Chapter 1

Nickel Catalysis in Asymmetric Reductive Cross-Coupling

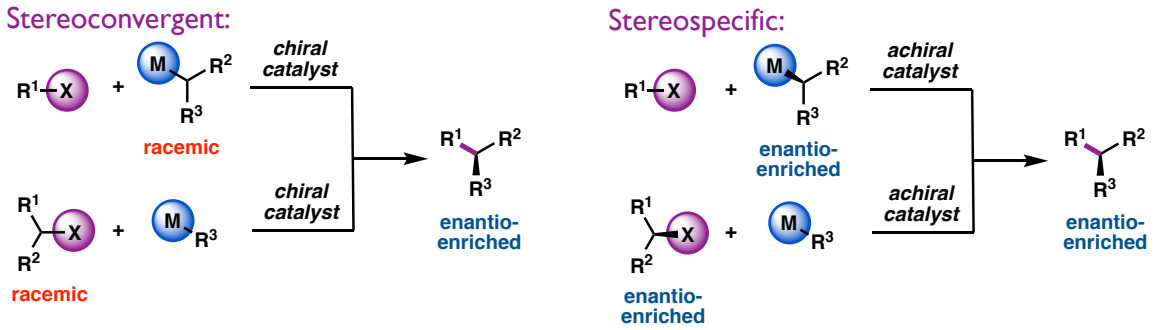
1.1 INTRODUCTION

Cross-coupling technology has become an incredibly powerful tool for forging C–C bonds in the synthesis of natural products and small molecules. An ongoing challenge for synthetic chemists is the stereocontrolled construction of these C–C bonds. Transition metal catalysis has opened up many new modes of reactivity for chemists that have redefined the synthetic strategies used for the preparation of enantioenriched molecules. In particular, the use of transition metal-catalyzed cross-coupling reactions, in which an organic electrophile (typically a halide or pseudo halide) is coupled to an organometallic reagent, has revolutionized organic chemistry.

These cross-coupling reactions, in which the stereogenic center is defined by the C–C bond forming event, can be organized in two categories, depending on the method in which the chiral information of the product is defined (Scheme 1.1).[1] In a *stereoconvergent* cross-coupling, one enantiomer of product is formed selectively from

an achiral and chiral racemic coupling partner, through the use of a chiral catalyst. In a *stereospecific* reaction, the stereochemistry of a chiral, enantioenriched coupling partner is transferred to the product with an achiral metal catalyst.

Scheme 1.1. *Strategies for enantioselective cross-coupling.*



While much focus has been placed on the use of palladium and other precious metals for these enantioselective cross-coupling reactions, processes involving alkyl coupling partners have been slow to develop due to the inherent challenges involved with Pd-catalyzed alkyl cross-coupling reactions. In these transformations, *sec*-alkyl organometallic reagents can be slow to undergo transmetalation,[2] while *sec*-alkyl electrophiles are often slow to undergo oxidative addition.[3] In either case, the resulting *sec*-alkyl Pd complex suffers from rapid β-hydride elimination.[4,5]

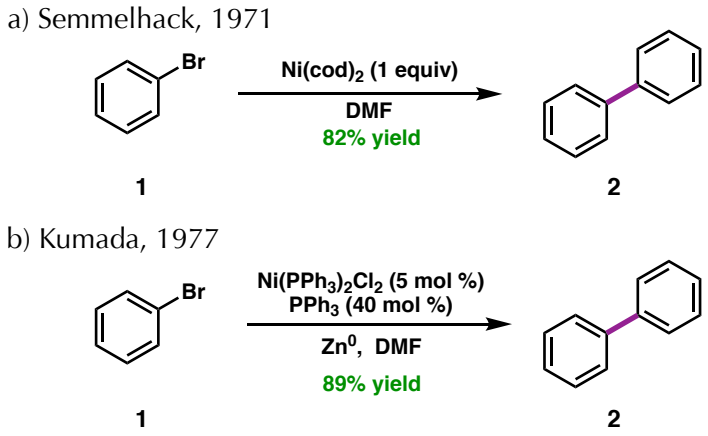
Due to these fundamental obstacles in reactivity, there has been much research into the alternative use of first-row transition metals for the enantioselective cross-coupling of alkyl substrates. In particular, the ability of nickel to engage in single electron processes makes it a desirable alternative to metals that proceed through polar, two electron mechanisms in the development of novel transformations.[4] Of these methods, reductive cross-coupling has recently emerged as a reliable and mild method to combine two electrophiles.

1.2 REDUCTIVE CROSS-COUPLING

1.2.1 Background and significance

In 1971, Semmelhack and coworkers reported the first reductive coupling of halide electrophiles using stoichiometric $Ni(cod)_2$ to form biaryl products (Scheme 1.2a).[6] Soon after, Kumada published the catalytic reductive homocoupling of aryl bromides using stoichiometric Zn as the chemical reductant (Scheme 1.2b).[7] Since then, renewed interest has led to the development of many catalytic reductive cross-couplings.

Scheme 1.2. *First reports of reductive homocoupling.*



Reductive cross-coupling offers many advantages over traditional redox-neutral transformations.[8–10] The mild nature of the reaction conditions allows for increased functional group tolerance and avoids racemization of newly formed stereogenic centers. Also, reductive coupling often utilizes halide electrophiles, from which many organometallic reagents are generated, rendering this approach more streamlined and efficient. Reductive cross-coupling is particularly advantageous for intramolecular coupling because it obviates the need to install both an electrophilic and organometallic functional group into the starting material.[11–14]

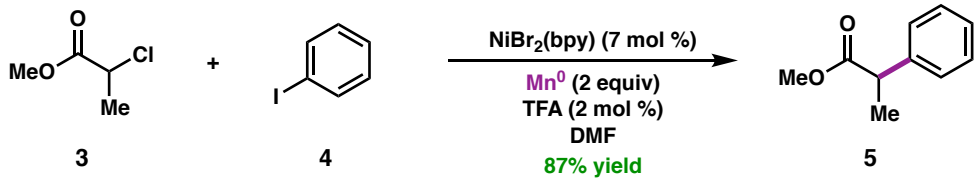
However, there are still many challenges associated with this new technology. The use of a stoichiometric amount of heterogeneous metal reductant renders these reactions sensitive to stirring and scale. Another major challenge in the development of reductive cross-coupling reactions is achieving cross-selectivity.[15,16] When employing two electrophilic coupling partners, there must be a way to differentiate them mechanistically to avoid undesired homocoupling. One strategy to address this is to leverage the hybridization of the electrophilic coupling partners. If differently-hybridized electrophiles react selectively with different oxidation states of Ni, then a careful sequencing of oxidative addition events could afford the desired cross-product, while minimizing the unwanted homo-coupled dimers. Optimization campaigns for these reactions require focus on this careful sequencing and the resultant product distribution.

1.2.2 Racemic $C(sp^3)$–$C(sp^2)$ bond formation

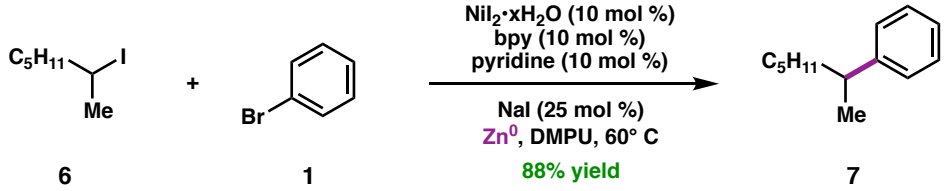
Since the first disclosure of Ni-mediated reductive homocoupling, there have been intensive efforts toward expanding this transformation to enable cross-selective couplings. In 2007, Durandetti and coworkers reported the first Ni-catalyzed reductive cross-coupling between α-chloroesters and aryl iodides with a chemical reductant (Scheme 1.3a).[17] Weix and coworkers followed that report in 2010 with the cross-coupling of *sec*-alkyl iodides and aryl halides, also utilizing a Ni(II) catalyst and bipyridine ligand (Scheme 1.3b).[18] Over the last 10 years, the labs of Weix,[15,19,20] Gong[21–27] and Molander[28,29] have greatly expanded the scope of this transformation, employing many different $C(sp^2)$ (aryl, alkenyl, acyl) and $C(sp^3)$ (activated and unactivated alkyl) coupling partners.

Scheme 1.3. *First reports of reductive cross-coupling using chemical reductants.*

a) Durandetti, 2007



b) Weix, 2010



1.3 STEREOCONVERGENT CROSS-ELECTROPHILE COUPLING

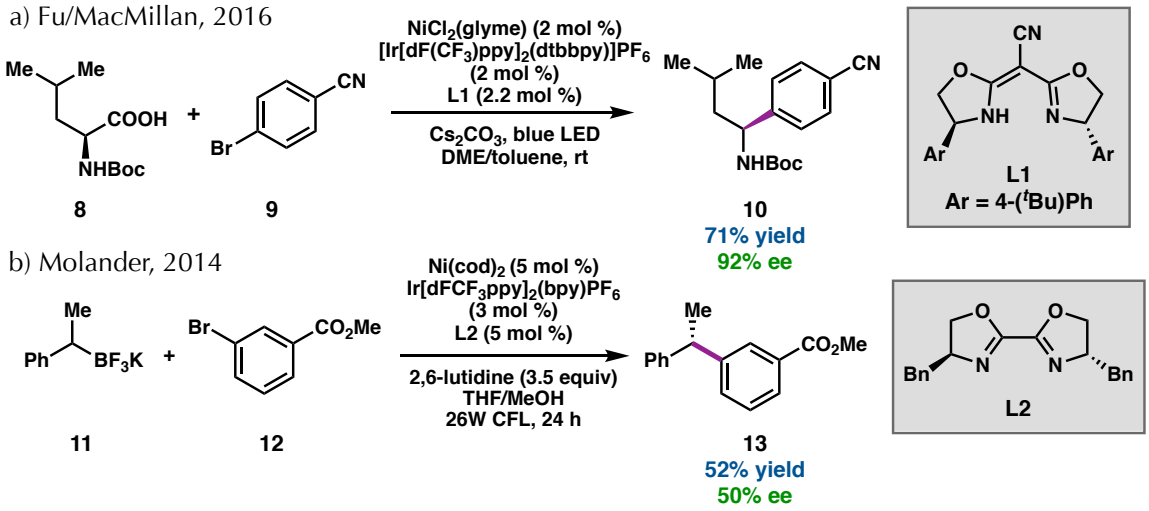
1.3.1 Strategic disconnection

Before the last decade, all examples of Ni-catalyzed asymmetric cross-coupling fell into the category of redox-neutral transformations. However, our group and others hypothesized that mechanisms active in stereoconvergent redox-neutral couplings could be leveraged toward the development of asymmetric reductive cross-couplings between two electrophilic partners. This effort requires control over the cross-selectivity of the reaction, as well as stereocontrol through an enantioconvergent transformation of the C(sp^3) electrophile.

Extensive methods development and mechanistic investigations by Fu and coworkers on the stereoconvergent cross-coupling of *sec*-alkyl electrophiles have demonstrated the feasibility of generating an alkyl radical through halide abstraction by a Ni(I) complex[30,31] and leveraging this species for asymmetric catalysis with a chiral ligand.[32] Beyond halide abstraction, there are several single electron processes that have been demonstrated to generate planar, prochiral radical intermediates that can be directed

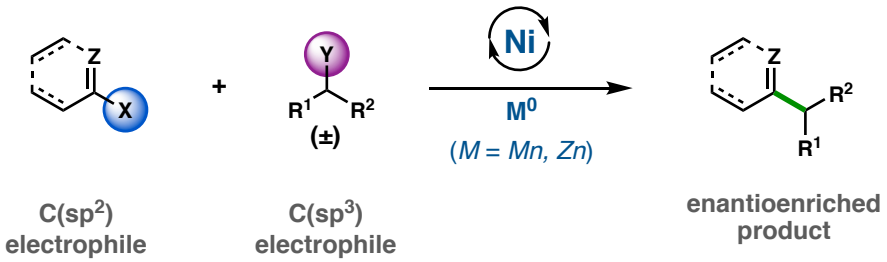
by chiral ligands for asymmetric catalysis. Decarboxylation and fragmentation of nucleophilic groups have been used for Ni-catalyzed photoredox dual catalysis (Molander,[33,34] Kozlowski,[35] Fu/MacMillan[36]) and reductive cross-electrophile (Reisman, Doyle[37]) stereoconvergent cross-couplings (Scheme 1.4).

Scheme 1.4. *Single electron chemistry in Ni-catalyzed cross-coupling.*



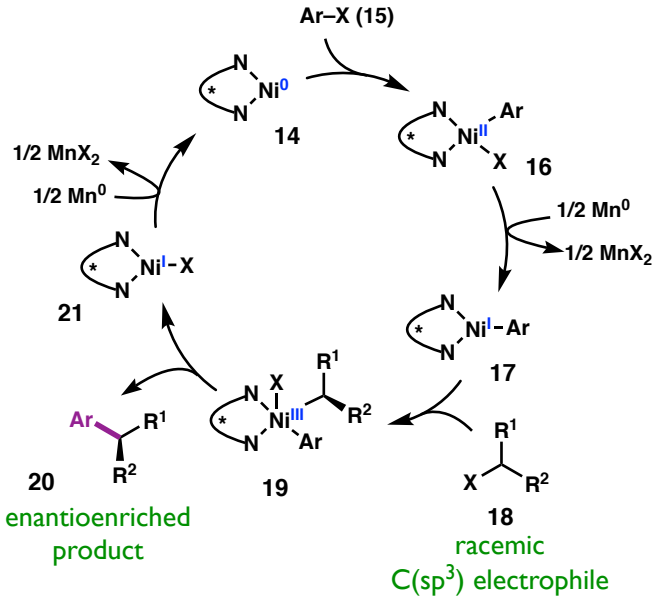
In order to achieve optimal cross-selectivity and enantiocontrol in reductive cross-couplings, our lab pairs C(sp^3) and C(sp^2)-hybridized electrophilic coupling partners for stereoconvergent reductive cross-coupling reaction development (Scheme 1.5). One of the advantages of a stereoconvergent approach is that after a single enantioselective preparation of a chiral ligand, many diverse enantioenriched product scaffolds can be readily accessed from racemic coupling partners. In a stereospecific approach, an enantioenriched coupling partner must be prepared beforehand for each corresponding desired product. However, it should be noted that achiral ligands are more often commercially available, and stereospecific reaction conditions can be easily adapted for diastereoselective transformations.[13,38–41]

Scheme 1.5. *General concept for stereoconvergent reductive cross-couplings.*



1.3.2 Mechanistic hypotheses

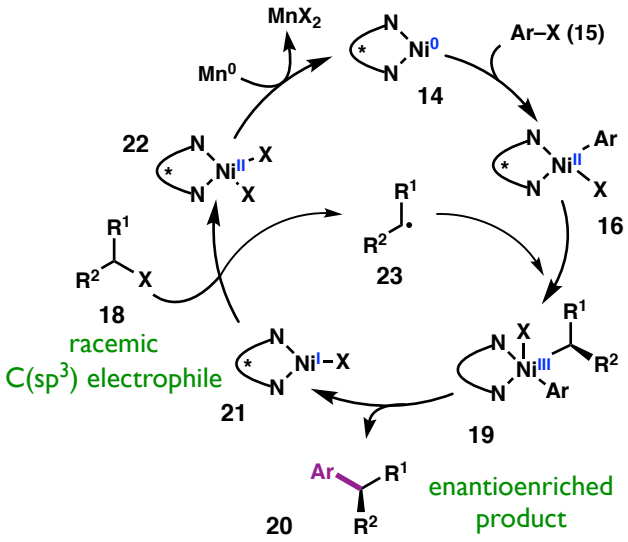
Figure 1.1. *Proposed sequential reduction mechanism.*



Mechanistic investigations into reductive cross-couplings have been conducted by several labs and can be primarily summarized by two related mechanistic hypotheses: a sequential reduction mechanism and a radical chain mechanism (Figure 1.1).[15,42,43] In a sequential reduction mechanism, we predict that the C(sp^2) electrophile undergoes concerted oxidative addition to Ni(0) species **14** to afford Ni(II)-aryl complex **16** (an aryl halide is shown as the C(sp^2) electrophile for clarity), which is then reduced by Mn^0 to a Ni(I)-aryl complex (**17**) (Figure 1.1).[44] **17** can then effect radical abstraction from

racemic *sec*-alkyl electrophile **18** to generate a prochiral radical, which undergoes radical addition with the metal center to give a Ni(III) intermediate (**19**).[30,31,45–47] Subsequent reductive elimination produces enantioenriched product **20** and a Ni(I)-halide complex (**21**), which can be reduced by Mn^0 to regenerate the Ni(0) catalyst and close the catalytic cycle.

Figure 1.2. *Proposed radical chain reaction mechanism.*



Our second mechanistic hypothesis involves a radical chain process (Figure 1.2). The C(sp^2) electrophile undergoes oxidative addition to Ni(0) complex **14**, as before. This Ni(II) intermediate **16** then combines with a free *sec*-alkyl radical (**23**) to give Ni(III) complex **19**, which reductively eliminates to give enantioenriched product **20** and the Ni(I)-halide complex **21**. The resulting Ni(I)-halide complex can abstract a halide from the C(sp^3) electrophile to generate long-lived *sec*-alkyl radical **23**.[48] The Ni(II)-dihalide (**22**) formed can be reduced by Mn^0 to regenerate the Ni(0) catalyst (**14**) and close the cycle.

The major difference between the sequential reduction and radical chain mechanism is the lifetime of the benzylic radical generated by halide abstraction, which is either short-lived and reacts via a radical-rebound process (sequential reduction mechanism), or long-lived and achieves cage escape (radical chain reaction mechanism). Mechanistic and computational data supports each mechanism in different systems, suggesting that the mechanism of Ni-catalyzed reductive cross-couplings may vary with different substrates, ligands, and reaction conditions. We can also imagine the two cycles working simultaneously for radicals of intermediate half-life. In these reactions, the enantiodetermining step could be radical combination with a Ni(II) complex to form the thermodynamically-preferred diastereomer of Ni(III), followed by facile reductive elimination. However, if radical combination to form a Ni(III) species is reversible, then reductive elimination through a Curtin-Hammett-type mechanism may be the enantiodetermining step.[35]

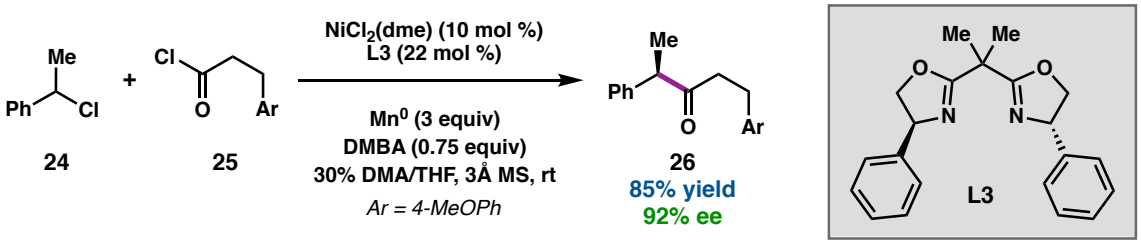
1.3.3 Stereoconvergent $C(sp^3)$–$C(sp^2)$ bond formation

With these general principles for cross-selectivity and enantioselectivity in mind, our lab aims to develop a number of general and highly selective Ni-catalyzed stereoconvergent reductive cross-coupling reactions. The first report of a Ni-catalyzed stereoconvergent reductive cross-coupling was published by our lab in 2013 (Scheme 1.6).[49] This report described the asymmetric cross-coupling of racemic benzyl chlorides and acyl chlorides using Mn^0 as a stoichiometric reductant, a Ni(II) catalyst, and a chiral bis(oxazoline) ligand. The mixed solvent system of DMA and THF provided the optimal balance of reactivity and selectivity; the highest ee's were observed in low yield in THF, while DMA provided higher conversion, though increased homocoupling. Importantly,

we found that the addition of dimethylbenzoic acid (DMBA) suppressed homocoupling of the C(sp^3) electrophile. While good functional group tolerance was observed for both coupling partners, we found that *o*-substituted benzyl chlorides were poor substrates, providing the products in low yield and ee.

Scheme 1.6. *First report of asymmetric reductive cross-coupling.*

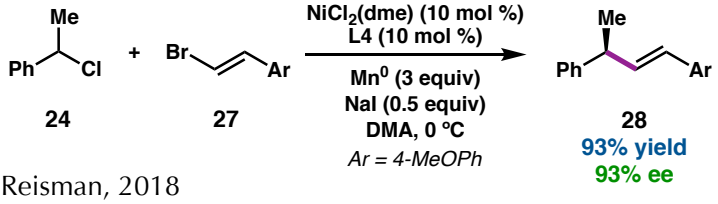
Reisman, 2013



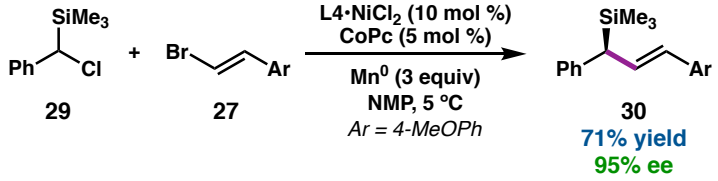
In 2014, we expanded the scope of the C(sp^2) coupling partner in the transformation to alkenyl bromides (Scheme 1.7a).[50] In DMA at 0 ºC, we identified chiral bis(oxazoline) **L4** as the optimal ligand for the reaction, giving the enantioenriched products bearing allylic stereogenic centers in excellent enantiomeric excess. We determined NaI to be an important additive in the reaction, improving the yield of **28** and decreasing the formation of the dibenzyl homodimer. NaI is known to enhance the reactivity in reductive cross-couplings, either through acceleration of electron transfer between Mn and Ni, or by *in situ* formation of iodide electrophiles.[51] In 2018, we were able to expand the scope of the benzyl chloride coupling partner to benzylic silanes,[52] extremely bulky electrophiles that required the addition of catalytic cobalt phthalocyanine (CoPc) to facilitate radical generation (Scheme 1.7b).[53]

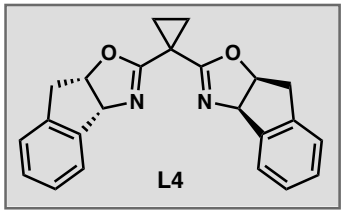
***Scheme 1.7**. Asymmetric reductive cross-coupling with alkenyl bromides.*

a) Reisman, 2014



b) Reisman, 2018

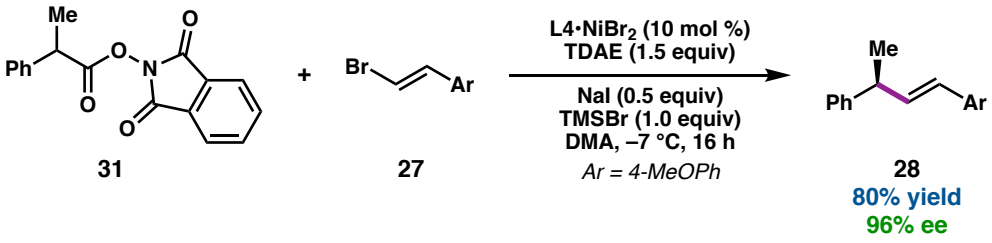




In 2017, we reported the use of a decarboxylative mechanism to generate a benzylic radical using *N*-hydroxyphthalimide (NHP) esters[54] for use in the asymmetric cross-coupling with alkenyl bromides (Scheme 1.8).[55] Interestingly, the organic reductant TDAE[56] was optimal in this reaction, with Mn^0 and Zn^0 providing the product in significantly lower yield. Intriguingly, we observed significant amounts of (*E*)-1-(2-chlorovinyl)-4-methoxybenzene when using a chloride-containing precatalyst or TMSCl as an additive, presumably due to a Ni-catalyzed halide exchange process.[57,58] This alkenyl chloride was inert in the cross-coupling reaction, and it was necessary to eliminate any source of chloride in the reaction to improve the yield.

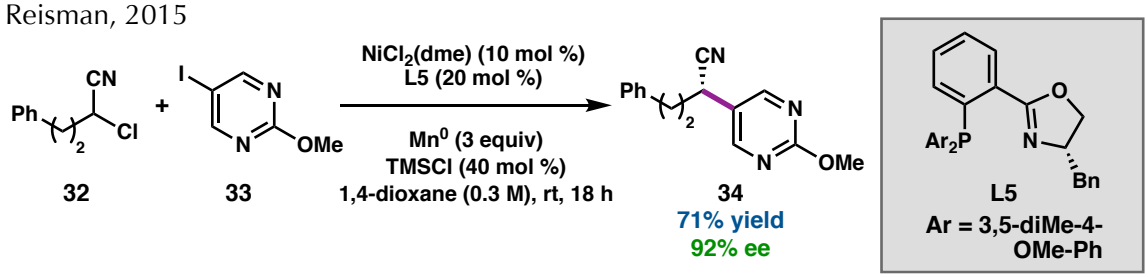
***Scheme 1.8**. Asymmetric reductive decarboxylative cross-coupling.*

Reisman, 2017 (Chapter 4)



While we had early success with benzyl chlorides as the C(sp^3) coupling partner, variation of the C(sp^3) electrophile has proven challenging and required the use of chiral ligands outside of the bis(oxazoline) family. In 2015, we published the Ni-catalyzed asymmetric reductive cross-coupling of α-chloronitriles and (hetero)aryl iodides (Scheme 1.9).[59] This reaction required a PHOX ligand and provided the highest yields and ee's of product in 1,4-dioxane with TMSCl as an additive, which has been proposed to activate the surface of the Mn.[15,60]

Scheme 1.9. *Asymmetric reductive cross-coupling with α-chloronitriles.*



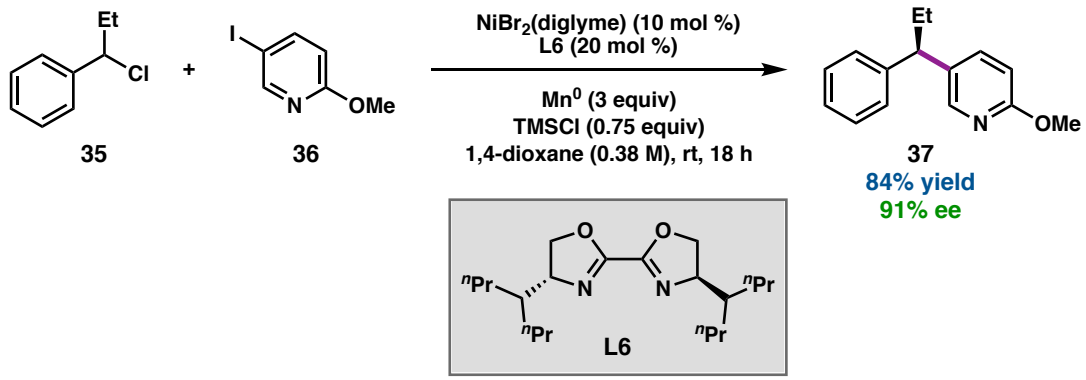
Interestingly, the asymmetric reductive cross-coupling of benzyl chlorides with aryl iodides proved to require significantly different reaction conditions from the corresponding reactions with alkenyl bromides, but similar conditions for the coupling of α-chloronitriles (Scheme 1.10a). This cross-coupling to access enantioenriched 1,1-diarylalkanes performed optimally in 1,4-dioxane with a novel bi(oxazoline) ligand bearing long alkyl chain substituents (**L6**).[61]

Invoking a similar stereoconvergent mechanism, Doyle and Sigman concurrently published the enantioselective reductive cross-coupling of racemic styrenyl aziridines with aryl iodides using **L6** developed by our lab (Scheme 1.10b).[37] Multivariate analysis of the effect of chiral bi(oxazoline) ligands on the reaction revealed ligand polarizability

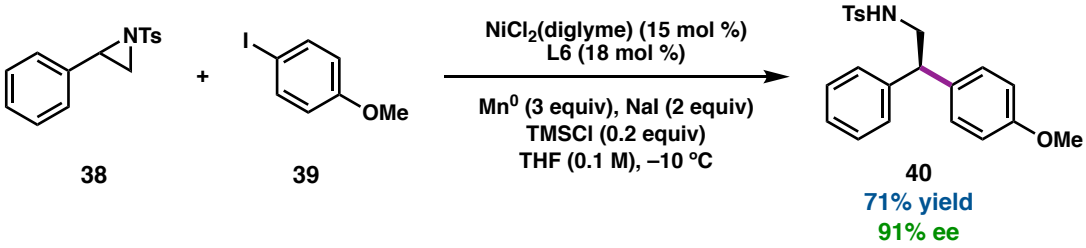
influences the enantioselectivity, suggesting the presence of noncovalent interactions, such as dispersion forces or CH–π interactions.

Scheme 1.10. *Asymmetric reductive cross-coupling with a novel BiOX ligand.*

a) Reisman, 2017 (Chapter 2)



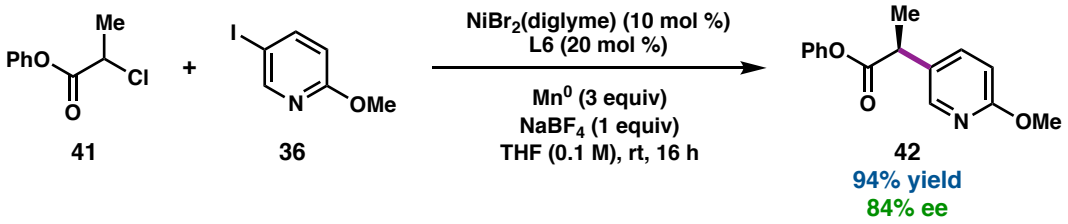
b) Doyle and Sigman, 2017



In an ongoing effort in our lab to expand the scope of the C(sp^3) coupling partner in this reaction, our lab is currently working on the development of the cross-coupling between α-chloroester substrates and (hetero)aryl iodides (Scheme 1.11). Toward this effort, we are collaborating with the Doyle and Sigman groups to identify the important features of the chiral bi(oxazoline) ligand in this system and direct the synthesis of novel alkyl-substituted bi(oxazoline) ligands.

Scheme 1.11. *Asymmetric reductive cross-coupling with α -chloroesters.*

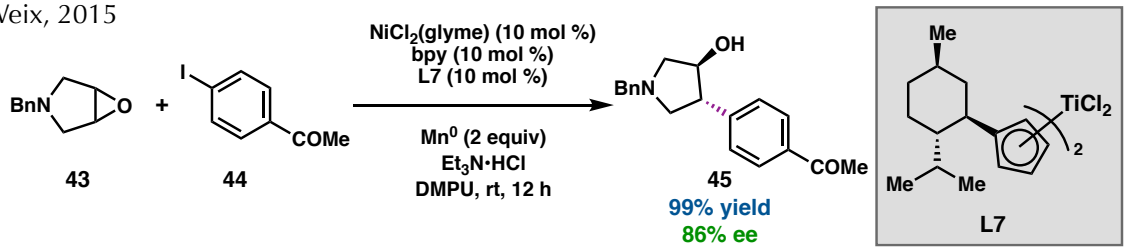
Reisman, unpublished (Chapter 3)



Outside of our lab's contributions to this field, the Weix group has published the enantioselective cross-coupling of *meso*-epoxides with aryl halides (Scheme 1.12).[42] In this transformation, a titanocene catalyst generates a chiral β-titanoxy carbon radical from the *meso*-epoxide, which can be intercepted by an Ar–Ni(II)bpy complex for reductive elimination from a Ni(III) species to give enantioenriched product.

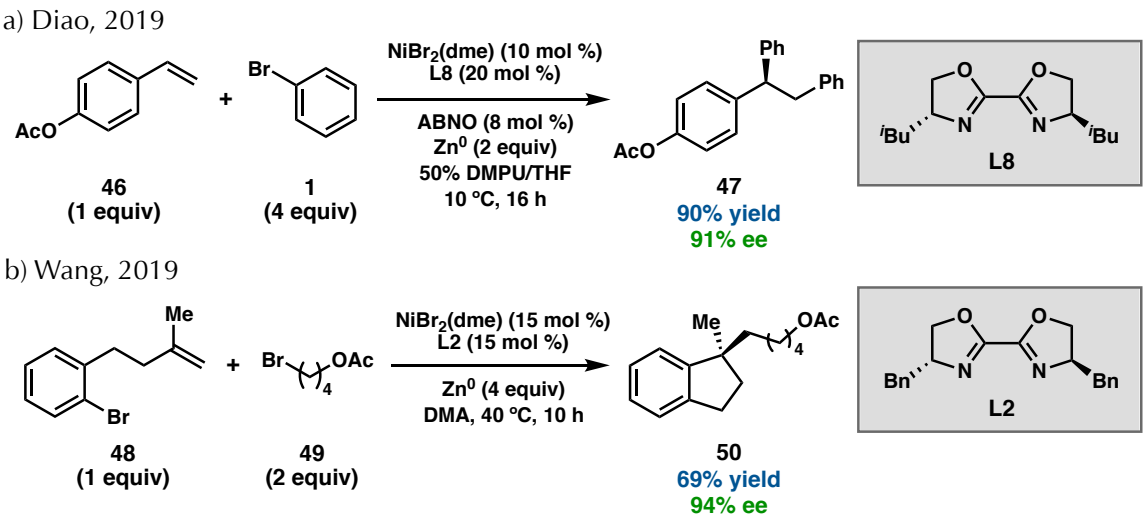
Scheme 1.12. *Reductive cross-coupling with Ni/Ti dual-catalysis.*

Weix, 2015



Recently, two reports of enantioselective Ni-catalyzed reductive cross-couplings with olefins have been reported. In 2019, Diao and coworkers disclosed the asymmetric reductive dicarbofunctionalization of styrenes utiliting a bi(oxazoline) ligand (**L8**) and Zn^0 as a stoichiometric reductant (Scheme 1.13a).[62] In this diarylation, a Ni(I)–aryl species is proposed to undergo radical addition across the olefin substrate to generate a Ni(I)–alkyl species. This complex can then undergo oxidative addition with a second equivalent of aryl halide and subsequent reductive elimination to form the enantioenriched product.

Scheme 1.13. *Enantioselective reductive cross-coupling with olefins.*



Soon after, Wang and coworkers published the asymmetric reductive arylalkylation of unactivated olefins to form enantioenriched benzene-fused cyclic products bearing quarternary centers using a chiral bi(oxazoline) ligand (**L2**) (Scheme 1.13b).[63] In this two-component coupling, an Ni(II)–aryl species can be reduced to Ni(I)–aryl, which could undergo 5-*exo*-trig cyclization with the pendent alkene. The resultant Ni(I)–alkyl species can then undergo oxidative addition with the alkyl bromide coupling partner to eventually furnish the final product.

1.4 CONCLUSION

While transition metal-catalyzed cross-coupling reactions remain an invaluable tool for the synthesis of natural products and other small molecules, the use of first-row transition metals has enabled the expansion of this methodology to allow for cross-electrophile couplings. The use of nickel in these reductive cross-couplings has enabled the development of mild reaction conditions that proceed to give the desired products in good yields with high levels of enantioselectivity. In particular, nickel-catalyzed

reductive cross-couplings have alleviated some of the challenges inherent to traditional, redox-neutral cross-coupling strategies. We anticipate that this field will continue to grow and revolutionize the way that carbon–carbon bonds are constructed in a stereoselective manner.

1.5 NOTES AND REFERENCES

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