Chapter 1

Enantioselective Transition Metal-Catalyzed Cross-Coupling Reactions of Organometallic Reagents to Prepare C–C Bonds[†]

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. The advent of transition metal catalysis has provided chemists with a broad range of new tools to forge C–C bonds and has resulted in a paradigm shift in synthetic strategy planning. The impact of these methodologies has been recognized with the awarding of the 2010 Nobel Prize in Chemistry to Richard Heck, Ei-ichi Negishi, and Akira Suzuki for their seminal contributions to the development of Pd-catalyzed cross-coupling.

[†] Portions of this chapter will be reproduced as a review written in collaboration with Prof. Sarah E. Reisman and Nathaniel T. Kadunce

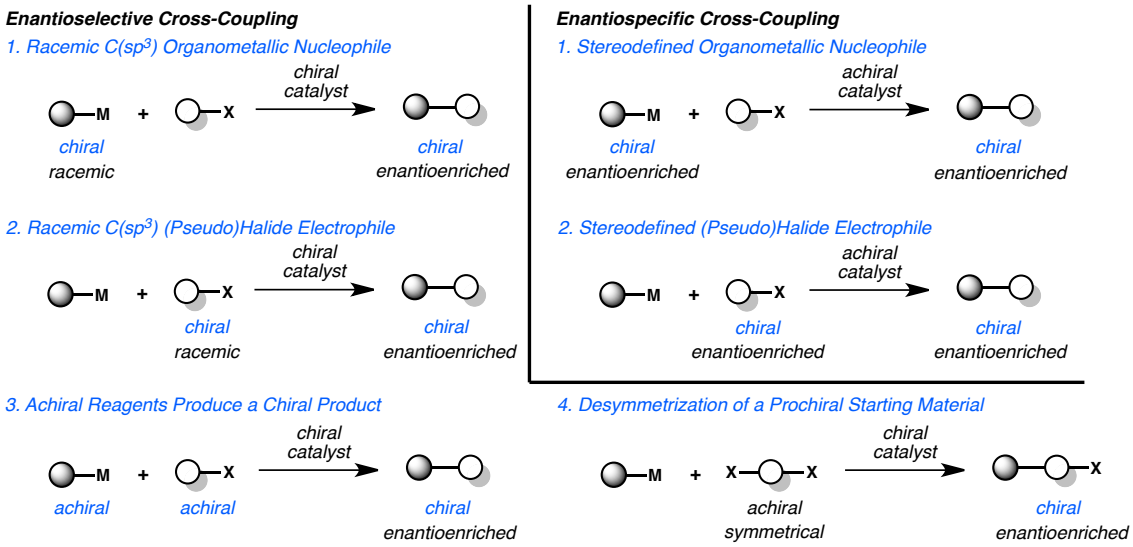
The potential of using transition metal-catalyzed C–C bond formation to prepare enantioenriched molecules was immediately recognized by the synthetic chemistry community. Indeed, the first forays into enantioselective cross-coupling reactions occurred contemporaneously with the development of the transition metal-catalyzed reactions themselves. Here we define *transition metal-catalyzed cross-coupling reactions* as C–C bond forming reactions between an organic electrophile (typically an organic halide or pseudo halide, which in this review includes alcohols, amines, and their derivatives) and an organometallic reagent, mediated by a transition metal catalyst.

Enantio-controlled transition metal-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> transition metal-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 metal 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.

The second group comprises <u>*enantiospecific*</u> transition metal-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. These types of enantioselective and enantiospecific reactions have been used to prepare molecules exhibiting centro, axial, and planar chirality. This review will encompass enantioselective transition metal-catalyzed cross-coupling reactions of organic electrophiles and organometallic reagents, covering the literature published through the end of the year 2014.

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

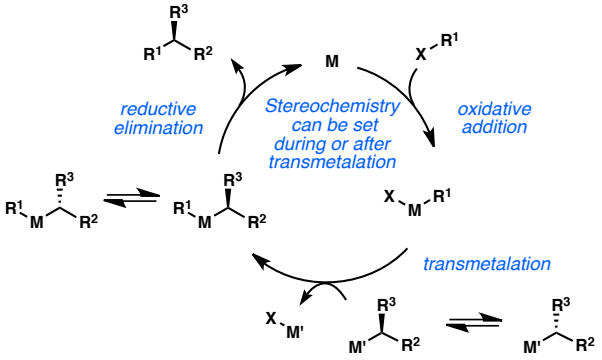
undergo transmetalation.[1] Similarly, *sec*-alkyl electrophiles are frequently slow to undergo oxidative addition to Pd.[2] Moreover, in either case, the resulting *sec*-alkyl transition metal complexes can suffer from rapid, non-productive β-hydride elimination. Thus, the successful realization of enantioselective transition metal-catalyzed alkyl cross-coupling reactions has resulted from fundamental studies of the factors, particularly ligands, which control and influence the efficiency of these transformations. In addition, 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.[3] 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.[4] 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.*



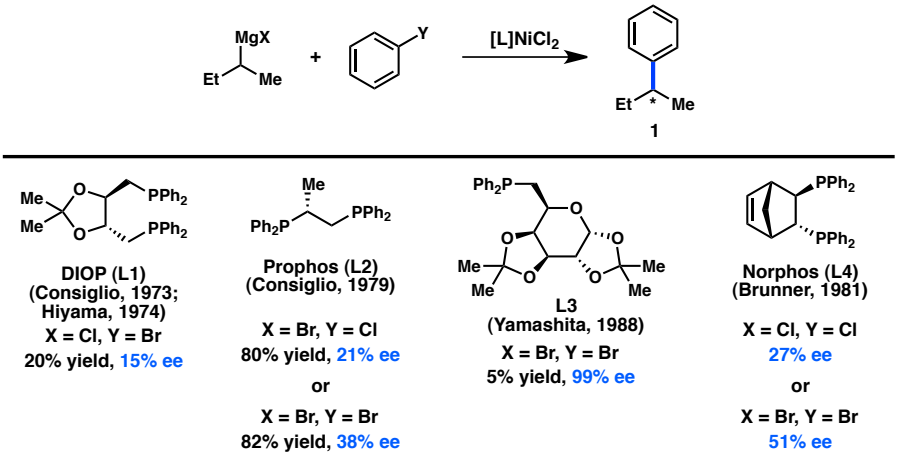
Enantioselective reactions of configurationally stable *sec*-alkyl organometallic reagents can arise from catalyst-controlled kinetic resolution processes, wherein the relative rates of transmetalation for the two enantiomers of the chiral organometallic reagent are substantially different. In this case, 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;[5] shortly thereafter the first studies aimed at utilizing chiral transition metal complexes to catalyze these reactions enantioselectively were reported.[6] 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).[7] 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**.[8] 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.[9] A carbohydrate-derived chiral ligand (**L3**) was also reported to deliver **1** in good ee, although with poor yields.[10]

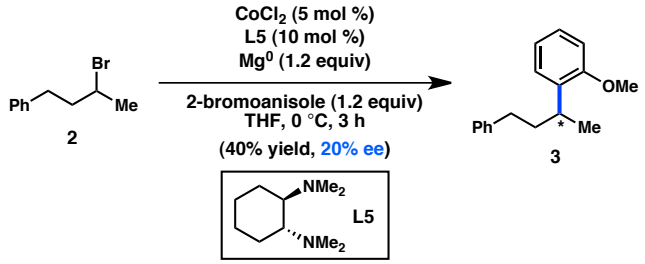
Figure 1.3. *Stereoconvergent arylation of ^{s}Bu Grignard reagents.*



In 2009, Jacobi von Wangelin and coworkers reported the in situ generation of a secondary Grignard reagent that can subsequently undergo a Co-catalyzed asymmetric cross-coupling with promising enantioinduction (Scheme 1.1).[11] Additional ligand

development and expansion of the substrate scope are imperative, but this initial result represents a solid advance for in situ Grignard formation in stereoconvergent cross-couplings.

Scheme 1.1. *Stereoselective coupling of a Grignard reagent prepared in situ.*



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.[7b,12] Following up on Kumada's studies, Brunner and coworkers reported that Norphos (**L4**) furnished **4** in 95% yield and 67% ee.[13]

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

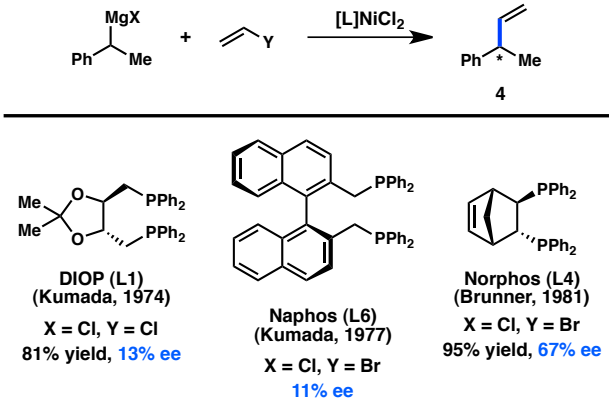
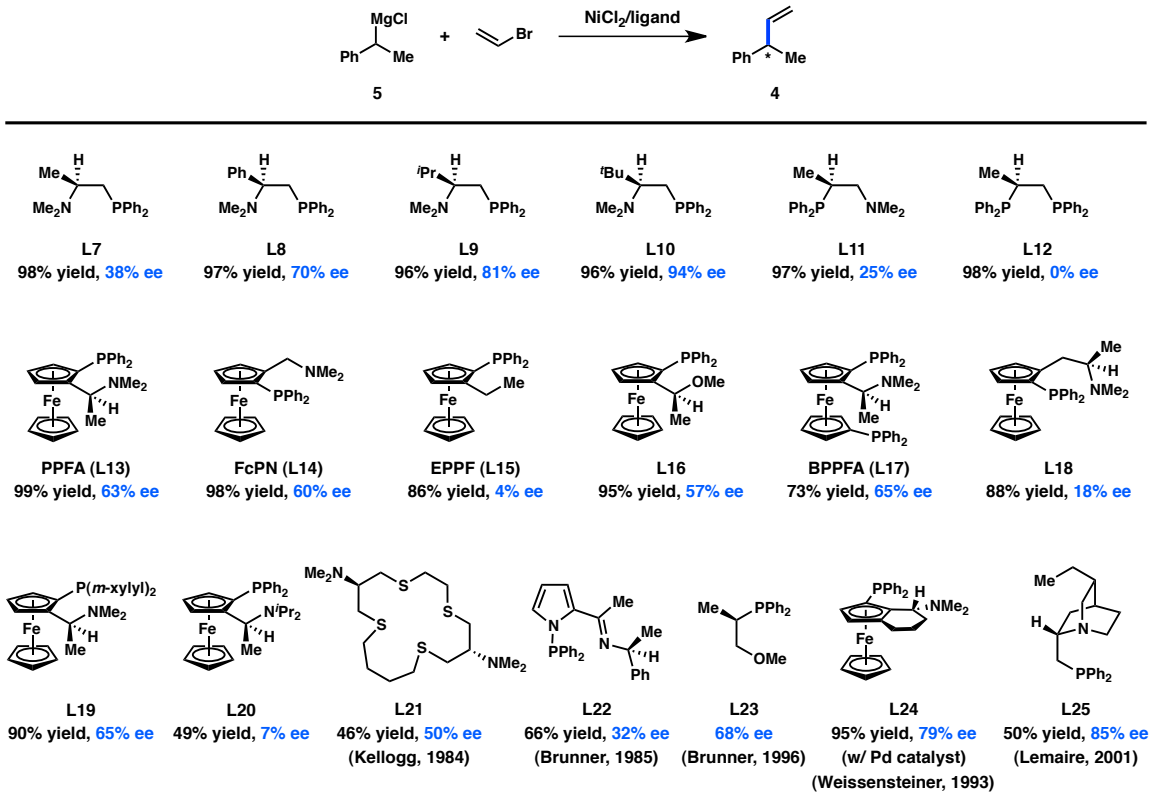


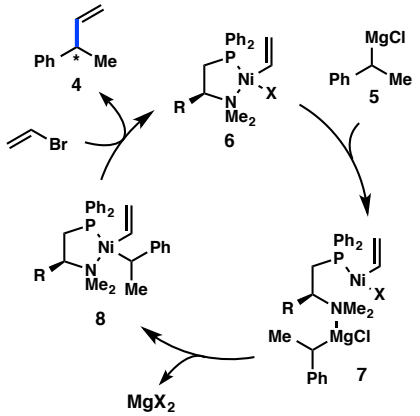
Figure 1.5. *Chiral ligands developed for the enantioselective cross-coupling of α-methylbenzyl Grignard reagents.*



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 (**5**) 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 **5** and vinyl bromide (Figure 1.5).[14] 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 (**L7**) to 94% when this group was ^{t}Bu (**L10**). In order to probe the origin of asymmetric induction, the isomeric P,N-ligand **L11** was designed. Under the same reaction conditions, **L11** delivered **4** in only 25% ee. Moreover, the analogous bis-phosphine **L12** 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 **5** and the amino group of the ligand to give complex **7**. 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.[15]

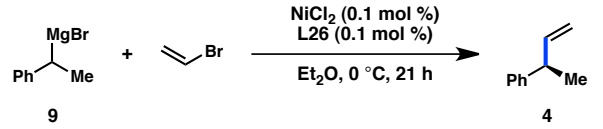
Figure 1.6. *Proposed catalytic cycle for the enantioselective coupling of α-methylbenzyl Grignard reagents.*



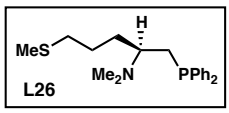
Elaborating on this concept, Kellogg and coworkers investigated the use of (β-aminoalkyl)phosphine ligands bearing pendant heteroatoms, such as those derived from lysine or methionine.[16] The authors reported a reversal of the stereochemical outcome in the presence of exogenous zinc halide salts (Figure 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* ***L26*** *is used.*



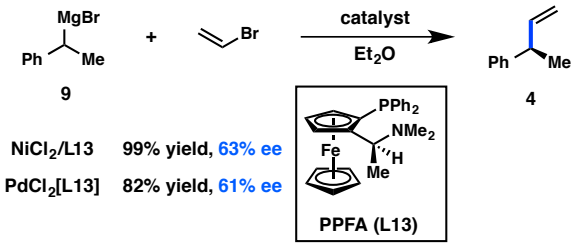
Lewis acid	yield (%)	ee (%)
none	95	61
$ZnBr_2$	71	–67
ZnI_2	16	–52



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 **5** and vinyl bromide (Figure 1.5). These bidentate P,N ligands possess both centrochirality at carbon as well as planar chirality. The ligand PPFA (**L13**), furnished **4** in an excellent 99% yield and 63% ee.[17] The ee of the product was determined to remain roughly constant over the course of the reaction.[18] A structure-activity relationship study revealed that FcPN (**L14**), while lacking centrochirality but maintaining planar chirality, gave **4** in 60% ee, demonstrating the dominant role of planar chirality in this system. EPPF (**L15**), which possesses neither centrochirality nor the dimethylamino group, delivered **4** 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 **L16**, which possesses a methoxy moiety instead of a dimethylamino group and provides **4** in 57% ee. Diphosphine BPPFA (**L17**), which could potentially coordinate through phosphorus in a bidentate fashion, also provides **4** in 65% ee. The similarity of the ee data obtained with **L13** and **L17** 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 **L13** gives a range of ee values for **4** (see **L20**), while changing the steric environment of the phosphine does not significantly perturb the selectivity (see **L19**). Homologated ligand **L18** delivers **4** in poor ee.[19] Pd catalysts were also investigated and were shown to give comparable results to Ni (Figure 1.8).[17c]

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

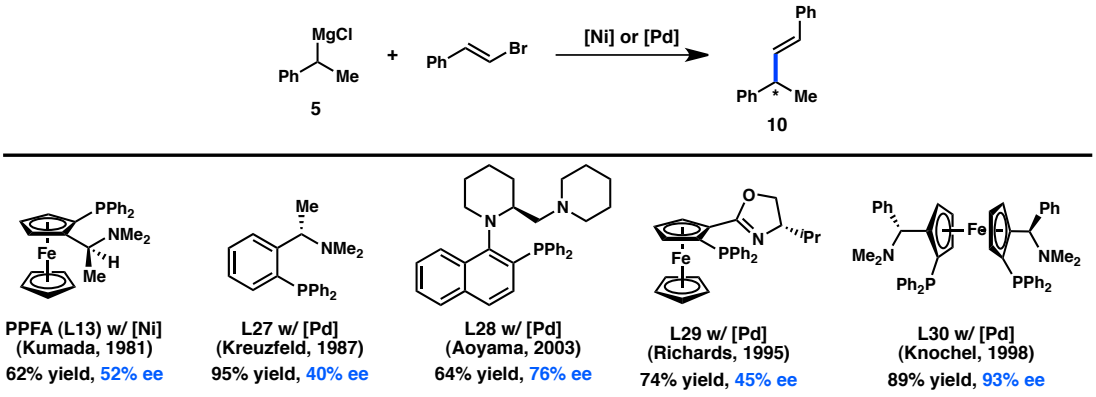


Several other ligand families have been developed for the enantioselective preparation of **4** (Figure 1.5). Catalysts generated from macrocyclic sulfides (**L21**) and nickel salts have been shown to impart moderate enantioselectivity, possibly through a simple kinetic resolution.[20] The use of pyrrole-containing P,N ligand **L22** or phosphine **L23** delivers **4** in 32% ee and 68% ee, respectively, under Ni catalysis.[21,22] Using Pd catalysis, the P,N ligand **L24**, which contains both planar and centrochirality, gives

improved results with respect to PPFA (**L13**).[23] High ee can also be achieved with phosphine-quincoridine **L25**.[24]

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 (**L13**) as the ligand delivered **10** in only 52% ee and moderate yield (Figure 1.9).[17c,25] While the yield could be improved using the simpler aminophosphine **L27**, the ee of **10** decreased.[26] **L28**, designed to induce axial chirality upon coordination to a transition metal, was able to induce 76% ee for **10**.[27] Moderate ee could also be attained with phosphine-oxazoline ligand **L29**.[28] Knochel and coworkers reported C_2-symmetric ferrocenyl phosphine **L30** as being capable of delivering excellent ee for the coupling of bromostyrene, although the reaction scope is still limited.[29]

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



The asymmetric cross-coupling of organomagnesium reagents has been extended to α-trialkylsilyl Grignard reagents (**11** and **13**). When vinyl halides are used as the coupling partners, the products are allylsilanes, which are versatile reagents for the construction of C–C bonds. In initial studies, Kumada, Hayashi, and coworkers reported

that Ni catalysts delivered poor yields of the desired allylsilane. However, the chiral $PdCl_2$[PPFA] complex furnished **12** in 93% yield and 95% ee (Scheme 1.2, a).[30] *E*-Vinyl bromides were found to provide higher selectivities than the corresponding *Z*-substrates, and the enantioselectivity was independent of the ratio of Grignard reagent to vinyl bromide. In contrast, the coupling of alkyl-substituted Grignard **13** proceeded in 93% ee when excess organomagnesium reagent was employed, but the ee fell precipitously when Grignard **13** was used as the limiting reagent (Scheme 1.2, b). These findings might suggest that for Grignard **13**, the rate of racemization is slow relative to the rate of C–C bond formation, resulting in a simple kinetic resolution instead of a DKR. A similar kinetic resolution had been observed previously in the diastereoselective coupling of non-benzylic Grignard reagents.[31] Lastly, an ee of 18% could be achieved in the alkynylation of **11** in the presence of $PdCl_2$[PPFA] (Scheme 1.2, c).[30b,32]

Scheme 1.2. *Diphosphine ligands in the coupling of α-silyl Grignard reagents.*

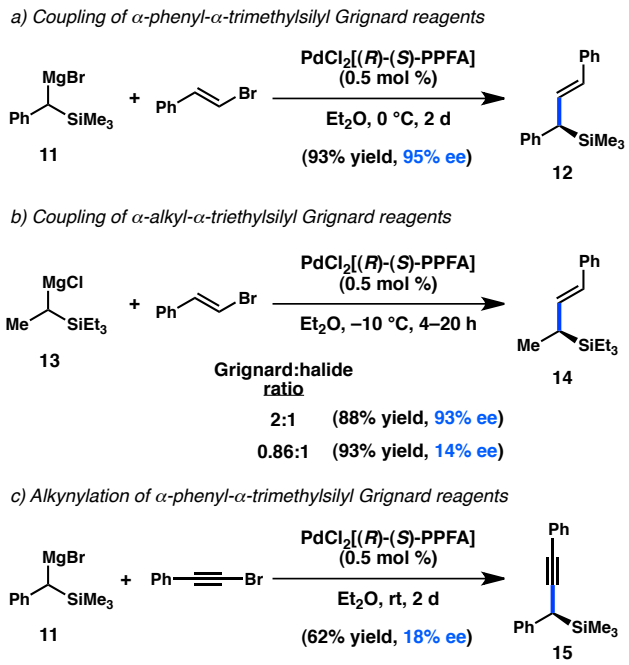
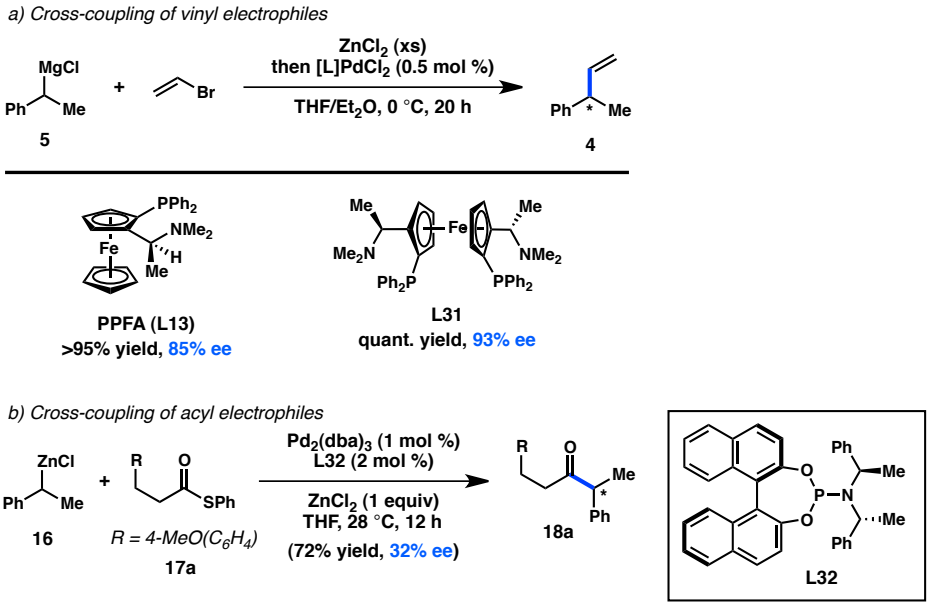


Figure 1.10. *Enantioselective alkyl Negishi-type cross-couplings.*

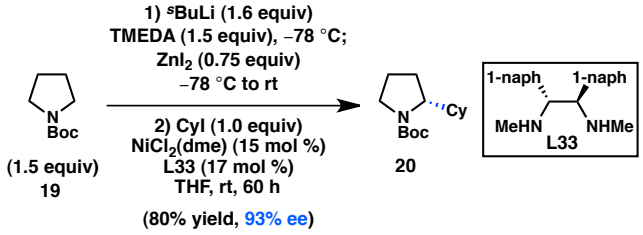


1.2.2 Organozinc Reagents

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.[33] Preliminary studies investigated the coupling of the organozinc chloride prepared from transmetalation of **5** with $ZnCl_2$; however, Ni catalysts were determined to be poorly reactive. On the other hand, the combination of Pd and PPFA (**L13**) delivered **4** in 85% ee (Figure 1.10, a). Significantly, when the organometallic was prepared by direct insertion of Zn^0 into the organic chloride, the same enantioselectivity is achieved, albeit with a lower yield. Such an

outcome implicates RZnCl as the transmetalating agent, rather than $ZnCl_2$ behaving as a Lewis acid to otherwise effect the transformation.[16a] Lower selectivities are obtained with the corresponding Grignard reagent under similar conditions. Additional improvements in ligand design revealed that **4** is formed in 93% ee when **L31** is used.[34] Despite a growing interest in the enantioselective 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. Recently, Reisman and coworkers reported the Pd-catalyzed coupling between thioester **17a** and organozinc **16** to form ketone **18a** using chiral phosphoramidite **L32** (Figure 1.10, b).[35] While the enantioselectivity of the transformation is still low, the study represents a proof of concept for the possibility of employing organozinc reagents in enantioselective acyl cross-coupling reactions.

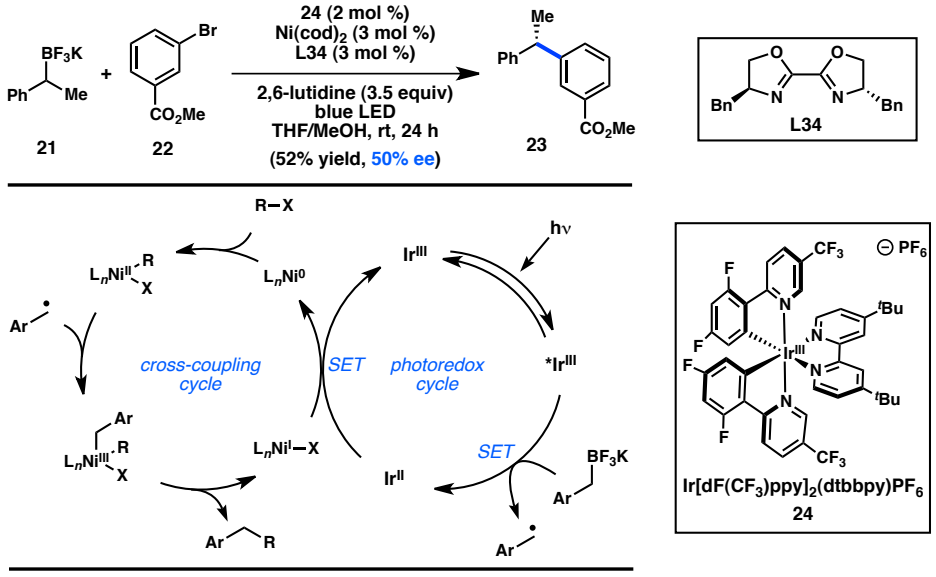
Scheme 1.3. *Enantioselective functionalization of pyrrolidine.*



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.[36] 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/**L33** complex was used as the catalyst, coupling of racemic **19** with cyclohexyl iodide furnished **20** with high ee

in a stereoconvergent fashion, representing the first enantioconvergent alkyl-alkyl coupling of a racemic organometallic reagent (Scheme 1.3).[37] 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 1.11. *Dual catalysis approach to asymmetric cross-coupling.*

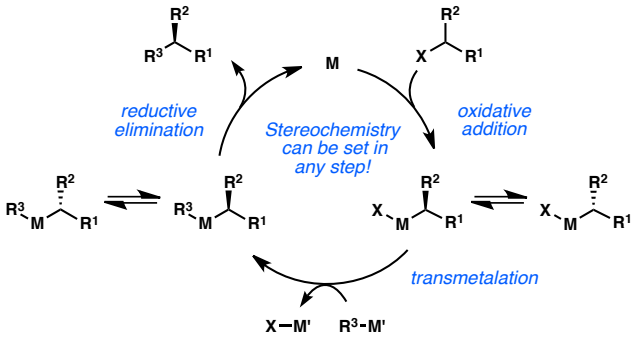


1.2.3 Organoboron Reagents

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, the authors

envisaged a dual catalysis mechanism in which Ni-catalyzed cross-coupling and Ir-catalyzed photoredox events occur synergistically (Figure 1.11).[38] In an important proof of concept, chiral bioxazoline (BiOX) **L34** was used to furnish **23** 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 1.12. *Stereochemical outcome of cross-coupling with secondary electrophiles.*

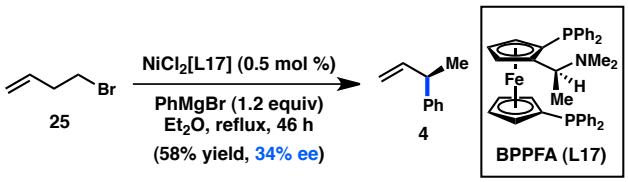


1.3 REACTIONS OF SECONDARY ALKYL ELECTROPHILES

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.[2] 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 1.12).

Scheme 1.4. *Primary-to-secondary isomerization in asymmetric cross-coupling.*

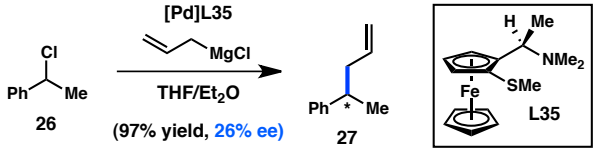


1.3.1 With Organomagnesium Reagents

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 **25** and PhMgBr (Scheme 1.4).[39] In the presence of the chiral catalyst $NiCl_2$[BPPFA], **4** 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.[40] Although this preliminary result was not further developed

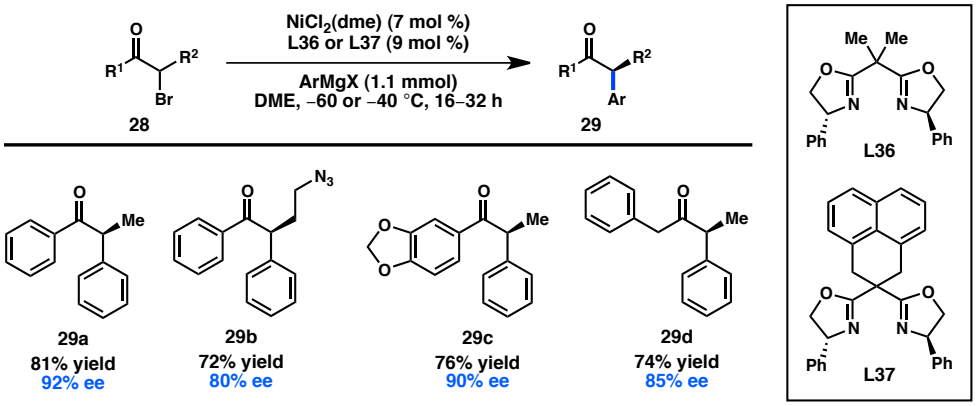
by Kumada and coworkers, it presaged the explosion of asymmetric cross-couplings of *sec*-alkyl electrophiles that would emerge in the literature nearly two decades later.

Scheme 1.5. *Asymmetric C(sp^3)–C(sp^3) Kumada–Corriu cross-coupling.*



In 1988, the Pd-catalyzed enantioselective cross-coupling between allylmagnesium chloride and racemic (1-chloroethyl)benzene (**26**) was reported by Brubaker and coworkers. A variety of bidentate S,N and Se,N ligands bearing planar and centrochirality were prepared and used to generate chiral Pd complexes.[41] The complex derived from **L35** catalyzed the formation of **27** in a high yield and modest, yet promising, ee (Scheme 1.5). Mechanistic studies to elucidate whether the enantioenriched product arises from a stereoconvergent process were not disclosed. The same group later studied Ni complexes of these ligands in the same transformation, obtaining similar levels of enantioinduction.

Figure 1.13. *Stereoconvergent Kumada–Corriu coupling of α-haloketones.*



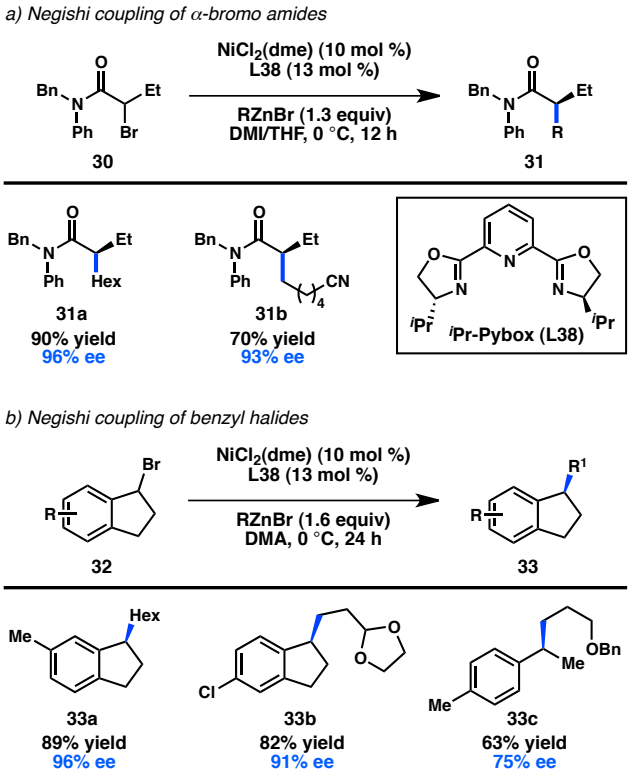
The first synthetically useful enantioselective, stereoconvergent cross-coupling between a *sec*-alkyl electrophile and a Grignard reagent was reported two decades later by Fu and coworkers. In this seminal report, the combination of $NiCl_2$(dme) and bidentate bis(oxazoline) ligand **L36** or **L37** was found to promote the coupling of α-haloketones **28** and arylmagnesium halides to give α-aryl ketones (Figure 1.13).[42] 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 **29** 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.[43]

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 **30** with an alkylzinc reagent and a Ni/**L38** catalyst delivered **31** in good yield and high ee (Figure 1.14, a).[44] 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/**L38**-catalyzed coupling of 1-bromoindanes and alkyl halides produced chiral indane **33** in good yield and high ee (Figure 1.14, b).[45] The use of acyclic 1-(1-bromoethyl)-4-methylbenzene furnished **33c** 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.[46] The enantioselectivity of the reaction was also correlated to the difference in free energy between the two transition states for reductive elimination.

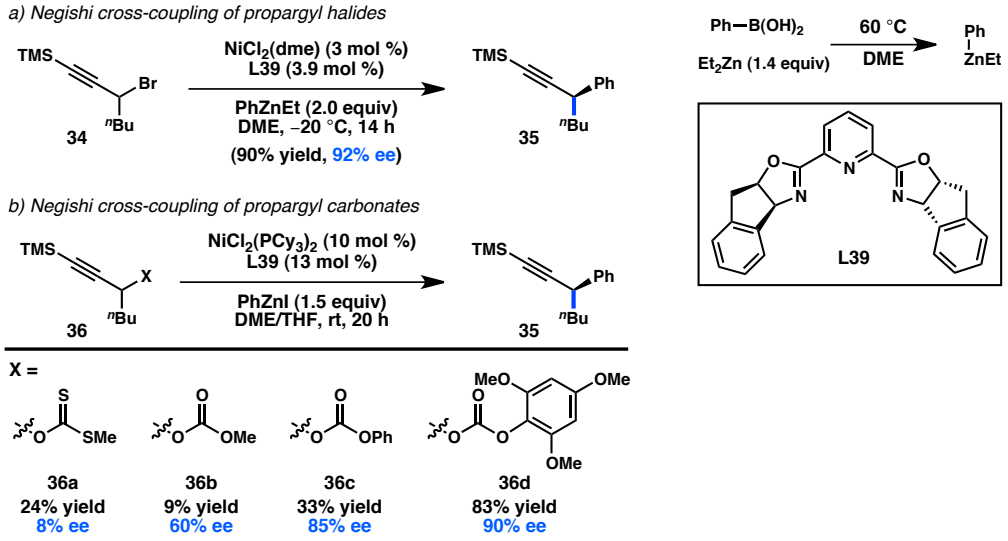
Figure 1.14. *Seminal stereoconvergent cross-couplings of secondary alkyl halides.*



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/**L39** complexes catalyze the cross-coupling between propargyl halide **34** and Ph_2Zn to furnish **35** in a high yield and ee (Figure 1.15, a).[47] 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.[48]

Figure 1.15. *Stereoconvergent Negishi cross-coupling of propargylic electrophiles.*

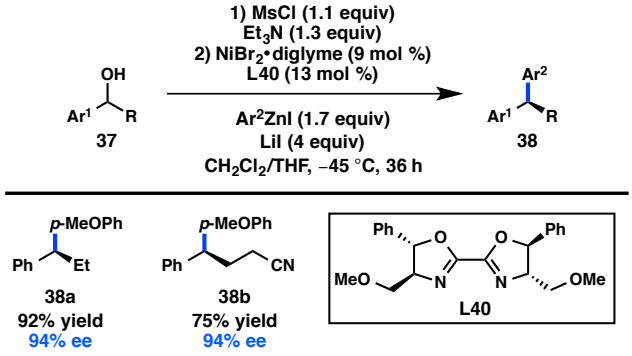


Organic halides are frequently prepared from the corresponding alcohols, and for certain substrates this functional group interconversion can be low yielding. Recognizing the synthetic advantage of using oxygen-based electrophiles directly in cross-coupling reactions, Fu and colleagues turned their attention 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 **35** in low yield and ee. (Figure 1.15, b).[49] On the other hand, simple carbonate **36b** 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 **36d** delivering **35** 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 chlorides and bromides.

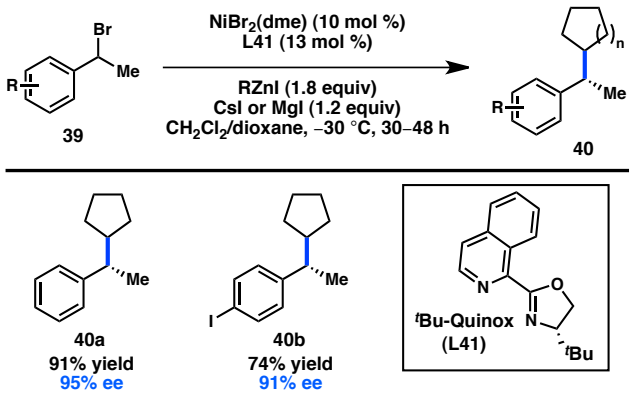
In 2013, Fu and coworkers published a stereoconvergent Negishi coupling of benzylic mesylates that could be prepared from the corresponding alcohols immediately prior to the coupling and used without purification (Figure 1.16).[50] Bi-oxazoline **L40** was identified as the optimal ligand, with more 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,[51] this reaction provides a complementary approach.

Figure 1.16. *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 **39** and cyclic organozinc halides (Figure 1.17).[40] Isoquinoline-oxazoline ligand **L41** 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.

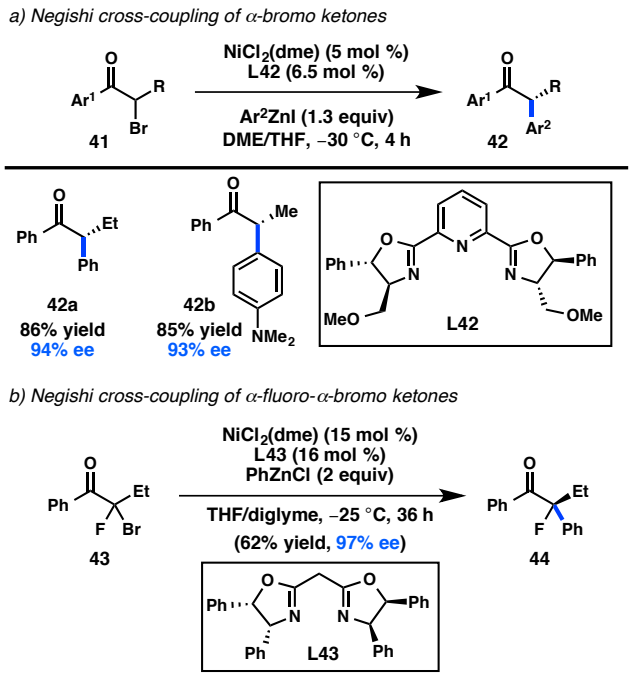
Figure 1.17. *Enantioconvergent Negishi cross-coupling of secondary organozinc reagents.*



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/**L42**-catalyzed asymmetric cross-coupling of α-bromoketones and arylzinc reagents (Figure 1.18, a).[43] 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 **42**. The synthesis of dialkyl ketones proceeded with lower

enantioinduction; however, this substrate limitation is addressed by their subsequently developed Kumada–Corriu conditions.[42] A recent modification of the reaction conditions has permitted the use of α-halo-α-fluoroketones, enabling the asymmetric formation of tertiary fluorides (Figure 1.18, b).[52]

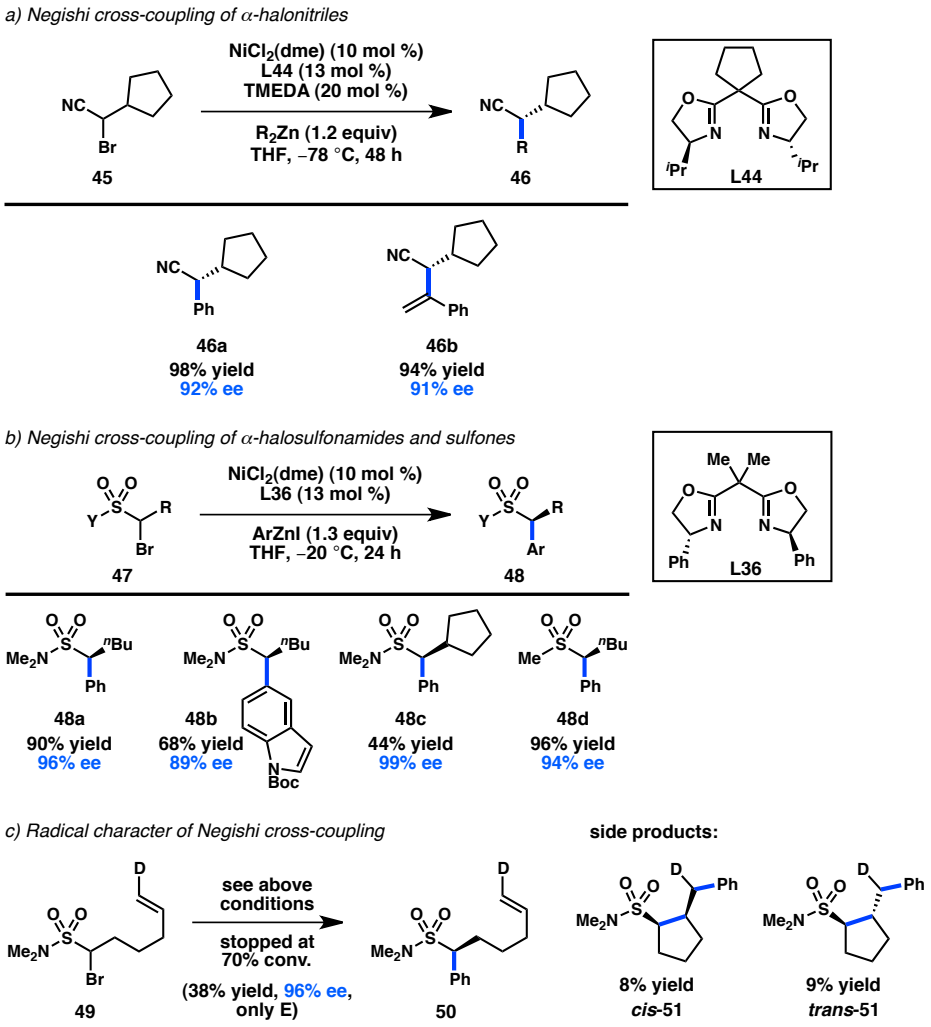
Figure 1.18. *Asymmetric Negishi cross-coupling of α-halo ketones.*



The Fu group has further expanded the scope of alkyl electrophiles amenable to Ni-catalyzed stereoconvergent Negishi cross-coupling to include α-bromonitriles.[53] Coupling of α-bromonitrile **45** and R_2Zn in the presence of $NiCl_2$(dme) and **L44** at –78 °C furnishes **46** in high yield and ee (Figure 1.19, a).[54] For the first time, alkenylzinc reagents were suitable coupling partners, delivering **46b** in 94% yield and 91% ee. Somewhat unexpectedly, a variant of **46** 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.[55] A more comprehensive mechanistic analysis is

thus required to elucidate the mechanism of oxidative addition for the given transformation.

Figure 1.19. *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 (**47**) and arylzinc reagents (Figures 1.19, b).[56] Since sulfonyl groups do not significantly stabilize

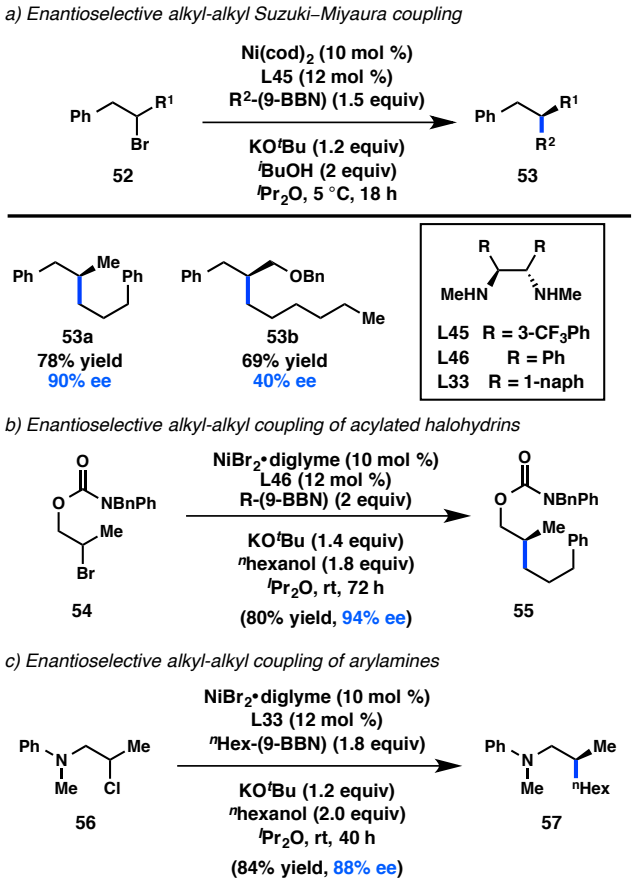
α-radicals, **47** can be considered as an unactivated electrophile. Investigations of the substrate scope revealed that sulfones are also suitable substrates without any change in the reaction conditions, furnishing **48d** in high yield and ee. Subjection of radical clock substrate **49** to the reaction conditions provided a mixture of **50**, cis-**51** and *trans*-**51**; the ratio of uncyclized product to cyclized product was found to increase linearly with increased Ni loading. These data could suggest that the reaction proceeds through a noncaged radical species, and also illustrates the dichotomy between the coupling of electrophiles **45** and **47**.

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,[57] Fu and coworkers reported that use of catalytic $Ni(cod)_2$ in conjunction with chiral 1,2-diamine ligand **L45** enabled the enantioselective coupling of homobenzylic bromides (**52**) with organoboranes (Figure 1.20, a).[58] The Ni catalyst was proposed to engage in a secondary interaction with the benzylic substituent on **52**, 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 **53b**. 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

(**54**) can also be coupled with alkylboranes in high enantioselectivity using a chiral 1,2-diamine **L46** (Figure 1.20, b).[59] Modified conditions permitted the enantioselective coupling of a homologated halohydrin. Further expansion of the substrate scope determined that halides (**56**) bearing proximal arylamines as directing groups can be coupled with alkylboranes in high enantioselectivity as well (Figure 1.20, c).[60] The reaction was found to be directed by the nitrogen atom of the arylamine group.

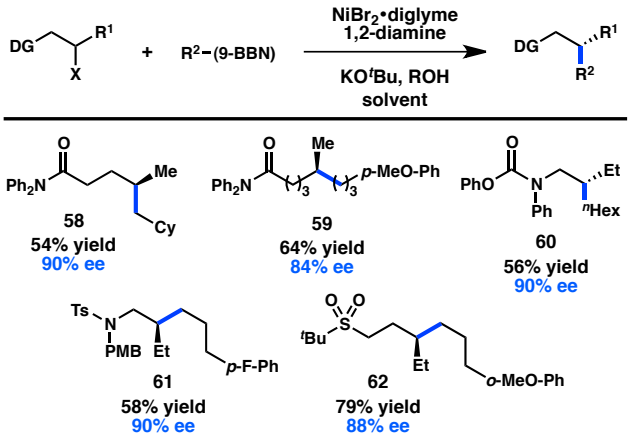
Figure 1.20. *Enantioconvergent Ni-catalyzed alkyl-alkyl Suzuki–Miyaura coupling.*



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 **58** and **59**, respectively (Figure 1.21).[61] Various halides proximal to protected amines, such as carbamates or sulfonamides, were also optimized toward enantioconvergent cross-coupling.[62] 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.[62a]

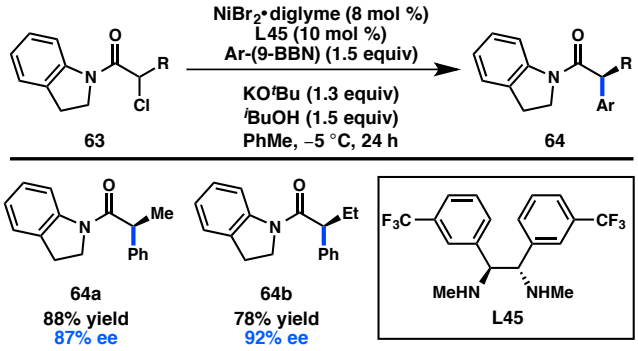
Figure 1.21. *Examples of directing groups for the enantioconvergent Suzuki–Miyaura coupling.*



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 enanatioselective coupling between α-haloamides and arylboron reagents. After first investigating several different amides, it was found that the combination of $NiBr_2$•diglyme and **L45** catalyzed the coupling between α-chloroamides

(**63**) and Ar-(9-BBN) reagents to furnish **64** in good yields and high ee's (Figure 1.22).[63] 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 **63** 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.[61]

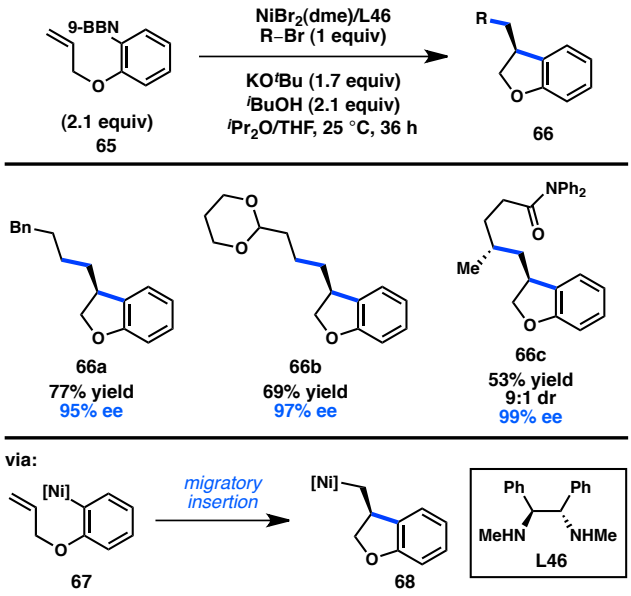
Figure 1.22. *Asymmetric Suzuki–Miyaura coupling of α-haloamides.*



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 1.23).[64] Key to this transformation was the insight that a "transmetalation first" mechanism could be operative, and that organonickel complex **67** 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 **65** and several simple alkyl bromides, in which heterocyclic products **66** were obtained in excellent ee. Realizing the compatibility of their reaction conditions with those previously optimized for coupling of

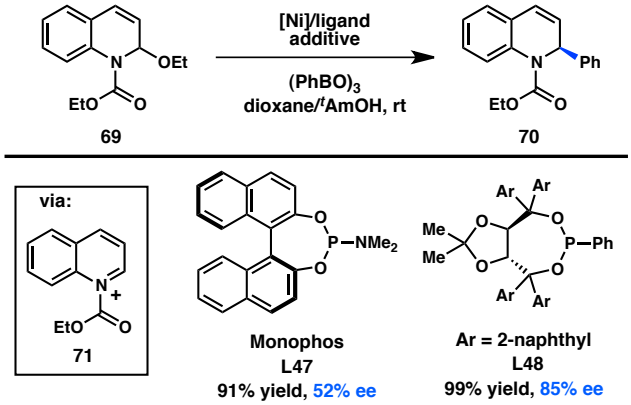
γ-haloamides (see Figure 1.21), a γ-haloamide was also used as an electrophile.[61] Remarkably, a single Ni complex controls the stereochemical outcome of two distinct C–C bond forming processes, giving product **66c** in good yield, good dr, and excellent ee.

Figure 1.23. *Asymmetric cascade cyclization/cross-coupling.*



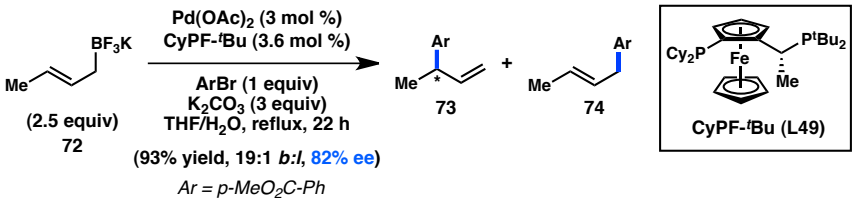
The Doyle laboratory has focused on expanding the scope of electrophiles suitable for transition metal catalysis, investigating the cross-coupling reactions of acetals and *N*,*O*-acetals. These efforts led to the discovery that $Ni(cod)_2$ catalyzes the addition of various aryl boroxines to *N*,*O*-acetal **69**, presumably via the intermediacy of quinolinium ion **71**.[65] When chiral phosphoramidite **L47** is used as a supporting ligand, **70** is formed in 52% ee (Figure 1.24). 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.[66] A wider survey of ligands showed that improved ee could be realized with TADDOL-based phosphonite **L48**.[67] In an extension, the addition of arylzinc reagents into pyridinium ions was subsequently reported.[68]

Figure 1.24. *Asymmetric addition into quinolinium ions.*



In 2006, Yamamoto, Miyaura, and coworkers reported a novel strategy for the preparation of enantioenriched products from achiral starting material. Bidentate phosphine ligands allowed for high γ-selectivity in the Pd-catalyzed coupling between allylic trifluoroborate salts and aryl bromides.[69] Bulky, Josiphos-type ligand **L49** promoted formation of **73** in 82% ee while still maintaining high selectivity for γ-addition (Scheme 1.6).[70] DFT studies support a S_E2' (open) transition state for transmetalation, whereas the corresponding closed transition state was of slightly higher energy;[71] transmetalation was also proposed to be the stereochemistry-determining step, followed by a fast reductive elimination to forge the desired product. Similar γ-selectivity was observed in the stereospecific couplings of allylic boronates[72] and silanes.[73]

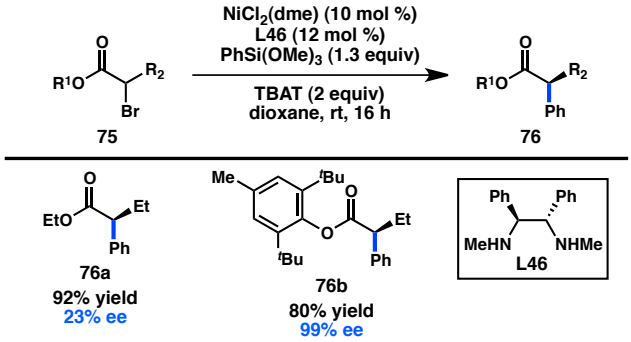
Scheme 1.6. *Enantioselective cross-coupling of allylic trifluoroborate salts.*



1.3.4 With Organosilicon Reagents

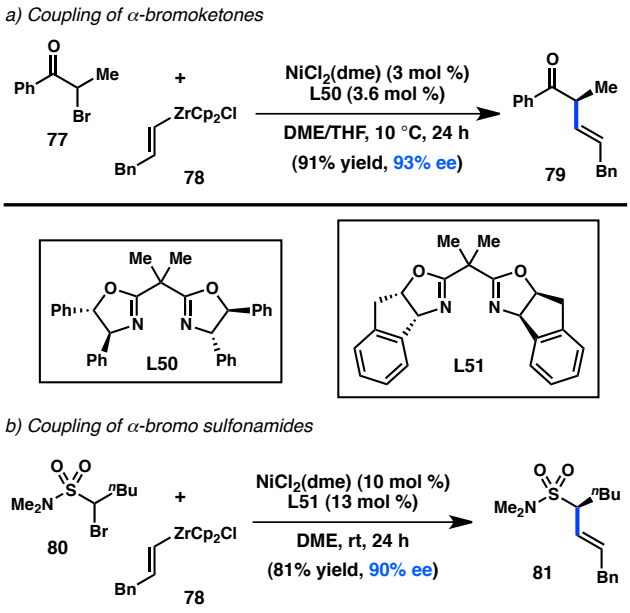
Only a single example of an asymmetric cross-coupling between *sec*-alkyl organic halides and organosilicon reagents has been reported to date. Fu and colleagues developed a Ni/**L46**-catalyzed stereoconvergent coupling of α-bromoesters (**75**) and aryl siloxanes to furnish α-aryl esters in good yields and with high enantioduction (Figure 1.25).[74] While simple ethyl esters gave good yield but poor ee, the use of the BHT ester resulted in formation of **76b** 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 extended to the coupling of alkenyl silanes as well.

Figure 1.25. *Stereoconvergent coupling of aryl silanes.*



coupling of alkenyl metal species, with alkenyl silicon[74] and zinc[54] reagents being the most promising. In 2010, Fu and coworkers published the Ni/**L50**-catalyzed asymmetric cross-coupling of alkenylzirconium reagents and α-bromoketones, allowing access to **79** in 93% ee (Figure 1.26, a).[75] 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 in high yield and ee (Figure 1.26, b).[56]

Figure 1.26. *Stereoconvergent coupling of alkenylzirconium reagents.*

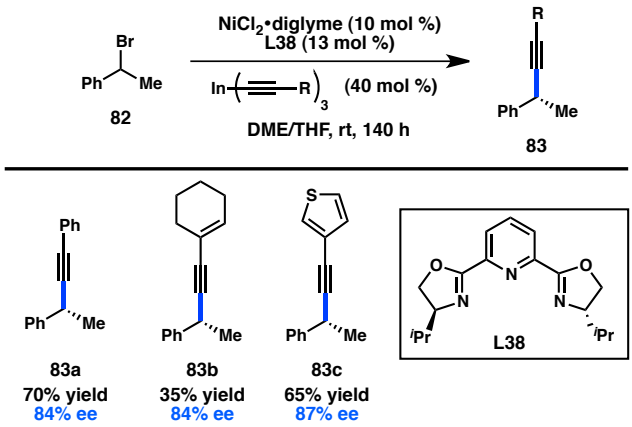


1.3.6 With Organoindium Reagents

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,[44-45] 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 **L38** was optimal, delivering cross-coupled product **83** in up to 87% ee for several different alkynes (Figure 1.27).[76] Further work on the asymmetric coupling of C(sp) organometallic reagents has not been disclosed.

Figure 1.27. *Alkynyl organometallic reagents in stereoconvergent cross-coupling.*

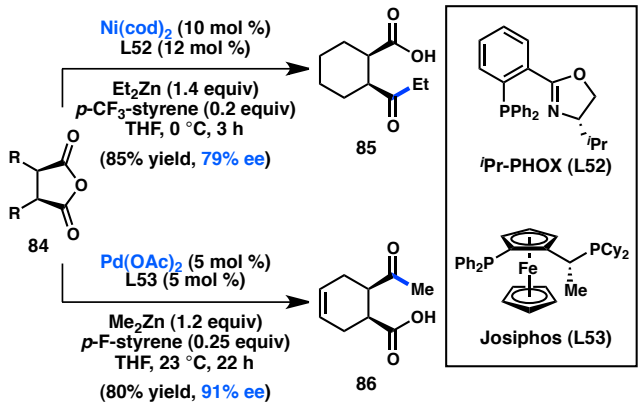


1.4 TRANSITION METAL-CATALYZED DESYMMETRIZATION REACTIONS

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 1.7. *Alkylative desymmetrization of meso-anhydrides.*

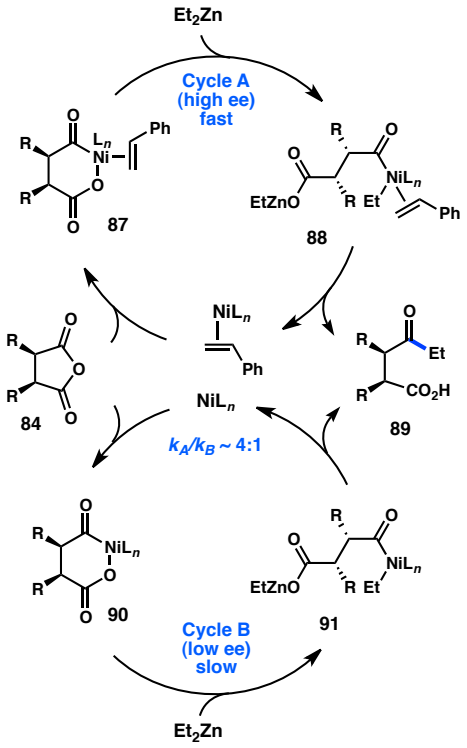


1.4.1 Organozinc Reagents

The desymmetrization of *meso*-anhydrides has emerged as a robust method for the synthesis of enantiopure products.[77] Rovis and coworkers[78] have developed a monofunctionalization of cyclic anhydrides through a Ni-catalyzed Negishi coupling with Et_2Zn.[79] 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.[80] Based on these initial findings, the authors sought to develop a desymmetrizing Negishi reaction of *meso*-cyclic anhydride **84**, and determined that the catalyst prepared from of $Ni(cod)_2$ and ^{i}Pr-PHOX (**L52**) furnished **85** in 79% ee (Scheme 1.7).[81] 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 1.28. *Competing mechanisms in the Ni-catalyzed desymmetrization of meso-anhydrides.*

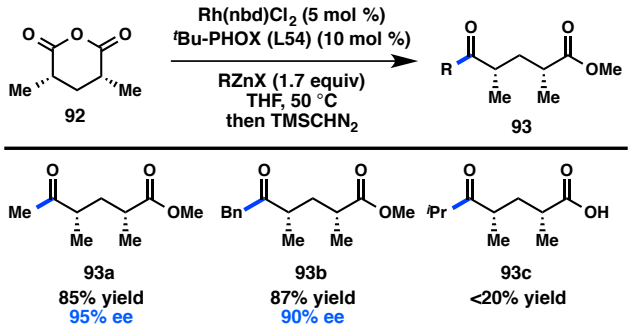


Kinetic analysis of the reaction revealed two competing mechanisms for the formation of **85** (Figure 1.28).[82] One occurred in the absence of styrene and proceeded with low enantioselectivity (cycle B). The other involved coordination of styrene and provided **89** in high ee (cycle A). For both reactions, 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.

The Pd-catalyzed desymmetrization of succinic anhydrides was also developed by Rovis and coworkers (Scheme 1.7). Treatment of **84** with Me_2Zn in the presence of $Pd(OAc)_2$ and the bidentate phosphine Josiphos (**L53**) furnished **86** in 91% ee; the use of *p*-F-styrene as an additive was crucial to achieving the high level of enantioselectivity.[83]

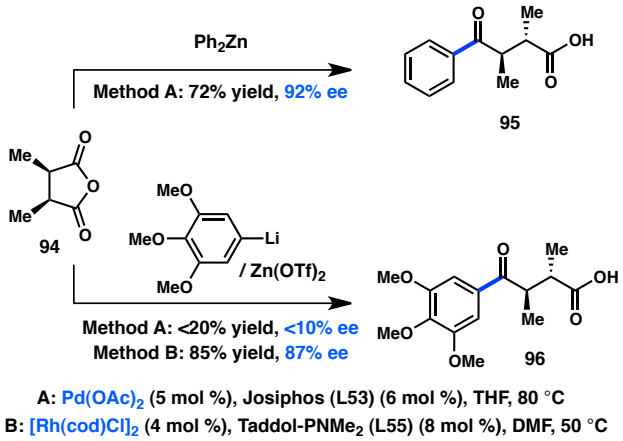
Figure 1.29. *Rh-catalyzed desymmetrization of glutaric anhydrides.*



One hurdle in the Pd-catalyzed desymmetrization was the catalyst's sensitivity to halide salts, meaning that the organozinc reagent could not be prepared in situ from the more readily available organomagnesium or -lithium reagents. Investigation of Rh catalysts in the desymmetrization of glutaric anhydride, a substrate that reacts poorly in the presence of Pd, revealed that high yields and good ee's could be attained, allowing access to *syn*-deoxypolypropionate synthons (Figure 1.29).[84] This reaction is proposed to proceed through a Rh^{I}/Rh^{III} catalytic cycle, with transmetalation occuring prior to oxidative addition of the anhydride. Furthermore, the organozinc reagent could now be prepared in situ. The desymmetrization of glutaric anhydrides is an enantioselective

alternative to Breit's enantiospecific Kumada–Corriu coupling for the synthesis of deoxypolypropionates.[85]

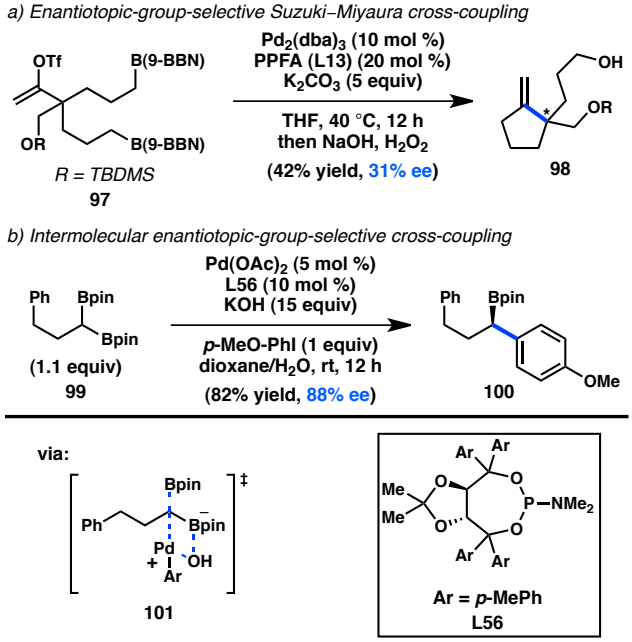
Figure 1.30. *Pd- and Rh-catalyzed desymmetrization with arylzinc reagents.*



Efforts by Rovis and coworkers to affect an alkylative desymmetrization of *meso*-anhydrides have been complemented by attempts to use arylzinc reagents in similar transformations. In the presence of a Pd/Josiphos catalyst system, 1,4-ketoacid **95** could be prepared from commercially available Ph_2Zn in good yield and high ee (Figure 1.30).[83] In contrast to Rovis' alkylation methodology, excess fluorostyrene is not necessary to achieve a high enantioinduction. While Ph_2Zn was reactive in the Pd-catalyzed transformation, lower yields and ee's were observed when the organozinc reagent was prepared in situ from the corresponding organolithium. In fact, simple exposure of **94** and Ph_2Zn to LiX under the standard reaction conditions led to a sharp drop in enantioselectivity. As a result, Rovis next turned to Rh complexes, which are well known to be less prone to interaction with Lewis bases like halides. After optimizing toward a chiral phosphoramidite ligand, **96** could be furnished in 85% yield and 87% ee.[84b,86] A variety of in situ-prepared arylzinc reagents can be coupled under the Rh-catalyzed

conditions with uniformly good enantioselectivity, leading the authors to propose that the stereochemistry-determining step occurs independent of the organometallic reagent. These reaction conditions could not be extended to the coupling of alkylzinc reagents.

Figure 1.31. *Enantiotopic-group-selective cross-coupling.*



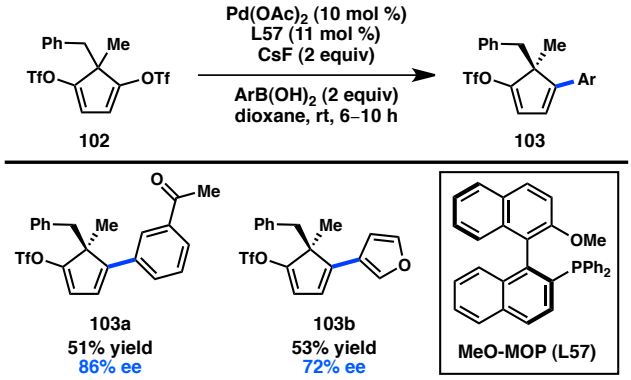
1.4.2 Organoboron Reagents

In 1998, Shibasaki and coworkers reported a Pd-catalyzed intramolecular enantiotopic group-selective Suzuki–Miyaura coupling of alkylboranes (**97**) to prepare exo-methylene cyclopentanes, but the highest ee value obtained was 31% (Figure 1.31, a).[87] More recently, Morken demonstrated that prochiral diboronate **99** can be cross-coupled with an aryl halide in the presence of $Pd(OAc)_2$ and phosphoramidite **L56** to forge benzylic boronate **100** with good enantioinduction (Figure 1.31, b).[88] Enantioenriched boronate **100** can undergo a subsequent stereospecific cross-coupling to

generate an enantioenriched diarylalkane.[51a] Prior studies by Shibata and coworkers had demonstrated that geminal bis(boronate) **99** is activated toward transmetalation and proposed that the "ate" complex of one boronate can coordinate to Pd and assist in an S_E2 transmetalation of the second boronate.[89] The resulting monoboronate **100** lacks this mode of activation, avoiding the formation of diarylated products.

In a distinct desymmetrization approach, Willis and coworkers reported the asymmetric Suzuki–Miyaura cross-coupling of *meso*-ditriflate **102**.[90] The catalyst generated from $Pd(OAc)_2$ and chiral biaryl phosphine **L57** furnished mono-arylated **103** bearing a stereodefined quaternary center (Figure 1.32). Even though the yield of the transformation was moderate, good enantioselectivity was still accomplished. The remaining triflate on **103** was shown to serve as a versatile handle for further diversification of the reaction products.

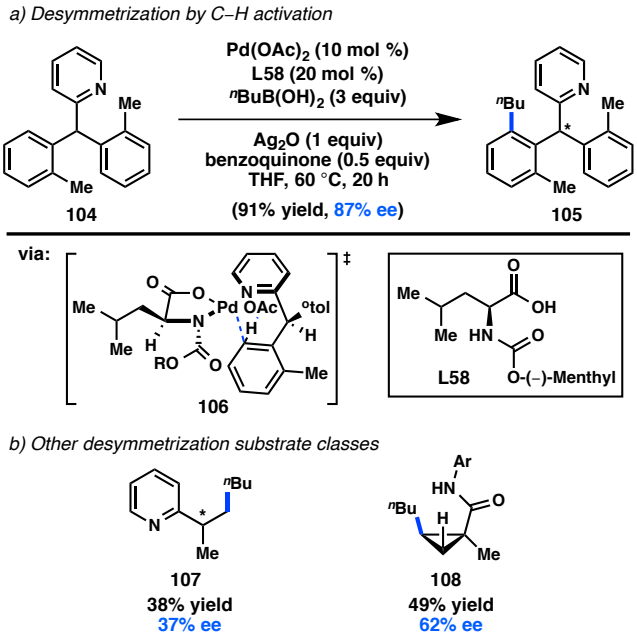
Figure 1.32. *Enantioselective desymmetrization of a meso-ditriflate.*



Yu and coworkers reported the first enantioselective C–H activation/cross-coupling via a desymmetrization process in 2008. Prochiral pyridyl-diarylmethane **104** was selected for these studies because of the relatively low temperatures required for C–H activation.[91] Following a thorough ligand study, the use of monoprotected amino

acid **L58** in conjunction with $Pd(OAc)_2$ was found to impart a high degree of asymmetric induction for the C-H activation/cross-coupling between **104** and butylboronic acid to give **105** (Figure 1.33, a). The *N*-protecting group on **L58** was a critical element for generating high ee. The reaction is hypothesized to proceed through concerted metalation/deprotonation transition state **106**, in which the unreactive aryl group is positioned *anti* to the carbamate protecting group of the ligand.[92]

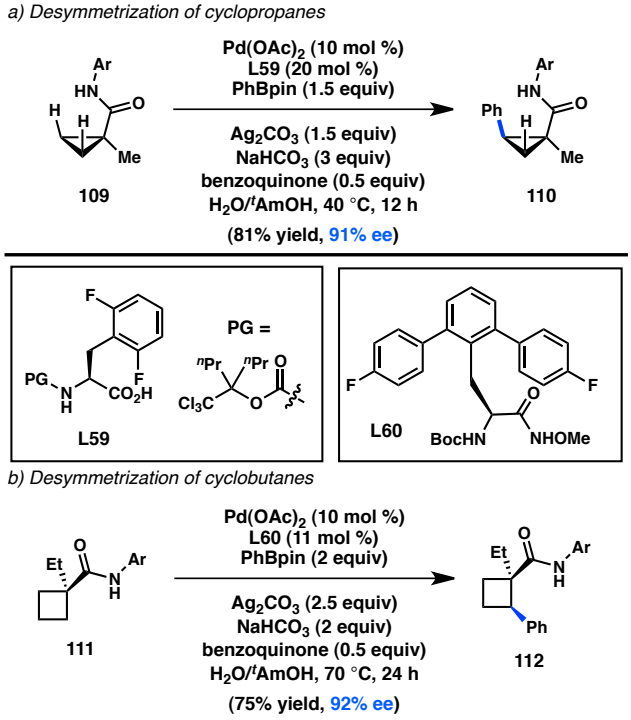
Figure 1.33. *Desymmetrizing enantioselective C–H activation/cross-coupling.*



Yu and coworkers were subsequently able to expand this chemistry to the desymmetrization of cyclopropanes and cyclobutanes. After extensive re-engineering of the ligand, the combination of $Pd(OAc)_2$ and monoprotected amino acid **L59** was found to catalyze C–H arylation of cyclopropyl amide **109** with phenyl boronate ester to produce **110** in good yield and high ee (Scheme 1.8, a).[92] Unfortunately, these conditions could not be extended toward the less acidic C–H bonds of a cyclobutane. The authors

hypothesized that a more strongly coordinating ligand could increase stereoselection and reactivity in the C–H activation of cyclobutylamide **111**. Using the more Lewis basic hydroxamic acid **L60**, **112** could be produced with a high level of enantioinduction (Scheme 1.8, b).[93] A related ligand also enabled the desymmetrization of prochiral methyl groups in acyclic amides to forge β-arylated products in modest ee.[93]

Scheme 1.8. *C–H activation of strained cycles.*



1.5 CONCLUDING REMARKS

The last several decades have seen a profound growth in cross-coupling methods, and the wealth of new tools for enantioselective C–C bond formation has revolutionized synthetic planning and practice. As this chapter encompasses, stereogenic structural motifs have become increasingly accessible through transition metal-catalyzed cross-

coupling, allowing chemists to leverage the flexibility of cross-coupling to streamline the synthesis of complex molecules. However, there remain challenges at the forefront of this field. Whereas enantiocontrolled cross-couplings of *sec*-alkyl partners with *n*-alkyl or C(sp^2) partners have been well-explored, the analogous asymmetric cross-coupling reactions of *tert*-alkyl partners represent a largely-undeveloped area of great synthetic promise. Similarly, the completely stereocontrolled cross-coupling of two *sec*-alkyl partners is yet to be realized. These reactions would provide entry to molecules with all carbon-quaternary centers or vicinal tertiary centers, respectively—motifs that are present in many bioactive small molecules and natural product targets. The promise of enantiocontrolled cross-coupling methodologies has been made clear in the years since their inception. We anticipate that their development and application will continue to address long-standing challenges in the field of organic synthesis.

1.6 NOTES AND REFERENCES

(1) Jana, R.; Pathak, T. P.; Sigman, M. S. *Chem. Rev.* **2011**, *111*, 1417.

(2) Rudolph, A.; Lautens, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 2656.

(3) (a) Whitesides, G. M.; Roberts, J. D. *J. Am. Chem. Soc.* **1965**, *87*, 4878. (b) Whitesides, G. M.; Witanowski, M.; Roberts, J. D. *J. Am. Chem. Soc.* **1965**, *87*, 2854. (c) Witanowski, M.; Roberts, J. D. *J. Am. Chem. Soc.* **1966**, *88*, 737.

(4) Hoffmann, R. W.; Hölzer, B.; Knopff, O.; Harms, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 3072.

(5) (a) Corriu, R. J. P.; Masse, J. P. *J. Chem. Soc., Chem. Commun.* **1972**, 144. (b) Tamao, K.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc.* **1972**, *94*, 4374. (c) Tamao, K. *J. Organomet. Chem.* **2002**, *653*, 23.

(6) Hayashi, T. *J. Organomet. Chem.* **2002**, *653*, 41.

(7) (a) Consiglio, G.; Botteghi, C. *Helv. Chim. Acta* **1973**, *56*, 460. (b) Kiso, Y.; Tamao, K.; Miyake, N.; Yamamoto, K.; Kumada, M. *Tetrahedron Lett.* **1974**, 3.

(8) Consiglio, G.; Piccolo, O. *J. Organomet. Chem.* **1979**, *177*, C13.

(9) (a) Consiglio, G.; Morandini, F.; Piccolo, O. *Tetrahedron* **1983**, *39*, 2699. (b) Consiglio, G.; Indolese, A. *J. Organomet. Chem.* **1991**, *417*, C36.

(10) Iida, A.; Yamashita, M. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2365.

(11) Czaplik, W. M.; Mayer, M.; Jacobi von Wangelin, A. *Synlett* **2009**, 2931.

(12) Tamao, K.; Yamamoto, H.; Matsumoto, H.; Miyake, N.; Hayashi, T.; Kumada, M. *Tetrahedron Lett.* **1977**, *18*, 1389.

(13) Brunner, H.; Pröbster, M. *J. Organomet. Chem.* **1981**, *209*, C1.

(14) (a) Hayashi, T.; Fukushima, M.; Konishi, M.; Kumada, M. *Tetrahedron Lett.* **1980**, *21*, 79. (b) Hayashi, T.; Nagashima, N.; Kumada, M. *Tetrahedron Lett.* **1980**, *21*, 4623. (c) Hayashi, T.; Konishi, M.; Fukushima, M.; Kanehira, K.; Hioki, T.; Kumada, M. *J. Org. Chem.* **1983**, *48*, 2195.

(15) Baker, K. V.; Brown, J. M.; Cooley, N. A.; Hughes, G. D.; Taylor, R. J. *J. Organomet. Chem.* **1989**, *370*, 397.

(16) (a) Cross, G. A.; Kellogg, R. M. *J. Chem. Soc., Chem. Commun.* **1987**, 1746. (b) Cross, G.; Vriesema, B. K.; Boven, G.; Kellogg, R. M.; van Bolhuis, F. *J. Organomet. Chem.* **1989**, *370*, 357.

(17) (a) Hayashi, T.; Tajika, M.; Tamao, K.; Kumada, M. *J. Am. Chem. Soc.* **1976**, *98*, 3718. (b) Tamao, K.; Hayashi, T.; Matsumoto, H.; Yamamoto, H.; Kumada, M. *Tetrahedron Lett.* **1979**, 2155. (c) Hayashi, T.; Konishi, M.; Fukushima, M.; Mise, T.; Kagotani, M.; Tajika, M.; Kumada, M. *J. Am. Chem. Soc.* **1982**, *104*, 180. (d) Hayashi, T.; Kumada, M. *Acc. Chem. Res.* **1982**, *15*, 395.

(18) Indolese, A.; Consiglio, G. *J. Organomet. Chem.* **1993**, *463*, 23.

(19) Hayashi, T.; Konishi, M.; Hioki, T.; Kumada, M.; Ratajczak, A.; Niedbala, H. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 3615.

(20) (a) Lemaire, M.; Buter, J.; Vriesema, B. K.; Kellogg, R. M. *J. Chem. Soc., Chem. Commun.* **1984**, 309. (b) Vriesema, B. K.; Lemaire, M.; Buter, J.; Kellogg, R. M. *J. Org. Chem.* **1986**, *51*, 5169.

(21) Brunner, H.; Li, W.; Weber, H. *J. Organomet. Chem.* **1985**, *288*, 359.

(22) Terfort, A.; Brunner, H. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1467.

(23) Jedlicka, B.; Kratky, C.; Weissensteiner, W.; Widhalm, M. *J. Chem. Soc., Chem. Commun.* **1993**, 1329.

(24) Pellet-Rostaing, S.; Saluzzo, C.; Halle, R. T.; Breuzard, J.; Vial, L.; Le Guyader, F.; Lemaire, M. *Tetrahedron: Asymmetry* **2001**, *12*, 1983.

(25) (a) Hayashi, M.; Takaoki, K.; Hashimoto, Y.; Saigo, K. *Enantiomer* **1997**, *2*, 293. (b) Yamago, S.; Yanagawa, M.; Nakamura, E. *J. Chem. Soc., Chem. Commun.* **1994**, 2093. (c) Yamago, S.; Yanagawa, M.; Mukai, H.; Nakamura, E. *Tetrahedron* **1996**, *52*, 5091.

(26) (a) Kreuzfeld, H. J.; Döbler, C.; Abicht, H. P. *J. Organomet. Chem.* **1987**, *336*, 287(b) Döbler, C.; Kreuzfeld, H. J. *J. Organomet. Chem.* **1988**, *344*, 249.

(27) (a) Horibe, H.; Kazuta, K.; Kotoku, M.; Kondo, K.; Okuno, H.; Murakami, Y.; Aoyama, T. *Synlett* **2003**, 2047. (b) Hideo, H.; Fukuda, Y.; Kondo, K.; Okuno, H.; Murakami, Y.; Aoyama, T. *Tetrahedron* **2004**, *60*, 10701.

(28) (a) Richards, C. J.; Hibbs, D. E.; Hursthouse, M. B. *Tetrahedron Lett.* **1995**, *36*, 3745(b) Lloyd-Jones, G. C.; Butts, C. P. *Tetrahedron* **1998**, *54*, 901.

(29) Schwink, L.; Knochel, P. *Chem. Eur. J.* **1998**, *4*, 950.

(30) (a) Hayashi, T.; Konishi, M.; Ito, H.; Kumada, M. *J. Am. Chem. Soc.* **1982**, *104*, 4962. (b) Hayashi, T.; Konishi, M.; Okamoto, Y.; Kabeta, K.; Kumada, M. *J. Org. Chem.* **1986**, *51*, 3772.

(31) Hayashi, T.; Kanehira, K.; Hioki, T.; Kumada, M. *Tetrahedron Lett.* **1981**, *22*, 137.

(32) Hayashi, T.; Okamoto, Y.; Kumada, M. *Tetrahedron Lett.* **1983**, *24*, 807.

(33) Hayashi, T.; Hagihara, T.; Katsuro, Y.; Kumada, M. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 363.

(34) Hayashi, T.; Yamamoto, A.; Hojo, M.; Ito, Y. *J. Chem. Soc., Chem. Commun.* **1989**, 495.

(35) Cherney, A. H.; Reisman, S. E. *Tetrahedron* **2014**, *70*, 3259.

(36) Campos, K. R.; Klapars, A.; Waldman, J. H.; Dormer, P. G.; Chen, C.-y. *J. Am. Chem. Soc.* **2006**, *128*, 3538.

(37) Cordier, C. J.; Lundgren, R. J.; Fu, G. C. *J. Am. Chem. Soc.* **2013**, *135*, 10946.

(38) Tellis, J. C.; Primer, D. N.; Molander, G. A. *Science* **2014**, *345*, 433.

(39) Zembayashi, M.; Tamao, K.; Hayashi, T.; Mise, T.; Kumada, M. *Tetrahedron Lett.* **1977**, *18*, 1799.

(40) Binder, J. T.; Cordier, C. J.; Fu, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 17003.

(41) (a) Okoroafor, M. O.; Ward, D. L.; Brubaker, C. H. *Organometallics* **1988**, *7*, 1504. (b) Naiini, A. A.; Lai, C.-K.; Ward, D. L.; Brubaker, C. H. *J. Organomet. Chem.* **1990**, *390*, 73. (c) Ali, H. M.; Brubaker, C. H. *J. Mol. Cat.* **1990**, *60*, 331.

(42) Lou, S.; Fu, G. C. *J. Am. Chem. Soc.* **2010**, *132*, 1264.

(43) Lundin, P. M.; Esquivias, J.; Fu, G. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 154.

(44) Fischer, C.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 4594.

(45) Arp, F. O.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 10482.

(46) Lin, X.; Sun, J.; Xi, Y.; Lin, D. *Organometallics* **2011**, *30*, 3284.

(47) Smith, S. W.; Fu, G. C. *J. Am. Chem. Soc.* **2008**, *130*, 12645.

(48) Partridge, B. M.; Chausset-Boissarie, L.; Burns, M.; Pulis, A. P.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2012**, *51*, 11795.

(49) Oelke, A. J.; Sun, J.; Fu, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 2966.

(50) Do, H.-Q.; Chandrashekar, E. R. R.; Fu, G. C. *J. Am. Chem. Soc.* **2013**, *135*, 16288.

(51) (a) Imao, D.; Glasspoole, B. W.; Laberge, V. S.; Crudden, C. M. *J. Am. Chem. Soc.* **2009**, *131*, 5024. (b) Taylor, B. L. H.; Swift, E. C.; Waetzig, J. D.; Jarvo, E. R. *J. Am. Chem. Soc.* **2011**, *133*, 389. (c) Greene, M. A.; Yonova, I. M.; Williams, F. J.; Jarvo, E. R. *Org. Lett.* **2012**, *14*, 4293. (d) Yonova, I. M.; Johnson, A. G.; Osborne, C. A.; Moore, C. E.; Morrissette, N. S.; Jarvo, E. R. *Angew. Chem., Int. Ed.* **2014**, *53*, 2422. (e) Zhou, Q.; Srinivas, H. D.; Dasgupta, S.; Watson, M. P. *J. Am. Chem. Soc.* **2013**, *135*, 3307. (f) Maity, P.; Shacklady-McAtee, D. M.; Yap, G. P. A.; Sirianni, E. R.; Watson, M. P. *J. Am. Chem. Soc.* **2013**, *135*, 280. (g) Shacklady-McAtee, D. M.; Roberts, K. M.; Basch, C. H.; Song, Y.-G.; Watson, M. P. *Tetrahedron* **2014**, *70*, 4257.

(52) Liang, Y.; Fu, G. C. *J. Am. Chem. Soc.* **2014**, *136*, 5520.

(53) He, A.; Falck, J. R. *J. Am. Chem. Soc.* **2010**, *132*, 2524.

(54) Choi, J.; Fu, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 9102.

(55) (a) Powell, D. A.; Maki, T.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 510. (b) Gonzalez-Bobes, F.; Fu, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 5360.

(56) Choi, J.; Martín-Gago, P.; Fu, G. C. *J. Am. Chem. Soc.* **2014**, *136*, 12161.

(57) Saito, B.; Fu, G. C. *J. Am. Chem. Soc.* **2007**, *129*, 9602.

(58) Saito, B.; Fu, G. C. *J. Am. Chem. Soc.* **2008**, *130*, 6694.

(59) Owston, N. A.; Fu, G. C. *J. Am. Chem. Soc.* **2010**, *132*, 11908.

(60) Lu, Z.; Wilsily, A.; Fu, G. C. *J. Am. Chem. Soc.* **2011**, *133*, 8154.

(61) Zultanski, S. L.; Fu, G. C. *J. Am. Chem. Soc.* **2011**, *133*, 15362.

(62) (a) Wilsily, A.; Tramutola, F.; Owston, N. A.; Fu, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 5794. (b) Jiang, X.; Sakthivel, S.; Kulbitski, K.; Nisnevich, G.; Gandelman, M. *J. Am. Chem. Soc.* **2014**, *136*, 9548.

(63) Lundin, P. M.; Fu, G. C. *J. Am. Chem. Soc.* **2010**, *132*, 11027.

(64) Cong, H.; Fu, G. C. *J. Am. Chem. Soc.* **2014**, *136*, 3788.

(65) Graham, T. J. A.; Shields, J. D.; Doyle, A. G. *Chem. Sci.* **2011**, *2*, 980.

(66) Sylvester, K. T.; Wu, K.; Doyle, A. G. *J. Am. Chem. Soc.* **2012**, *134*, 16967.

(67) Shields, J. D.; Ahneman, D. T.; Graham, T. J. A.; Doyle, A. G. *Org. Lett.* **2014**, *16*, 142.

(68) Chau, S. T.; Lutz, J. P.; Wu, K.; Doyle, A. G. *Angew. Chem., Int. Ed.* **2013**, *52*, 9153.

(69) Yamamoto, Y.; Takada, S.; Miyaura, N. *Chem. Lett.* **2006**, *35*, 704.

(70) Yamamoto, Y.; Takada, S.; Miyaura, N. *Chem. Lett.* **2006**, *35*, 1368.

(71) Yamamoto, Y.; Takada, S.; Miyaura, N.; Iyama, T.; Tachikawa, H. *Organometallics* **2009**, *28*, 152.

(72) Chausset-Boissarie, L.; Ghozati, K.; LaBine, E.; Chen, J. L.-Y.; Aggarwal, V. K.; Crudden, C. M. *Chem. Eur. J.* **2013**, *19*, 17698.

(73) (a) Hatanaka, Y.; Goda, K.-I.; Hiyama, T. *Tetrahedron Lett.* **1994**, *35*, 1279. (b) Denmark, S. E.; Werner, N. S. *J. Am. Chem. Soc.* **2010**, *132*, 3612.

(74) Dai, X.; Strotman, N. A.; Fu, G. C. *J. Am. Chem. Soc.* **2008**, *130*, 3302.

(75) Lou, S.; Fu, G. C. *J. Am. Chem. Soc.* **2010**, *132*, 5010.

(76) Caeiro, J.; Pérez Sestelo, J.; Sarandeses, L. A. *Chem. Eur. J.* **2008**, *14*, 741.

(77) (a) Willis, M. C. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1765. (b) Chen, Y.; McDaid, P.; Deng, L. *Chem. Rev.* **2003**, *103*, 2965. (c) Díaz de Villegas, M. D.; Gálvez, J. A.; Etayo, P.; Badorrey, R.; López-Ram-de-Víu, P. *Chem. Soc. Rev.* **2011**, *40*, 5564.

(78) Johnson, J. B.; Rovis, T. *Acc. Chem. Res.* **2008**, *41*, 327.

(79) Bercot, E. A.; Rovis, T. *J. Am. Chem. Soc.* **2005**, *127*, 247.

(80) (a) Giovannini, R.; Stüdemann, T.; Dussin, G.; Knochel, P. *Angew. Chem., Int. Ed.* **1998**, *37*, 2387. (b) Giovannini, R.; Stüdemann, T.; Devasagayaraj, A.; Dussin, G.; Knochel, P. *J. Org. Chem.* **1999**, *64*, 3544.

(81) Bercot, E. A.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 174.

(82) Johnson, J. B.; Bercot, E. A.; Rowley, J. M.; Coates, G. W.; Rovis, T. *J. Am. Chem. Soc.* **2007**, *129*, 2718.

(83) Bercot, E. A.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 10248.

(84) (a) Cook, M. J.; Rovis, T. *J. Am. Chem. Soc.* **2007**, *129*, 9302. (b) Johnson, J. B.; Cook, M. J.; Rovis, T. *Tetrahedron* **2009**, *65*, 3202. (c) Cook, M. J.; Rovis, T. *Synthesis* **2009**, 335.

(85) Brand, G. J.; Studte, C.; Breit, B. *Org. Lett.* **2009**, *11*, 4668.

(86) Johnson, J. B.; Bercot, E. A.; Williams, C. M.; Rovis, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 4514.

(87) Cho, S. Y.; Shibasaki, M. *Tetrahedron: Asymmetry* **1998**, *9*, 3751.

(88) Sun, C.; Potter, B.; Morken, J. P. *J. Am. Chem. Soc.* **2014**, *136*, 6534.

(89) Endo, K.; Ohkubo, T.; Hirokami, M.; Shibata, T. *J. Am. Chem. Soc.* **2010**, *132*, 11033.

(90) Willis, M. C.; Powell, L. H. W.; Claverie, C. K.; Watson, S. J. *Angew. Chem., Int. Ed.* **2004**, *43*, 1249.

(91) Shi, B.-F.; Maugel, N.; Zhang, Y.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2008**, *47*, 4882.

(92) Wasa, M.; Engle, K. M.; Lin, D. W.; Yoo, E. J.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 19598.

(93) Xiao, K.-J.; Lin, D. W.; Miura, M.; Zhu, R.-Y.; Gong, W.; Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2014**, *136*, 8138.

1.7