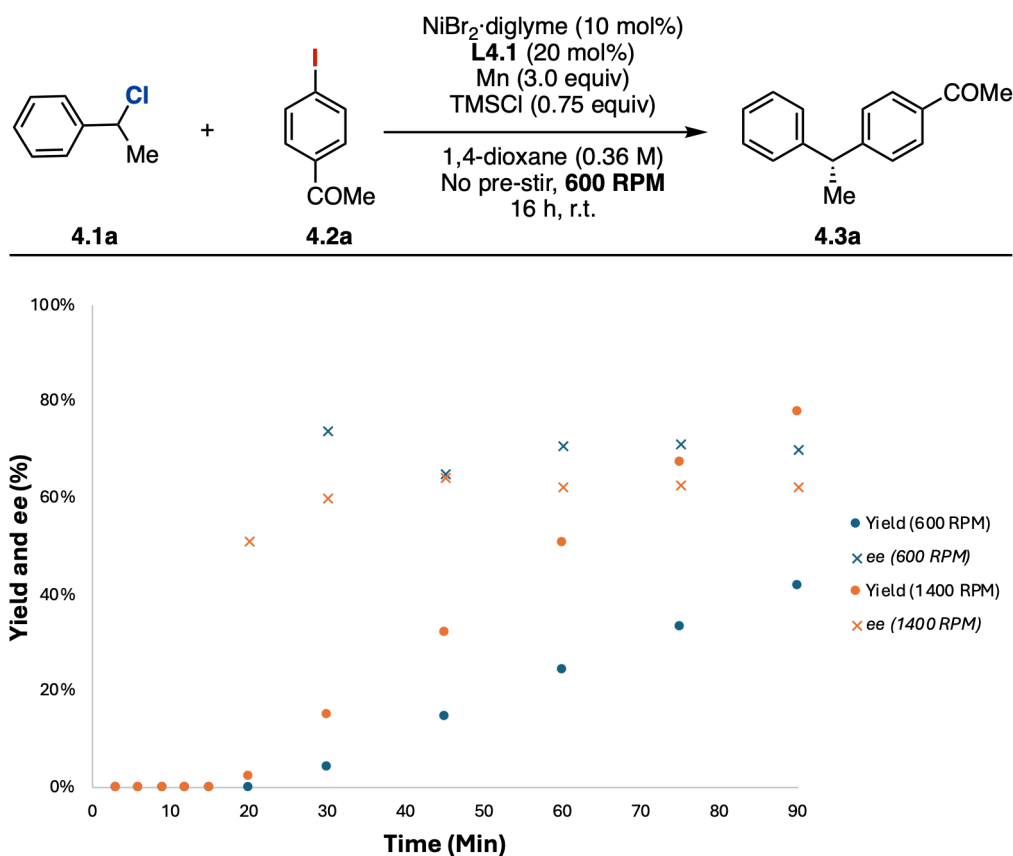


Figure 4.11: Time points at different stir rates. 600 RPM (blue) 1400 RPM (orange).

The induction period was slightly longer for the reaction run at 600 RPM, with the detected product formed by 30 min. This is consistent with either of the hypotheses to explain the induction period. Additionally, compared with the reaction performed at 1400 RPM, the ee was noticeably higher and remained consistent throughout the reaction. It should be noted that while the ee difference is moderate,

this experiment has been repeated multiple times, and the results have been consistent throughout.

Our current working hypothesis as to why the ee is affected by stir rate is that it is due to the buildup of localized concentration gradients at lower stirring rates. To further ensure that this can occur across different XEC reactions, we are currently investigating this reaction with different high-performing ligands, varying the benzyl chloride, and varying the aryl iodide.

Our priority then shifted to finding reaction conditions that did not give an induction period. This is not only to obtain more time points as the reaction begins, but also to determine whether other unknown byproducts are being generated and affecting the reaction mechanism. We decided to pre-ligate **L4.1** to the NiBr₂·diglyme pre-catalyst to see if the reaction would proceed without the induction period.

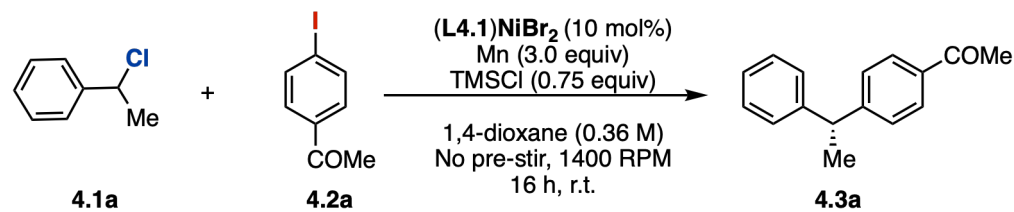
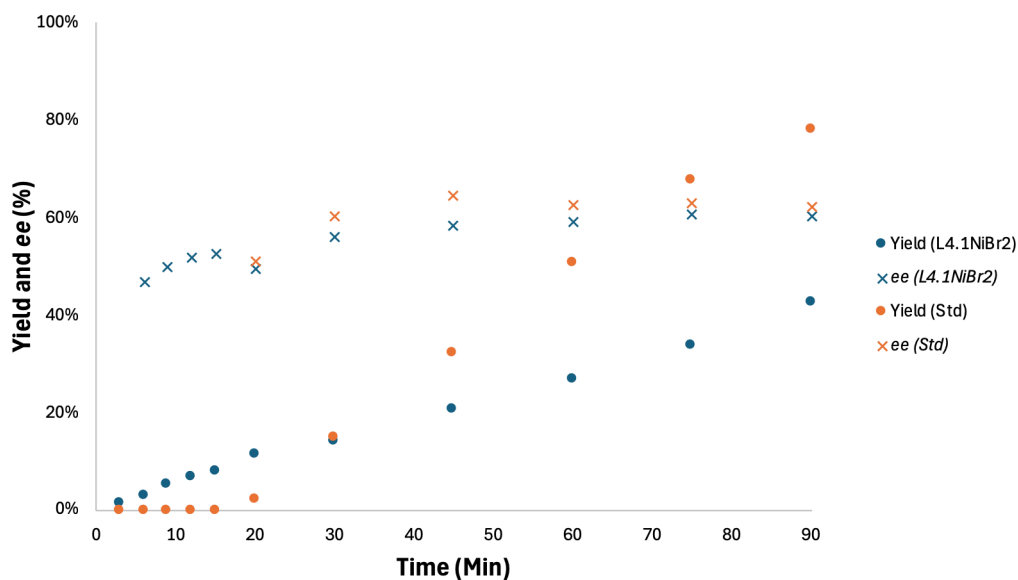


Figure 4.12: Comparison of (L4.1)NiBr₂ (blue) against L4.1 (20 mol%) and NiBr₂-diglyme (10 mol%) (orange).

To our delight (L4.1)NiBr₂ completely removed the induction period (**Figure 4.12**). However, this came at the cost of a diminished yield and a seemingly diminished ee to 60%. Additionally, the graph showed a gradual increase in ee. However, this may be due to an error in collecting early time points when yield is low, resulting in a more inaccurate measurement. Reproducibility for this experiment has proven difficult due to trace oxygen poisoning of the catalyst.

Additionally, the reaction proceeded at a much slower rate than under standard conditions, where the Ni is not pre-ligated. Because, under standard conditions, an excess of ligand relative to Ni is used, we decided to test whether running the reaction

with (**L4.1**)NiBr₂ and an additional 10 mol% **L4.1** to mimic the standard setup would improve reaction performance. While this raised yield, it reintroduced the induction period, and product formation once again stalled at ~90 min (**Figure 4.13**). We decided to move forward with this data for a point of comparison against other nickel sources.

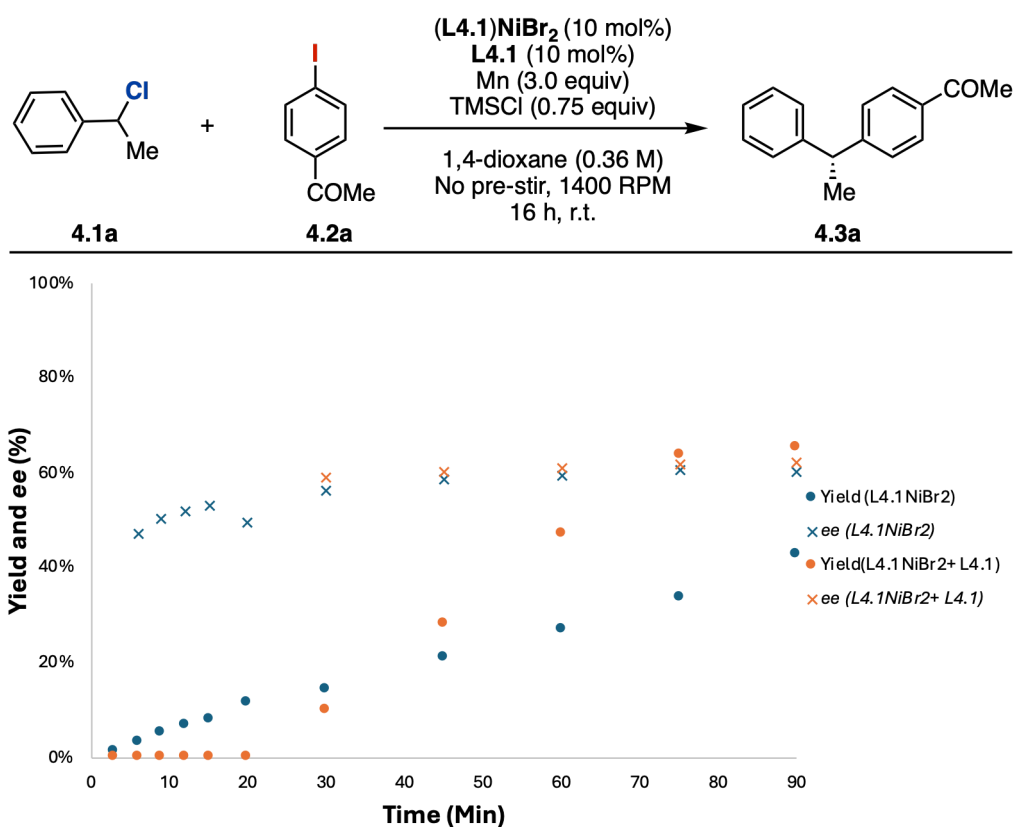


Figure 4.13: Comparison of (**L4.1**)NiBr₂ + 10 mol% **L4.1** (orange) against (**L4.1**)NiBr₂ (blue).

Subsequently, we decided to evaluate the effect of performing the reactions with Ni pre-catalysts in different oxidation states. The following time point experiments we performed used Ni(0), mixtures of Ni(II) and Ni(0), which are known to generate Ni(I) *in situ*, and (**L4.1**)Ni(II) aryl iodide complex made with **4.2a**).

Our first comparison was between (**L4.1**)NiBr₂ and (**L4.1**)Ni(0) (**Figure 4.14**). In our previous studies, we found that using Ni(COD)₂ as a pre-catalyst with an exogenous ligand resulted in no conversion. However, pre-ligating the BOX ligand to Ni(COD)₂ enabled reactivity.³ Hence, we also pre-ligated the BiOX ligand to Ni(COD)₂ to assess whether a reaction was possible using a Ni(0) source.

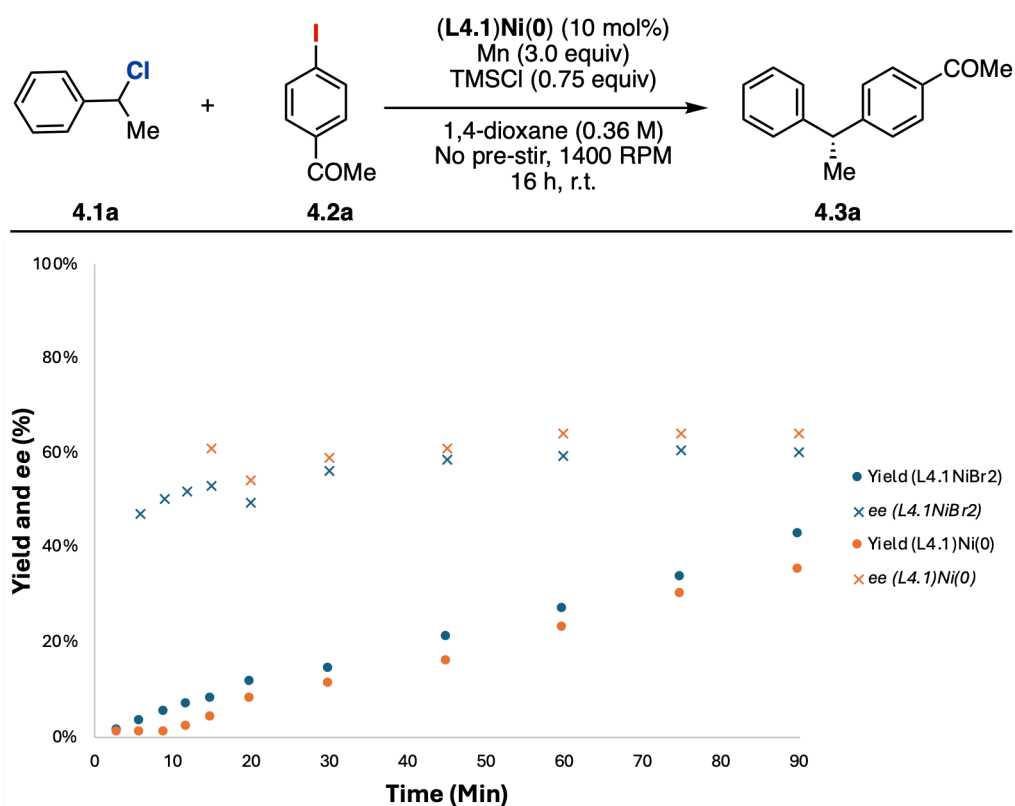


Figure 4.14: Comparison of **L4.1**Ni(0) (orange) and **L4.1**NiBr₂ (blue).

Using (**L4.1**)Ni(0) pre-catalyst, we observed a relatively stable product enantioselectivity throughout the course of the reaction, which was comparable to the optimized conditions. We propose that under these conditions, immediate oxidative addition into the aryl iodide generates **II.11**. This is due to the ease of oxidative addition into electron-poor aryl iodides.^{76, 77} Previous studies have

demonstrated that Ni(I) species preferentially engage aryl iodides before alkyl halides.^{5, 7} Additionally, the reaction turns a deep red, comparable to solutions containing **II.11**.⁴

Previous work by the Diao group suggests that the **II.11** cannot be directly reduced by Mn(0) powder, yet our reaction still proceeded to a 35% yield. However, the observed reactivity could be explained in line with Diao's proposal (see **Figure 4.5**). Upon formation of **II.11**, this complex may act as a Lewis acid to rapidly form a benzyl radical, which can then be trapped and reductively eliminated to form the product. Another pathway, consistent with our observations in the THF arylation study, would be oxidative addition followed by comproportionation with the remaining Ni(0), thereby generating Ni(I) as the active catalyst *in situ*.³

To test whether the observed reactivity is indeed related to the quick formation of **II.11** and rule out the formation of other species under these conditions, we decided to independently synthesize **II.11** and see if we observe a similar reactivity profile when employing it as a pre-catalyst (**Figure 4.15**).

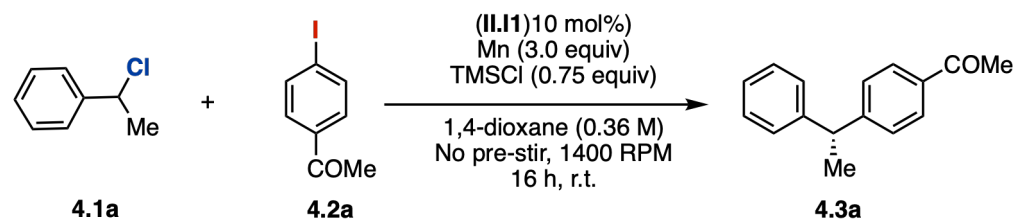
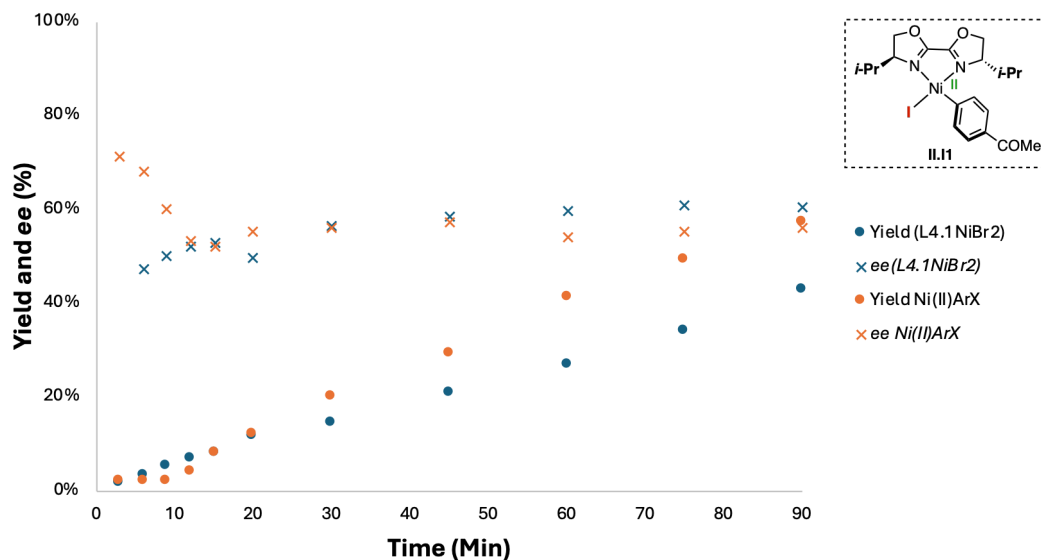


Figure 4.15: Comparison of **II.11** (orange) and **(L4.1)NiBr₂** (blue).

The runs we conducted using **II.11** showed a completely different reactivity profile, unlike anything we had previously seen. Product formation occurs almost immediately, with a high ee of 71% at the initial time points. This result suggests that this intermediate engages in an alternative pathway that gradually converges to the main mechanistic pathway, as evidenced by the gradual decrease in ee until stagnation. Our mechanistic hypothesis in this scenario is that benzylic radical formation (from **4.1a** in the presence of Mn, TMSCl, and Ni) is accelerated with **II.11** acting as additional Lewis acid, as proposed in the Diao group's work (see **Figure**

4.5).⁶ The radical is immediately trapped by **II.I1**, followed by reductive elimination to form the product and continuing the mechanism via a Ni(I) species.

Comparing the results of **Figure 4.14** using (**L4.1**)Ni(0) as the pre-catalyst and **Figure 4.15** using **II.I1** as the pre-catalyst, these reactions do not afford the same reactivity profile. We hypothesize that when using (**L4.1**)Ni(0) as the pre-catalyst, we are generating **II.I1**, but it is rapidly comproportionating to make other active Ni-species. This also explains why reproducing the (**L4.1**)Ni(0) time points is so difficult, because even in the short time between adding the (**L4.1**)Ni(0) solution to the solids and adding **4.1a** and TMSCl, the Ni(0) species can react and form a wide variety of Ni species. This results in a markedly different reactivity compared to using **II.I1** as a pre-catalyst. We believe that conducting EPR studies will be useful for determining the possible Ni species we form under these conditions, as in our previous mechanistic investigation.³

Finally, we wanted to assess how another low-valent Ni species, such as Ni(I) generated *in situ*, would fare as a pre-catalyst and if it would afford the same reactivity profile as using Ni(0).

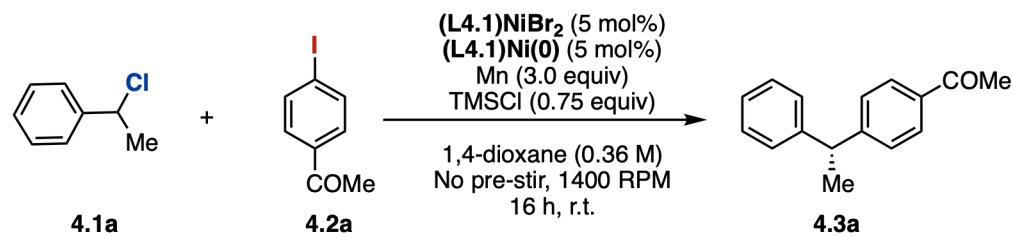
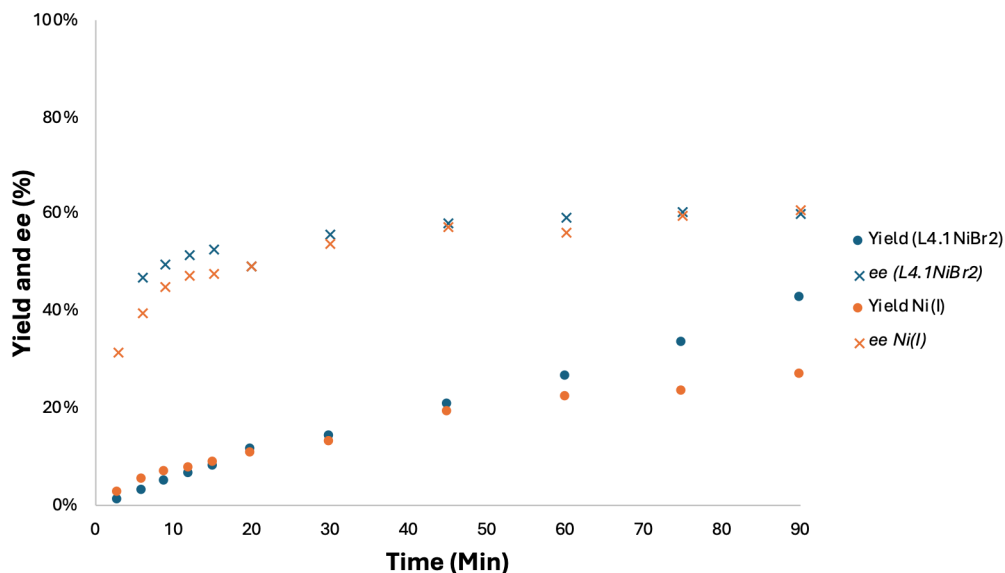


Figure 4.16: Comparing **(L4.1)NiBr₂** (blue) and **(L4.1)Ni(I)** (orange).

This mixture provided a reaction profile seemingly inverse to that of **II.11** as the pre-catalyst, at least in the first turnovers. The ee starts much lower at 32% but appears to converge to the same trend observed with the **(L4.1)Ni(II)** bromide complex (**Figure 4.16**). This suggests that starting from this Ni(I) species has an alternative enantioselectivity-determining step. Additionally, reproducing these results has been much more consistent than our attempts at using **(L4.1)Ni(0)**, indicating the transient nature of Ni(0) species compared to Ni(I) and especially Ni(II).

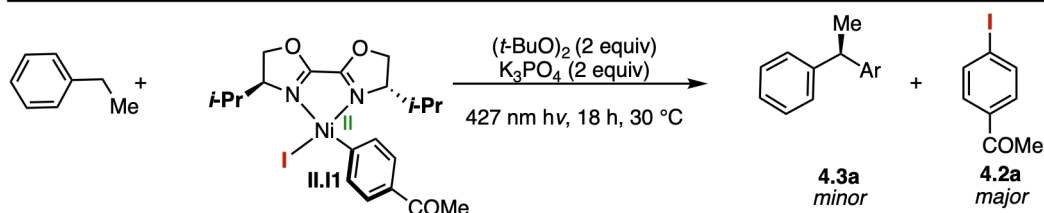
The time-point reactions I have performed so far have given us insight into multiple possible pathways by which this reaction can proceed. Hai and N.

Coddington will continue to pursue time point reactions to both ensure reproducibility of our current results and investigate other possible combinations of pre-catalysts.

Section 4.7: Stoichiometric Experiments

Another key component of our studies is conducting stoichiometric experiments to investigate the step that determines the reaction's enantioselectivity. Our initial attempts were to follow an identical procedure to our THF-arylation stoichiometric experiments, but with the complex replaced by **II.11** and the solvent replaced by ethylbenzene.³ Despite the successful synthesis of our desired **II.11** aryl iodide complex (detailed in **Chapter 2**), I've found these complexes to be much less soluble in solvents like ethylbenzene and *d*₆-benzene, ultimately leading to rapid decomposition within an h timescale. Running the stoichiometric experiment under the conditions described in **Figure 4.17a** yields varying yields and ee for **4.3a** due to inconsistent solubilization and decomposition (**Figure 4.17b**). The major product I have observed is aryl iodide **4.2a**, consistent with the light-induced reductive elimination of Ni(II) aryl halide complexes described in **Chapter 3**.⁷⁸

a) Stoichiometric Experiment for **4.11a**



b) Photo-induced Reductive Elimination

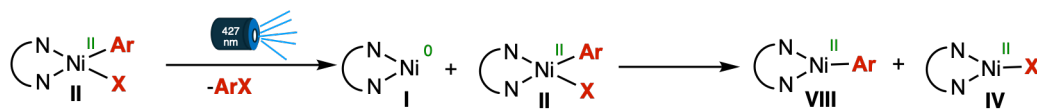


Figure 4.17: Attempts at stoichiometric studies for this system.

Hai is currently working on a flow setup in which a mixture of peroxide and ethylbenzene is irradiated to generate a benzylic radical, then delivered to the complex, which is kept in a Schlenk tube away from the irradiation. This is an effort to negate light-induced reductive elimination while maintaining conditions that generate the benzylic radical. We also plan to attempt these reactions with ortho-substituted complexes, as they will persist longer *in situ* and are likely to make Ni(II) reductive elimination more challenging. Before doing this, though, we want to ensure the ortho-substituted aryl iodides are comparable coupling partners in the catalytic reaction and develop conditions that will give us consistent results.

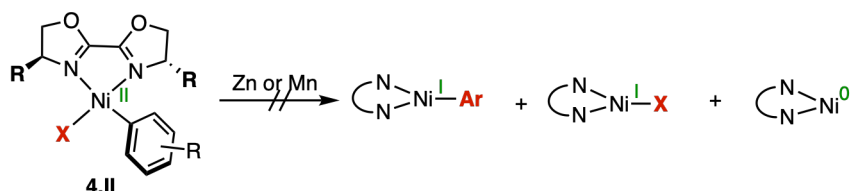
To address solubility issues, Hai is currently working on this system using 1,4-dioxane as a cosolvent (in which we know **11.11** is soluble) and ethylbenzene (1:5 v/v) in the stoichiometric reactions to fully dissolve the complex and ultimately obtain reproducible results. The potential drawback of utilizing the dioxane cosolvent is the possibility of HAT on the 1,4-dioxane, which has a comparable BDE (91 kcal/mol) to

the benzylic C(sp³)-H of ethylbenzene (86-88 kcal/mol), but we hope that since ethylbenzene is in higher concentration, this will be the favored site of carbon-centered radical generation.

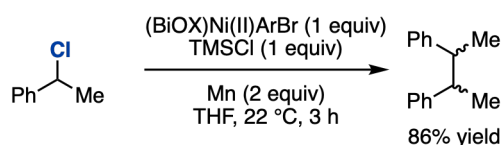
In addition to our HAT-mediated stoichiometric experiments, I have recently developed a new plan to assess the relevance of the Ni(II) aryl halide intermediate in this reaction system. In the 2021 Diao report,⁶ the group claims that due to the lack of redox activity in BiOX ligands, both (BiOX)NiBr₂ and BiOXNi(II) aryl bromide complexes cannot be reduced in the presence of Mn or Zn, even with the addition of TMSCl (**Figure 4.18a**). We may be able to use this to our advantage to directly test how the reductant influences the enantioselectivity-determining step. The Diao and Reisman groups both independently characterized the formation of benzyl radical (by dimer formation) from **4.1a** when using Mn, TMSCl, and Ni(II) (presumably acting as a Lewis Acid) (**Figure 4.18b** and **Figure 4.18c**). Despite successful dimer formation, there is no mention of the fate of the aryl group that was initially part of the Ni(II) in Diao's report, leading us to believe that a cross-coupled product is formed before dimer formation.⁶ This suggests that we might be able to generate the benzylic radical directly from the benzyl chloride electrophile **4.1a** in the presence of **II.11** by utilizing these conditions (**Scheme 4.18d**). Additionally, given the precedent that **II.11** cannot be reduced in the presence of Mn or Zn, we can run the stoichiometric reaction with the expectation that the Mn or Zn will react exclusively with **4.1a** (and other benzyl halide/ NHP ester analogs), we could expect that **II.11** will remain untouched while

the benzyl radical is being generated. This will mimic the trapping step of **II**→**III** shown in all the radical chain proposals (**Figures 4.4, 4.5, 4.6**)⁵⁻⁷.

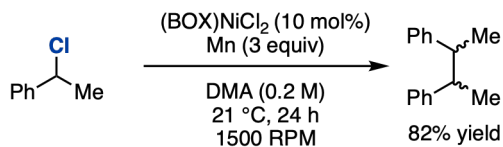
*a) Redox Inactivity of **4.II** Complexes*



b) Proposed Generation of Benzyl Radical (Diao 2021)



c) Proposed Generation of Benzyl Radical (Reisman 2023)



d) Proposed Stoichiometric Experiment 1: Use of Reductant for Benzyl Radical Generation

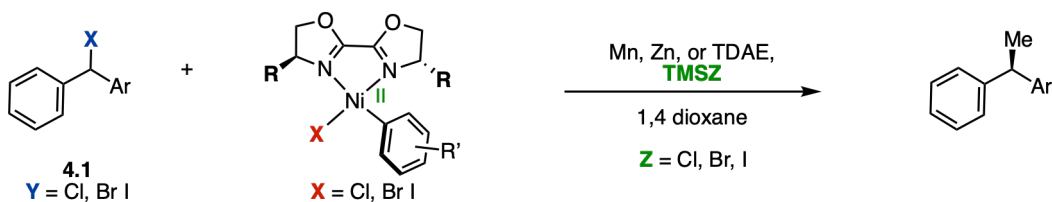


Figure 4.18: Proposed stoichiometric experiments using **4.1a** and other analogs.

Additionally, under these conditions, we'll be able to screen the other Lewis acids as well (TESCl, TBSCl, TESBr) to further investigate if the Lewis acids are also involved in the enantioselectivity-determining step. Finally, we can change the halide on the complex itself to investigate if the halides do or do not affect ee, how the reductants affect the ee, and how the Lewis acids affect the ee. A combination of

these experiments should answer our main hypothesis on how the reductant can affect the enantioselectivity-determining step.

Section 4.8: Future Work and Outlook

This chapter describes our initial experiments towards a better understanding of the mechanism of XEC reactions. As anticipated, we have observed a change in ee with reductant. However, we have also found that other reaction components, such as stirring and Lewis acids, affect the ee. Additionally, the identity of the aryl halide is independent of product ee, contrary to our previous work.³ Our path forward in elucidating the mechanistic scenario will involve conducting additional time point reactions, stoichiometric experiments, and possibly kinetic analyses.

Section 4.9: General Information and Procedures

Section 4.9.1: Reagent List

To ensure reproducibility, a detailed list of reagents and general preparations is provided. All reagents were purchased from commercial suppliers and used without further purification unless otherwise noted.

Oven-drying: All glassware and stir bars were oven-dried at 130 °C for at least one h before use. No other drying was performed on glassware unless otherwise noted.

Ni(COD)₂: 2 g bottles of bis (1,5-cyclooctadiene)nickel (0), 98+% were purchased from STREM and used without any further purification (catalog number 18-0010). The Ni(COD)₂ was immediately cycled into the glovebox and stored in the freezer at -30 °C. Between uses, the bottle cap was sealed with electrical tape.

NiBr₂·diglyme: 10 g bottles of Nickel(II) bromide ethylene glycol dimethyl ether complex, 98% were purchased from Ambeed and used without any further purification (catalog number A896886). The NiBr₂·diglyme was immediately cycled into the glovebox and stored at ambient temperature.

NiBr₂·glyme: 10 g bottles of Nickel(II) bromide, dimethoxyethane adduct, min. 97% were purchased from Strem and used without any further purification (catalog number 28-1145). The bottle, while still sealed, was immediately cycled into the glovebox and stored at ambient temperature.

Manganese: 100 g bottles of Manganese powder (99+%) were purchased from Stem (catalog number 25-0100). The bottle, while still sealed, was immediately cycled into the glovebox. Roughly 10 g of manganese were transferred to a scintillation vial charged with a pill-shaped stir bar. The manganese powder was stirred for at least 120 h at 1400 rpm before use in any reactions.

Zinc: 250 g bottles of Zinc flake, ~325 mesh, were purchased from Thermo Fisher Scientific (catalog number AA1378930). The bottle, while still sealed, was immediately cycled into the glovebox. Roughly 10 g of zinc were transferred to a scintillation vial charged with a pill-shaped stir bar. The zinc powder was stirred for at least 120 h at 1400 rpm before use in any reactions.

Aryl halides: The aryl halide used in this study ((1-(4-iodophenyl)ethan-1-one) was purchased in 25 g quantity bottles from Ambeed (product number A344622). The aryl halide was brought into the glovebox in 20 mL scintillation vial secondary containers and stored at ambient temperature with limited exposure to light. Experimental results were reproducible whether the reagent was used directly or aryl iodide purified via flash column chromatography was used.

Benzyl chloride: 25 mL bottles of 1-chloroethyl)benzene were purchased from TCI Chemicals (catalog number C0166) and used without any further purification. The bottles were immediately cycled into the glovebox and stored at ambient temperature.

Trichloromethylsilane (TMSCl): 25 mL bottles of TMSCl were purchased from either Oakwood Chemical or TCI Chemicals (product number C0306) and used without any further purification. The bottles were immediately cycled into the glovebox and sealed with electrical tape between uses. This reagent was found to be particularly air sensitive, which led to skewed ee data if used in the glovebox with an O₂ concentration >0.5 ppm. Replacing bottles frequently led to rectified reproducibility issues.

Bi-oxazoline(BiOX) ligands: BiOX ligands used in this study (**L4.1**, **L4.2**, **L4.3**) were synthesized using a slightly modified literature procedure and are also commercially available through Ambeed. Once synthesized, each BiOX ligand was stored in a 20 mL scintillation vial and cycled into the glovebox. The ligands were stored in the freezer at -30 °C between uses. Additionally, the scintillation vial cap was sealed with electrical tape between uses.

1,4-Dioxane: 1 L bottles of 1,4-dioxane, 99.5%, Extra Dry over Molecular Sieve, stabilized, AcroSeal were purchased from Thermo Fisher Scientific (*catalog number 364340010*). *The dioxane, while still sealed, was cycled into the glovebox and used without further purification.*

Pentane: 1 L bottles of *n*-pentane, anhydrous, 99.5+%, over molecular sieves, packaged under argon in resealable ChemSeal™ bottles were purchased from

Thermo Fisher Scientific (catalog number 047115.K2). The pentane, while still sealed, was cycled into the glovebox and used without any further purification.

Diethyl ether: a 2.5 L bottle of diethyl ether, 99.5%, extra dry, stabilized with BHT, Acroseal® was purchased from Thermo Fisher Scientific (currently unavailable). The bottle, while still sealed, was cycled into the glovebox and used without any further purification.

Tetrahydrofuran: THF was dispensed from our solvent system into a 1L oven-dried Straus flask over activated 3 Å molecular sieves. When sealed, the Straus-flask was cycled into the glovebox and the THF was allowed to sit over the mol sieves for 12 h. The THF was then filtered into a secondary container to remove any residual mol sieve dust and used without any further purification.

Deuterated benzene: Bottles of d_6 -benzene >99% were purchased from Oakwood Chemical (catalog number 099808) in 10 mL and 25 mL quantities. While still sealed, the bottles were cycled into the glovebox overnight upon arrival and then used as NMR solvents without further purification. Between uses, the bottle was sealed with electrical tape, and the glovebox was freshly purged before opening every time to prevent solvent vapor contamination.

Stir bar: Pill-shaped stir bar L x diam. 10.0 mm x 5.0 mm (product number HS120547) were purchased from Millipore Sigma. Before use in any reaction, the stir bars were oven-dried at 130 °C for at least 1 h, then cycled into the glovebox and used for all

stirring. After each use, the stir bars were cleaned in water and acetone, then stirred in an aqua regia solution overnight, followed by a sodium bicarbonate wash to remove any excess acid.

Schlenk tube: Wide 10 mL Synthware Schlenk tubes 2.64"D x 3.54"W x 5.12"H (product number F891410) were purchased from Amazon. Before use in any reaction, the stir bars were oven-dried at 130 °C for at least 1 h before being cycled into the glovebox. To ensure the removal of any trace metals (particularly Zn or Mn plating on the glassware), the Schlenk tubes were cleaned with water, acetone, hydrochloric acid, and finally aqua regia overnight, followed by a sodium bicarbonate wash to remove any excess acid.

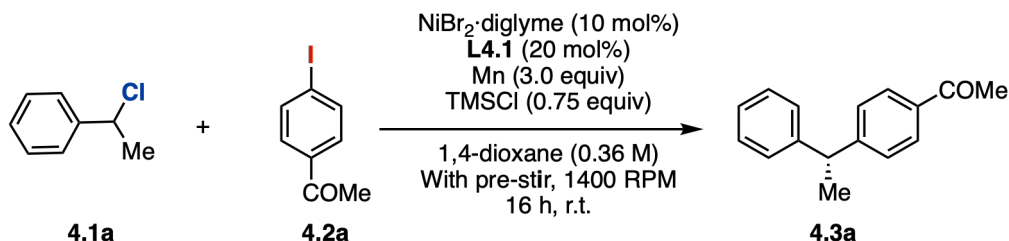
All syringe filters used were purchased from VWR (product number 76479-016). These have a 33 mm diameter and a 0.22 μm pore-size PES membrane.

^1H NMR spectra were obtained in CDCl_3 or C_6D_6 at 400 MHz or 600 MHz using Bruker instruments. Chemical shifts are reported in ppm and referenced to the residual CHCl_3 singlet ($\delta = 7.26$ ppm) or C_6H_6 singlet ($\delta = 7.16$ ppm).

Chiral Traces: Enantiomeric excess and yield were determined with an ACQUITY UPC² System using chiral stationary phase TrefoilTM AMY1, 2.5 μm 3.0 x 150 mm column.

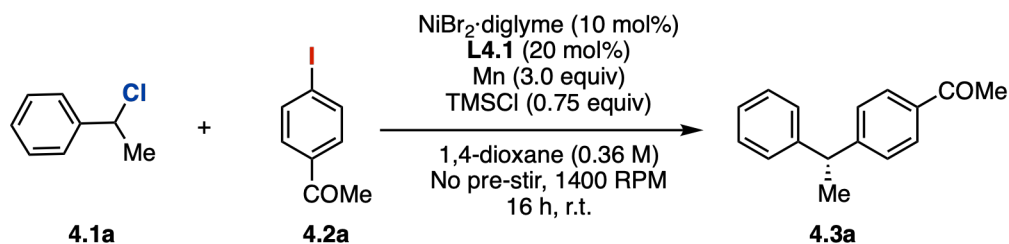
Section 4.9.2: Procedures

General Procedure 4A



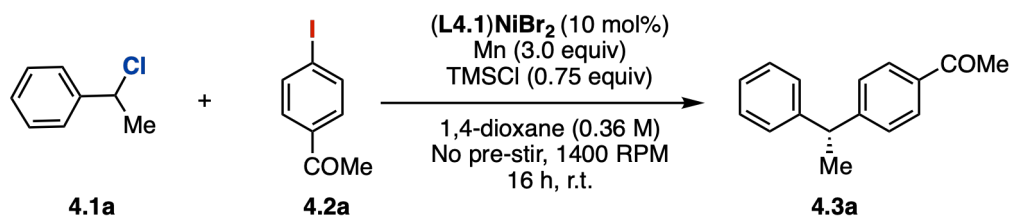
Inside a nitrogen-filled glovebox, an oven-dried 10 mL Schlenk tube was charged with a pill-shaped stir bar. Solid reagents were then added to the Schlenk tube in the following order: Mn (0.6 mmol, 3.0 equiv, 33.0 mg), 1-(4-iodophenyl)ethan-1-one (**4.2a**) (0.2 mmol, 1.0 equiv, 49.2 mg), $\text{NiBr}_2 \cdot \text{diglyme}$ (0.02 mmol, 0.1 equiv, 7.1 mg), and BiOX ligand (0.04 mmol, 0.2 equiv). Then 1,4-dioxane (0.36 M, 0.56 mL) was added to the Schlenk tube. The Schlenk tube was capped with a rubber septum, and the solution was stirred for 20 min at 1400 RPM. After 20 min, (1-chloroethyl)benzene **4.1a** (0.24 mmol, 1.2 equiv, 32.0 μL) was added to the reaction. The mixture was stirred for 1 min before adding TMSCl (0.15 mmol, 0.75 equiv, 20 μL).

General Procedure 4B



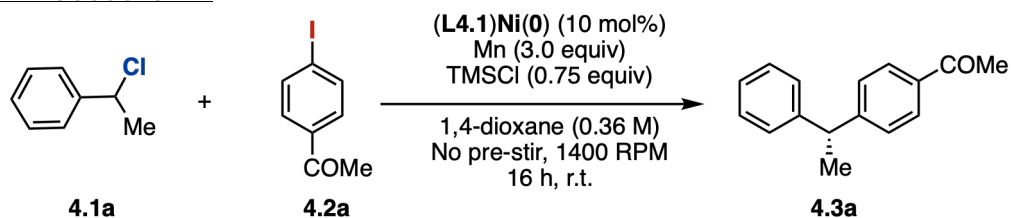
Inside a nitrogen-filled glovebox, an oven-dried 10 mL Schlenk tube was charged with a pill-shaped stir bar. Solid reagents were then added to the Schlenk tube in the following order: Mn (0.6 mmol, 3.0 equiv, 33.0 mg), 1-(4-iodophenyl)ethan-1-one (**4.2a**) (0.2 mmol, 1.0 equiv, 49.2 mg), $\text{NiBr}_2 \cdot \text{diglyme}$ (0.02 mmol, 0.1 equiv, 7.1 mg), and **L4.1** (0.04 mmol, 0.2 equiv, 9.0 mg). Finally, benzophenone was added as an internal standard (between 0.2-0.75 equiv). Then, 1,4-dioxane (0.36 M, 0.56 mL) was added to the Schlenk tube. Immediately, (1-chloroethyl)benzene (**4.1a**) (0.24 mmol, 1.2 equiv, 32.0 μL) was added to the reaction, followed by TMSCl (0.15 mmol, 0.75 equiv, 20 μL). The Schlenk tube was then placed on the stir plate and mixed at 1400 RPM.

General Procedure 4C



Inside a nitrogen-filled glovebox, an oven-dried 10 mL Schlenk tube was charged with a pill-shaped stir bar. Solid reagents were then added to the Schlenk tube in the following order: Mn (0.6 mmol, 3.0 equiv, 33.0 mg), 1-(4-iodophenyl)ethan-1-one (**4.2a**) (0.2 mmol, 1.0 equiv, 49.2 mg), and (**L4.1**)NiBr₂ (0.02 mmol, 0.1 equiv, 8.9 mg). Finally, benzophenone was added as an internal standard (between 0.2-0.75 equiv). Then, 1,4-dioxane (0.36 M, 0.56 mL) was added to the Schlenk tube. Immediately, (1-chloroethyl)benzene (**4.1a**) (0.24 mmol, 1.2 equiv, 32.0 μ l) was added to the reaction, followed by TMSCl (0.15 mmol, 0.75 equiv, 20 μ L). The Schlenk tube was then placed on the stir plate and mixed at 1400 RPM.

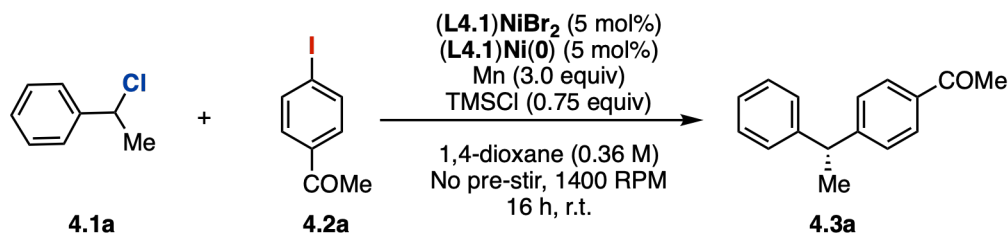
General Procedure 4D



Inside a nitrogen-filled glovebox, an oven-dried 10 mL Schlenk tube was charged with a pill-shaped stir bar. Solid reagents were then added to the Schlenk tube in the following order: Mn (0.6 mmol, 3.0 equiv, 33.0 mg), 1-(4-iodophenyl)ethan-1-one (**4.2a**) (0.2 mmol, 1.0 equiv, 49.2 mg), and benzophenone was added as an internal standard (between 0.2-0.75 equiv). Simultaneously, a dioxane stock solution

of (**L4.1**)Ni(0) was made from a 0.2 mmol scale (0.036 M, 5.6 mL). The stock solution was stirred for 10 min to ensure full solubility of the nickel species, resulting in a dark turquoise solution. The stock solution was then added to the contents of the Schlenk tube (0.036 M, 0.56 mL), almost immediately turning the solution deep red. This was followed by adding (1-chloroethyl)benzene (**4.1a**) (0.24 mmol, 1.2 equiv, 32.0 μ L) to the reaction, followed by TMSCl (0.15 mmol, 0.75 equiv, 20 μ L). The Schlenk tube was then placed on the stir plate and mixed at 1400 RPM.

General Procedure 4E



Inside a nitrogen-filled glovebox, an oven-dried 10 mL Schlenk tube was charged with a pill-shaped stir bar. Solid reagents were then added to the Schlenk tube in the following order: Mn (0.6 mmol, 3.0 equiv, 33.0 mg), 1-(4-iodophenyl)ethan-1-one (**4.2a**) (0.2 mmol, 1.0 equiv, 49.2 mg), and benzophenone was added as an internal standard (between 0.2-0.75 equiv). Simultaneously a dioxane stock solution of (**L4.1**)Ni(0) was made from a 0.2 mmol scale (0.036 M, 5.6 mL). The stock solution was stirred for 10 min to ensure full solubility of the nickel species, resulting in a dark turquoise solution. In a separate vial (**L4.1**)NiBr₂ (0.04 mmol, 17.8 mg) was weighed out. Then, 1.11 mL of the 0.036 M Ni(0) stock solution was added to (**L4.1**)NiBr₂, resulting in a dark red solution. The mixture was stirred for 2 min before 0.56 mL of

the solution was added to the Schlenk tube. This was followed by adding (1-chloroethyl)benzene (**4.1a**) (0.24 mmol, 1.2 equiv, 32.0 μ l), which was added to the reaction, followed by TMSCl (0.15 mmol, 0.75 equiv, 20 μ L).

Section 4.9.3: Time Point Reactions

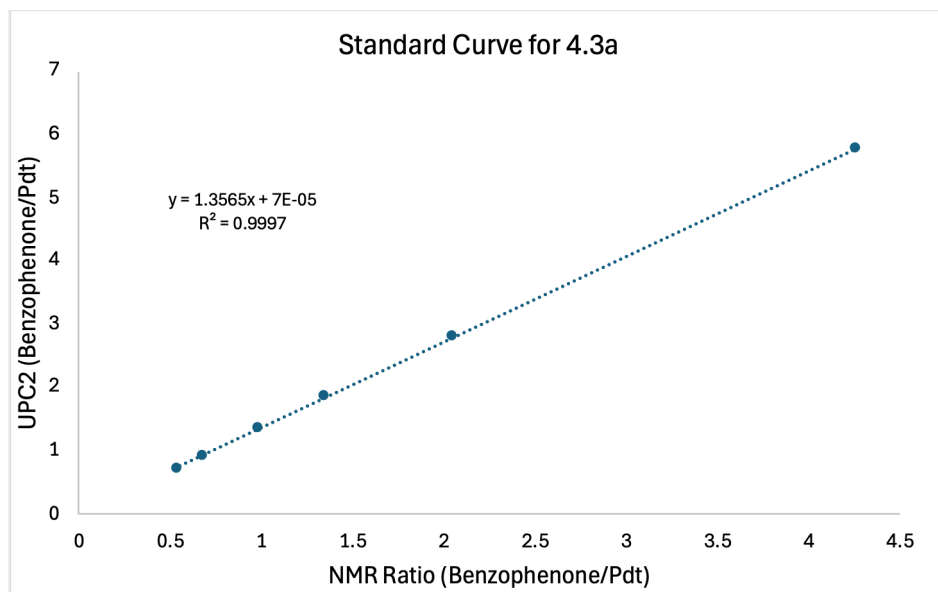
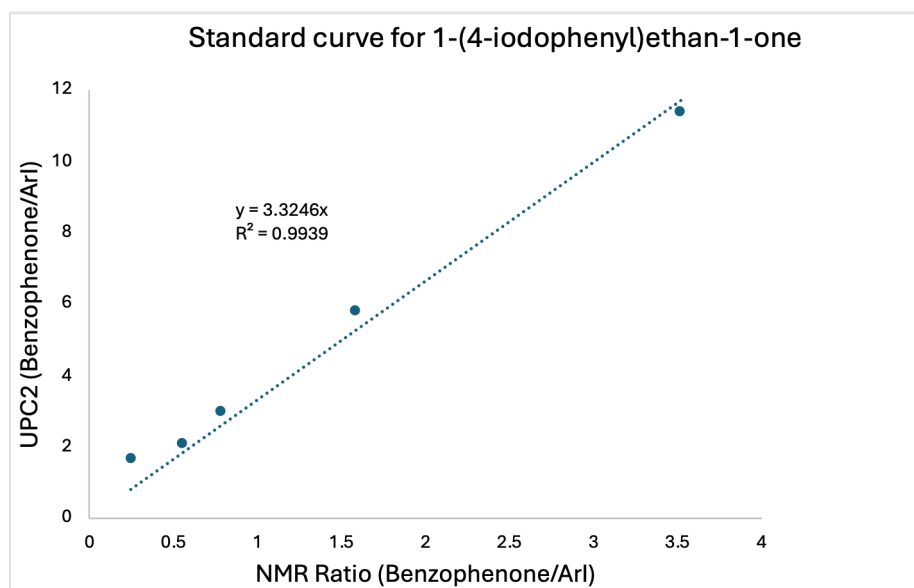
General Procedure 4F: Time Points Procedure

Immediately after the TMSCl was added to the Schlenk tube, a timer was started. The Schlenk tube was then capped with a rubber septum and removed from the glovebox. The tube was then connected to a Schlenk line, placed over a stir plate, and began stirring at 1400 RPM at room temperature. Exactly three min after the addition of TMSCl, the Schlenk tube was uncapped, and an aliquot was taken by dipping a 9" glass pipette into the solution (the stirring was not stopped during this time). The glass pipette was then flushed with 2 mL of HPLC-grade acetonitrile into a previously prepared celite plug (made in a 5.75" glass pipette) into a 2 mL LCGC screw neck vial. This process was repeated at 6, 9, 12, 15, 20, 30, 45, 60, 75, and 90 min post-TMSCl addition. One final time point was taken after the reaction had stirred overnight. The 2 mL vials were then analyzed via UPC², and yield and enantioselectivity data were calculated.

Standard Curve for Analytical Runs

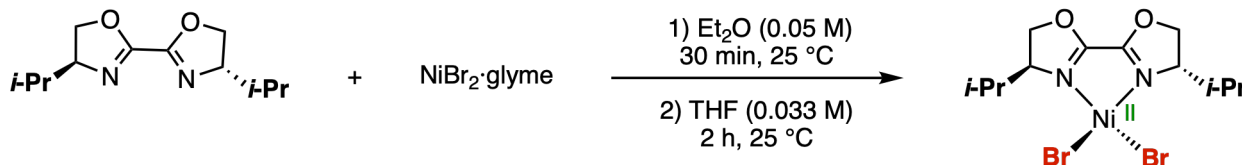
Two separate equimolar solutions of racemic 1-(4-(1-phenylethyl)phenyl)ethan-1-one (**4.3a**) or 1-(4-iodophenyl)ethan-1-one (**4.2a**) and benzophenone were made in deuterated chloroform. The ratio of the benzophenone peak integration to diaryl alkane peak integration were recorded. The deuterated

chloroform mixture was then concentrated and redissolved in 2 mL of HPLC grade acetonitrile. The acetonitrile solution was then analyzed by ACQUITY UPC² System using chiral stationary phase column Trefoil™. UPC² Conditions: 5.0 µL injection volume, 1.5 mL/min flow rate. Mobile phase comprised of 95% solvent A (CO₂) and 5% solvent B (MeOH). A calibration curve was then generated by comparing the NMR integration ratio (benzophenone/**4.3a**) as the X axis to the ratio of peak areas in the UPC² traces as the Y axis.



Section 4.9.4: Synthesis of Ni Pre-Catalysts

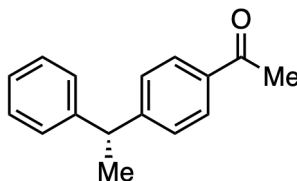
General Procedure 4G



(**L4.1**) NiBr_2 was prepared according to a slightly modified procedure from the Diao group.⁶ In a nitrogen-filled glovebox, **L4.1** (0.5 mmol, 1 equiv, 112.2 mg) followed by $\text{NiBr}_2 \cdot \text{glyme}$ (0.5 mmol, 1 equiv, 154.3 mg) were measured into a 20 mL scintillation vial equipped with a stir bar. Diethyl ether (0.05 M, 10 mL) was subsequently added, followed by intense stirring at 1400 rpm for 30 min. Under these conditions, the ligand dissolves, but a large excess of the $\text{NiBr}_2 \cdot \text{glyme}$ remained suspended in solution. Subsequently, 5 mL of THF was added to the suspension. The solution turned from light orange to dark brown until all the $\text{NiBr}_2 \cdot \text{glyme}$ dissolved. The solution was stirred for an additional 2 h, at which point a light green solid precipitated. The contents of the scintillation vial were then poured over a fine porosity frit, with the mother liquor collected in a filter flask. The mother liquor was then fully concentrated by introducing a vacuum until a sticky green solid remained on the sides of the filter flask. This was then redissolved in 2 mL of THF and transferred to a 20 mL scintillation vial. Subsequent addition of pentane resulted in precipitation of additional green solid, which was poured over the fine porosity frit. This process was repeated until the mother liquor became clear. The contents of the fine porosity frit were then washed

with 5 x 6 mL of pentane, and the contents were placed in a fresh scintillation vial to afford the desired (**L4.1**)NiBr₂. Characterization of this complex via ¹H NMR is consistent with the Diao reported characterization data.⁶

Section 4.9.5: Characterization of Diaryl Alkanes



Diaryl alkane **4.3a** was prepared via *General Procedure 4A* and isolated as a clear, colorless oil. (98:2 Hexanes:Et₂O) **¹H NMR** (400 MHz, CDCl₃) δ 7.88 (d, *J* = 8.6 Hz, 2H), 7.34 – 7.27 (m, 4H), 7.21 (m, 3H), 4.21 (q, *J* = 7.4 Hz, 1H), 2.57 (s, 3H), 1.66 (d, *J* = 7.2 Hz, 4H). The characterization data matches the previously reported data.⁷⁹

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