Chapter 1

Nickel Catalysis in Cross-Coupling: A Review of Applications in Asymmetric Catalysis and the Rise of Reductive Cross-Coupling[◊]

1.1 INTRODUCTION

The stereocontrolled construction of C–C bonds remains one of the foremost challenges in organic synthesis. At the heart of any chemical synthesis of a natural product or designed small molecule is the need to carefully orchestrate a series of chemical reactions to prepare and functionalize a carbon framework. Transition metal catalysis, most notably by Pd, has transformed the palette of tools available to the synthetic chemist, enabling new disconnections and streamlining access to complex scaffolds. While the incredible versatility and reliable predictability of Pd-mediated reactions has made them a mainstay of synthetic organic chemistry (and earned their inventors a Nobel prize), the unique reactivity of Ni and other base metals has brought

[◊] Portions of this chapter have been reproduced from a published review coauthored with Prof. Sarah E. Reisman and Dr. Alan H. Cherney (see reference 1).

about a resurgence of interest in these catalysts as well, particularly to effect stereoselective transformations.

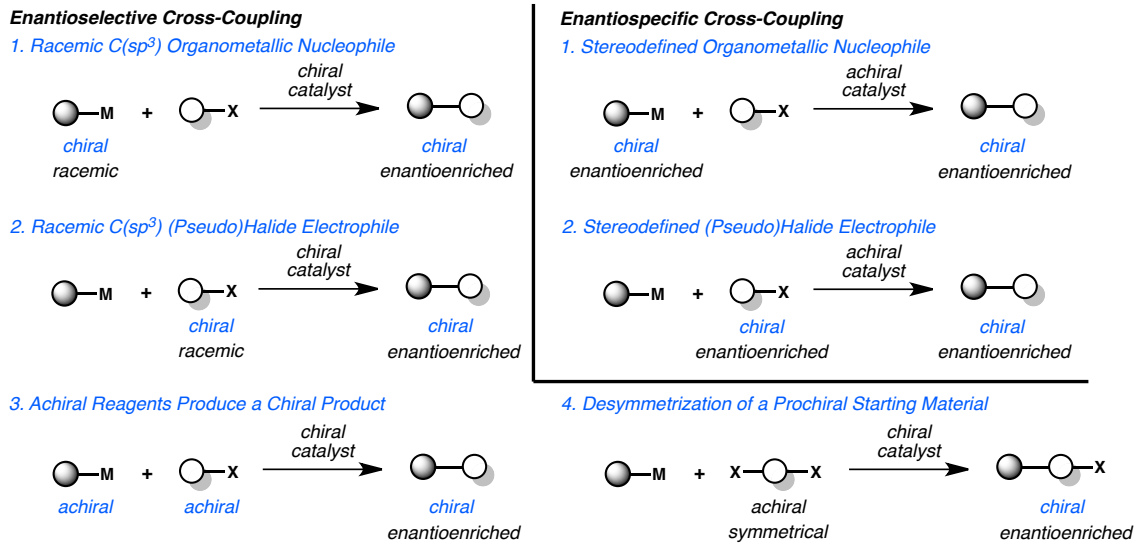
The potential of using transition metal-catalyzed C–C bond formation to prepare enantioenriched molecules was immediately recognized by the synthetic chemistry community. Indeed, the first forays into enantioselective cross-coupling reactions occurred contemporaneously with the development of the transition metal-catalyzed reactions themselves. Though some of the earliest and most foundational studies in cross-coupling (including asymmetric reactions, *vide infra*) were conducted using Ni catalysis, much of this field has been dominated by precious metals until recently. Below we have collected the Ni-catalyzed asymmetric cross-coupling reactions reported over the last five decades, highlighting the utility of this base metal in catalysis and underscoring its role in the history of asymmetric cross-coupling. Here we define *Ni-catalyzed cross–coupling reactions* as C–C bond forming reactions between an organic electrophile (typically an organic halide or pseudo halide, such as alcohols, amines, and their derivatives) and an organometallic reagent, mediated by a nickel catalyst.

Enantio-controlled Ni-catalyzed cross-coupling reactions to form C–C bonds, in which the stereogenic unit is defined by the C–C bond forming event, can be organized into two general categories. The first group comprises <u>*enantioselective*</u> Ni-catalyzed cross-coupling reactions, which we define as *reactions in which there is selective formation of one enantiomer over the other as defined by a non-racemic chiral Ni catalyst*. There are several different types of enantioselective cross-coupling reactions: those in which (a) racemic, $C(sp)^3$ organometallic reagents are stereoconvergently coupled to organic electrophiles; (b) racemic, $C(sp)^3$ organic electrophiles are

stereoconvergently coupled to organometallic reagents; (c) achiral organic electrophiles are coupled to achiral organometallic reagents to produce chiral, non-racemic products; and (d) a prochiral starting material (either the organic electrophile or organometallic reagent) is desymmetrized. These reactions are schematically represented in **Figure 1.1**. These types of enantioselective reactions have been used to prepare molecules exhibiting centro, axial, and planar chirality. Our discussion here will encompass enantioselective Ni-catalyzed cross-coupling reactions of organic electrophiles and organometallic reagents, covering the literature published through the end of the year 2014.[1]

Although not discussed further in this chapter, it is important to note that the second group comprises *enantiospecific* Ni-catalyzed alkyl cross-coupling reactions, which we define as *chirality exchange reactions in which the stereochemistry of a chiral, enantioenriched substrate defines the stereochemistry of the product*. These reactions can be further categorized into those which involve the cross-coupling of (a) a stereodefined organometallic reagent with an electrophile, or (b) a stereodefined electrophile with an organometallic reagent. While much of this field has been dominated by the stereospecific coupling of enantioenriched organometallic reagents by Pd, Ni has received significant recent attention for its ability to stereospecifically cross-couple pseudohalide electrophiles such as benzylic ethers, carbamates, esters, and ammonium salts.[2] These reactions are an area of substantial current interest and represent a valuable alternative approach to access chiral products.

Figure 1.1. *Strategies for enantiocontrolled cross-coupling.*

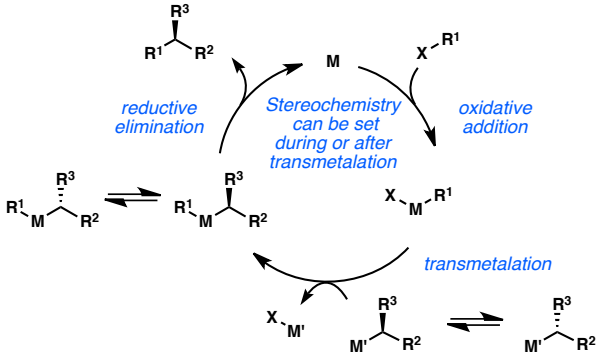


Despite promising initial reports, highly enantioselective transition metal-catalyzed alkyl cross-coupling reactions were slow to develop, in part because of the general challenges encountered in Pd-catalyzed alkyl cross-coupling reactions. For Pd and other metals that react by polar, two-electron mechanisms, *sec*-alkyl organometallic reagents are typically slower than their *n*-alkyl or C(sp)^2 hybridized counterparts to undergo transmetalation.[3] Similarly, *sec*-alkyl electrophiles are frequently slow to undergo oxidative addition to Pd.[4] Moreover, in either case, the resulting *sec*-alkyl transition metal complexes can suffer from rapid, non-productive β-hydride elimination. Thus, the successful realization of enantioselective transition metal-catalyzed alkyl cross-coupling reactions has resulted from fundamental studies of the factors, especially ligands, which control and influence the efficiency of these transformations. In particular, a renewed interest in Ni catalysts, which can engage with *sec*-alkyl halides through single electron oxidative addition mechanisms, has resulted in a rapidly increasing number of enantioselective alkyl cross-coupling reactions.

1.2 REACTIONS OF SECONDARY ALKYL ORGANOMETALLIC REAGENTS

Early efforts to develop enantioselective transition metal-catalyzed alkyl cross-coupling reactions focused primarily on the use of configurationally labile *sec*-alkyl organometallic species such as organomagnesium and organozinc reagents. In general, the configurational stability of an organometallic reagent correlates to the electronegativity of the metal, with less electronegative metals resulting in more configurationally labile *sec*-alkyl reagents.[5] For example, *sec*-alkyl magnesium reagents have been shown to racemize above –10 °C, while the corresponding *sec*-alkyl boron reagents are configurationally stable indefinitely at room temperature.[6] In principle, fast equilibration between the two enantiomers of a *sec*-alkyl organometallic reagent or between two diastereomers of a chiral transition metal complex could enable enantioselective cross-coupling through a dynamic kinetic asymmetric transformation (DYKAT), in which the newly formed stereogenic center is controlled by the chirality of the metal catalyst (**Figure 1.2**).

Figure 1.2. *Stereochemical outcome of cross-coupling with secondary nucleophiles.*



Enantioselective reactions of configurationally stable *sec*-alkyl organometallic reagents can arise from catalyst-controlled kinetic resolution processes, wherein the

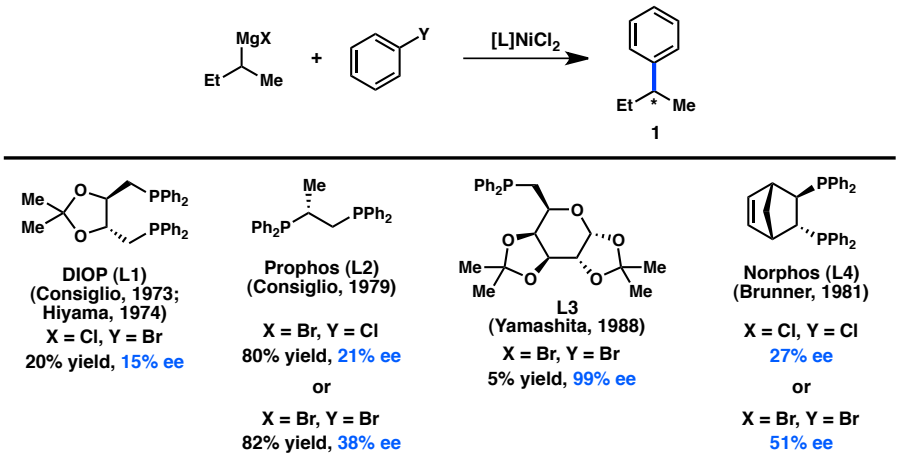
relative rates of transmetalation for the two enantiomers of the chiral organometallic reagent are substantially different. In this case, an excess of the organometallic reagent must be used to obtain the cross-coupled product in good yield. A third possibility involves a stereoablative mechanism, in which the initial configuration of the starting material is destroyed and then reset by the chiral catalyst during the reaction.

1.2.1 Organomagnesium Reagents

In 1972 Corriu and Kumada independently reported the Ni-catalyzed cross-coupling between alkyl organomagnesium halides and aryl or vinyl halides;[7] shortly thereafter the first studies aimed at utilizing chiral transition metal complexes to catalyze these reactions enantioselectively were reported.[8] In 1973 and 1974, respectively, Consiglio and Kumada independently reported that the complex generated from Ni-halide salts and the chiral bidentate phosphine ligand DIOP (**L1**) catalyzes the reaction between *sec*-butylmagnesium bromide or chloride and bromo- or chlorobenzene to give product **1** with promising enantioinduction (**Figure 1.3**).[9] These results were an important proof of concept for the area of enantioselective cross-coupling; however, since low yields of product were obtained, it remains ambiguous whether these reactions proceed by kinetic resolution of the *sec*-alkylmagnesium reagent or through a DYKAT. It was subsequently reported that Prophos (**L2**) provides improved enantioinduction and higher yields of **1**.[10] The identity of the halogen on both the organic halide and the organometallic reagent was shown to significantly influence the absolute configuration and the ee of **1**. Further improvements were observed when Norphos (**L4**) was employed as the chiral ligand,

providing **1** in 50% ee.[11] A carbohydrate-derived chiral ligand (**L3**) was also reported to deliver **1** in good ee, although with poor yields.[12]

Figure 1.3. *Stereoconvergent arylation of ^{s}Bu Grignard reagents.*



Concurrent to their efforts to develop enantioselective cross-coupling reactions of *sec*-butyl Grignard reagents, Kumada and coworkers investigated the Ni-catalyzed enantioselective coupling between α-methylbenzyl Grignard reagents and vinyl halides (**Figure 1.4**). DIOP (**L1**) and the axially chiral Naphos (**L6**) ligand systems provided the product with low enantioinduction.[9b,13] Following up on Kumada's studies, Brunner and coworkers reported that Norphos (**L4**) furnished **2** in 95% yield and 67% ee.[14]

Figure 1.4. *Stereoconvergent vinylation of benzylic Grignard reagents.*

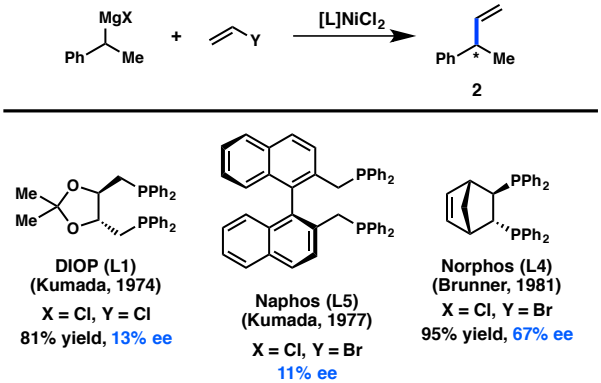
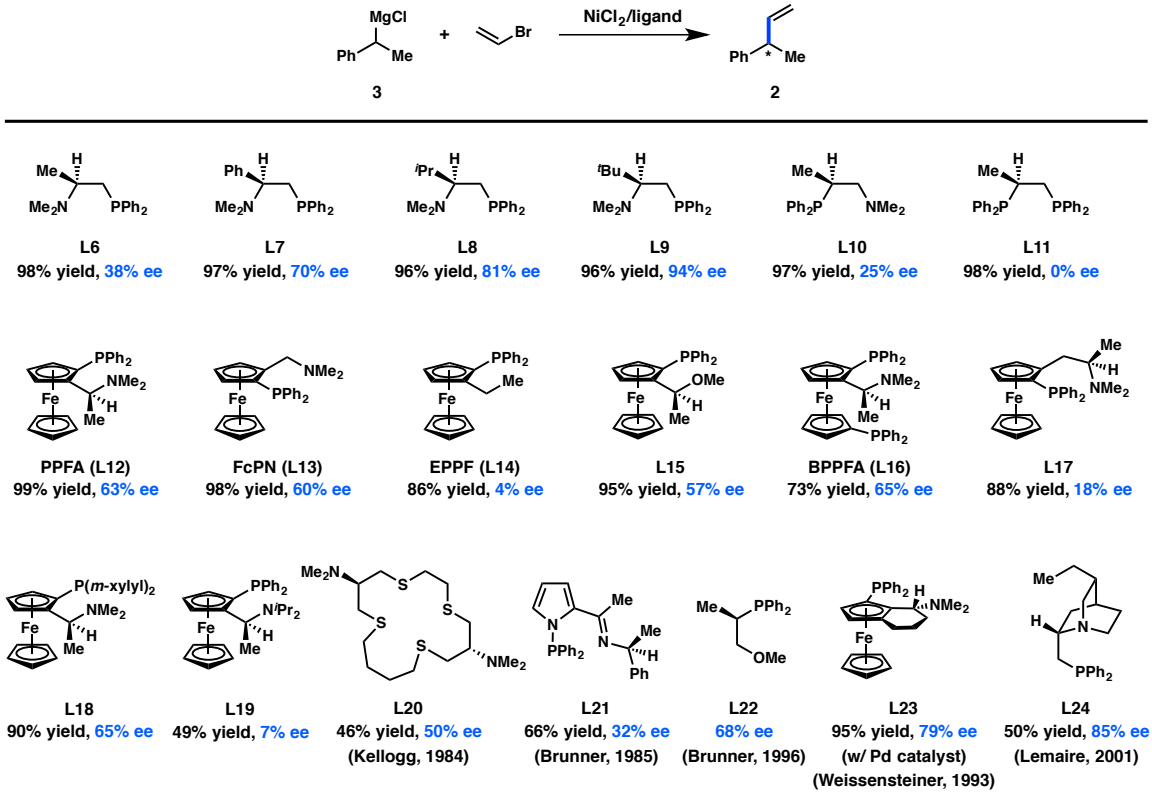


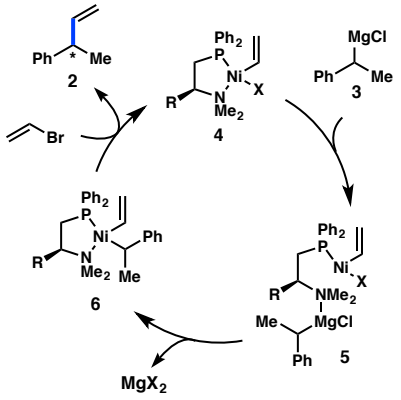
Figure 1.5. *Chiral ligands developed for the enantioselective cross-coupling of α-methylbenzyl Grignard reagents.*



Since Kumada's initial report, the majority of studies have focused on identifying new ligands to improve the selectivity in the coupling between α-methylbenzyl Grignard reagents (**3**) and vinyl bromide. Whereas the early studies focused on the use of bidentate bis-phosphine ligands, which delivered modest levels of enantioinduction, later efforts turned to chiral P,N ligands. Kumada, Hayashi, and coworkers reported that chiral (β-aminoalkyl)phosphines—easily prepared from enantiopure amino acids—delivered exceptionally high yields for the cross-coupling between **3** and vinyl bromide (**Figure 1.5**).[15] Interestingly, whereas the alkyl substitution on the ligand backbone exhibited little influence on the yield of the reaction, it dramatically impacted the enantioselectivity: increasing the steric profile of the ligand raised the ee from 38% when the chiral tertiary

substituent was Me (**L6**) to 94% when this group was ^{t}Bu (**L9**). In order to probe the origin of asymmetric induction, the isomeric P,N-ligand **L10** was designed. Under the same reaction conditions, **L10** delivered **4** in only 25% ee. Moreover, the analogous bis-phosphine **L11** provided no enantioinduction, suggesting a critical role for the amino group. A proposed catalytic cycle for this reaction is shown in **Figure 1.6** and involves precoordination between Grignard reagent **3** and the amino group of the ligand to give complex **5**. The authors hypothesize that this coordination could selectively direct the transmetalation of a single enantiomer of the organometallic reagent, although the importance of this interaction has been debated.[16]

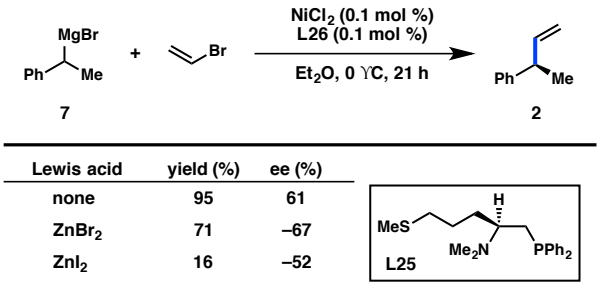
Figure 1.6. *Proposed catalytic cycle for the enantioselective coupling of α-methylbenzyl Grignard reagents.*



Elaborating on this concept, Kellogg and coworkers investigated the use of (β-aminoalkyl)phosphine ligands bearing pendant heteroatoms, such as those derived from lysine or methionine.[17] The authors reported a reversal of the stereochemical outcome in the presence of exogenous zinc halide salts (**Figure 1.7**). Control experiments using pre-generated α-methylbenzylzinc bromide did not support the intermediacy of an organozinc species; instead it is possible that coordination between the Lewis acidic zinc halide and

the sidechain heteroatom could alter or disrupt the ability of the amino group to direct the transmetalation event.

Figure 1.7. *Addition of exogenous zinc halide salts reverses the sense of enantioinduction when sulfur-containing ligand* ***L25*** *is used.*

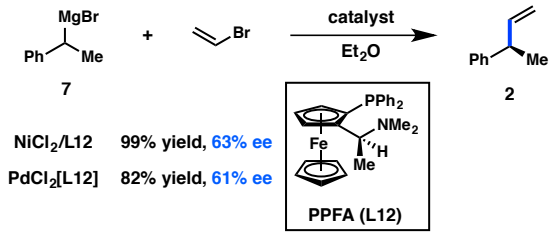


Lewis acid	yield (%)	ee (%)
none	95	61
$ZnBr_2$	71	–67
ZnI_2	16	–52

The importance of an amino directing group on the chiral ligand was also reported by Kumada, Hayashi, and coworkers, during their investigations of ferrocenyl phosphines in the Ni-catalyzed coupling between α-methylbenzyl Grignard reagent **3** and vinyl bromide (**Figure 1.5**). These bidentate P,N ligands possess both centrochirality at carbon as well as planar chirality. The ligand PPFA (**L12**), furnished **2** in an excellent 99% yield and 63% ee.[18] The ee of the product was determined to remain roughly constant over the course of the reaction.[19] A structure-activity relationship study revealed that FcPN (**L13**), while lacking centrochirality but maintaining planar chirality, gave **2** in 60% ee, demonstrating the dominant role of planar chirality in this system. EPPF (**L14**), which possesses neither centrochirality nor the dimethylamino group, delivered **2** in only 4% ee, validating the importance of the amino group and supporting a role for pre-coordination as proposed in **Figure 1.6**. Further evidence for the significance of a coordinating group comes from **L15**, which possesses a methoxy moiety instead of a dimethylamino group and provides **2** in 57% ee. Diphosphine BPPFA (**L16**), which could potentially coordinate through phosphorus in a bidentate fashion, also provides **2** in 65% ee. The

similarity of the ee data obtained with **L14** and **L16** suggests that they both coordinate the metal in the same fashion, likely through a P-N mode. Consistent with this observation, changing the steric bulk on the amine of **L12** gives a range of ee values for **2** (see **L19**), while changing the steric environment of the phosphine does not significantly perturb the selectivity (see **L18**). Homologated ligand **L17** delivers **2** in poor ee.[20] Pd catalysts were also investigated and were shown to give comparable results to Ni (**Figure 1.8**).[18c]

Figure 1.8. *The use of the P-N ligand PPFA provides similar results in both Ni- and Pd-catalyzed transformations.*

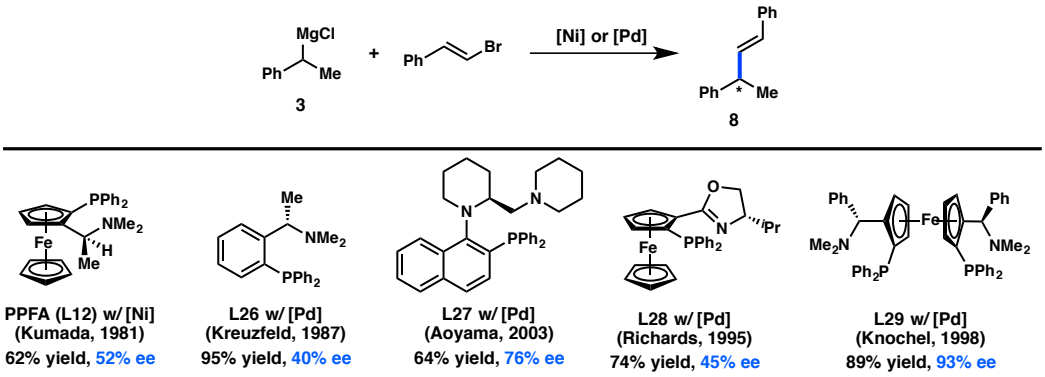


Several other ligand families have been developed for the enantioselective preparation of **2** (**Figure 1.5**). Catalysts generated from macrocyclic sulfides (**L20**) and nickel salts have been shown to impart moderate enantioselectivity, possibly through a simple kinetic resolution.[21] The use of pyrrole-containing P,N ligand **L21** or phosphine **L22** delivers **2** in 32% ee and 68% ee, respectively, under Ni catalysis.[22,23] Using Pd catalysis, the P,N ligand **L23**, which contains both planar and centrochirality, gives improved results with respect to PPFA (**L12**).[24] High ee can also be achieved with phosphine-quincoridine **L24**.[25]

Despite the advances made through ligand tuning when vinyl bromide is used as an electrophile, the scope of the asymmetric alkyl cross-coupling is poor. Disubstituted alkenes were typically found to be less enantioselective; for example, the reaction of *E*-

bromostyrene using PPFA (**L12**) as the ligand delivered **8** in only 52% ee and moderate yield (**Figure 1.9**).[18c,26] While the yield could be improved using the simpler aminophosphine **L26**, the ee of **8** decreased.[27] **L27**, designed to induce axial chirality upon coordination to a transition metal, was able to induce 76% ee for **8**.[28] Moderate ee could also be attained with phosphine-oxazoline ligand **L28**.[29] Knochel and coworkers reported C_2-symmetric ferrocenyl phosphine **L29** as being capable of delivering excellent ee for the coupling of bromostyrene, although the reaction scope is still limited.[30]

Figure 1.9. *Asymmetric Kumada–Corriu cross-coupling of bromostyrene.*

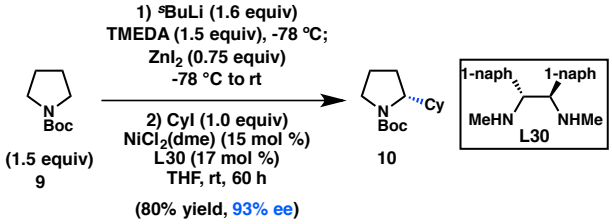


1.2.2 Organozinc Reagents

The pioneering studies of enantioselective transition metal-catalyzed alkyl cross-coupling reactions were initially performed using Ni catalysts and organomagnesium reagents—a species expected to exhibit configurational lability. Advances in the development of the Negishi cross-coupling subsequently enabled the use of organozinc reagents in asymmetric alkyl cross-coupling reactions, with Hayashi, Kumada, and coworkers reporting the first examples in 1983.[31] Preliminary studies investigated the coupling of the organozinc chloride prepared from transmetalation of **3** with $ZnCl_2$; however, Ni catalysts were determined to be poorly reactive. On the other hand, the

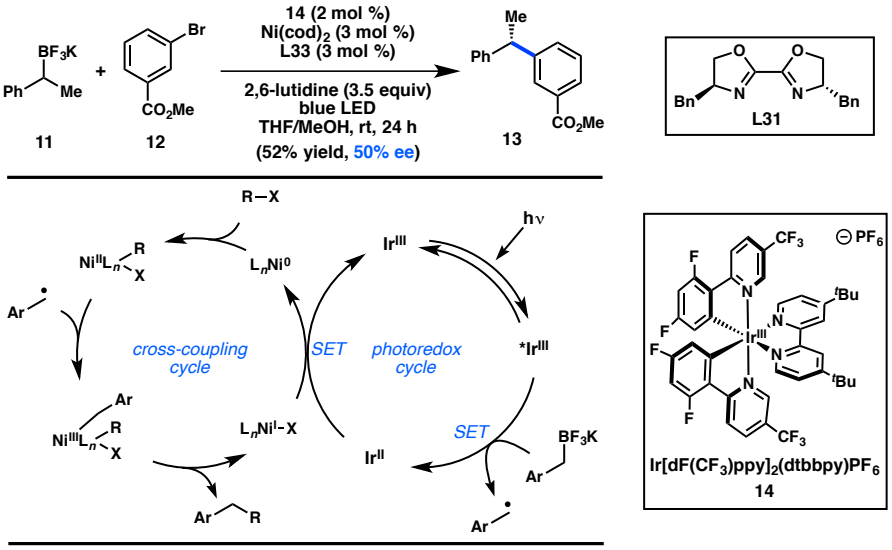
combination of Pd and PPFA (**L12**) delivered **2** in 85% ee. Despite a growing interest in the enantioselective Ni-catalyzed cross-coupling reactions of organozinc reagents over the past three decades, successful efforts to further expand upon the enantioselective alkyl Negishi cross-coupling have been limited.

Scheme 1.1. *Enantioselective functionalization of pyrrolidine.*



However, in a seminal 2013 report, Fu reinvestigated the Negishi cross-coupling of α-zincated *N*-Boc-pyrrolidine, which Campos and coworkers had previously shown can undergo stereospecific Pd-catalyzed cross-coupling to deliver enantioenriched α-arylpyrrolidine products.[32] Under Ni catalysis, in the absence of a chiral ligand, coupling of the stereodefined organozinc reagent with cyclohexyl iodide produced the coupled product in almost racemic form. Alternatively, when the chiral Ni/**L30** complex was used as the catalyst, coupling of racemic **9** with cyclohexyl iodide furnished **10** with high ee in a stereoconvergent fashion, representing the first enantioconvergent alkyl-alkyl coupling of a racemic organometallic reagent (**Scheme 1.1**).[33] Mechanistic studies have determined that this stereoconvergence does not arise from a series of β-hydride elimination/alkene insertion processes of the organometallic reagent.

Figure 1.10. *Dual catalysis approach to asymmetric cross-coupling.*

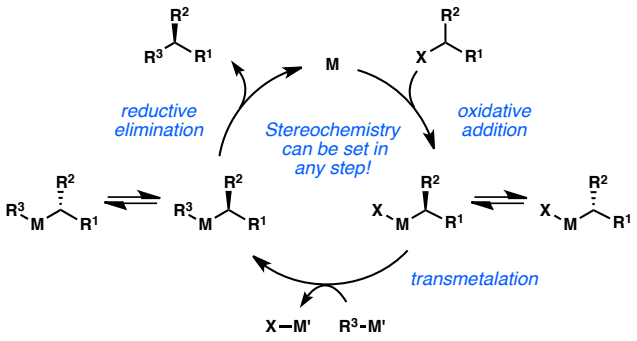


1.2.3 Organoboron Reagents

Trifluoroborate salts are often used in the Suzuki–Miyaura cross-coupling due to their improved stability with respect to boronic acids and esters. The two-electron mechanism of transmetalation typically believed to be operative in Suzuki–Miyaura reactions innately favors transmetalation in a stereospecific manner. However, Molander and coworkers hypothesized that transmetalation through a single electron pathway could favor transfer of a C(sp^3)-hybridized alkyl fragment via a stereoconvergent, radical process. In order to generate a radical from an organoboron reagent (**11**), the authors envisaged a dual catalysis mechanism in which Ni-catalyzed cross-coupling and Ir-catalyzed photoredox events occur synergistically (**Figure 1.10**).[34] In an important proof of concept, chiral bioxazoline (BiOX) **L31** was used to furnish **13** in 50% ee. Electron transfer to an excited state $*Ir^{III}$ complex from an organoboron species would generate an alkyl radical. The alkyl radical can then combine with a chiral Ni^{II} complex to form a Ni^{III}

species that can reductively eliminate the desired product. The resulting Ni^{I} can be reduced by Ir^{II} to complete both catalytic cycles. Additional investigations toward asymmetric catalysis would be valuable.

Figure 1.11. *Stereochemical outcome of cross-coupling with 2° electrophiles.*

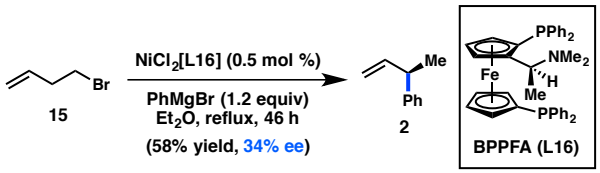


1.3 REACTIONS OF SECONDARY ALKYL ELECTROPHILES

The challenges associated with oxidative addition of *sec*-alkyl electrophiles, as well as the propensity for alkyl transition metal complexes to undergo rapid β-hydride elimination, conspired to make the cross-coupling of these electrophiles difficult to realize using Pd, which had emerged as the metal of choice for cross-coupling in the 1980s. In the early 2000's, researchers began re-investigating first-row transition metals for the cross-coupling of *sec*-alkyl halides and organometallic reagents.[4] Following the first reports of alkyl cross-coupling to form stereogenic $C(sp^3)$ centers, the systematic examination of asymmetric induction in these processes became a chief objective. In these systems, catalysts that favor a single-electron oxidative addition mechanism may undergo a stereoconvergent oxidative addition to set the ultimate stereochemistry of the product. Alternatively, rapidly equilibrating mixtures of diastereomeric transition metal

complexes can result in preferential transmetalation or reductive elimination of one diastereomer over the other (**Figure 1.11**).

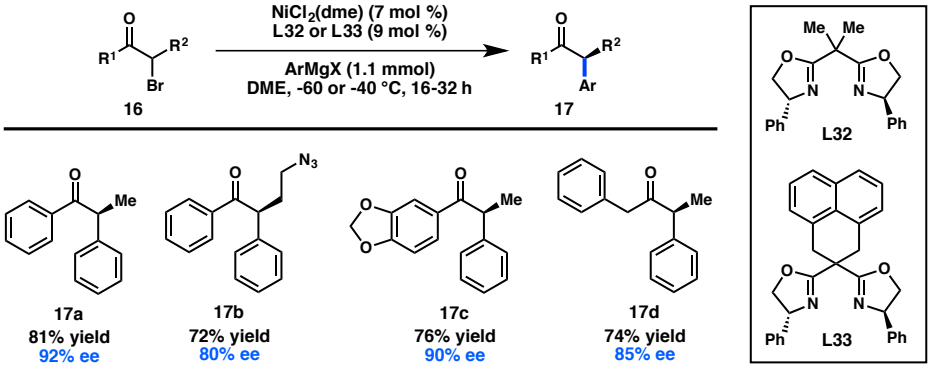
Scheme 1.2. *Primary-to-secondary isomerization in asymmetric cross-coupling.*



1.3.1 With Organomagnesium Reagents

The earliest example of an enantioselective transition metal-catalyzed cross-coupling reaction between an alkyl electrophile and an organomagnesium reagent was disclosed by Kumada and coworkers in 1977, the result of a surprising alkyl group isomerization observed during the coupling between homoallylic halide **15** and PhMgBr (**Scheme 1.2**).[35] In the presence of the chiral catalyst $NiCl_2$[BPPFA], **2** was formed in 34% ee. While the isomerization of secondary organometallic reagents to primary species is a well-known side reaction in cross-coupling chemistry, the inverse isomerization is much more rarely observed.[36] Although this preliminary result was not developed further by Kumada and coworkers, it presaged the explosion of asymmetric cross-couplings of *sec*-alkyl electrophiles that would emerge in the literature nearly two decades later.

Figure 1.12. *Stereoconvergent Kumada–Corriu coupling of α-haloketones.*



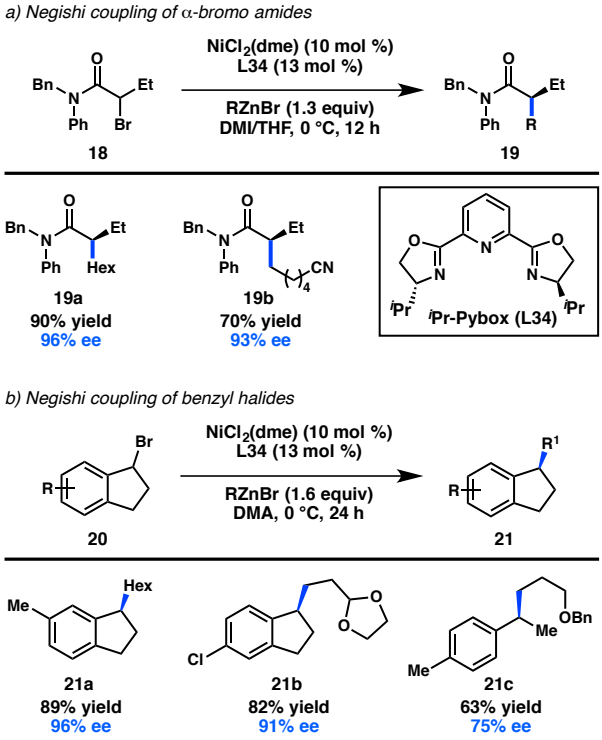
The first synthetically useful enantioselective, stereoconvergent cross-coupling between a *sec*-alkyl electrophile and a Grignard reagent was developed by Fu and coworkers in 2010. In this seminal report, the combination of $NiCl_2$(dme) and bidentate bis(oxazoline) ligand **L32** or **L33** was found to promote the coupling of α-haloketones **16** and arylmagnesium halides to give α-aryl ketones **17** (**Figure 1.12**).[37] Notably, the reaction can be run at some of the lowest temperatures reported for the cross-coupling of alkyl electrophiles (–60 °C); the low temperature prevents the racemization of ketone product **17** through enolization by the Brønsted basic Grignard reagent. Both alkyl and aryl ketones can be prepared by this method, and these products can be diastereoselectively derivatized to access chiral alcohols and amines.[38]

1.3.2 With Organozinc Reagents

In 2005, two reports from the Fu laboratory demonstrated the first utilization of secondary alkyl electrophiles in highly enantioselective cross-coupling reactions. In one example, treatment of α-bromo amide **18** with an alkylzinc reagent and a Ni/**L34** catalyst delivered **19** in good yield and high ee (**Figure 1.13**, **a**).[39] The identity of the amide substituents played a key role in achieving high enantioselectivity. When the organozinc reagent is used as a limiting reagent, the α-bromo amide is recovered as a racemate, suggesting that the reaction does not proceed by a kinetic resolution. In a second example by Fu and coworkers, the Ni/**L34**-catalyzed coupling of 1-bromoindanes and alkyl halides produced chiral indane **20** in good yield and high ee (**Figure 1.13**, **b**).[40] The use of acyclic 1-(1-bromoethyl)-4-methylbenzene furnished **21c** with more modest enantioselectivity. In both cases, only primary organozinc reagents were compatible with

the reaction conditions. A computational investigation by Lin and coworkers proposed that a Ni^{I}/Ni^{III} mechanism consisting of transmetalation/oxidative addition/reductive elimination is more energetically favorable than a Ni^{0}/Ni^{II} mechanism.[41] The enantioselectivity of the reaction was also correlated to the difference in free energy between the two transition states for reductive elimination.

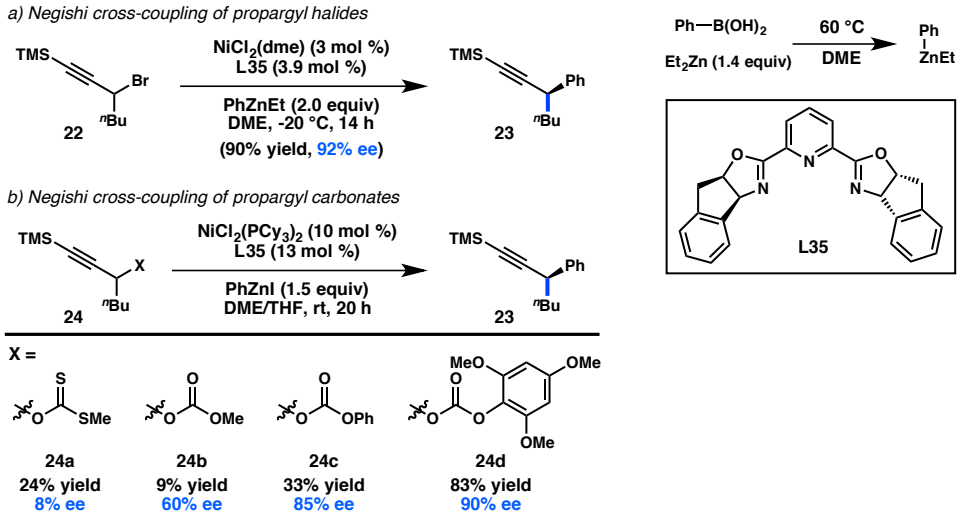
Figure 1.13. *Seminal stereoconvergent cross-couplings of secondary alkyl halides.*



In spite of Fu's promising results for the asymmetric, stereoconvergent Negishi cross-coupling of *alkyl*zinc reagents, the extension to *aryl*zinc species proved challenging. After a lengthy investigation, it was discovered that Ni/**L35** complexes catalyze the cross-coupling between propargyl halide **22** and Ph_2Zn to furnish **23** in a high yield and ee (**Figure 1.14**, **a**).[42] Since relatively few diarylzinc reagents are commercially available, the group sought to identify other arylzinc reagents that were effective for this transformation. Unfortunately, the use of arylzinc halides or *in situ*-

prepared diarylzincs, generated from transmetalation of the corresponding organolithium or –magnesium reagent, was unsuccessful. However, the group determined that ArZnEt, prepared from $ArB(OH)_2$ and Et_2Zn, could react to provide comparable results. In contrast to the stereospecific Pd-catalyzed coupling of propargyl halides, no allene formation arising from S_N2' oxidative addition was observed.[43] Fu and coworkers reported a detailed mechanistic study of this transformation in 2014, showing that the oxidative addition of the propargylic electrophile proceeds via a radical chain pathway, with the stabilized prochiral radical intermediate facilitating enantioconvergence.[44]

Figure 1.14. *Stereoconvergent Negishi cross-coupling of propargylic electrophiles.*

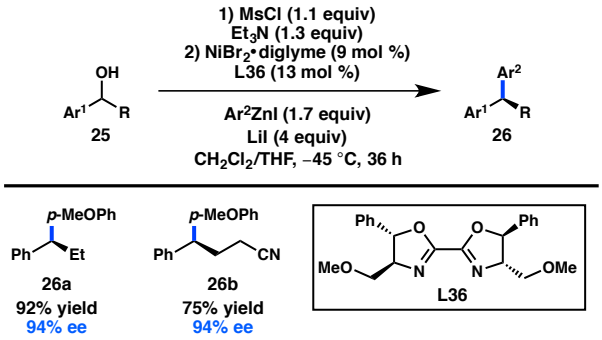


Organic halides are frequently prepared from the corresponding alcohols, and for certain substrates this functional group interconversion can be low yielding. Recognizing the synthetic advantage of using oxygen-based electrophiles directly in cross-coupling reactions, Fu and colleagues turned their attention to the asymmetric cross-coupling of propargylic alcohol derivatives. Hypothesizing that the reaction would proceed through a radical-based oxidative addition to Ni, a xanthate was chosen as a potential leaving group, due to its propensity toward radical cleavage in Barton-McCombie-type

transformations. However, these substrates performed poorly, producing **23** in low yield and ee (**Figure 1.14**, **b**).[45] On the other hand, simple carbonate **24b** underwent cross-coupling with improved enantioselectivity. Further investigation revealed that both the yield and ee could be improved by use of aryl-substituted carbonates, with **24d** delivering **23** in 83% yield and 90% ee. The optimized reaction conditions proved to be general not just for propargyl carbonates, but also for the coupling of propargyl halides.

In 2013, Fu and coworkers published a stereoconvergent Negishi coupling of benzylic mesylates that could be prepared from the corresponding alcohols immediately prior to the coupling and used without purification (**Figure 1.15**).[46] Bi-oxazoline **L36** was identified as the optimal ligand, with more traditional Pybox and Box ligands delivering poor enantioselectivity. LiI was employed to allow *in situ* displacement of the mesylate to form a reactive benzylic iodide. A wide substrate scope was demonstrated for the cross-coupling; a slight erosion of ee is observed when R = Me. Although several stereospecific routes to diarylalkanes have been developed to date,[47] this reaction provides a complementary approach.

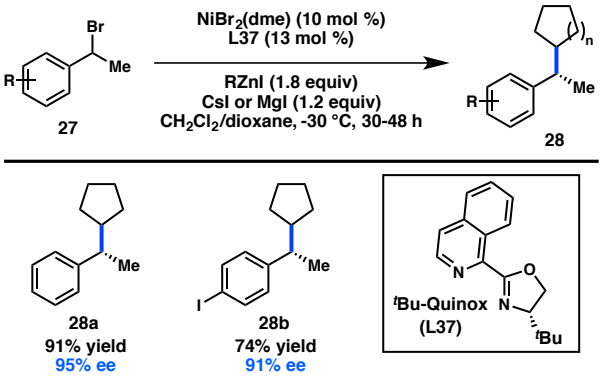
Figure 1.15. *Stereoconvergent Negishi cross-coupling of benzyl alcohol derivatives.*



A long-term objective in the area of enantioselective alkyl cross-coupling is to couple *sec*-alkyl electrophiles with *sec*-alkyl organometallic reagents. The Fu laboratory

made a significant advance toward this objective in 2012 when they reported the asymmetric Negishi cross-coupling between benzylic bromide **27** and cyclic organozinc halides (**Figure 1.16**).[36] Isoquinoline-oxazoline ligand **L37** delivered the products in high yields and ee's, in contrast to the more commonly employed PyBox and Box ligands. Acyclic secondary organozinc halides resulted in a mixture of branched and linear products; surprisingly, primary organozinc halides also resulted in a mixture of branched and linear products.

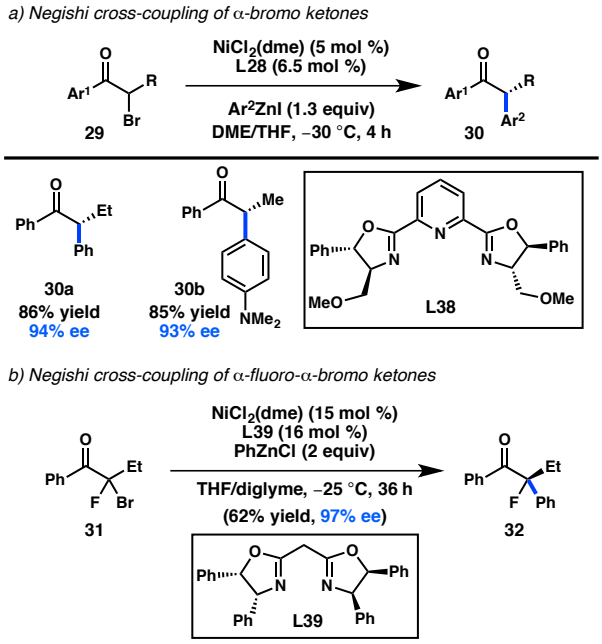
Figure 1.16. *Enantioconvergent Negishi cross-coupling of secondary organozinc reagents.*



Prior to their disclosure of the enantioselective cross-coupling between α-bromoketones and aryl Grignard reagents (see Figure 1.13), the Fu laboratory developed a Ni/**L38**-catalyzed asymmetric cross-coupling of α-bromoketones and arylzinc reagents (**Figure 1.17**, **a**).[38] The low basicity of the organozinc reagent, as well as a reduced reaction temperature, accounts for the configurational stability of the potentially sensitive tertiary stereocenter in **30**. The synthesis of dialkyl ketones proceeded with lower enantioinduction; however, this substrate limitation is addressed by their subsequently developed Kumada–Corriu conditions.[37] A recent modification of the reaction conditions

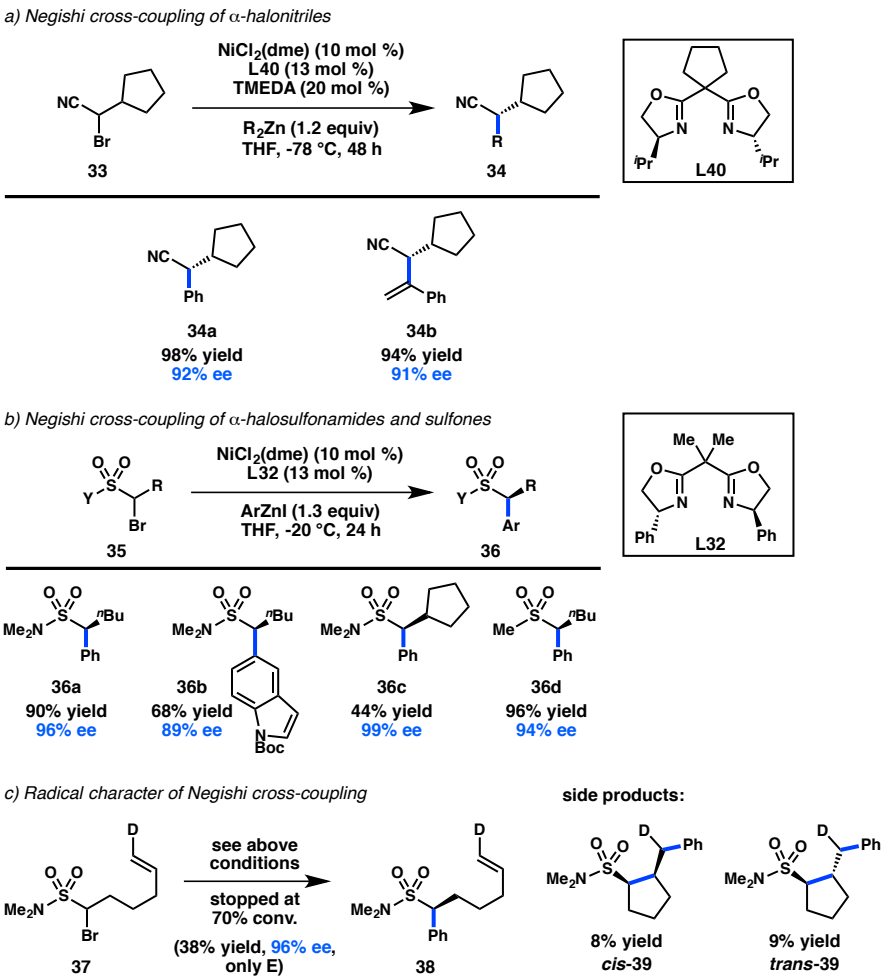
has permitted the use of α-halo-α-fluoroketones **31**, enabling the asymmetric formation of tertiary fluorides **32** (**Figure 1.17**, **b**).[48]

Figure 1.17. *Asymmetric Negishi cross-coupling of α-halo ketones.*



The Fu group has further expanded the scope of alkyl electrophiles amenable to Ni-catalyzed stereoconvergent Negishi cross-coupling to include α-bromonitriles.[49] Coupling of α-bromonitrile **33** and R_2Zn in the presence of $NiCl_2$(dme) and **L40** at –78 °C furnishes **34** in high yield and ee (**Figure 1.18**, **a**).[50] For the first time, alkenylzinc reagents were suitable coupling partners, delivering **34b** in 94% yield and 91% ee. Somewhat unexpectedly, a variant of **34** containing a pendant alkene failed to cyclize under the reaction conditions, in contrast to what was observed in the related coupling of simple unactivated halide electrophiles.[51] A more comprehensive mechanistic analysis is thus required to elucidate the mechanism of oxidative addition for the given transformation.

Figure 1.18. *Other directing groups in asymmetric Ni-catalyzed Negishi cross-coupling.*



The previous examples of Ni-catalyzed stereoconvergent Negishi cross-coupling reactions from the Fu laboratory have focused on the use of activated secondary electrophiles; in 2014, they reported the coupling between α-halosulfonamides (**35**) and arylzinc reagents (**Figure 1.18**, **b**).[52] Since sulfonyl groups do not significantly stabilize α-radicals, **35** can be considered as an unactivated electrophile. Investigations of the substrate scope revealed that sulfones are also suitable substrates without any change in the reaction conditions, furnishing **36d** in high yield and ee. Subjection of radical clock

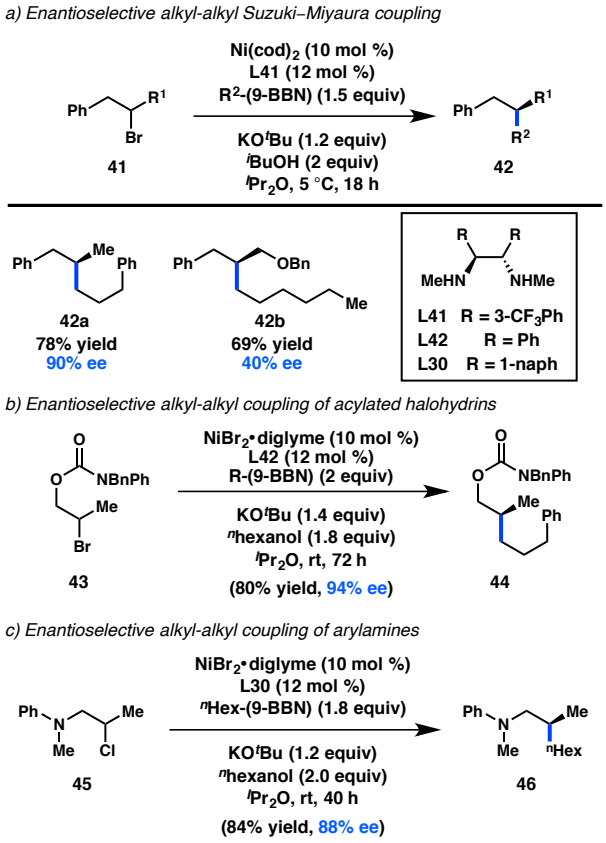
substrate **37** to the reaction conditions provided a mixture of **38**, cis-**39** and *trans*-**39**; the ratio of uncyclized product to cyclized product was found to increase linearly with increased Ni loading (**Figure 1.18**, **c**). These data could suggest that the reaction proceeds through a noncaged radical species, and also illustrates the dichotomy between the coupling of electrophiles **33** and **35**.

1.3.3 With Organoboron Reagents

Seminal contributions to the transition metal-catalyzed enantioselective cross-coupling of *sec*-alkyl electrophiles with organoboron reagents have been made by the Fu laboratory. Shortly after disclosing the Ni-catalyzed cross-coupling of *sec*-alkyl electrophiles with alkylboranes to prepare racemic products,[53] Fu and coworkers reported that use of catalytic $Ni(cod)_2$ in conjunction with chiral 1,2-diamine ligand **L41** enabled the enantioselective coupling of homobenzylic bromides (**41**) with organoboranes (Figure **1.19**, **a**).[54] The Ni catalyst was proposed to engage in a secondary interaction with the benzylic substituent on **41**, allowing for differentiation between the two alkyl groups of the starting material. While a variety of homobenzylic bromides were tolerated, poor enantioselectivity was attained in the formation of **42b**. Fu hypothesized that the ether might also interact with the Ni catalyst, leading to poor asymmetric induction. Based on this hypothesis, the group subsequently reported that carbamate-protected halohydrins (**43)** can also be coupled with alkylboranes in high enantioselectivity using a chiral 1,2-diamine **L42** (**Figure 1.19**, **b**).[55] Modified conditions permitted the enantioselective coupling of a homologated halohydrin. Further expansion of the substrate scope determined that halides (**45**) bearing proximal arylamines as directing groups can be

coupled with alkylboranes in high enantioselectivity as well (**Figure 1.19**, **c**).[56] The reaction was found to be directed by the nitrogen atom of the arylamine group.

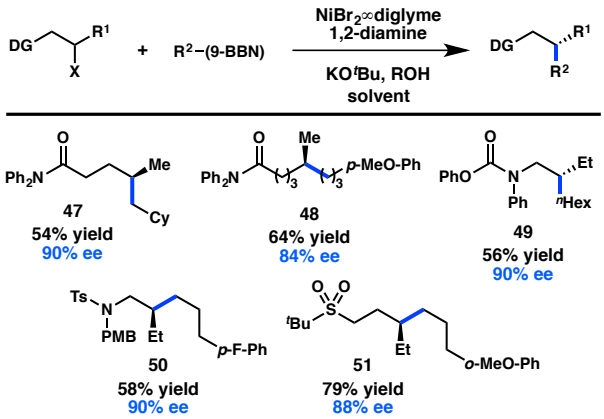
Figure 1.19. *Enantioconvergent Ni-catalyzed alkyl-alkyl Suzuki–Miyaura coupling.*



The early examples of enantioconvergent alkyl-alkyl Suzuki–Miyaura couplings all involved alkyl halide substrates with a directing group capable of coordinating the Ni center. Subsequent efforts turned to identifying new directing groups and to exploring how far removed the directing group could be from the reacting C–halide bond. Illustrating that distal functional groups are still capable of directing highly enantioselective reactions, both γ- and δ-chloroamides were shown to undergo Suzuki–Miyaura cross-coupling with good asymmetric induction to form **47** and **48**, respectively (**Figure 1.20**).[57] Various halides proximal to protected amines, such as carbamates or

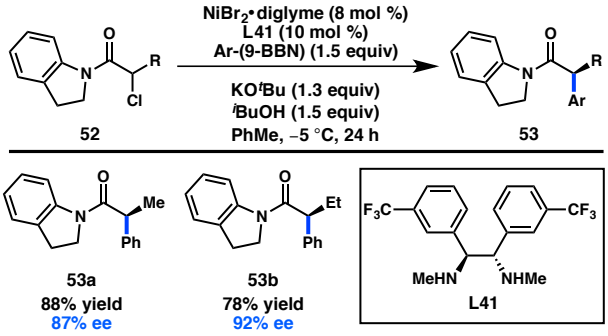
sulfonamides, were also optimized toward enantioconvergent cross-coupling.[58] After confirming that the oxygen of the sulfonamide was the key directing atom, Fu and coworkers examined sulfone-containing electrophiles and reported that good enantioselectivity can still be maintained for these substrates.[58a]

Figure 1.20. *Examples of directing groups for the enantioconvergent Suzuki–Miyaura coupling.*



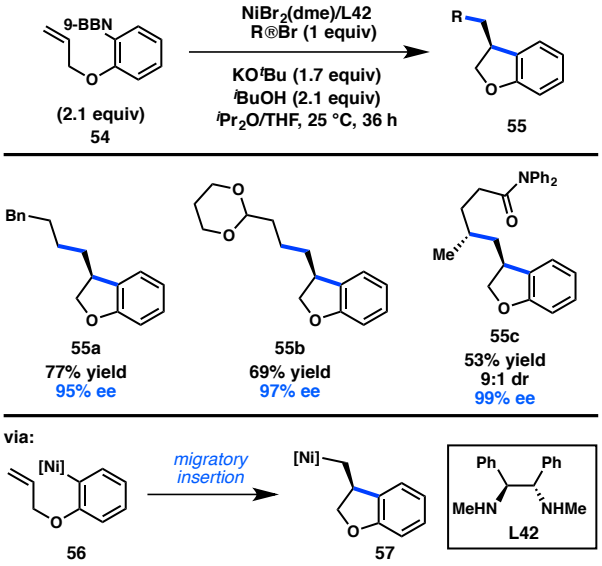
In addition to the Ni-catalyzed cross-coupling of organomagnesium and organozinc reagents to α-halocarbonyl compounds, the Fu laboratory has identified conditions for the enantioselective coupling between α-haloamides and arylboron reagents. After first investigating several different amides, it was found that the combination of $NiBr_2$•diglyme and **L41** catalyzed the coupling between α-chloroamides (**52**) and Ar-(9-BBN) reagents to furnish **53** in good yields and high ee's (**Figure 1.21**).[59] The identity of the amide substituents was important for good enantioinduction: diphenyl amides and Weinreb amides delivered nearly racemic products. In contrast to previous stereoconvergent couplings of secondary electrophiles, a modest kinetic resolution of **52** was observed. Further studies confirmed an irreversible oxidative addition step. γ-Haloamides can also be arylated with Ph-(9-BBN) in good ee but only moderate yield.[57]

Figure 1.21. *Asymmetric Suzuki–Miyaura coupling of α-haloamides.*



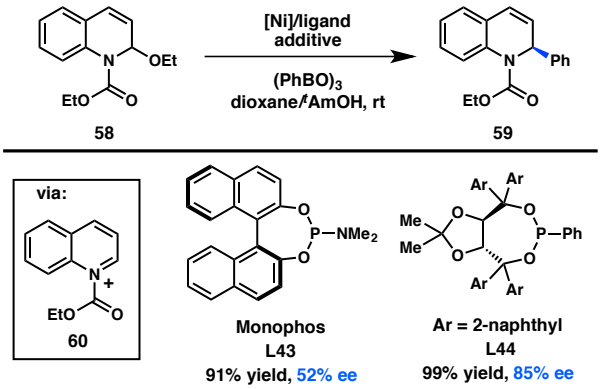
Building off their growing mechanistic understanding of Ni-catalyzed stereoconvergent alkyl cross-coupling reactions, Fu and coworkers have developed a cascade cyclization/cross-coupling to forge two C–C bonds in one step with both excellent ee and high dr (**Figure 1.22**).[60] Key to this transformation was the insight that a "transmetalation first" mechanism could be operative, and that organonickel complex **56** might undergo migratory insertion faster than oxidative addition of the alkyl halide electrophile. This theory was validated in the Ni-catalyzed asymmetric cascade cyclization/cross-coupling reaction between arylborane **54** and several simple alkyl bromides, in which heterocyclic products **55** were obtained in excellent ee. Realizing the compatibility of their reaction conditions with those previously optimized for coupling of γ-haloamides (see **Figure 1.20**), a γ-haloamide was also used as an electrophile.[57] Remarkably, a single Ni complex controls the stereochemical outcome of two distinct C–C bond forming processes, giving product **55c** in good yield, good dr, and excellent ee.

Figure 1.22. *Asymmetric cascade cyclization/cross-coupling.*



The Doyle laboratory has focused on expanding the scope of electrophiles suitable for transition metal catalysis, investigating the cross-coupling reactions of acetals and *N*,*O*-acetals. These efforts led to the discovery that $Ni(cod)_2$ catalyzes the addition of various aryl boroxines to *N*,*O*-acetal **58**, presumably via the intermediacy of quinolinium ion **60**.[61] When chiral phosphoramidite **L43** is used as a supporting ligand, **59** is formed in 52% ee (**Figure 1.23**). A unique oxidative addition mechanism, in which the Lewis acidic boroxine promotes ionization of the leaving group and results in an S_N1-type addition of Ni^0, was discovered for this coupling.[62] A wider survey of ligands showed that improved ee could be realized with TADDOL-based phosphonite **L44**.[63] In an extension, the addition of arylzinc reagents into pyridinium ions was subsequently reported.[64]

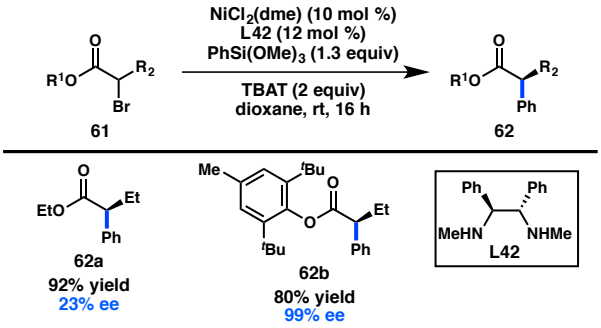
Figure 1.23. *Asymmetric addition into quinolinium ions.*



1.3.4 With Organosilicon Reagents

Only a single example of an asymmetric cross-coupling between *sec*-alkyl organic halides and organosilicon reagents has been reported to date. Fu and colleagues developed a Ni/**L42**-catalyzed stereoconvergent coupling of α-bromoesters (**61**) and aryl siloxanes to furnish α-aryl esters in good yields and with high enantioduction (**Figure 1.24**).[65] While simple ethyl esters gave good yield but poor ee, the use of the BHT ester resulted in formation of **62b** in a remarkable 99% ee. The nature of the fluoride source and the steric profile of R^2 also affected the level of enantioinduction. In the same report, the optimized reaction conditions were also extended to the coupling of alkenyl silanes.

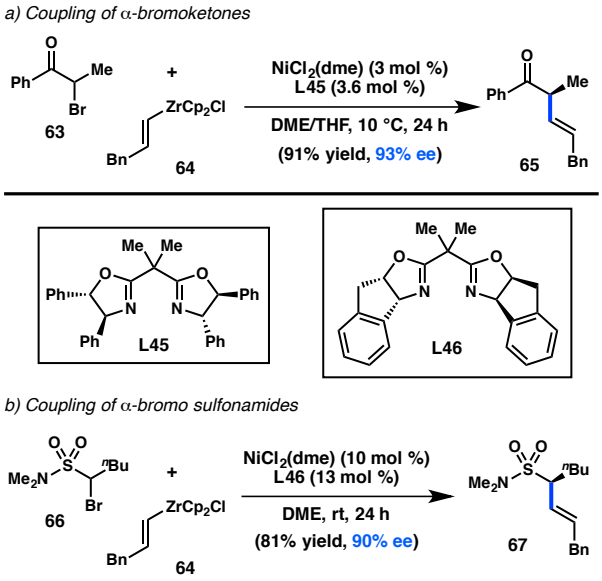
Figure 1.24. *Stereoconvergent coupling of aryl silanes.*



1.3.5 With Organozirconium Reagents

Alkenylzirconium complexes are attractive vinyl organometallic species for use in organic synthesis because they can be easily prepared from Schwartz's reagent and an alkyne. While Fu has disclosed a remarkable variety of stereoconvergent arylation reactions, most of the reaction conditions could not easily be extended to the cross-coupling of alkenyl metal species, with alkenyl silicon[65] and zinc[50] reagents being the most promising. In 2010, Fu and coworkers published the Ni/**L45**-catalyzed asymmetric cross-coupling of alkenylzirconium reagents and α-bromoketones, allowing access to **65** in 93% ee (**Figure 1.25**, **a**).[66] The versatility of this approach has been exemplified by the efficient coupling of both aryl-alkyl ketones and dialkyl ketones under the same conditions. Alkenylzirconium complexes have also been shown to react with α-bromosulfonamides **66** in high yield and ee (**Figure 1.25**, **b**).[52]

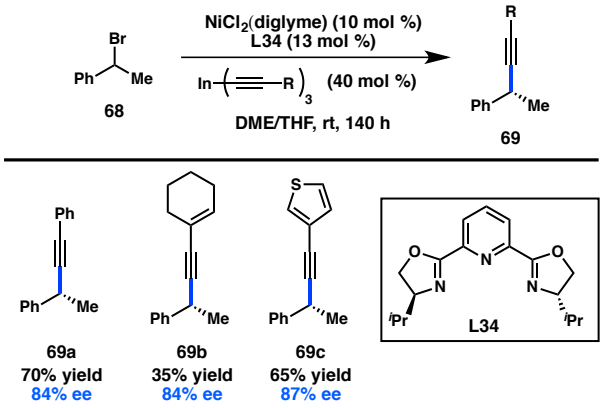
Figure 1.25. *Stereoconvergent coupling of alkenylzirconium reagents.*



1.3.6 With Organoindium Reagents

Shortly after the publication of Fu's seminal examples of Ni-catalyzed stereoconvergent cross-coupling reactions between *sec*-alkyl electrophiles and either C(sp^3)- or C(sp^2)-hybridized organometallic reagents,[39-40] Sestelo, Sarandeses, and coworkers investigated the asymmetric coupling between C(sp)-hybridized organometallic reagents and benzylic bromides. Alkynylindium reagents exhibited clean cross-coupling under Ni-catalysis, and were selected for further study. Pybox ligand **L34** was optimal, delivering cross-coupled product **69** in up to 87% ee for several different alkynes (**Figure 1.26**).[67] Further work on the asymmetric coupling of C(sp) organometallic reagents has not been disclosed.

Figure 1.26. *Alkynyl organometallic reagents in stereoconvergent cross-coupling.*

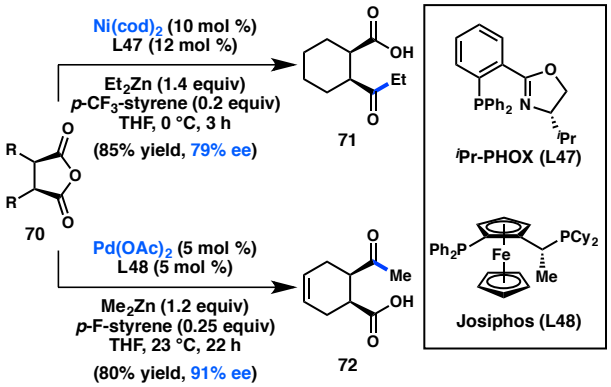


1.4 NICKEL-CATALYZED DESYMMETRIZATION REACTIONS

One approach to generating enantioenriched products through transition metal-catalyzed alkyl cross-coupling reactions is to perform desymmetrization reactions of *meso* compounds. In this case, the C(sp^3)-hybridized carbon at the site of C–C bond formation is not necessarily stereogenic; instead, the C–C bond formation is used to break

symmetry through a catalyst-controlled process, giving rise to a molecule with centrochirality. Most of the work in this area has focused on the desymmetrization of *meso* electrophiles; however, some researchers have investigated the desymmetrization of *meso* bis-organometalic reagents or processes that involve desymmetrization by C-H functionalization.

Scheme 1.3. *Alkylative desymmetrization of meso-anhydrides.*

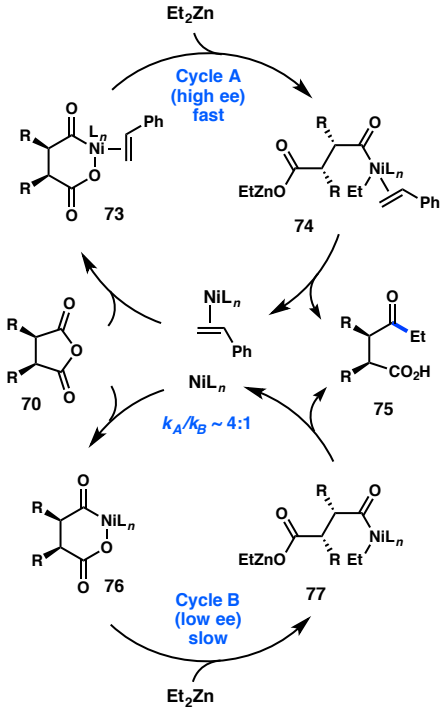


1.4.1 Organozinc Reagents

The desymmetrization of *meso*-anhydrides has emerged as a robust method for the synthesis of enantiopure products.[68] Rovis and coworkers[69] have developed a monofunctionalization of cyclic anhydrides through a Ni-catalyzed Negishi coupling with Et_2Zn.[70] The transformation was sensitive to the bite angle of the ligand and required an electron-deficient styrene additive, which has been demonstrated by Knochel to accelerate reductive elimination over β-hydride elimination.[71] Based on these initial findings, the authors sought to develop a desymmetrizing Negishi reaction of *meso*-cyclic anhydride **70**, and determined that the catalyst prepared from $Ni(cod)_2$ and ^{i}Pr-PHOX (**L47**) furnished **71** in 79% ee (**Scheme 1.3**).[72] Surprisingly, omission of the *p*-CF_3-

styrene additive reduced the ee to 4%, prompting Rovis and coworkers to more closely examine the mechanism of the reaction.

Figure 1.27. *Competing mechanisms in the Ni-catalyzed desymmetrization of meso-anhydrides.*



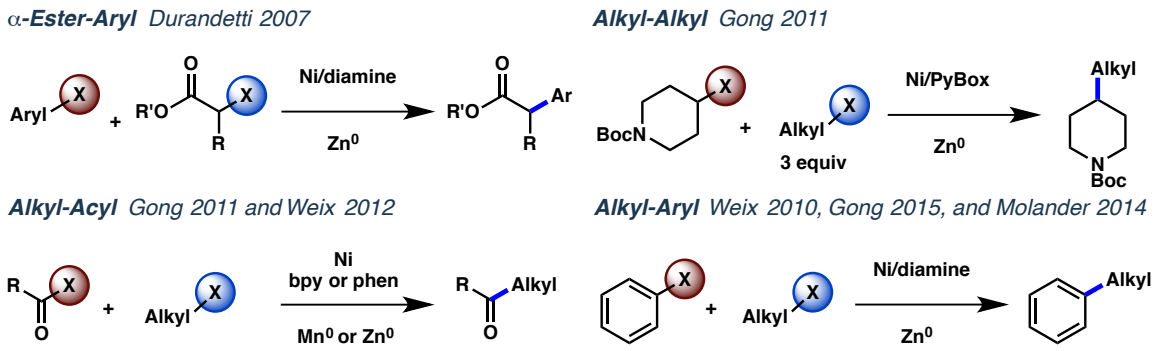
Kinetic analysis of the reaction revealed two competing mechanisms for the formation of **75** (**Figure 1.27**).[73] One occurred in the absence of styrene and proceeded with low enantioselectivity (cycle B). The other involved coordination of styrene and provided **75** in high ee (cycle A). For both reactions, the rate-determining step was realized to be oxidative addition. However, in contrast to the initial proposal that *p*-CF_3-styrene would accelerate reductive elimination, it was instead shown to increase the rate of oxidative addition. While the origin of this rate enhancement is unclear, it was hypothesized that *p*-CF_3-styrene might coordinate to Ni and facilitate deligation of cod, providing a three-coordinate Ni complex capable of undergoing oxidative addition. The

kinetic analysis determined that cycle A proceeds approximately four times faster than cycle B and is roughly consistent with the somewhat modest enantioselectivities obtained under these conditions.

1.5 CROSS-ELECTROPHILE COUPLING

The methodologies discussed above are limited to enantioselective cross-couplings of electrophiles (halides and pseudohalides) with organometallic reagents. Indeed, until very recently, all examples of Ni-catalyzed asymmetric cross-coupling fell into this category of redox-neutral transformations. However, our group realized that mechanisms at play in the stereoconvergent redox-neutral couplings described in the previous sections could also be leveraged toward the development of asymmetric reductive cross-couplings between two electrophilic partners. Indeed, recent work by our laboratory has led to the development of cross-electrophile coupling reactions that afford the products in excellent enantioselectivity. These efforts will be the focus of subsequent chapters of this thesis. However a brief introduction to the precedents and mechanistic hypotheses underlying these campaigns will be provided here.

Scheme 1.4. *Selected examples of Ni-catalyzed reductive cross-couplings.*

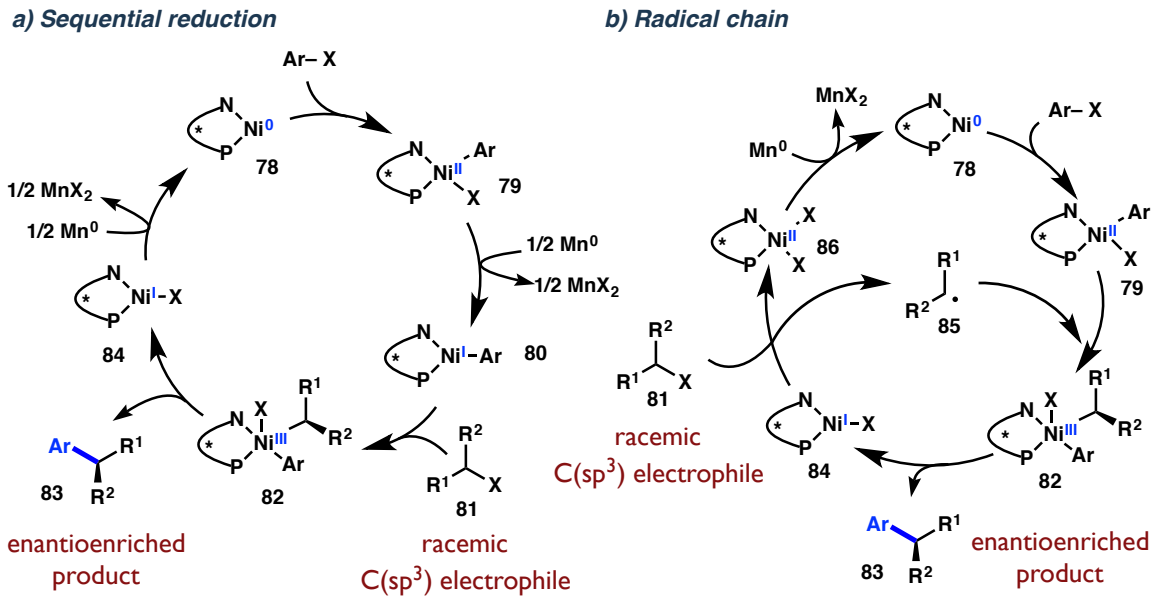


While the first disclosure of Ni-mediated reductive homocoupling of halide electrophiles was by Semmelhack and coworkers in 1971, renewed interest has seen the development of many reductive catalytic cross-couplings over the last ten years.[74] Reductive cross-coupling to form C–C bonds under Ni catalysis and employing chemical reductants debuted in 2007, with a seminal report by Durandetti and coworkers.[75] Employing aryl halides and α-haloesters, the cross-coupling is effected by a catalytic Ni^{II} source and stoichiometric Zn metal. This archetypal transformation has been expounded upon by the Weix, Gong, and Molander labs, with new couplings employing many $C(sp^2)$ (aryl, vinyl, acyl) and $C(sp^3)$ (activated and unactivated alkyl) partners (**Scheme 1.4**).[76] These reactions benefit from their exceedingly mild conditions and from the lack of organometallic functionality. As a result, excellent functional group tolerance is routinely observed in these reports, which would be incompatible with conventional organometallic preparations. It is also worth noting that many organometallic reagents are generated from the corresponding halides, in which case reductive cross-coupling offers a shorter, streamlined disconnection.

However a key challenge in the development of reductive cross-couplings, especially in contrast to conventional redox-neutral couplings, is the need to achieve cross-selectivity.[77] Employing two electrophilic partners, some means of differentiation between the partners must be identified in order to avoid a statistical mixture of homo- and cross-coupled products. While a simple solution to this challenge is to manipulate the stoichiometry of the reagents, this does not circumvent the formation of dimers and requires an undesirable excess of one coupling partner.[76c] A preferable means of distinguishing the electrophilic partners relies instead on their hybridization. If differently

hybridized halides can selectively react with different oxidation states of Ni, then a sequencing of oxidative addition events can be envisioned that affords cross-selectivity.

Scheme 1.5. *Two hypothetical mechanisms for asymmetric reductive cross-couplings (shown with aryl halide as the C(sp²) electrophile for clarity).*

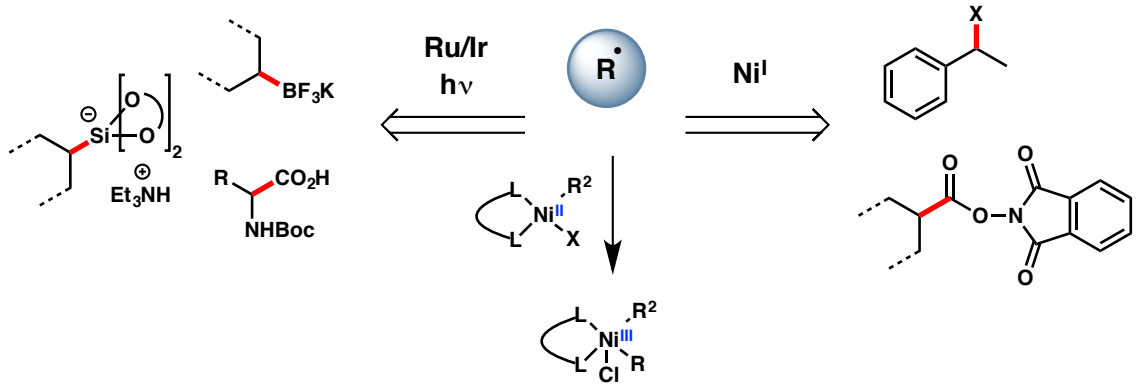


Computational studies and experimental mechanistic investigations by the Weix, Gong, and Reisman groups have led to coalescence about two related mechanistic hypotheses for these transformations (**Scheme 1.5**).[76a,78] A sequential reduction mechanism can be proposed in which a C(sp^2) halide undergoes concerted oxidative addition to a Ni^0 center (**78**) (or a primary alkyl halide capable of undergoing an S_N2-type oxidative addition). Reduction to Ni^I **80** then facilitates halide abstraction from the C(sp^3) electrophile (**81**) to generate a solvent-caged alkyl radical. Recombination of this prochiral radical with the Ni^{II} center generates a Ni^{III} complex (**82**). Reductive elimination then affords the cross-coupled product (**83**) and subsequent reduction of the resulting Ni^I halide **84** regenerates Ni^0 **80** to reenter the catalytic cycle. If the radical generated by halide abstraction is sufficiently long-lived to escape the solvent cage (**85**),

then a radical chain mechanism can be initiated, as shown in **Scheme 1.5**.[79] These are essentially two ends of a mechanistic spectrum and we can also imagine them working simultaneously for some radicals of intermediate half-life.

While this mechanistic paradigm provides an entry to cross-selectivity, efforts to advance reductive cross-coupling into the realm of asymmetric catalysis require an additional level of control. Such reactions must retain cross-selectivity, while also achieving stereocontrol via an enantioconvergent transformation of the C(sp^3) electrophile. In considering this problem, we looked to the stereoconvergent couplings of secondary alkyl electrophiles developed by Fu and coworkers, as well as the fundamental inorganic chemistry underlying their work. Critically, Vicic and coworkers have shown that an isolable Ni^I complex will abstract a halide to generate an alkyl radical.[80] Subsequent mechanistic work by Fu and coworkers has demonstrated the feasibility of this step in catalysis, and recent work by Baran has seen single-electron reduction by Ni(I) employed in decarboxylative couplings as well.[44,81] Most importantly for asymmetric catalysis, the radicals generated by this process have been exploited as an entry to stereoconvergence of the racemic halide precursors.

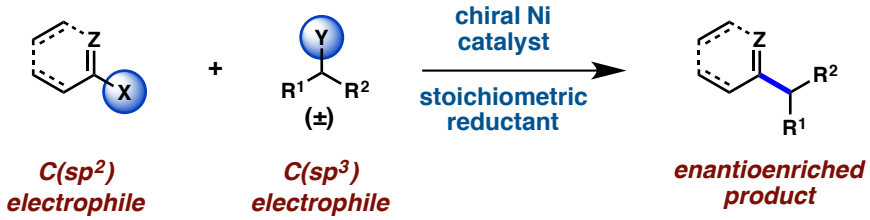
Figure 1.28. *Radical chemistry of Ni in recent cross-couplings.*



In either of the pathways described above, it is the single electron processes involved that we hypothesize enable asymmetric Ni-catalyzed reductive cross-couplings. Radical intermediates are planar, prochiral species and have been generated via halide abstraction (as above),[76a] decarboxylation,[81-82] or fragmentation of suitable nucleophiles[83] (**Figure 1.28**). In all of these cases, an appropriate chiral ligand has been shown to successfully direct its combination with a Ni center to afford a thermodynamically preferred diastereomer of the resulting complex that can reductively eliminate the enantioenriched product. In this process, the enantiodetermining step may be radical combination with the Ni^{II} center followed by fast reductive elimination. However, if radical combination is reversible, then reductive elimination may be enantiodetermining via a Curtin-Hammett-type mechanism.[84] This stereoconvergent process has been exploited in redox-neutral conventional couplings as described above (Fu), photoredox-enabled couplings (Molander, Kozlowski, MacMillan/Fu),[84-85] and, as detailed in the following chapters, reductive cross-electrophile couplings (Reisman).[86]

1.6 CONCLUDING REMARKS

Figure 1.29. *General disconnection for asymmetric reductive cross-couplings.*



The history of asymmetric cross-coupling is rich in examples of stereoselective reactivity being uniquely promoted by Ni and other base metals. Besides being earth-abundant and inexpensive, Ni has the advantage of accessible odd-electron oxidation

states. This enables Ni to perform radical chemistry not easily replicated by Pd or its noble metal cousins, promoting stereoconvergent reactions of $C(sp^3)$ electrophiles. More recently, a surge of Ni-catalyzed cross-electrophile couplings has been disclosed. These reactions obviate the need for organometallic reagents and occur under uncommonly mild conditions. However the synthesis of these fields remained unknown until the work described herein. We are delighted here to report the successful development of a series of Ni-catalyzed asymmetric reductive cross-couplings (**Figure 1.29**).

1.7 NOTES AND REFERENCES

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