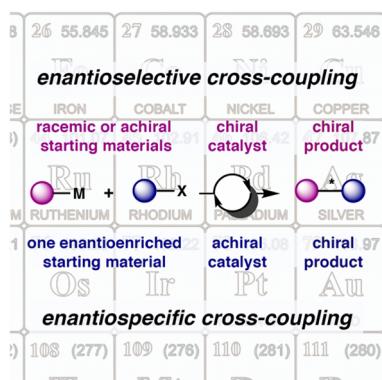


Enantioselective and Enantiospecific Transition-Metal-Catalyzed Cross-Coupling Reactions of Organometallic Reagents To Construct C–C Bonds

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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 orchestrate a series of chemical reactions to prepare and functionalize a carbon framework. The advent of transition-metal catalysis has provided chemists with

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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 methods was 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.

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 pseudohalide, which in this review includes alcohols, amines, and their derivatives) and an organometallic reagent, mediated by a transition-metal catalyst.

This review will focus on 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. These reactions can be organized into two general categories.

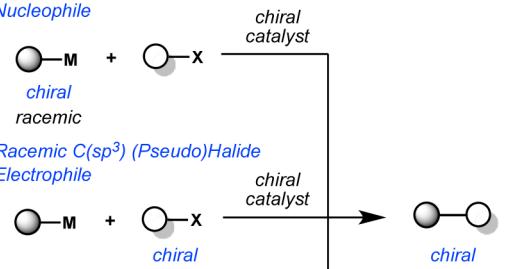
The first group comprises *enantioselective* transition-metal-catalyzed cross-coupling reactions, which we define as *reactions in which there is selective formation of one enantiomer over the other as defined by a nonracemic chiral metal catalyst*. There are several different types of enantioselective cross-coupling reactions: those in which (a) racemic, C(sp³) organometallic reagents are stereoconvergently coupled to organic electrophiles, (b) racemic, C(sp³) organic electrophiles are stereoconvergently coupled to organometallic reagents, (c) achiral organic electrophiles are coupled to chiral organometallic reagents to produce chiral, nonracemic products, and (d) a prochiral starting material (either the organic electrophile or organometallic reagent) is desymmetrized. These reactions are schematically represented in Figure 1.

The second group comprises *enantiospecific* 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.

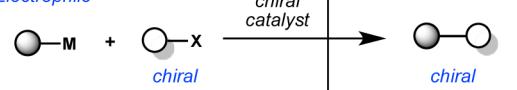
This review will encompass enantioselective and enantiospecific transition-metal-catalyzed cross-coupling reactions of organic electrophiles and organometallic reagents, covering the literature published through the end of the year 2014. Carbon–carbon bond forming reactions that provide products with centro, axial, and planar chirality will be discussed. Diastereoselective reactions, in which an existing stereocenter in the substrate controls the formation of a second chiral center in the product, will not be evaluated. Correspondingly, the discussion of stereospecific reactions will be limited to substrates bearing only a single stereogenic center. Processes involving coupling reactions of isolated alkenes, α,β -unsaturated carbonyl compounds, or isolated alkynes will not be discussed here, including asymmetric Heck¹ and oxidative Heck² reactions, conjugate addition reactions, and asymmetric ring-opening reactions of oxabicyclic compounds.³ Stoichiometric transition-metal-mediated reactions will also not be covered. Although allylic substitution reactions using enolates and

Enantioselective Cross-Coupling

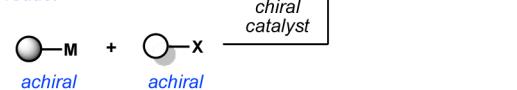
1. Racemic C(sp³) Organometallic Nucleophile



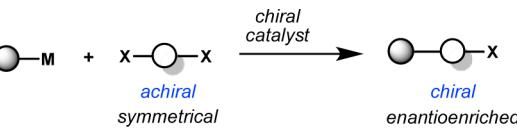
2. Racemic C(sp³) (Pseudo)Halide Electrophile



3. Achiral Reagents Produce a Chiral Product

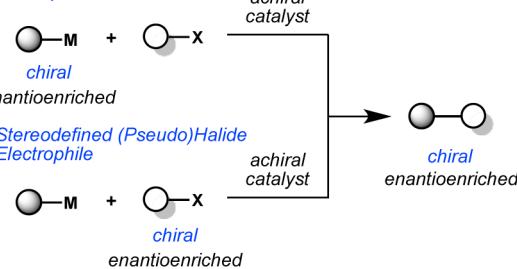


4. Desymmetrization of a Prochiral Starting Material



Enantiospecific Cross-Coupling

1. Stereodefined Organometallic Nucleophile



2. Stereodefined (Pseudo)Halide Electrophile

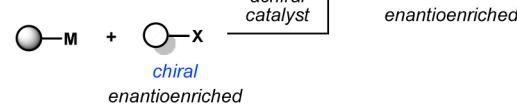


Figure 1. Strategies for enantiocontrolled cross-coupling.

related soft nucleophiles are beyond the scope of this review, transition-metal-catalyzed allylic substitution reactions using organometallic reagents will be discussed. Cu-catalyzed asymmetric allylic substitution reactions prior to 2008 have been well-reviewed elsewhere and will not be included here.^{4–6}

2. ENANTIOSELECTIVE TRANSITION-METAL-CATALYZED ALKYL CROSS-COUPLING REACTIONS

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*-alkylmetallic reagents are typically slower than their *n*-alkyl or C(sp²)-hybridized counterparts to undergo transmetalation.⁷ Similarly, *sec*-alkyl electrophiles are frequently slow to undergo oxidative addition to Pd.⁸ Moreover, in either case, the resulting *sec*-alkyl transition-metal complexes can suffer from rapid, nonproductive 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, that control and influence the efficiency of these elementary steps. 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.

2.1. Reactions of Secondary Alkylmetallic Reagents

Early efforts to develop enantioselective transition-metal-catalyzed alkyl cross-coupling reactions focused primarily on the use of configurationally labile *sec*-alkylmetallic 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.^{9–11} For example, *sec*-alkylmagnesium reagents have been shown to racemize above -10°C , whereas the corresponding *sec*-alkylboron reagents are configurationally stable indefinitely at room temperature.¹² In principle, fast equilibration between the two enantiomers of a *sec*-alkylmetallic 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 2).

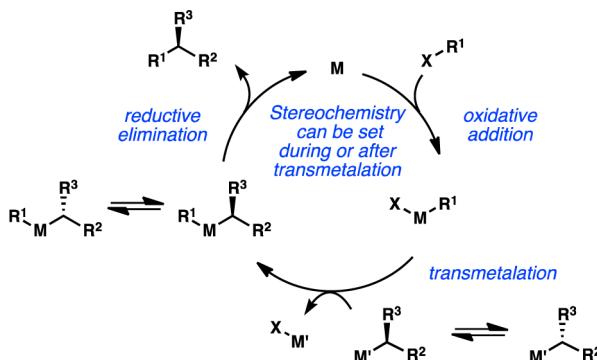


Figure 2. Stereochemical outcome of cross-coupling with secondary nucleophiles.

Enantioselective reactions of configurationally stable *sec*-alkylmetallic 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 stereoab ablative mechanism, in which the initial configuration of the starting material is destroyed and then reset by the chiral catalyst during the reaction.

2.1.1. Organomagnesium Reagents. In 1972 Corriu and Kumada independently reported the Ni-catalyzed cross-coupling between alkylmagnesium halides and aryl or vinyl halides;^{13–15} shortly thereafter the first studies aimed at utilizing chiral transition-metal complexes to catalyze these reactions enantioselectively were reported.¹⁶ In 1973 and 1974, respectively, Consiglio and Kumada independently reported that the complex generated from nickel 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 3).^{17,18} These results were an important proof of concept for the area of enantioselective cross-coupling; however, because low yields of product were

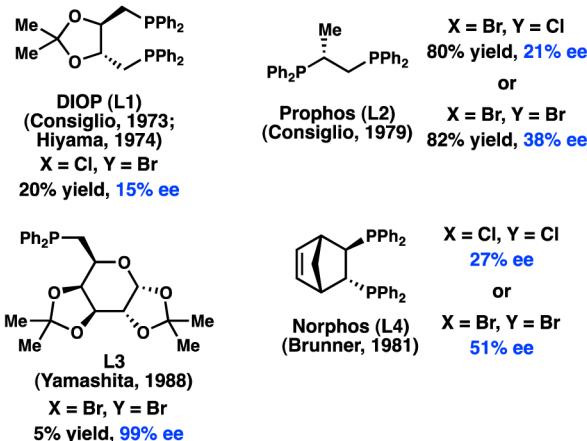
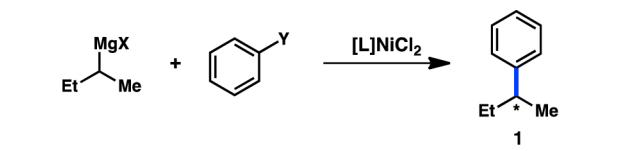
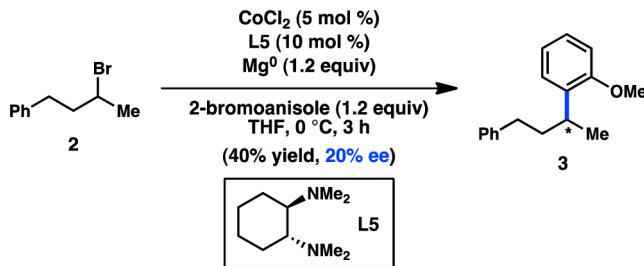


Figure 3. Stereoconvergent arylation of ${}^3\text{Bu}$ Grignard reagents.

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**.¹⁹ The identity of the halogen on both the organic halide and the organometallic reagent significantly influenced the absolute configuration and the enantiomeric excess (ee) of **1**. Further improvements were observed when Norphos (L4) was employed as the chiral ligand, providing **1** in 50% ee.^{20,21} A carbohydrate-derived chiral ligand (L3) was also reported to deliver **1** in good ee, although with poor yields.²²

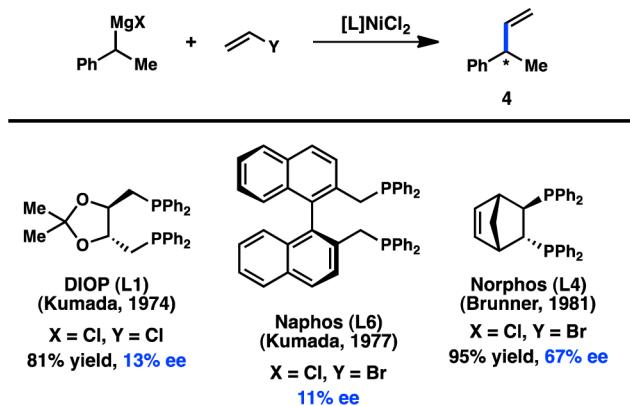
In 2009, Jacobi von Wangenin and co-workers reported the in situ generation of a secondary Grignard reagent that can subsequently undergo a Co-catalyzed asymmetric cross-coupling with promising enantioinduction (Scheme 1).²³

Scheme 1. Stereoselective Coupling of a Grignard Reagent Prepared in Situ



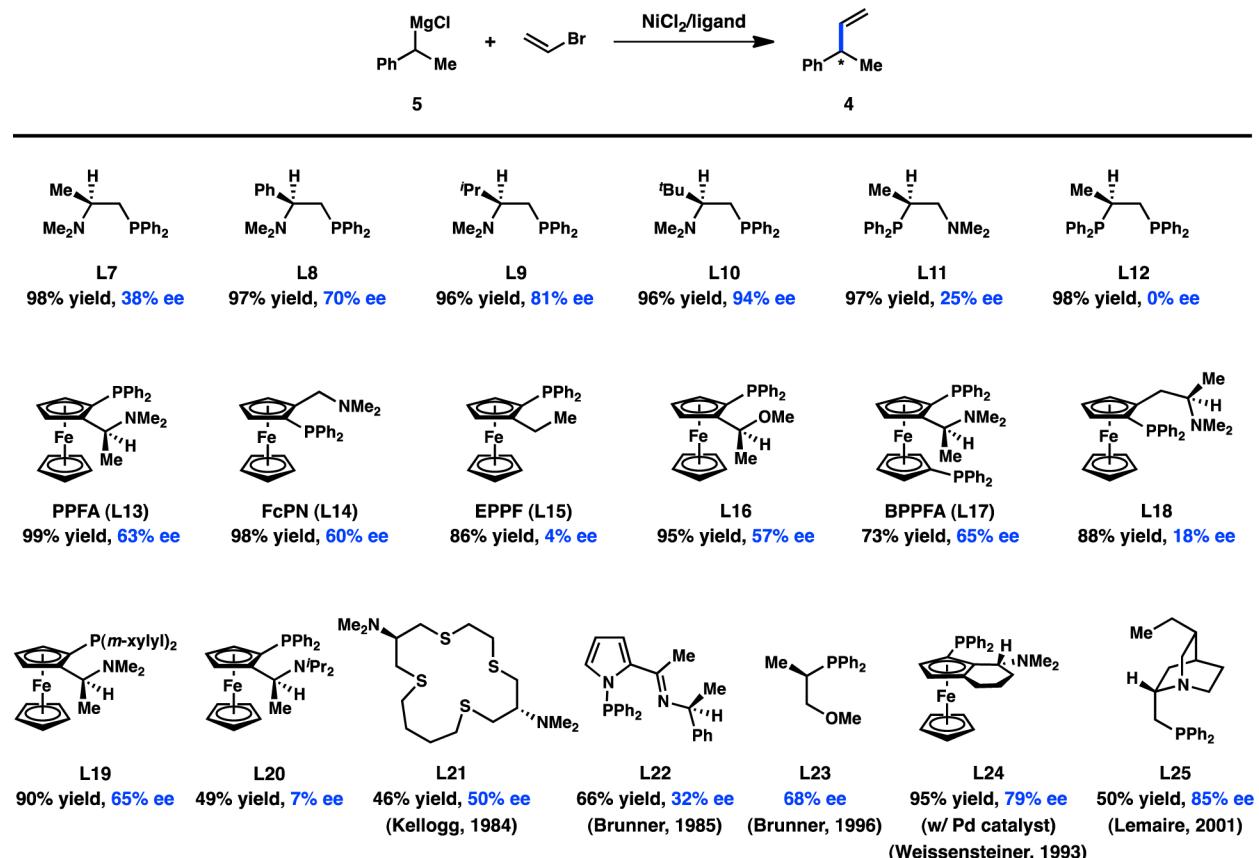
Additional ligand development and expansion of the substrate scope are imperative, but this initial result represents a solid advance for in situ Grignard formation in stereoconvergent cross-couplings.

Concurrent with their efforts to develop enantioselective cross-coupling reactions of *sec*-butyl Grignard reagents, Kumada and co-workers investigated the Ni-catalyzed enantioselective coupling between α -methylbenzyl Grignard reagents and vinyl halides (Figure 4). DIOP (L1) and the axially chiral Naphos (L6) ligand systems provided the product with low



enantioinduction.^{18,24} Following up on Kumada's studies, Brunner and co-workers reported that the use of Norphos (**L4**) in this reaction furnished **4** in 95% yield and 67% ee.²⁵

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 bisphosphine ligands, which delivered modest levels of enantioinduction, later efforts turned to chiral P,N ligands. Kumada, Hayashi, and co-workers 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 5).^{26–28}



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**). 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 bisphosphine **L12** provided no enantioinduction, suggesting a critical role for the amino group. A proposed catalytic cycle for this reaction is shown in Figure 6, which

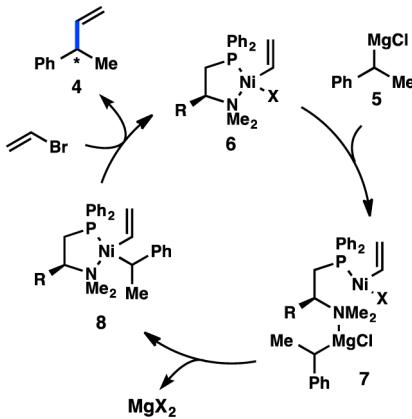


Figure 6. Proposed catalytic cycle for the enantioselective coupling of α -methylbenzyl Grignard reagents.

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.²⁹

Elaborating on this concept, Kellogg and co-workers investigated the use of (β -aminoalkyl)phosphine ligands bearing pendant heteroatoms, such as those derived from lysine or methionine.^{30,31} The authors reported a reversal of the stereochemical outcome in the presence of exogenous zinc halide salts (Figure 7). Control experiments using pregenerated

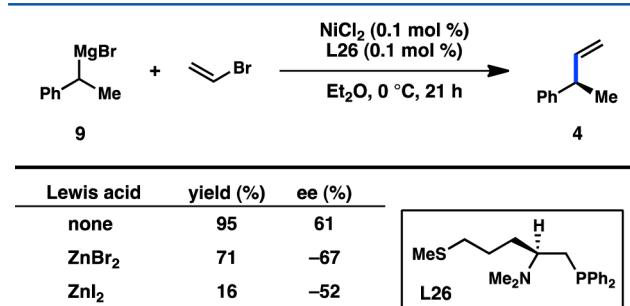


Figure 7. Addition of exogenous zinc halide salts reverses the sense of enantioinduction when sulfur-containing ligand **L26** is used.

(α -methylbenzyl)zinc bromide did not support the intermediacy of an organozinc species; instead it is possible that coordination between the Lewis acidic zinc halide and the side chain heteroatom could alter or disrupt the ability of the amino group to direct the transmetalation event.

The importance of an amino directing group on the chiral ligand was also reported by Kumada, Hayashi, and co-workers, during their investigations of ferrocenylphosphines in the Ni-catalyzed coupling between α -methylbenzyl Grignard reagent **5** and vinyl bromide (Figure 5). These bidentate P,N ligands possess both centrochirality at carbon and planar chirality. The ligand PPFA (**L13**) furnished **4** in an excellent 99% yield and 63% ee.^{32–35} The ee of the product was determined to remain roughly constant over the course of the reaction.³⁶ A structure–activity relationship study revealed that FcPN (**L14**), 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 precoordination as proposed in Figure 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**), whereas changing the steric environment of the phosphine does not significantly perturb the selectivity (see **L19**). Homologated ligand **L18** delivers **4** in poor ee.³⁷ Pd catalysts were also investigated and were shown to give results comparable to those of Ni (Figure 8).³⁴

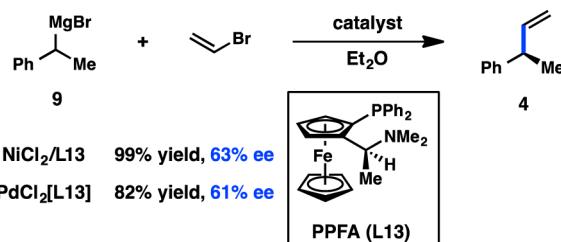


Figure 8. Use of the P–N ligand PPFA provides similar results in both Ni- and Pd-catalyzed transformations.

Several other ligand families have been developed for the enantioselective preparation of **4** (Figure 5). Catalysts generated from macrocyclic sulfides (**L21**) and nickel salts have been shown to impart moderate enantioselectivity, possibly through a simple kinetic resolution.^{38,39} The use of pyrrole-containing P,N ligand **L22** or phosphine **L23** delivers **4** in 32% and 68% ee, respectively, under Ni catalysis.^{40,41} Using Pd catalysis, the P,N ligand **L24**, containing both planar and centrochirality, gives improved results with respect to PPFA (**L13**).⁴² High ee can also be achieved with phosphine–quincoridine **L25**.⁴³

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 9).^{34,44–46} Although the yield could be improved using the

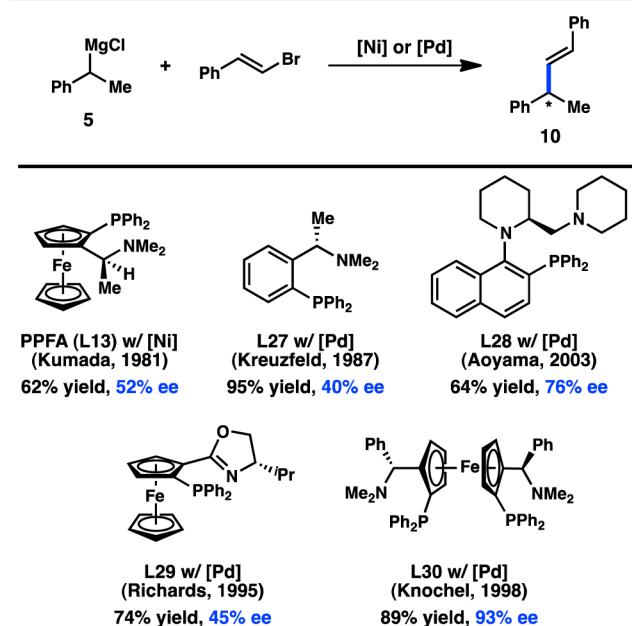


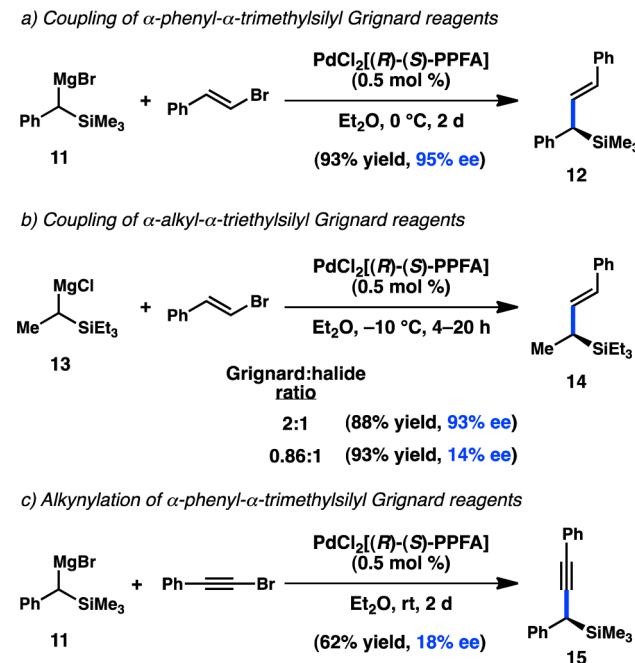
Figure 9. Asymmetric Kumada–Corriu cross-coupling of bromostyrene.

simpler aminophosphine **L27**, the ee of **10** decreased.^{47,48} **L28**, designed to induce axial chirality upon coordination to a transition metal, was able to induce 76% ee for **10**.^{49,50} Moderate enantioselectivity could also be attained with phosphine–oxazoline ligand **L29**.^{51,52} Knochel and co-workers have reported *C*₂-symmetric ferrocenylphosphine **L30** as

capable of delivering excellent ee for the coupling of bromostyrene, although the reaction scope is still limited.⁵³

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, versatile reagents for the construction of C–C bonds. In initial studies, Kumada, Hayashi, and co-workers reported that Ni catalysts delivered poor yields of the desired allylsilane. However, the chiral PdCl₂[PPFA] complex furnished **12** in 93% yield and 95% ee (Scheme 2a).^{54,55} (E)-Vinyl bromides were found to provide

Scheme 2. Diphosphine Ligands in the Coupling of α -Silyl Grignard Reagents

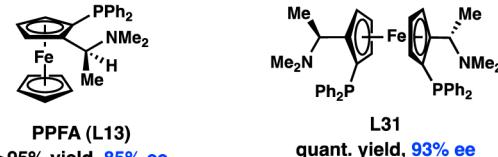
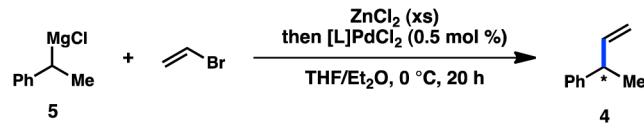


higher selectivities than the corresponding (*Z*)-substrates, and the enantioselectivity was independent of the ratio of Grignard reagent to vinyl bromide. In contrast, the coupling of alkyl-substituted Grignard **13** proceeded in 93% ee when excess organomagnesium reagent was employed, but the ee fell precipitously when Grignard **13** was used as the limiting reagent (Scheme 2b). 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 nonbenzylic Grignard reagents.⁵⁶ Lastly, an ee of 18% could be achieved in the alkynylation of **11** in the presence of PdCl₂[PPFA] (Scheme 2c).^{55,57}

2.1.2. Organozinc Reagents. The pioneering studies of enantioselective transition-metal-catalyzed alkyl cross-coupling reactions were initially performed using Ni catalysts and organomagnesium reagents—species expected to exhibit configurational lability (see section 2.1.1). 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 co-workers reporting the first examples in 1983.⁵⁸ Preliminary studies were carried out on the coupling of the organozinc chloride prepared from transmetalation of **5** with ZnCl₂,

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 10a). Significantly, when the

a) Cross-coupling of vinyl electrophiles



b) Cross-coupling of acyl electrophiles

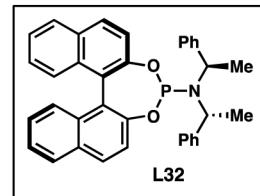
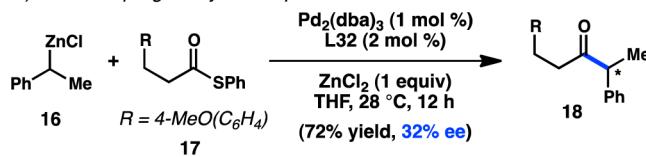


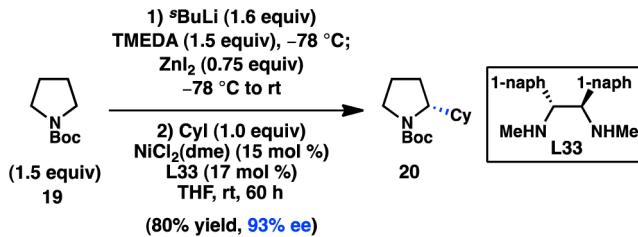
Figure 10. Enantioselective alkyl Negishi-type cross-couplings.

organometallic was prepared by direct insertion of Zn⁰ into the organic chloride, the same enantioselectivity was achieved, albeit with a lower yield. Such an outcome implicates RZnCl as the transmetalating agent, rather than ZnCl₂ behaving as a Lewis acid that can otherwise affect the transformation.⁵⁹ 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.⁵⁹ Despite a growing interest in the enantioselective cross-coupling reactions of organozinc reagents over the past three decades, successful efforts to expand further upon the enantioselective alkyl Negishi cross-coupling have been limited. Recently, Reisman and co-workers reported the Pd-catalyzed coupling between thioester **17** and organozinc **16** to form ketone **18** using chiral phosphoramidite **L32** (Figure 10b).⁶⁰ Although 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.

In a seminal 2013 report, Fu reinvestigated the Negishi cross-coupling of α -zincated *N*-Boc-pyrrolidine, which Campos and co-workers had previously shown can undergo stereospecific Pd-catalyzed cross-coupling to deliver enantioenriched α -arylpiperidine products (see section 3.1.5).⁶¹ 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 3).⁶² Mechanistic studies have determined that this stereoconvergence does not arise from a series of β -hydride elimination/alkene insertion processes of the organometallic reagent.

Scheme 3. Enantioselective Functionalization of Pyrrolidine



2.1.3. Organoboron Reagents. Trifluoroborate salts are often used in the Suzuki–Miyaura cross-coupling because of 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 co-workers hypothesized that transmetalation through a single-electron pathway could favor transfer of a $C(sp^3)$ -hybridized alkyl fragment via a stereoconvergent, radical process. 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 11).⁶³ 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.

2.2. 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 2000s, researchers began reinvestigating first-row transition metals for the cross-coupling of *sec*-alkyl halides and organometallic reagents.⁸ 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 (Figure 12). Alternatively, rapidly equilibrating mixtures of diastereomeric transition-metal complexes can result in preferential transmetalation or reductive elimination of one diastereomer over the other.

2.2.1. 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 co-workers in 1977, the result of a surprising alkyl group

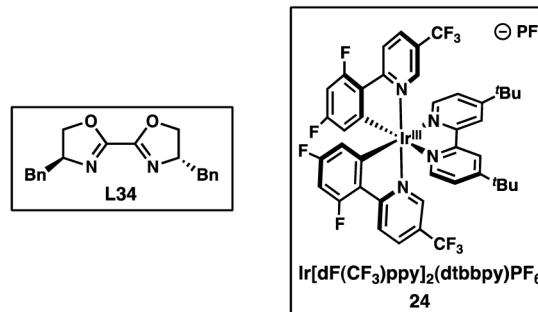
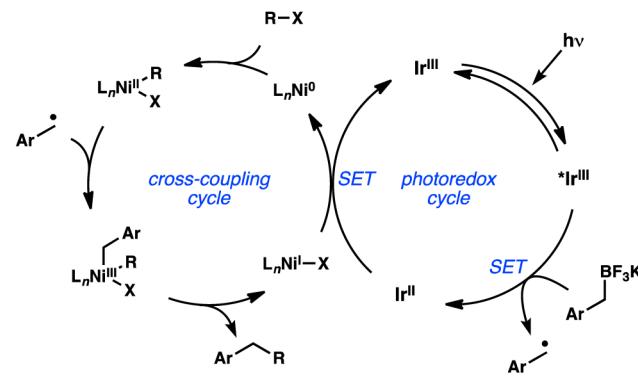
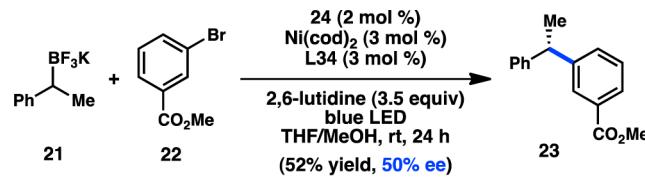


Figure 11. Dual catalysis approach to asymmetric cross-coupling.

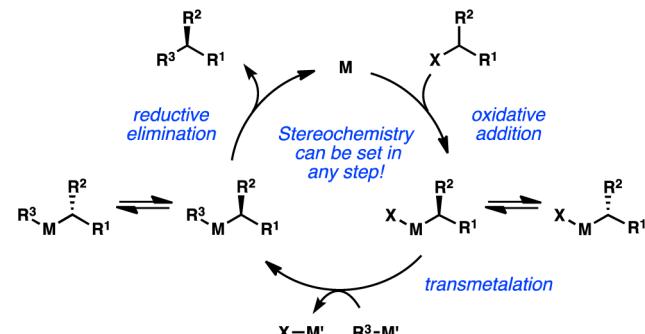
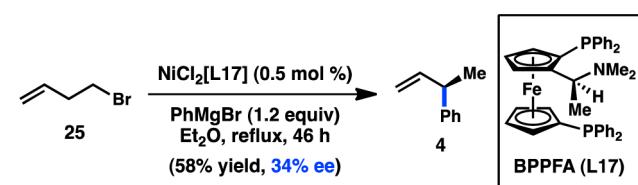


Figure 12. Stereochemical outcome of cross-coupling with secondary electrophiles.

isomerization observed during the coupling between homallylic halide **25** and $PhMgBr$ (Scheme 4).⁶⁴ In the presence of the chiral catalyst $NiCl_2[BPPFA]$, **4** was formed in 34% ee. Whereas the isomerization of secondary organometallic

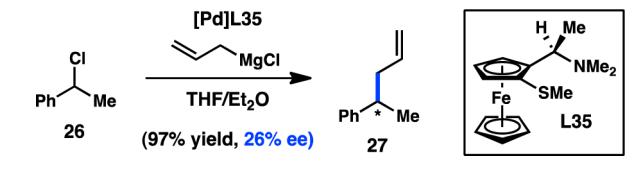
Scheme 4. Primary-to-Secondary Isomerization in Asymmetric Cross-Coupling



reagents to primary species is a well-known side reaction in cross-coupling chemistry, the inverse isomerization is much more rarely observed.⁶⁵ Although this preliminary result was not further developed by Kumada and co-workers, it presaged the explosion of asymmetric cross-couplings of *sec*-alkyl electrophiles that would emerge in the literature nearly two decades later.

In 1988, the Pd-catalyzed enantioselective cross-coupling between allylmagnesium chloride and racemic (1-chloroethyl)-benzene (**26**) was reported by Brubaker and co-workers. A variety of bidentate S,N and Se,N ligands bearing planar and centrochirality were prepared and used to generate chiral Pd complexes.^{66–68} The complex derived from L35 catalyzed the formation of **27** in a high yield and modest, yet promising ee (Scheme 5). Mechanistic studies to elucidate whether the

Scheme 5. Asymmetric C(sp³)–C(sp³) Kumada–Corriu Cross-Coupling



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.

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 co-workers. In this seminal report, the combination of NiCl₂(dme) and bidentate bis(oxazoline) ligand L36 or L37 was found to promote the coupling of α -halo ketones **28** and arylmagnesium halides to give α -aryl ketones (**29**) (Figure 13).⁶⁹ Notably, the reaction can be run at some of the lowest temperatures reported for the cross-coupling of alkyl electrophiles (-60°C);

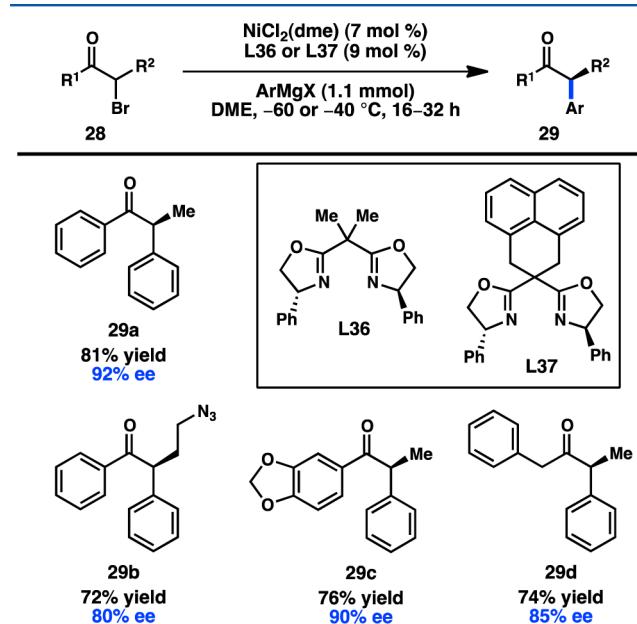
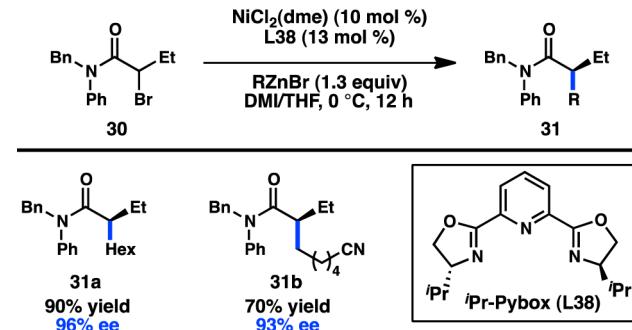


Figure 13. Stereoconvergent Kumada–Corriu coupling of α -halo ketones.

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.⁷⁰

2.2.2. 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 14a).⁷¹ The

a) Negishi coupling of α -bromo amides



b) Negishi coupling of benzyl halides

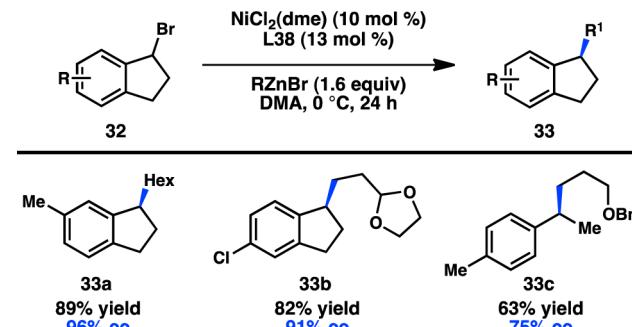


Figure 14. Seminal reports of stereoconvergent cross-couplings of secondary alkyl halides.

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 raceme, suggesting that the reaction does not proceed by a kinetic resolution. In a second example by Fu and co-workers, the Ni/L38-catalyzed coupling of 1-bromoindanes and alkyl halides produced chiral indane **33** in good yield and high ee (Figure 14b).⁷² 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 co-workers proposed that a Ni^I/Ni^{III} mechanism consisting of transmetalation/oxidative addition/reductive elimination is more energetically favorable than a Ni⁰/Ni^{II} mechanism.⁷³ The enantioselectivity of the reaction was also correlated to the difference in free energy between the two transition states for reductive elimination.

Despite 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 Ph₂Zn to furnish **35** in a high yield and ee (Figure 15a).⁷⁴ Because

a) Negishi cross-coupling of propargyl halides

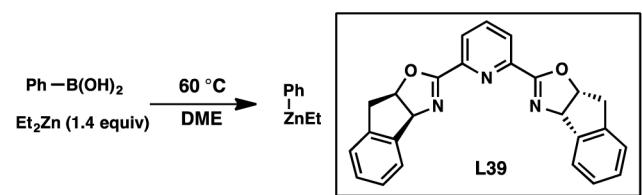
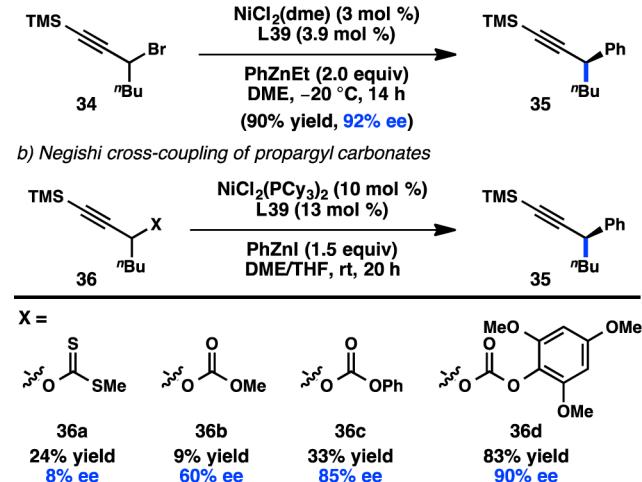


Figure 15. Stereoconvergent Negishi cross-coupling of propargylic electrophiles.

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 Et₂Zn, could react to provide comparable results. A recent mechanistic investigation supports a radical chain pathway in which a bimetallic oxidative addition to propargyl bromide **34** takes place.⁷⁵ In contrast to the stereospecific Pd-catalyzed coupling of propargyl halides, no allene formation, arising from S_N2' oxidative addition, was observed.⁷⁶

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 because of its propensity toward radical cleavage in Barton–McCombie-type transformations. However, these substrates performed poorly, producing **35** in low yield and ee (Figure 15b).⁷⁷ 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 co-workers 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 16).⁷⁸ Bioxazo-

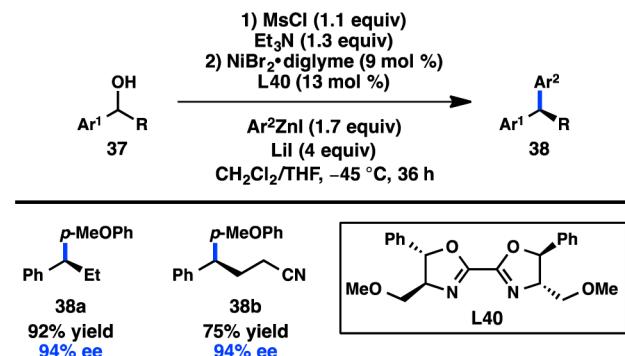


Figure 16. Stereoconvergent Negishi cross-coupling of benzylic alcohol derivatives.

line **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,^{79–85} this reaction provides a complementary approach.

A long-term objective in the area of enantioselective alkyl cross-coupling is to couple *sec*-alkyl electrophiles with *sec*-alkylmetallic 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 17).⁶⁵ Isoquinoline-

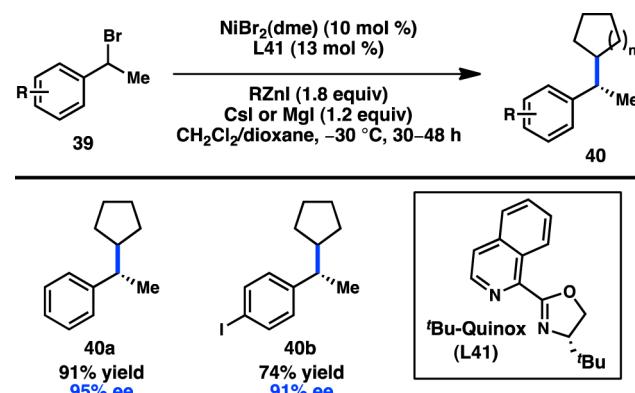


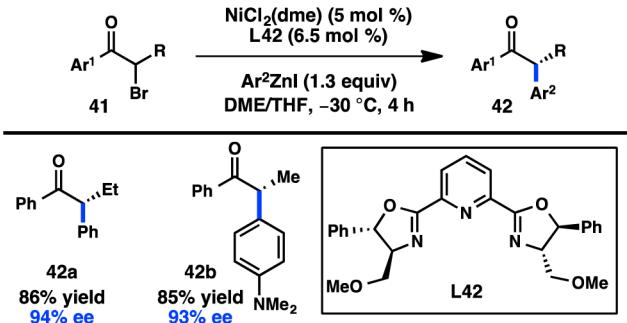
Figure 17. Enantioconvergent Negishi cross-coupling of secondary organozinc reagents.

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.

Prior to their disclosure of the enantioselective cross-coupling between *α*-bromo ketones and aryl Grignard reagents

(see Figure 13), the Fu laboratory developed a Ni/L42-catalyzed asymmetric cross-coupling of α -bromo ketones and arylzinc reagents (Figure 18a).⁷⁰ The low basicity of the

a) Negishi cross-coupling of α -bromo ketones



b) Negishi cross-coupling of α -fluoro- α -bromo ketones

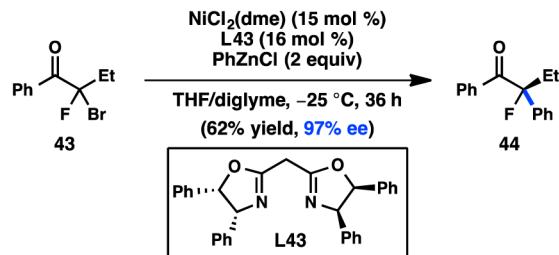


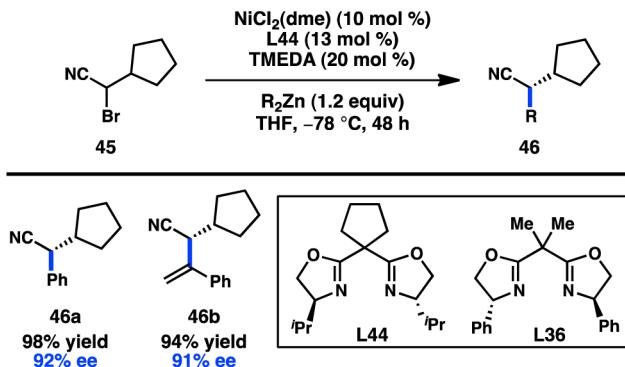
Figure 18. Asymmetric Negishi cross-coupling of α -halo ketones.

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.⁶⁹ A recent modification of the reaction conditions has permitted the use of α -halo- α -fluoro ketones, enabling the asymmetric formation of tertiary fluorides (Figure 18b).⁸⁶

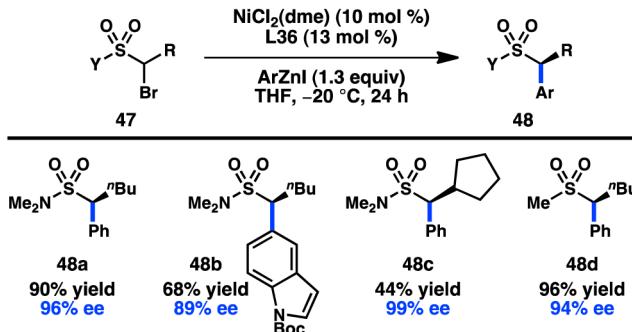
The Fu group has further expanded the scope of alkyl electrophiles amenable to Ni-catalyzed stereoconvergent Negishi cross-coupling to include α -bromo nitriles.⁸⁷ Coupling of α -bromo nitrile 45 and R₂Zn in the presence of NiCl₂(dme) and L44 at -78°C furnishes 46 in high yield and ee (Figure 19a).⁸⁸ 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.^{89,90} A more comprehensive mechanistic analysis is thus required to elucidate the mechanism of oxidative addition for the given transformation.

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 -halo sulfonamides (47) and arylzinc reagents (Figures 19b).⁹¹ Because 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

a) Negishi cross-coupling of α -halonitriles



b) Negishi cross-coupling of α -halosulfonamides and sulfones



c) Radical character of Negishi cross-coupling

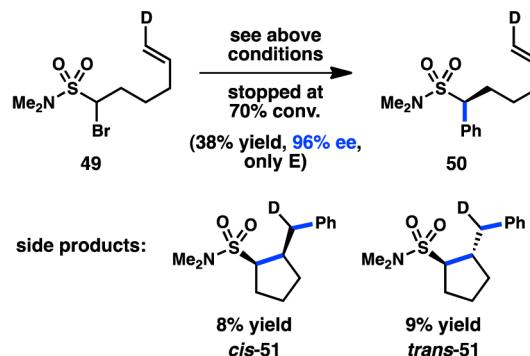


Figure 19. Other directing groups in asymmetric Ni-catalyzed Negishi cross-coupling.

50, cis-51, and trans-51; the ratio of uncyclized product to cyclized product was found to linearly increase 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.

2.2.3. 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,⁹² Fu and co-workers 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 20a).⁹³ The Ni catalyst was proposed to engage in a secondary interaction with the benzylic substituent on 52, allowing differentiation between the two alkyl groups of the starting material. Although a variety of homobenzylic bromides

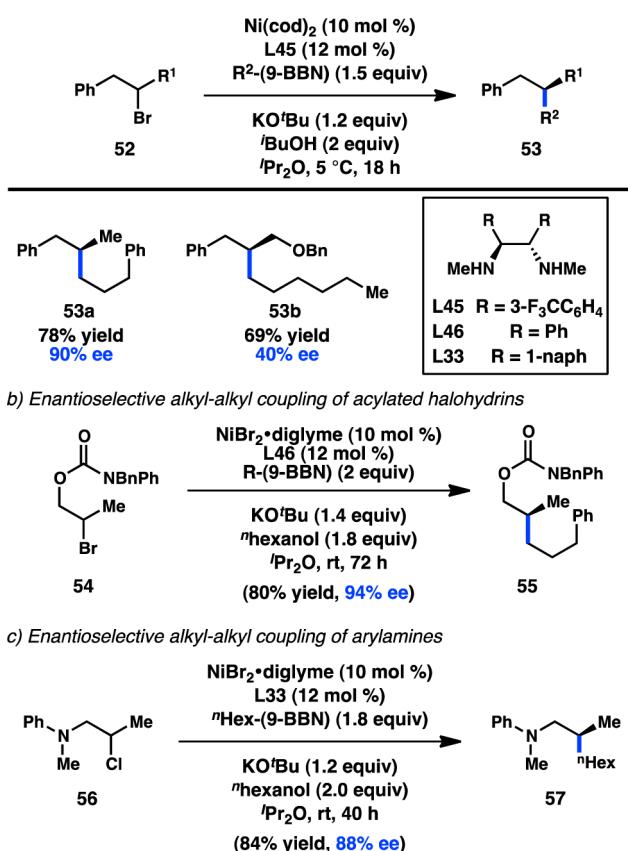
a) Enantioselective alkyl–alkyl Suzuki–Miyaura coupling

Figure 20. Enantioconvergent Ni-catalyzed alkyl–alkyl Suzuki–Miyaura coupling.

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. On the basis of 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 20b).⁹⁴ 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 20c).⁹⁵ The reaction was found to be directed by the nitrogen atom of the arylamine group.

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 -chloro amides were shown to undergo Suzuki–Miyaura cross-coupling with good asymmetric induction to form **58** and **59**, respectively (Figure 21).⁹⁶ Various halides proximal to protected amines, such as carbamates or sulfonamides, were also optimized toward enantioconvergent cross-coupling.^{97,98} After confirming that the oxygen of the sulfonamide was the key directing atom, Fu and co-workers examined sulfone-containing electrophiles and

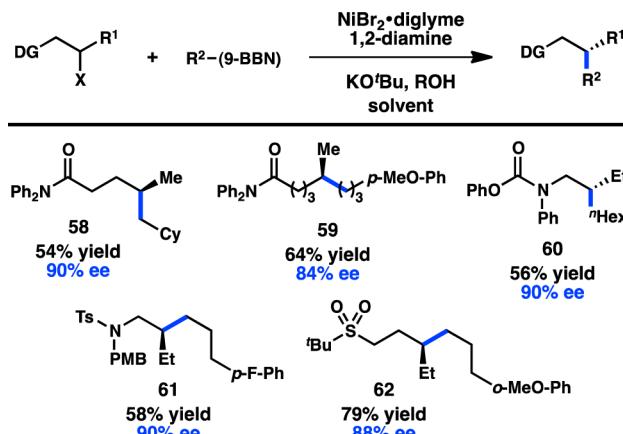


Figure 21. Examples of directing groups for the enantioconvergent Suzuki–Miyaura coupling.

reported that good enantioselectivity can still be maintained for these substrates.⁹⁷

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 -halo amides and arylboron reagents. After first investigating several different amides, it was found that the combination of $\text{NiBr}_2\text{-diglyme}$ and **L45** catalyzed the coupling between α -chloro amides (**63**) and Ar(9-BBN) reagents to furnish **64** in good yields and high ee's (Figure 22).⁹⁹ The identity of the amide substituents was

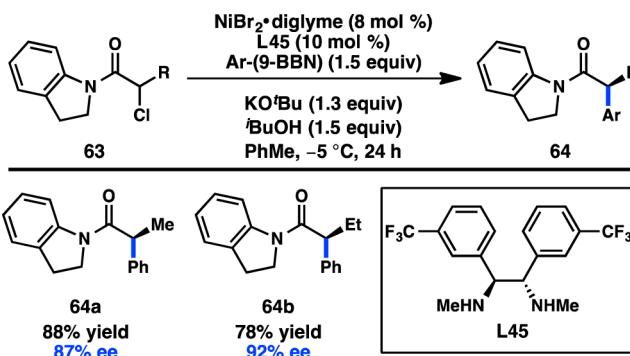


Figure 22. Asymmetric Suzuki–Miyaura coupling of α -halo amides.

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. The Fu laboratory has also shown that γ -halo amides can be arylated with Ph(9-BBN) in good ee but only moderate yield.⁹⁶

Building off their growing mechanistic understanding of Ni-catalyzed stereoconvergent alkyl cross-coupling reactions, Fu and co-workers have developed a cascade cyclization/cross-coupling to forge two C–C bonds in one step with both excellent ee and high diastereomeric ratio (dr) (Figure 23).¹⁰⁰ Key to this transformation was the insight that a “trans-metallation 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

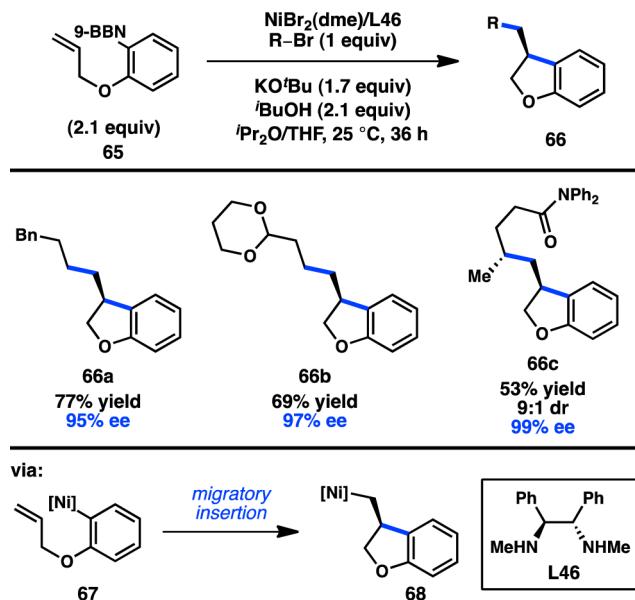


Figure 23. Asymmetric cascade cyclization/cross-coupling.

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 -halo amides (see Figure 21), a γ -halo amide was also used as an electrophile.⁹⁶ Remarkably, a single Ni complex controls the stereochemical outcome of two distinct C–C bond forming processes, providing product 66c in good yield, good dr, and excellent ee.

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 $\text{Ni}(\text{cod})_2$ catalyzes the addition of various arylboroxines to N,O -acetal 69, presumably via the intermediacy of quinolinium ion 71.¹⁰¹ When chiral phosphoramidite L47 is used as a supporting ligand, 70 is formed in 52% ee (Figure 24). A unique oxidative addition mechanism, in

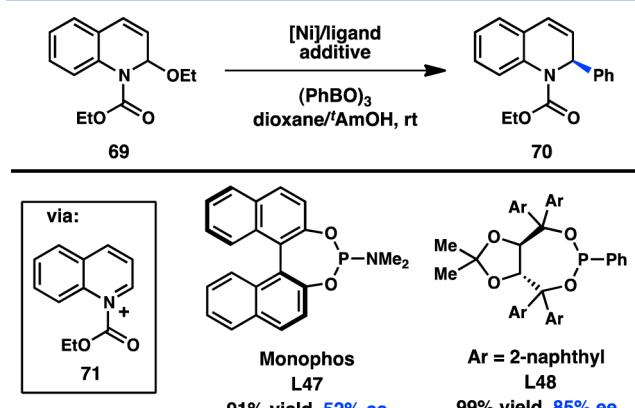


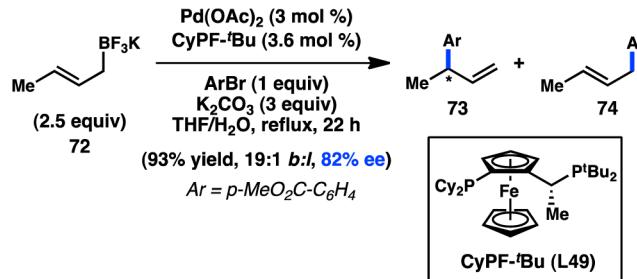
Figure 24. Asymmetric addition into quinolinium ions.

which the Lewis acidic boroxine promotes ionization of the leaving group and results in an $S_{\text{N}}1$ -type addition of Ni^0 , was discovered for this coupling.¹⁰² A wider survey of ligands showed that improved ee could be realized with TADDOL-based phosphonite L48.¹⁰³ In an extension of this work, the

addition of arylzinc reagents into pyridinium ions was subsequently reported.¹⁰⁴

In 2006, Yamamoto, Miyaura, and co-workers reported a novel strategy for the preparation of enantioenriched products from achiral starting material. Bidentate phosphine ligands were used to allow high γ -selectivity in the Pd-catalyzed asymmetric cross-coupling between allylic trifluoroborate salts and aryl bromides.¹⁰⁵ A subsequent evaluation of bulky, chiral ferrocenylphosphine ligands revealed that Josiphos-type ligand L49 could promote formation of 73 in 82% ee while still maintaining a high selectivity for γ -addition (Scheme 6).¹⁰⁶

Scheme 6. Enantioselective Cross-Coupling of Allylic Trifluoroborate Salts



DFT studies support an $S_{\text{E}}2'$ (open) transition state for transmetalation, whereas the corresponding closed transition state was of slightly higher energy;¹⁰⁷ transmetalation was also proposed to be the stereochemistry-determining step, which is followed by a fast reductive elimination to forge the desired product. Similar γ -selectivity was observed in the stereospecific couplings of allylic boronates¹⁰⁸ and silanes (see sections 3.1.1 and 3.1.3).^{109,110}

2.2.4. 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 $\text{Ni}/\text{L46}$ -catalyzed stereoconvergent coupling of α -bromo esters (75) and arylsiloxanes to furnish α -aryl esters in good yields and with high enantioinduction (Figure 25).¹¹¹ Although simple ethyl

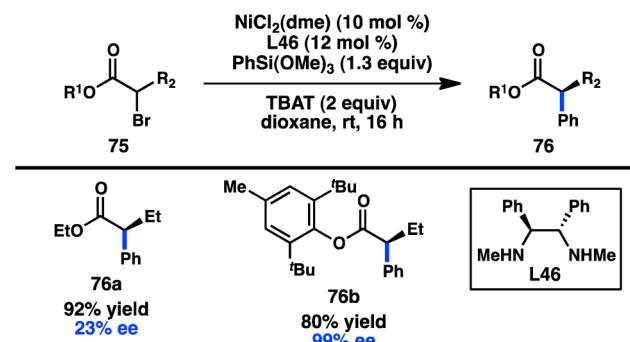
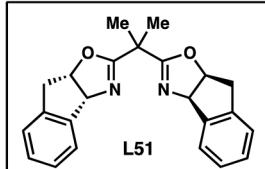
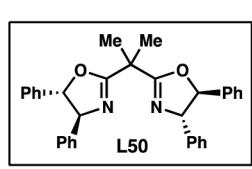
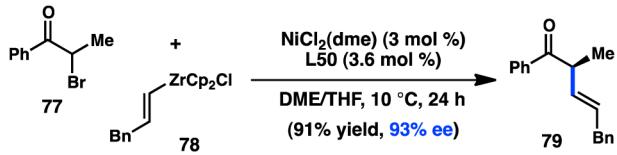


Figure 25. Stereoconvergent coupling of arylsilanes.

esters gave good yield but poor ee, the use of the BHT (butylated hydroxytoluene) 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 paper, the optimized reaction conditions were extended to the coupling of alkenylsilanes as well.

2.2.5. With Organozirconium Reagents. Alkenylzirconium complexes are attractive alkenylmetallic species for use in organic synthesis because they can be easily prepared from Schwartz's reagent and an alkyne. Although 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 alkenylmetallic species, with alkenylsilicon¹¹¹ and -zinc⁸⁸ reagents being the most promising. In 2010, Fu and co-workers published the Ni/L50-catalyzed asymmetric cross-coupling of alkenylzirconium reagents and α -bromo ketones, allowing access to **79** in 93% ee (Figure 26a).¹¹²

a) Coupling of α -bromoketones



b) Coupling of α -bromo sulfonamides

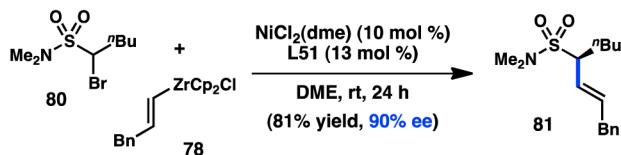


Figure 26. Stereoconvergent coupling of alkenylzirconium reagents.

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 -bromo sulfonamides in high yield and ee (Figure 26b).⁹¹

2.2.6. 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(sp³)- or C(sp²)-hybridized organometallic reagents,^{71,72} Sestelo, Sarandeses, and co-workers 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 27).¹¹³ Further work on the asymmetric coupling of C(sp) organometallic reagents has not been disclosed.

2.3. 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(sp³)-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 centrochir-

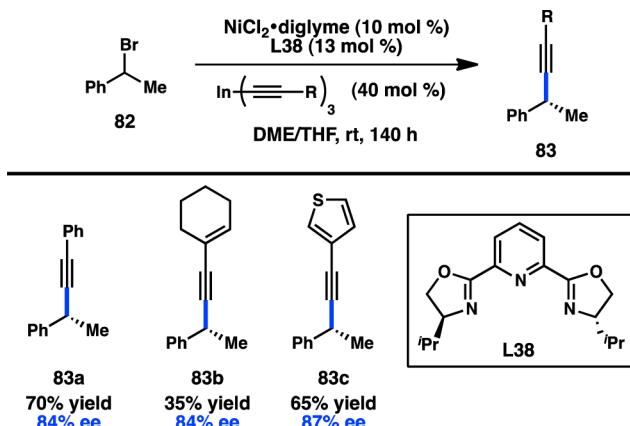
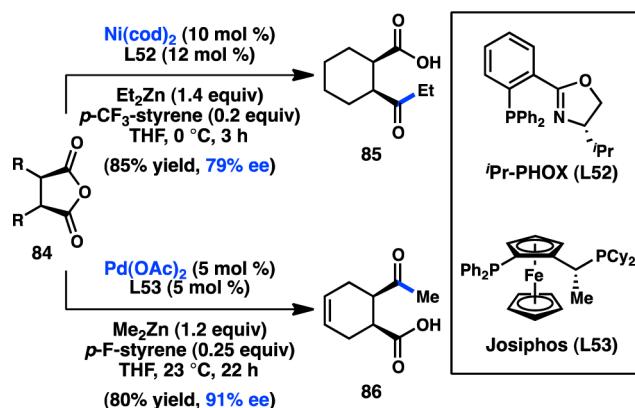


Figure 27. Alkynylmetallic reagents in stereoconvergent cross-coupling.

ality. Most of the work in this area has focused on the desymmetrization of *meso*-electrophiles; however, some researchers have investigated the desymmetrization of *meso*-bisorganometallic reagents or processes that involve desymmetrization by C–H functionalization.

2.3.1. Organozinc Reagents. The desymmetrization of *meso*-anhydrides has emerged as a robust method for the synthesis of enantiopure products.^{114–116} Rovis and co-workers¹¹⁷ have developed a monofunctionalization of cyclic anhydrides through a Ni-catalyzed Negishi coupling with Et₂Zn.¹¹⁸ 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.^{119,120} On the basis of 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 7).¹²¹

Scheme 7. Alkylative Desymmetrization of *meso*-Anhydrides



Surprisingly, omission of the *p*-(trifluoromethyl)styrene additive reduced the ee to 4%, prompting Rovis and co-workers to examine the mechanism of the reaction more closely. Kinetic analysis of the reaction revealed two competing mechanisms for the formation of **85** (Figure 28).¹²² 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 found to be oxidative

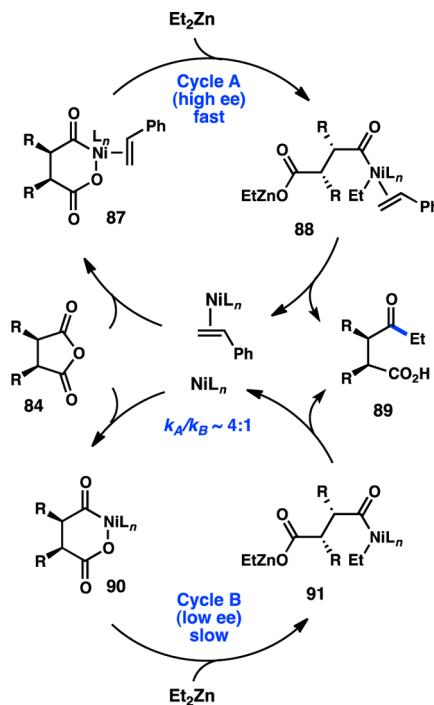


Figure 28. Competing mechanisms in the Ni-catalyzed desymmetrization of *meso*-anhydrides.

addition. However, in contrast to the initial proposal that *p*-(trifluoromethyl)styrene would accelerate reductive elimination, it was instead shown to increase the rate of oxidative addition. Although the origin of this rate enhancement is unclear, it was hypothesized that *p*-(trifluoromethyl)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 4 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 co-workers (Scheme 7). Treatment of **84** with Me_2Zn in the presence of $\text{Pd}(\text{OAc})_2$ and the bidentate phosphine Josiphos (**L53**) furnished **86** in 91% ee; the use of *p*-fluorostyrene as an additive was crucial to achieving the high level of enantioselectivity.¹²³

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 29).^{124–126} This reaction is proposed to proceed through a $\text{Rh}^{\text{I}}/\text{Rh}^{\text{III}}$ catalytic cycle, with transmetalation occurring 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.¹²⁷

Efforts by Rovis and co-workers to effect an alkylative desymmetrization of *meso*-anhydrides have been complemented by attempts to use arylzinc reagents in similar transformations.

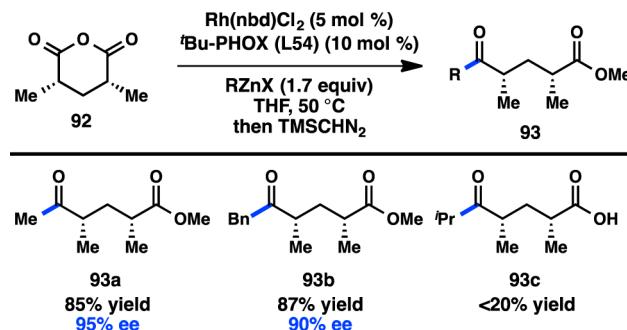
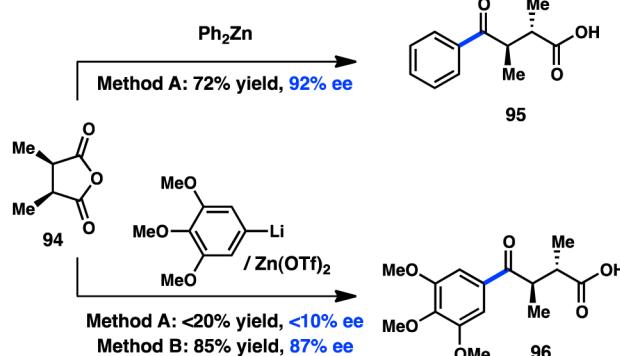


Figure 29. Rh-catalyzed desymmetrization of glutaric anhydrides.

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 30).¹²³ In contrast to Rovis's



A: $\text{Pd}(\text{OAc})_2$ (5 mol %), Josiphos (**L53**) (6 mol %), THF, 80 °C
B: $[\text{Rh}(\text{cod})\text{Cl}]_2$ (4 mol %), Taddol-PNMe₂ (**L55**) (8 mol %), DMF, 50 °C

Figure 30. Pd- and Rh-catalyzed desymmetrization with arylzinc reagents.

alkylation method, excess fluorostyrene is not necessary to achieve a high enantioinduction. Although 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 such as halides. After optimization toward a chiral phosphoramidite ligand, **96** could be furnished in 85% yield and 87% ee.^{125,128} 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.

2.3.2. Organoboron Reagents. In 1998, Shibasaki and co-workers reported a Pd-catalyzed intramolecular enantiotopic group-selective Suzuki–Miyaura coupling of alkylboranes (**97**) to prepare *exo*-methylenecyclopentanes, but the highest ee value obtained was 31% (Figure 31a).¹²⁹ More recently, Morken demonstrated that prochiral diboronate **99** can be cross-coupled with an aryl halide in the presence of $\text{Pd}(\text{OAc})_2$ and phosphoramidite **L56** to forge benzylic boronate **100** with good enantioinduction (Figure 31b).¹³⁰ Enantioenriched boronate **100** can undergo a subsequent stereospecific cross-

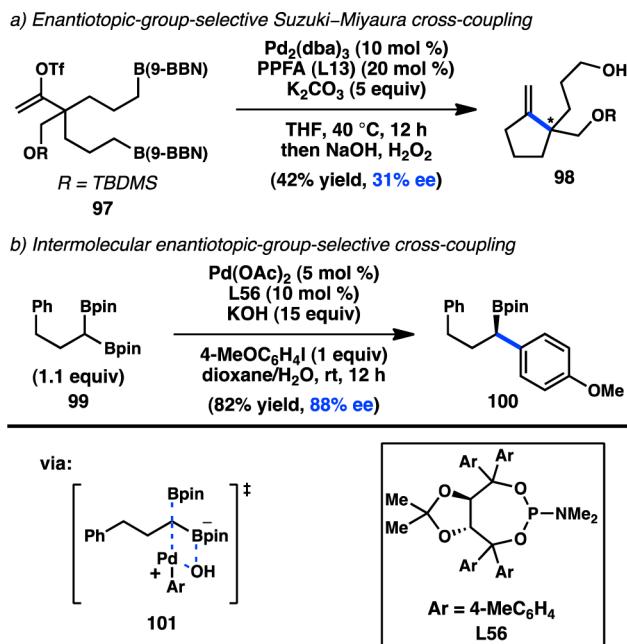
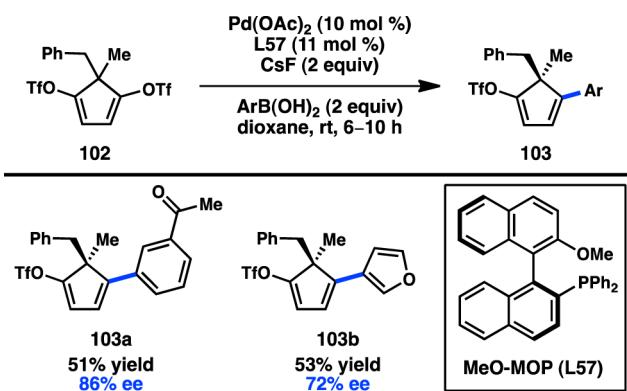


Figure 31. Enantiotopic-group-selective cross-coupling.

coupling to generate an enantioenriched diarylalkane.⁷⁹ Prior studies by Shibata and co-workers had demonstrated that geminal diboronic **99** is activated toward transmetalation and proposed that the “ate” complex of one boronate can coordinate to Pd and assist in an $S_{\mathrm{E}2}$ transmetalation of the second boronate.¹³¹ The resulting monoborionate **100** lacks this mode of activation, avoiding the formation of diarylated products.

In a distinct desymmetrization approach, Willis and co-workers reported the asymmetric Suzuki–Miyaura cross-coupling of *meso*-ditriflate **102**.¹³² The catalyst generated from Pd(OAc)₂ and chiral biarylylphosphine **L57** furnished monoarylated **103** bearing a stereodefined quaternary center (Figure 32). Even though the yield of the transformation was

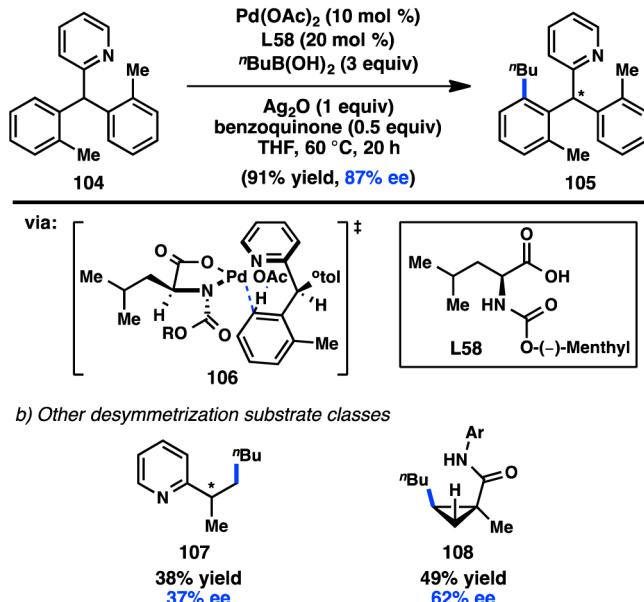
Figure 32. Enantioselective desymmetrization of a *meso*-ditriflate.

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.

Yu and co-workers reported the first enantioselective C–H activation/cross-coupling via a desymmetrization process in 2008. Prochiral pyridyldiarylmethane **104** was selected for these studies because of the relatively low temperatures required for C–H activation.¹³³ 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 33a). The N-

a) Desymmetrization by C–H activation



b) Other desymmetrization substrate classes

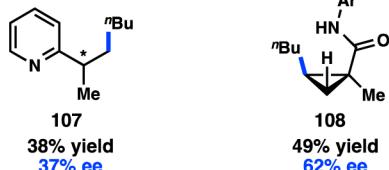


Figure 33. Desymmetrizing enantioselective C–H activation/cross-coupling with alkyl boronic acids.

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.¹³⁴

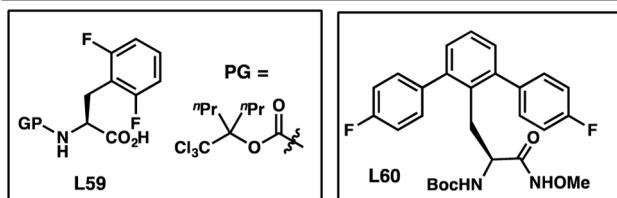
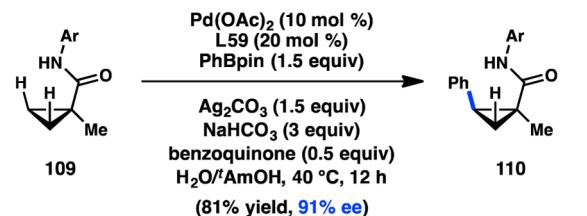
Yu and co-workers were subsequently able to expand this chemistry to the desymmetrization of cyclopropanes and cyclobutanes. After extensive re-engineering of the ligand, the combination of Pd(OAc)₂ and monoprotected amino acid **L59** was found to catalyze C–H arylation of cyclopropanamide **109** with phenylboronate ester to produce **110** in good yield and high ee (Scheme 8a).¹³⁴ 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 cyclobutanamide **111**. Using the more Lewis basic hydroxamic acid **L60**, **112** could be produced with a high level of enantioinduction (Scheme 8b).¹³⁵ A related ligand also enabled the desymmetrization of prochiral methyl groups in acyclic amides to forge β -arylated products in modest ee.¹³⁵

3. ENANTIOSPECIFIC TRANSITION-METAL-CATALYZED ALKYL CROSS-COUPLING REACTIONS

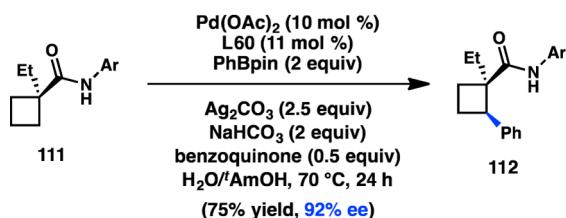
The considerations taken into account to invoke enantiospecific cross-coupling reactions are similar to those discussed for enantioselective C–C bond formation. Configurationally stable *sec*-alkylsilicon, -boron, and -tin species have received more attention than harder to access organometallic reagents derived from magnesium and zinc. In the transmetalation step, competition between open and closed transition states can

Scheme 8. C–H Activation of Strained Cycles

a) Desymmetrization of cyclopropanes with aryl boronates



b) Desymmetrization of cyclobutanes with aryl boronates



erode the ee of the final product. Following transmetalation, fast reductive elimination is needed to outcompete racemization pathways that would deliver products with reduced stereofidelity. With respect to secondary electrophiles, catalysts that undergo two-electron oxidative addition are more likely to proceed with high stereospecificity; retention or inversion can be influenced by the presence of coordinating groups proximal to the site of oxidative addition. Although Pd is the most studied transition metal for enantiospecific cross-coupling, Ni catalysis has recently gained popularity for its ability to cross-couple unconventional pseudohalide electrophiles.

3.1. Reactions of Secondary Alkylmetallic Reagents

3.1.1. Organosilicon Reagents. The first investigation of a transition-metal-catalyzed cross-coupling of an enantioenriched *sec*-alkylmetallic reagent was reported by Hiyama and co-workers in 1990 and focused on the coupling of C(sp³) organosilanes. The high configurational stability of organosilanes, coupled to the development of asymmetric hydro-silylation reactions in the 1980s, allowed ready access to the requisite enantioenriched organosilane starting materials.¹³⁶ Pd-catalyzed arylation of benzylic trifluorosilane 113 at 50 °C in THF produced 115 with nearly complete retention of configuration (Figure 34).¹³⁷ Alternatively, increasing the reaction temperature to 90 °C furnished *ent*-115, formed with inversion of configuration in moderate enantiospecificity (es). An analysis of solvent effects for the reaction showed that incorporating HMPA as a polar cosolvent also led to inversion of configuration but with reduced stereochemical fidelity. To explain the divergent stereochemical outcomes, the authors propose two competing modes of transmetalation. At lower temperatures, transmetalation is hypothesized to occur through a four-centered, S_E2(cyclic) transition state (116), resulting in retention of configuration. The transition state is organized by a critical fluoride bridge between Pd and a pentacoordinate silane. Treatment with a large excess of TBAF leads to

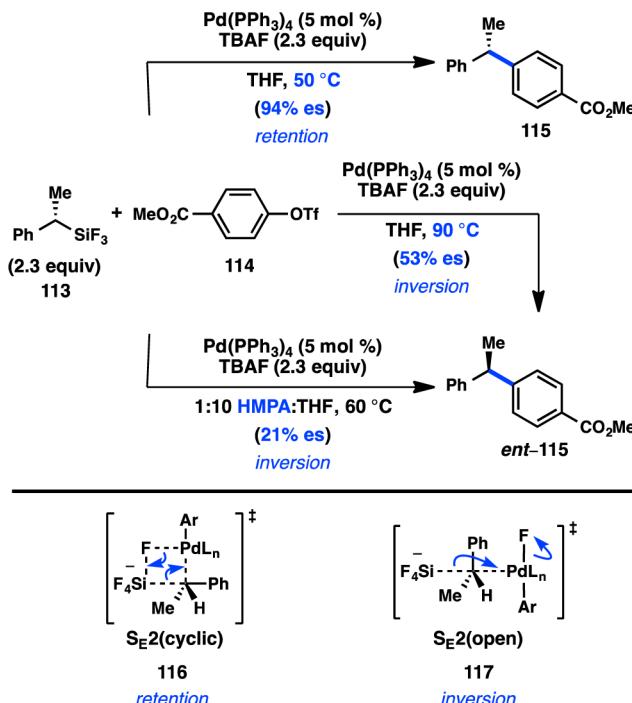


Figure 34. Stereochemical outcome of secondary silanes in the Hiyama cross-coupling.

inhibition of product formation, presumably because of the presence of a hexacoordinate silane incapable of accommodating transition state 116. Raising the reaction temperature is thought to facilitate cleavage of the fluoride bridge and accelerate transmetalation through an S_E2(open) transition state (117), leading to inversion of configuration via backside attack. Similarly, polar cosolvents such as HMPA can also disrupt the cyclic transition state and favor an S_E2(open) mechanism.

Following their studies of Pd-catalyzed enantiospecific cross-coupling reactions of benzyltrifluorosilanes, in 1994, Hiyama and co-workers reported the stereospecific coupling of enantioenriched allyltrifluorosilanes with aryl triflates (Figure 35).¹⁰⁹ Coupling of silane 118 and triflate 119 using Pd(PPh₃)₄ as the catalyst and CsF as a fluoride source furnished 120 with retention of configuration. However, the solvent polarity and the nature of the fluoride source determined the stereospecificity of the reaction. Replacing CsF with the nonmetallic fluoride source TASF delivered *ent*-120, the product of inversion. In addition, the use of DMF as a polar coordinating solvent provides *ent*-120 with inversion regardless of the fluoride source. As in the coupling of benzylic trifluorosilanes,¹³⁷ two competing models for transmetalation were proposed by Hiyama. In the presence of CsF, a fluoride bridge between Pd, Cs, and the trifluorosilane promotes syn S_E' transmetalation to Pd, leading to retention of configuration. Disruption of the fluoride bridge in polar, coordinating solvents, or by use of nonmetallic fluoride sources, would result in anti S_E' transmetalation to Pd, resulting in inversion of stereochemistry.

More recently, Denmark and co-workers extended Hiyama's work to more synthetically tractable allylic silanoate salts.¹¹⁰ High γ -selectivity in the Pd-catalyzed enantiospecific coupling of 123 with bromobenzene was achieved by using π -acidic diene L61 as the ligand, which is hypothesized to accelerate

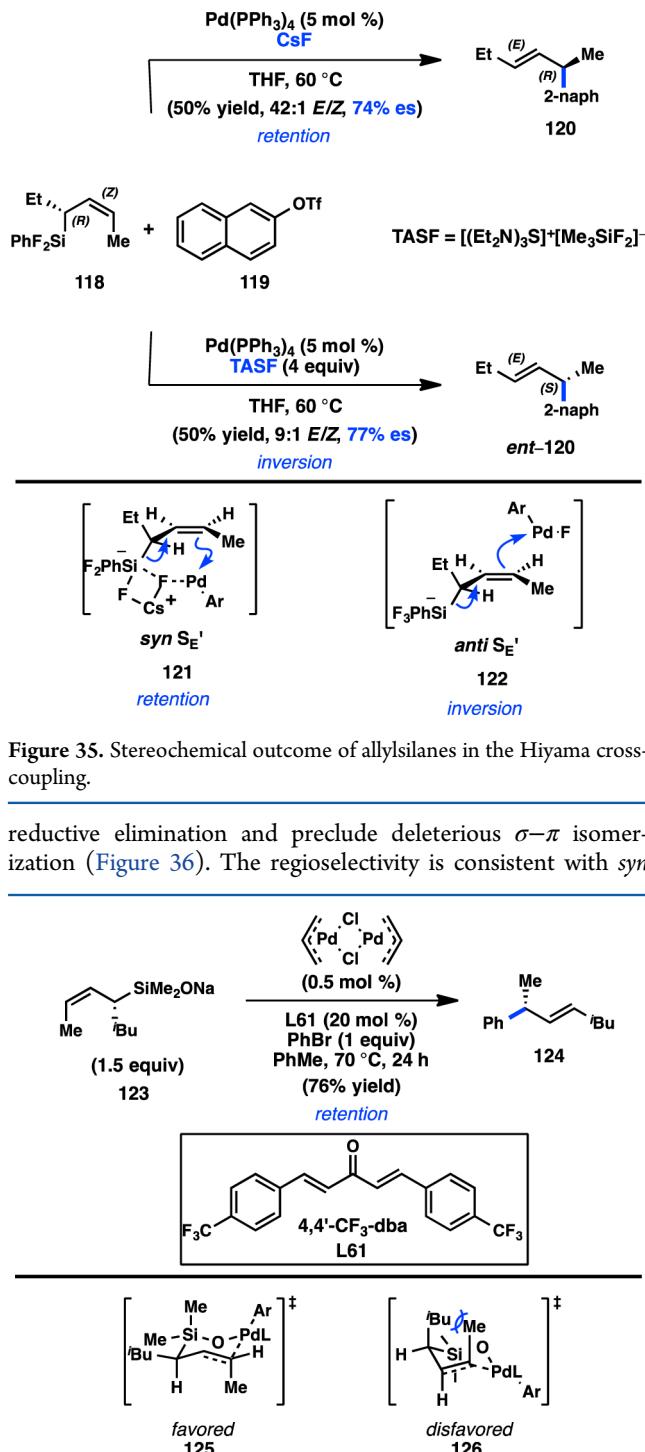
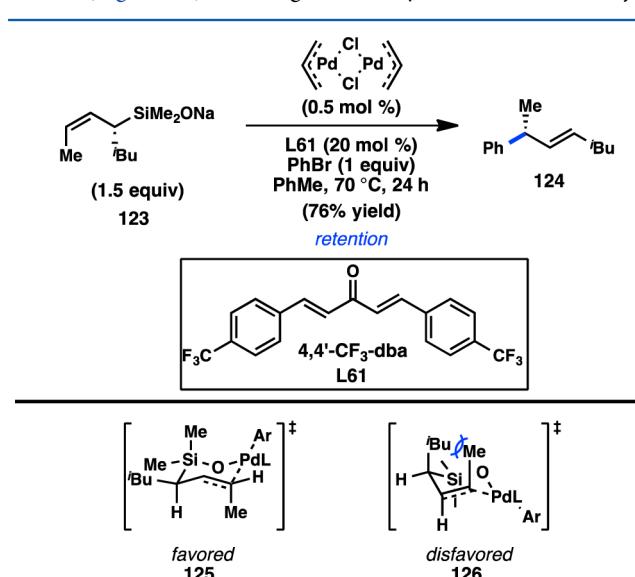


Figure 35. Stereochemical outcome of allylsilanes in the Hiyama cross-coupling.

reductive elimination and preclude deleterious $\sigma-\pi$ isomerization (Figure 36). The regioselectivity is consistent with *syn*



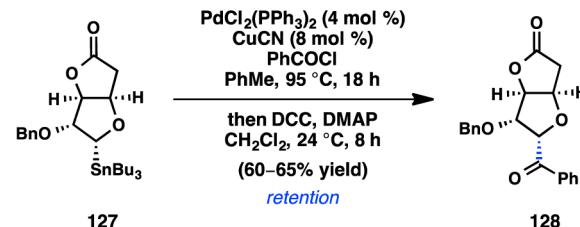
S_E' transmetalation via pseudochair conformation 125, in which the Si—O—Pd linkage directs addition of Pd to the γ -position. Favored transition state 125 places the *t*Bu group in a pseudoequatorial position, leading to retention of stereochemistry and formation of the (*E*)-alkene; transition state 126, which would furnish the (*Z*)-alkene, suffers from a destabilizing 1,3-diaxial interaction.

3.1.2. Organotin Reagents. The first study of an enantiospecific alkyl Stille cross-coupling to generate a tertiary stereogenic center was reported in 1993 by Falck and co-

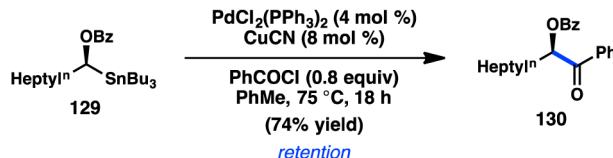
workers as part of their synthetic efforts toward the anticancer natural product (+)-goniofufurone. In a key step of the synthesis, enantiopure α -stannylated tetrahydrofuran 127 was coupled with benzoyl chloride in the presence of catalytic PdCl₂(PPh₃)₂ and CuCN to deliver 128 with retention of configuration (Scheme 9a). This result was in contrast to

Scheme 9. Seminal Stereospecific Stille Cross-Couplings

a) Total synthesis of (+)-goniofufurone



b) Exploration of α -heteroatom-substituted nucleophiles



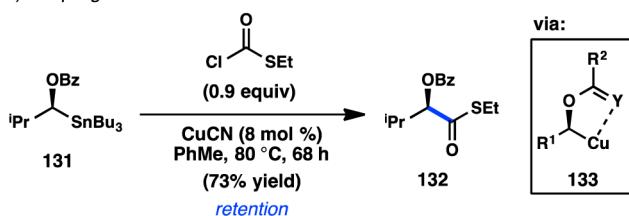
Stille's initial studies of organostannane transmetalation using ((*S*)-(*–*)-(α -deuteriobenzyl)tributyltin, which underwent transmetalation with inversion of configuration.¹³⁸ A follow-up investigation revealed that enantioenriched α -stannylated benzoate 129 also underwent Pd-catalyzed stereoretentive cross-coupling with benzoyl chloride (Scheme 9b).¹³⁹ An investigation of scope revealed that both aryl chlorides and alkanoyl chlorides bearing coordinating groups couple smoothly under the reaction conditions. A Cu-free reaction afforded the product in lower yield but with no erosion of stereochemistry. Coordinating groups have been demonstrated to accelerate the rate of transmetalation of alkylstannane reagents;¹⁴⁰ it is possible that the α -alkoxy substituent favors transmetalation through an S_E 2(cyclic) transition state.

Subsequently, Falck disclosed that use of Cu as the sole catalyst also provided good yields for the coupling of α -stannylated benzoate 131 with *S*-ethyl chlorothioformates (Scheme 10a).^{141,142} The resulting products exhibited retention of configuration. The reaction scope was studied using racemic Sn reagents bearing an array of α -heteroatom directing groups; good yields were obtained for reactive electrophiles such as allyl bromides and chloroformates, but lower yields were attained with aryl and vinyl halides. Sulfur substituents on either coupling partner were found to increase yields and reaction rates and could suggest the intermediacy of chelated organocopper species such as 133 during the catalytic cycle. Alkylation of 134, bearing a proximal thionocarbamate group, occurs in excellent yield and with retention of configuration (Scheme 10b).^{143,144} The reaction proceeds without any β -elimination of stannane 134.

In collaboration with Liebeskind and co-workers, Falck investigated the Cu-catalyzed cross-coupling of complex α -amino thioesters 136 with α -stannylated thionocarbamate 137 (Figure 37).¹⁴⁵ The formation of $\alpha,\alpha,\alpha'\alpha'$ -tetrasubstituted ketone 138 occurred in excellent yield and dr, with retention of configuration at the thionocarbamate-bearing stereocenter.

Scheme 10. Cu-Catalyzed Stereospecific Stille Cross-Coupling

a) Coupling of α -heteroatom-substituted stannanes



b) Coupling of α -stannyli thionocarbamates

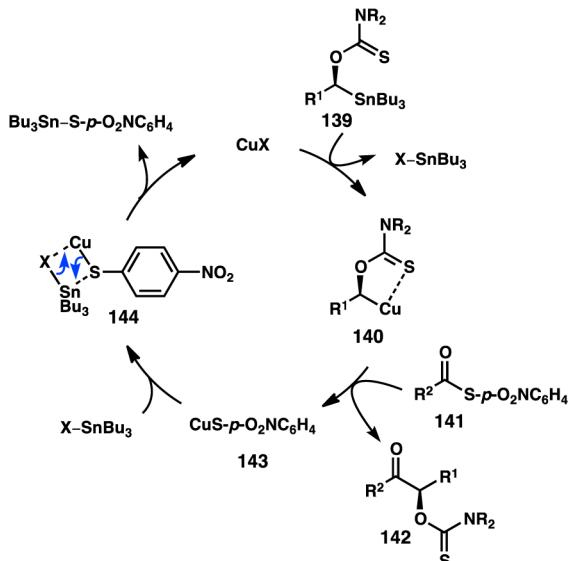
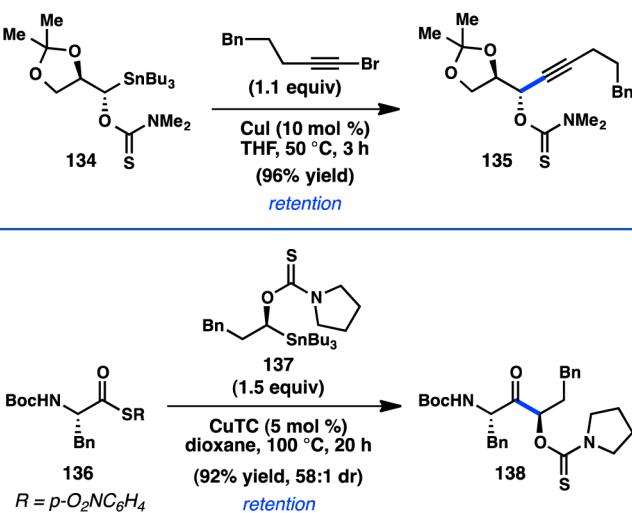


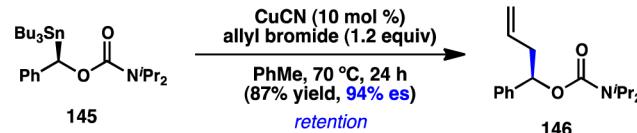
Figure 37. Cu-catalyzed cross-coupling of α -amino thioesters.

Surprisingly, the reaction proceeded efficiently with catalytic CuTC, despite the very strong Cu–S bond that was expected to form following oxidative addition. The authors propose a mechanism in which Sn/Cu transmetalation takes place to provide stabilized organocopper intermediate 140. An oxidative addition/reductive elimination sequence furnishes coupled product 142 and a copper thiolate complex (143). Typically, copper thiolates of this type are catalytically unreactive; however, in this case a second transmetalation between 144 and SnBu₃X forms a tin thiolate and regenerates the active

copper catalyst. The second transmetalation is presumably driven by the strength of the Sn–S bond (464 kJ mol⁻¹) relative to the Cu–S bond (274 kJ mol⁻¹).

Hoppe and co-workers have developed an enantioselective preparation of α -carbamoyl benzylstannanes (e.g., 145) and explored the use of these nucleophiles in Cu-catalyzed stereospecific allylic alkylations. Using CuCN as the catalyst, coupling of 145 and allyl bromide proceeds in good yield and with retention of configuration (Scheme 11).¹⁴² Good levels of

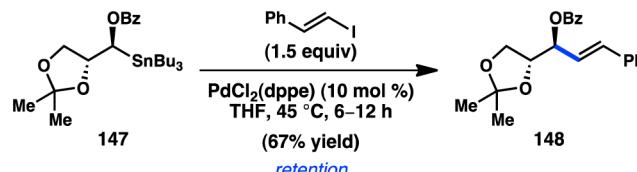
Scheme 11. Stereospecific Substitution of α -Carbamoyl Benzylstannanes



es were observed. The carbamate group was postulated to stabilize the organocopper intermediate through coordination, promoting configurational stability at the stereogenic C–Cu bond. Substituted allylic electrophiles reacted with low dr but maintained excellent stereospecificity at the benzylic center.

Despite the advances made in Cu catalysis, these conditions still performed relatively poorly when utilized to couple aryl or vinyl electrophiles. Falck and co-workers then turned to other transition-metal catalyst systems and discovered that α -stannylated benzoate 147 and β -iodostyrene readily undergo stereospecific Pd-catalyzed cross-coupling (Scheme 12).¹⁴⁶ A

Scheme 12. Pd-Catalyzed and Cu-Free Stereospecific Stille Cross-Coupling

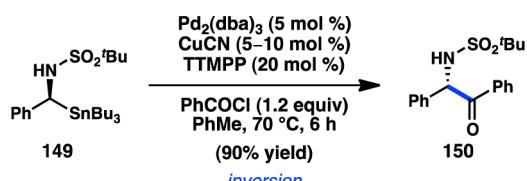


control experiment revealed that the adjacent stereocenter in 147 had no effect on the stereochemical outcome of the reaction. Alkenyl bromides and triflates, as well as aryl iodides and bromides, cross-couple in moderate yield and with retention of configuration.

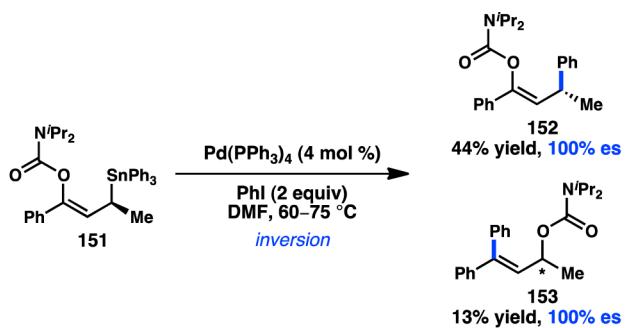
The stereospecific Stille cross-coupling reactions developed by Falck and co-workers focused primarily on the use of α -oxygenated organostannanes. In contrast, the coupling of α -amino organostannanes has received less attention. Chong and co-workers have disclosed a diastereoselective addition of Bu₃SnLi to imines bearing a chiral *tert*-butanesulfonamide auxiliary.¹⁴⁷ The sulfinamide products of the reaction were not active toward Stille cross-coupling conditions. Fortunately, oxidation to sulfonamide 149 allowed cross-coupling with benzoyl chloride in the presence of catalytic Pd₂(dba)₃ and ligand tris(2,4,6-trimethoxyphenyl)phosphine (TTMPP) (Scheme 13). The high donicity of the ligand was thought to prevent deleterious β -hydride elimination. Significantly, analysis of the reaction products revealed that 150 was formed with inversion of configuration, consistent with an S_{E2}(open) transition state and Stille's original mechanistic studies.

Whereas the previous examples of cross-coupling reactions of sec-alkylstannanes benefit from α -heteroatoms that enforce the

Scheme 13. Stereoinvertive Stille Cross-Coupling



stereospecificity of transmetalation, Hoppe and co-workers have reported a stereospecific Stille coupling of allylstannane **151**, which benefits from a γ -directing group (Figure 38).



153 via:

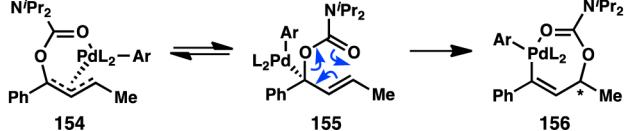


Figure 38. Stille cross-coupling of allyltin reagents.

Treatment of **151** with iodobenzene and catalytic Pd(PPh_3)₄ provides **152**, the result of inversion of configuration, as the major product.¹⁴⁸ Unfortunately, the yields are modest because of the competing formation of **153**. The minor product, **153**, is presumably formed via π -allyl complex **154**; isomerization of **154** to γ -substituted Pd complex **155** can then result in [3,3] rearrangement to **156**. Reductive elimination from vinyl-palladium complex **156** furnishes minor product **153**, which is notably formed with complete enantiospecificity. Thus, a direct S_{E2'} mechanism is not proposed for the formation of **153**.

Recently, Biscoe and co-workers reported the first enantiospecific Stille cross-coupling of simple alkylstannanes. Integral to the success of the reaction was the use of alkylazastannatranes as the organotin coupling partner. Most Stille couplings utilize trialkylstannyll groups, wherein the alkyl groups act as dummy ligands because of their slow rate of transfer to a transition-metal catalyst. However, alkylazastannatranes have been shown to transfer alkyl groups selectively; intramolecular coordination of the nitrogen to tin activates the apical alkyl group toward transmetalation.¹⁴⁹ Reaction optimization for the coupling between **157** and aryl halides identified JackiePhos (**L62**) as providing good levels of conversion and minimal alkane isomerization (Figure 39).¹⁵⁰ The coupling proceeds with retention of configuration and is notably tolerant of a range of heteroaryl halide partners. New methods for the enantioselective construction of simple alkylazastannatranes are necessary to realize the full potential of this method.

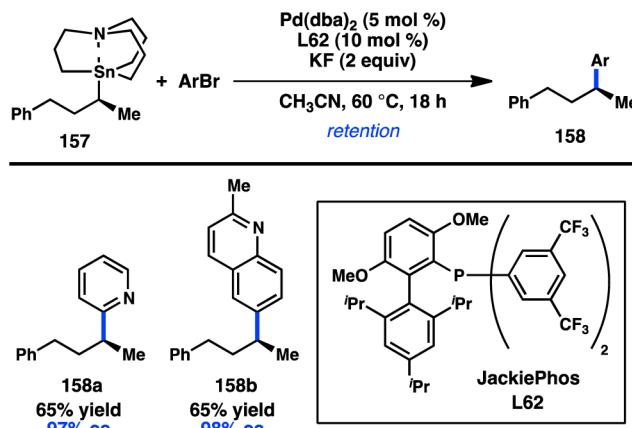


Figure 39. Stereospecific Stille cross-coupling of unactivated secondary alkyltin reagents

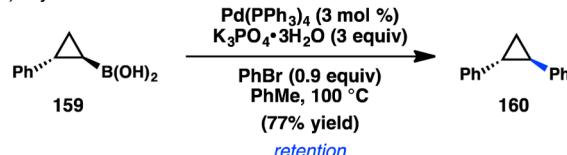
3.1.3. Organoboron Reagents. The alkyl cross-coupling of stereodefined C(sp³) organoborane reagents is a synthetically appealing transformation that, for several reasons, has been somewhat challenging to develop. In general, alkylboron species undergo transmetalation at a slower rate than their vinyl, aryl, and alkynyl counterparts. The increased steric hindrance of the *sec*-alkylboron species required for stereo-specific cross-coupling reactions further exacerbates the challenge of the transmetalation step. Moreover, until the past decade, there were relatively few methods to prepare these reagents in enantioenriched form.

Early efforts to develop cross-coupling reactions of *sec*-alkylboron reagents focused on cyclopropylboronic acids because the Walsh orbitals of a cyclopropyl ring impart extra p character to the C–C bonds, resulting in a greater C(sp²) character of the C–B bond. Cyclopropylmetallic species also benefit from a high-energy barrier for β -hydride elimination. In 1996, Deng and co-workers reported a Suzuki–Miyaura cross-coupling of cyclopropylboronic acids and aryl bromides, observing that *trans*-cyclopropyl starting materials provided *trans*-products.¹⁵¹ Later, both Deng and Charette demonstrated that racemic *cis*-cyclopropyl trifluoroborates also react with retention of configuration.^{152,153} In 1998, Deng disclosed an asymmetric route to **159** via a diastereoselective cyclopropanation of an alkenylboronate ester followed by hydrolysis to form the free boronic acid.¹⁵⁴ Treatment of **159** with bromobenzene under Deng's previously optimized conditions delivered **160** in good yield and with retention of stereochemistry, indicating that transmetalation from boron to Pd occurs with retention of configuration at the carbon atom (**Scheme 14a**).^{155–158} This example represented the first report of a stereoretentive Suzuki–Miyaura cross-coupling reaction of a secondary organoboron species. Later studies illustrated that both aryl and heteroaryl triflates were competent coupling partners;^{159,160} acylation of **161** was also achieved using Ag₂O as a base (**Scheme 14b**).¹⁶¹

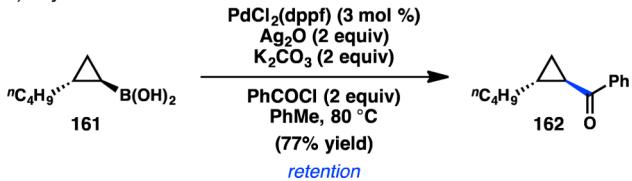
Despite the promising reactivity of cyclopropylboronic acids, it was not until 2009 that Cradden and co-workers were able to develop the first stereospecific Suzuki–Miyaura cross-coupling of acyclic, stereodefined *sec*-alkylboronates. Prior studies in the Cradden laboratory had established an enantioselective Rh-catalyzed hydroboration of styrenes to furnish secondary benzylic boronates in high ee.¹⁶² Exposure of hydroboration product 163 to Pd-catalyzed cross-coupling conditions delivered 164 with retention of configuration (Scheme

Scheme 14. Stereospecific Suzuki–Miyaura Coupling of Cyclopropylboronic Acid

a) Arylation



b) Acylation



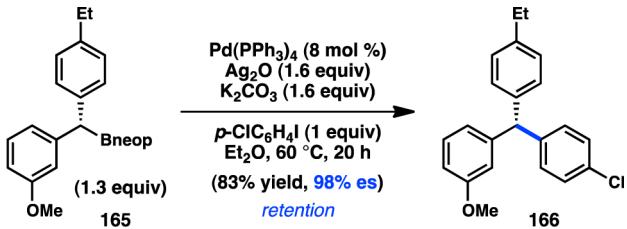
15a).⁷⁹ Ag_2O was critical to enhance the rate of transmetalation of the *sec*-alkylboronate; it was later found that the combination

Scheme 15. Suzuki–Miyaura Cross-Coupling of Benzylic Boronates

a) Preparation of Diarylmethanes



b) Preparation of Triarylmethanes



of Ag_2O and K_2CO_3 enhances enantiospecificity.¹⁶³ An 8:1 ligand:metal ratio was required to maintain good yields, although further increasing the phosphine loading led to reduced enantiospecificity. Whereas primary benzylic boronate esters react in yields comparable to that of 163, primary alkylboronates were shown to be unreactive under the optimal conditions;¹⁶⁴ these results highlight the importance of the adjacent aryl group of 163 to promote transmetalation. Employing similar reaction conditions, triarylmethane 166 could be prepared from boronate ester 165 (Scheme 15b).¹⁶⁵ The use of 2,2-dimethylpropanediol-derived boronic esters (Bneop) instead of pinacol boronates was required to synthesize starting material 165 efficiently via Aggarwal's asymmetric 1,2-metallate rearrangement.¹⁶⁶

Realizing the important role of adjacent π -unsaturation for efficient cross-coupling of secondary organoboronate esters, Crudden and co-workers next investigated the cross-coupling of secondary allylic boron species. After developing a cross-coupling of racemic allylic boronate esters,¹⁶⁴ Crudden collaborated with the Aggarwal laboratory to prepare enantioenriched 167 from the corresponding carbamate by a lithiation–borylation route.¹⁰⁸ Pd-catalyzed reaction of 167

with iodobenzene provided 168 with complete retention of stereochemistry and high γ -selectivity (Figure 40). The authors

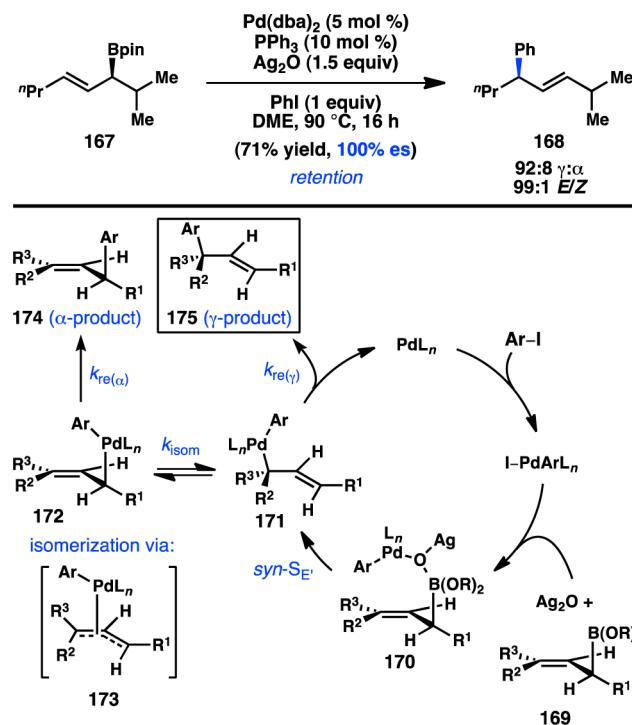


Figure 40. Regioselective cross-coupling of allylic boronates.

propose that the cross-coupling proceeds through a *syn S_{E'}* mechanism wherein the Pd–O–B linkage in 170 directs γ -addition to form 171. Reductive elimination from 171 forms γ -product 175; alternatively, isomerization through π -allylpalladium complex 172 would lead to α -product 174. Deuterium labeling studies confirmed that the rate of reductive elimination is faster than the rate of isomerization. The aforementioned mechanism is consistent with proposals for the coupling of stereogenic allyl trifluorosilanes and allylsilanoates (see section 3.1.1).^{109,110} Sugino and co-workers have disclosed a cross-coupling of homoallylic boronates that also proceeds with retention of configuration.¹⁶⁷

Aggarwal and co-workers concurrently investigated the asymmetric preparation of tertiary propargylic boronate esters through their lithiation–borylation method. After synthesis of 176 in high ee, the tertiary boronate was subjected to modified Crudden conditions to deliver γ -addition product 177 exclusively with minimal formation of the protodeboronated product (Figure 41).⁷⁶ This reaction represented the first example of a tertiary organoboron species being employed in a stereospecific Suzuki–Miyaura coupling. In analogy to the coupling of allylic boronates, the reaction is expected to proceed through a *syn S_{E'}* mechanism in which the “ate” complex of 178 can direct Pd toward γ -addition.

Following the early reports by Crudden, Sugino and co-workers disclosed the Pd-catalyzed cross-coupling of enantioenriched [α -(acylamino)benzyl]boronic ester 181. Optimization studies of the Suzuki–Miyaura cross-coupling of 181a and aryl bromides established that use of Pd/L63 and K_2CO_3 delivered the product with moderate stereofidelity (Figure 42).¹⁶⁸ Incorporation of a bulkier protecting group on nitrogen, as in 181b, increased the enantiospecificity to 97%. Aryl and heteroaryl bromides, as well as aryl chlorides, could thus be

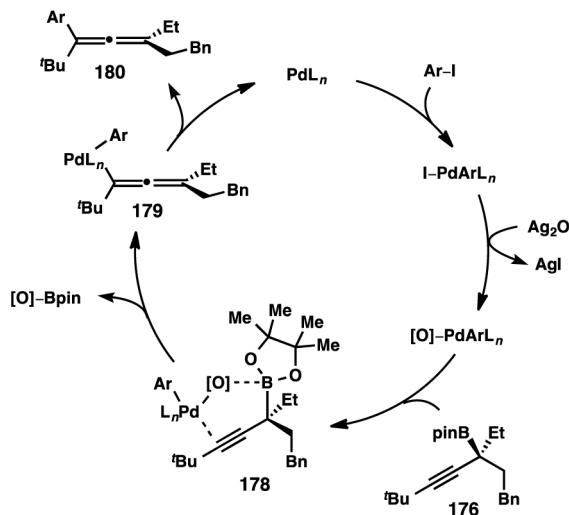
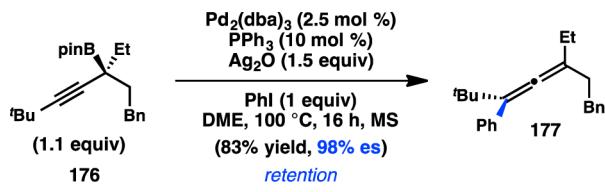


Figure 41. Tetrasubstituted allene formation from Suzuki–Miyaura cross-coupling.

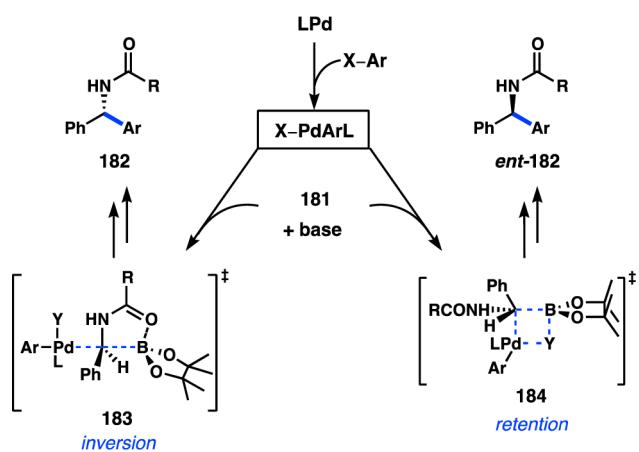
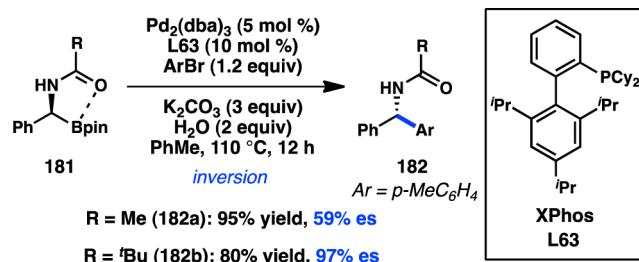


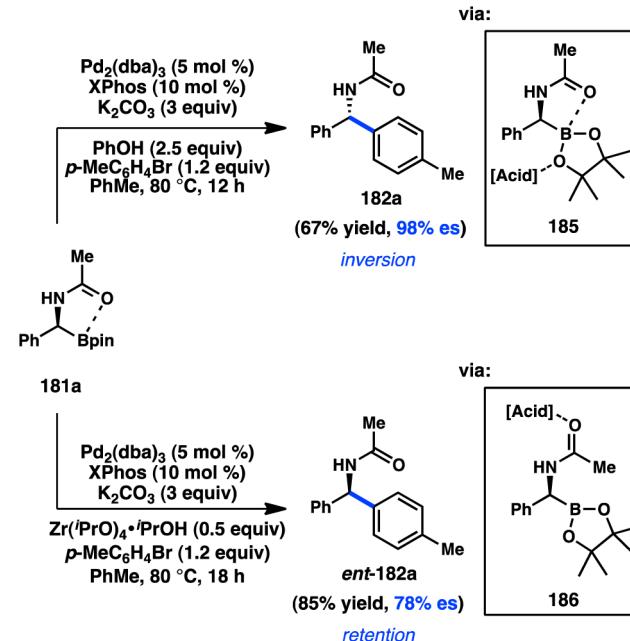
Figure 42. Stereoinvertive cross-coupling of $[\alpha$ -(acylamino)benzyl]boronic esters.

coupled with **181b** in high yields and excellent es. Stereochemical assignment of the amide products revealed that the reaction occurred with inversion of configuration. Suginome proposed that strong intramolecular coordination between the carbonyl and the boron atom of **181** would enforce

transmetalation to Pd through an $S_{\text{E}2}(\text{open})$ mechanism, as shown in **183**. In contrast, a stereoretentive cross-coupling would proceed by transmetalation via four-centered $S_{\text{E}2}(\text{cyclic})$ transition state **184**, which would require decoordination of the carbonyl group from the boron atom of **181**.

In a follow-up study, Suginome investigated how additives might affect the stereochemical course of cross-coupling reactions of **181a**. Addition of protic acids was found to increase the es of the stereoinvertive coupling of **181a**, with phenol providing **182a** in 98% es (Scheme 16).¹⁶⁹ The authors

Scheme 16. Additive Effects in Coupling of $[\alpha$ -(Acylamino)benzyl]boronic Esters



propose that phenol hydrogen bonds to the oxygen atom of the pinacol ligand (**185**), making the boron more electropositive and strengthening the dative interaction between the carbonyl and boron, thereby enforcing an $S_{\text{E}2}(\text{open})$ transition state. On the other hand, the Lewis acid $\text{Zr}(\text{iPrO})_4 \cdot \text{iPrOH}$ was found to reverse the stereochemical outcome of the reaction, delivering **ent-182a** in 78% es and with retention of configuration. In this case, coordination of the amide of **181a** to the exogenous Lewis acid is proposed to disrupt the intramolecular coordination of the carbonyl to boron (**186**), favoring instead stereoretention through an $S_{\text{E}2}(\text{cyclic})$ transition state.

A second stereoinvertive Suzuki–Miyaura cross-coupling was concurrently developed by Molander and co-workers in 2010. Enantioenriched trifluoroborates such as **187** are readily prepared by asymmetric β -borylation of the corresponding α,β -unsaturated amides.¹⁷⁰ Trifluoroborate **187** was found to undergo Pd-catalyzed cross-coupling with chlorobenzene to give **188** in high yield and es, and with inversion of stereochemistry (Figure 43). The use of the bulky Buchwald ligand XPhos (**L63**) was found to prevent the formation of products resulting from β -hydride elimination or isomerization.¹⁷¹ Amide **187** can be coupled with a variety of aryl and heteroaryl chlorides; a reduced yield is obtained using bromobenzene, and no product is observed when using iodobenzene.¹⁷² However, substrates containing a ketone or ester in place of the amide in **187** did not deliver any of the

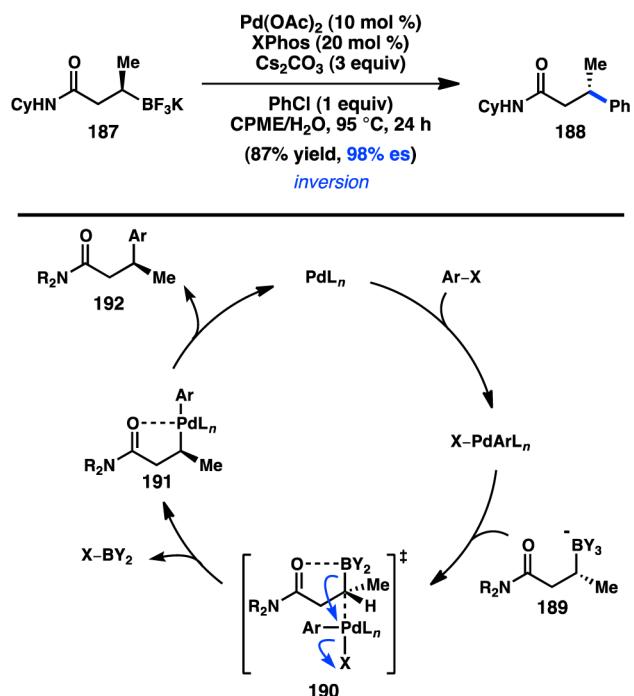


Figure 43. Stereoinvertive Suzuki–Miyaura coupling of β -trifluoroborato amides.

desired cross-coupling products. To explain the key role of the amide, Molander proposes a stereochemical model similar to that of Sugimoto, in which intramolecular dative coordination between boron and the carbonyl of 187 favors an S_{E2} (cyclic)-type mechanism for stereoinvertive transmetalation. In addition, formation of five-membered chelate 191 might stabilize the resulting organometallic complex, preventing β -hydride elimination by precluding formation of the required *syn*-coplanar conformation. Janesko and co-workers used DFT calculations to find that the bulky XPhos protects the coordinatively unsaturated Pd^{II} intermediate from β -hydride elimination while also accelerating reductive elimination from 191 by interrupting the five-membered chelate.¹⁷³

Molander also investigated the cross-coupling of [1-(benzyloxy)alkyl]boron species 193 with aryl chlorides using the Pd precatalyst system cataCXium A-Pd-G2 (Figure 44). Prior research by Falck and others demonstrated that Stille cross-couplings of α -heteroatom-substituted organotin reagents can proceed with high stereospecificity (see section 3.1.2). In the present case, a benzyl ether was utilized to facilitate coordination to Pd in an η^2 binding mode following oxidative addition (195).¹⁷⁴ It was hypothesized that this interaction could stabilize the organometallic intermediate, disfavoring β -hydride elimination. Indeed, a variety of aryl and heteroaryl chlorides could be coupled in high yield and with excellent stereospecificity. These cross-coupling reactions proceed with retention of stereochemistry, in analogy to the cross-coupling of benzylic, allylic, and propargylic boronates studied by Crudden and Aggarwal.^{76,79,108,163–165}

Recent advances in catalytic asymmetric borylation reactions have provided access to an array of new enantioenriched C(sp³) organoboron compounds. In 2011, Hall and co-workers disclosed the enantioselective preparation of geminally substituted 1,1-diboron compound 196, which contains differentially protected boron groups (Figure 45).¹⁷⁵ Subsequent exposure of 196 to Suzuki–Miyaura cross-coupling

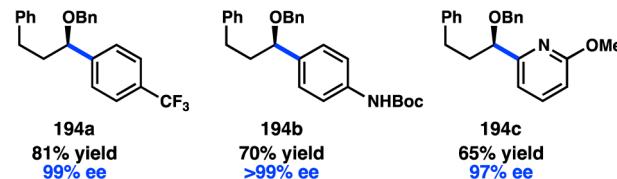
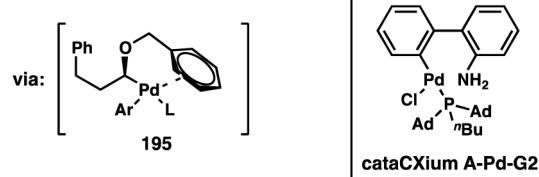
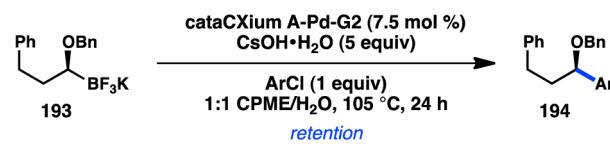


Figure 44. Stereoretentive coupling of a [1-(benzyloxy)alkyl]boron compound.

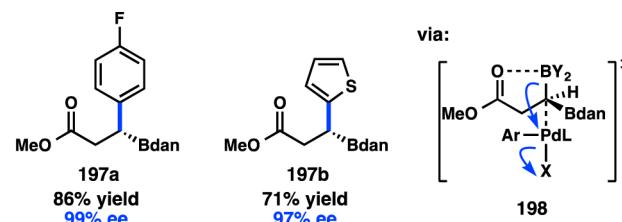
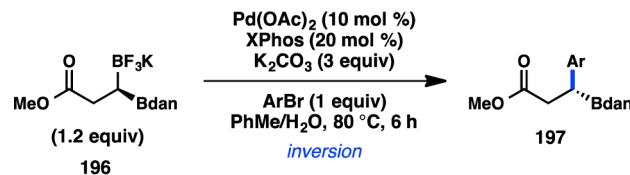


Figure 45. Stereoinvertive coupling of geminal diborons.

conditions resulted in a chemoselective arylation of the BF_3K group to form 197 with inversion of configuration. Notably, a substrate bearing a Bpin group in place of the BF_3K group results in a racemic product. As previously discussed by Molander in the coupling of β -boryl amides, the cross-coupling is proposed to proceed through an S_{E2} (open) transition state (198). Although Molander observed poor reactivity with ester directing groups, it is hypothesized that the α -Bdan group exerts a cooperative effect with the ester to stabilize transition state 198.¹³¹ However, when a simple homobenzylic 1,1-diboron compound was subjected to the reaction conditions, the cross-coupled product was obtained in only 15% yield and reduced enantiospecificity, illustrating the importance of the ester directing group.¹⁷⁶

All of the above examples employ enantioenriched organoboron reagents activated by a proximal π -system or Lewis basic directing group. The Biscoe laboratory has focused on the development of enantiospecific cross-coupling reactions of simple, secondary organometallic reagents.¹⁵⁰ Building from pioneering work by Molander¹⁷⁷ and van der Hoogenband,¹⁷⁸ Biscoe and co-workers discovered that $Pd/P(tBu)_3$ precatalyst 201 catalyzed the cross-coupling of *sec*-alkyl trifluoroborates (199) with aryl chlorides to provide products with branched to

linear ratios as high as >200:1 (Figure 46).¹⁷⁹ Both boronic acids and trifluoroborate salts were competent reaction

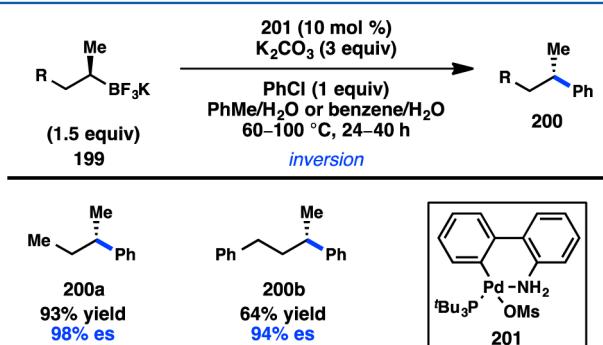
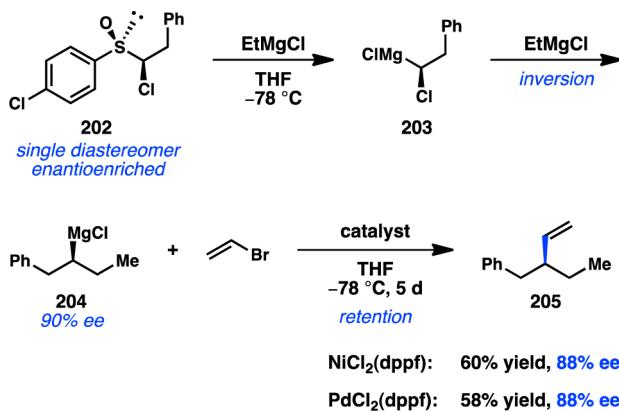


Figure 46. Stereoinvertive coupling of unactivated acyclic organoboron reagents.

partners, and products bearing interesting heterocyclic scaffolds could be prepared with good efficiency. Examination of the stereochemical outcome revealed that the transformation proceeds with inversion of stereochemistry. Previous stereospecific Suzuki–Miyaura cross-couplings have been shown to proceed with either retention or inversion of stereochemistry; it is possible that the stereochemical outcome of this transformation reflects the innate mechanism of transmetalation for unactivated secondary alkylboron reagents.

3.1.4. Organomagnesium Reagents. The configurational lability of the C–Mg bond has hindered the development of stereospecific cross-coupling reactions of stereodefined sec-alkylmagnesium reagents. Although the racemization of hard organometallic compounds can be attenuated at low temperatures and in certain solvents,^{9,180} most syntheses of Grignard reagents proceed via alkyl radicals and preclude formation of enantioenriched material.¹⁸¹ Hoffmann and co-workers developed a route to stereodefined Grignard reagent 204 by employing a sulfoxide/Mg exchange followed by a carbenoid homologation reaction (Scheme 17).¹² The half-life of 204 was

Scheme 17. Stereospecific Coupling of Secondary Organomagnesium Compounds

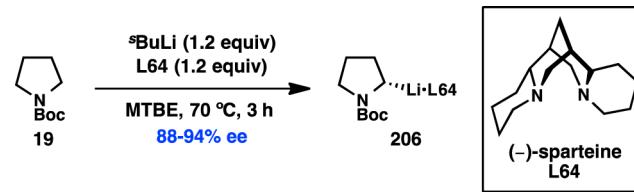


measured to be ~5 h at -10 °C. Hoffmann utilized the stereogenicity of 204 as a mechanistic probe for transition-metal-catalyzed Kumada–Corriu cross-couplings.¹⁸² Under Ni or Pd catalysis, stereochemical information is maintained throughout the reaction, supporting a polar mechanism for transmetalation. On the other hand, Fe- and Co-catalyzed

reactions provided 205 in reduced ee, indicating the presence of single-electron transfer pathways.

3.1.5. Organozinc Reagents. As with organomagnesium reagents, stereospecific cross-coupling of enantioenriched sec-alkylzinc reagents has been limited by the asymmetric preparation of the organozinc coupling partner. Oxidative addition of Zn into C–X bonds often occurs via a radical process and does not proceed with stereochemical fidelity. In contrast, transmetalation of Zn^{II} salts with organolithium or organoboron compounds occurs with retention of configuration. Knochel and co-workers have pioneered a boron/zinc exchange for diastereoselective cross-couplings, but progress toward using these reagents in enantiospecific processes has been slow.^{183–186} Lithium/zinc transmetalation has enjoyed more success in enantiospecific cross-coupling. Studies by Beak and co-workers demonstrated that treatment of N-Boc-pyrrolidine 19 with ⁶BuLi and (-)-sparteine (L64) results in stereodefined organolithium complexes that are stable at low temperatures (Scheme 18).¹⁸⁷ These complexes can react with an array of electrophiles to form C–C bonds; they also readily undergo transmetalation with Zn^{II} to form stereodefined organozinc compounds.

Scheme 18. Asymmetric Deprotonation To Form Chiral Lithium Reagents



In 2006, Campos and co-workers reported the synthesis and coupling of organozinc reagent 207, which could be warmed to room temperature without loss of configurational integrity (Figure 47).^{61,188} In the presence of Pd(OAc)₂ and P('Bu)₃, a variety of aryl and heteroaryl halides could be cross-coupled in good yields and with excellent enantiospecificity. Use of the bulky, electron-rich, monodentate ligand P('Bu)₃ enables oxidative addition of the aryl halide at low temperature, while also mitigating the β-hydride elimination pathway. The reaction was applied to the synthesis of a glucokinase activator and

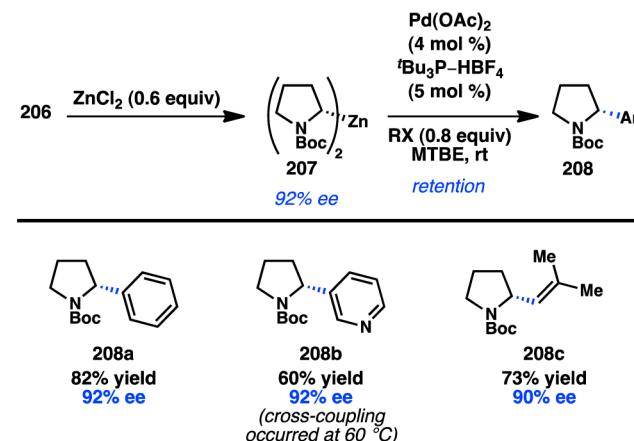


Figure 47. Pyrrolidine functionalization via stereoretentive Negishi cross-couplings.

performed on the kilogram scale.¹⁸⁹ Efforts to increase the scope of the reaction demonstrated that **207** could be coupled with alkenyl bromides in good yield and retention of stereochemistry to form **208c**.¹⁹⁰

Although asymmetric deprotonation allows access to enantioenriched pyrrolidine **206**, challenges have been encountered when attempting to apply this procedure to similar heterocycles, such as piperidines.¹⁹¹ An alternative approach involves a dynamic thermodynamic resolution (DTR) of 2-lithiopiperidines.^{192,193} In the DTR of **209**, racemic organolithium **210** is prepared at low temperature by treatment with ⁷BuLi (Figure 48). Chiral ligand L* is added, and the

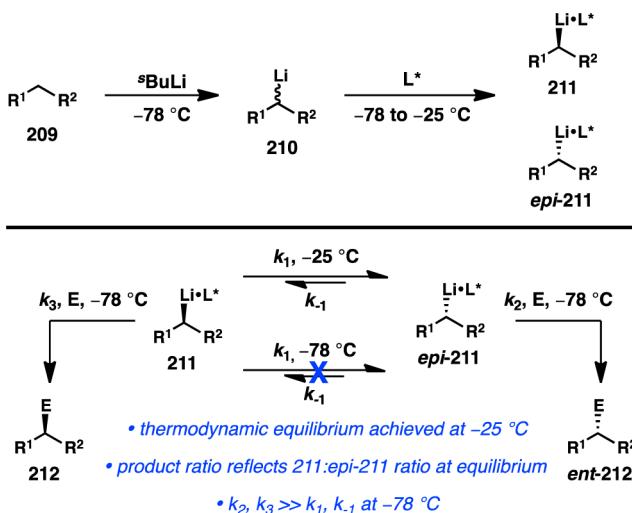
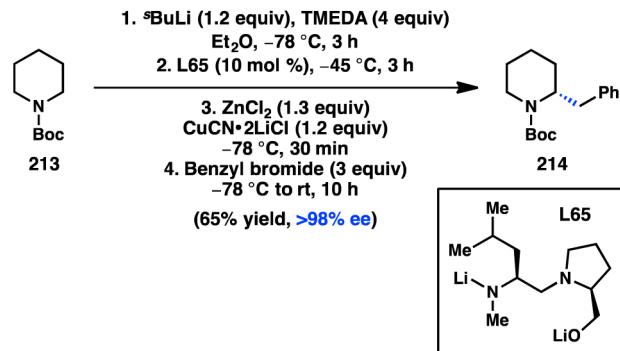


Figure 48. Dynamic thermodynamic resolution (DTR).

reaction temperature is subsequently raised. Diastereomers **211** and *epi*-**211** may reach a thermodynamic equilibrium by carbanion inversion, permitting a single stereoisomer (in this case, *epi*-**211**) to be preferentially populated. The reaction temperature is then lowered to a point of configurational stability ($k_2, k_3 \gg k_1, k_{-1}$), effectively freezing the thermodynamic equilibrium. Treatment with an electrophile leads to product formation with an ee similar to the ratio of **211** and *epi*-**211** present from the thermodynamic equilibrium.

Gawley and co-workers have applied a DTR technique to prepare enantioenriched piperidylzinc species. Dilithiated diaminoalkoxide ligand **L65** was employed catalytically in the presence of superstoichiometric achiral TMEDA, enabling a catalytic dynamic resolution (CDR)¹⁹⁴ of 2-lithiopiperidine. Transmetalation to Zn followed by a Cu-mediated Negishi cross-coupling afforded benzylolation product **214** in moderate yield and excellent ee (Figure 49a).^{195,196} The Cu-catalyzed protocol was useful for benzylolation and allylation but was not amenable to cross-coupling with aryl or vinyl halides. However, Pd-catalyzed cross-coupling under the conditions developed by Campos for the arylation of pyrrolidines furnished the 2-aryl- or 2-vinylpiperidines in good ee (Figure 49b).^{197,198} Although heteroaryl bromides were reactive under the coupling conditions, conversion was sluggish and heating to 60 °C was required. Enantioselectivity studies reveal a moderate loss of stereochemical integrity as the reaction temperature is increased from 22 to 60 °C, implicating a slow racemization process for the intermediate organozinc reagent. In contrast, Campos's coupling of pyrrolidines occurs at 60 °C without any erosion of ee.⁶¹

a) Benzylation



b) Arylation and vinylation

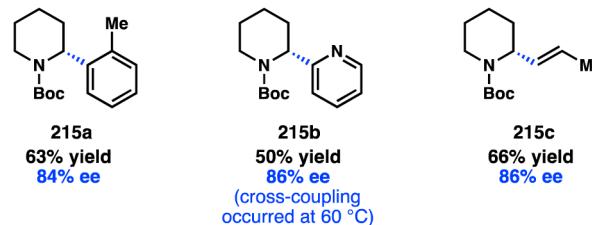
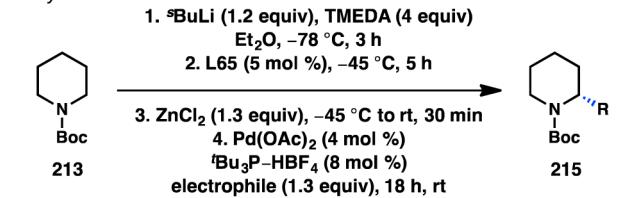


Figure 49. Piperidine functionalization via stereoretentive Negishi cross-couplings.

3.2. Reactions of Secondary Alkyl Electrophiles

3.2.1. With Organomagnesium Reagents. Although the Kumada–Corriu coupling was first reported over 40 years ago, the development of stereospecific reactions between enantioenriched *sec*-alkyl electrophiles and organometallic reagents has only recently gained traction. In 1990, Larchevêque and co-workers demonstrated that α -hydroxy esters react with stoichiometric cuprate reagents with inversion of configuration.¹⁹⁹ Building off this work, Breit and co-workers reported a Zn-catalyzed cross-coupling of enantioenriched α -hydroxy ester triflates and alkylmagnesium chlorides in 2008 (Figure 50).²⁰⁰ The enantioenriched triflate electrophiles were easily accessed from enantiopure lactic acid or α -amino acids. The cross-coupling proceeded with excellent transfer of chirality and inversion of configuration. In an extension of this method, an iterative cross-coupling protocol was developed for the preparation of (oligo)deoxypiproniates.¹²⁷ The reaction is proposed to proceed through a triorganozincate species that is generated *in situ* from the $ZnCl_2$ catalyst and the Grignard reagent. The triorganozincate is thought to be more nucleophilic than a simple dialkylzinc because of its enhanced polarization of the C–Zn bond. The reaction likely also benefits from activation of the triflate by coordination to Mg. S_N2 displacement of the triflate provides product **219** with inversion of configuration.

In 2009, Carretero and co-workers reported a Pd-catalyzed cross-coupling between enantioenriched secondary benzylic bromides and aryl or vinyl Grignard reagents (Scheme 19).²⁰¹ Xantphos (**L66**), possessing a very wide bite angle of 111°, was

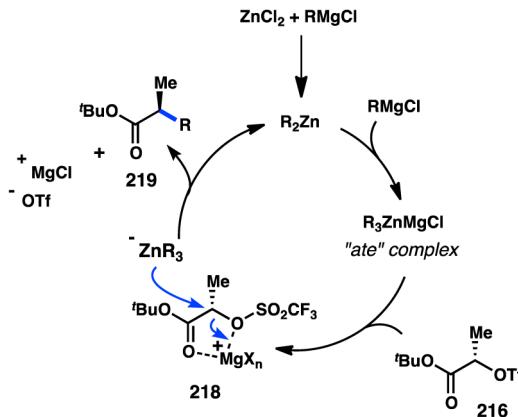
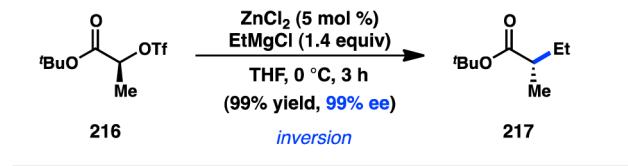
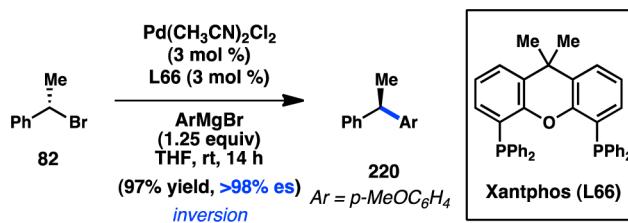


Figure 50. Zn-catalyzed enantiospecific $\text{C}(\text{sp}^3)\text{-C}(\text{sp}^3)$ cross-coupling.

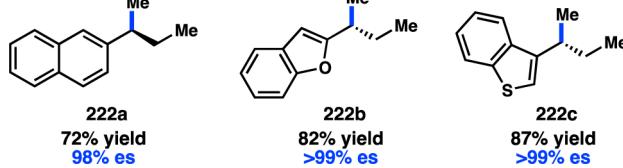
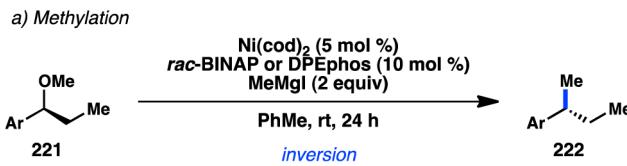
Scheme 19. Stereospecific Kumada–Corriu Coupling of Secondary Benzyl Bromides



crucial to preventing β -hydride elimination. The cross-coupling of enantioenriched bromide **82** proceeded with good enantiospecificity and full inversion of configuration. Although this was an important demonstration of an enantiospecific cross-coupling of a *sec*-alkyl electrophile, the required enantioenriched benzylic bromides can be challenging to prepare in high enantiomeric excess.

In 2011, Jarvo and co-workers reported the first stereospecific Ni-catalyzed Kumada–Corriu cross-coupling of a *sec*-alkyl ether.⁸⁰ In the presence of Ni/phosphine complexes, enantioenriched benzylic ethers (**221**) could be coupled to MeMgI in good yields and high ee and with inversion of configuration (Figure 51a). The initially disclosed reaction scope was limited to electrophiles bearing extended aromatic systems that promote efficient oxidative addition through π -benzyl formation. The method was also limited to Grignard reagents that lacked β -hydrogens because of competing β -hydride elimination. A second-generation protocol was developed for the more general coupling of alkylmagnesium halides and benzylic ethers (Figure 51b).⁸² The ability to use easy-to-prepare enantioenriched *sec*-alkyl ethers as electrophiles provides practical advantages over the previously discussed coupling by Carretero and co-workers.

The aforementioned Kumada–Corriu coupling suffered from a limited substrate scope because of the inability of the Ni catalyst to add oxidatively into benzylic ethers that lacked a π -extended system. To promote cross-coupling of simple benzylic ethers, Jarvo and co-workers hypothesized that incorporation of



b) Alkylation (containing β -hydrogen atoms)

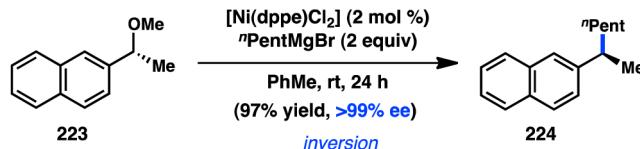


Figure 51. Stereospecific Kumada–Corriu cross-coupling of benzylic ethers.

a more coordinating leaving group could facilitate oxidative addition by a traceless activation strategy. Following electrophile optimization, the use of 2-methoxyethoxy ethers (**225**) was found to enable Kumada–Corriu coupling of simple benzylic substrates; bidentate chelation of Mg is proposed to activate the C–O bond toward oxidative addition (Figure 52).⁸¹ Under these conditions, both diphenyl- and phenylcarbinol derivatives could be coupled enantiospecifically with inversion of configuration.

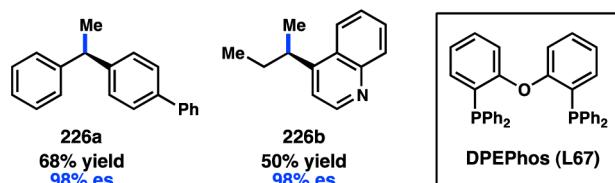
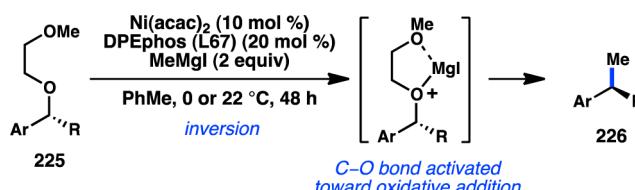


Figure 52. Traceless directing group in the Kumada–Corriu cross-coupling.

Jarvo and co-workers have recently succeeded in further extending their Ni-catalyzed enantiospecific cross-coupling method^{80,81} to the arylation of diarylmethanol derivatives. The yield and enantiospecificity of the transformation were heavily dependent on both the identity of the phosphine ligand and the electrophile (Figure 53).²⁰² When DPEPhos was employed in the cross-coupling of methyl ether **227a**, product was obtained in modest yield and poor ee. The main side product was the homodimer of **227a**. Modification of the electrophile to a traceless 2-methoxyethoxy directing group (**227b**) improved the yield of **228**, but with only a slight

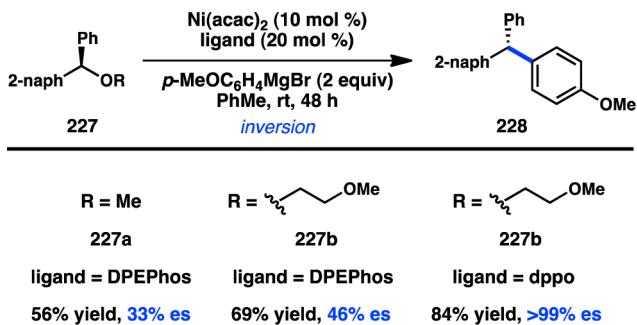


Figure 53. Preparation of enantioenriched triarylmethanes by Kumada–Corriu coupling.

increase in es. However, the combination of substrate **227b** and 1,8-bis(diphenylphosphino)octane (dppo) resulted in clean coupling to deliver **228** in good yield and perfect es. The reaction is limited to substrates containing π -extended systems and cannot be used in the synthesis of diarylalkanes. Jarvo's strategy to prepare triarylmethanes represents a conceptually similar but reverse-polarity approach compared to that of Crudden.¹⁶⁵

In a rare example of a cross-coupling to give products with vicinal tertiary centers, Liu and co-workers reported the stereospecific Cu-catalyzed reaction of secondary tosylates with primary or secondary alkylmagnesium halides; the reactions proceed with complete inversion of configuration (Figure 54).²⁰³ These findings are consistent with mechanistic

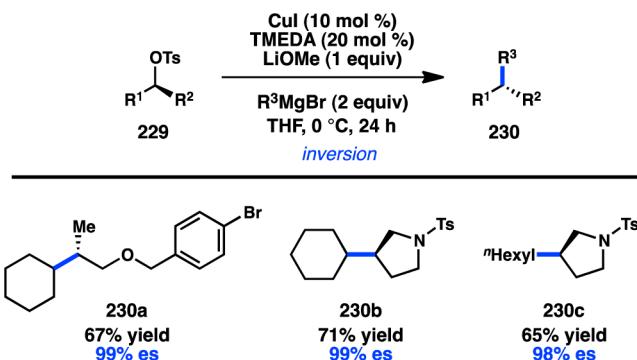
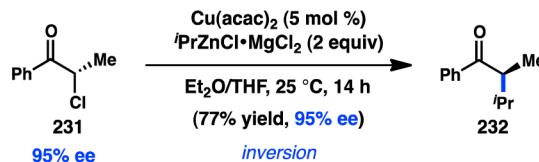


Figure 54. Cu-catalyzed stereospecific Kumada–Corriu cross-coupling.

studies by Kambe and co-workers, which had previously demonstrated that Cu-catalyzed cross-couplings of primary alkyl halides with Grignard reagents occur in an S_N2 fashion.²⁰⁴ Excellent chemoselectivity was realized in the Cu-catalyzed reaction: competition studies indicated that secondary alkyl bromides or tosylates selectively underwent cross-coupling in the presence of an aryl bromide.

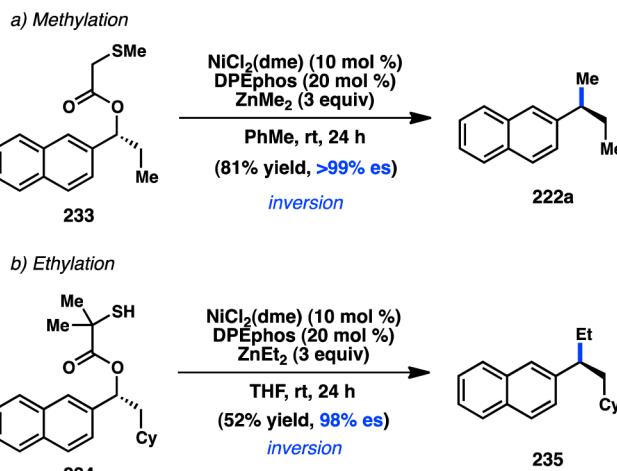
3.2.2. With Organozinc Reagents. The first stereocontrolled Cu-catalyzed cross-coupling of an alkylzinc reagent was reported by Ready and co-workers in 2004.²⁰⁵ Treatment of α -chloro ketone **231** with an alkylzinc species in the presence of catalytic $\text{Cu}(\text{acac})_2$ furnished **232** with inversion of configuration (Scheme 20). It was imperative for the zinc reagent to be prepared via transmetalation of the corresponding Grignard compound for the reaction to proceed efficiently. The observed inversion of configuration supports an S_N2 mechanism for the alkylation and disfavors intermediate enolate formation.

Scheme 20. Stereospecific Cu-Catalyzed Negishi Cross-Coupling



In addition to their development of the cross-coupling between *sec*-alkyl ethers and organomagnesium reagents (see Figure 51), Jarvo and co-workers have investigated Ni-catalyzed cross-coupling reactions with ZnMe_2 .²⁰⁶ Whereas their previous Kumada–Corriu coupling proceeded with simple methyl ether electrophiles, it was reasoned that the decreased nucleophilicity of organozinc species would require a more reactive electrophile as a coupling partner. A traceless directing group strategy was adopted, and a screen of leaving groups bearing different chelating moieties identified 2-methylthio ester **233** as optimal (Scheme 21a). The complex generated from $\text{NiCl}_2(\text{dme})$ and

Scheme 21. Traceless Directing Group for Alkylation of Benzylic Esters



DPPEPhos catalyzed the cross-coupling between electrophiles such as **233** and ZnMe_2 in high yields and with complete inversion of configuration. To extend the transformation to ZnEt_2 , ester **234** was employed to mitigate β -hydride elimination and hydrogenolysis products that were observed when using **233** (Scheme 21b). Unfortunately, the decreased reactivity of organozinc reagents currently limits the method to activated electrophiles bearing π -extended systems.

Having identified that esters behave as feasible electrophiles for stereospecific Negishi couplings, Jarvo and co-workers turned their attention to the cross-coupling of aryl-substituted lactones. The authors demonstrated that treatment of lactone **236** with their modified Negishi methylation conditions delivered ring-opened product **237** in good yield and excellent enantiospecificity (Figure 55).²⁰⁷ Several heteroaryl-substituted lactones were also shown to react well under the optimized reaction conditions.

3.2.3. With Organoboron Reagents. Despite the general popularity of Suzuki–Miyaura cross-coupling reactions, examples of stereospecific couplings of *sec*-alkyl electrophiles have only recently been studied. In 2007, Asensio and co-workers reported the Pd-catalyzed Suzuki–Miyaura coupling of

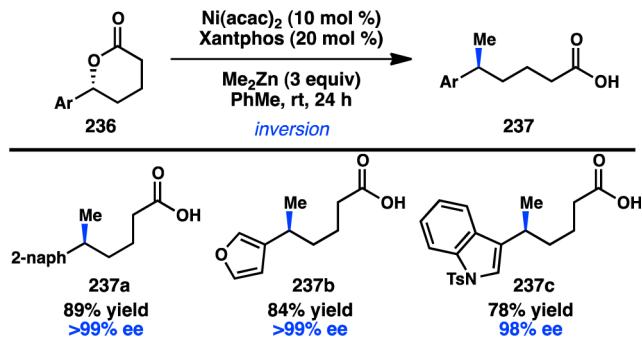
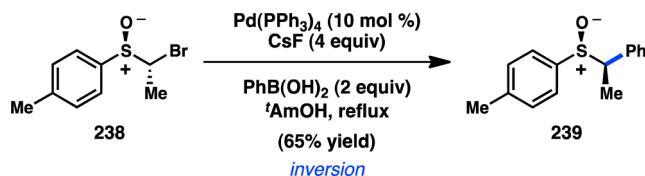


Figure 55. Stereospecific ring-opening of aryl-substituted lactones.

enantioenriched α -bromo sulfoxide 238 with $\text{PhB}(\text{OH})_2$ (Scheme 22).²⁰⁸ The α -arylated sulfoxides 239 were produced

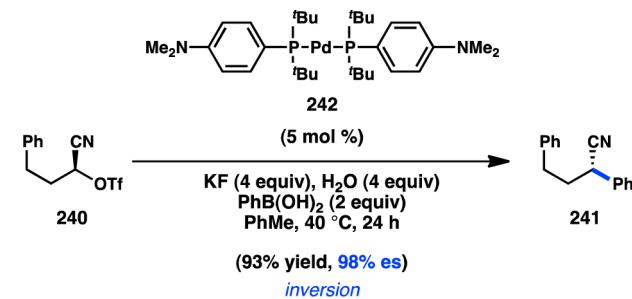
Scheme 22. Stereospecific Suzuki–Miyaura Cross-Coupling of a Secondary Electrophile



with inversion of configuration. Surprisingly, the diastereomer of 238 does not deliver any desired product. The authors hypothesize that coordination of Pd to the sulfinyl group is important for oxidative addition; an unfavorable *gauche* interaction could potentially destabilize the transition state for oxidative addition of the unreactive diastereomer. A computational study supports this hypothesis, finding that coordination of the sulfinyl group to Pd lowers the energy barrier for oxidative addition to the C–Br bond through an $\text{S}_{\text{N}}2$ mechanism.²⁰⁹

Employing a similar strategy, Falck and co-workers developed the first enantiospecific Suzuki–Miyaura cross-coupling of a *sec*-alkyl halide in 2010. Key to their success was the use of an α -cyanohydrin triflate, where the proximal nitrile can accelerate oxidative addition by coordinating to Pd in a fashion analogous to that of the sulfinyl group in Asensio's system. Exposure of 240 and $\text{PhB}(\text{OH})_2$ to Pd complex 242 delivered 241 in excellent yield and with inversion of configuration, while minimizing formation of acrylonitrile side products (Scheme 23).⁸⁷ Subsequent computational studies by Janesko and Pudasaini support the critical role of the Lewis basic nitrile in both accelerating the rate of oxidative addition to

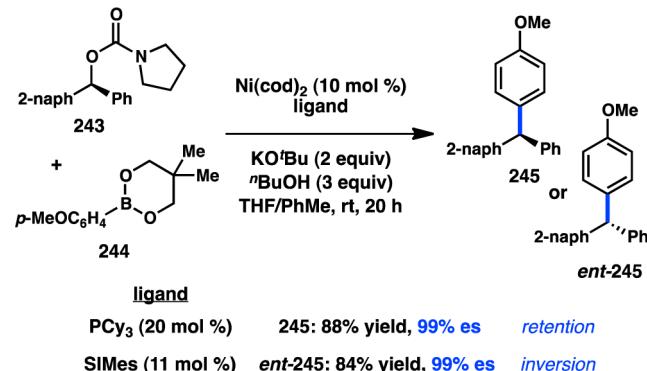
Scheme 23. Enantiospecific Suzuki–Miyaura Cross-Coupling of α -Cyanohydrin Triflate



Pd and slowing the rate of β -hydride elimination from alkylpalladium intermediates.²¹⁰ Other organoborons such as boronate esters, BF_3K salts, and MIDA boronates were unreactive under the reported conditions.

Given the abundance of commercially available organoboron reagents, Jarvo and co-workers sought to extend the scope of their Ni-catalyzed stereospecific cross-coupling reactions to the use of organoboron coupling partners.²⁰² However, Suzuki–Miyaura cross-coupling reactions of *sec*-alkyl ethers were expected to require harsher conditions because of the slower rates of transmetalation with organoboron reagents. Nonetheless, when diaryl carbamates (e.g., 243) and strong base are employed, Ni-catalyzed enantiospecific cross-coupling to boronate esters is possible (Scheme 24).²¹¹ Systems lacking

Scheme 24. Stereodivergent Synthesis of Triarylmethane

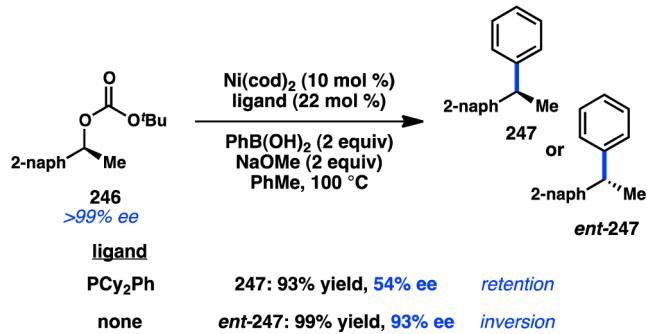


an extended π -system could be coupled when pivalates were used as the leaving group. Surprisingly, the identity of the ligand completely overturned the stereochemical outcome of the reaction. When PCy_3 was used, the cross-coupling proceeded with retention of configuration, contrary to Jarvo's previous findings in the Kumada–Corriu coupling. The use of $n\text{BuOH}$ as an additive played a key role in enhancing the enantiospecificity. When SIMes , an NHC ligand, was employed, *ent*-245 was produced with inversion of configuration. Although additional studies are necessary, a preliminary proposal by the authors suggests that PCy_3 -mediated reactions of 243 occur through initial coordination of Ni to the carbamate followed by a *syn*, or retentive, oxidative addition; alternatively, the SIMes -mediated reaction could proceed through a stereoinvertive $\text{S}_{\text{N}}2'$ -type oxidative addition.

Concurrent with the studies by Jarvo described above, Watson and co-workers reported similarly intriguing stereodivergent behavior in the cross-coupling of benzhydryl pivalates and arylboronic acids. Treatment of pivalate 246 and $\text{PhB}(\text{OH})_2$ with $\text{Ni}/\text{PCy}_2\text{Ph}$ furnished 247 with retention of configuration and moderate es (Scheme 25).⁸³ In contrast, nearly exclusive inversion of configuration was observed under ligand-free coupling conditions. These results are consistent with Jarvo's hypothesis that Ni/phosphine complexes can coordinate to carbamate or ester groups and provide a *syn* oxidative addition. Under Watson's ligand-free conditions, both diaryl- and triarylalkanes can be accessed in high yield and with inversion of configuration.

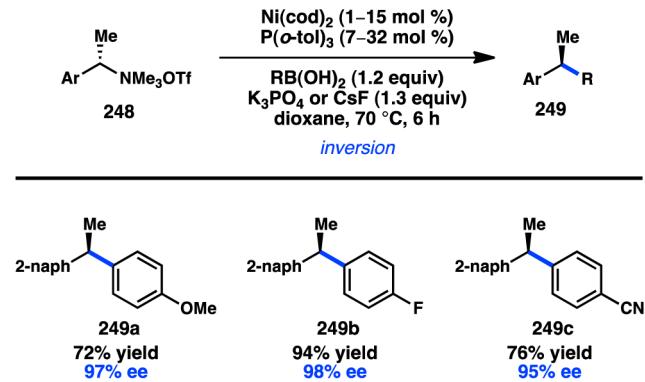
Watson and co-workers have also investigated the stereospecific Suzuki–Miyaura cross-coupling reactions of benzylammonium salts in an interesting example of oxidative addition to a $\text{C}(\text{sp}^3)\text{C–N}$ bond. Employing $\text{Ni}/\text{P}(o\text{-tol})_3$ as the catalyst, a

Scheme 25. Stereodivergent Coupling of Benzyl Pivalates



variety of diarylalkanes could be prepared in good yield and high ee, with inversion of configuration (Figure 56a).⁸⁴ The

a) First-generation coupling of benzylammonium salts



b) Second-generation coupling of benzylammonium salts

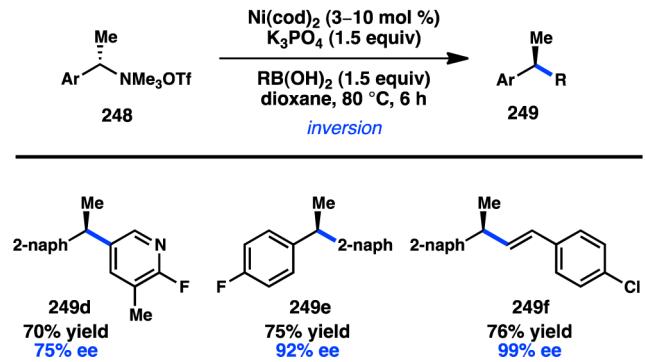
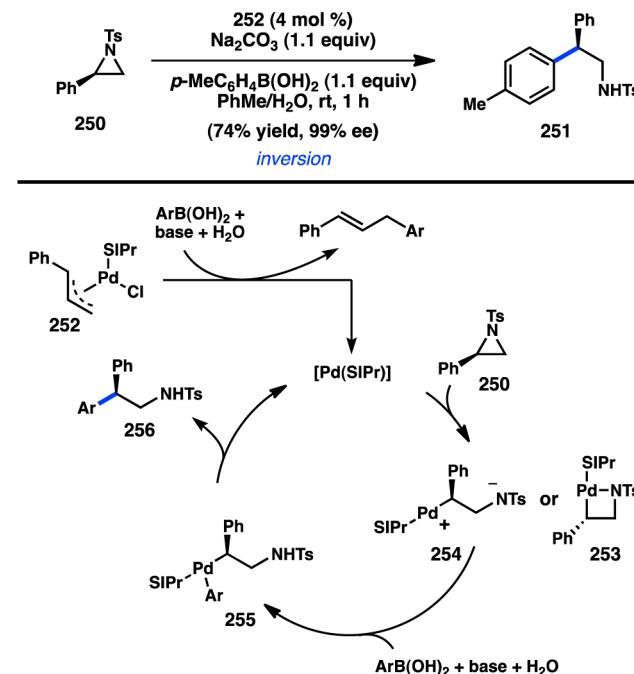


Figure 56. Stereospecific cross-coupling of benzylammonium triflates.

stereochemical outcome is opposite that observed with benzylic pivalates when Ni/phosphine complexes are utilized. Subsequent efforts to extend the scope of the reaction to heterocycles and substrates lacking π -extended systems revealed that Ni(cod)₂, in the absence of an exogenous ligand, catalyzes the desired cross-coupling reaction with high enantiospecificity (Figure 56b).⁸⁵ Under these modified conditions, heterocyclic and alkenylboronic acids were coupled in good yields and simple α -phenylammonium triflates could also be coupled.

Recently, Takeda, Minakata, and co-workers reported a stereospecific Suzuki–Miyaura cross-coupling of arylaziridines. Ni-catalyzed couplings of aziridines have previously been reported to proceed with stereochemical scrambling,^{212,213} so the authors instead investigated Pd catalysts for this trans-

formation. Although phosphine ligands tended to promote β -hydride elimination, NHC ligands favored generation of the cross-coupled product, with C–C bond formation occurring at the benzylic position.²¹⁴ Thus, treatment of aziridine 250 with a boronic acid and Pd-NHC precatalyst 252 furnished 251 in high yield and regioselectivity and with complete inversion of configuration (Figure 57). The authors propose that S_N2-type

Figure 57. Stereospecific cross-coupling of *N*-tosylaziridines.

oxidative addition to 250 can form either metallacycle 253 or acyclic species 254. Transmetalation followed by reductive elimination releases product 256 as a single enantiomer and regioisomer.

4. TRANSITION-METAL-CATALYZED ENANTIOCONTROLLED ALLYLIC SUBSTITUTION

Over the past several decades, enantiocontrolled allylic substitution has emerged as a fundamental process in organic synthesis, allowing efficient formation of C–C, C–N, and C–O bonds with concomitant production of a versatile alkene functional group.^{215,216} As a general rule, these transformations proceed through π -allylmetal complexes. With respect to carbon-based nucleophiles, allylic functionalizations can be categorized into two groups (Figure 58): (1) reactions with stabilized or “soft” nucleophiles, defined here as nucleophiles for which the pK_a of the conjugate acid is less than 25, and (2) reactions with unstabilized or “hard” nucleophiles, typically comprising organometallic reagents. Whereas soft nucleophiles usually undergo direct attack at the carbon atom of a π -

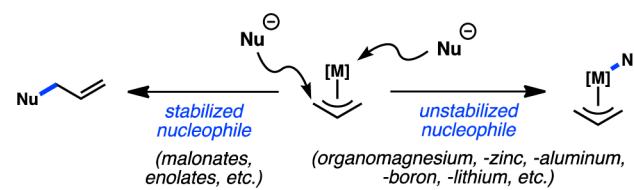


Figure 58. Stabilized vs unstabilized nucleophiles.

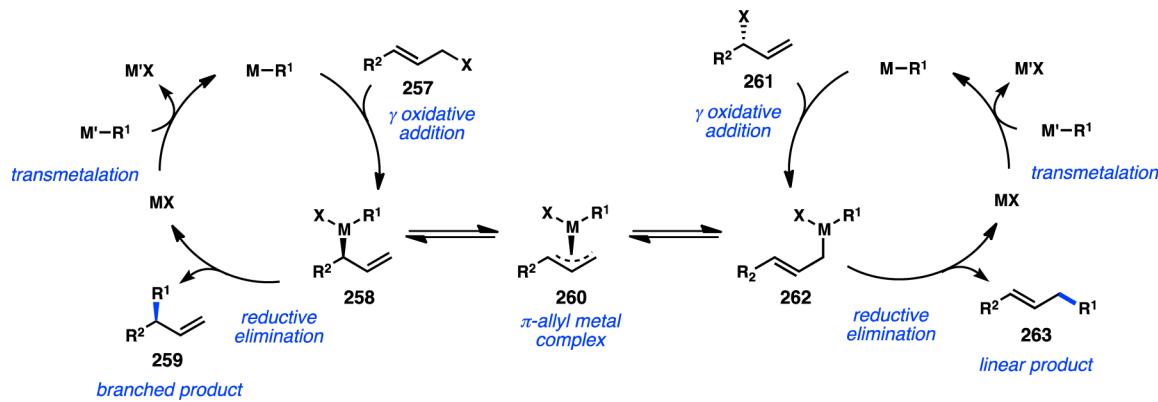


Figure 59. General principles of allylic substitution with hard nucleophiles.

allylmetal complex, hard nucleophiles typically react first with the metal catalyst through a transmetalation mechanism. Following transmetalation, reductive elimination from the metal center forges the C–C bond. Depending on the choice of transition-metal catalyst and ligand, transmetalation may occur either before or after oxidative addition to an allyl electrophile.

In many ways, the principles of stereocontrolled cross-coupling remain relevant when discussing enantioselective or enantiospecific allylic substitution reactions. In a simplified case, allylic substitution with hard nucleophiles can proceed via transmetalation, S_N2' (or γ) oxidative addition (these two steps can also occur in the reverse order), and reductive elimination to deliver the desired product (Figure 59). Controlling the facial selectivity for oxidative addition of allyl electrophile 257 can provide enantioenriched material. A critical complication occurs when the rate of π -allyl formation becomes competitive with reductive elimination: in this case, isomerization from σ -allyl complex 258 to π -allyl complex 260 allows generation of linear product 263. The rate of π -allyl formation is often influenced by the nature of the transition-metal catalyst and ligand.

Controlling the regioselectivity of stereocontrolled allylic substitution remains an active area of research. In the case of enantiospecific allylic substitution, transformation of stereogenic starting material 261 to branched product 259 can proceed through an *anti* S_N2' oxidative addition and π -allylmetal complex 260. Unselective reductive elimination yields a mixture of linear (263) and branched (259) products. Moreover, σ -bond rotation of allylmetal 262 can form a π -allylmetal complex on the opposite enantiotopic face, leading to erosion of enantiospecificity.

Although a number of transition metals have been shown to catalyze allylic substitution reactions, copper²¹⁷ has received special attention for its ability to promote the coupling of hard nucleophiles and for delivering γ -substituted products with high regiochemical fidelity.^{4–6,218} With respect to stereospecific and stereoselective reactions, several aspects of Cu-catalyzed allylic substitution are worthy of mention. Electron-deficient copper complexes typically undergo faster reductive elimination to favor the γ -adduct with little stereochemical scrambling. Therefore, the use of electron-rich dialkyl cuprates is usually avoided when γ -selectivity is desired. To establish asymmetric variants of allylic substitution with high regio- and enantiocontrol, the above mechanism has been harnessed and modified in a number of different applications.

This review will cover the transition-metal-catalyzed enantioselective and enantiospecific union of unstabilized, organometallic reagents with allylic and propargylic electrophiles. Copper-catalyzed substitution has been thoroughly reviewed in the past; this paper will only focus on developments in Cu catalysis since 2008.^{4–6,218} Elegant work in the desymmetrizing ring opening of oxabicyclic electrophiles,³ which typically proceeds via carbometalation and β -oxy elimination, is considered outside the scope of this review.

4.1. Enantioselective Allylic Substitution Reactions

4.1.1. Organomagnesium Reagents. As in the development of transition-metal-catalyzed asymmetric cross-coupling reactions, the first explorations of asymmetric allylic substitution involved the Ni-catalyzed reaction of organomagnesium reagents in the presence of chiral phosphines. In 1980, Consiglio and co-workers showed that Ni in conjunction with bidentate chiral phosphine DIOP (L1) catalyzed the formation of 265 in 16% ee from allylic alcohol 264 (Figure 60).²¹⁹

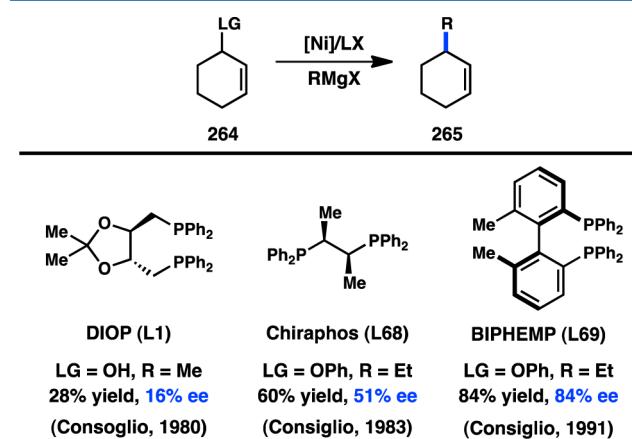


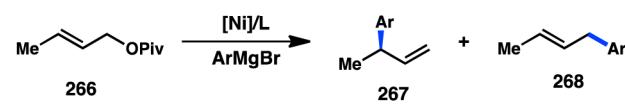
Figure 60. Seminal Ni-catalyzed substitution of cyclic allylic alcohol derivatives.

Further studies using the allylic phenyl ether determined that use of Chiraphos (L68)^{220,221} or axially chiral BIPHEMP (L69)^{222,223} as a ligand provides 265 in improved 51% and 84% ee, respectively. Under similar conditions, low enantioselectivity was obtained for acyclic allylic alcohols.²²⁴ In a separate approach, racemic secondary Grignard reagents could be resolved through an enantioselective allylation to deliver products with low ee.^{21,221}

Shortly after their initial reports of Ni-catalyzed asymmetric allylic substitution reactions with alkyl Grignard reagents, Consiglio and co-workers turned to develop the analogous reactions of arylmagnesium species. However, the decreased nucleophilicity of arylmetallic reagents compared to their alkyl counterparts makes allylic *arylation* challenging, and the early studies by Consiglio^{220,221} and Hiyama²²⁵ demonstrated both the promise and the challenge of asymmetric allylic arylation. Using Ni as a catalyst, allylic electrophiles and ArMgBr could be coupled to provide a mixture of branched and linear products (**Scheme 26a**). When acyclic pivalate **266** was utilized, **267** was

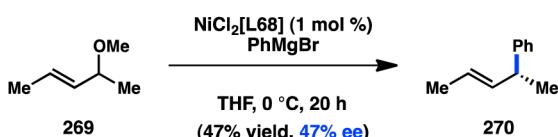
Scheme 26. Ni-Catalyzed Asymmetric Allylic Arylation with Grignard Reagents

a) Coupling of acyclic electrophiles

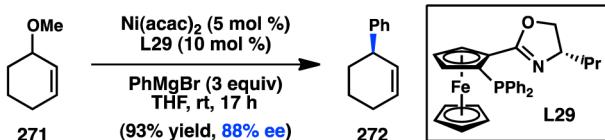


 <p>Chiraphos (L68)</p>	 <p>L70</p>
75% yield 67:33 <i>b/l</i> 89% ee	92% yield 63:37 <i>b/l</i> 80% ee

b) Coupling of symmetrical electrophiles



c) Coupling of cyclic electrophiles

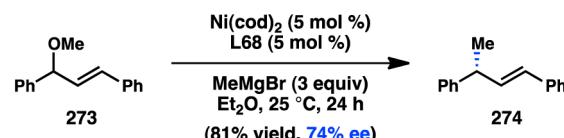


obtained in a promising 89% ee, but as a mixture with the linear coupling product **268**. Similar regioselectivity was observed when diphosphine **L70** was employed.²²⁶ Symmetrical acyclic electrophiles were instead required to avoid the formation of regiosomers (**Scheme 26b**). Whereas cyclic substrates reacted with poor enantioselectivity under Consiglio's conditions, Uemura and co-workers determined that Ni/**L29** delivers cyclic product **272** in high ee (**Scheme 26c**).²²⁷ Control experiments revealed that removal of the planar chirality in **L29** furnished products with only moderate enantioinduction. Interestingly, Uemura's method could not be readily extended to acyclic systems.

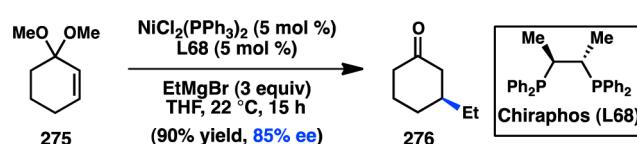
In 1997, RajanBabu and co-workers disclosed an enantioselective Ni/L68-catalyzed alkylation of acyclic diphenylallyl ether **273** (**Scheme 27a**).²²⁸ Methyl ethers were found to provide better results than phenyl ethers, whereas EtMgBr delivered slightly higher ee than MeMgBr. Quenching of the reaction mixture prior to complete conversion led to recovery of enantioenriched **273**, implicating a kinetic resolution of the allyl ether in the oxidative addition step. Shortly after these results, Hoveyda and co-workers reported the Ni-catalyzed addition of alkyl Grignard reagents to unsaturated cyclic acetal **275** (**Scheme 27b**).²²⁹ Following acidic workup, ketone **276**

Scheme 27. Ni-Catalyzed Addition to Allyl Ethers

a) Kinetic resolution of diphenyl allyl ethers



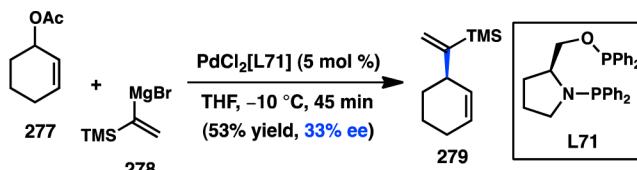
b) Asymmetric addition to unsaturated cyclic acetals



was obtained in high yield and good ee. Although Chiraphos (L68) was identified as the optimal chiral ligand, the authors were intrigued to find that the presence of an achiral phosphine, such as PPh_3 , increased the enantioselectivity of the reaction. Importantly, the reaction conditions permitted both alkyl and aryl Grignard reagents to be incorporated without a difference in enantioinduction.

The first Pd-catalyzed asymmetric allylic substitution using Grignard reagents was reported by Buono and co-workers in 1990. The researchers found that a Pd/L71 complex could catalyze the alkenylation of cyclic electrophile 277 in moderate yield and promising ee (**Scheme 28**).²³⁰ Reaction with simple

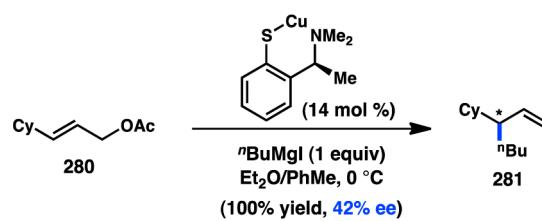
Scheme 28. Pd-Catalyzed Asymmetric Allylic Alkenylation with Grignard Reagents



vinylmagnesium bromide only formed reduction products. The related Pd-catalyzed asymmetric allylic arylation with Grignard reagents has yet to be accomplished.

Despite the pioneering examples of asymmetric Ni- and Pd-catalyzed coupling of Grignard reagents and allylic electrophiles, the attention of the scientific community has shifted toward Cu catalysis over the past two decades. The Cu-catalyzed addition to linear allylic electrophiles is widely known to proceed with excellent regioselectivity for the branched, stereogenic isomer. In 1995, Bäckvall, van Koten, and co-workers reported the first asymmetric Cu-catalyzed coupling of alkylmagnesium reagents with allylic electrophiles (**Scheme 29**).²³¹ In successive years, a range of different leaving groups and chiral ligand scaffolds have been exploited to deliver

Scheme 29. Seminal Example of Cu-Catalyzed Asymmetric Allylic Substitution with Alkyl



branched products in excellent yield, ee, and regioselectivity; these developments have previously been reviewed by others and will not be discussed here.^{4–6,218} Since 2008, efforts have focused on diversifying the toolbox of nucleophiles and electrophiles that can deliver high enantioinduction.

The asymmetric allylic substitution of cinnamyl electrophiles with organomagnesium reagents has served as a model system to test new chiral ligand scaffolds for Cu catalysis (Figure 61).

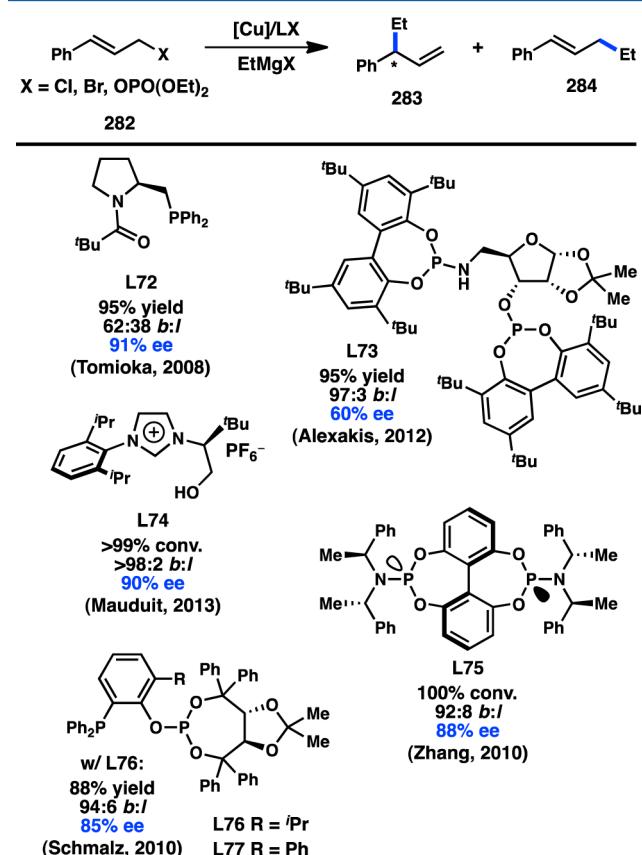


Figure 61. Cu-catalyzed asymmetric allylic alkylation of cinnamyl electrophiles.

In 2008, Tomioka and co-workers applied chiral amidophosphane **L72**, which had previously been used in asymmetric conjugate addition reactions, to the allylic substitution of cinnamyl bromide.²³² High enantioselectivity was observed for the reaction with ethylmagnesium bromide, but the regioselectivity was poor. Nonetheless, **L72** proved to be quite versatile, delivering the branched product in high ee when either alkyl or aryl Grignard reagents were employed.

The laboratories of Schmalz and Zhang independently showed that phosphite or phosphoramidite ligands improve the regioselectivity in the Cu-catalyzed coupling of cinnamyl halides with organomagnesium reagents (Figure 61).^{233,234} Although **L76** was the optimal ligand identified by Schmalz for higher alkyl Grignard reagents, related phosphine–phosphite **L77** delivered better results in the coupling of **282** with MeMgBr. Zhang's novel ligand **L75**, a rare example of a *D*₂-symmetric ligand being used in asymmetric catalysis, provides the substitution product **283** with good regioselectivity and in good ee. Alexakis subsequently reported phosphite–phosphoramidite **L73** in which the ligand chirality is derived from a

furanoside core;²³⁵ **L73** imparts excellent regioselectivity favoring **283**, but the enantioinduction is modest.

In 2013, Mauduit and co-workers investigated the use of NHC ligands in the Cu-catalyzed substitution of cinnamyl phosphates with alkyl Grignard reagents.²³⁶ The chelating, yet relatively simple, NHC **L74** produced **283** in high yield and ee and with excellent regioselectivity (Figure 61). Moreover, the reaction conditions could be extended to the formation of all-carbon quaternary centers with little erosion of ee (Scheme 30).

Scheme 30. Preparation of All-Carbon Quaternary Centers by Asymmetric Allylic Alkylation

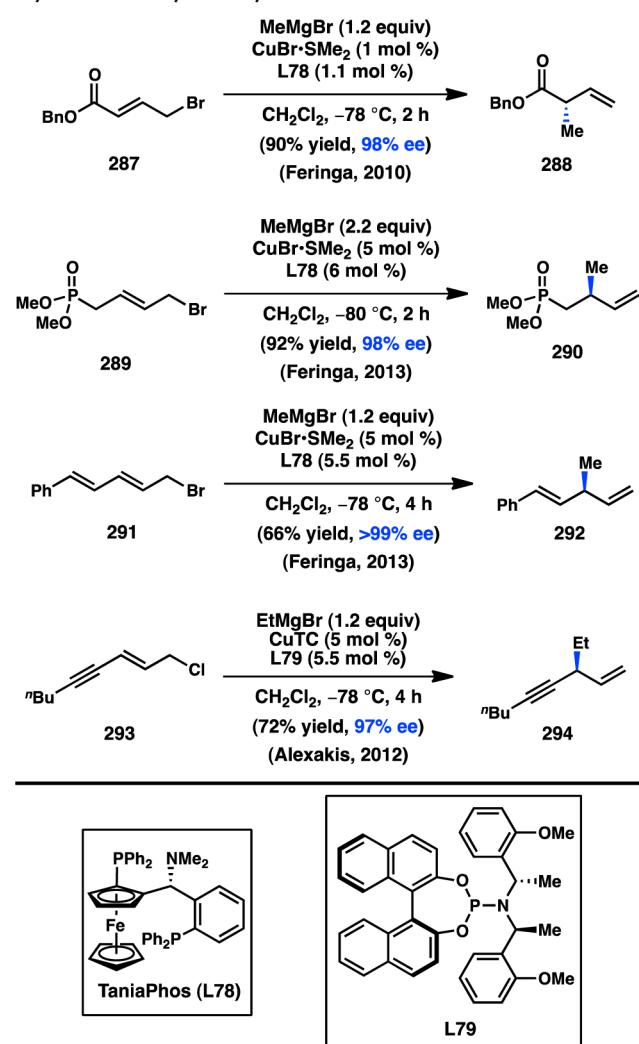


In addition to cinnamyl electrophiles, a concerted effort has been made by the Feringa group to develop Cu-catalyzed reactions between organomagnesium reagents and allylic electrophiles bearing synthetically useful functional groups. Halocrotonate **287** reacts with MeMgBr in the presence of Taniaphos (**L78**) to deliver the desired *S*_N2' product **288** in excellent ee and without formation of 1,2- or 1,4-addition products (Scheme 31).²³⁷ Using the same ligand, Feringa reported the reaction of phosphonate **289** and dienyl bromide **291** with MeMgBr to give products **290** and **291**, respectively, in good yields and with excellent enantioinduction.^{238,239} Recent work by Alexakis and co-workers has demonstrated that skipped enynes can be prepared from enynyl chloride **293** and alkyl Grignard reagents upon exposure to Cu and **L79**.²⁴⁰ Whereas good selectivity for the *S*_N2' product is observed for most higher alkylmagnesium reagents, poor regioselection is obtained in the reaction of MeMgBr. A number of recent reports have also demonstrated the utility of tandem asymmetric allylic alkylation/cross-metathesis for the generation of enantioenriched cyclic species.^{241–244} A tandem asymmetric allylic alkylation/Heck coupling has been realized to form chromene products as well.²⁴⁵

The coupling of more functionalized allylic electrophiles has been extended to include geminal disubstituted electrophiles bearing two leaving groups. In 2010, Feringa and co-workers studied the Cu-catalyzed asymmetric allylic substitution of α -halo acetates (**296**), which can be prepared in situ from aldehyde **295** (Figure 62a).²⁴⁶ Treatment of **296** with CuTC and **L32** delivers **297** with high enantioinduction and exclusive formation of the chloride-displacement product. Higher alkylmagnesium reagents heavily favored *S*_N2' addition, with good selectivity for the (Z)-alkene in most cases; MeMgBr resulted in decreased regioselectivity. Exposure of **297** to base delivered **298**, formally a conjugate addition product. The high Z-selectivity observed in the formation of **297** prompted Feringa and co-workers to investigate the substitution of *gem*-dichloride **299** (Figure 62b).²⁴⁷ Slightly modified reaction conditions provided chloroalkene **300** with excellent ee and 99:1 Z:E-selectivity. To explain the selectivity for the (Z)-isomer, the authors propose that dative coordination between one of the chlorines of **299** and Cu results in oxidative addition through π -complex **301** to give (Z)- σ -allyl complex **302**.

The development of highly enantio- and regioselective Cu-catalyzed allylic substitution reactions with arylmagnesium

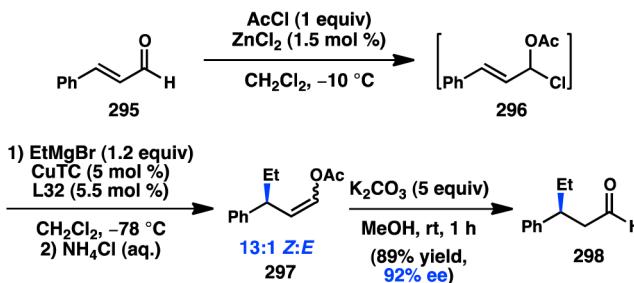
Scheme 31. Expansion of the Scope of Cu-Catalyzed Asymmetric Allylic Alkylation



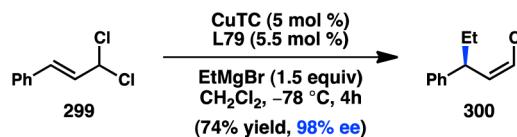
reagents has proven more challenging than the reactions of the corresponding alkylmagnesium species. In 2009, Tomioka and co-workers were able to improve on their previous studies, which utilized Cu/L72 (see Figure 61), by employing chiral NHC ligands. The preformed copper complex derived from L80 catalyzed the reaction between cinnamyl bromide and PhMgBr to furnish diarylalkene 304 in excellent yield, ee, and branch selectivity (Scheme 32).²⁴⁸ A bulky *o*-tol group on L80 was hypothesized to increase the steric hindrance of the γ - σ -allylcopper(III) intermediate, thus facilitating a fast reductive elimination and precluding isomerization via π -allyl formation. Using this principle, bulky NHC ligands were applied to the coupling of aliphatic allyl bromides, delivering the $S_{N}2'$ products in up to 96% branch selectivity and up to 98% ee.²⁴⁹

Asymmetric allyl–allyl cross-couplings provide access to versatile intermediates, but they have been slow to develop because of challenges associated with the dual coordination modes of allylmetal species. In 2013, Feringa and co-workers reported an enantioselective Cu-catalyzed coupling of allylmagnesium halides and allyl bromides (Figure 63).²⁵⁰ The use of phosphoramidite (*R,S,S*)-L32 provided 306 in high ee. A noncoordinating counterion on Cu was necessary to enhance the selectivity for branched product 306; however, the regioselectivity of the reaction was still only modest. The

a) Asymmetric allylic alkylation of α -haloacetates



b) Asymmetric allylic alkylation of gem-dichlorides



Origin of Z-selectivity:

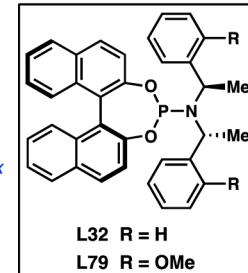
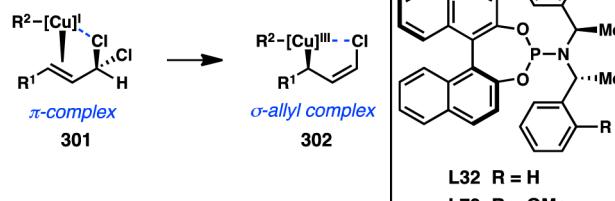
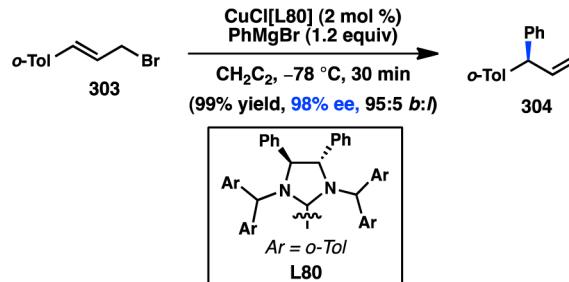


Figure 62. Coupling of allylic electrophiles bearing two leaving groups.

Scheme 32. Cu-Catalyzed Asymmetric Allylic Arylation with Grignard Reagents



authors propose that oxidative addition of allyl-[Cu]^I to an allylic bromide potentially gives rise to a mixture of Cu σ , σ - and σ , π -complexes (308, 309, and 311). Fast reductive elimination from 308 would produce branched product 310, whereas equilibration to π , σ -complex 311 would lead to linear product 312.

The majority of Cu-catalyzed asymmetric allylic substitution reactions of alkyl Grignard reagents employ nonstereogenic allyl electrophiles. High enantioinduction arises from catalyst differentiation of the pro-chiral faces of the substrate. However, in 2009, Alexakis reported a highly enantioselective allylic substitution of racemic cyclic bromide 313, wherein both enantiomers of starting material converge to a single enantiomer of product (Figure 64).^{251,252} A subsequent computational study proposed that this reaction is an example of a direct enantioselective transformation (DET). In a DET, each enantiomer of starting material proceeds according to a distinct reaction pathway to provide ultimately the identical enantiomer of product. In the present example, Cu/L32

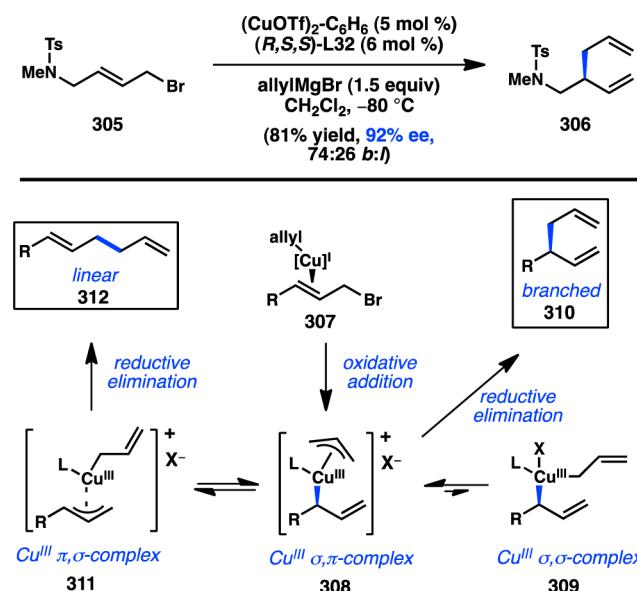


Figure 63. Cu-catalyzed allyl–allyl coupling.

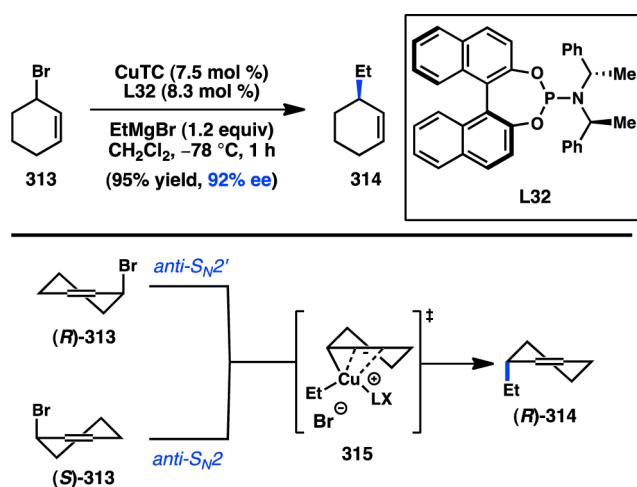


Figure 64. Direct enantioselective transformation (DET) of a racemic allylic electrophile.

engages (*R*)-313 through an $S_{N}2'$ oxidative addition, whereas (*S*)-313 reacts by an $S_{N}2$ oxidative addition, both converging to Cu^{III} complex 315.²⁵³

When this method was extended to acyclic systems and L81 was employed as the ligand, the authors obtained a ~1:1 mixture of (*R,E*)-317 and (*R,Z*)-317, both of which were formed in high ee (Figure 65).²⁵⁴ To explain this behavior, the authors propose that the reaction proceeds by a stereodivergent kinetic resolution (SKR), in which the chiral catalyst favors an *anti S_N2'* oxidative addition to the *Si* face of the alkene. To satisfy these mechanistic conditions, (*S*)-316 must react in the pro-*E*-conformation, whereas (*R*)-316 must react in the pro-*Z*-conformation.

4.1.2. Organozinc Reagents. In 1985, Fiaud and co-workers reported their investigations of the Pd-catalyzed substitution of allylic acetates with arylzinc halides (Scheme 33).^{255,256} When phosphine L82 was used as the chiral ligand, the reaction between 277 and PhZnCl provided 272 in 60% yield but with poor enantioinduction. Nearly 15 years later, the first enantioselective allylic substitution reaction of organozinc

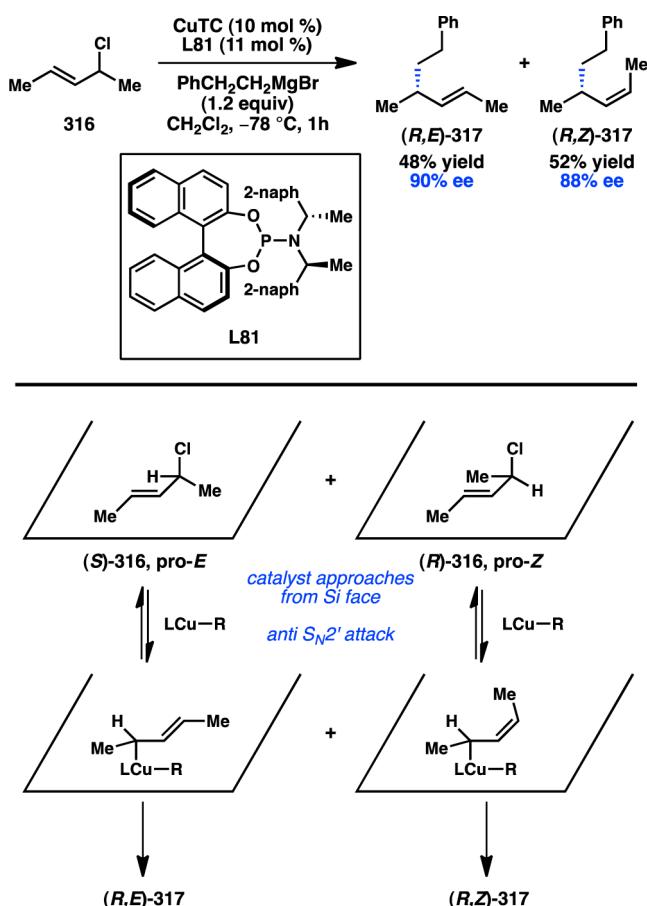
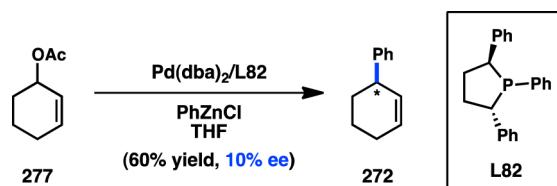


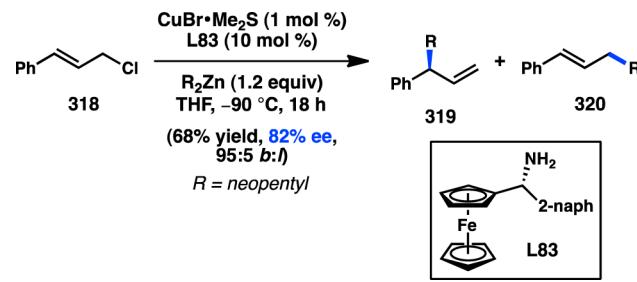
Figure 65. Stereodivergent kinetic resolution (SKR) of an acyclic racemic electrophile.

Scheme 33. Seminal Enantioselective Pd-Catalyzed Substitution of Cyclic Allylic Acetates



reagents was reported by Knochel and co-workers (**Scheme 34**).²⁵⁷ Subsequent developments have expanded the scope of leaving groups and the degree of enantioinduction to prepare both tertiary and quaternary centers, primarily using Cu catalysts.^{4–6,218}

Scheme 34. Seminal Enantioselective Cu-Catalyzed Substitution of Allylic Chlorides



Beginning in 2007, researchers began to reinvestigate transition metals other than Cu for the cross-coupling between allylic electrophiles and organozinc reagents. In 2008, Fu and co-workers disclosed a Ni-catalyzed stereoconvergent coupling of alkylzinc halides and branched allylic halides (Figure 66).²⁵⁸

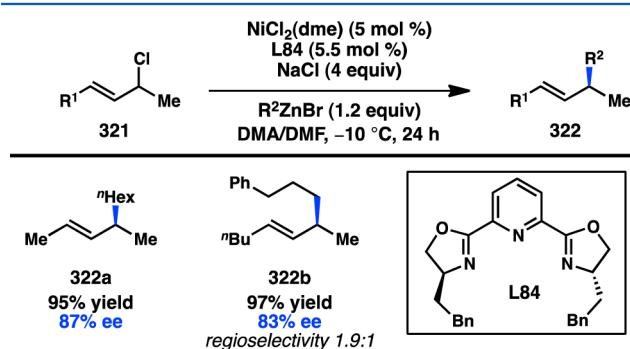


Figure 66. Stereoconvergent Ni-catalyzed coupling of internal allylic electrophiles.

With Pybox L84 as the ligand, a variety of primary alkylzinc halides and unsymmetrical allylic halides could be coupled with high enantio- and regioselectivity, favoring C–C bond formation at the less hindered position. Only in the case of 322b, in which a Me group must be distinguished from an *n*Bu group, was there poor regiodifferentiation. The advantage of this method over many of the Cu-catalyzed reactions lies in its ability to promote stereoconvergent couplings of racemic, stereogenic allylic electrophiles.

The first highly enantioselective Pd-catalyzed allylic substitution reaction using organozinc reagents was developed by Maulide and co-workers in 2014. This transformation has been challenging to achieve because of the well-precedented umpolung reactivity of allylpalladium complexes in the presence of dialkylzinc reagents.^{259,260} Upon exposure to R₂Zn, allylpalladium species typically acquire nucleophilic character and can react with electrophiles through undesired pathways (Figure 67). Maulide discovered that phosphoramidite L85 imparts unique reactivity to the allylpalladium complex, favoring allylic substitution to provide coupled product 324 in both good yield and good ee.

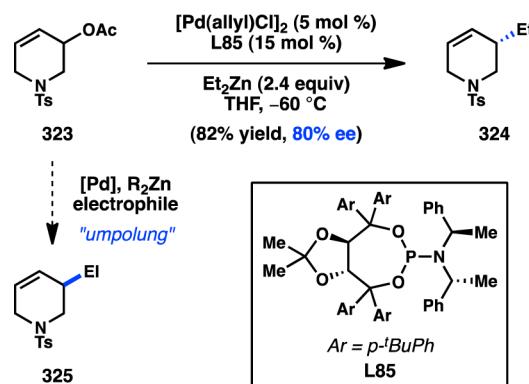


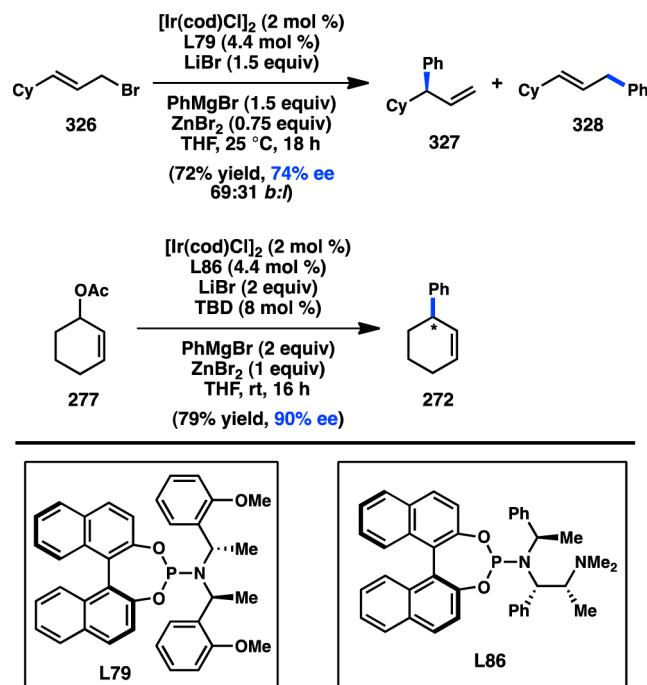
Figure 67. Stereoconvergent Pd-catalyzed coupling of cyclic allylic electrophiles.

Ligand L85 imparts unique reactivity to the allylpalladium complex, favoring allylic substitution to provide coupled product 324 in both good yield and good ee.²⁶¹ Although a variety of cyclic allylic electrophiles were found to be competent reaction partners, only hydrodehalogenation was observed with an acyclic electrophile. The mechanism and

origin of enantioinduction have yet to be explored for this intriguing transformation.

Although the Cu-catalyzed asymmetric allylic substitution using *alkyl*metallic reagents had been extensively developed throughout the early 2000s, examples using *aryl*metallic reagents were still quite rare. In 2007, Alexakis and co-workers examined the ability of different transition-metal catalysts to promote the branch-selective and enantioselective coupling of aliphatic allylic carbonates and arylmetal reagents.^{262,263} Iridium was chosen for further study because of its propensity to deliver λ -substituted products in the allylic substitution of stabilized nucleophiles.^{264,265} Treatment of 326 with PhMgBr in the presence of Ir/L79 as the catalyst led to deprotection of the electrophile but no formation of coupled product. In contrast, transmetalation to the aryl zinc reagent and addition of excess LiBr enabled the desired substitution reaction, providing 327 in good yield and ee, albeit with low selectivity for the branched product (Scheme 35). A variety of phosphoramidite ligands

Scheme 35. Ir-Catalyzed Asymmetric Allylic Arylation with Organozinc Reagents



were studied in place of L79, but none delivered enhanced regioselectivity. Modified reaction conditions could be applied to cyclic allylic acetates (277), generating products in as high as 90% ee without any complications from regiosomeric mixtures.

Notwithstanding the recent developments with other transition-metal catalysts, Cu has remained the workhorse of enantioselective allylic substitution reactions of organozinc reagents. Advances in ligand design continue to expand the scope and selectivity of these transformations. In 2009, Nakamura and co-workers disclosed amino hydroxy phosphine L87, with which the Cu-catalyzed reaction between cinnamyl phosphate 329 and dialkylzinc reagents proceeds in modest yield but high ee and regioselectivity (Figure 68).²⁶⁶ The authors suggest that the multiple chelating sites on L87 permit the formation of a Cu/Zn bimetallic complex. Simultaneous π -complexation by Cu and phosphate coordination by Zn forges a closed transition state that can promote an *anti S_N2'* oxidative

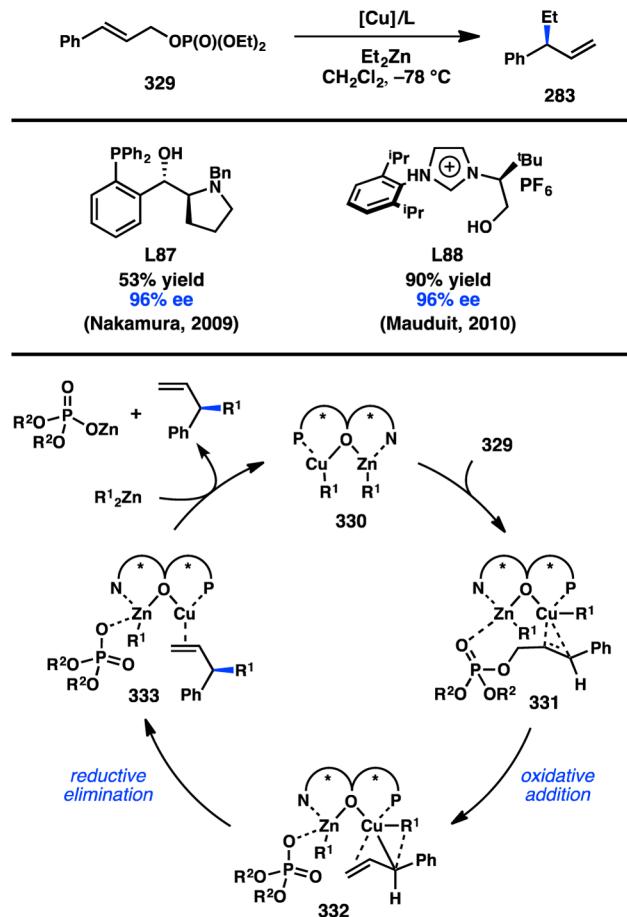
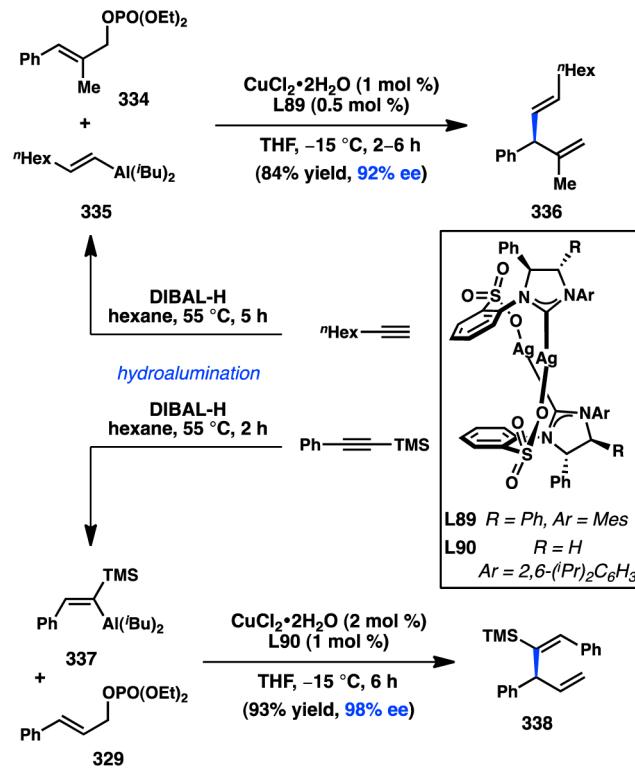


Figure 68. Cu-catalyzed coupling of allylic phosphates.

addition. The following year, Mauduit and co-workers revealed that hydroxyalkyl NHC L88 can provide 283 in both high yield and high ee.²⁶⁷ The reaction scope was later extended to include the synthesis of skipped dienes as well as the use of Grignard reagents.²³⁶

4.1.3. Organoaluminum Reagents. Trimethylaluminum was first studied in asymmetric allylic alkylation in 2000 by Woodward and co-workers, but both isolated yields and ee's below 10% were obtained.²⁶⁸ In 2008, Hoveyda and co-workers showed that Cu–NHC complexes catalyze the coupling between allylic phosphates and alkenylaluminum species, which were prepared in situ from an alkyne and DIBAL-H (Scheme 36).²⁶⁹ NHC L89 was unique in delivering both high regioselectivity and high enantioselectivity; furthermore, ¹Bu group transfer was low. If the reaction was conducted using the imidazolium salt precursor to L89, lower conversion was observed. Unfortunately, the reaction scope was limited to alkenylaluminum species that could be prepared by hydroalumination, which excluded *cis*-alkenylaluminum species, or vinyl groups with aryl substitution. To overcome these issues, Hoveyda investigated the hydroalumination of phenylacetylene derivatives and discovered that trimethyl(phenylethynyl)silane underwent clean hydroalumination with DIBAL-H.²⁷⁰ Moreover, depending on the reaction conditions, either the (*E*)- or the (*Z*)-isomer of the vinylmetal could be accessed. Subsequent reaction of 337 and phosphate 329 with Cu/L90 delivered 338 in high yield and excellent ee. The TMS group could be removed under mild conditions to deliver a disubstituted *cis*-alkene; correspondingly, *trans*-alkenes could be generated from

Scheme 36. Cu-Catalyzed Asymmetric Allylic Vinylation with Organoaluminum Reagents



the (*Z*)-isomer of 337. Subsequent studies by Hoveyda have established that both alkyl- and aryl-substituted vinylaluminum reagents can also be applied to the synthesis of all-carbon quaternary stereocenters.²⁷¹

Following their success using vinylaluminum reagents, the Hoveyda laboratory investigated whether arylaluminum reagents could participate in a rare example of transition-metal-catalyzed asymmetric allylic arylation. The requisite organometallic reagents are prepared by treatment of aryllithium species with Et₂AlCl (Figure 69).²⁷² The authors expected that the aryl group on Al would be more likely to transmetalate to Cu than the alkyl group.^{273–276} Cu-catalyzed coupling of an arylaluminum and allylic phosphate 339, using NHC L91 as the

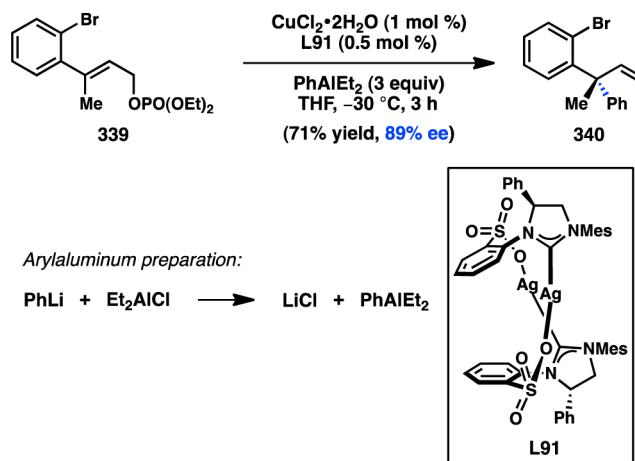


Figure 69. Cu-catalyzed asymmetric allylic arylation with organoaluminum reagents.

ligand, furnished **340** in good yield and high ee. A variety of aryl- and heteroarylaluminum reagents could be used to generate products bearing all-carbon quaternary stereocenters.

In 2011, Hoveyda and co-workers discovered that Cu/L90 catalyzes the asymmetric cross-coupling of alkynylaluminum reagents with allylic phosphates to form all-carbon quaternary stereocenters (**Figure 70**).^{277,278} The authors were surprised to

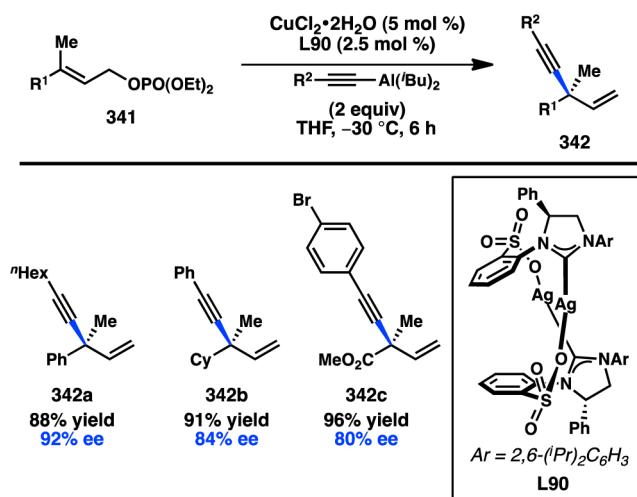


Figure 70. Cu-catalyzed asymmetric allylic alkynylation with alkynylaluminum reagents.

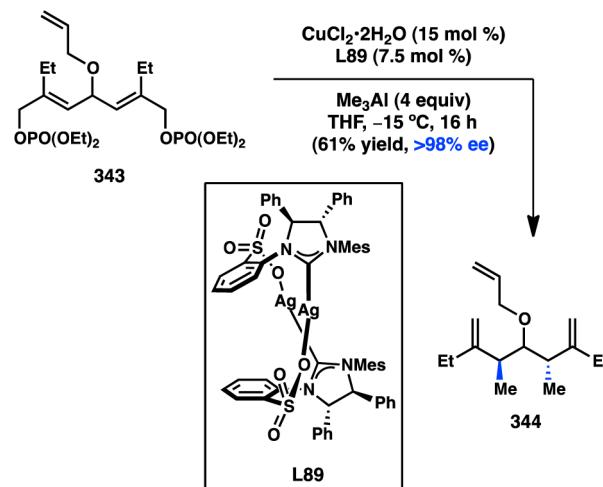
see good chemoselectivity for alkynyl transfer, because alkynes are sometimes used as dummy ligands on copper. The organoaluminum reagents could easily be prepared *in situ* by treatment of an alkyne with DIBAL-H and Et₃N.

C(sp³) organoaluminum reagents have been less frequently utilized in asymmetric allylic substitution reactions than their organozinc counterparts. However, in 2007, Hoveyda and co-workers showed that AlMe₃ provided better results than Me₂Zn in Cu/L89-catalyzed S_N2' substitution reactions of allylic phosphates. This reactivity was exploited in an elegant example of a double S_N2' reaction toward a total synthesis of baconipyrone C (**Scheme 37a**).²⁷⁹ A Ni-catalyzed allylic substitution was also developed by Woodward and co-workers, in which Baylis–Hillman adduct **345** could be coupled with AlMe₃ (**Scheme 37b**).^{280,281} Axially chiral Ferrocite **L92** imparted high enantioinduction, but good control of regioselectivity remains an unsolved obstacle.

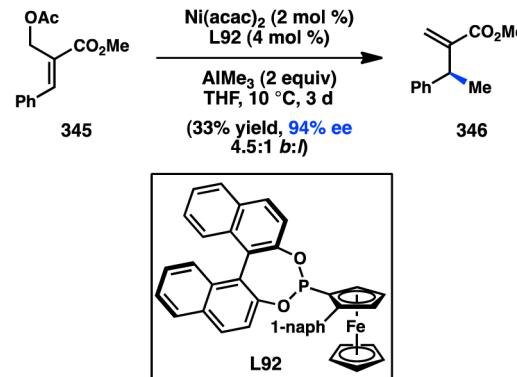
4.1.4. Organoboron Reagents. Of the various organometallic nucleophiles utilized for asymmetric allylic substitution reactions, organoboron reagents have been successfully implemented with the most diverse array of transition-metal catalysts, including Ni, Rh, Ir, Pd, and Cu. In 2000, Uemura studied the reactivity of both organoboron and organomagnesium reagents in the Ni-catalyzed asymmetric allylic arylation of cyclohex-2-en-1-yl acetate (**277**). The use of (oxazolinylferrocenyl)phosphine **L29** enabled formation of **272** in good yield and moderate ee, representing the first example of an arylboron reagent being used in asymmetric allylic arylation (**Scheme 38**).²⁸² In comparison to Uemura's related coupling of Grignard reagents (see **Scheme 26**),²²⁷ several points are worth noting: (1) the lower nucleophilicity of organoboron reagents requires the addition of base and for the reaction to be conducted at elevated temperatures, (2) a smaller range of leaving groups participate in the coupling with arylboron

Scheme 37. AlMe₃ in Ni-Catalyzed Asymmetric Allylic Alkylation

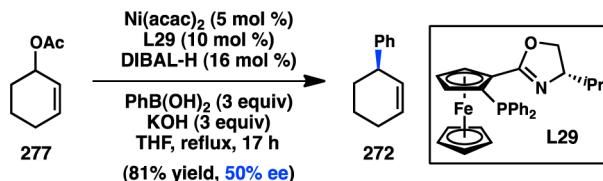
a) Double S_N2' reaction of Me₃Al toward baconipyrone C



b) S_N2' reaction of Me₃Al with Baylis–Hillman adducts



Scheme 38. Ni-Catalyzed Asymmetric Allylic Arylation with Organoboron Reagent



species, and (3) lower levels of enantioinduction by **L29** are observed. Both methods suffer from reduced ee and poor regioselectivity when applied to acyclic substrates.

Building on earlier studies of Rh-catalyzed asymmetric 1,4-addition reactions of boronic acids to nitrocyclohexene,²⁸³ in 2005, Gong and co-workers reported the Rh-catalyzed substitution of nitroallyl acetate **347** with PhB(OH)₂ (**Figure 71**).²⁸⁴ The authors reasoned that, following insertion into the olefin of **347**, a β -elimination of the acetate group might deliver the desired allylic substitution product. Rh-catalyzed coupling of **347** and PhB(OH)₂ with BINAP as a chiral ligand furnished **348** in excellent enantioselectivity. Subsequent studies revealed that higher yields but slightly lower enantioselectivity could be obtained when more reactive arylzinc halides were employed as the nucleophile.²⁸⁵

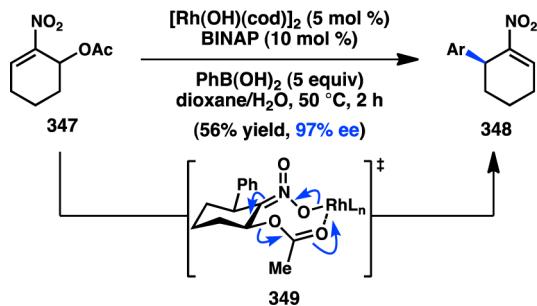


Figure 71. Rh-catalyzed reactivity of nitroallyl acetates.

Allylic diols have also been studied as electrophiles in Rh-catalyzed allylic substitution reactions with arylboron reagents. Murakami and co-workers discovered that Rh catalyzes the reaction of *cis*-diol 350 with phenylboroxine to give enantioenriched homoallylic alcohol 351 when chiral diene L93 is employed as the ligand (Figure 72).²⁸⁶ It was observed

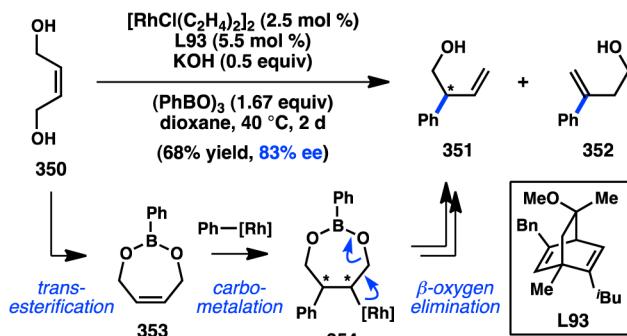


Figure 72. Allylic substitution by carborhodation.

that allylic *cis*-diol 350 first reacts with phenylboroxine to generate cyclic allyl boronate ester 353. Subsequent carbometalation followed by β -oxygen elimination yields alcohol 351. The production of minor constituent 352 was rationalized by a β -hydride elimination/reinsertion/ β -oxygen elimination sequence. A limited scope of arylboroxines was demonstrated for the transformation.

In 2012, Oi and co-workers reported the Rh/DTBM-SEGPHOS-catalyzed coupling of allyl aryl ethers (355) with arylboronic acids to give allylic substitution product 4 (Figure 73).²⁸⁷ A variety of arylboronic acids were found to react in good yields and with high enantioselectivity. The authors proposed a carborhodation/ β -oxygen elimination mechanism analogous to that suggested by Murakami for the reaction of allylic *cis*-1,4-diols.

Lautens and co-workers have studied a closely related reaction, the Rh-catalyzed asymmetric arylation of allylic *cis*-dicarbonates.²⁸⁸ Rh/L94-catalyzed substitution of dicarbonate 358 with PhB(OH)₂ delivered branched product 359 in high yield and ee (Figure 74). The minor product was found to be the isomeric, linear carbonate 360; notably, the alkene corresponding to 352, detected by Murakami in the previously discussed reaction (see Figure 72), was not observed. This finding prompted Lautens to propose instead an oxidative addition/reductive elimination mechanism that proceeds through σ -enyl intermediate 361. Slow isomerization to linear organorhodium complex 362 would explain formation of 360, where the relative rates of reductive elimination from 361 versus isomerization to 362 would determine the product

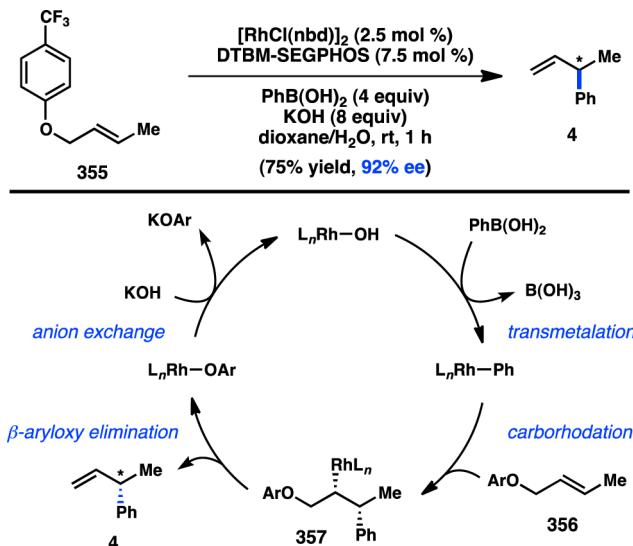


Figure 73. Allylic substitution of allyl aryl ethers.

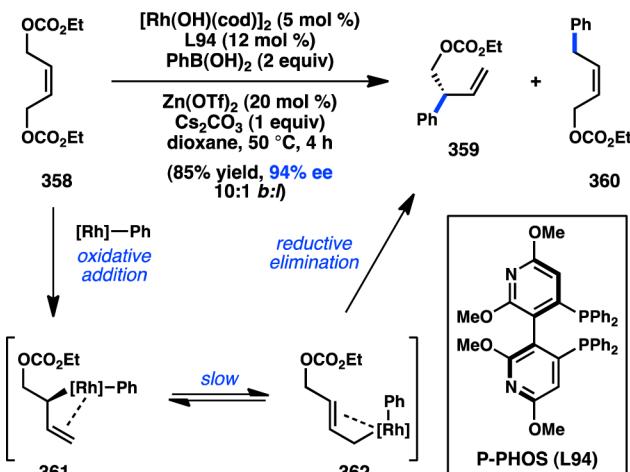


Figure 74. Allylic substitution by oxidative addition of Rh complexes.

distribution. The Rh-catalyzed desymmetrization of *meso*-cyclopentene-1,4-diol dicarbonates with arylboron reagents has also been developed by the same group.^{289,290}

Until recently, there have been few reports of Cu-catalyzed stereoselective couplings of allylic electrophiles and C(sp²)-hybridized organoboron reagents. In 2011, Shintani, Hayashi, and co-workers discovered that CuCl, in conjunction with Mauduit-type NHC ligand L95^{236,267} bearing a pendant hydroxyl group, catalyzes the union of allylic phosphate 329 and boronate ester 363 (Figure 75).^{291,292} The use of NaOMe was important to favor formation of the branched product over the linear isomer. A wide scope of arylboron reagents were well tolerated, and trisubstituted allylic phosphates could be employed to deliver all-carbon quaternary stereocenters. Moreover, a cyclohexenylboronate was coupled with only a small erosion of ee. The authors propose a mechanism in which transmetalation proceeds via complex 365, in which the alcohol of L95 undergoes transesterification with the boronic acid. B to Cu transmetalation, followed by oxidative addition to phosphate 368, would generate σ -allylcopper complex 369. Reductive elimination would then provide product 370 and regenerate the Cu catalyst.

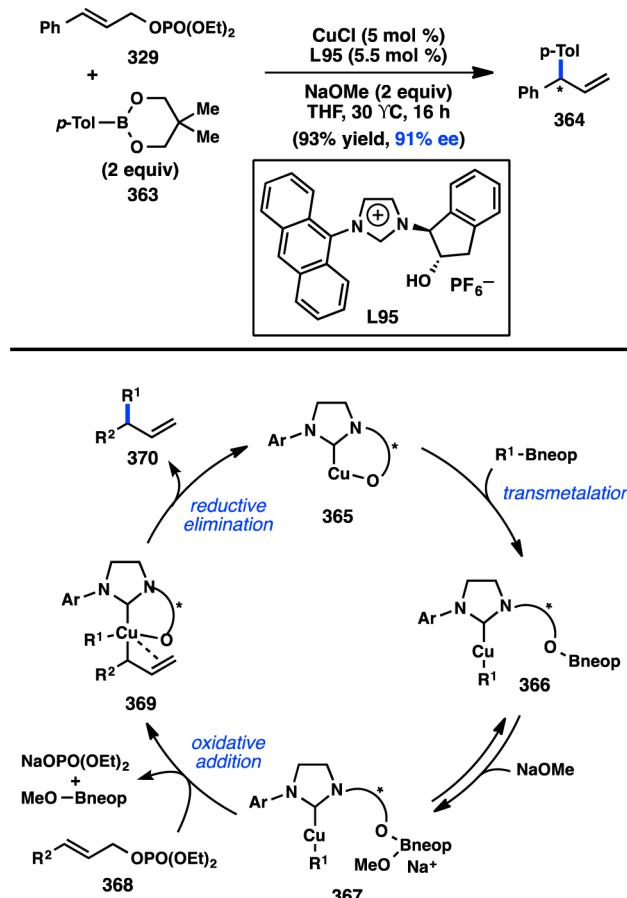


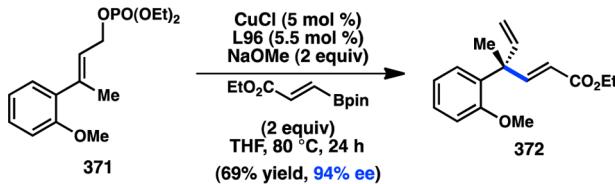
Figure 75. Cu-catalyzed asymmetric allylic arylation with arylboron reagents.

In 2012, Hoveyda and co-workers turned their attention from alkenylaluminum reagents to alkenylboron reagents for Cu-catalyzed asymmetric allylic substitution.^{293,294} Using NHC ligand L96, allylic phosphate 371 could be coupled with alkenylboron esters in good yield and high enantio- and regioselectivity (Scheme 39a). Compared to the coupling of vinylaluminum species, these reactions require higher temperatures because of the decreased nucleophilicity of the organoboron. However, the method tolerated functional groups that were not compatible with the vinylaluminum chemistry. Both (*Z*)-alkenylboron and trisubstituted alkenylboron reagents couple efficiently, readily enabling the synthesis of several natural products. More recently, the Cu/L97-catalyzed coupling of allenylboron reagents with allylic phosphates was disclosed (Scheme 39b).²⁹⁵ These reactions could be conducted at lower temperatures, presumably because of the decreased steric hindrance at the nucleophile. Excellent fidelity for allenylation over propargylation was observed in all cases. A study of ligand effects illustrated the importance of the sulfonate group on L97 for providing γ -selectivity.

Iridium complexes have emerged as privileged catalysts that provide branched products in a wide variety of allylic substitution reactions with heteronucleophiles and stabilized nucleophiles.^{264,265} Carreira and co-workers were able to extend this reactivity to alkenyl trifluoroborates, finding that Ir/L98 catalyzes the reaction of simple allylic alcohols (374) with alkenyl trifluoroborates to furnish skipped diene products in good yields and remarkable levels of enantioinduction (Figure 76).²⁹⁶ The $^n\text{Bu}_4\text{HSO}_4$ was proposed to perform two

Scheme 39. Cu-Catalyzed Asymmetric Allylic Substitution with Other C(sp²)-Hybridized Boron

a) Asymmetric allylic alkenylation



b) Asymmetric allylic allenylation

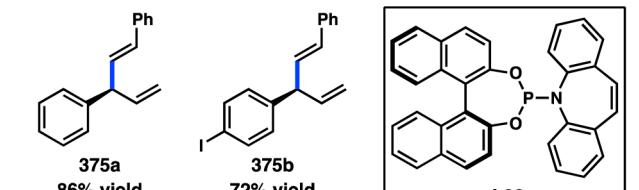
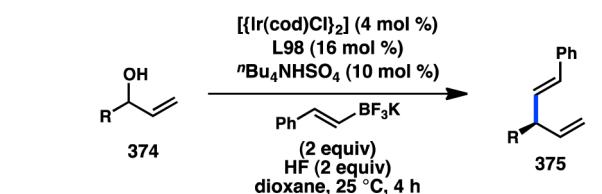
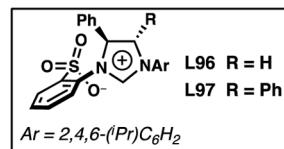
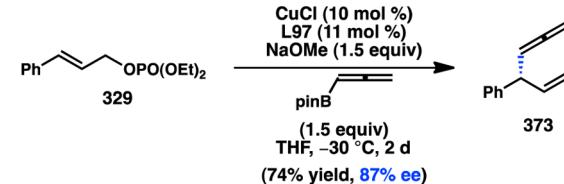


Figure 76. Ir-catalyzed asymmetric allylic vinylation with vinylboron reagents.

functions: Brønsted acid activation of the allylic alcohol and solubilization of the trifluoroborate salt through phase-transfer catalysis. Both aryl and aliphatic vinyl trifluoroborates are competent in the reaction; however, the scope of electrophiles was limited to aryl- and heteroaryl-substituted allylic alcohols.

Building on their successful Ir-catalyzed asymmetric allylic vinylation, Carreira and co-workers turned to developing the analogous alkynyl coupling reaction. Using the same Ir/L98 catalyst system, allylic alcohol 376 could be coupled to a variety of aryl- and alkyl-substituted alkynyl trifluoroborates (Figure 77).²⁹⁷ Slight modifications to the previously disclosed vinylation conditions were required: instead of using $n\text{Bu}_4\text{HSO}_4$ as an additive, the combination of phase transfer catalyst $n\text{Bu}_4\text{NBr}$ and Brønsted acid $\text{CF}_3\text{CO}_2\text{H}$ was used. The ability to form tertiary stereocenters is complementary to Hoveyda's Cu-catalyzed coupling of alkynylaluminum reagents, a method that was limited to the synthesis of all-carbon quaternary centers.^{277,278}

The asymmetric allylic functionalization by C(sp³)-hybridized boron reagents has only recently witnessed success in

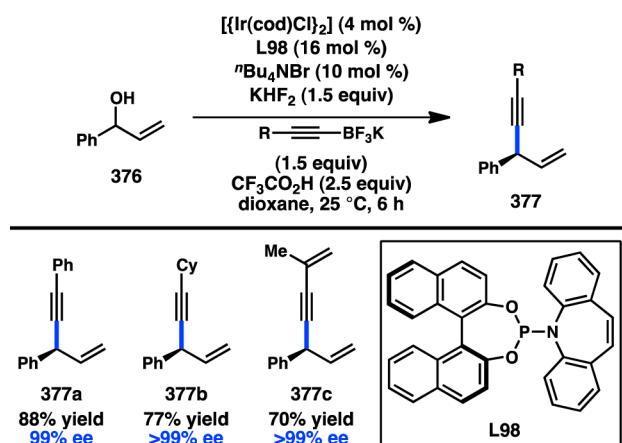


Figure 77. Ir-catalyzed asymmetric allylic alkynylation.

both Pd- and Cu-catalyzed reactions. In 2010, Morken and co-workers disclosed the use of allylboron reagents in Pd-catalyzed asymmetric allyl–allyl couplings. Using BIPHEP ligand L99, the Pd-catalyzed coupling of allyl carbonate 378 and allylboronate delivered 379 in good yield and high ee; notably, both isomers of the allyl carbonate starting material were found to converge to the same product (Figure 78). The authors

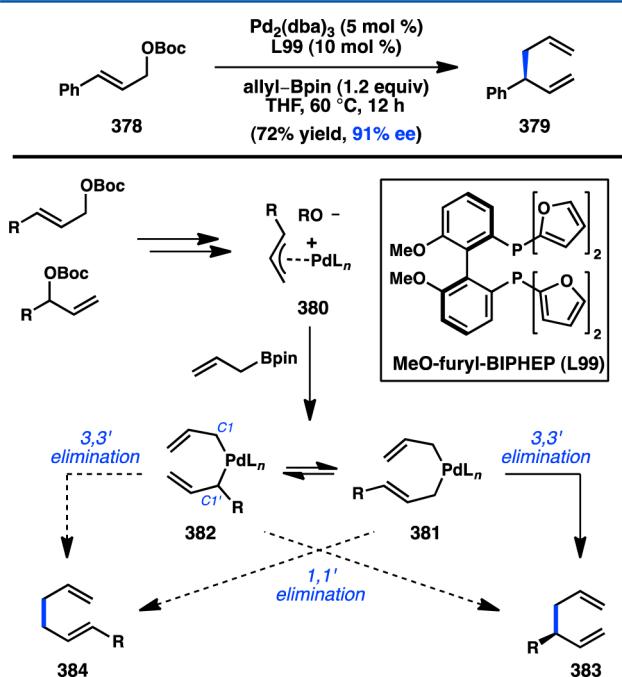


Figure 78. Pd-catalyzed enantioselective allyl–allyl coupling.

propose that bidentate ligand **L99** forces the allyl groups of a bisallylpalladium complex **381** to adopt η^1 rather than η^3 binding modes. Complex **381** is now poised to undergo a 3,3' reductive elimination to furnish stereogenic product **383**.²⁹⁸ The authors hypothesize that equilibration between **381** and **382** should favor the less sterically demanding metal complex. Furthermore, the bite angle of the ligand could affect the ratio of branched (**383**) to linear (**384**) products, with small-bite-angle ligands increasing the C1–C1' separation and disfavoring 1,1' reductive elimination. Indeed, ligands with small bite angles favored branched products, and those with larger bite angles were unselective.

Having devised a paradigm for allyl–allyl coupling, Morken and co-workers subsequently expanded the scope of the transformation to form products with all-carbon quaternary or vicinal tertiary centers. Substituted allylboronates were found to react with allylic chlorides (385) to form coupled products (e.g., 388) with both enantio- and diastereoccontrol (Figure 79).²⁹⁹ The increased steric hindrance of the boronate

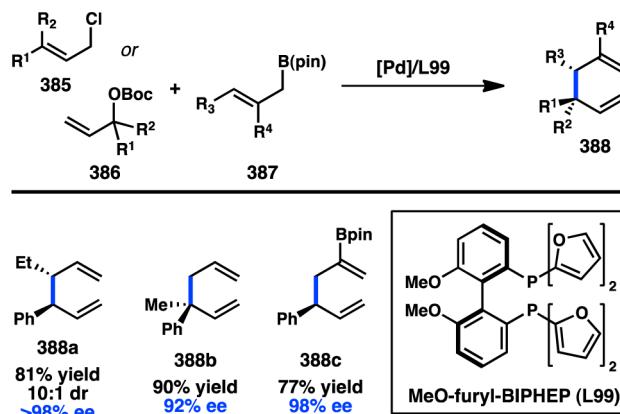


Figure 79. Pd-catalyzed enantioselective allyl–allyl coupling: expansion of the substrate scope.

nucleophile required the addition of CsF to accelerate transmetalation. Products with all-carbon quaternary centers (**388b**) could be generated from tertiary allylic carbonates (**386**) with little erosion of ee.³⁰⁰ Lastly, a bisboronate starting material can be employed, leading to synthetically versatile **388c** in high ee.³⁰¹ Alkyl-substituted allylic electrophiles were also tolerated when a quinoxaline ligand was utilized. A mechanistically distinct Cu-catalyzed allyl–allyl coupling was later reported by Feringa and co-workers.²⁵⁰

Morken's studies on allylboron reagents prompted the discovery of the first enantioselective intramolecular coupling of an allylboronate and an aryl halide. Phosphoramidite **L100** was identified as the optimal ligand, providing indane **390** in 80% ee (Figure 80).³⁰² Interestingly, the reversed-polarity intramolecular coupling of an allyl halide and an arylboronate proceeded with similar enantioselectivity. Additional studies revealed that reductive elimination is the stereochemistry-determining step, which occurs after equilibration of trans-

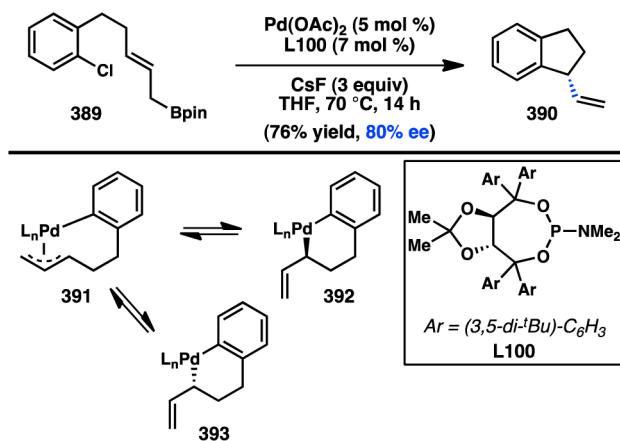


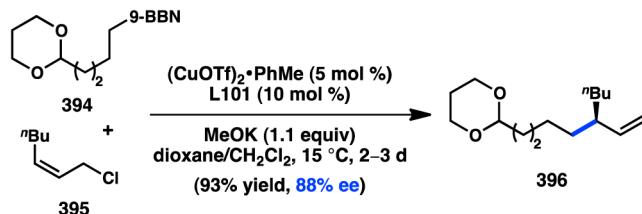
Figure 80. Enantioselective intramolecular coupling of an allylboronate.

metalation adducts **392** and **393**. Reaction conditions that either slowed reductive elimination or accelerated isomerization delivered higher ee's of **390**. The origin of enantioselectivity stands in stark contrast to the intermolecular coupling of allylboron reagents developed by Yamamoto and Miyaura.¹⁰⁷

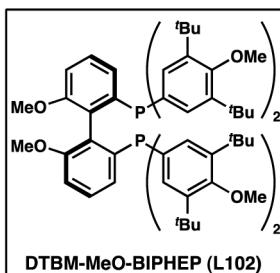
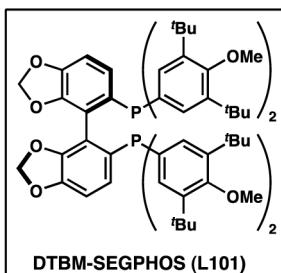
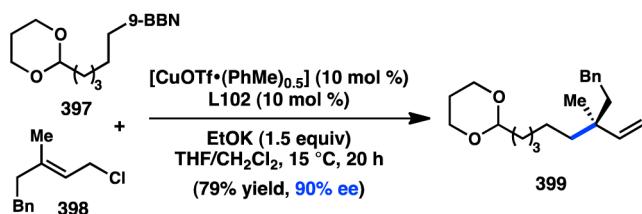
In 2012, Sawamura and co-workers reported the first enantioselective allylic alkylation using simple alkylboron reagents. Under Cu-catalyzed conditions derived from their previously reported stereospecific coupling of allylic phosphates and alkylboron reagents,³⁰³ the authors were able to couple allylic chloride **395** with alkylborane **394** to deliver **396** in excellent yield with high enantio- and regioselectivity (Scheme 40a).³⁰⁴ The DTBM group on **L101** was necessary for both

Scheme 40. Cu-Catalyzed Enantioselective Allylic Alkylation Using Unactivated Alkylborons

a) Preparation of tertiary centers



b) Preparation of quaternary centers



high selectivity and high reactivity; it was proposed this moiety might assist in deaggregation of alkylcopper species, increasing the concentration of active monomeric Cu complexes. Under similar conditions that instead utilize **L102**, trisubstituted allylic electrophile **398** reacts with alkylboron **397** to form a compound bearing an all-carbon quaternary center in 90% ee (Scheme 40b).³⁰⁵

The authors propose that the aforementioned reactions proceed by an addition/elimination mechanism (Figure 81). Transmetalation of the Cu catalyst with the “ate” complex of the alkylboron reagent would give neutral alkylcopper species **400**, which would engage allylic chloride **401** through carbocupration, rather than *anti* S_N2' oxidative addition. Asymmetric induction is thought to arise from differentiation of the two prochiral faces of the olefin by the catalyst. β -Elimination of Cl, possibly assisted by Lewis acidic 9-BBN-OR,

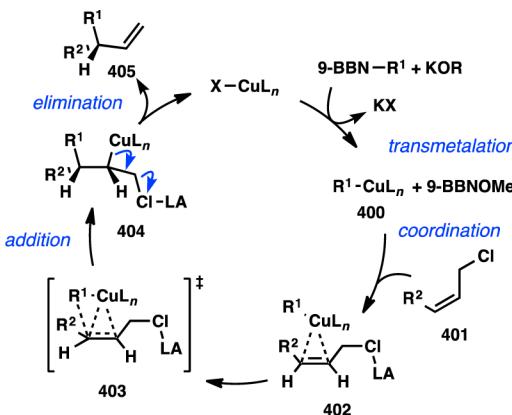


Figure 81. Mechanism of allylic alkylation using alkylboron reagents.

would produce the observed product and re-form the active catalyst.

4.1.5. Organolithium Reagents. The high reactivity of organolithium reagents has traditionally prevented their use in asymmetric allylic alkylation reactions: any successful transformations would require conditions that avoid or outcompete unselective background reactivity. By performing spectroscopic studies to understand the parameters that favor catalytically active alkylcopper species and disfavor reactive organolithium aggregates or lithium cuprates, Feringa and co-workers were able to develop the first enantioselective cross-coupling of alkylolithium reagents.³⁰⁶ The key was to exclude ethereal solvents and lower the temperature to –80 °C, under which conditions ligated alkylcopper species could be selectively formed. Thus, slow addition of an organolithium reagent to a dichloromethane solution of allylic halide (**406**) and Cu/L78 at –80 °C provided alkylated product **407** in high yield with good regioselectivity and excellent enantioinduction (Figure 82).^{306,307} High chemoselectivity was demonstrated through the coupling of substrates bearing aryl halides and even a free alcohol. The use of phosphoramidite **L103** also delivered products with good enantioselectivity: in addition to tertiary centers, the method could be expanded to the synthesis of all-carbon quaternary centers.³⁰⁸ A recent study has shown that

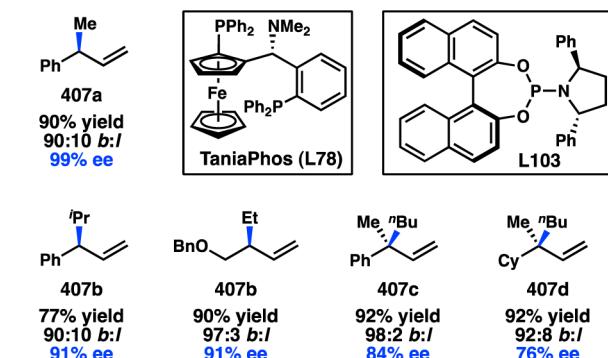
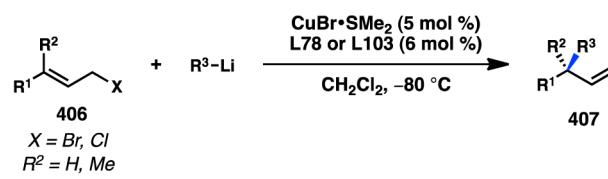


Figure 82. Asymmetric allylic alkylation using organolithium reagents.

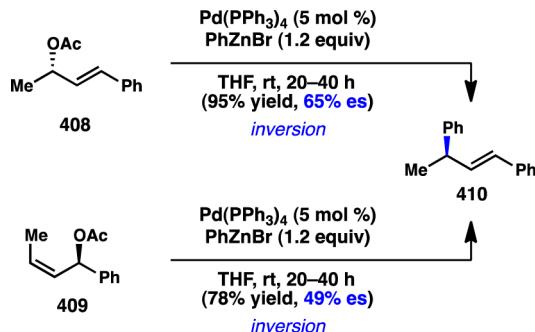
addition of a Lewis acid can enable the use of methyl or benzyl ethers as leaving groups, increasing the scope of the electrophile.³⁰⁹

4.2. Enantiospecific Allylic Substitutions

Early efforts toward developing stereospecific substitution reactions of allylic electrophiles focused on the use of soft nucleophiles, such as malonates, or hard nucleophiles, such as alkoxides. Whereas enantiospecific allylic substitution reactions using stoichiometric copper nucleophiles have been known for decades and have been exhaustively studied, the corresponding transition-metal-catalyzed reactions of organometallic reagents were much slower to develop.

4.2.1. Organozinc Reagents. The first report of a transition-metal-catalyzed stereospecific allylic substitution reaction using an organometallic nucleophile was disclosed in Hayashi and co-workers' investigations of Pd-catalyzed reactions of allylic acetates (Scheme 41).³¹⁰ Pd-catalyzed

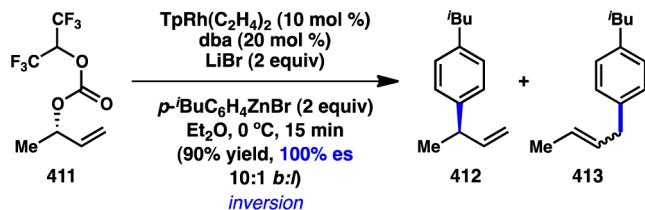
Scheme 41. Pd-Catalyzed Stereospecific Allylic Arylation with Arylzinc Reagents



reaction of acetate 408 with phenylzinc bromide delivered arylation product 410 in good yield and with modest es favoring inversion of stereochemistry. Exposure of isomeric acetate 409 to the same conditions also produced 410 as the major product, albeit with lower es. Although both processes proceed with inversion of stereochemistry, the observation that both 408 and 409 converge to a common product suggests that they proceed through a similar π -allylpalladium intermediate.

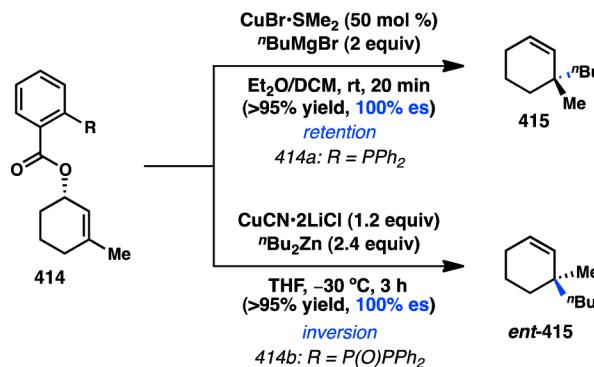
Nearly two decades later, Evans and Uraguchi reported the Rh-catalyzed arylation of allyl carbonates with arylzinc halides to give product 412 in good yield and good regioselectivity (Scheme 42).³¹¹ This transformation was found to be completely enantiospecific, giving the product with inversion of configuration. Optimization of additives was critical to achieving good regiospecificity and reproducible yields, with the combined use of LiBr and the exogenous diene ligand dibenzylideneacetone (dba) providing the best results.

Scheme 42. Rh-Catalyzed Stereospecific Allylic Arylation with Arylzinc Reagents



4.2.2. Organomagnesium Reagents. Investigations of transition-metal-catalyzed stereospecific allylic substitution reactions with organomagnesium reagents have focused on rendering the long-established chemistry of *stoichiometrically* generated cuprate reagents *catalytic*. The Breit group has focused on developing allylic electrophiles with phosphine-containing leaving groups for γ -selective coupling reactions.^{312–315} Treatment of enantioenriched *o*-(diphenylphosphino)benzoyl (*o*-dppbz) ester 414a with *n*BuMgBr in the presence of substoichiometric CuBr·SMe₂ furnished cyclohexene 415, bearing an all-carbon quaternary center (Scheme 43). The product is formed in high yield with

Scheme 43. o-dppbz-Directed Stereospecific Allylic Alkylation with Grignard Reagents



excellent regioselectivity and perfect enantiospecificity for the *syn*-substitution product. The high selectivity for γ -*syn*-addition of the nucleophile is proposed to result from the ability of the *o*-dppbz ester to direct the approach of the copper nucleophile. Consistent with this proposal, (stoichiometric) cuprate addition to the analogous phosphine oxide (414b) provides exclusively the γ -*anti*-product. The Breit group has employed this method in the synthesis of various polyketide motifs and natural products, including (+)-bourgeanic acid and (*R,R,R*)- α -tocopherol, to demonstrate its utility.^{316–319}

Several groups have investigated Cu-catalyzed stereospecific α -selective allylic substitution reactions. In 2010, Bäckvall and co-workers reported their investigations of the Cu^I-catalyzed coupling of enantioenriched cinnamaldehyde-derived ester 416 with alkyl and aryl Grignard reagents to give styrenyl products 417 and 418 with inversion of stereochemistry (Figure 83a). High levels of α -selectivity and excellent es were reported for a range of nucleophiles, although alkyl Grignard reagents reacted with somewhat lower levels of regioselectivity.^{320–322} Bäckvall rationalized that the α : γ -selectivity of the transformation is determined by the relative rates of reductive elimination (k_1) versus π -allyl formation (k_2 , k_2') (Figure 83, b). If $k_1 > k_2$, then γ -alkylated product 421 is obtained; however, if the rate of reductive elimination is slow, formation of π -allyl 422 can give rise to the thermodynamically stable α -product, 423. The intermediacy of an electron-rich cuprate is expected to slow reductive elimination further, favoring delivery of the α -product. The authors ascribe the erosion of enantiospecificity in some substrates to π -allyl formation via conformation 424, giving rise to undesired 426.

In addition to the allylic esters investigated by the Bäckvall group, other laboratories have begun exploring alternative electrophiles for α -selective Cu-catalyzed allylic substitution reactions with organomagnesium reagents. Tian and co-workers

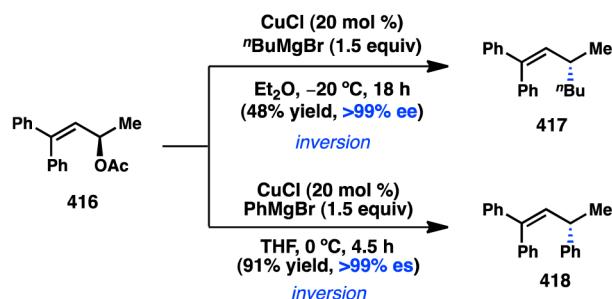
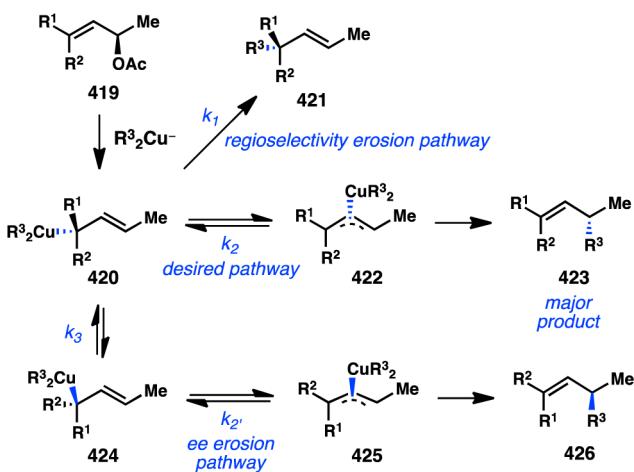
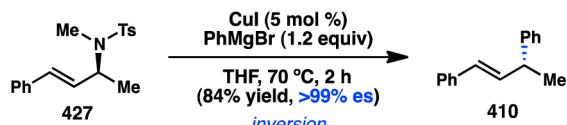
a) α -Selective allylic substitution of enantiopure estersb) Mechanism giving rise to α -selectivity

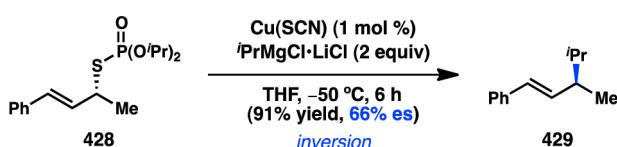
Figure 83. α -Selective stereospecific allylic substitutions with organomagnesium reagents.

disclosed the Cu-catalyzed arylation of styrenyl sulfonamide 427 with PhMgBr to prepare 410 in good yield, high α -selectivity, and perfect es (Scheme 44).³²³ Although 427 is the only reported substrate, these preliminary results show promise for the use of sulfonamides as leaving groups.

Scheme 44. α -Selective Allylic Arylation of Enantioenriched Sulfonamides

Wu and co-workers reported a Cu-catalyzed α -selective allylic substitution of phosphorothioate ester 428 (Scheme 45).³²⁴ These studies focused on the use of alkylmagnesium reagents as nucleophiles. The authors propose that reaction through dialkylcopper species bearing an electron-rich ligand favors equilibration to the π -allyl complex, ultimately delivering the thermodynamic product, 429. The phosphorothioate

Scheme 45. Stereospecific Allylic Alkylation of Phosphorothioate Esters



leaving group was critical for imparting both excellent α -selectivity and high yields. It was hypothesized that the phosphorothioate serves as an electron-rich ligand on Cu, further favoring α -selectivity. A single enantioenriched substrate (428) was shown to react with modest es to furnish the stereoinverted product. This transformation is currently limited by a lack of methods to prepare the enantioenriched substrates.

4.2.3. Organoboron Reagents. The Sawamura laboratory has pioneered the development of transition-metal-catalyzed stereospecific allylic substitution reactions using arylboron nucleophiles.^{325–328} In 2008, they reported that cationic (phen) $Pd^{II}(OAc)\cdot SbF_6$ (432) catalyzes the reaction between allylic benzoate 430 and an arylboronic acid to give γ -arylation product 431 with retention of stereochemistry (Figure 84).

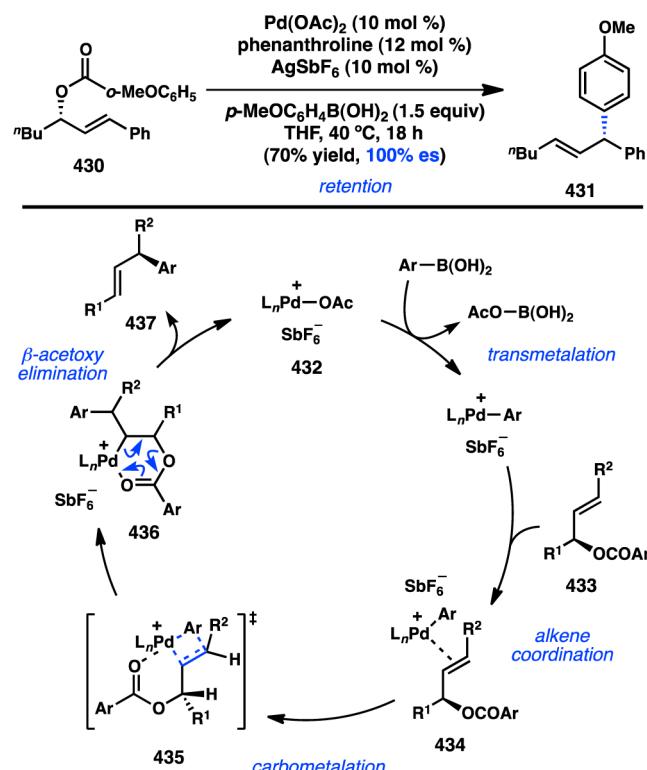


Figure 84. Pd-catalyzed allylic γ -arylation with arylboron nucleophiles.

Product 431 is obtained in good yield and excellent enantiospecificity. The authors propose a mechanism involving ester-directed allylpalladation of the alkene to give 436, followed by preferential β -acetoxy elimination as opposed to β -hydride elimination. The reaction exhibits broad functional group tolerance for both coupling partners. Moreover, the γ -selectivity to form *gem*-diaryllalkanes, which overrides the thermodynamic preference for conjugated products via α -arylation, represents complementary selectivity to many of the Cu-catalyzed methods.

The Zhang group has investigated α -selective Pd-catalyzed enantiospecific allylic substitution reactions with arylboron nucleophiles. In 2012, they reported the Pd/*rac*-BINAP-catalyzed reactions of allyl carbonates (438) with arylboronic acids to give α -substitution products (410) in good yield and perfect enantiospecificity (Figure 85a).³²⁹ Oxidative addition of Pd to the carbonate electrophile proceeds with extrusion of carbon dioxide to afford π -allyl complex 440 (Figure 85b). This activation mode of the allyl electrophile is distinct from the

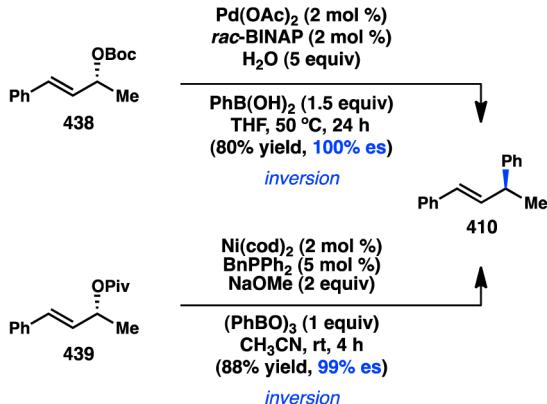
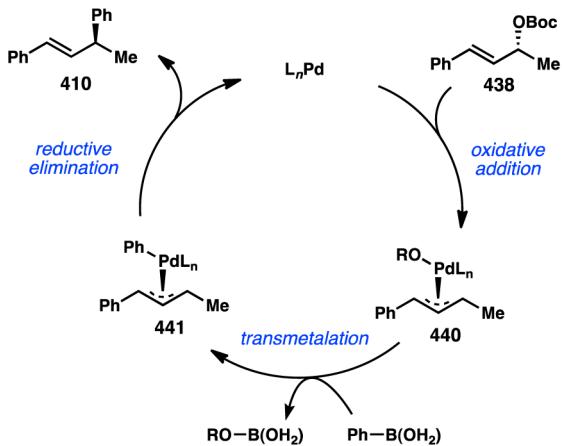
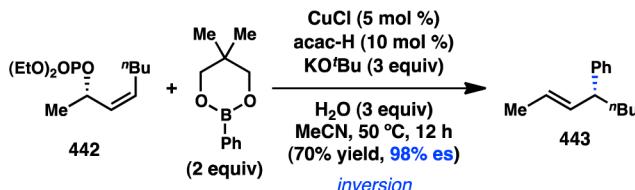
a) α -Selective allylic substitution with arylboron reagents*b) Mechanism giving rise to α -selectivity*

Figure 85. Carbonate leaving groups in allylic arylation.

carbometalation previously invoked by Sawamura.³²⁵ Transmetalation of phenylboronic acid delivers intermediate 441, which undergoes reductive elimination to furnish the more thermodynamically favored conjugated α -substitution product 410. This transformation was demonstrated to be general, tolerating a variety of functional groups and sterically encumbered substrates. The authors have subsequently reported that the reaction can be conducted in aqueous conditions and without exogenous ligand.³³⁰

Recently, the Watson group has reported that the same transformation can be achieved using Ni catalysis. When Ni/Bn₂PPH₂ is used as the catalyst, allylic pivalate 439 can be coupled to phenylboroxine in good yield and high es (Figure 85a).³³¹ As in the Pd-catalyzed transformation developed by Zhang, the product is formed with inversion of stereochemistry. The reaction is conducted under mild conditions and exhibits a broad substrate scope.

A limitation of the Pd-catalyzed reactions discussed above is that (*Z*)-allylic substrates react with poor stereochemical fidelity. To address this shortcoming, Sawamura and co-workers have disclosed a related Cu-catalyzed reaction of (*Z*)-allylic phosphates (e.g., 442) and arylboronates (Scheme 46).³³² Using a simple catalyst system generated from CuCl and acetylacetone, the coupled products are formed in good yield with high γ -selectivity and enantiospecificity. As is often observed in Cu-catalyzed allylic substitution, the products are formed with inversion of stereochemistry.

Scheme 46. Cu-Catalyzed Allylic γ -Arylation with Arylboron Nucleophiles

In an effort to simplify substrate preparation and minimize waste, attention has recently turned to the development of γ -selective arylations of electrophiles with Lewis-basic leaving groups. Tian and co-workers reported the arylation of allylic amines (444), whereas both Zhang and Tian have independently disclosed the analogous reaction of free allylic alcohols (445) (Figure 86).^{333–335} These reactions are proposed to

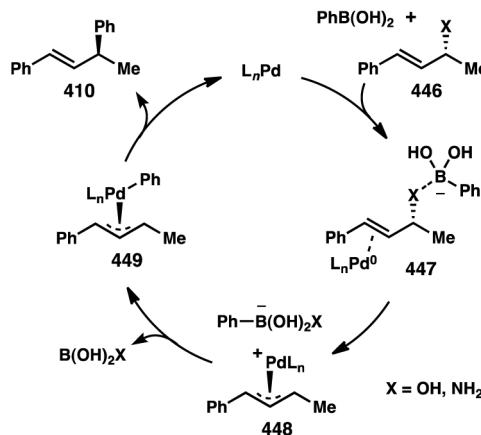
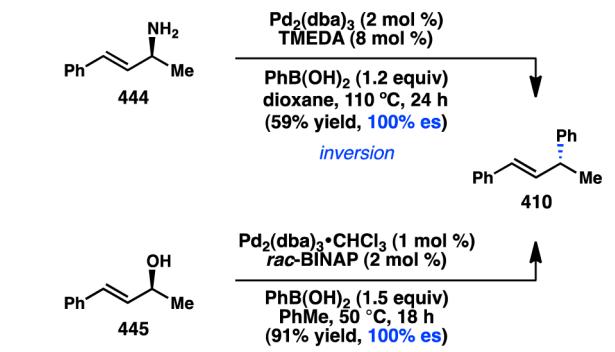


Figure 86. Amine and alcohol leaving groups in allylic arylation.

proceed by complexation of the leaving group to the boronic acid nucleophile to form “ate” complex 447, activating the electrophile toward S_N2' oxidative addition. Following transmetalation of π -allyl complex 448 with the arylboronate, reductive elimination furnishes the α -selective products (410). These reactions generally proceed with high enantiospecificity and regioselectivity when bidentate ligands such as TMEDA or *rac*-BINAP are employed.

Building on this mechanism, the Sigman group has developed a novel Pd-catalyzed cross-coupling between homoallylic tosylates and arylboronic acids.³³⁶ Using a Pd/L104 complex as the catalyst, tosylate 450 can be coupled with phenylboronic acid to give 451, with inversion of stereochemistry, in good yield and high es (Figure 87). The authors

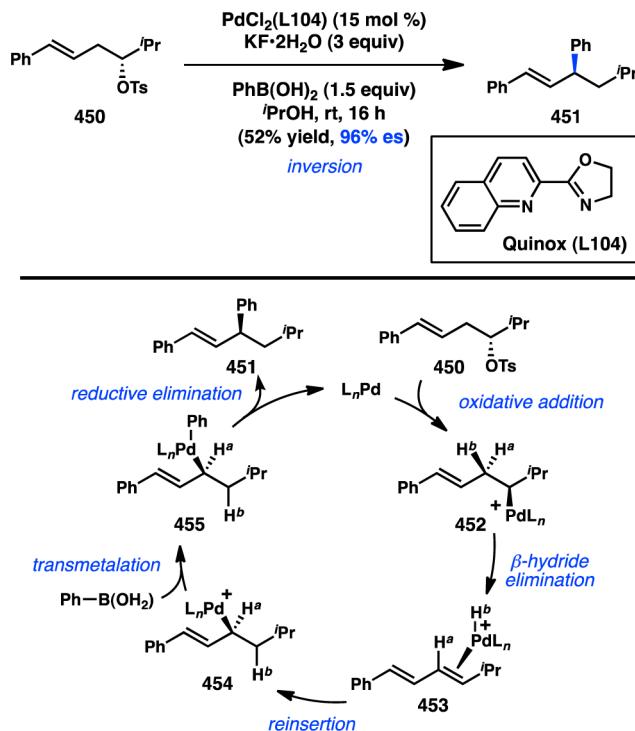
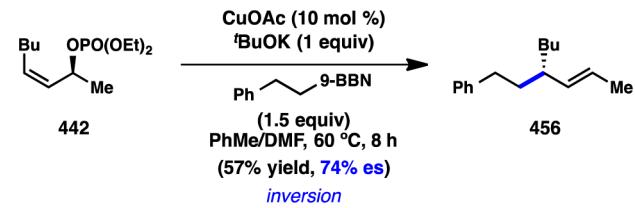


Figure 87. Stereospecific coupling of homoallylic tosylates.

propose that, following oxidative addition, the alkylpalladium intermediate **452** undergoes β -hydride elimination to afford **453**, which can reinser Pd to generate **454** and intercept the standard allylic coupling mechanism. Importantly, the good levels of es observed in this transformation suggest that the olefin remains tightly bound to Pd following β -hydride elimination. It was determined that bulky substituents α to the original position of the tosylate were critical to observe high es in this substitution reaction.

The use of alkylboron nucleophiles in transition-metal-catalyzed stereospecific allylic substitution reactions has only recently been developed. In 2010, Sawamura and co-workers disclosed a γ -selective Cu-catalyzed reaction of alkyl-9-BBN reagents and enantioenriched (*Z*)-allylic phosphates (**442**) (Scheme 47).³⁰³ The stereochemical course of the reaction proceeded with overall inversion of configuration and high selectivity for the (*E*)-alkene, but modest enantiospecificity.

Scheme 47. Initial Report of Enantiospecific Allylic Substitution with Alkylboron Reagents



The same group subsequently investigated how reaction parameters such as the solvent and base influenced the enantiospecificity of the reaction. Employing silyl-substituted electrophile **457**, two sets of conditions that enable stereospecific formation of either (*S*)-**458** or (*R*)-**458** were developed (Figure 88).³³⁷ Thus, Cu-catalyzed coupling of (*Z*)-allylic phosphate **457** and an alkyl-9-BBN in THF with ${}^t\text{BuOK}$ as the

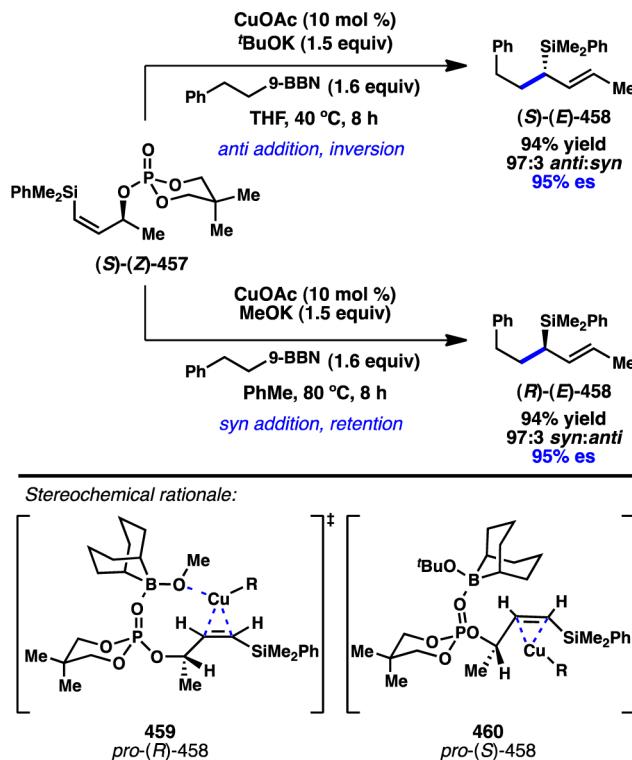


Figure 88. Enantiodivergent allylic alkylation with alkylboron reagents.

base furnished (*S*)-**458** in good yield and high es, whereas conducting the same reaction in toluene with MeOK provides (*R*)-**458** with similar levels of es. It is proposed that use of a small base, MeOK, enables coordination of Cu to the leaving group, which directs a *syn* oxidative addition (i.e., to the same face as the leaving group) via cyclic transition state **459**. On the other hand, the bulky base ${}^t\text{BuOK}$ precludes coordination of Cu to the “ate” complex, instead favoring *anti* oxidative addition according to open transition state **460**. Along with alkyl-substituted alkenes, this method tolerates both di- and trisubstituted alkenylsilanes, furnishing the corresponding secondary and tertiary chiral silanes, respectively.

Morken and co-workers have reported Pd-catalyzed stereospecific allylic substitution reactions of propargylic and allylic electrophiles, giving rise to 1,5-enynes and -dienes, respectively. In the former case, Pd/*rac*-BINAP-catalyzed substitution of propargylic acetate **461** with allyl pinacol boronate is proposed to occur by *anti* $\text{S}_{\text{N}}2'$ oxidative addition of Pd^0 to **461**, followed by transmetalation to generate η^1 -allenylpalladium species **463** (Figure 89a). Subsequent 3,3' reductive elimination affords alkyne **462** with excellent es and selectivity for formation of the alkyne over the allene.³³⁸ Consistent with this mechanism, the reaction proceeds with inversion of stereochemistry. The authors have also disclosed a related kinetic resolution, in which a chiral ligand enables the selective allylation of one enantiomer of the propargylic substrate, allowing recovery of enantioenriched starting material.³³⁹ More recently, the Morken laboratory reported the Pd-catalyzed stereospecific substitution of allylic acetate **464** with allyl pinacol boronate to deliver enantioenriched 1,5-diene **465** in good yield and with excellent es (Figure 89b).³⁴⁰ This reaction can also be applied to tertiary acetates, which enables the production of 1,5-dienes bearing all-carbon quaternary centers. This transformation provides a notable alternative to the Cope rearrangement for

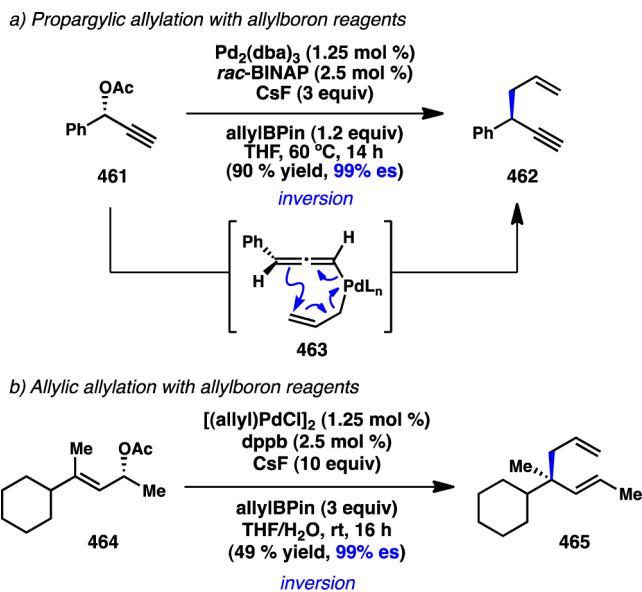


Figure 89. Allylation with allylboronates to form 1,5-dienes and -enyne.

the synthesis of chiral 1,5-dienes, particularly because there are no enantioselective examples of Cope rearrangements of unfunctionalized substrates (such as those required to produce 465).

5. ENANTIOCONTROLLED CROSS-CO尤LING REACTIONS TO PREPARE MOLECULES WITH AXIAL OR PLANAR CHIRALITY

Although centrochirality—arising from a stereogenic $C(sp^3)$ -hybridized atom—is most commonly encountered in small organic molecules, other chirality modes include axial and planar chirality. In the case of allenes, axial chirality arises from hindered rotation about a $C=C$ double bond. Alternatively, in atropoisomerism, axial chirality emerges as a result of hindered rotation about a $C-C$ single bond because of either conformational constraints (as in some macrocyclic natural products) or significant steric encumbrance about the bonding axis. Most commonly for biaryl systems, *ortho* substitution prevents rotation about the biaryl axis, allowing isolation of enantiopure atropisomers. Atropisomers maintain a half-life to racemization of at least 1000 s, corresponding to a minimum energy barrier of 93.5 kJ/mol at 300 K.³⁴¹ Stable atropisomers are expected in biaryls containing four *ortho* substituents and, in many cases, those with only three substituents. Isolable atropisomers can be found in molecules with only two *ortho* groups if those groups are sufficiently large.³⁴² The energy of interconversion has been shown to be well-correlated with the van der Waals radii of the blocking groups, demonstrating the steric nature of the effect.³⁴³ Similarly, planar chirality may result from the unsymmetrical arrangement of groups about a plane of symmetry. Although a range of elegant diastereoselective and oxidative approaches to control atropochirality have been developed, this discussion will be limited to strategies involving enantioselective and enantiospecific cross-coupling.

5.1. Enantiocontrolled Preparation of Axially Chiral Biaryls

Three general strategies have been developed for the enantioselective preparation of axially chiral biaryl scaffolds using transition-metal-catalyzed cross-coupling: (1) $C(sp^3)-C(sp^2)$ coupling in which axial chirality is produced in the

formation of the biaryl linkage, (2) enantioposition-selective cross-coupling of a prochiral bisfunctionalized biaryl scaffold, usually a biaryl ditriflate, and (3) dynamic kinetic asymmetric transformation by cross-coupling of a racemic, axially chiral starting material.

5.1.1. Organomagnesium Reagents. In 1975, Kumada and co-workers reported the Ni-catalyzed cross-coupling of *ortho*-substituted aryl electrophiles and *ortho*-substituted aryl Grignard reagents to make biaryl products.³⁴⁴ Recognizing that this chemistry could provide atroposelective entry to molecules with axial chirality, several chiral ligands were investigated in the coupling of naphthyl partners 466 and 467 (Figure 90).

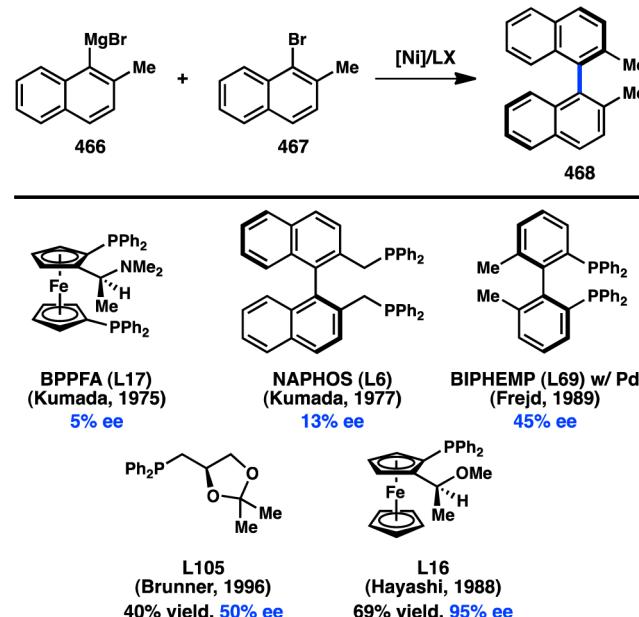


Figure 90. Early ligands for asymmetric $C(sp^2)-C(sp^2)$ Kumada–Corriu coupling.

BPPFA (L17) was found to deliver 468 in 5% ee, a low but potentially promising value. Several years later, Kumada reported that NAPHOS (L6) provides 468 in 13% ee,²⁴ whereas Brunner found that phosphine L105 delivers 468 in 50% ee.³⁴¹ Subsequent to Kumada’s work, Frejd investigated the related Pd-catalyzed cross-coupling which produced 468 in 45% ee when BIPHEMP (L69) was used as the ligand.³⁴⁵

The first highly atroposelective examples of Ni-catalyzed biaryl formation emerged from the work of Hayashi, Ito, and co-workers in 1988, when they reinvestigated chiral ferrocenylphosphine ligands for the coupling between 466 and 467.^{346,347} After observing that monodentate ligands were more catalytically active than bidentate ligands, they identified methoxy-containing ligand L16, which produced binaphthyl 468 in good yield and excellent ee. Critically, a ligand lacking the methoxy group delivered racemic coupling products. The methoxy substituent was proposed to precoordinate the Grignard reagent during a selectivity-determining transmetalation step. A similar proposal was put forth for the DYKAT/cross-coupling of $C(sp^3)$ organomagnesium reagents.³⁴⁸

Hayashi and co-workers also investigated transition-metal-catalyzed desymmetrizing cross-coupling reactions to generate enantioenriched biaryl compounds. When chiral Pd complex 471 was used as a catalyst, cross-coupling of prochiral ditriflate 469 with PhMgBr furnished monofunctionalized product 470

in 84% yield and 90% ee (Figure 91).^{348,349} The major byproduct was diarylated compound 472. The ee of 470 was

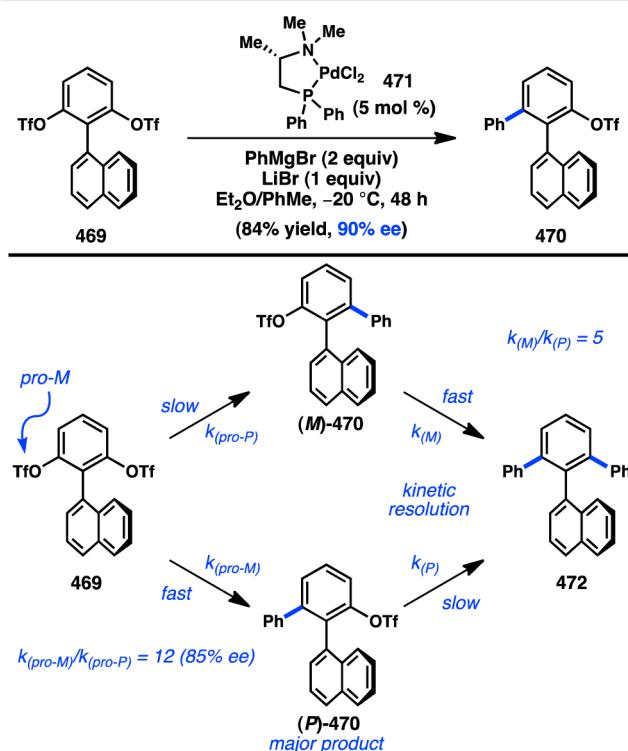


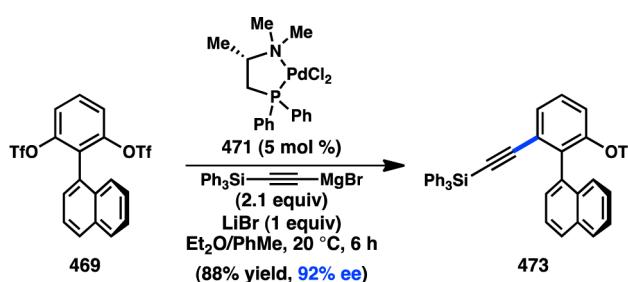
Figure 91. Enantioposition-selective Kumada–Corriu coupling.

found to be 85% at low conversion, which increased over the course of the reaction because of a subsequent kinetic resolution of the two monoarylated atropisomers. The minor enantiomer was observed to react approximately 5 times faster than the major enantiomer to form 472, leading to an enhancement in the ee of 470. LiBr was found to increase both the reaction rate and the enantioselectivity.

Following the successful development of the Pd-catalyzed enantioposition-selective arylation of ditriflate 469,^{348,349} Hayashi and co-workers investigated the analogous atroposelective alkynylation. Using the same chiral Pd catalyst, 471, cross-coupling of biaryl ditriflate 469 and alkynylmagnesium bromide delivered 473 in 92% ee after 6 h (Scheme 48).³⁵⁰ Increasing the reaction time furnished 473 in enantiopure form, albeit in lower yield, because of the kinetic resolution of the monofunctionalized product in a second cross-coupling event.

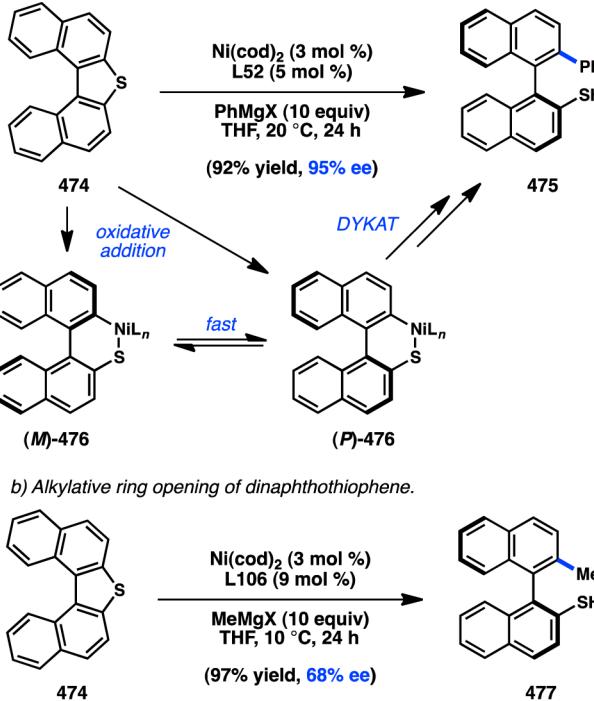
Exploiting the ability of Ni to insert into the C–S bond of benzothiophene, Hayashi and co-workers explored the Ni-

Scheme 48. Enantioposition-Selective Cross-Coupling of Alkynyl Coupling Partners



catalyzed Kumada–Corriu coupling of 474 with aryl Grignard reagents to give enantioenriched biaryl thiols (Figure 92a).^{351,352} Dinaphthothiophene (474) is generally considered

a) Arylative ring opening of dinaphthothiophene.



b) Alkylative ring opening of dinaphthothiophene.

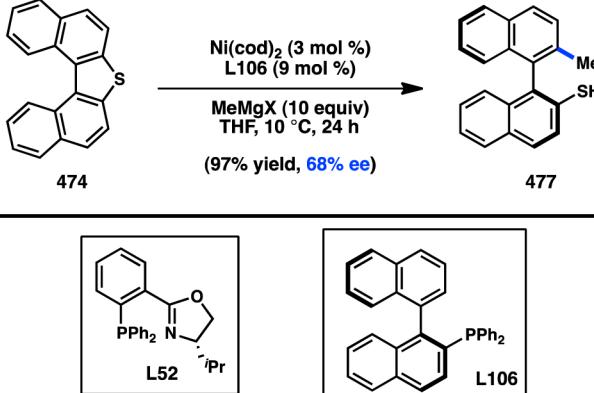
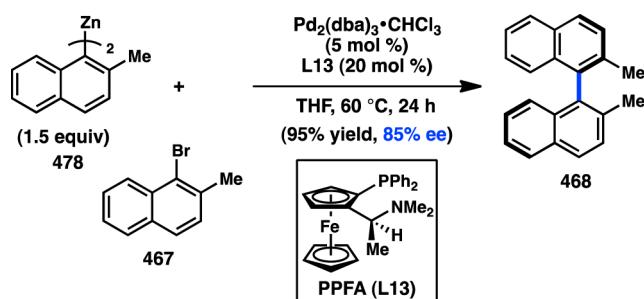


Figure 92. Atroposelective ring openings of dinaphthothiophene.

to be an achiral compound because of the low barrier to flipping about the axial axis of symmetry. When PHOX ligand L52 was employed, the Ni-catalyzed ring-opening/cross-coupling proceeded in high yield and ee. The atroposelectivity was strongly influenced by the identity of the Grignard reagent; alkylmagnesium reagents reacted with poor selectivity. On the basis of this observation, the authors propose that the reaction proceeds by a DYKAT of the rapidly equilibrating oxidative addition products (M)-476 and (P)-476, in which the transmetalation step sets the axial chirality. The reaction could also be extended to dibenzothiophene coupling partners to generate axially chiral biphenyl products. Despite efforts to improve the selectivity of the reaction between 474 and alkyl Grignard reagents, the best conditions identified to date, which utilize chiral phosphine L106, deliver 477 with only moderate enantioselectivity (Figure 92b).

5.1.2. Organozinc Reagents. The first atroposelective Negishi cross-coupling to prepare an axially chiral biaryl was reported in 2006 by Espinet and co-workers.³⁵³ Using $Pd_2(dbu)_3$ and chiral ferrocenylphosphine L13, diarylzinc 478 was coupled to bromonaphthalene 467 to furnish 468 in excellent yield and 85% ee (Scheme 49). This result was comparable to that of a related Pd/L13-catalyzed Suzuki–Miyaura coupling to form 468 (see Scheme 50), but a shorter

Scheme 49. Stereoselective Negishi Coupling of Naphthylzinc Reagents

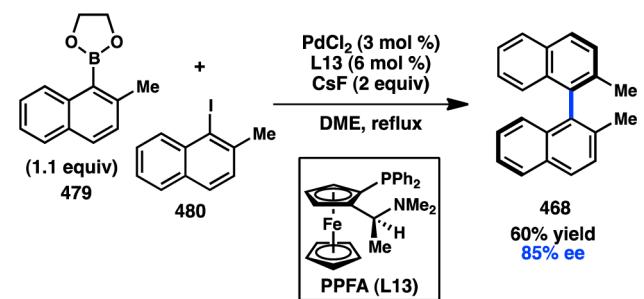


reaction time was achieved.³⁵⁴ The reaction conditions were modified to allow microwave-heating-induced acceleration of the transformation; although the coupling is complete within 1 h, the ee of 468 falls to 60%.³⁵⁵

5.1.3. Organoboron Reagents. Arylboron reagents are attractive partners for cross-coupling reactions because they are easy to handle and store, generate nontoxic byproducts, and are highly functional group tolerant. On the other hand, transition-metal-catalyzed cross-coupling reactions of hindered, *ortho*-substituted arylboron species often require long reaction times and high temperatures and can suffer from competitive protodeborylation. Likely because of these reasons, atroposelective Suzuki–Miyaura cross-couplings have only emerged in the past 15 years. In contrast, asymmetric variants of the Kumada–Corriu coupling have been known for twice as long. Refinements in ligand design and improved reaction conditions for the racemic formation of hindered biaryls were key to the ultimate discovery of an asymmetric variant.^{356–358}

Following a report from Nicolaou and co-workers describing the use of chiral ligands to enhance the atropodiastereoselectivity of a Pd-catalyzed Suzuki–Miyaura aryl–aryl cross-coupling in the synthesis of vancomycin,³⁵⁹ the laboratories of Cammidge and Buchwald independently disclosed enantioselective reactions to prepare simple biaryl systems. In 2000, Cammidge and co-workers reported the Pd-catalyzed coupling of boronate 479 and iodonaphthalene 480, delivering 468 in 85% ee when L13 was used as a chiral ligand (Scheme 50).^{354,355,358,360,361} The authors propose that the axial chirality

Scheme 50. Cammidge's Approach to Asymmetric Biaryl Formation



is set in the transmetalation step and that the overall reaction occurs under kinetic control. Consistent with Hayashi's proposal, the authors hypothesize that the nitrogen atom of L13 can coordinate to the organoboron reagent during or before transmetalation.³⁴⁶

Concurrent with Cammidge's study, Buchwald and co-workers reported a Pd-catalyzed atroposelective Suzuki–Miyaura cross-coupling between 1-bromonaphthalene 481 and arylboronic acids. When chiral biarylphosphine L107 was employed, the coupling with (*o*-methylphenyl)boronic acid provided biaryl 483 in 87% ee (Figure 93).^{362,363} The presence

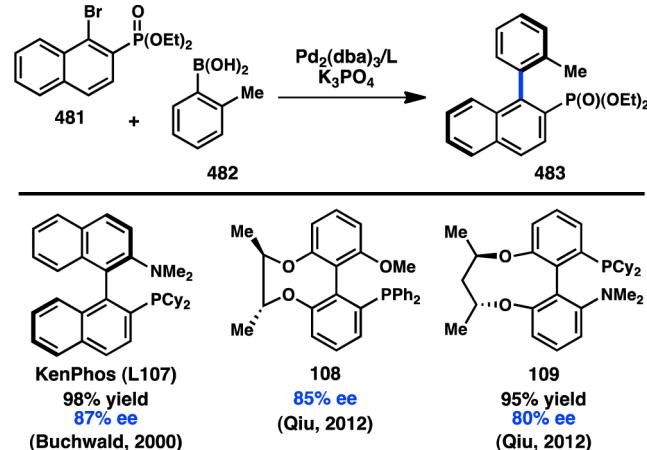


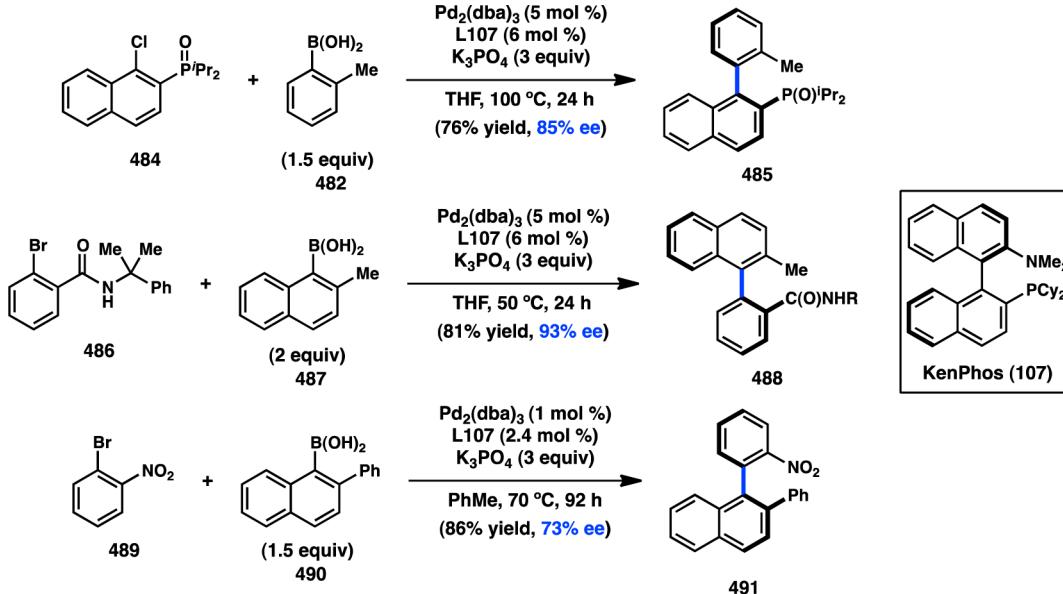
Figure 93. Buchwald's approach to asymmetric biaryl formation.

of the adjacent phosphonate ester was important for achieving high selectivity. A crystal structure of an oxidative addition product revealed a potential interaction between Pd and the oxygen atom of the phosphorus substituent.³⁶⁴ The authors proposed that this dative interaction might guide a selectivity-determining reductive elimination. Qiu and co-workers have subsequently developed bridged, axially chiral ligands (L108 and L109) to effect the same transformation in similar ee.^{365,366} Likewise, Suginome and co-workers have synthesized chiral helical polymers capable of catalyzing the formation of phosphonate-bearing products in the presence of Pd.^{367–369} In addition to accomplishing high enantioselectivity, Suginome showed that the sense of chiral induction can be reversed simply through a change of solvent.

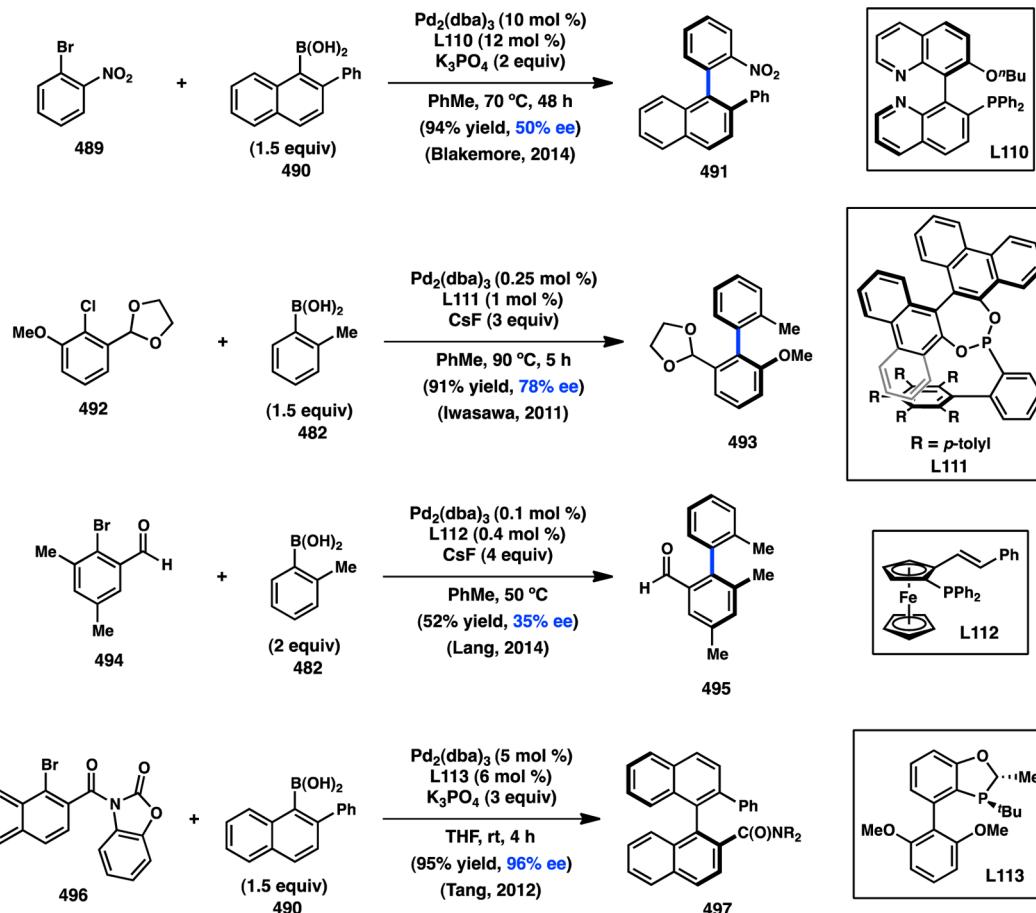
On the basis of the hypothesis that the phosphonate of 481 coordinates to Pd and enhances the atroposelectivity of biaryl bond formation, Buchwald and co-workers investigated the asymmetric Suzuki–Miyaura cross-coupling of other substrates bearing proximal coordinating groups, including amide and nitro functional groups (Scheme 51).^{364,370,362,371} A more recent report by Blakemore and co-workers disclosed that biquinoline-derived phosphine L110 provides biaryl 491 in good yield but modest ee (Scheme 52). Iwasawa and Lang have prepared new ligands for the coupling of substrates 489 and 492, respectively, but with varied results.^{372–374} In collaboration with the process group at Boehringer-Ingelheim, Tang and co-workers have identified P-chiral ligand L113 as providing high atroposelectivity in the Pd-catalyzed cross-coupling of carbonylbenzoxazolidinone 496 with arylboronic acids. Excellent yields and ee's are obtained for several different boronic acid substrates;³⁷⁵ optimization of the reaction enabled its application in the efficient total synthesis of several biaryl natural products.³⁷⁶

Despite advances in the asymmetric Suzuki–Miyaura cross-coupling of aryl halides bearing proximal coordinating groups, the development of highly atroposelective cross-coupling reactions of simple substrates has remained challenging. The coupling between 1-naphthylboronic acid 487 and 1-halonaph-

Scheme 51. Coordinating Groups Developed by Buchwald for Asymmetric Biaryl Couplings



Scheme 52. Other Coordinating Functional Groups in Asymmetric Suzuki–Miyaura Couplings



thalene 498 has emerged as a test reaction for new chiral ligands (Figure 94). Often, *o*-Me groups in the starting materials provide higher ee's, but their presence can also decrease the yield of the coupling. High temperatures and long reaction times are typical of these methods. Nonetheless, in 2009, Uozumi and co-workers identified an imidazoindole

phosphine that facilitates production of 468 in high yield and ee.³⁷⁷ Tethering the ligand to a polymer support, as in L115, permits 468 to be made in water and under heterogeneous conditions without loss of enantioinduction. Additional experiments confirmed that the polymer-supported ligand could be recycled through multiple reaction runs. Notably, ferrocenyl-

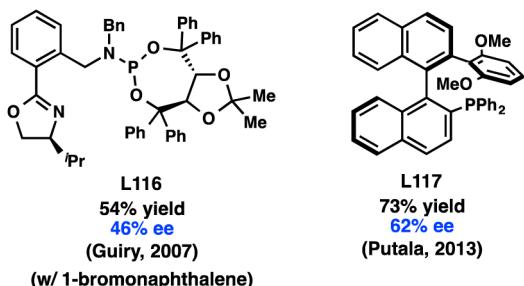
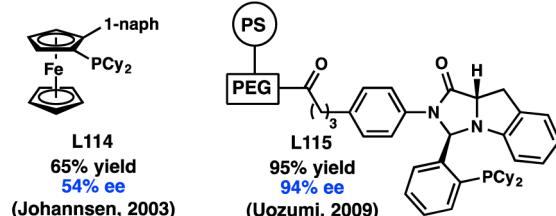
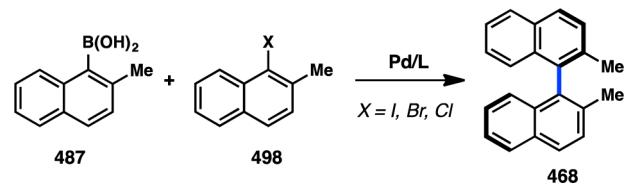


Figure 94. Other ligands for the formation of tetrasubstituted biaryls.

phosphine **L114**, lacking the dimethylamino group in **L13**, delivers the desired product in moderate enantioselectivity;³⁷⁸ similar enantioinduction has been demonstrated by Guiry³⁷⁹ and Putala.³⁸⁰

With respect to the formation of trisubstituted biaryl compounds lacking polar directing groups, Lin and co-workers have developed a chiral diene to promote generation of **500** in up to 90% ee and good yield (Figure 95).³⁸¹ Kündig and co-

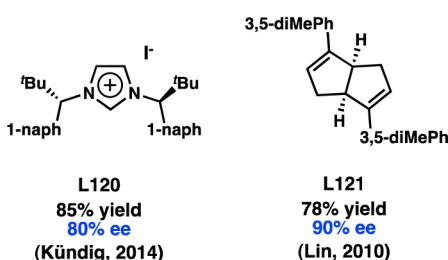
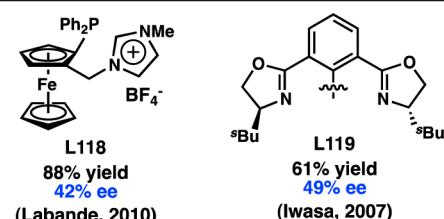
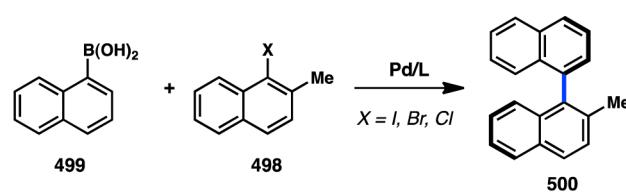


Figure 95. Other ligands for the formation of trisubstituted biaryls.

workers have recently demonstrated that NHC **L120** can be used as part of a chiral PEPPSI complex to forge **500** in good ee.³⁸² Phebox **L119**³⁸³ and phosphine–NHC **L118**^{384,385} deliver more modest atroposelectivity.

The Pd-catalyzed Suzuki–Miyaura cross-coupling between 2-methoxyhalonaphthalenes (**501**) and 1-naphthylboronic acid (**499**) is another cross-coupling reaction that serves as a testing ground for new ligands (Figure 96). Binaphthyl **502** can be

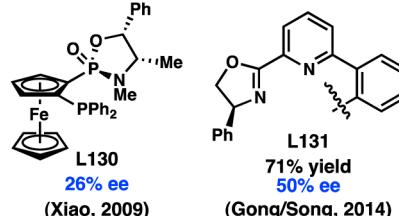
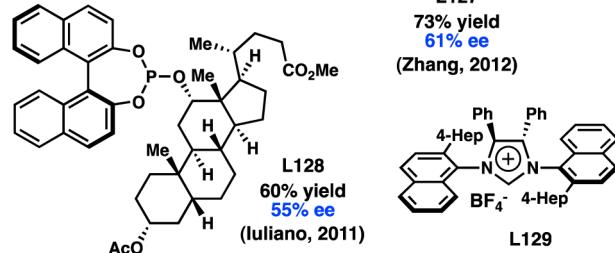
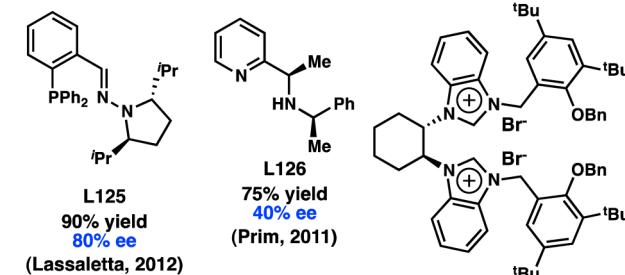
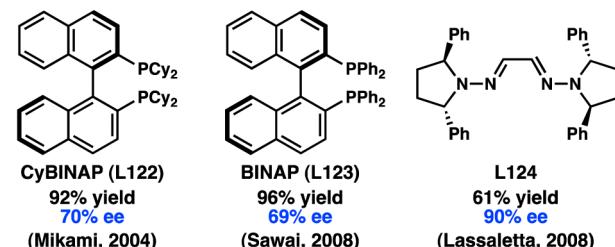
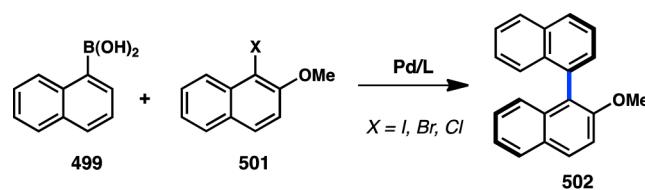
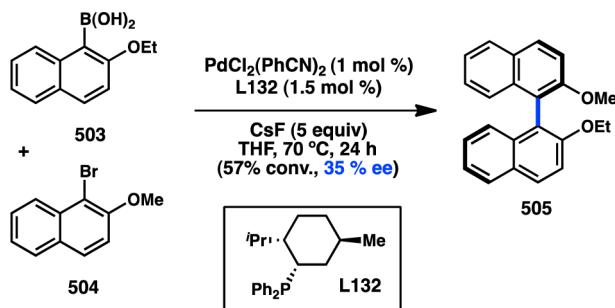


Figure 96. Other ligands for the asymmetric Suzuki–Miyaura coupling of alkoxynaphthalys.

obtained in high yields and moderate ee when BINAP ligands **L122** and **L123** are employed.^{386–388} Lassaletta achieved higher atroposelectivity in the Pd-catalyzed coupling of **499** and **501** through the use of bishydrazone **L124** and phosphino hydrazone **L125**: the improved result with **L124** was proposed to arise from π -stacking interactions between the substrate and the ligand.^{389,390} Notably, Pd/L124-catalyzed biaryl formation

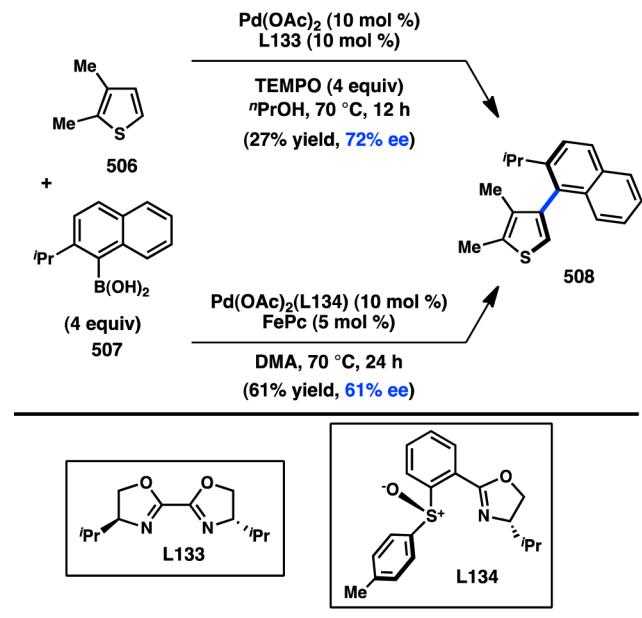
exhibited a relatively broad substrate scope, enabling the atroposelective cross-coupling of 1-bromonaphthalene or 1-bromo-2-methylnaphthalene with a variety of arylboronic acids. Several additional ligands that have proven less successful are shown in Figure 96.^{391–398} Enantioenriched dialkoxybinaphthalenes have also been targeted through an asymmetric Suzuki–Miyaura coupling (Scheme 53).

Scheme 53. Preparation of Dialkoxybinaphthyls



Pd-catalyzed oxidative cross-coupling of unfunctionalized aryl substrates with arylboronic acids can provide direct access to enantioenriched biaryl compounds without the need to prepare the intermediate organo(pseudo)halide. In 2012, Yamaguchi, Itami, and co-workers examined the Pd-catalyzed oxidative cross-coupling of thiophenes with *ortho*-substituted naphthylboronic acids. Using TEMPO as the stoichiometric oxidant and chiral bioxazoline ligand L133, the C–H activation/cross-coupling between 506 and 507 proceeds in poor yield but with promising atroposelectivity (Scheme 54).³⁹⁹ In a second-

Scheme 54. Atroposelective Oxidative Cross-Coupling



generation approach, an aerobic oxidation using iron phthalocyanine (FePc) as a cocatalyst was developed.⁴⁰⁰ Realizing that DMSO can coordinate to Pd under the reaction conditions, the authors developed a bidentate sulfoxide–oxazoline ligand (L134) that was capable of furnishing 508 in a better yield than the first-generation strategy, although the enantioinduction was still modest.

The majority of research toward atropoenantioselective Suzuki–Miyaura cross-couplings has focused on reactions in which the axial chirality is produced in the formation of the biaryl linkage. Alternatively, Lassaletta and co-workers recently reported a Pd-catalyzed arylation of triflate 509 that is an example of a DYKAT (Figure 97).⁴⁰¹ When TADDOL-based

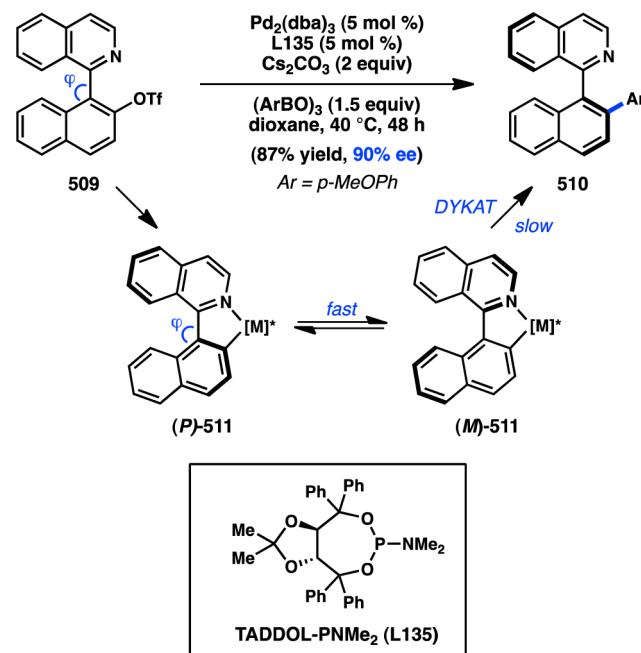


Figure 97. DYKAT approach to enantioenriched biaryls.

phosphoramidite L135 is used as a ligand, coupling of triflate 509 with arylboroxines occurs in good yields and with a high level of enantioinduction. Control experiments confirmed the inability of 509 to racemize on the time scale of the reaction, ruling out a dynamic kinetic resolution of the starting material. Instead, the authors hypothesized that oxidative addition of 509 to Pd would be accompanied by chelation of the proximal isoquinoline. This bidentate coordination to Pd was proposed to distort the biaryl C–C bond, widening the angle φ , and decreasing the configurational stability of the complex. In this scenario, fast racemization about the axis of chirality, followed by selective transmetalation of one atropisomer ((P)-511), would ultimately lead to high atroposelectivity. A similar DYKAT approach has been disclosed by Virgil, Stoltz, and co-workers for the preparation of C–P bonds on QUINAP scaffolds.⁴⁰²

5.1.4. Organoindium Reagents. Organoindium reagents are also viable nucleophiles in transition-metal-catalyzed biaryl formation, prompting the group of Sarandeses to investigate atroposelective variants of these reactions.⁴⁰³ Surprisingly, low ee was observed when the chiral Buchwald ligand KenPhos (L107) was employed (Figure 98). On the other hand, PPFA (L13), which is known to promote similar atroposelective cross-coupling reactions of organozinc reagents,³⁵³ delivers 500 in good ee. Further studies are needed to assess the full scope and synthetic utility of these organoindium cross-coupling reactions.

5.2. Enantiocontrolled Preparation of Allenes

The synthesis of axially chiral allenes has garnered attention because of their presence in bioactive natural products and the

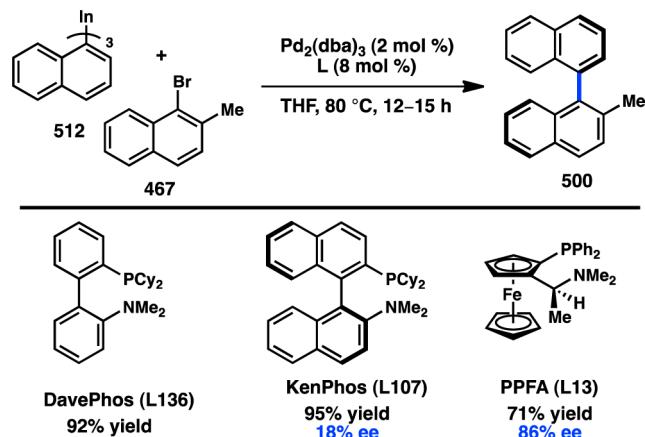
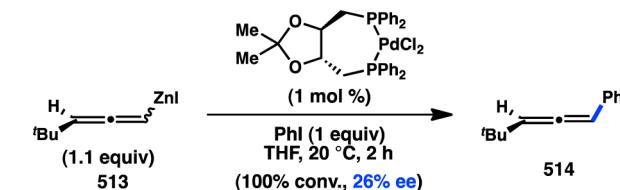


Figure 98. Atroposelective cross-coupling of organoindium reagents.

intriguing chiroptical properties of cumulenes in general.⁴⁰⁴ Both enantioselective and enantiospecific transition-metal-catalyzed reactions have been developed for the synthesis of chiral allenes. For each approach, as in the case of allylic substitution, oxidative addition to allenyl or propargyl electrophiles can occur either by an S_N2 mechanism or by an S_N2' mechanism, resulting in a potential mixture of regio- and stereochemical outcomes. A second key challenge arises from the possible equilibrium between the allenylmetal and its isomeric propargylmetal species prior to reductive elimination.

5.2.1. Enantioselective Preparation of Allenes. Boersma, Elsevier, and co-workers have investigated a Pd-catalyzed asymmetric Negishi reaction for the synthesis of enantioenriched allenes. When a chiral Pd complex was used as the catalyst, the coupling of racemic allenylzinc iodide **513** with iodobenzene furnished chiral allene **514** in 26% ee (Scheme 55).⁴⁰⁵ Other allenylmetal species, such as organomagnesium

Scheme 55. Stereoselective Negishi Coupling of Allenylzinc Halides



and -copper reagents, resulted in lower enantioselectivity. The reversed-polarity cross-coupling of an arylzinc halide and a haloallene was simultaneously investigated, but enantioinduction higher than 9% ee could not be accomplished.

Transition-metal-catalyzed coupling of an organometallic reagent to a propargyl electrophile represents a direct and powerful method for the preparation of chiral allenes. Alexakis and co-workers recently reported the Cu-catalyzed asymmetric addition of alkyl Grignard reagents to propargylic dichloride **515** (Figure 99).⁴⁰⁶ The complex generated from CuBr and phosphoramidite **L137** catalyzed the enantioselective reaction to provide chloroallenes **516** in high yield and ee. Both primary and secondary organomagnesium reagents were well tolerated; however, t BuMgBr only delivered racemic product. The authors demonstrated that the newly formed chiral chloroallene could undergo a Cu-catalyzed enantiospecific cross-coupling with aryl

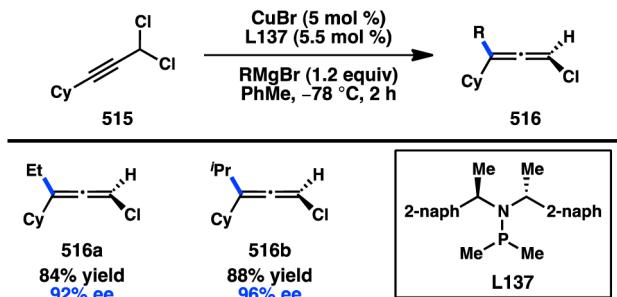


Figure 99. Cu-catalyzed enantioselective propargylic alkylation.

Grignard reagents to afford cross-coupled products without loss of stereochemical information.

5.2.2. Enantiospecific Preparation of Allenes. In 1984, Vermeer and co-workers investigated the stereochemical outcome of Pd-catalyzed cross-coupling reactions of enantioenriched allenyl halide **517** (Figure 100).^{407,408} The authors

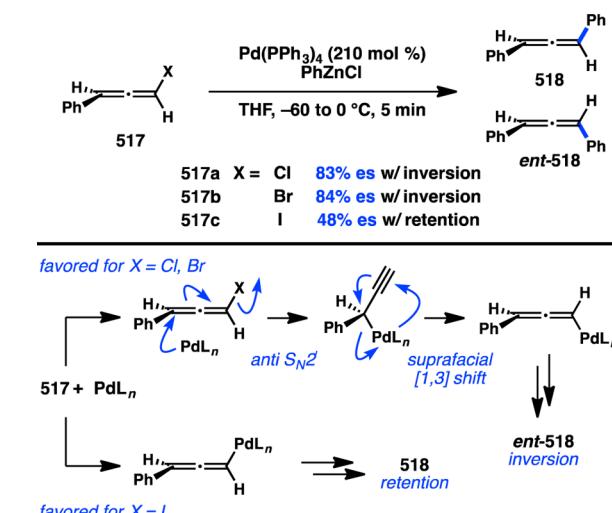


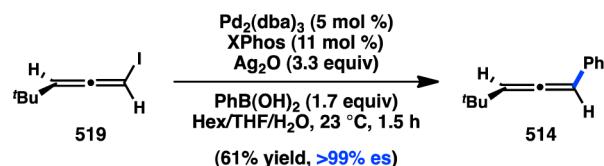
Figure 100. Stereochemical outcome of the coupling of enantioenriched allenyl halides.

initially anticipated haloallenes would behave like haloalkenes and react with retention of configuration in the presence of Pd⁰. To the contrary, the coupling of either **517a** or **517b** delivered **518** with good enantiospecificity and *inversion* of configuration. Iodoallene **517c** furnished the desired product with stereoretention, albeit the degree of es was lower. The nature of the organozinc reagent and the catalyst had smaller effects on the stereospecificity.

The authors rationalize this behavior by proposing two competing mechanisms for the cross-coupling. In the case of **517a** and **517b**, Pd precoordinates to the allene, resulting in oxidative addition by an *anti S_N2'* mechanism to give a propargylmetal species. A [1,3]-suprafacial Pd shift would furnish an allenylmetal complex with net inversion of configuration, which following reductive elimination would provide product **518**. For **517c**, the weaker C–I bond could result in direct oxidative addition of Pd, which upon reductive elimination would furnish the product with retention of stereochemistry.

In 2010, Burke and co-workers performed a similar analysis for the Suzuki–Miyaura coupling of haloallenes and PhB(OH)₂ (Scheme 56).⁴⁰⁹ In analogy to Negishi couplings discussed

Scheme 56. Suzuki–Miyaura Cross-Coupling of Enantioenriched Haloallenes



above, allenyl bromides and chlorides delivered products with net inversion. However, increasing steric profiles of the substituents at C3 and employing large supporting ligands, such as XPhos (L63), can disfavor the *anti* S_N2' pathway, as demonstrated in the coupling of allenyl iodide 519 to produce 514 exclusively with stereoretention. A DFT study on the Stille coupling of enantiopure haloallenes has supported a similar conclusion.⁴¹⁰

Enantiospecific allylic functionalization is a versatile tool for the preparation of chiral allenes from propargylic electrophiles. Readily prepared enantiopure propargylic electrophiles make stereospecific transformations especially attractive. Whereas Pd-catalyzed substitutions with organozinc reagents have been known for many years, only recently have Cu-catalyzed transformations, as well as reactions that use organoboron nucleophiles, emerged.

In the early 1980s, Vermeer and co-workers examined the stereochemical outcome for the Pd-catalyzed coupling of arylzinc reagents and enantioenriched propargylic acetates. Initial studies revealed that allene 518 could be generated in modest enantiospecificity and with inversion of configuration (Figure 101).^{411,412} The authors hypothesized that acetate 520

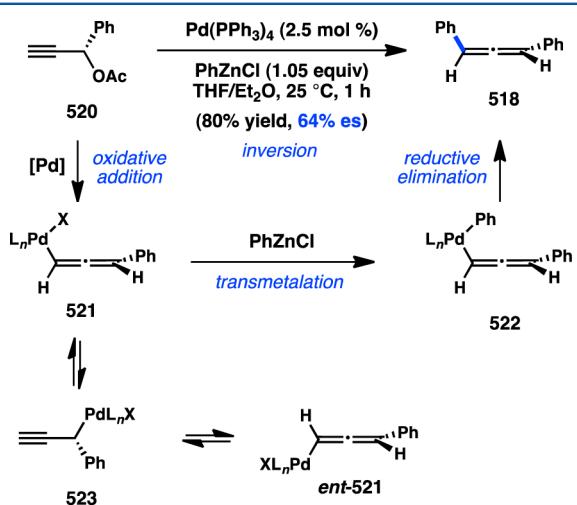


Figure 101. Pd-catalyzed enantiospecific functionalization with arylzinc reagents.

undergoes a stereoinvertive S_N2' oxidative addition to form η^1 -allenylpalladium complex 521. Transmetalation with PhZnCl and a stereoretentive reductive elimination would deliver allene 518 with overall inversion. Isomerization of 521 to propargyl complex 523 is one potential mechanism for the racemization of the product. Vermeer's protocol continues to be a robust method for the synthesis of enantioenriched aryl-substituted allenes.^{413,414}

Yoshida, Ihara, and co-workers reported the Pd-catalyzed enantiospecific arylations of propargylic electrophiles using

arylboronic acid nucleophiles. Using Pd(PPh₃)₄ as the catalyst, the reaction of carbonate 524 with arylboronic acids proceeds with perfect invertive transfer of chirality to furnish allene 525 (Scheme 57).^{415,416} In comparison to arylzinc reagents,

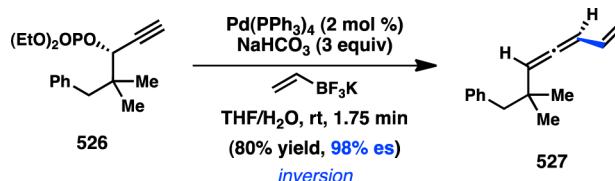
Scheme 57. Pd-Catalyzed Enantiospecific Functionalization with Arylboronic Acids



relatively high temperatures are required to obtain good yields. The identity of the leaving group influenced the degree of enantiospecificity, with the parent propargyl alcohols delivering nearly racemic products. In an interesting extension of the reaction, propargylic oxiranes can also be coupled with arylboronic acids to form products in high yield and with good es.⁴¹⁷

In 2006, Molander reported the Pd-catalyzed vinylation of propargylic phosphates to prepare enylallenes. Using Pd(PPh₃)₄ as the catalyst, propargylic phosphate 526 could be coupled with vinyl trifluoroborate under mild conditions at room temperature to give 527 with good levels of enantiospecificity (Scheme 58). The use of less reactive

Scheme 58. Pd-Catalyzed Enantiospecific Functionalization with Vinyl-BF₃K



electrophiles, such as propargylic carbonates, or an increase in the reaction time notably decreased the ee of the product through an off-pathway racemization process. Unfortunately, a limited scope of vinylboron nucleophiles was reported.

Sawamura and co-workers reported a Cu-catalyzed enantiospecific synthesis of chiral allenes in 2011. Building off their prior investigations of stereospecific coupling reactions between allylic phosphates and alkylboron nucleophiles,³⁰³ it was found that CuOAc catalyzed the reaction of propargylic phosphate 528 with alkyl-9-BBN reagents to deliver allene 529 with excellent γ -selectivity and high point-to-axial chirality transfer (Figure 102).^{418,419} The authors propose that the reaction proceeds via initial transmetalation between Cu and the “ate” complex of the nucleophile to form neutral Cu¹ complex 530, which is only mildly nucleophilic. π -Complexation of the alkyne followed by carbometalation would provide 533. *anti*-Elimination from 533 would deliver the desired allene without stereochemical scrambling. A similar transformation was developed by Lalic and co-workers the following year, in which a Cu–NHC complex catalyzes the stereospecific substitution of a propargylic phosphate with both alkyl- and arylboron nucleophiles.⁴²⁰

A year later, Sawamura and Lalic independently reported the Cu-catalyzed stereospecific coupling of propargylic phosphates 528 with either aryl- or vinylboronate reagents (Figure

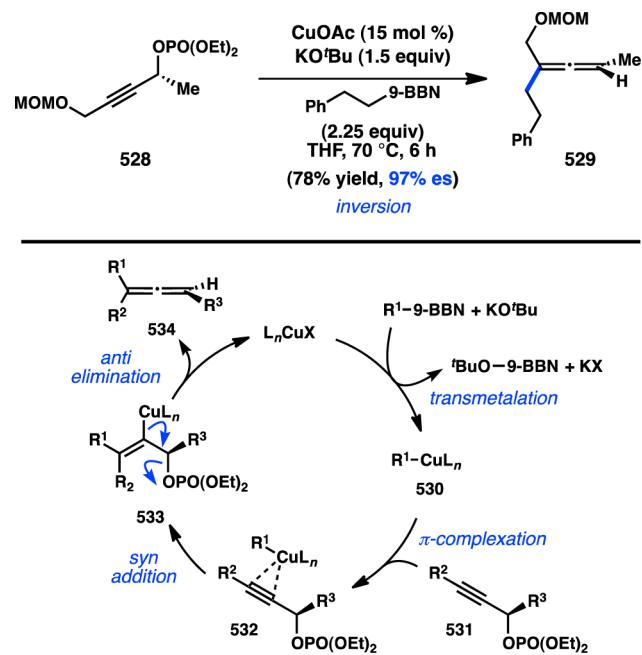


Figure 102. Cu-catalyzed enantiospecific functionalization of propargyl phosphates.

103a).⁴²¹ The Sawamura coupling employed either CuCl or CuCl₂ as the catalyst, under conditions similar to those utilized

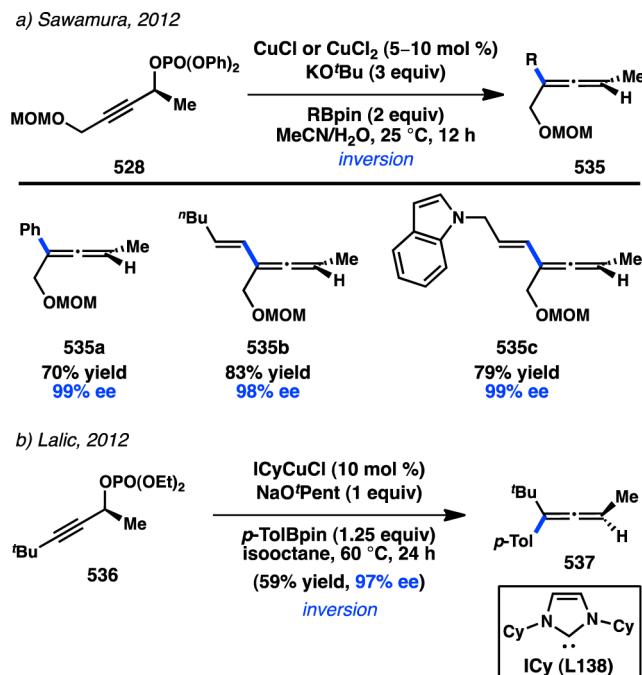


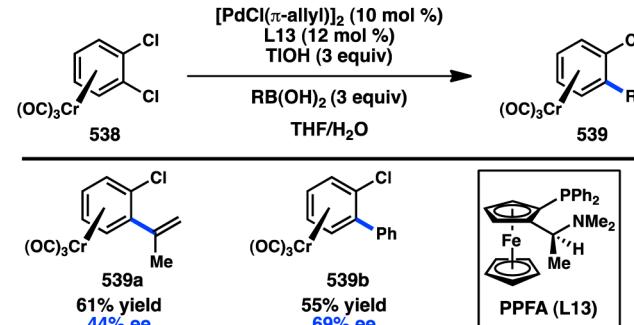
Figure 103. Cu-catalyzed propargylic arylation and vinylation with organoboronates.

in the previously reported enantiospecific arylation of allylic phosphates.³³² On the other hand, Lalic and co-workers identified a Cu–NHC catalyst that provided the enantioenriched allene in good yield and with excellent point-to-axial chirality transfer (Figure 103b).⁴²⁰ Under Lalic's conditions, both aryl- and alkylboron reagents were found to react with high stereochemical fidelity.

5.3. Enantioselective Preparation of Planar Chiral Compounds

Few catalytic asymmetric methods have been developed for the synthesis of molecules with planar or helical chirality; most routes focus on classical resolutions or chiral auxiliary approaches.⁴²² Tricarbonyl(η^6 -arene)chromium complexes have found utility in the synthesis of planar chiral compounds because the complexes can exist in two enantiomeric forms when the arene is not symmetrically substituted. The first enantioselective cross-coupling to generate a planar chiral compound was reported by Uemura, Hayashi, and co-workers in 1993, in which *meso*-dichloride 538 was desymmetrized to give 539 (Figure 104a).⁴²³ Screening an array of chiral ligands

a) Desymmetrization of dihalobenzene



b) Desymmetrization of dihalonaphthalene

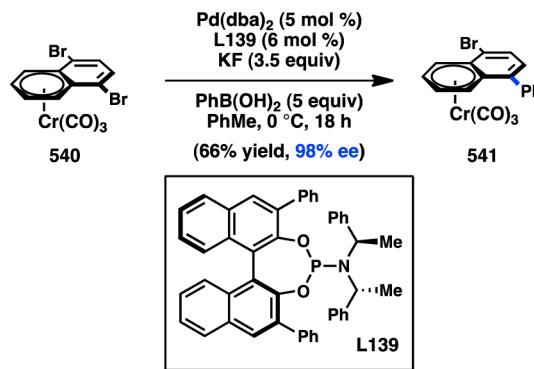


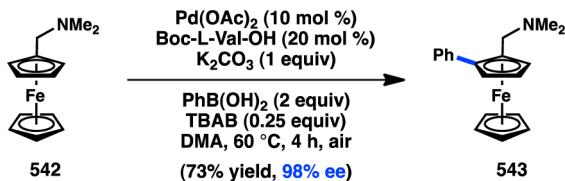
Figure 104. Desymmetrization of tricarbonyl(η^6 -arene)chromium complexes.

and alkenylmetallic species while using [PdCl- π -allyl]₂ as the palladium source revealed that the combination of PPFA (L13) as the ligand and prop-1-en-2-ylboronic acid as the coupling partner provides product 539a in 61% yield and 44% ee. Poor enantioinduction was observed when organotin and organomagnesium reagents were employed. Under similar conditions, arylboronic acids can be coupled with 538 to afford 539b in up to 69% ee.⁴²⁴ In 2011, Kündig and co-workers reported a similar strategy for the desymmetrization of 1,4-dibromonaphthalene complexes. Upon exposure to Pd(dba)₂ and phosphoramidite L139, 540 and phenylboronic acid can be coupled to prepare 541 with excellent enantioselectivity (Figure 104b).⁴²⁵ Additional experiments confirmed that the ee increased at longer reaction times, suggesting a kinetic resolution of the product enantiomers takes place during a second cross-coupling to give the *meso*-compound. Oxidative addition was presumed to be the enantio-determining step. In a separate report, *meso*-

cobalt metallocenes could be desymmetrized in up to 24% ee through an asymmetric Suzuki–Miyaura cross-coupling.⁴²⁶

In 2013, Gu, You, and co-workers reported an asymmetric C–H activation approach to planar chiral ferrocenes. Building on reports from Yu and co-workers that chiral monoprotected amino acids were competent ligands for asymmetric C–H activation/cross-coupling techniques,^{133,134} the authors subjected **542** and PhB(OH)₂ to Pd(OAc)₂ and a series of different amino acid-derived ligands (**Scheme 59**).⁴²⁷ Boc-L-Val-

Scheme 59. Synthesis of Planar Chiral Ferrocenes by C–H Activation



OH was found to effect formation of 543 with excellent enantioinduction and a minimal amount of the bisarylated product. The authors propose that the Lewis basic dimethylamino group acts as a directing group to facilitate the C–H activation event.

6. CONCLUSION AND FUTURE OUTLOOK

The past several decades have seen a profound growth in cross-coupling methods, and the wealth of new tools for enantioselective and enantiospecific C–C bond formation has revolutionized synthetic planning and practice. As this review illustrates, more and more stereogenic structural motifs have become accessible through transition-metal-catalyzed cross-coupling, allowing chemists to leverage the flexibility of cross-coupling to streamline the synthesis of complex molecules. However, several challenges remain at the forefront of this field. Whereas enantiocontrolled cross-couplings of *sec*-alkyl partners with *n*-alkyl or C(sp²) 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. Stereospecific cross-couplings of enantiopure C(sp³) boron and tin nucleophiles show great promise but are currently limited by the difficulty of preparing such substrates. Despite considerable research in the area of allylic substitution, reactions using aryl nucleophiles to prepare all-carbon quaternary centers remain underdeveloped yet valuable. Finally, although atroposelective methods to provide axially chiral products have blossomed in recent years, few ligands have been shown to support a broad substrate scope with high selectivity. More general methods would be of great utility in accessing these atropoisomeric products. The promise of enantiocontrolled cross-coupling methods 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.

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Notes

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ABBREVIATIONS

9-BBN	9-borabicyclo[3.3.1]nonane
acac	acetylacetone
Boc	tert-butoxycarbonyl
Bz	benzoyl
CDR	catalytic dynamic resolution
cod	1,5-cyclooctadiene
CPME	cyclopentyl methyl ether
dan	1,8-diaminonaphthalene
dba	dibenzylideneacetone
DCC	N,N'-dicyclohexylcarbodiimide
DET	direct enantioselective transformation
DFT	density functional theory
DIBAL-H	diisobutylaluminum hydride
DKR	dynamic kinetic resolution
DMA	N,N-dimethylacetamide
DMAP	p-(dimethylamino)pyridine
DME	1,2-dimethoxyethane
DMF	N,N-dimethylformamide
dppb	1,4-bis(diphenylphosphino)butane
dppf	1,1'-bis(diphenylphosphino)ferrocene
dppo	1,8-bis(diphenylphosphino)octane
DTBM	3,5-di- <i>tert</i> -butyl-4-methoxyphenyl
DTR	dynamic thermodynamic resolution
DYKAT	dynamic kinetic asymmetric transformation
ee	enantiomeric excess
es	enantiospecificity
HMPA	hexamethylphosphoramide
MS	molecular sieves
MTBE	methyl <i>tert</i> -butyl ether
nbd	norbornadiene
Neop	neopentanediol, 2,2-dimethyl-1,3-propanediol
NHC	N-heterocyclic carbene
PEPPSI	pyridine-enhanced precatalyst preparation stabilization and initiation
phen	1,10-phenanthroline
Pin	pinacol, 2,3-dimethyl-2,3-butanediol
PMB	<i>p</i> -methoxybenzyl
SiMes	1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene
SKR	stereodivergent kinetic resolution
TADDOLs	α,α',α' -tetraaryl-1,3-dioxolane-4,5-dimethanol
TASF	tris(dimethylamino)sulfonium difluorotrimethylsilicate

TBAB	tetrabutylammonium bromide
TBAF	tetrabutylammonium fluoride
TBAT	tetrabutylammonium difluorotriphenylsilicate
TBD	1,5,7-triazabicyclo[4.4.0]dec-5-ene
TC	thiophene-2-carboxylate
TEMPO	2,2,6,6-tetramethylpiperidine 1-oxyl
THF	tetrahydrofuran
TMEDA	N,N,N',N'-tetramethylethylenediamine
Ts	tosyl, <i>p</i> -toluenesulfonyl

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