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Advances in Transition Metal (Pd, Ni, Fe)-Catalyzed Cross-Coupling Reactions Using Alkyl-Organometallics as Reaction Partners

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1. Introduction

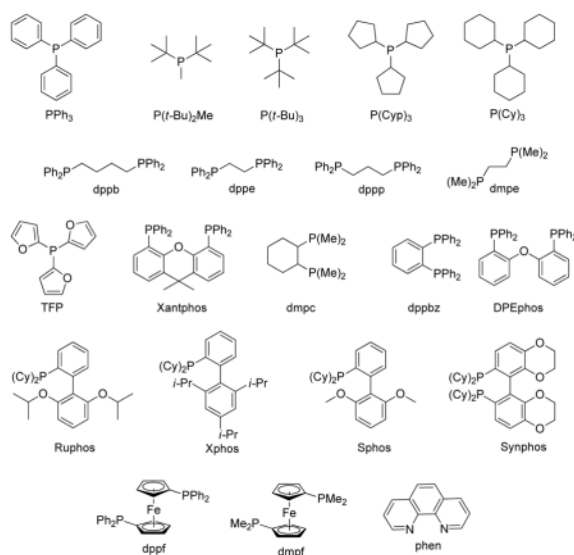
Transition metal-catalyzed cross-coupling reactions of organic electrophiles and organometallic reagents have emerged as a tremendously powerful synthetic tool and the development has reached a level of sophistication that allows for wide range of coupling partners to be combined efficiently.^{1–3} In the last three decades, this paradigm for carbon-carbon bond construction has allowed chemists to assemble complex molecular frameworks of diversified interests encompassing total synthesis of natural products, medicinal chemistry, and industrial process development as well as chemical biology, materials, and nanotechnology. The emergence of cross-coupling as a popular method in synthesis arises from both the diversity of organometallic reagents utilized in these reactions and the broad range of functional groups which can be incorporated into these reagents.^{4–11} Since initial submission of this review, the importance of this general class of reactions was recognized by the awarding of the Nobel prize in chemistry to Richard Heck, Ei-ichi Negishi and Akira Suzuki “*for palladium-catalyzed cross-couplings in organic synthesis*”. This review details transition metal-catalyzed cross-coupling of C(sp³) organometallics with various organic electrophiles (Figure 1a).

Historically, the use of C(sp³)-organometallics in cross-coupling reactions has suffered from several serious problems, making its development much slower than related C(sp²)-couplings. The issues include but are not limited to: (1) the spontaneous decomposition of alkyl organometallics via β -elimination or by proto-demetalation,¹² (2) the necessity to pre-form the organometallic reagents without purification as they are not air stable, making the use of superstoichiometric (3–4 equiv.) amounts necessary to achieve satisfactory conversions, and (3) often slow transmetalation (*vide infra*), thereby requiring various additives.¹³ Additionally, evaluation of the general proposed mechanism reveals several features which can lead to undesired side products, especially when considering the emerging area of C(sp³)-C(sp³) cross-couplings between alkyl halides or pseudohalides and alkyl organometallics (Figure 1b,1c).^{14–18} In general, metal-catalyzed cross-coupling reactions proceed through three critical organometallic processes: (1) oxidative addition of an electrophilic carbonheteroatom bond into the low valent transition metal, (2) transmetalation or displacement of a heteroatom leaving group by the nucleophilic partner and finally, (3) reductive elimination to form a new C-C bond. The use of C(sp³)-electrophiles generally results in slower oxidative addition, which is proposed to be either a nucleophilic substitution (S_N2) with Pd-complex¹⁹ or radical in nature with Ni^{20,21} or Fe^{22,23}.

Comparatively, oxidative addition of sp or sp^2 analogues is faster and generally proceeds in a concerted manner. As illustrated in Figure 1b-c, slow oxidative addition with alkyl electrophiles leads to the formation of homo-coupling products, or β -hydride elimination generating various possible side products. Finally, sluggish reductive elimination also can lead to competing β -hydride elimination.

These issues have made it necessary to identify sometimes complex combination of ligands, metals, and conditions to effectively promote cross-coupling reactions of $C(sp^3)$ -organometallics especially with $C(sp^3)$ -electrophiles. The $C(sp)$ - $C(sp^3)$ coupling between alkynyl electrophile and alkyl organometallic nucleophiles is rarely seen in the literature,^{24,25} whereas alkynyl organometallics in these cross-coupling reactions are very common. In this review, the synthesis, stability, and transition metal-catalyzed (Pd, Ni, Fe) cross-coupling reactions of sp^3 -organometallics possessing β -hydrogen(s) using alkylzinc (Negishi-protocol), alkylboron (Suzuki-Miyaura-protocol), alkylmagnesium (Kumada-protocol), alkyltin (Stille-protocol), alkylsilicon (Hiyama protocol) and alkylindium will be discussed. Besides their detailed development and mechanistic investigations, extension to asymmetric catalysis and applications in total synthesis will be described. It should be noted that organometallic reagents that cannot undergo β -hydride elimination will not be reviewed comprehensively. Co-catalyzed cross-coupling reactions will not be covered in this article as they have been reviewed recently.²⁶ Cu-catalyzed coupling reactions will also not be covered in this review as this could be a subject of a distinct review.

1.1 List of Common Ligands



2. Alkylzinc Reagents

Organozinc reagents of type R_2Zn or $RZnX$ are some of the most widely used organometallic reagents in cross-coupling reactions.²⁷ The preparation and systematic studies of their reactivity in addition reactions to general electrophiles such as acid chlorides, aldehydes, ketones, and esters was reported initially in the 1880's.²⁸ During this time, it was realized that organozinc reagents in general possess low reactivity in addition reactions because of the highly covalent character of the carbon-zinc bond, and zinc has a mild Lewis acidic character to activate electrophiles.²⁹ This low reactivity presents considerable advantages in the preparation of functionalized organozinc reagents to perform

chemoselective reactions for the direct introduction of desired functionality into organic scaffolds. Additionally, the empty low-lying p orbitals of zinc make these reagents susceptible to transmetalation reactions with various transition metals. These combined characteristics have allowed organozinc reagents to be a reaction partner for a vast number of cross-coupling reactions, as highlighted by the Pd-catalyzed cross-coupling reactions pioneered by Negishi.³⁰ After smooth transmetalation of a Ni or a Pd salt with organozinc reagents, a reactive intermediate **1** is formed, which readily undergoes reductive elimination to provide cross-coupling products (Scheme 1).^{31–42} This section will be devoted to the synthesis and reactivity of C(sp³)-alkylzinc reagents in cross-coupling reactions.

2.1. Synthesis of Alkylzinc Reagents

The zinc insertion into alkyl halides represents the most convenient and widely used method for the preparation of alkylzinc reagents.⁴³ In 1849, Frankland discovered that the heating of ethyl iodide with zinc produces highly pyrophoric diethylzinc that could be safely stored under a hydrogen atmosphere.^{44,45} During preparation of zinc reagents, a faster rate of insertion was observed by activating zinc successively with 1,2-dibromoethane (4–5 mol %)^{46,47} and/or chlorotrimethylsilane (3 mol %)^{46,47,48–50} prior to addition of the alkyl halide in THF. The Normant group reported the preparation of alkylzinc using Et₂O as solvent.⁵¹ Alternative methods of metal activation include washing with aqueous HCl,⁵² using Zn-Cu^{53–56} Zn-Cu-Ag couples,^{57,58} or Zn-Hg alloys,⁵⁹ ultrasound irradiation,⁶⁰ metal-solvent co-condensation,^{61,62} sacrificial Zn-anodes,⁶³ pulsed sonoelectro-chemical reduction of zinc salts,⁶⁴ and reduction of zinc salts on titanium dioxide.⁶⁵ A wide range of organic functionalities, such as esters,^{46,66–86} ketones,^{46,66} cyanides,^{46,66–73,78,80–84,86–89} halides,^{46,66,73,79,82,86} *N,N*-bis(trimethylsilyl)amino groups,⁹⁰ primary and secondary amino groups,⁹¹ amides and phthalimides,^{91,92} sulfoxides,⁹³ sulfides,⁹³ sulfones,^{93,94} thioesters,⁹⁴ boronic esters,^{76,79,82} enones^{95,96} and phosphates^{70,97} are compatible under this mild zinc insertion protocol (Figure 2a). In contrast, carboxylic acid, hydroxyl, nitro and azide groups present in the alkyl moiety potentially prevent zinc insertion. It is feasible to generate Rieke zinc metal *in situ* by reduction of zinc chloride with lithium naphthalenide in THF (Figure 2b).^{98–104} Using catalytic amount of alkali metal iodides or stoichiometric amount of alkali metal bromides, zinc insertion into alkyl chlorides, bromides, sulfonates, phosphates etc... was achieved in polar solvents (Figure 2c).¹⁰⁵ Huo reported an efficient and general procedure for the preparation of alkylzinc reagents and Ni-catalyzed coupling with aryl halides (Figure 2d).¹⁰⁶ An interesting example of the preparation of alkylzinc reagents directly from zinc metal and primary alkyl halides in water at room temperature was reported using diamines as promoter, followed by Pd-catalyzed cross-couplings with aryl bromides (Figure 2e).^{112,113,107} Transition metal salts also catalyze the zinc insertion process.^{108–110} Boron-zinc exchange to afford functionalized dialkylzinc reagents is another attractive methodology.^{111,112}

2.2. Stability of Alkylzinc Reagents

The stability of the preformed organometallics is an important factor for the optimization of subsequent reaction conditions and yield. It is a general observation that most cross-coupling reactions require an excess (3–4 equiv) of alkylzinc reagents to achieve satisfactory yields. At the same time, alkylzinc reagents have usually been prepared in solvents of moderate Lewis basicity such as THF¹¹³ or DMA,¹¹⁴ and the benefits of using polar aprotic solvents as a minor component of the solvent mixture such as DMSO/THF, NMP/THF have been highlighted.³⁹ Another crucial parameter for stability is the structure of the alkylzinc reagents. Functionalized alkylzinc reagents containing one or multiple functionalities have differing degrees of decomposition tendency, depending on the nature and position of the functional group. Generally, they undergo decomposition via β -hydride elimination to form olefins, or via protonation to form alkanes.

Amino acid-derived alkylzinc reagents are an important class of reaction partners in Negishi coupling reactions as they provide concise routes to the synthesis of numerous biologically active molecules.¹¹⁵ The Jackson group has studied the structure stability relationship as well as the solvent dependent stability of these functionalized alkylzinc reagents.^{12,116} In this study, a series of functionalized alkylzinc reagents derived from α -amino acids were prepared by gentle heating (35 °C) in THF and the zinc was activated by 1,2-dibromoethane or chlorotrimethylsilane (Figure 3).

From NMR studies in THF-*d*₈, it was evident that samples undergo decomposition at different rates upon heating at 50 °C to form alkanes and alkenes through protonation and β -elimination, respectively. The zinc reagents **2** and **3** are the most stable (relatively) whereas **4** is susceptible to β -elimination. This high stability of **2** and **3** is best accounted for invoking an internally chelated structure **5** that voids the necessary conformation for elimination (either a *syn* or *anti* arrangement of the C-Zn and C-NHBoc bonds) (Figure 3). In contrast, compound **4** contains zinc remote to the α -center, which diminishes the potential for chelating possibilities.

Interestingly, the stability of these reagents is relatively high in DMF as compared to THF. It has been observed that the intramolecular coordination of the carbamate carbonyl group to zinc is responsible for the faster β -elimination since zinc can act as an internal Lewis acid. The intramolecular coordination of the carbamate carbonyl group to zinc appears to be completely suppressed in DMF to improve their stability. Their reactivity in subsequent cross-coupling reactions is also enhanced in DMF as compared to THF.

It has been found that decomposition of β -benzamido alkylzinc iodide **6** occurs by self-protonation of the carbon-zinc bond to form **7** through first-order kinetics.¹² In contrast, the carbamate derivative **8** decomposes by a first-order elimination process to form **9** (Figure 4). The homologous reagent also decomposes at a faster rate compared to **8** by β -elimination. In conclusion, the structure of alkylzinc reagents and the solvent used for their preparation have a pronounced effect on their stability and reactivity.

2.3. Cross-Coupling Reactions of Alkylzinc Reagents

Typically, transition metal-catalyzed cross-coupling reactions proceed through three consecutive steps as outlined in the introduction: (1) oxidative addition, (2) transmetalation and (3) reductive elimination to afford product (Figure 1). The alkylzinc reagents exhibit an excellent ability to undergo transmetalation due to the presence of an empty low-lying p orbital of zinc. Consequently, Pd(II) and Ni(II)-catalyzed cross-coupling reactions of alkylzinc reagents with aryl or alkenyl,¹¹⁷ acyl,¹¹³ or alkyl halides^{118–120} or pseudohalides¹²¹ have proved to be powerful tools in vast areas of synthesis.

The cross-coupling of secondary and tertiary alkyl reagents has been found to be especially difficult because it is accompanied by the isomerization of the alkyl group and/or reduction of the halide.¹²² This isomerization and reduction must occur via σ - π interconversions of σ -alkylmetal intermediates through β -hydride elimination to give a hydrido-olefin complex followed by readdition to the olefin.^{123–125} Therefore, selective cross-couplings are realized by faster reductive elimination than β -hydride elimination. The undesired side reactions could be suppressed to some extent by an appropriate choice of catalyst that could potentially accelerate the reductive elimination pathway, providing a lower energy transition state or elevating the ground state energy.^{126–130} The isomerization of the coupling partners from a *trans* arrangement to *cis* is necessary for reductive elimination to occur.¹³¹ Bidentate phosphine ligands with a large bite angle (P-Pd-P) enforce the coupling partners into a *cis* geometry in a squareplanar Pd(II) complex, thereby increasing the rate of reductive elimination. Thus, PdCl₂(dppf), was expected to be an excellent catalyst for cross-coupling

as it has a large bite angle ($\angle\text{P-Pd-P} = 99.07^\circ$) to facilitate reductive elimination (Scheme 2).¹³² Indeed, the Hayashi group found that $\text{PdCl}_2(\text{dppf})$ is a highly active catalyst compared to similar Pd-catalysts with other bidentate phosphine ligands providing excellent product selectivity in the cross-coupling of bromobenzene and primary or secondary butylzinc chloride (Table 1).

2.4. Pd-Catalyzed Cross-Coupling Reactions of Alkylzinc Reagents

In 1977, Negishi reported that organozinc reagents undergo Ni- or Pd-catalyzed cross-coupling reactions, providing a general and mild procedure for the synthesis of biaryls and diarylmethines with high chemo- and regioselectivity as well as high cross- versus homocoupling ratios.³⁰ Although this Negishi protocol has been extensively studied using alkynyl,¹³³ aryl, alkenyl,^{34,117,134} methyl,¹³⁵ allyl,¹³⁶ and benzylzinc^{30,65,90,137} reagents, the frequent use of more challenging alkylzinc reagents containing β -hydrogen(s) as a cross-coupling partner has only evolved more recently. Our discussion in this section will be limited to the use of alkylzinc reagents as cross-coupling partners in Pd(0) catalysis and are generally presented in chronological order.

2.4.1. Pd-Catalyzed $\text{C}(\text{sp}^2)\text{-C}(\text{sp}^3)$ Negishi Coupling with Alkylzinc Reagents—

The 1,5-diene moiety can be prepared via allyl-allyl coupling reactions.^{138–140} Negishi reported a Pd-catalyzed cross-coupling reactions of homoallylic and homopropargylic alkylzinc reagents with alkenyl halides, which provides an effective route for the synthesis of 1,5-dienes and 1,5-enynes (Scheme 3) that constitute the core structure of several terpenoids.^{141,142} It was also observed that primary and secondary alkylzinc reagents are more selective towards cross-coupling compared to the corresponding alkylmagnesium reagents (Table 2, entries 1 vs. 2 and 3 vs. 4). Homoallylic and homopropargylic alkylzincs are even better coupling partners, providing cross-coupling products in high yields (Table 2, entries 5 & 7).³¹ The highly regio- and stereoselective product formation through this protocol is noteworthy.¹⁴³

Symmetrical 2,5-disubstituted benzoquinones are synthesized in a convenient route by Pd-catalyzed double Negishi coupling reactions between simple or functionalized alkylzinc and 2,5-dibromo-1,4-dimethoxy benzene, followed by oxidative demethylation with ceric ammonium nitrate (CAN) (Figure 5).¹⁴⁴ The precursor 2,5-dibromo-1,4-dimethoxy benzene was easily synthesized by bromination (Br_2/AcOH) of 1,4-dimethoxybenzene.

Perfluorinated organometallics are an important class of coupling partners as fluorine can be easily introduced into the organic backbone via cross-coupling reactions.^{145,146} The Qing group prepared the fluorine containing alkylzinc reagent **10** from the corresponding alkyl bromide by the treatment with zinc dust in anhydrous DMF at ambient temperature.¹⁴⁷ It undergoes Pd(0)/Cu(I)-cocatalyzed Negishi cross-coupling with aryl or alkenyl iodides or bromides to produce β -fluoro- α , β -unsaturated ester **12** (Figure 6). Mechanistic studies revealed that the alkylzinc reagents first produce (*Z*)-1-fluoro-2-(ethoxycarbonyl)-ethenylzinc reagent **11** via Cu(I)-catalyzed stereoselective elimination and this subsequently undergoes the Pd-catalyzed cross-coupling to produce **12** in lieu of direct cross-coupling to produce **13** (Figure 6).

Organotellurium species undergo efficient Te/metal-exchange reactions in a regio- and stereoselective manner.¹⁴⁸ This unique property is utilized for the preparation of organozinc reagents by reaction with dimethyl or diethylzinc reagents. Although this Te/Zn-exchange reaction is not quite a general method to obtain vinylzinc reagents, a new carbon-carbon bond is formed when the reaction is carried out employing $\text{CuI}/\text{Pd}(\text{PPh}_3)_4$ in DMF (Figure 7).¹⁴⁹

Negishi reported a Pd-catalyzed monosubstitution of cyclic α -iodoenones with organozinc reagents. Several five and six membered α -iodoenones underwent cross-coupling reactions with a number of dialkylzinc or alkylzinc halide reagents in the presence of a catalytic amount of $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (Figure 8).¹⁵⁰

Dibromothiazole compounds undergo Pd-catalyzed Negishi cross-coupling reactions in a regio-selective manner as reported by Bach and coworkers. The bromine atom at C-2 is more susceptible to oxidative addition, allowing for a mild reaction with alkylzincs using $\text{Pd}_2(\text{dba})_3/\text{dppf}$ to provide a series of 2-alkyl-substituted thiazole analogues leaving the other C-Br intact for further functionalization (Figure 9).¹⁵¹

Pd-catalyzed cross-coupling reactions were applied to the synthesis of azamacrocycles. Suitably functionalized 2-bromopyridines were reacted with alkylzinc reagents in the presence of catalytic $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ in THF to produce 2,6-difunctionalized pyridines which were converted to azamacrocycles after a couple of functional group interconversions followed by intramolecular *N*-alkylation (Scheme 4).¹⁵²

Two Negishi couplings were performed consecutively for the stereoselective synthesis of enynes from the corresponding 1,1-dibromo-1-alkenes or 1,1-dichloro-1-alkenes. A *trans*-selective alkenylation was accomplished with alkenylzinc chloride or bromide catalyzed by $\text{Pd}(\text{DPEPhos})\text{Cl}_2$ followed by a $\text{Pd}(\text{Pt-Bu})_2$ -catalyzed stereospecific methylation or ethylation with dimethylzinc/methylzinc halide or diethylzinc/ethylzinc halide respectively (Figure 10). Alternatively, a $[\text{Pd}_2(\text{dba})_3]/\text{NHC}$ ligand combination could be used to alkylate the second halide stereospecifically.¹⁵³ Following almost the same protocol, (1*E*)-2-methyl-1,3-ene-yne were synthesized from the *trans*-selective Negishi coupling of 1,1-dibromo-1-alkenes with alkynylzinc reagents followed by stereospecific alkylation with alkylzincs.¹⁵⁴

1-Fluoro-1-haloalkenes undergo Pd-catalyzed Negishi cross-couplings with primary alkylzinc bromides to give fluoroalkenes. Excellent *trans*-stereoselectivity is observed to provide the *Z*-fluoroalkenes in most cases.¹⁵⁵ Interestingly, tertiary alkylzincs also produce the desired fluoroalkenes in high yields (Figure 11). Although $\text{PdCl}_2(\text{dppb})$ gave the highest yields, the best stereochemical outcome was observed with $\text{Pd}(\text{PPh}_3)_4$ in favor of *Z*-fluoroalkene.

The catalytic system using tetraphosphine *cis,cis,cis*-1,2,3,4-tetrakis(diphenylphosphinomethyl)cyclopentane (tedicyp) as a ligand and $[\text{Pd}(\text{C}_3\text{H}_5)\text{Cl}]_2$ as the metal precatalyst are active for Negishi cross-coupling reactions between aryl halides and alkylzinc bromides as reported by Doucet and coworkers (Figure 12).¹⁵⁶ A wide variety of aryl bromides react with aryl or alkylzinc reagents providing good yields and high turnover numbers (TONs up to 1×10^6).

A series of aryl or alkyl vinyl phosphates undergo $\text{Pd}(0)$ -catalyzed Negishi cross-coupling reactions with alkylzinc reagents to produce the corresponding 1,1-aryl,alkyl or 1,1-alkyl,alkyl disubstituted alkenes respectively.¹⁵⁷ In this coupling, the counter ion (chloride or bromide) of the alkylzinc reagent has a pronounced effect. It was found that alkylzinc bromides, in the presence of LiCl , are active towards the cross-couplings whereas alkylzinc bromides by themselves are less reactive or inactive. This is in good agreement with the observation of Buchwald and coworkers.¹⁵⁸ It is assumed that during the preparation of the organozinc chloride from the corresponding organochloride via lithium-zinc exchange at least an equivalent amount of lithium chloride is formed that augments the concentration of a more reactive anionic $\text{Pd}(0)$ complex in equilibrium with its neutral species. As a mechanistic probe, addition of an excess (5 equiv) of lithium chloride was found to effectively promote cross-couplings with alkylzinc bromides in combination with $\text{Pd}_2\text{dba}_3/$

dppf in THF at 70 °C (Figure 13). Furthermore, it was observed that alkylzinc reagents are less reactive compared to their arylzinc counterparts.

C(sp²)-centers with higher electronegativity or adjacent double bonds have an accelerating effect on the rate of cross-coupling reactions. This is proposed to arise from faster reductive elimination via the transfer of metal d electrons to the π^* orbitals of the olefin or aryl group.^{159,160} As a result, competitive β -hydride elimination is suppressed. Based on this concept, the Lei group designed a chelating ligand containing a phosphine and an electron-deficient olefin for Pd-catalyzed Negishi couplings (Figure 14). Superior effects of the ligands were observed not only in terms of higher yields but also faster reaction rates under mild conditions.¹⁶¹ Thus, a series of aryl iodides underwent cross-couplings with primary, secondary and even tertiary alkylzincs at ambient temperature. A kinetic study with a 1:1 mixture of ligand **14** and PdCl₂(CH₃CN)₂ was performed using the cross-coupling between ethyl-2-iodobenzoate and cyclohexylzinc chloride as the model reaction.¹⁶² The kinetic data revealed that the rate constant for reductive elimination of [Ar-Pd-C_{sp3}] was $> 0.3 \text{ s}^{-1}$, which was about 4 or 5 orders of magnitude greater than values using [Pd-(dppbz)] or [Pd(PPh₃)₂] (dppbz = 1,2-bis(diphenylphosphino)-benzene). The rate enhancement was proposed to be a result of the π -acidity of the ligand. As expected the same reaction with the saturated analog of the ligand resulted in not only a slower rate but also the formation of a substantial amount of ethyl benzoate. The formation of ethyl benzoate was a clear indication that the ligand promotes reductive elimination and suppresses competitive β -hydride elimination. During a subsequent mechanistic investigation by Lei and coworkers, a second transmetalation step in the Negishi coupling was revealed and its competition with reductive elimination was disclosed.¹⁶³ The isomerization of the secondary dialkylzinc such as *i*-Pr₂Zn to a linear one was significantly suppressed using the catalytic combination of [Pd(CH₃CN)₂Cl₂] and ligand **14** (Figure 14). Similarly, ligand **15** was used for the Negishi coupling between aryl bromides and alkylzinc chlorides. Using the same concept, a highly electron-deficient diene ligand **16** was also employed for the Pd-catalyzed cross-couplings of aryl iodides and alkylzinc reagents.¹⁶⁴

A library of biologically active 5-fluoroalkylated pyrimidine nucleosides was synthesized by a Pd(*Pt*-Bu₃)₂-catalyzed cross-coupling reaction between protected 5-iodo-2'-S-deoxyuridine nucleosides and fluorinated, unactivated alkylzinc reagents (Figure 15).¹⁶⁵ This methodology provides a direct route to synthesize F¹⁸-radiolabeled 5-fluoroalkylated pyrimidine nucleosides that could be used as probes for noninvasive *in vivo* molecular imaging.^{166–168} Although yields are modest, mild reaction conditions for the cross-coupling reactions of sensitive and densely functionalized molecules are noteworthy.

Wolf and coworkers recently reported the Negishi cross-coupling of organozinc reagents and aryl halides catalyzed by Pd-phosphinous (POPd7) acid in NMP (Figure 16). A wide range of functional groups were compatible under the reaction conditions.¹⁶⁹

The cross-coupling of unsaturated halides bearing acidic protons with organozinc reagents is an ongoing challenge. The Knochel group reported that Pd(OAc)₂/SPhos is an excellent catalyst combination for the Negishi cross-coupling reactions of substrates bearing acidic protons (Figure 17).^{170,171} Thus a variety of bromo- or iodo-anilines, alcohols, and acidic phenols underwent cross-coupling upon slow addition (90 min) of the organozinc reagents at 25 °C. The relative kinetic basicity of the organozinc reagents is in the order: arylzinc halide $>$ alkylzinc halide $>$ benzylzinc halide as determined by the addition of *i*-PrOH to the organozinc reagents and subsequent quenching with CuCN/allyl bromide in THF.¹⁷⁰

A highly chemoselective Negishi cross-coupling reaction between alkylzinc reagents and 2-bromo- 5(or 6)-tri-*n*-butylstannylpyridines was reported by Twieg group.¹⁷² The Pd(PPh₃)₄-

catalyzed cross-coupling occurred at ambient temperature selectively at the 2-position, leaving the tri-*n*-butylstannyl group intact for further Stille couplings (Scheme 5).

The Knochel group observed a positive effect of tetra-*n*-butylammonium iodide on Pd(0)- and Ni-catalyzed Negishi cross-couplings. A series of aryl or alkenyl triflates underwent a Pd(dba)₂/dppf (7 mol%)-catalyzed cross-coupling with benzyl¹⁷³ and/or alkylzinc halides using three equivalents of Bu₄NI.¹⁷⁴ To explore the impact of Bu₄NI on the conversion of the starting material, experiments were performed with differing amounts of Bu₄NI. It was found that the cross-coupling between benzylzinc bromides and *p*-Cl-phenyl triflate produced 2.4% of the coupling product with 0.1 equiv, 38% with 1.0 equiv and 90% with 3.0 equiv of Bu₄NI. More recently, Marder and Lei reported that Pd-nanoparticles were formed from Pd(OAc)₂ and Bu₄NBr under these reaction conditions (Figure 18).¹⁷⁵ Transition metal nanoparticles can provide a more accessible and active surface area to interact with substrates that increase the catalytic activity.¹⁷⁶ Suitable stabilizers such as commercially available tetraalkylammonium halides are frequently used in nano-Pd catalysis to prevent agglomeration and precipitation of the catalyst.¹⁷⁷ Thus, a combination of Pd(OAc)₂ and Bu₄NBr catalyzed the cross-coupling between aryl iodide and alkylzinc efficiently at room temperature as well as at -20 °C in excellent yield within 1 h (Figure 18). Presumably, Pd(OAc)₂ was reduced to Pd(0) by the alkylzinc reagent under the reaction conditions. The Pd(0)-species was then suspended as nanoparticles (PdNPs) and stabilized by Bu₄NBr. The reaction between ethyl-2-iodobenzoate and CyZnCl was monitored by *in situ* IR. It was found that the reaction reached 60% completion after 30 seconds and 100% after 2 min. Several experiments support that Pd(NPs) are formed including the observation that PPh₃ acts as a catalyst poison.

Yang and Lei identified a highly efficient alkylated pincer thioimido-Pd complex intermediate in Negishi coupling by *in situ* IR, ¹H and ¹³C NMR studies. Contrary to the Pd(OAc)₂/Bu₄NBr catalytic system that forms Pd(NPs) as a true active species, the thioimido-Pd(II) complex **17** reacted with CyZnCl to form an alkylated, anionic species **19** that catalyzed cross-coupling further with ethyl-2-iodobenzoate (Scheme 6).¹⁷⁸ The long induction time (~ 60 min) was due to the formation of **18**. Once it was formed the subsequent coupling is complete within 20 min.

The Buchwald group reported an efficient Negishi coupling between secondary alkylzinc halides and aryl bromides and chlorides catalyzed by Pd(OAc)₂ and an electron-rich ligand CPhos (Figure 19). Excellent selectivity for branched versus linear products using CPhos was observed due to the slow relative rates of β-hydride elimination-reinsertion versus reductive elimination.¹²⁵

In 1979, the Wenkert group first reported the transmetalation of Grignard reagents containing unsaturated thioethers in transition metal-catalyzed cross-coupling reactions.¹⁷⁹ The Fukuyama coupling is another illustration of this concept that converts thioesters to ketones by reacting with organozincs in the presence of catalytic Pd.¹⁸⁰ The Knochel group exploited this concept of C-S bond activation to show that various thiomethyl-substituted *N*-heterocycles, i.e. pyridines, pyrimidines, pyrazines, pyridazines, benzothiazoles etc., undergo Pd-catalyzed cross-coupling reactions with organozinc reagents using Pd(OAc)₂/SPhos (Figure 20).¹⁸¹ For alkylzincs, the cross-couplings required heating at 50 °C for completion. More recently, the same group reported that Ni(acac)₂/DPEPhos could catalyze this reaction at room temperature. Several 2-substituted oxazoles were synthesized using a Ni-catalyzed cross-coupling of 2-methylthio-oxazole and various organozinc reagents.¹⁸² A Pd-catalyzed cross-coupling with thiomethylated alkynes and alkylzinc reagents was also reported by this group.¹⁸³ Furthermore, Stambuli reported the synthesis of unsymmetrical 2,5-disubstituted oxazoles from the corresponding 2,5-dimethylthio-oxazole by

chemoselective Pd- and Ni-catalyzed cross-couplings with organozinc reagents in one pot.
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Lipshutz and coworkers reported the *in situ* preparation of alkylzinc reagents in water catalyzed by tetramethylethylenediamine (TMEDA) and subsequent cross-coupling reactions with arylbromides. A combination of a sterically hindered and electron-rich Pd-catalyst along with a surfactant (PTS) in water formed a highly active aqueous micellar catalyst for the Negishi cross-coupling (Figure 21).¹⁰⁷ This methodology offers a low-waste technology for C(sp²)-C(sp³) bond constructions in the absence of stoichiometrically *preformed* organometallic coupling partners and organic solvents. Similarly, a one pot protocol using a Pd-PEPPSI-catalyst for a cross-coupling between aryl chlorides, bromides and triflates and alkylzinc reagent was reported by the Knochel group.¹⁸⁵

2.4.2. Pd-Catalyzed C(sp³)-C(sp³) Negishi Coupling with Alkylzinc Reagents—

Over the past two decades, significant progress has been achieved in the area of C(sp³)-C(sp³) cross-coupling between alkyl organometallics and alkyl electrophiles. The Fu group has made key contributions by identifying a set of electron-rich hindered ligands capable of promoting oxidative addition and reductive elimination to furnish cross-coupling products. As an example, Pd₂(dba)₃/PCyp₃/NMI was found to be an effective catalyst combination for the cross-coupling of alkylzinc reagents with alkyl halides and tosylates (Figure 22).¹²¹ The addition of NMI improved yields to some extent, perhaps through activation of alkylzinc halides toward transmetalation.

As discussed earlier, one of the main problems in alkyl-alkyl cross-coupling is the reluctance of saturated carbon-halogen bonds to undergo oxidative addition compared to aryl, vinyl, benzyl, or allyl halides and competing β-hydride elimination from the organometallic intermediates. To overcome these obstacles, an electron-rich Pd-center is often employed for effective oxidative addition, wherein *N*-heterocyclic carbenes (NHCs) are an alternative to electron-rich phosphine ligands due to their σ-donicity and steric properties.^{186,187} Fu and coworkers reported low yields when a NHC ligand having modest sized substituents was used in a Negishi coupling.¹²¹ In contrast, Organ and coworkers reported good to excellent yields using sterically more hindered NHC ligands (Figure 23).
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The use of an NHC ligand (*Ii*-Pr) in an oxidative Pd(II)-catalyzed C(sp³)-C(sp³) cross-coupling was recently reported by the Sigman group (Figure 24).¹⁸⁹ In this chemistry, styrenes were utilized as synthons for alkyl halides in an overall hydroalkylation process with alkylzinc reagents to form primary-secondary carbon-carbon bonds under oxidative conditions. The reaction is proposed to proceed by transmetalation to form complex **23** followed by β-hydride elimination to form a Pd-hydrido species **24**. Insertion of the Pd-hydride into the conjugated alkene presumably generates a π-benzyl species **25** which undergoes transmetalation to form the product. Benzoquinone was used as a terminal oxidant that regenerates the active Pd(II)-species to complete the catalytic cycle (Figure 24). The cationic nature of the metal center was found to be crucial in this transformation, which is in contrast to the involvement of electron-rich metal centers in C(sp³)-C(sp³) couplings with alkyl halides. To illustrate the origin of hydrogen in the product, a deuterated alkylzinc reagent was subjected to the cross-coupling reaction. Nearly one deuterium incorporation was observed predominantly (94%) at the methyl position, and at the methine position to some extent (11%). This phenomenon indicates that the insertion of alkene occurs with either regiochemistry, but the resultant Pd-alkyl species likely rearranges to the more stabilized π-benzyl intermediate via β-hydride elimination-reinsertion.

2.4.3. Pd-Catalyzed C(sp)-C(sp³) Negishi Coupling with Alkylzinc Reagents—

Although C(sp²)-C(sp³) couplings have been studied extensively, there are few examples of C(sp)-C(sp³) couplings using alkynyl electrophiles and alkyl organometallics.¹⁹⁰ One such example is the Pd-catalyzed oxidative cross-coupling of terminal alkynyltin reagents with alkylzincs to generate alkylated alkynes through double transmetalation (Figure 25).²⁴ Mechanistically, the oxidative addition of decyl chloride to Pd(0) generates C-bound Pd-enolate chloride **26** that undergoes tautomerization into the O-bound Pd-enolate chloride **27**. Sequential transmetalation with zinc and tin reagents produces the C(sp)-Pd-C(sp³) intermediate **29**, which undergoes reductive elimination to yield the desired cross-coupling product **30** (Figure 25). Kinetic studies by *in situ* IR revealed that the rate of cross-coupling is much faster than that of the corresponding homocoupling. In addition, the rate of stilbenyloxylzinc chloride formation is almost equal to the consumption of desyl chloride and the formation of the cross-coupling product (R¹-R²).

Similarly, C(sp)-C(sp³) coupling of terminal alkynes with alkylzincs using Pd(dba)₂ were accomplished under oxidative conditions by the same group (Figure 26).²⁵ A substantial amount of diyne formation was observed using air as the oxidant along with Pd(dba)₂. However, cross-coupling products were obtained in good to high yields using a (10:1) mixture of air/CO. Presumably, the well-known π -acidic ligand CO facilitates the reductive elimination in this process. A similar accelerating effect was observed using dibenzylideneacetone (dba) in lieu of CO. A nice practical advantage of using CO as the π -acidic ligand was that no rigorous column chromatography for separation was required.

2.4.4. Formation of Ketones via Pd-Catalyzed Negishi Coupling with Alkylzinc Reagents—

The Pd-catalyzed acylation of organozinc reagents using carboxylic acid chlorides was reported in early 1980's.^{113,191} As a recent example, pyridine carboxylic acid chlorides were coupled with alkylzinc reagents catalyzed by Pd(phen)Cl₂ to afford pyridyl ketones. Interestingly, only the acid chlorides react while the 2-chloroazine moiety remains intact under the reaction conditions (Figure 27).¹⁹²

2.5. Ni-Catalyzed Cross-Coupling Reactions of Alkylzinc Reagents

The use of Ni-complexes in Negishi type cross-coupling reactions was initially reported simultaneously with the Pd variants. As described below, the Ni-catalyzed variants are quite powerful on an array of substrate types.

2.5.1. Ni-Catalyzed C(sp²)-C(sp³) Negishi Coupling with Alkylzinc Reagents—

Liebesskind reported a biologically relevant, Ni-catalyzed cross-coupling of a thioglycolate series with organozinc reagents based on the principle of metal-thiolate activation. A series of thioglycolic acids were synthesized conveniently by base-catalyzed thioether formation of thioarenes and 2-bromoethanesulfonic acid and underwent cross-coupling with organozincs in the presence of catalytic (MePPh₂)₂NiCl₂ in THF at 25–50 °C (Figure 28).¹⁹³ Control experiments suggested the crucial role of Zn²⁺ presumably as a thiolate ion scavenger to prevent poisoning of the metal catalyst in these cross-coupling reactions.

The Yang group reported Pd-catalyzed cross-coupling reactions of arene and vinyl-sulfonates with organozincs to produce 4-substituted coumarins.¹⁹⁴ Switching from Pd to Ni resulted in the facile coupling of organozinc reagents with vinyl-phosphates. Thus, a series of 4-substituted coumarins were obtained from the corresponding 4-phosphate-coumarins (Figure 29).

Ni-catalyzed Negishi coupling of amino-heteroaryl chlorides with alkylzinc reagents was reported by Walters (Figure 30).¹⁹⁵ The alkylzinc reagents could be commercially available dialkylzincs or alkylzinc halides, or they could be conveniently generated *in situ* from

diethylzinc and primary alkyl bromides in the presence of $\text{NiCl}_2(\text{dppp})$ as catalyst, which also catalyzes the cross-coupling reaction.

Pd-catalyzed Negishi coupling of substrates bearing basic nitrogen substituents has proved to be unsuccessful in general. The Knochel group has developed a Ni-catalyzed protocol for aminoalkylations of arenes. The lithium salts of amino alkyl Grignard reagents were converted to the corresponding alkylzinc reagents *in situ* by treatment with ZnBr_2 . Subsequently, $\text{Ni}(\text{acac})_2/\text{DPEPhos}$ -catalyzed cross-coupling with an aryl or a heteroaryl (pseudo)halides introduced the aminoalkyl moiety into the arene system (Scheme 7).¹⁹⁶

Recently, the Terao group reported a Ni-catalyzed regioselective three-component coupling of alkyl halides, arylacetylenes, or enynes with organomagnesium or organozinc reagents (Figure 31).¹⁹⁷ Mechanistically, it was proposed that alkyl radicals are generated *in situ* from the alkyl halides by single electron transfer from nickelate complex **31**. The alkyl radical undergoes addition to the unsaturated C-C system forming **32** (at terminal double bond in the case of enynes) followed by generation of **34** through combination of **32** and Ni-complex **33**. Finally, reductive elimination from Ni-complex **34** provides trisubstituted olefins **35** (or allenes).

2.5.2. Ni-Catalyzed Carboxylations with Alkylzinc Reagents—A Ni(0)-mediated three component coupling of alkynes, alkylzinc reagents and CO_2 has been reported to yield β,β' -disubstituted, unsaturated carboxylic acids (Figure 32).¹⁹⁸ Mechanistically, the reaction of Ni, alkyne, and CO_2 forms an oxonickelacycle **36** that undergoes transmetalation with alkylzinc reagents to produce intermediate **38**. Reductive elimination of the β,β' -disubstituted, unsaturated carboxylate **39** is followed by hydrolysis to release the product **40** (Figure 32). Various functionalized alkylzinc reagents also underwent this alkylative carboxylation of alkynes whereas diethylzinc produced corresponding β -monosubstituted acids via β -hydride elimination.

Oshima and coworkers reported an efficient Ni-catalyzed carboxylation of alkylzinc reagents for the production of saturated carboxylic acids. Lithium chloride salts of alkylzinc reagents underwent carboxylations smoothly under ambient pressure of CO_2 , catalyzed by $\text{Ni}(\text{acac})_2$ and PCy_3 (Figure 33).¹⁹⁹ The mechanism is proposed to proceed by initial reduction of $\text{Ni}(\text{acac})_2$ with the organozinc reagent. Ni(0) subsequently reacts with CO_2 to produce η^2 -coordinated complex **41**, which undergoes transmetalation with the organozinc reagent to generate reactive intermediate **42** upon a rapid reductive elimination, alkylcarboxylate **43** and active Ni(0) species are formed (Figure 33). The transmetalation and reductive elimination are thought to be facilitated by the highly electron-rich and bulky PCy_3 ligand. Recently, this protocol has been revisited by the Dong group and they found that $[\text{Ni}(\text{PCy}_3)_2(\text{N}_2)]$ is an efficient catalyst for the carboxylation of alkylzinc halides as well as alkylzinc halide-lithium salts.²⁰⁰

2.5.3. Ni-Catalyzed $\text{C}(\text{sp}^3)\text{-C}(\text{sp}^3)$ Negishi Coupling with Alkylzinc Reagents—

The Ni-catalyzed cross-coupling reaction between an alkyl organometallic reagent and an alkyl halide has been an active area of research during the past two decades. During the study of Ni-catalyzed Negishi couplings, the Knochel group observed that the presence of unsaturation or an electron withdrawing functional group on the alkyl halide accelerates the rate of reaction and produces the desired cross-coupling product in higher yields. Therefore, it was suspected that the remote double bond could act as an additional ligand for the Ni intermediates in the cross-coupling reaction. To gain more insight, the corresponding saturated alkylzinc reagent was submitted to the same cross-coupling conditions where a negligible amount of product formation was observed. Based on these observations, it is proposed that the catalytically active species $\text{L}_2\text{Ni}(0)$ generated by *in situ* reduction of

Ni(acac)₂ undergoes an oxidative addition of the alkyl halide to produce a Ni(II) complex **46**, in which the double bond is coordinated to the metal center (Scheme 8). After ligand exchange with diethyl zinc, complex **47** is formed where the double bond accepts the d electrons of the Ni (**51**), resulting in a faster reductive elimination reaction. In the absence of the double bond (or if it is sterically encumbered), a Ni complex of type **49** is formed that undergoes further transmetalation to generate a new alkylzinc reagent **50**, which can also undergo cross-coupling to give the undesired product. Alkyl halides bearing double bonds can be utilized in a substrate-controlled cross-coupling with dialkylzinc reagents as demonstrated by the Knochel group (Figure 34).²⁰¹

Similarly, functional groups such as ketones, cyanides, esters, and amides have positive effects on related cross-couplings. Besides the strategic control over reductive elimination by substrates that contain double bond(s), external additives were also effective in promoting cross-coupling reactions. It was found that additives such as acetophenones, benzophenones, and styrenes with electron withdrawing substituents accelerate the reaction (Figure 35).¹⁵⁹ Among all of these additives, *p*- and *m*-trifluoromethyl substituted styrenes were the most effective in affording high yields at fast rates (Figure 35).¹⁵⁹

The Knochel group reported a Ni(II)-catalyzed cross-coupling of benzyl zinc reagents with alkyl iodides in combination with *p*-fluorostyrene and Bu₄Ni as additives (Figure 36).¹⁷⁴ The role of *p*-fluorostyrene was quite evident based on the preceding discussion; however, the role of Bu₄Ni is not clear although it is necessary for improved rates and yields. The same protocol was applied to the coupling of functionalized primary and secondary alkylzincs with primary alkyl halides.¹⁷⁴ Recently, the same group has discovered that isopropyl iodide accelerates Negishi cross-couplings.²⁰²

Fu and coworkers reported Ni-catalyzed C(sp³)-C(sp³) cross-coupling reactions of diverse alkylzinc reagents with unactivated secondary alkyl halides under very mild conditions. Ni(cod)₂ and *s*-Bu-Pybox catalyzed the Negishi couplings in DMA at room temperature (Figure 37). Gratifyingly, the same catalytic system was also employed in the Negishi coupling with primary alkyl halides highlighted by the use of neopentyl iodide as a reaction partner.²⁰³

A number of primary alkyl halides and a tosylate underwent cross-coupling with dialkylzinc reagents at room temperature in NMP using catalytic NiCl₂ in combination with MgBr₂ and tetraene **52** (Figure 38).²⁰⁴ It was found that the electron-withdrawing tetraene additive **52** has a pronounced effect on reaction outcome, compared to conventional additives such as Bu₄NBr, Bu₄Ni, *p*-fluorostyrene, isoprene, and *i*-PrI. It was speculated that a bis- π -allyl-Ni structure **53** is formed by oxidative cycloaddition of Ni(0) with the two butadiene moieties of 1,3,8,10-tetraene **52**. An organomagnesium or zinc reagent attacks the bis- π -allyl-Ni complex to generate the η,η -octadienediylnickelate complex **54**, which then reacts with the alkyl halide to yield complex **55**. Cross-coupling product **56** is obtained via the subsequent reductive elimination of complex **55**, and complex **53** is regenerated to complete the catalytic cycle (Figure 38).

Gagné and coworkers reported another example of a Ni-catalyzed Negishi coupling between functionalized alkylzinc reagents and secondary glycosidic halides.²⁰⁵ It was observed that NiCl₂ with an achiral Pybox ligand lead to good product yields, and mannosyl halides were diastereoselective for retentive *CI*-alkylation. In the case of acetyl-protected glycosides, α -bromides were the reaction partners, whereas benzyl-protected α -bromoglycosides were more reactive and in that case α -chlorides provided good yields and selectivity (Figure 39).

The Cárdenas group utilized the proposed intermediacy of alkyl radicals in a Ni-catalyzed radical cyclization/cross-coupling process. This lead to the successful construction of

substituted cyclic ethers via cascade formation of C(sp³)-C(sp³) bonds by cyclization and cross-coupling reactions of iodoalkanes with alkylzinc halides (Figure 40).²⁰⁶

Cross-coupling reactions between secondary electrophiles and secondary alkyl organometallics are very problematic due to the presumed steric interactions associated with the process. The Ready group reported a Cu-catalyzed α -alkylation of α -chloro ketones with secondary alkylzinc reagents at room temperature.²⁰⁷ Fu and coworkers developed a Ni-catalyzed Negishi coupling with secondary alkylzinc reagents and secondary propargylic halides at room temperature using a combination of 10 mol% Ni-complex, and 10 mol% terpyridine **57** in DMA.²⁰⁸ More hindered alkylzinc reagents required the use of 5 mol% of Ni-complex and 5 mol% of 2,6-bis(*N*-pyrazolyl)pyridine **58** as ligand in THF. Bulky substituents on the alkyne were found to be crucial to avoid diyne formation via homocoupling. This methodology has been extended into the formal total synthesis of α -cembra-2,7,11-triene-4,6-diol (Scheme 9).

2.5.4. Mechanistic Insights in Ni-Catalyzed Cross-Couplings—Alkyl halides are known to undergo oxidative addition to Ni-catalysts via a radical pathway.²⁰⁹ Cárdenas and coworkers conducted tandem cyclization-cross-coupling reactions.²⁰⁶ It was observed that the *cis* and *trans*-isomers of a secondary alkyl halide containing a tethered olefin underwent intramolecular cyclizations followed by cross-coupling to give the same degree of *cis/trans* selectivity, indicating loss of stereochemical fidelity (Scheme 10).²⁰⁶ The same type of selectivity is observed under reported radical cyclization conditions,²¹⁰ implicating the formation of a planar radical intermediate.

The same phenomenon was also observed under Fu's conditions where cross-coupling of both *exo*- and *endo*-2-bromonorbornane with various organometallic reagents produced the *exo* product predominantly.²¹¹ Therefore, enantioselective cross-coupling reactions, which are discussed later, with racemic secondary alkyl halides, undergo stereoconvergence rather than a kinetic resolution.

Vicic and coworkers carried out an extensive study to probe the mechanism of Ni-catalyzed Negishi couplings.^{20,212} It was observed that a (terpyridine)nickel(0) complex does not react with alkyl halides by simple oxidative addition (two electron process) followed by transmetalation to afford cross-coupling product.²¹ The mono methyl Ni-complex is formed by ligand-induced loss of ethane followed by a comproportionation with another molecule of a dimethyl Ni(II) species (Scheme 11).²¹²

In contrast, the mechanism involving a secondary alkyl iodide and (terpyridyl)Ni(alkyl) complex **59** was proposed to proceed via a single electron transfer from the ligand to the alkyl halide generating a new metal complex **60** and an alkyl radical (Scheme 12). In EPR investigations, it was observed that the radical in the complex remains mainly on the ligand ($g = 2.021 \pm 0.002$), and the alkyl radical remains in close proximity to the metal center. A subsequent oxidative radical addition to the metal center gives a putative Ni(III)-dialkyl complex **61** that yields the cross-coupling product via reductive elimination along with the complex **62**.

Further DFT calculations performed by Phillips and coworkers also suggest the involvement of a single electron process in Ni-catalyzed alkyl-alkyl Negishi couplings.²¹³ It was computed that the traditional two-electron redox mechanism is energetically unfavorable. Moreover, the halogen atom transfer to the metal center is the rate-determining step. The use of secondary electrophiles led to a faster decomposition of a Ni(III) complex compared to the reductive elimination.

Finally, a plausible mechanism for the cyclization/coupling reaction described by Cárdenas was proposed based on computational and experimental results.^{206,214} Free radicals of type **63** are readily formed from alkyl iodides in the presence of Ni salts, which in some cases cyclize to yield intermediate **64**. If the cyclization is slow, faster coordination to a Ni^{II}-complex to give a dialkyl-Ni(III) intermediate **68** may occur. This species would then undergo reductive elimination to give simple coupling product **69**. Alternatively, intermediate **64** could react with the starting iodide to give **63** and **66** that could undergo subsequent coupling to give final product **67** (Scheme 13).

The role of additives in alkyl-alkyl Negishi couplings has also been investigated.¹⁹⁹ The Organ group performed a titration study with the various amounts of LiBr doped into the alkyl-alkyl cross-coupling reaction mixture.²¹⁵ It was observed that the rate of cross-coupling increases with the amount of LiBr added, and a sharp increase was observed at approximately 1.0 equiv of LiBr added. In addition to the presumed break up of polymeric zinc aggregates, LiBr converts it to the tetracoordinated zincate complexes, which is an active transmetalating agent.

3. Cross-Coupling with Alkylboron Reagents

3.1. Introduction

In the context of transition metal-catalyzed C-C bond forming reactions, the Suzuki-Miyaura coupling using organoboron compounds has emerged as a powerful tool due to its operational simplicity, environmentally benign nature, and the thermal stability of the transmetalating agents.^{117,216,217} The broad functional group tolerance compared to Negishi or Kumada protocols, which utilize organozinc and organomagnesium reagents respectively, is an added advantage of this protocol.^{117,216} Although organoboron compounds are highly electrophilic, the organic groups on boron are weakly nucleophilic. Additionally, the coordination of a negatively charged base to the boron atom can increase the nucleophilicity of the organic moiety on boron.²¹⁸ Interestingly, Suzuki and Miyaura simultaneously realized that organoboron compounds, even organoboronic acids and esters, have sufficient reactivity for the transmetalation to various metals such as silver(I),²¹⁹ magnesium(II),²²⁰ zinc(II),^{221–223} aluminum(II),^{224,225} tin(IV),²²⁶ copper(I)^{227,228} and mercury(II).²²⁹ Since the first report in 1986 of the cross-coupling reaction between alkylboron reagents and aryl and alkenyl halides in the presence of Pd(0) and a base,²³⁰ the *B*-alkyl Suzuki-Miyaura cross-coupling has become one of the most popular cross-coupling protocols in organic synthesis.^{231,232}

Primary alkyl borane compounds are easily synthesized by hydroboration of terminal alkenes in a highly chemo-, regio- and stereoselective manner.²³³ They are generally reactive species and undergo cross-couplings under diverse reaction conditions, but secondary alkylborons, especially secondary alkylboronic acids or trifluoroborates, are less reactive with the exception of cyclopropylboron derivatives that possess significant sp²-character.²³⁴ In spite of their low reactivity, the use of alkylboronic acids or trifluoroborates has become common practice in cross-coupling reactions due to their excellent compatibility with a wide range of functional groups.

3.2. Synthesis of Alkylboron Reagents

Classically, alkylboron reagents have been synthesized from the corresponding alkyllithium or alkylmagnesium reagents by reaction with suitable boron compounds. The Brown group reported a simple and efficient preparation of boronic esters, in which the corresponding alkyl halides were treated with methyllithium and quenched with trialkoxyborane at low temperature (−78 °C).²³⁵ Acidification with anhydrous HCl at 0 °C furnished the corresponding alkylboronic acids. Triisopropylborate was found to be the most effective

furnishing diisopropylborates in quantitative yields. Similarly, treatment of alkyl iodides with *t*-BuLi followed by trapping with 9-methoxy-9-borabicyclo[3.3.1]nonane produces the corresponding alkylboron compounds *in situ*, which undergo cross-coupling reactions without further purification.²³⁶ Soderquist and coworkers used (TIPS)S-9-BBN instead of *B*-MeO-9-BBN. (Figure 43).²³⁷ A more common and popular approach to the synthesis of alkylboron reagents is through hydroboration of the corresponding alkene, which offers operational simplicity and a high degree of chemo-, regio-, and diastereoselectivity (Figure 43). The terminal alkylboron compounds are formed selectively through the *anti*-Markovnikov addition of the boron from the less hindered side of the alkene. Catecholborane (HBcat)^{238,239} or pinacolborane (HBpin)²⁴⁰ can also be used to synthesize the corresponding alkyl boronic ester under rhodium- or iridium-catalysis respectively (Figure 43). The Hartwig group also reported the Ti-catalyzed hydroboration of alkenes.²⁴¹ Mioskowski and coworkers reported the synthesis of polymer-bound alkylboranes that could be purified by filtration, washing with anhydrous THF, and drying under vacuum for subsequent Pd-catalyzed cross-coupling reactions.²⁴² Alkylboronic acids are prepared by the reaction of Grignard reagents or alkyllithium reagents with trihaloboranes and trialkoxyboranes, followed by acidification. Instead of the acidic work up, the reaction can be quenched with different alcohols to form the corresponding esters in high yields (Figure 43).²³⁵ The Brown group reported a convenient preparation of alkyl boronic acids and esters by the hydroboration of alkenes with dibromoborane-dimethylsulfide, followed by treatment with water or alcohols (Figure 43).^{235,243} A recent literature account described the preparation of alkyl trifluoroborates via halomethyltrifluoroborates.²⁴⁴

3.3. Stability of Alkylboron Reagents

Alkylation reactions can be achieved under Suzuki-Miyaura conditions using alkylboron components as the coupling partner that transfers the alkyl group to the organic framework. One of the leading candidates to serve this purpose is *B*-alkyl-9-BBN. However, this reagent is not air stable, which makes it relatively difficult to handle, isolate, and purify.²⁴⁵ Typically, cross-coupling reactions with *B*-alkyl-9-BBN are carried out *in situ* immediately after hydroboration of the alkene. In addition, carrying out a cross-coupling reaction with alkyl-9-BBN produces significant waste. As an alternative to alkyl-9-BBN, alkylboronic acids, esters, as well as trifluoroborates are extremely useful. They can be easily prepared as described in the previous section and stored (Figure 43). Alkylboronic acids are frequently used in superstoichiometric amounts to achieve satisfactory yields of the cross-coupling products. This is due to the fact that under the cross-coupling conditions, they can decompose either via protodeboration, or β -elimination. The corresponding esters of boronic acids can be employed as coupling partners, but very often they require activation by thallium bases, such as TlOH or Tl₂CO₃.²⁴⁶ In contrast, potassium organotrifluoroborates are stable under air and moisture indefinitely without any special precautions. Several functionalized organotrifluoroborates can be easily synthesized from various organoboron intermediates by addition of KHF₂.^{244,247}

3.4. General Mechanistic Aspects

In 1986, Suzuki and Miyaura reported the cross-coupling between alkylboron reagents and aryl halides.²³⁰ Since its disclosure, it has been an attractive solution to challenging synthetic problems and has been used frequently in total synthesis for the construction of complex molecular frameworks.^{231,232} Like other cross-coupling reactions, this reaction typically proceeds through (1) oxidative addition of aryl, alkenyl or alkyl halides or pseudohalides to a low-valent metal complex; (2) transmetalation with the alkylboron component; and (3) reductive elimination to give the cross-coupling product and metal complex for use in the next catalytic cycle. In most cases, oxidative addition is the turnover limiting step. The electronic character of the alkyl groups as well as the nature of the halide

or pseudohalide greatly influences the rate of oxidative addition. Fu and coworkers have shown that the relative rate of oxidative addition of the electrophile is in the order $I \gg Br > OTf \gg Cl$.²⁴⁸

3.4.1. Catalysts for Suzuki-Miyaura Cross-Coupling Reactions—A rigorous literature survey revealed that among all other electrophiles^{217,249} the alkyl electrophiles^{16,120} are the most challenging in *B*-alkyl Suzuki-Miyaura coupling due to the sluggish oxidative addition and deleterious β -hydride elimination. The most frequently used catalysts in *B*-alkyl Suzuki-Miyaura coupling with aryl, alkenyl, benzyl and allyl halides and triflates are $PdCl_2(dppf)$ and $Pd(PPh_3)_4$,²⁴⁹ but they have been found to be unsuccessful for alkyl-alkyl couplings. In the last decade, the Fu group has made significant progress in this field using electron-rich and sterically hindered phosphine ligands, as well as replacing Pd with Ni-catalysts.²⁴⁸ The Buchwald group also developed a series of electron-rich ligands for the Pd-catalyzed Suzuki couplings of various substrates including aryl chlorides and alkylboranes that were previously considered to be unreactive.^{250,251}

3.4.2. Role of Bases in the Suzuki-Miyaura Cross-Coupling Reaction—It has been found that the choice of base(s) is crucial in the Suzuki-Miyaura coupling reaction. In their initial reports, the Suzuki group demonstrated the solvent and base dependence of the conversion for different boron derivatives.^{246,252} Stronger bases such as NaOH, TIOH, and NaOMe perform well in THF/H₂O solvent systems, whereas K₂CO₃ and K₃PO₄ are more efficient in DMF. Soderquist and coworkers²⁵³ have shown that the base is involved in several steps, such as (1) formation of the borate complex, (2) hydrolysis of the $RPd^{II}X$ intermediate to the more reactive $RPd^{II}OH$ species, which was evident from ³¹P NMR spectroscopy (Scheme 15). (The chemical shift in the ³¹P NMR for $Pd(PPh_3)_4$ appears at $\delta = 18.0$ (broad singlet) whereas it shifts to $\delta = 26.1$ after oxidative addition (**70**)). The adduct is then hydrolyzed by base to form **71** with $\delta = 23.6$) (3) complexation of HOBR₂ byproducts that can compete for base with the trialkyl borane, (4) acceleration of the rate of reaction for the OBBD derivatives (Scheme 16), and (5) regeneration of the catalyst.

Based on Soderquist's study, it was proposed that the oxidative addition of phenyl bromide is the rate limiting step in the case of alkyl-9-BBN derivatives. The halide ion is displaced by the base to form a hydroxo μ_2 -bridged intermediate **73**. The coordination of the Pd species with the hydroxyl group of the intermediate **73** accelerates the transmetalation with boron with retention of configuration through a four-centered transition state (Scheme 18). After fast reductive elimination, the cross-coupling product is formed. In contrast, the formation of $PdPh(PPh_3)_2OH$ is rate-limiting in the case of less Lewis acidic OBBD-derivatives. The reaction proceeds through the formation of the μ_2 -bridged species **73'** that collapses spontaneously to **74**, which on reductive elimination gives the cross-coupling product. Thus, a more detailed catalytic cycle for the *B*-alkyl Suzuki coupling was proposed, which demonstrates the crucial role of base and boron derivatives (Scheme 16).

3.4.3. Boron Derivatives in the Suzuki-Miyaura Cross-Coupling Reactions—Generally, unhindered electron-rich organoboranes and electron-deficient vinyl or aryl halides or triflates are the most efficient reaction partners for the *B*-alkyl Suzuki reaction. Although 9-BBN-H is the most commonly used hydroborating agent, disiamylborane and dicyclohexylborane are also used in this reaction. The rate of transmetalation of a primary alkyl group on boron is much higher than that of a secondary alkyl group. The coupling reactions with secondary alkylborons provide only moderate yields (Table 3).^{246,252}

The Soderquist group observed differences in rate when varying the structure of boron reagents. The *B*-alkyl-9-BBN derivative was found to be significantly more reactive towards bromobenzene than the corresponding *B*-alkyl-OBBD counterpart.²⁵³ Their different Lewis

acidities accounted for the observed reactivity, which was examined in the study of borane-borate equilibria. The boranes were titrated with NaOH and the changes in chemical shift in their ^{11}B NMR spectra were recorded (Figure 44). The corresponding chemical shift of 9-BBN-H (**76**) was shifted from $\delta = 87.7$ to $\delta = 12.0$, $\delta = 6.0$ and $\delta = 3.3$ upon the addition of one, two, and three equivalents of NaOH respectively. No change in chemical shift was observed upon further addition of NaOH. In contrast, there was no observable change in ^{11}B chemical shift of the OBBD counterpart (**78**) upon treatment with NaOH. These results clearly indicate that the 9-BBN derivative is much more Lewis acidic than OBBD. Therefore, the borate of the corresponding 9-BBN participates in the transmetalation step, whereas OBBD-derivatives undergo transmetalation without further complex formation with base (Scheme 16).

Soderquist and coworkers also observed differences in reaction kinetics under Suzuki coupling conditions. For the reaction of PhBr with $[(\text{HO})\text{Bu-9-BBN}]^-$, a first-order rate dependence on [PhBr] was observed, indicating that the oxidative addition was the turnover-limiting step. In contrast, a first-order dependence on base and zero-order dependence on [PhBr] and [Bu-OBBD] was observed for Bu-OBBD derivative. Therefore, the hydrolysis of $[\text{BrPdPh}(\text{PPh}_3)_2]$ is the proposed turnover-limiting step in this case (Figure 44).

3.4.4. Stereochemistry of Oxidative Addition—The stereochemistry at the oxidation step in the *B*-alkyl Suzuki-Miyaura coupling is highly dependent on the metal complexes used for the cross-coupling. Recently, Fu and coworkers demonstrated that the oxidative addition process in Pd-catalyzed Suzuki-Miyaura cross-couplings proceeds predominantly via inversion of configuration.¹⁹ In their mechanistic investigation (Scheme 17), the diastereomerically pure tosylate **80** was subjected to the optimized reaction conditions without alkyl-9-BBN. From NMR analysis, it was determined that the oxidative addition was predominantly associated with inversion of configuration [inversion (**81**)/retention (**82**) = 10:1], and the primary kinetic isotope effect for the subsequent β -hydride elimination was found to be $k_{\text{H}}/k_{\text{D}} = 3$. In the next step, Ph-9-BBN was added to the reaction mixture and the cross-coupling products (**83**, **84**) were obtained with inversion of configuration, indicating retention of configuration at the reductive elimination step.¹⁹

3.4.5. Stereochemistry of Transmetalation—Woerpel²⁵⁴ and Soderquist²⁵³ independently studied the stereochemistry of transmetalation in the *B*-alkyl Suzuki-Miyaura coupling. The Soderquist group proposed that the transmetalation proceeds with retention of configuration through the formation of a four-membered cyclic transition state **87** (Scheme 18).²⁵³ From deuterium-labeling experiments, the Woerpel group also showed that transmetalation to Pd proceeds with retention of configuration (Scheme 19).²⁵⁴ In this experiment, diastereomeric dideuterioalkenes *cis*-**89** and *trans*-**89** were synthesized, and underwent hydroboration followed by Pd-catalyzed cross-coupling with α -iodocyclohexenone. The stereochemistry of the corresponding coupling products was assigned by ^1H NMR coupling constants (for *syn* isomer $J_{ab} = 5.8$ Hz, *anti* isomer $J_{ab} = 9.1$ Hz). The *syn*-coupling product (*syn*-**91**) was obtained from the *cis*-**90** isomer, whereas the *trans*-coupling product (*trans*-**91**) was obtained from the corresponding *trans*-**90**. As the hydroboration is a *syn*-addition process, it was concluded that transmetalation in *B*-alkyl Suzuki-Miyaura cross-coupling proceeds through retention of configuration, which is in agreement with Soderquist's findings.

3.4.6. Choice of Bases and Boron Substituents in Suzuki-Miyaura Couplings—Various alkylboranes have been used in the *B*-alkyl Suzuki-Miyaura cross-coupling reactions (See Table 3). 9-BBN-derivatives are the most commonly used. Different bases are used to activate them, and no reaction is observed in the absence of base.^{246,252} Therefore, selection of a suitable base is crucial to obtain high yields. The Kishi group first observed

rate-enhancing effect of thallium salts in the C(sp²)-C(sp³) Suzuki reactions.²⁵⁵ In their early reports, Suzuki and Miyaura also observed a dramatic effect of different bases with different boron compounds. Therefore, thallium salts were found to be important for several Suzuki-Miyaura coupling reactions.^{256–258}

3.5. *B*-Alkyl Suzuki-Miyaura Cross-Coupling with Alkyl Boranes

3.5.1. *B*-Alkyl Suzuki-Miyaura Cross-Coupling with Aryl and Alkenyl Halides—

Generally, aryl or alkenyl iodides or bromides are the most frequently used coupling partners in Suzuki-Miyaura cross-couplings,²⁴⁹ whereas aryl or alkenyl chlorides have traditionally been less common due to their low reactivity. However, the development of electron-rich and sterically hindered catalysts has overcome the slow oxidative addition of these substrates and made these cross-coupling reactions more effective.¹⁶

In their seminal report in 1989, Suzuki and Miyaura reported the cross-coupling reaction of *B*-alkyl-9-BBNs readily generated *in situ* from the corresponding alkenes and 9-BBN-H with a range of aryl and alkenyl halides, performed in the presence of a catalytic amount of PdCl₂(dppf) and base, such as sodium hydroxide, potassium carbonate, and phosphates.²⁵² High stereoselectivity was observed for the alkene products obtained from the reaction of alkenyl halides and *B*-alkyl boranes. Several common functional groups were found to be compatible under these mild reaction conditions. The stereoselective hydroboration of a C20-C21-methylene steroid **92** with 9-BBN-H produced predominantly C21-boryl steroid **93**. This underwent cross-coupling with ethyl (*E*)-β-bromomethacrylate to give **94** in 75% yield (Scheme 20). Interestingly, the hydroboration occurred chemoselectively at the less hindered C19-C20 double bond in the presence of C5-C6 double bond.

The Buchwald group developed an exceptional Pd catalyst for the Suzuki-Miyaura cross-coupling of challenging aryl halides (Scheme 21).²⁵⁹ An electron-rich biaryl ligand **95** was designed to provide the necessary steric interactions and electron density. Furthermore, X-ray analysis suggests an important interaction of the *ipso*-carbon of the arene with Pd. Employing this ligand, cross-coupling between sterically hindered aryl halides and aryl boronic acids or alkylboranes was accomplished with low catalyst loadings.²⁵⁹

The Taylor group demonstrated the synthesis of non-natural amino acids via *B*-alkyl Suzuki-Miyaura cross-coupling (Figure 45).²⁶⁰ The precursor olefin for the hydroboration was synthesized by Wittig olefination of Garner's aldehyde. The alkylboranes formed *in situ* underwent cross-coupling with alkenyl or aryl halides in the presence of K₃PO₄ and a catalytic amount of PdCl₂(dppf). The coupling products could easily be converted to the corresponding amino esters via Jones oxidation followed by methylation with diazomethane.

Johnson and coworkers subsequently reported the synthesis of nonproteinogenic α-amino acids and amino alcohols following a similar protocol (Figure 46).²⁶¹ In this case, it was observed that a catalytic amount of Pd(PPh₃)₄ was more efficient than PdCl₂(dppf). Aryl triflates were found to be excellent coupling partners under these reaction conditions, whereas in the Taylor's report, they were inefficient and only a small amount (11%) of the coupling product was isolated. All coupling products were converted to their corresponding amino acids using various oxidation protocols. Following the same procedure, Overman and Kamatani reported the synthesis of phenethyl and homoallylic amines from protected vinyl amines and aryl or alkenyl halides, respectively.²⁶²

A *B*-alkyl Suzuki-Miyaura coupling procedure for the synthesis of biologically active 4-benzyl piperidines and related substances was reported by Vice and coworkers (Figure 47).²⁶³ The hydroboration of *N*-Boc-4-methylene piperidine, followed by reaction with aryl bromides, iodides, and triflates in the presence of a catalytic amount of PdCl₂(dppf)/AsPh₃

produced a series of biologically relevant coupling products. Interestingly, 2,5-dibromopyridine underwent cross-coupling regioselectively at the 2-position, producing the corresponding coupling product in high yield.

A Pd-catalyzed direct alkylation of 2-halopurines with Et₃B or Bu₃B was developed by Piersanti and coworkers (Scheme 22).²⁶⁴ The alkylation of these particular substrates was challenging but highly desirable, as it offers a concise route for the synthesis of ST1535, a potent adenosine A_{2A} receptor antagonist. Fortunately, applying a *B*-alkyl Suzuki-Miyaura cross-coupling in the presence of Cs₂CO₃ and catalytic Pd(dppf)Cl₂ in THF afforded 2-alkylated purines in high yields. A comparative study with other organometallics revealed that, with the exception of tetra-*n*-butyltin, no other organometallics, including *n*-butylboronic acids, were successful in producing the desired product.

Tan and coworkers developed a flexible and efficient method to convert glycals to C1-substituted glycals using a *B*-alkyl Suzuki-Miyaura cross-coupling approach (Figure 48).²⁶⁵ A wide range of C1-iodo substituted glycals were alkylated directly with a variety of *in situ* generated alkylboranes in the presence of NaOH (aq) and a catalytic amount of Pd(dppf)Cl₂. It was observed that upon preincubation of the alkylborane with base prior to the addition of a mixture of C1-iodoglycal and Pd(dppf)Cl₂, the Pd-mediated reduction of the alkene iodide product was substantially suppressed.

Interestingly, when 1,1-dichloro-1-alkenes were cross-coupled with *B*-alkyl-9-BBN, the chloride *trans* to the alkene chain reacted preferentially (Figure 49).²⁶⁶ A detailed ligand study was performed, which showed that the larger bite angle of the ligand resulted in an improved ratio of the monoalkylation product. Thus, moving from dppb (\angle P-Pd-P = 98°) to DPEPhos (\angle P-Pd-P = 102°), the yield as well as selectivity were dramatically improved. Finally, using XantPhos (\angle P-Pd-P = 111°) in combination with Pd₂(dba)₃ and K₃PO₄-KF as base couple afforded excellent yields of the monoalkylated products. The stereoselectivity was also very good in most cases (*Z/E* = 90/10-98/2). Interestingly, when the monoalkylation product was subjected to further alkylation with Pd(dppp)Cl₂ or 2-(dicyclohexylphosphino)biphenyl, the unsymmetrical dialkylation product was obtained in good yields (Figure 50).²⁶⁶

3.5.2. Cross-Coupling with Aryl and 1-Alkenyl Triflates—Aryl or 1-alkenyl triflates are also an efficient class of coupling partners in *B*-alkyl Suzuki-Miyaura cross-coupling reactions. Suzuki and coworkers first reported that 1-alkenyl or aryl triflates underwent cross-coupling reactions with various alkylboranes in the presence of K₃PO₄ and a catalytic amount of Pd(PPh₃)₄ or PdCl₂(dppf) in dioxane in high yields.²⁵² Alkylboranes containing several functional groups, derived *in situ* from the reaction of the corresponding alkene with 9-BBN-H were also compatible under the reaction conditions.

Narukawa and coworkers reported an efficient synthesis of 2-alkyl carbapenems via Pd-catalyzed alkylation of carbapenem-2-yl triflate with *B*-alkyl-9-BBN (Figure 51).²⁶⁷ The alkylboranes were prepared *in situ* by reaction of 9-BBN-H with an alkene. Since the hydroboration occurs stereoselectively from the less hindered side of the olefin, the alkylborane obtained from the corresponding chiral olefin gave a single isomer that was incorporated into the carbapenem moiety without racemization through the subsequent cross-coupling reaction.

The Pd-catalyzed *B*-alkyl Suzuki coupling has been successfully employed for the construction of the *trans*-fused polyether framework that constitutes the core of several natural products.²⁶⁸ Sasaki and coworkers reported that cyclic vinyl triflates and a highly

functionalized *B*-alkyl-9-BBN underwent cross-coupling in the presence of Cs_2CO_3 , KBr, and a catalytic amount of $\text{Pd}(\text{dppf})\text{Cl}_2/\text{AsPh}_3$ (Figure 52).²⁶⁹

The Stevens group applied the *B*-alkyl Suzuki-Miyaura cross-coupling reaction in the synthesis of functionalized 8-methylquinoacridines, which were methylated with methyl iodide to generate telomerase-inhibitors, 8,13-dimethylquinoacridinium iodides (Scheme 23). Alkylboranes were prepared *in situ* by reaction of 9-BBN-H with allyl acetate or *N*-allyltrifluoroacetamide, which was subsequently treated with chloro- and triflate-substituted 8-methylquinoacridines. The cross-coupling occurred chemoselectively with the triflate functionality leaving the chloride intact when Cs_2CO_3 and catalytic amount of $\text{Pd}(\text{OAc})_2$ and PPh_3 were used.²⁷⁰

An interesting example of Suzuki-Miyaura cross-coupling between arenediazonium *o*-benzenesulfonamides and alkylboranes was reported by the Dughera group.²⁷¹ In this study, arenediazonium *o*-benzenesulfonamides were reacted with triethyl- or tri-*n*-butylborane in the presence of $\text{Pd}(\text{OAc})_2$, $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$, or $\text{Pd}(\text{dppf})\text{Cl}_2$ to afford ethyl or *n*-butyl arenes in high yields (Figure 53). No base was required for this transformation. It was observed that although high yields of the cross-coupling products were obtained using tetramethyltin reagents, ethyl or *n*-butyl analogues produced mainly protonated arenes via β -hydride elimination.

3.5.3. Intramolecular Suzuki-Miyaura Cross-Coupling and Macrocyclization—

An interesting extension of the Suzuki-Miyaura cross-coupling process is the formation of five- or six-membered rings via intramolecular cross-coupling.²⁵² The Suzuki group first reported the intramolecular reaction of aryl or alkenyl halides with *B*-alkyl-9-BBN derivatives to form five- and six-membered rings. However, the authors were unable to construct larger rings through this protocol due to oligomerization of the coupling partners at high substrate concentration. Compounds containing a vinyl halide and a terminal olefin linked through a two- or three-carbon tether can also be cyclized to form five- and six-membered exocyclic alkenes (Table 4 and 5).²⁷²

Soderquist and coworkers extended this idea when they performed tandem cross-coupling reactions with symmetrical bis-boranes and geminal dibromides (Figure 54).²⁷³ The intermolecular followed by intramolecular cross-couplings produced six-membered ring systems with exocyclic double bonds in moderate to good yields. The construction of five-membered rings was unsuccessful using this protocol.

Applying a high dilution technique (0.003 M), macrocyclization was achieved via intramolecular *B*-alkyl Suzuki-Miyaura cross-coupling with substrates containing aryl or alkenyl iodides and terminal double bonds. The double bond was converted to the corresponding terminal *B*-alkyl component *in situ* for subsequent cross-coupling in the presence of Cs_2CO_3 and a catalytic amount of $\text{Pd}(\text{dppf})\text{Cl}_2/\text{AsPh}_3$ in THF (Table 6).²⁵⁸ The Halcomb group accomplished the total synthesis of (+)-phomactin *via* late stage *B*-Alkyl Suzuki macrocyclization.²⁷⁴

3.5.4. Carbonylative Suzuki-Miyaura Cross-Coupling Reactions—In 1991, Suzuki and coworkers reported a carbonylative cross-coupling for the synthesis of α,β -unsaturated ketones from alkenyl halides and *B*-alkylboranes using a catalytic amount of Pd.²⁷⁵ In the same year, they reported the synthesis of unsymmetrical ketones via carbonylative cross-coupling between alkyl iodides and alkylboranes under an atmosphere of carbon monoxide (Figure 55). It was found that the reaction was accelerated by visible light, which could be due to the involvement of a radical process in the oxidative addition step.²⁷⁶ Tan

and coworkers reported a carbonylative Suzuki-Miyaura cross-coupling for the synthesis of C1-substituted glycals from the corresponding iodo-glycals (Scheme 25).²⁶⁵

3.5.5. Suzuki-Miyaura Alkyl-Alkyl Cross-Coupling Reactions—As in many other cross-coupling reactions, alkyl electrophiles are the most problematic substrates, and difficulties are especially exasperated in C(sp³)-C(sp³) couplings. In 1992, the Suzuki group first reported the C(sp³)-C(sp³) couplings using *B*-alkyl-9-BBN and alkyl halides (Figure 56). In a previous report, rate acceleration was observed for the carbonylative cross-coupling reaction in the presence of light,²⁷⁶ which suggested that the oxidative addition to the alkyl halide proceeds through a radical process. Although there was no induction of light in the cross-coupling of 9-octyl-9-BBN with 6-iodo-1-hexene, the formation of nonylcyclopentane as a byproduct along with the cross-coupling product suggests a radical pathway.²⁷⁷ To explore the effect of organometallic reagents, a series of *n*-butyl organometallic reagents were subjected to cross-coupling with 1-iododecane under the optimized reaction conditions, and 9-butyl-9-BBN was found to be the best coupling partner, providing 50% of the desired product.

Fu and coworkers have made substantial progress in the field of alkyl-alkyl Suzuki-Miyaura cross-coupling. Exploiting PCy₃ as the ligand, the oxidative addition of the Pd complex to alkyl halides was accelerated and cross-couplings with *B*-alkyl-9-BBN were accomplished at room temperature. Gratifyingly, it was discovered that Pd(OAc)₂/PCy₃ (1:2) in the presence of K₃PO₄•H₂O provided cross-coupling products in high yields (Figure 57).²⁷⁸ Besides the mild reaction conditions, triumph over β-hydride elimination, which is a major challenge of using alkyl electrophiles bearing β-hydrogens, was a major achievement of this protocol. Under a slightly modified catalytic combination of Pd₂(dba)₃ and PCy₃ in the presence of CsOH•H₂O, alkyl-alkyl Suzuki-Miyaura cross-couplings with more challenging alkyl chlorides were also accomplished at elevated temperature (90 °C) in dioxane (Figure 58).²⁷⁹

Although alkyl bromides and chlorides underwent cross-coupling successfully using PCy₃ as the ligand, alkyl tosylates were unreactive using the same reaction conditions. After optimization of the reaction conditions for these substrates, it was observed that a slightly different trialkylphosphine ligand, Pt-Bu₂Me, was able to provide cross-coupling products in high yields (Figure 59). During this study, it was observed that the reaction was exceptionally sensitive towards the cone angle of the ligands employed. Finally, a bench-stable trialkyl phosphonium salt, [HPt-Bu₂Me]BF₄, and Pd(OAc)₂ in the presence of NaOH were discovered to be effective for the cross-coupling between alkyl tosylates and *B*-alkyl-9-BBN.¹⁹

The Capretta group synthesized a series of phosphadamantane ligands via *P*-arylation of 1,3,5,7-tetramethyl-2,4,8-trioxa-6-phosphadamantane and employed them in Pd-catalyzed cross-coupling reactions. A highly active catalyst combination was found for the alkyl-alkyl Suzuki-Miyaura cross-coupling using alkyl halides and tosylates as electrophiles. Thus, catalytic Pd(OAc)₂ in combination with 1,3,5,7-tetramethyl-6-(2,4-dimethoxyphenyl)-2,4,8-trioxa-6-phosphadamantane in the presence of K₃PO₄•H₂O facilitated the C(sp³)-C(sp³) coupling in high yields (Figure 60).²⁸⁰

Caddick and coworkers first reported the use of *N*-heterocyclic carbenes in a Pd-catalyzed alkyl-alkyl Suzuki-Miyaura coupling. Using this protocol, alkyl bromides were treated with *B*-alkyl-9-BBNs to provide cross-coupling products in modest yields (Figure 61).²⁸¹ Later, a modified NHC-based catalyst, Pd-PEPPSI-IiPr, was used to obtain high yields from the corresponding alkyl bromides and *B*-alkyl-9-BBN (Figure 62).^{282,283}

The use of secondary alkyl halides as the electrophile in cross-coupling reactions is extremely rare due to their unreactive nature. Fu and coworkers were able to accomplish this challenging transformation, utilizing a Ni-catalyzed Suzuki-Miyaura cross-coupling. It was found that a catalytic amount of $\text{NiCl}_2 \cdot \text{glyme}$, in combination with commercially available *trans*-*N,N'*-dimethyl-1,2-cyclohexanediamine in the presence of $\text{KO}t\text{-Bu}$ and *i*-BuOH at room temperature is the best catalytic system for this reaction (Figure 63).²⁸⁴ Thus, a series of *B*-alkyl-9-BBN was cross-coupled with a wide variety of secondary alkyl bromides under the optimized reaction conditions affording high yields. From a ^{11}B NMR study, it was confirmed that $\text{KO}t\text{-Bu}$ and *i*-BuOH activate the alkylborane for transmetalation with Ni *via* the formation of a tetravalent ate complex, which is in good agreement with Soderquist's earlier observation.²⁵³ Recently, the same group reported that after modification of the Ni-source, ligand, and the solvent that unreactive secondary alkyl chlorides also underwent Suzuki coupling at room temperature providing high yields.²⁸⁵

In summary, alkyl-alkyl Suzuki-Miyaura cross-couplings have been successfully accomplished using several metal complexes and electron-rich as well as sterically hindered ligands. The electron-rich metal center generally overcomes slow oxidative addition to alkyl halides and steric crowding of the ligands provides the necessary interactions to stabilize the metal center and suppress β -hydride elimination. In addition to primary alkyl halides, secondary alkyl halides were also successfully coupled with alkylboranes. Ultimately, the use of bench stable ligands for such challenging cross-coupling reactions has made the protocols accessible to the entire community.

3.5.6. *B*-Alkyl Suzuki-Miyaura Cross-Coupling for the Synthesis of Ketones and Amides—The direct ketone or amide formation from organometallic reagents with acid chlorides, activated esters or potentially formamide derivatives is an attractive method owing to its simplicity and reliability. However, organometallic reagents used for this approach have been limited mainly to magnesium, lithium, or alkylzinc reagents (Fukuyama coupling).¹⁸⁰ The use of less reactive alkylboron reagents for these transformations is highly desirable due to their high functional group tolerance.

The Liebeskind group reported the synthesis of ketones from activated thioesters *via* C-S bond scission and C-C bond formation. Coupling of thiol esters and *B*-alkyl-9-BBN derivatives was achieved in the presence of stoichiometric Cu(I)-thiophene-2-carboxylate (CuTc) and catalytic $\text{Pd}(\text{PPh}_3)_4$ (Figure 64). Unlike in the case of boronic acids, *B*-alkyl-9-BBN required only activation by base for this transformation, and no oxygen source was found to be necessary. A series of alkyl-alkyl and aryl-alkyl ketones were prepared in high yields from the corresponding thioesters.²⁸⁶

The Takemoto group reported a one pot amidation of alkenes *via* Pd-catalyzed coupling of carbamoyl chlorides with alkylboranes derived from the *in situ* reaction of alkenes and 9-BBN-H in a highly stereoselective manner (Figure 65). A series of functionalized alkylboranes was prepared and reacted to afford good to excellent yields.²⁸⁷

3.6. Suzuki-Miyaura Cross-Coupling Reactions with Alkylboronic Acids

Alkyl or arylboronic acids exist in equilibrium with their trimeric cyclic anhydrides, boroxines.²⁸⁸ The equilibrium has some influence on the coupling process, but it is difficult to determine the concentrations of boronic acid and boroxine during the catalytic reactions. Furthermore, boronic acids can degrade *via* hydrolysis or protonolysis. Consequently, most of the Suzuki-Miyaura coupling protocols employ superstoichiometric amounts of boronic acids to ensure complete conversion of the electrophilic coupling partner. Advantages of using organoboronic acids in cross-coupling reactions are the ease of purification *via*

recrystallization prior to reaction, compatibility with air and moisture, and generally long shelf-life.

3.6.1. Suzuki-Miyaura Coupling with Primary Alkylboronic Acids—In 1989, Suzuki and coworkers reported the cross-coupling between alkyl boronic esters with 1-alkenyl or aryl halides in the presence of thallium hydroxide or thallium carbonate and catalytic $\text{PdCl}_2(\text{dppf})$ or $\text{Pd}(\text{PPh}_3)_4$ (Figure 66).²⁴⁶ A serious limitation of this protocol is the use of toxic thallium bases that was found to be crucial, as in their absence extremely low conversion was observed. In search for alternative bases, Falck and coworkers found that high yields of the cross-coupling products with alkylboronic acids and aryl bromides were achieved using $\text{PdCl}_2(\text{dppf})$ as a catalyst and K_2CO_3 as a base. The reaction unfortunately required a superstoichiometric (2.5 equiv) amount of Ag_2O as an additive.¹³ In the same year, Bellina and coworkers also reported the regioselective cross-coupling of 3,4-dibromofuranones with alkylboronic acids in the presence of 5 mol% $\text{PdCl}_2(\text{MeCN})_2$, 20 mol% AsPh_3 and 3.0 equiv of Ag_2O to afford the corresponding 4-alkylation product.²⁸⁹

In 2002, the Molander group developed reaction conditions for the Suzuki-Miyaura cross-coupling with phenethylboronic acids and aryl triflates or halides, which do not require Ag_2O . A catalytic amount of $\text{Pd}(\text{dppf})\text{Cl}_2 \cdot \text{CH}_2\text{Cl}_2$ in combination with 3.0 equiv K_2CO_3 in THF/ H_2O furnished the cross-coupling products in high yields (Figure 67).²⁹⁰ Electron-deficient aryl triflates led to high yields while electron-rich triflates were less effective.

To overcome the problem of slow oxidative addition to electron-rich aryl triflates and chlorides, the Hartwig group developed an air stable, sterically-hindered ferrocenyl dialkylphosphine ligand for Pd-catalyzed cross-coupling reactions.²⁹¹ With this catalyst, a series of alkyl boronic acids were coupled successfully with various aryl chlorides and bromides. Gratifyingly, the cross-coupling of electron-rich, 2-chloroanisole with *n*-butylboronic acid catalyzed by a 1:1 mixture of $\text{Pd}(\text{dba})_2$ and the ferrocenyl ligand in the presence of K_3PO_4 also afforded high yields at 100 °C in toluene (Figure 68). A secondary boronic acid was coupled with *p*-*t*-butylbromobenzene to afford the unisomerized coupling product in moderate yield, although the secondary alkylboronic acids are prone to isomerize to the linear form via β -hydride elimination and reinsertion. A similar ferrocene-based ligand and reaction protocol was reported by the Chan and Kwong group.²⁹²

Phosphite ligands have also been used in *B*-alkyl Suzuki-Miyaura cross-coupling reactions. The bulky ligands undergo facile orthopalladation *in situ*, which forms an active species for the cross-coupling reactions. Therefore, a catalytic amount (0.5 mol%) of $\text{Pd}(\text{OAc})_2$ and $\text{P}(\text{OC}_6\text{H}_3-2,4-*t*\text{-Bu}_2)_3$ in the presence of K_3PO_4 constituted effective conditions to carry out the cross-coupling between electron-rich 4-bromo anisole and *n*-butylboronic acid (Figure 69).²⁹³ High turnover numbers were observed when electron-deficient aryl bromides, such as 4-bromoacetophenone (TON = 10 000), was used. An indolyl phosphine ligand coordinated to $\text{Pd}_2(\text{dba})_3$ catalyzed the same reaction to afford excellent yields.²⁹⁴

Cross-coupling reactions in aqueous media are often desirable in the field of organic and organometallic chemistry, as they provide a manifold to develop more environmentally benign protocols for the incorporation of desired functionality. To perform a reaction in an aqueous medium, water soluble ligands, as well as suitable additives, are necessary for optimal performance.²⁹⁵ Nájera and coworkers developed a water soluble di-(2-pyridyl)methylamine-based Pd-dichloride complex for the Suzuki-Miyaura cross-coupling and related reactions in aqueous medium (Figure 70).²⁹⁶ Utilizing this catalyst, trimethylboroxine and *n*-butylboronic acid were coupled with bromo- and chloroarenes in refluxing water with K_2CO_3 and Bu_4NBr as additives. The reaction was accomplished in a shorter reaction time under microwave irradiation, providing comparable yields.

Doucet and coworkers reported the use of $[\text{PdCl}(\text{C}_3\text{H}_5)]_2/\text{cis,cis,cis-1,2,3,4-tetrakis(diphenylphosphinomethyl)cyclopentane}$ (tedicyp) in Suzuki-Miyaura cross-coupling reactions of alkylboronic acids with aryl bromides or chlorides (Figure 71).^{297,298} The low catalyst loading and high turnover number (TON up to 10,000) of this protocol are noteworthy. A wide range of functional groups were well tolerated under the reaction conditions.

The Buchwald group developed an electron-rich biaryl ligand for general Suzuki-Miyaura cross-coupling reactions.^{250,251} Ma et al. used the same ligand, along with catalytic $\text{PdCl}_2(\text{PhCN})_2$, for the cross-coupling of *n*-butylboronic acids with chlorobenzylidenelactone in refluxing toluene (Scheme 26).²⁹⁹

Delaude and coworkers tested the cross-coupling between *n*-butylboronic acid and unprotected 3-bromo-2,4,6-trimethylaniline under Fu's conditions, using the sterically hindered and electron-rich $\text{P}(t\text{-Bu})_3$ ligand along with $\text{Pd}_2(\text{dba})_3$ (Scheme 27).³⁰⁰ The corresponding cross-coupled product was isolated in 63% yield after refluxing in dioxane for 24 h. Although the yield was far from quantitative, the result was encouraging, considering the steric hindrance imposed by the two methyl groups flanking the bromine as well as the unprotected aniline moiety.

The Ranu group also reported a simple and efficient ligand-free Suzuki coupling in aqueous medium. The sodium tetrachloropalladate (Na_2PdCl_4) precatalyst is reduced to $\text{Pd}(0)$ by organoboronic acids in aqueous medium to form Pd nanoparticles (PdNPs), which were stabilized by sodium dodecyl sulfate (Figure 72). Using K_3PO_4 as a base, the cross-coupling reaction between aryl bromides and iodides and alkylboronic acids was accomplished at 100 °C within 25 min.³⁰¹

The Fu group has reported a $\text{C}(\text{sp}^3)\text{-C}(\text{sp}^3)$ Suzuki-Miyaura cross-coupling of alkyl halides with alkylboronic acids at room temperature. It was observed that a catalytic amount of $\text{Pd}(\text{OAc})_2/\text{P}(t\text{-Bu})_2\text{Me}$ in the presence of $\text{KO}t\text{-Bu}$ afforded alkyl-alkyl cross-coupling products in high yields (Figure 73).³⁰² Interestingly, the oxidative addition of alkyl halides was accomplished under very mild conditions, furnishing intermediates that were stable enough to undergo transmetalation instead of decomposition via β -hydride elimination. One such oxidative addition product **96** was isolated and characterized by X-ray crystallography. When the oxidative addition product **96** was treated with a boronic acid, the cross-coupling product was formed with comparable yield.

3.6.2. Suzuki-Miyura Coupling with Secondary Alkylboronic Acids—While primary alkylboronic acids have been explored in Suzuki-Miyaura cross-coupling reactions, secondary alkylboronic acids have been sparsely studied. This is due to the fact that transmetalation of these hindered substrates is extremely slow failing to yield cross-coupling products. In contrast, cyclopropyl boronic acids have been used successfully, as they possess a substantial amount of s-character on the exocyclic C-B bond, and their geometry prevents β -hydride elimination.

Deng and Wang reported Suzuki couplings of *trans*-2-butylcyclopropylboronic acid with aryl bromides. The reactions gave stereodefined *trans*-2-cyclopropylarenes in high yields with both electron-rich and electron-deficient aryl bromides.³⁰³ Cyclopropaneboronic acid itself has also been coupled with aryl bromides, irrespective of their electronics, in the presence of catalytic $\text{Pd}(\text{OAc})_2$ and the electron-rich PCy_3 (Figure 74).³⁰⁴

Fu and coworkers reported a Suzuki-Miyaura cross-coupling between cyclopentylboronic acid and *p*-chlorotoluene (Scheme 28). This challenging transformation was made possible by employing $P(t\text{-Bu})_3$ with catalytic $\text{Pd}_2(\text{dba})_3$.²⁴⁸

3.7. Suzuki-Miyaura Cross-Coupling with Alkylboronic Esters

In general, alkylboronic esters are even less reactive than alkylboronic acids and often fail to produce cross-coupling products. Higher catalyst loadings and more forcing reaction conditions are often required for these cross-couplings to proceed. However, alkylboronic esters are important coupling partners in Suzuki coupling reactions, as they can offer neutral reaction conditions ($\text{p}K_{\text{a}}$ of boronic acid ~ 9), and only the monomeric form is the active species. In addition, high yields of boronic esters are isolated by the simple addition of an alcohol or diol to the boronic acids.

After the first report in 1989 by the Suzuki group, several examples of Suzuki coupling with alkylboronic esters have been reported (Figure 75).²⁴⁶ In 1996, Marsden and Hildebrand reported the stereoselective coupling of a cyclopropylboronate with several *p*-substituted electron-deficient or electron-rich aryl bromides in the presence of catalytic $\text{Pd}(\text{PPh}_3)_4$ (Figure 76).³⁰⁵ In 1997, Charette and coworkers reported the cross-coupling between cyclopropylboronate and iodocyclopropanes to generate contiguous cyclopropanes (Figure 77).³⁰⁶ These reactions proceed smoothly in the presence of $\text{Pd}(\text{OAc})_2$ with PPh_3 in DME with *t*-BuOK as base. In 2001, de Meijere and coworkers reported the same reaction between 2-cyclopropylborolane and aryl halides under identical reaction conditions. Although a wide range of aryl iodides were tolerated and furnished cross-coupling products, electron-deficient *p*-bromonitrobenzene or methyl-2-iodobenzoate gave no coupling products.³⁰⁷

In line with the previous observations, alkylboronic acids are poorer nucleophiles than alkenyl- and arylboronic acids, and alkylboronic esters are even less reactive in Suzuki-Miyaura cross-couplings. This is demonstrated in the Suzuki-couplings of vinyl triflates derived from *N*-alkoxycarbonyl lactams and alkylboron derivatives (Table 7).³⁰⁸ An accelerating effect of $\text{Ag}(\text{I})$ salt was also observed in these transformations.

Andrus and coworkers demonstrated that *N,N*-bis-(2,6-diisopropylphenyl)dihydroimidazolium chloride with $\text{Pd}(\text{OAc})_2$ was an effective catalytic system for the cross-coupling between aryldiazonium tetrafluoroborates and alkyl catecholborane at room temperature in the absence of base.³⁰⁹ The aryldiazoniumtetrafluoroborates were generated *in situ* by the treatment of aryl amines with *t*-butyl nitrite followed by $\text{BF}_3 \cdot \text{OEt}_2$ at 0 °C in THF (Figure 78). Interestingly, despite having bromine in the alkyl catechol borane moiety, cross-coupling with aryldiazonium salts occurs selectively, leaving the bromine intact. This suggests that oxidative addition of allyl bromide is slow under these reaction conditions, whereas aryldiazonium salts readily furnish cross-coupling products in high yields.

In the same year, Falck and coworkers demonstrated that when a mixed alkylboronate containing primary and secondary alkyl chains was subjected to Suzuki-Miyaura cross-coupling conditions with aryl bromides or alkenyl triflates, the *n*-alkylaryl product was isolated in excellent yield (Scheme 29).³¹⁰ This suggests that the secondary alkyl group undergoes β -hydride elimination and reinsertion to give the *n*-alkyl isomer under the reaction conditions, followed by a normal cross-coupling reaction. Aryl triflates were also tested with this mixed alkylboronate and similar results were consistently observed.

In summary, alkylboronic esters are used as coupling partners less frequently due to their lower reactivity. In many cases, they afford modest yields and sometimes fail to give

products, whereas their alkylboronic acid counterparts give better yields of the cross-coupling products under the same reaction conditions.

3.8. Suzuki-Miyaura Cross-Coupling with Alkyltrifluoroborates

Organotrifluoroborates are an interesting class of coupling partners in Suzuki-Miyaura cross-coupling reactions.³¹¹ The Molander group has made substantial contributions to their preparation and applications in cross-couplings. Potassium organotrifluoroborates are easily synthesized by addition of KHF_2 to various organoboron intermediates, and several functionalized trifluoroborates can be synthesized easily from readily available starting materials. Nearly all organotrifluoroborates synthesized to date can be stored indefinitely without special precautions.

In 2001, Molander and coworkers reported the Pd-catalyzed *B*-alkyl Suzuki-Miyaura cross-coupling between potassium alkyltrifluoroborates and aryl or alkenyltriflates.³¹² Besides the simple potassium alkyltrifluoroborates, a number of functionalized variants were also synthesized and readily underwent the cross-coupling reaction with aryl or alkenyltriflates. It was observed that electron-deficient aryl and alkenyl triflates underwent cross-couplings efficiently in the presence of catalytic amounts of $\text{Pd}(\text{dppf})\text{Cl}_2 \cdot \text{CH}_2\text{Cl}_2$ and Cs_2CO_3 as a base (Figure 79). Electron-rich triflates were not suitable coupling partners. The aqueous conditions for this transformation were found to be necessary presumably due to the formation of alkylboronic acid *in situ*, which undergoes the coupling process.³¹³ To probe this hypothesis, an ^{11}B NMR study was performed. When the potassium-3-phenylpropylfluoroborate was exposed to water for 4 days at room temperature, the ^{11}B NMR revealed a new peak at δ 33.5 ppm in addition to the original resonance at δ 5.6 ppm. This observation indicated that the alkylboronic acid (whose ^{11}B NMR signal typically appears at δ 31.5 ppm) or a fluorinated active species such as RBF_3^- , $\text{RBF}_2(\text{OH})^-$, and/or $\text{RBF}(\text{OH})_2^-$ could be generated *in situ*, and be the active species in fluoride-mediated coupling of boronic acids. Interestingly, it was observed that the corresponding alkylboronic acid and ester also underwent cross-coupling under identical reaction conditions, affording similar yields. This observation has great synthetic potential as it implies that the cross-coupling reactions in general could be performed with potassium alkyltrifluoroborates instead of the corresponding alkyl boronic acid or esters.

In 2003, the same group demonstrated the synthesis of alkyltrifluoroborates and their use in the Pd-catalyzed Suzuki-Miyaura coupling with aryl halides and triflates. Along with potassium methyltrifluoroborate and potassium trimethylsilyltrifluoroborate, potassium-3-substituted-propyltrifluoroborates were also reacted with electron-deficient aryl halides and triflates to afford moderate to good yields.³¹⁴ Similarly to the previous results, electron-rich electrophiles proved to be more difficult substrates. In general, the products were formed efficiently in refluxing THF or THF- H_2O . Further heating led to the formation of protodehalogenation and protodeboration products, and ultimately resulted in an inseparable mixture of several products and poor yields of the desired cross-coupling product. During the coupling of aryl triflates with various alkylboron reagents it was observed that potassium alkyltrifluoroborates provided better yield (Scheme 30).³¹²

The Deng group reported the reaction of substituted potassium cyclopropyltrifluoroborates with aryl bromides. A series of electron-deficient as well as electron-rich aryl bromides underwent Pd-catalyzed cross-coupling with retention of configuration to provide the corresponding disubstituted cyclopropanes in high yields (Figure 80).³¹⁵ Subsequently, the Charette group also reported a stereospecific cross-coupling between disubstituted cyclopropyltrifluoroborates and aryl bromides to furnish trisubstituted cyclopropanes in high yields (Figure 81).³¹⁶

The Molander group reported the synthesis of ketone-, ester-, and amide- containing potassium trifluoroboratoenolates and their cross-coupling reactions with aryl halides and triflates. These boron salts are particularly challenging in cross-coupling processes due to the formation of metallacyclopropanoxides and facile β -hydride elimination that leads to Heck-type products. Gratifyingly, it was observed that aryl bromides, chlorides, triflates and alkenyl bromides afforded high yields irrespective of their electronic nature (Figure 82). A series of functionalized potassium alkyltrifluoroborates underwent coupling with relatively unreactive aryl chlorides to furnish excellent yields.³¹⁷

In 2008, Molander and coworkers demonstrated the rare cross-coupling of secondary alkyltrifluoroborates with aryl chlorides (Figure 83).³¹⁸ The reaction conditions for this challenging transformation were optimized using parallel microscale experimentation. Aryl chlorides, irrespective of electron-donating or electron-withdrawing substituents, underwent cross-coupling efficiently under the optimized reaction conditions. In the case of branched acyclic alkyltrifluoroborates, e.g. with potassium *i*-propyltrifluoroborate, a mixture of branched and linear (1.4:1 for 2-chloroanisole, 8.2:1 for 4-chloroanisole) products were isolated. During the course of this study, enhanced nucleophilicity of the alkyltrifluoroborates compared to their alkylboronic acid and boronic ester counterparts was experienced and the reactivity order for the aryl or alkenyl component was found to be $\text{Br} > \text{OTf} \gg \text{Cl}$.

3.9. Conclusion

It is quite evident that considerable progress has been achieved in *B*-alkyl Suzuki-Miyaura cross-coupling reactions. Various boron sources have been used successfully as coupling partners. Several catalyst systems with high activity and chemo- and regioselectivity are now available for this widely used process. The success in alkyl-alkyl Suzuki-Miyaura cross-coupling is also noteworthy. However, a number of challenges still need to be addressed. Although there are a few examples of Suzuki-Miyaura cross-coupling with relatively inert and inexpensive aryl chlorides, general catalytic systems for these substrates are in high demand. Additionally, an efficient catalytic system for the general class of secondary alkylboron reagents has yet to be developed. A more detailed mechanistic understanding is essential for less efficient alkylboronic acids or esters to make them effective towards cross-coupling. At the same time, cost-effective catalysts are in high demand for successful application in industrial processes.

4. Cross-Couplings with Alkylmagnesium Reagents

4.1. Introduction

Organomagnesium reagents were first discovered by Grignard in 1900^{319,320} and since then, they have occupied a central role in synthetic organic chemistry.^{1–3,18,321–324} Despite their extensive use, the main focus of these reagents has been on nucleophilic addition and substitution reactions. The pioneering studies of Kharasch and Fuchs opened new synthetic avenues for Grignard reagents.³²⁵ In 1972, Kumada and coworkers and Corriu and Masse independently demonstrated the synthetic utility of Grignard reagents in Ni-catalyzed cross-coupling reactions. However, the modest functional group tolerance of Grignard reagents compared to that of corresponding boron and zinc reagents has limited their use in synthesis. In this section of the review, the synthesis, stability, and cross-coupling reactions of alkylMg reagents will be discussed. This will exclude cross-coupling reactions of reagents unable to undergo β -hydride elimination such as ArMgX , MeMgX , PhCH_2MgX , TMSCH_2MgX and alkynylMgX .

4.2. Synthesis and Stability

The most common method to synthesize organomagnesium reagents is via Mg-halogen exchange. Though there have been significant developments in the preparation of functionalized arylMgX and alkenylMgX, the preparation of functionalized alkylMgX has not received much attention. Since the preparation of functionalized arylMgX, alkenylMgX and heteroarylMgX is discussed in detail by Knochel and coworkers in their review,³²⁶ this will be excluded from discussion here.

Unfunctionalized alkylMgX can be synthesized via Mg-halogen exchange reactions with the corresponding alkyl halides. Similar methods can be applied to the synthesis of the polyfunctionalized alkylMgX but few examples of such processes have been reported.^{327–332}

4.3. Ni-Catalyzed Cross-Coupling Reactions with Alkylmagnesium Reagents

4.3.1. Kumada Cross-Coupling Reactions *via* Carbon-Halogen Bond

Activation—In 1972, Kumada and coworkers^{333–335} as well as Corriu and Masse³³⁶ independently reported the Ni-catalyzed coupling reaction with organomagnesium reagents. This transformation has come to be known as the Kumada-Corriu cross-coupling.^{1–3,15,1718,335–337} Corriu and Masse used vinyl bromides, chlorides and aryl bromides with arylMgBr and Ni(acac)₂ as a catalyst (Figure 84).³³⁶

In the same year, Kumada and coworkers reported the cross-coupling of aryl and vinyl chlorides with alkyl- and arylMgBr using Ni(dppe)Cl₂ in high yields (Figure 85).^{123,335} It was also observed that only bidentate ligands gave reasonable yields of the cross-coupled products. The reaction was not found to be highly stereospecific.

Use of *sec*-alkylMgX resulted in mixture of products as shown in Figure 86.¹²³ It was postulated that more electron-rich ligands favored the formation of the linear over the branched product. The proposed mechanism for the undesired (linear) product formation is depicted in Figure 86a. Oxidative addition of PhCl followed by transmetalation with *i*-PrMgCl gives intermediate **97**. Intermediate **97** can either undergo reductive elimination to give the desired branched product **100**, or it can β-hydride eliminate to give **98**, which then rearranges to intermediate **99**, which upon reductive elimination gives undesired product **102**.

In 1976, Kumada and coworkers reported a full account of this work.³³⁷ The proposed mechanism is described in figure 86b, starting with the reaction of L₂NiX₂ with 2 equiv of RMgX to give a diorganonickel species, which undergoes reductive elimination to produce Ni(0). The resulting Ni(0) undergoes oxidative addition to give Ni-complex **103**. Intermediate **103** transmetalates with another equiv of RMgX to give intermediate **104**, which then coordinates with an alkyl halide to give penta-coordinated Ni-species **105**. Intermediate **105** undergoes reductive elimination to give the cross-coupled product as well as regenerate the active catalyst **103**. The scope of this transformation is extremely broad with one major limitation, namely that substitution of organic halides and on the Grignard reagents are restricted to those that cannot react with Grignard reagents. The most striking feature of this chemistry is that even alkyl Grignard reagents containing β-hydrogens are compatible under the reaction conditions to give cross-coupled product and do not undergo β-hydride elimination (Figure 87).³³⁷ In the same year, Kumada and coworkers extended this methodology to include β-bromovinylethers as substrates to give the corresponding aldehyde after coupling and hydrolysis (Figure 88).³³⁸

Mono and dichlorinated benzenes were used by Kumada to give corresponding mono and dialkylated products respectively. Tamborski and coworkers extended this work to

trichlorinated benzenes to give trialkyl benzenes (Figure 89).³³⁹ They observed a significant decrease in the rate of the reaction when monoalkylated dichlorobenzene was used as a substrate, which indicates that the substitutions do not occur in a stepwise fashion (Figure 89). Furthermore, this limits sequential functionalization to obtain unsymmetrical tri-alkyl benzenes. Bochmann reported the Ni-catalyzed alkylation of di-, tri- and polychlorobiphenyls.³⁴⁰

Though these reactions are useful, the selective alkylation of one halogen atom, for dihalobenzenes that possess two identical halo groups, was not achieved. In 1983, Tam and Reddy developed a Ni catalyst that gave high selectivity for the monoalkylation of dichlorobenzene with 1 equiv of R-MgX (Scheme 31).³⁴¹ The use of the tridentate ligand “triphos” [triphos = *bis*(2-(diphenylphosphino)ethyl)phenylphosphine] was necessary to achieve high selectivity. Manabe and Wang addressed the issue of selectivity by using phenol as the directing group to achieve a highly selective cross-coupling reaction, where the halogen next to the phenol is activated and reacts to give the corresponding alkylated product (Scheme 32).³⁴² Interestingly, the *o*-fluoro group was more reactive than a *p*-bromo group (**106**), which indicates that the directing effects of hydroxyl group take priority over the inherent reactivity of the halo groups. The proposed transition state is shown in scheme 37, where the coordination of Mg to the phenol is postulated to facilitate oxidative addition of Ni to the adjacent C-X bond.³⁴²

Liao and coworkers reported a unique tridentate amido diphosphino ligand for Ni-catalyzed cross-coupling. Using this pincer-type complex, they were able to couple EtMgCl and *n*-BuMgCl with aryl halides in moderate yields (Scheme 33).³⁴³ Saint-Jalmes and Roques reported a unique use of the Kumada coupling reaction to synthesize 3-alkyl-trifluoromethylbenzenes, where NiCl₂/Xantphos is used as the catalyst and the reaction can be scaled up to 2L (Scheme 34).³⁴⁴

Claesson and coworkers initially reported the Ni-catalyzed synthesis of multi-substituted 1,3-butadienes from the corresponding phosphates.³⁴⁵ Shi and Shao reported the use of Ni(dppp)Cl₂ as an effective catalyst for the synthesis of multi-substituted 1,3-butadienes.³⁴⁶ In this case, diiodo-substrates of type **108** were first treated with DBU to give the corresponding dienes **109**, which were subsequently treated with the Ni catalyst and R-MgX to give the desired cross-coupled products in good yields (Figure 90). To probe the role of the diene, the following control experiments were conducted: the use of a substrate lacking the diene (**111**) resulted in only dehalohydrogenation to give product (**112**), whereas a substrate with a diene (**113**) gave the desired product (**114**). These experiments suggest that the diene is necessary to promote the Kumada coupling reaction under these conditions.^{346,347}

4.3.2. Kumada Cross-Coupling Reactions *via* Carbon-Sulfur Bond Activation—

Cross-coupling reactions with organosulfur compounds³⁴⁸ are promising because of their ease of synthesis and availability; however, such reactions are not well developed. The strong carbon-sulfur and metal-sulfur bonds result in slow oxidative addition and transmetalation compared to organic halides. Hence, strong σ -donating ligands as well as higher temperatures are required for a successful reaction.³⁴⁸

In 1979, Takei and coworkers first reported the cross-coupling between aryl and alkenyl sulfides and arylMgBr (Figure 91).³⁴⁹ The use of 3 mol% Ni(PPh₃)₂Cl₂ was found to be effective for the coupling of various organosulfides with Grignard reagents. Under these conditions, no reaction with alkyl sulfides as substrates was observed. Interestingly, excellent retention of stereochemistry was observed when isomerically pure alkenes were used.

Later, the scope was expanded to include allyl sulfides and heterocyclic sulfides.³⁵⁰ Ni(dppp)Cl₂ (3 mol%) was the catalyst of choice for the coupling of various alkylMgBr with heterocyclic sulfides. The use of bidentate dppp was essential for the successful cross-coupling with alkylMgX, presumably because of its ability to prevent β-hydride elimination of the alkyl Grignard as demonstrated by Kumada.¹²³ Thiols and disulfides were also successfully coupled to give products in good yields (Figure 92). Interestingly, for the reaction of 2,2'-dipyridyl disulfide with PhCH₂CH₂MgBr, formation of PhCH₂CH₂SH was observed. Based on this observation, a mechanism for the reaction with disulfides was proposed (Figure 92).³⁵⁰

In 1985, Takei and coworkers reported the synthesis of 6-substituted purine bases via cross-coupling between 6-(methylthio)-purine and Grignard reagents (Figure 93).³⁵¹ In the same year, Wenkert and coworkers reported the preparation of 4-alkylpyridines from the corresponding thiopyridines and 2-alkylindoles from the corresponding thioindoles (Figure 94).³⁵²

In 2005, Ila and coworkers reported the synthesis of an unsymmetrical quinoxaline.³⁵³ To demonstrate the synthetic utility of their method they showcased the cross-coupling of 2-thioquinoxaline with *n*-BuMgBr to give 2-butylquinoxaline in good yield (Scheme 35).³⁵³ In 2008, Oshima and coworkers reported Ni-catalyzed (5 mol%) cross-coupling of sulfides with alkyl Grignards.³⁵⁴ The use of bidentate (*Z*)-3,3-dimethyl-2-bis(diphenylphosphino)but-1-ene ligand was optimal for coupling (Figure 95). The most striking feature of this protocol is the use of *sec*-alkyl Grignards as coupling partners. Moreover, the reaction of an alkenylsulfide and an alkylMgBr occurs with retention of configuration under the reaction conditions.

In 2005, Park and coworkers demonstrated that neopentyl arenesulfonates could be used in Ni-catalyzed cross-coupling reactions (Scheme 36).³⁵⁵ Interestingly, arenesulfonates are unreactive in the Pd-catalyzed variant, allowing for stepwise functionalization of the bromoarenesulfonates. Under the optimized conditions, MeMgBr, *t*-BuCH₂MgBr and BnMgBr undergo the cross-coupling reaction in good yields. It should be noted that only alkylMgBr reagents with no β-hydrogens are used in this report. This methodology was later extended to the use of a Ni-NHC (IiPr) system.³⁵⁶ NHC ligands are better σ-donors than phosphines, which facilitates oxidative addition of the relatively unreactive C-S bond.

4.3.3. Kumada Cross-Coupling Reactions *via* Carbon-Oxygen Bond Activation

—The conversion of a C-O bond to the corresponding C-C bond holds high synthetic value because of their ease of synthesis and high stability. In 1981, Kumada and coworkers reported a Ni-catalyzed cross-coupling reaction between aryl phosphonates with various arylmagnesium reagents.³⁵⁷ Only *n*-BuMgBr was used as an alkyl coupling partner in this seminal publication (Scheme 37).

In 1999, Fiaschisi and coworkers reported the Ni-catalyzed cross-coupling of vinyl triflates with alkylMgBr.³⁵⁸ They observed a significant impact of the ligand's bite angle on the reaction outcome, which was more pronounced in the case of coupling with *sec*-alkylMgBr (Figure 96). The use of *sec*-alkylMgBr is complicated by the formation of *n*-alkyl product **116**, which was suppressed by use of ligands with smaller bite angles (dppe, dppp) as compared to ligands with larger bite angles (dppf, dppb) (Figure 97). Moreover, under the optimized conditions, trisubstituted vinyl triflates also react to give the corresponding products in good yield.

Bäckvall and coworkers have reported the cross-coupling of dienyl phosphates with Grignard reagents in the presence of 1 mol% Ni(dppe)Cl₂ or Ni(dppp)Cl₂ (Figure 98).³⁵⁹

Under the optimized conditions, various alkylMgBr, including *sec*-alkylMgBr, react to give satisfactory yields of the corresponding products. In addition to cyclic dienyl phosphates, one acyclic substrate was found to give the product in 77% yield. Aryltriflates are also viable coupling partners for a Ni-catalyzed cross-coupling as demonstrated by Busacca and coworkers.³⁶⁰

In 2005, DuBois and coworkers first reported the Ni(dppp)Cl₂-catalyzed cross-coupling of cyclic sulfamates with organomagnesium reagents (Figure 99).³⁶¹

4.3.4. C(sp³)-C(sp³) Cross-Coupling with Alkylmagnesium Reagents—C(sp³)-C(sp³) cross-coupling reactions are challenging for the reasons described in the preceding sections of this review. Thus, it was not until 2002, almost 30 years after the initial report of the Kumada-Corriu coupling, that the first successful Ni-catalyzed C(sp³)-C(sp³) coupling reaction was reported by Kambe and coworkers (Figure 100).^{118,347,362}

In 2002, Kambe and coworkers reported the successful cross-coupling of alkyl bromides, chlorides and tosylates with alkylMgBr using a Ni-catalyst. Interestingly, it was found that the use of 1,3-butadiene rather than phosphine ligands led to a competent catalyst. Under the optimized conditions (NiCl₂ (1–3 mol %) and butadiene (10–100 mol %)), the products were obtained in good to excellent yields. The butadiene ligand was essential for the observed reaction, as in the absence of butadiene reduction and/or elimination of the substrates was mainly observed (Scheme 38).³⁴⁷

The proposed mechanism for this transformation is shown in scheme 43. NiCl₂ is reduced to Ni(0) by reacting with 2 equiv of *n*-BuMgCl. The resulting Ni(0) complex reacts with 2 equiv of 1,3-butadiene to afford bis- π -allyl Ni complex **117**. Intermediate **117** is proposed to react with Grignard reagents to form η^1, η^3 -octadiene-diylnickelate complex **118**, which then undergoes oxidative addition of alkyl halides and tosylates to yield dialkylnickel complex **119**. Complex **119** reductively eliminates to give desired product **120**. In 2010, Fang and coworkers reported DFT calculations on the model substrate for Ni(allyl)₂-catalyzed cross-coupling.³⁶³ Their study suggested a weak but persistent interaction between Mg and the allyl moiety throughout the catalytic cycle. Moreover, oxidative addition is proposed to be the turnover limiting step and competing β -hydride elimination is much higher in energy compared to reductive elimination.³⁶³ Subsequently, Kambe and coworkers reported the use of *bis*-(η^3 -allyl)nickel complex as a catalyst for the coupling of alkyl bromides and alkyl tosylates with alkyl Grignard reagents.³⁶⁴

Kambe and coworkers extended this methodology to alkyl fluorides, where the use of Ni/butadiene as a catalyst provided excellent yields of the cross-coupled products as shown in scheme 39.³⁶⁵ Surprisingly, the reactivity of the alkyl halides increased in the order Cl < F < Br. This trend cannot be explained by the bond energies of the alkyl halides and the magnesium salts formed.

Despite substantial advancements in Kumada cross-coupling reactions, functional group tolerance has always been an issue. This can be attributed to the high nucleophilicity/basicity of Grignard reagents. Recently, Kambe and coworkers reported a C(sp³)-C(sp³) cross-coupling reaction using NiX₂/butadiene system, where improved functional group tolerance was observed (Figure 101).³⁶⁶

In 2008, Hu reported a Ni-catalyzed Kumada-Corriu coupling with a unique pincer amido-*bis*-(amine) ligand.^{367–371} They observed an unusual reaction of CH₂Cl₂ and CHCl₃ with *n*-BuMgBr to give the dialkylated or trialkylated products respectively (Scheme 40).³⁷²

The reaction involves cleavage of up to three C-Cl bonds to form three new C-C bonds at the same carbon center. The reaction is proposed to follow a radical pathway based on the following observations: 1) the reactions of CH_2Cl_2 and CHCl_3 were faster than octyl-Cl, 2) TEMPO inhibits the reaction of **121** with CH_2Cl_2 , and the formation of TEMPO- CH_3 was observed; 3) the reaction of **121** with bromomethylcyclopropane gave 1-pentene as the product. The scope of this transformation was later expanded to include other alkyl Grignard reagents (Table 8).^{368,369} This system was found to be general for the cross-coupling between various alkyl halides and alkylMgCl, and exhibits good functional group tolerance. Interestingly, Grignard reagents containing functional groups also undergo smooth reactions in the presence of 3–9 mol% catalyst in DMA at -35°C .

4.4. Fe-Catalyzed Kumada Cross-Coupling Reactions

Cross-coupling reactions are typically catalyzed by Pd and Ni salts. But the higher cost of these metals, as well as environmental issues, demand cheaper and more environmentally friendly metals for this transformation. Iron being less expensive than Pd and Ni, as well as its lower toxicity makes it an ideal choice for cross-coupling reactions.^{373–378}

4.4.1. $\text{C}(\text{sp}^2)\text{-C}(\text{sp}^3)$ Cross-Coupling with Alkylmagnesium Reagents—In 1971, Kochi and coworkers^{378–384} first reported Fe-catalyzed cross-coupling reactions.^{379,380,383,384} In this seminal report, they described the coupling of vinyl bromides with alkyl Grignard reagents catalyzed by FeCl_3 (Figure 102). Utilizing this protocol, Kochi obtained good yields, but the requirement of a large excess of vinyl halide to effect the reaction limited its synthetic utility. Furthermore, they observed decomposition of the catalyst on standing (catalyst aging), which led to diminished yields of products.

Several years later, Kochi published a subsequent report aimed at improving this reaction by employing *tris*(dibenzoylmethido)iron(III) as the catalyst.³⁸¹ Indeed, this improved the reaction stoichiometry and catalyst stability to some degree; however, excess vinyl halide was still required. The proposed reaction mechanism is shown in scheme 41.^{381,382} The catalytically active Fe(I) species is formed *in situ* by reduction of Fe(III) with 2 equiv of RMgX . The resultant Fe(I) species undergoes oxidative addition of R-X followed by transmetalation with RMgX to give intermediate **122**, which upon reductive elimination yields product and regenerates the catalyst.

The following experiments provide support for the formation of a Fe(I) complex.³⁸¹ First, a careful study of the amount of methane and ethane gases generated in the reaction with methylmagnesium bromide suggested a stoichiometric relationship $\text{Fe(III)} + n\text{CH}_3\text{MgBr} = \text{Fe(III-n)} + \text{XCH}_4 + \text{YC}_2\text{H}_6$, where $n = \text{X} + 2\text{Y}$. The value of n according to the above equation provides the change in oxidation state of iron. The value of n was found to be close to 2, which supports reduction of Fe(III) to Fe(I). Secondly, the ESR spectrum of $\text{Fe}(\text{dbm})_3$ after treatment with excess EtMgBr gave $\langle g \rangle = 2.08$. This value matches the well-characterized HFe(I)(dppe)_2 complex,³⁸⁵ providing additional evidence for the presence of Fe(I).

Vinyl sulfones and allyl phosphates can also serve as viable coupling partners with Grignard reagents as demonstrated by Julia³⁸⁶ and Yamamoto,^{387,388} respectively. Despite this early report of a Fe-catalyzed cross-coupling reaction with alkylMgX, almost 30 years passed from the original report before the development of synthetically useful protocols. Cahiez and Avedissia reported that the reaction of a vinyl bromide with octylMgBr in the presence of 3 mol% $\text{Fe}(\text{acac})_3$ in THF afforded the desired alkene in only 40% yield (Scheme 42).³⁸⁹ However, the addition of *N*-methyl-2-pyrrolidinone (NMP) as a co-solvent enhanced the yield to 87%. An even more drastic increase in yield was observed for the reaction between a vinyl chloride and BuMgX (Scheme 42).³⁸⁹

Surprisingly, the nature of the iron salt had little effect on the reaction outcome. The only requirement found was that the catalyst should be soluble in THF, as illustrated by the ability of various iron catalysts ($\text{Fe}(\text{acac})_3$, $\text{Fe}(\text{dpm})_3$, $\text{Fe}(\text{dbm})_3$, and FeCl_3), to catalyze the reaction with isolated yields in excess of 85%. In contrast, $\text{Fe}_2(\text{SO}_4)_3$, gave a poor yield of 31%, as it is sparingly soluble in THF (Figure 103). Interestingly, the nature of the halide also had little effect on product yield. The scope of the reaction is broad with tolerance for a vast array of functional groups including esters and ketones. Vinyl phosphonates are also viable substrates under these conditions. Furthermore, this protocol is highly stereospecific, (*Z*)- and (*E*)-1-chlorooct-1-enes afforded the corresponding *Z*- and *E*-olefins with excellent stereoisomeric purity.

In 2002, Fürstner and coworkers reported the reaction of aryl chlorides, tosylates and triflates with alkylMgBr, which represents substrate classes that were unreactive prior to this report.^{378,390,391} In this report, they proposed a modified mechanism for the Fe-catalyzed coupling reaction in the presence of Grignard reagents. FeCl_2 reacts with 4 equiv of RMgX to give a new species of the formal composition $[\text{Fe}(-\text{II})(\text{MgX})_2]$, an “inorganic Grignard reagent”, which is readily soluble in ethereal solvents.³⁹² In complex **123**, the iron is proposed to have a formal charge of -2 .³⁹¹ The nucleophilic iron “super-ate” complex is proposed to oxidatively add to aryl chlorides to give species **124**. Intermediate **124** undergoes transmetalation with another equivalent of RMgX to form species **125**, which upon reductive elimination gives product and regenerates the active catalyst (Scheme 43).

To support their mechanistic proposal, Fürstner and coworkers conducted a key control experiment. When nonpassivated iron metal $\text{Fe}(0)^*$ powder was used, which was prepared by reduction of FeCl_3 with potassium, no reaction with substrate was observed (Scheme 44). Whereas, when excess Grignard reagent was added to the reaction mixture containing $\text{Fe}(0)^*$, the desired product was formed. These experiments rule out an active catalytic species with Fe in the zero oxidation state and support their proposed mechanism.³⁹¹

The scope of this transformation was found to be broad, and commercially available, air and moisture stable $\text{Fe}(\text{acac})_3$ could be used as the pre-catalyst (Figure 104). Of most interest, the reaction of **126** in the presence of a Ni-catalyst proceeds in 6 h at reflux in ether, whereas with a Fe-catalyst it was completed in 5 min with a better yield (Scheme 45).³⁹¹ Vinyl triflates were also found to undergo the cross-coupling under the reported conditions (Figure 105).³⁹³ Furthermore, monoalkylation of a dichloroarene was also achieved using $\text{Fe}(\text{acac})_3$ as a catalyst in THF/NMP as solvent.³⁹³ Hocek and coworkers utilized Fe-catalyzed cross-coupling for preparation of 6-methyl purine bases and nucleosides (Scheme 46).³⁹⁴ Tam and coworkers reported the synthesis of 2-substituted bicyclic alkenes utilizing an Fe-catalyzed cross-coupling of alkenyl triflates with alkyl Grignard reagents.³⁹⁵

Alami and coworkers utilized an Fe-catalyzed cross-coupling for the synthesis of substituted quinolines, which show anti-retroviral activity against HIV-1 and HTLV-1 transformed cells (Scheme 47).³⁹⁶ The optimized reaction conditions were also effective for the reaction of substituted chloroenynes with alkyl Grignards. Using similar conditions, Olsson and coworkers reported the cross-coupling of imidoyl chlorides with Grignard reagents (Scheme 48).³⁹⁷ Vogel and Volla reported the cross-coupling of alkenyl sulfonyl chlorides with Grignard reagents using $\text{Fe}(\text{acac})_3$ as catalyst.^{348,398,399}

Skrydstrup reported the cross-coupling of heteroaromatic sulfonates and phosphates with alkyl Grignards using FeCl_3 using a THF/NMP mixture as a solvent (Scheme 49).⁴⁰⁰

Recently, Shi and coworkers reported the cross-coupling of alkenyl carboxylates with Grignard reagents in the presence of FeCl_2 (1 mol%) and $\text{H}_2\text{IMes}\cdot\text{HCl}$ (2 mol%) as a ligand (Figure 106).⁴⁰¹ Interestingly, the counterion of the Grignard reagent was highly important,

as *n*-hexylMgCl reacts cleanly, but *n*-hexylMgBr gave no product, which can be overcome by addition of excess LiCl.⁴⁰¹

4.4.2. C(sp³)-C(sp³) Cross-Coupling with Alkylmagnesium Reagents—Iron-catalyzed C(sp³)-C(sp³) coupling reactions of unactivated alkyl electrophiles face various issues, including homocoupling, disproportionation, and β -elimination. These issues hinder the development of a successful iron-catalyzed C(sp³)-C(sp³) cross-coupling. In 2007, Chai and coworkers reported the first C(sp³)-C(sp³) coupling of unactivated alkyl halides with alkyl Grignard reagents.⁴⁰² In their optimization study, they found that use of 3 mol% of Fe(OAc)₂ and 6 mol% of Xantphos in Et₂O gave the best results. Using these conditions, various unfunctionalized alkyl bromides coupled with alkyl Grignards in moderate yields of 46–64% (Figure 107). The reaction is proposed to proceed via a radical pathway based on the results shown in Scheme 50.⁴⁰² Reaction of alkylMgBr with hexylbromide and cyclopropylbromide gave radical-induced cyclization and ring opened products, respectively. Both of these experiments suggest the formation of an alkyl radical from the corresponding alkyl halide.

4.4.3. Mechanistic Considerations—Despite these impressive advances, the mechanistic understanding of iron-catalyzed cross-coupling reactions is not well developed. Various proposals with catalytic cycles shuttling between Fe(-2)/Fe(0),^{22,374,390,391,393,403} Fe(0)/Fe(+2)^{382,404} or Fe(+1)/Fe(+3)^{381,382,405,406} have been proposed and discussed briefly above. Moreover, the catalyst is generated *in situ* and is prone to rapid degradation on isolation attempts. Kochi proposed a catalytic cycle where the active catalytic species is formally a Fe(I) species.^{389,391–393} Recently, Norrby and coworkers supported this claim based on their findings.²³ From computational studies the authors found unfavorable thermodynamics for reductive elimination of Fe(-II) to Fe(0), while the energy barrier for reductive elimination in the case of Fe(III) to Fe(I) was only 10 kJ/mol. The energy barrier for reductive elimination of Fe(II) to Fe(0) was also found to be prohibitively high. Based on these findings as well as systematic study of change in oxidation state of iron and Hammett plots suggest Fe(I) as the active catalyst in Fe-catalyzed cross-coupling reaction with alkylMgX.²³

In contrast, Fürstner proposed a catalytic cycle,³⁹¹ in which the active catalytic species is formally in the -2 oxidation state. Recently, Fürstner reported a full account of their mechanistic study and proposed two different active species for different Grignard reagents (with and without β -hydrogens) based on the following observations.²²

Fürstner and coworkers observed that the treatment of methyl 4-chlorobenzoate with EtMgBr (or higher alkyl Grignard reagents) in the presence of Fe(acac)₃ or FeCl_{*n*} (*n* = 2, 3) as the precatalyst affords the desired product in excellent yield at 0 °C, whereas MeMgBr fails to react even under more forcing conditions (Scheme 51). Interestingly, the appearance of the reaction mixtures is also noticeably different: the reaction containing MeMgBr leads to a yellow-colored solution that slowly darkens, whereas the reaction containing EtMgBr instantaneously generates a brown/black and turbid mixture, which eventually transforms to black-violet as the reaction proceeds. This observation indicates the presence of two different active catalytic species for Grignard reagents with β -hydrogens as compared to reagents without β -hydrogens.²²

To gain insight into the nature of the catalytic species, Fürstner and coworkers isolated the Fe complex. On treatment of ethereal solutions of FeCl₃ with excess MeLi at low temperatures a red Fe-complex was isolated, which was exceptionally sensitive. X-ray analysis provided the structural composition as [(Me₄Fe)(MeLi)][Li(OEt₂)₂] (**129**). This complex was found to exhibit similar reactivity as observed with the reaction of MeMgBr in

presence of FeX_3 , suggesting that **129** might be the reactive iron species which acts as the nucleophilic partner in methylation reactions. It was postulated that other analogs such as aryl Grignards, vinyl Grignards, etc. (not containing β -hydrogen) might also lead to similar reactive species.²²

Bogdanovi and coworkers have proposed that Grignard reagents containing a β -hydrogen react with FeX_2 to give dark-brown bimetallic clusters of the formal composition $[\text{Fe}(\text{-II})(\text{MgX})_2]_n$.³⁹² Various attempts to further characterize the iron species failed. Based on a model study conducted by Fürstner and coworkers, $[\text{Fe}(\text{-II})(\text{MgX})_2]_n$ is proposed to be the active catalytic species for Grignard reagents containing β -hydrides. The proposed mechanism for the Fe-catalyzed cross-coupling with various alkylMgX is shown in scheme 53.

4.4.4. Kumada Cross-Coupling for Ketone Formation—Direct addition of Grignard reagents to acid chlorides is limited by the subsequent addition to the product ketones to give the *tert*-alcohol products. Addition of metal salts was found to be effective to improve selectivity for the ketone product over the tertiary alcohol.¹⁹¹ In 2000, Taurino and coworkers reported a polymer-supported Fe-catalyst, $\text{Fe}(\text{AAEMA})_3$, which was effective for the coupling reaction between hexanoyl chloride and butylmagnesium chloride (Figure 109).⁴⁰⁷ This catalyst showed similar activity to the homogeneous $\text{Fe}(\text{acac})_3$ catalyst. Furthermore, low leaching of iron was observed and the recovered $\text{Fe}(\text{AAEMA})_3$ gave similar results on subsequent uses.

In 2004, Fürstner reported a $\text{Fe}(\text{acac})_3$ system, which showed excellent functional group tolerance. Representative examples are shown in figure 110.³⁹³

4.5. Pd-Catalyzed Kumada Cross-Coupling Reactions with Alkylmagnesium Reagents

In 1975, Murahashi and coworkers^{408–410} were the first to demonstrate the use of Pd in cross-coupling reactions of vinyl halides with CH_3MgBr .⁴⁰⁸ Despite significant advances in Ni- and Fe-catalyzed Kumada cross-couplings, Pd-catalyzed alkyl Kumada cross-couplings are limited. This could be attributed to the high reactivity of Grignard reagents and the higher propensity of Pd-alkyl species to undergo β -hydride elimination compared to the corresponding Ni-alkyl species.

4.5.1. $\text{C}(\text{sp}^2)\text{-C}(\text{sp}^3)$ Cross-Coupling with Alkylmagnesium Reagents—In 1984, Hayashi and coworkers demonstrated a significant effect of ligand bite angle on the reaction outcome for primary and secondary alkyl Grignards and zinc reagents (see section 2.3).¹³² The use of dppf as ligand gave optimal results for both primary and secondary alkyl Grignards. Since, this initial report dppf has become a very common ligand in both Pd-catalyzed Kumada and Negishi coupling reactions.

In 1991, Katayama and coworkers used $\text{Pd}(\text{dppf})\text{Cl}_2$ as a catalyst to selectively monoalkylate, dichlorobenzenes (Figure 111).⁴¹¹ They observed that the use of additional dppf ligand gave better results for reactions with alkyl Grignard reagents. It was postulated that the additional ligand blocks the open coordination site on Pd.

In 2002, Miller reported the Pd-catalyzed cross-coupling of Grignard reagents with enol phosphonates, which were formed *in situ* from the corresponding ketones using hindered Grignard reagents and used as substrates for sequential cross-coupling reactions with separate Grignard reagents (Figure 112).⁴¹² The reaction of the ketone with MesitylMgBr and $\text{ClP}(\text{O})(\text{OPh})_2$ gave the corresponding enol phosphonate, which was then treated with *n*-BuMgBr in the presence of $\text{Pd}(\text{dppf})\text{Cl}_2$ to give the product in 79% yield.

In 2005, Hartwig and coworkers reported a Pd-catalyzed cross-coupling between aryl and vinyl tosylates with Grignard reagents.⁴¹³ The use of an electron-rich phosphine ligand allows for oxidative addition of aryl and vinyl tosylates (Figure 113). Under the optimized conditions, alkenyl, *n*-alkyl, branched alkyl, cycloalkyl and benzyl Grignard reagents all couple with electron-rich anisyl tosylates in good to excellent yields. Moreover, vinyl tosylates also react with *sec*-alkyl Grignards to give products in good yields.⁴¹³

Recently, Eycken and coworkers utilized a Pd-catalyzed desulfitative Kumada cross-coupling reaction to generate libraries of 2-(1*H*)-pyrazinones (Figure 114).⁴¹⁴ In this report, few examples using alkyl Grignards are demonstrated. Interestingly, the use of Ni- and Fe-catalysts in the desulfitative Kumada cross-coupling reaction resulted in the formation of homocoupling products, whereas Pd(dba)₂ (5 mol%), TFP (tri-2-furylphosphine) (10 mol%) in THF/NMP mixtures gave the desired products in good yields.

4.5.2. C(sp³)-C(sp³) Cross-Coupling with Alkylmagnesium Reagents—In 2003, Kambe and coworkers were the first to report a Pd-catalyzed C(sp³)-C(sp³) coupling with alkylMgX.⁴¹⁵ The use of 1,3-butadiene as a ligand was found to be essential for this reaction to proceed, similar to the Ni-catalyzed transformation.^{347,362,364} Under the optimized conditions (1–3 mol% Pd(acac)₂, 30–100 mol% butadiene, THF), alkyl bromides and tosylates react with alkylMgX to give products in excellent yields (Figure 115). To showcase the superiority of Pd over Ni as the catalyst, parallel reactions of a chloroalkyltosylate with EtMgBr were conducted (Scheme 54). The Pd-catalyst reacts exclusively with the –OTs leaving the –Cl intact, whereas Ni reacts with partial selectivity.

4.6. Conclusion

From its discovery in 1972, the Kumada-Corriu cross-coupling has come a long way. Key contributions by scientists in the Ni- and Fe-catalyzed Kumada cross-coupling have made it more synthetically useful. Additionally, recent developments in C(sp³)-C(sp³) cross-coupling as well as the successful use of functionalized reagents are promising and showcase the potential to make this methodology even more general.

5. Cross-Coupling with Alkylindium Reagents

5.1. Introduction

Transition metal-catalyzed cross-coupling reactions of alkyl organometallics and organoelectrophiles are a field of growing interest due to their potential applications in the synthesis of target-oriented molecular frameworks.^{3,416} Although traditional organometallic reagents are frequently used in cross-couplings, they sometimes suffer from serious limitations, particularly in the case of alkyl transfer reactions.⁴¹⁷ In recent years, the synthetic scope of these types of reactions has been continuously expanded by the use of new organic electrophiles, catalysts, and organometallics. Besides the chemo- and stereoselectivity issues they also generate a stoichiometric amount of metal waste that can display serious toxicity. Organoindium reagents were introduced as cross-coupling partners that offer a protocol for C–C bond formation. Importantly, unlike other organometallics, triorganoindiums generate substoichiometric (1/3) metal waste in the alkylation processes. In addition, indium organometallic reagents are substantially less nucleophilic reagents, compared to alkylzinc and alkylmagnesium reagents but possess sufficient transmetalation properties for cross-coupling reactions.⁴¹⁸

5.2. Preparation of Trialkylindium Reagents

Indiumorganometallics are readily accessible by different approaches. (1) Transmetalation of dimethylmercury with indium metal in the presence of mercuric chloride leads to the

formation of the trimethylindium reagent, but this method is not practically useful due to the involvement of highly toxic materials (Figure 116).⁴¹⁹ (2) The metathesis reaction of lithium, magnesium, sodium, aluminum, or zinc organometallics with indium halides is a frequently used protocol for the preparation of triorganoindium reagents. Anhydrous indium(III) chloride is added to a solution of alkyllithium or alkylmagnesium reagents in THF at $-78\text{ }^{\circ}\text{C}$, the reaction mixture is warmed to room temperature and the subsequent cross-coupling reaction is performed without further purification.⁴²⁰⁻⁴²¹ (3) Oxidative addition of indium metal to an organic halide is one of the most common procedures for the preparation of organoindium reagents.⁴²² The Hill group isolated an indium metal complex which was formed from the oxidative addition of methyl iodide to indium(I)-species. From an electron paramagnetic resonance (EPR) study, it became evident that the indium insertion to the alkyl halide bond is a radical process.⁴²³

5.3. Cross-Coupling Reactions of Alkylindium Reagents

Due to low bond strengths in triorganoindiums and the large difference between the heats of formation of trialkylindiums and indium halides, indium has the ability to transfer all three groups in cross-coupling reactions.⁴²⁴ Nevertheless, the highly Lewis acidic character of the indium reagents may lead to an alternative mechanism that involves the formation of Pd–In complex prior to transmetalation.⁴²⁵

Initially, the Nomura group reported a catalyst-free addition of trialkylindium to chloroalkenes. Subsequently, several groups have made significant progress on the use of triorganoindium reagents in metal-catalyzed cross-coupling reactions.^{424,426} The Sarandeses group reported a Pd-catalyzed cross-coupling of triorganoindiums with aryl or alkenyl iodide and triflate (Figure 117).⁴²¹ It was revealed that in addition to aryl, alkenyl, and alkynylindium organometallics, trialkylindiums also undergo cross-coupling reactions with a variety of organic electrophiles, such as aryl halides and triflates, vinyl triflates, benzyl bromides, and acid chlorides in the presence of Pd or Ni catalysts. A systematic study revealed that tri-*n*-butyl, trimethyl, and triallylindium underwent cross-coupling with *p*-iodotoluene in the presence of 1 mol% $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ in refluxing THF, affording high yields. In addition, the trialkylindiums are able to deliver all three alkyl groups for effective cross-coupling with electrophiles. Therefore, the ratio of trialkylindium reagents to electrophiles could be reduced to 1:3, still obtaining almost quantitative yields. Aryl bromides and triflates as well as alkenyl triflates were also successful coupling partners under the same reaction conditions (Figure 118). In contrast, relatively inert aryl chlorides did not afford any cross-coupled products using Pd catalysts, even with Buchwald or Fu ligands.^{248,250,427} However, a combination of 5 mol% $\text{Ni}(\text{PPh}_3)_2\text{Cl}_2$ and DIBAL-H/ PPh_3 generates Ni(0) *in situ*, which catalyzes the cross-coupling between *p*-chlorotoluene and triphenyl or tri-*n*-butylindium (Scheme 56). Similar to Pd catalysis, all three alkyl groups were transferred to the electrophiles under Ni catalysis. A comparative reactivity study was performed with an aryl iodide, bromide and triflate and the reactivity order was observed as $\text{I} > \text{Br} \cong \text{OTf}$. The same order of reactivity is observed in the case of Pd-catalyzed cross-coupling with other organometallics reagents. Therefore, the oxidative addition is proposed to be the turnover-limiting step similar to many other cross-coupling processes.

In 2002, utilizing the chemoselective nature of organoindium reagents, a sequential one-pot cross-coupling with oligohaloarenes was accomplished. For example, *p*-iodobromobenzene was reacted first with TMS-protected triacetyleneindium in the presence of catalytic $\text{Pd}(\text{PPh}_3)_4$ followed by a second cross-coupling with tributylindium to afford disubstituted benzene in high yields (Scheme 57).⁴²⁸

Considering the low reactivity of indium organometallics, the Oshima group hypothesized that cross-couplings could be performed in aqueous media (Scheme 58).⁴²⁹ As a proof of

concept, 1.0 equiv of triphenylindium was reacted with 3.0 equiv of 3-iodoanisole in aqueous THF (THF:H₂O = 6:1). After work-up and purification, 2.1 equiv of the cross-coupled product was isolated along with 0.9 equiv of unreacted 3-iodoanisole. This observation led to the conclusion that at least two of the three phenyl groups could participate in the cross-coupling reaction under these aqueous reaction conditions. It was further confirmed by NMR experiments that triphenylindium converted to diphenylindium hydroxide upon addition of water. The cross-coupling of diethylindium chloride with *p*-nitro-iodobenzene in the presence of Pd₂(dba)₃•CHCl₃ afforded excellent yield under the optimized reaction conditions.

The Sarandeses group reported a regio- and stereoselective Pd-catalyzed cross-coupling reaction of indium organometallics with 1,1-dihaloalkenes and stereo-defined 1-haloalkenes (Figure 119, 120).⁴³⁰ Triorganoindium reagents were stereospecifically coupled with stereodefined alkenyl iodides in good yields and short reaction times using Pd catalysts. Additionally, the Pd-catalyzed cross-coupling reaction of R₃In (0.9 equiv) with 1,1-dibromo-1-alkenes gave coupling products in high yields (Figure 120). Interestingly, when the reaction was performed with 0.4 equiv of aryl-, vinyl- or alkynylindium derivatives, *trans*-monosubstituted products were obtained selectively in moderate to good yields. These selective cross-couplings were performed with [Pd₂dba₃]/P(2-furyl)₃ (1:1, 2 mol%) at room temperature. The resulting (*Z*)-monobromoalkenes were further functionalized by cross-coupling reactions with various triorganoindium reagents at room temperature in the presence of [Pd(*t*-Bu₃P)₂] as a catalyst, to provide trisubstituted olefins in good yields.

In 2009, the same group reported the synthesis of unsymmetrical 3,4-disubstituted maleimides by a sequential one-pot Pd-catalyzed cross-coupling reaction of indium organometallics with 3,4-dihalomaleimides (Figure 121). Disubstituted products were obtained in high yields and selectivity.⁴³¹

5.4. Carbonylative Cross-Coupling With Trialkylindium Reagents

In 2003, the Lee group reported a Pd-catalyzed cross-coupling of aryl halides, triflates, benzyl bromides and acid chlorides with tetraorganoindate complexes.⁴³² The tetraorganoindates were prepared *in situ* by the reaction of indium trichloride and alkyl, aryl or alkenyl lithium or magnesium bromides. It was observed that 0.28 equiv of indate complexes were able to furnish almost quantitative yields of the cross-coupled products. Primary as well as secondary alkyl groups were transferred successfully, whereas tertiary alkyls did not form any cross-coupling products. When the coupling reaction was performed under CO atmosphere the corresponding carbonylative cross-coupling product was obtained in good yield (Figure 122).⁴³³

The same group also reported a Pd-catalyzed synthesis of unsymmetrical ketones using trialkyl- and triarylindiums via carbonylative cross-coupling with a variety of organic electrophiles.⁴³⁴ Only 0.37 equivalents of alkylindium were required to afford high yields of ketones using one atmosphere of CO (Figure 123). Interestingly, when *p*-bromiodobenzene was reacted with 0.37 equiv of trimethylindium under a CO atmosphere in the presence of 4 mol% Pd(PPh₃)₄, *p*-bromoacetophenone was formed selectively. The subsequent addition of 0.37 equiv of triphenylindium generated 4-phenylacetophenone in 75% overall yield. In the following year, modified conditions for ketone formation were reported using tetraorganoindate complexes.⁴³⁴ This protocol allows for the use of secondary alkyl groups to afford unsymmetrical ketones in high yields.

5.5. Oxidative Cross-Couplings with Trialkylindium Reagents

The Lei group reported a Pd-catalyzed oxidative carbonylation protocol for a broad range of primary and secondary alkyl and aryl indium reagents under mild conditions.⁴³⁵ The alkyl indium reagents exhibited compatibility to a wide range of functional groups, whereas the alkyl Grignard precursor precludes their involvement in such reactions in many cases because of the high reactivity and basicity. Unlike conventional cross-coupling protocols, desyl chloride was used as an oxidant to avoid slow oxidative addition and β -hydride elimination. Mechanistic investigations under stoichiometric and catalytic conditions provided evidence for the oxidative addition of desyl chloride to Pd(0) followed by rapid tautomerization to give Pd species **131** (Figure 124). Subsequent displacement of the enolate group in **131** by ROH, followed by CO insertion gave alkoxycarbonyl Pd complex **132**. Transmetalation with alkylindium and reductive elimination furnished the desired alkyl esters **134**.

Exploiting the oxidative addition of desyl chloride to Pd(0) complex, the C(sp²)-C(sp³) cross-coupling of arylzinc reagents with trialkylindium reagents was accomplished in the following year by the same group. Analysis of the preliminary kinetic data revealed that alkylindium reagents rapidly undergo transmetalation after oxidation with desyl chloride. A second transmetalation with an arylzinc reagent and reductive elimination yields the cross-coupling product (Scheme 59).⁴³⁶

5.6. Formation of Ketones from Acid Chlorides

Sarandeses reported ketone formation via the cross-coupling of triorganoindium and acid chlorides. Besides triaryl and alkynylindium reagents, trimethylindium also afforded a near quantitative yield with benzoyl chloride (Scheme 60).⁴²¹

The Liebeskind group reported the synthesis of ketones via a Pd-catalyzed cross-coupling of thioesters and alkylindium reagents (Figure 125).⁴³⁷ This protocol offers an advantage over other existing methods, in that due to the thiophilicity of indium, no added Cu was required and no base activation was necessary. It was observed that with 0.40 equiv of a trialkylindium reagent less than 5% yield was observed, whereas upon increasing the amount of the indium reagent to 1.2 equiv, very high yields (95%) were achieved. Unfortunately, this process requires 3.6 equiv of the alkyl group from the indium reagent. This problem was addressed by using a non-transferring *tert*-butyl “dummy ligand” on indium. Employing 0.6 equiv of this mixed trialkylindium bearing two transferring alkyl groups, good yields of the ketones were achieved.

5.7. Conclusion

Triorganoindium reagents have been successfully used in cross-coupling reactions. Due to their low reactivity, alkylindium reagents provide a high degree of chemo-, regio and stereoselectivity and good functional group compatibility. Above all, they are attractive alternatives as they are environmentally benign and generate substoichiometric (0.33 equiv) metal waste. In addition, due to their water compatibility, aqueous conditions can be used to perform cross-coupling reactions.

6. Cross-Coupling Reactions with Alkylsilicon Reagents

Hiyama first reported the use of an organosilicon in a cross-coupling reaction in 1988.⁴³⁸ Since then, substantial advancements have been made in the cross-coupling of alkynylsilicons and arylsilicons, while the use of alkylsilicons is still limited.^{439–442} The strong C-Si bond requires higher temperatures along with activation of the organosilicon reagent for successful transmetalation, which restricts their use. However, alkylsilicons have

several advantages over other alkylmetals: 1) low toxicity, 2) high stability to air and moisture and 3) easy handling and preparation. In this part of the review, the seminal report on the use of alkylsilicons in cross-coupling as well as significant advancements will be discussed in chronological order.

In 1988, Hiyama and coworkers reported the first example of alkylation of aryl halides with alkylsilicon.⁴³⁸ They showcased the use of *tris*(diethylamino)sulfonium difluorotrimethylsilicate (TASF) as a source of a methyl group in cross-coupling with various aryl halides. The $[\text{Pd}(\text{allyl})\text{Cl}]_2$ was an effective catalyst for this transformation. The Pd-catalyzed methylation reaction using TASF has excellent functional group tolerance (Figure 126).

Several years later, Hiyama and coworkers reported the use of vinyl and aryl triflates in the cross-coupling reaction with various organosilicons.^{443,444} TBAF as the source of fluoride was essential for the successful reaction. Fluoride is proposed to react with the organosilicon reagent to generate pentavalent silicon, which undergoes transmetalation with the palladium complex. The Hiyama group expanded the scope of this transformation to various functionalized aryl halides and organosilicons (Figure 127–128).^{445–447} They observed that $\text{Pd}(\text{PPh}_3)_4$ in THF at 100 °C was the best catalyst for the desired transformation. Moreover, excess TBAF was required for activation of the alkylsilicon.

The proposed mechanism for this transformation is depicted in scheme 61.⁴⁴⁶ The oxidative addition of the aryl halide results in the formation of Pd-aryl complex **136**, which undergoes transmetalation with activated alkylsilicon **138** to give Pd complex **141** and SiF_4 . Upon reductive elimination, the product is released and the active catalyst **135** is regenerated. The SiF_4 is proposed to react with an equivalent of TBAF to either form SiF_5^- (**139**) or SiF_6^{2-} (**140**) species. The existence of these species was confirmed by ^{19}F -NMR.^{448,449}

Recently, Bach and Schweizer reported a highly regioselective monoalkylation of dibromo heteroarenes.⁴⁵⁰ Bidentate phosphine ligands gave mainly the undesired hydrodebromination product, whereas monodentate phosphines gave the desired product. $\text{P}(\text{2-furyl})_3$ was the optimal ligand, giving the best selectivity for the desired product. Extended reaction times and elevated temperatures were required due to slow transmetalation of alkylsilicon. Under the optimized conditions, an array of dibromo-substituted heterocycles was successfully employed.⁴⁵⁰

In 2010, Hiyama and coworkers reported the use of 2-(2-hydroxyprop-2-yl)phenyl-substituted alkylsilanes in cross-coupling reactions (Figure 129).⁴⁵¹ These reagents have advantages over the widely used polyfluorinated alkylsilicons such as stability under acidic as well as basic conditions. The authors observed that the use of $\text{Cu}(\text{hfacac})_2$ as a cocatalyst gave improved results, which suggests that an alkyl Cu species formed *in situ* from alkylsilicon might be the active transmetalating agent. Under the optimized conditions, various functionalized alkylsilicon reagents cross-coupled to give products in good yields. Furthermore, challenging *sec*-alkylsilicons also yielded the desired products.

7. Cross-Coupling Reactions with Alkyltin Reagents

Stille cross-couplings with organotin reagents are some of the most frequently used methods to form C–C bonds.^{3,416} In practice though, aryl- or alkenyltin reagents are commonly used as coupling partners, while alkyl transfer is mostly limited to methyl group transfer using SnMe_4 .⁴⁵² Although there are a few examples of benzyl or methoxymethyl group transfer from tin reagents, alkyl groups containing β -hydrogens such as *n*-butyl are extremely rare⁴⁵³ and very often they provide low yields or fail to give any cross-coupling products.^{417,452,454} This is in contrast to the SnMe_4 reagent, which produces the corresponding coupling

products in high yields under the same reaction conditions. Alkyltin reagents can be prepared conveniently via the oxidative addition of alkyl halides, or Grignard additions to ClSnMe_3 .⁴⁵⁵

In 1983, the Tam group reported the Pd-catalyzed Stille coupling of 2,3-dichloro-1,4-naphthoquinones to afford 2-alkylated products (Figure 130).⁴⁵⁶ During alkylation it was observed that tetraalkyltin reagents containing alkyl groups such as methyl or *n*-butyl, were reactive enough to provide high yields, however, the reaction was slow with larger alkyl groups. For example, tetra-dodecyltin provided only 25% of the cross-coupling product after refluxing in dioxane for six days. The same order of reactivity was also observed in the case of alkylation of arenediazonium *o*-benzenedisulfonamides.²⁷¹ Using Pd-catalysis, tetramethyltin afforded substituted toluenes in high yields, whereas tetra-*n*-butyltin afforded only low or moderate yields under identical reaction conditions.

Ohta and coworkers demonstrated alkylations of pyrazines by a Pd-catalyzed Stille coupling. Pyrazine or pyrazine *N*-oxides were alkylated using tetra-*n*-butyltin, tetra-*n*-pentyltin and tetra-*n*-octyltin reagents, providing good to high yields (Figure 131).⁴⁵⁷

Fouquet and coworkers illustrated an attractive advancement in Stille couplings.⁴⁵⁸ Considering the low reactivity, inherent toxicity and difficulties in separation of tetraalkyltin reagents, they prepared activated tin reagents *in situ* by simple oxidative addition of alkyl halides to low valent tin, which underwent a subsequent $\text{Pd}_2(\text{dba})_3$ -catalyzed cross-coupling reaction (Figure 132). Gratifyingly, only TBAF was used as an additive, no additional ligand was required on Pd, and relatively less toxic inorganic tin byproducts were separated from the organic materials by simple filtration. A number of *n*-alkyl iodides and bromides underwent cross-couplings with aryl iodides and bromides providing high yields. Unfortunately, secondary alkyl bromides did not furnish any products. Perfluorinated alkyls were also tested and afforded the corresponding cross-coupling products under even milder reaction conditions. Chiappe and coworkers also reported ligandless Stille couplings in ionic liquids.⁴⁵⁹ A single example of Stille cross-coupling between an alkyltin chloride and an aryl chloride appeared in Fu's general protocol for Stille couplings.⁴⁶⁰

In conclusion, although alkylative Stille couplings with SnMe_4 are well demonstrated, higher alkyltin reagents are limited in use due to their low reactivity and alkyl transfer capability. In addition, due to the toxicity of tin, Stille couplings for alkylations have been substantially substituted by Negishi and Suzuki protocols.

8. Asymmetric Cross-Coupling Reactions with Alkyl Organometallics

8.1. Introduction

The synthesis of both natural and unnatural organic compounds in optically active form is a central challenge in chemistry. Enantioselective cross-coupling reactions are powerful tools for the assembly of diverse building blocks in a stereocontrolled manner via C-C bond formation.⁴⁶¹ Strategically, it can be 1) reagent-controlled, where the organometallic reagent itself is stereo- or diastereoselective; or 2) catalyst-controlled. The latter is the most powerful method for chiral induction, as it requires only a catalytic amount of precious chiral ligands on the metal centers and is highly tunable.⁴⁶² Cross-coupling with reactants containing remote stereocenters on their backbone will not be discussed in this section.

8.2. Organometallic Reagent-Controlled Enantioselective Cross-Coupling Reactions

In reagent-controlled enantioselective cross-coupling, an alkyl organometallic reagent with a well-defined stereocenter is prepared and undergoes a subsequent cross-coupling with a prochiral substrate to provide an optically active product. The downside to this strategy is

that depending on the reaction mechanism and reaction conditions, the stereochemical fidelity can be poor or inversion may occur. In 1990, the Hiyama group observed the influence of temperature and solvent on the stereochemistry of the cross-coupling reaction of chiral alkylsilanes with aryl triflates.⁴⁶³ The cross-coupling between (*S*)-phenyl-1-(trifluorosilyl)ethane (34% ee) with 4-acetylphenyl triflate took place smoothly in the presence of 5 mol% Pd(PPh₃)₄ and 2.0 equiv of TBAF in THF to afford the cross-coupled product with retention of configuration at 50 °C (32% ee), and an inversion of configuration at 75 °C (Figure 133). Furthermore, the inversion of configuration was observed predominantly in a polar solvent system (HMPA-THF) even at 50 °C, whereas retention was still maintained in comparatively less polar DMF and DMSO at 50 °C. Presumably, the Pd-catalyzed cross-coupling of an organosilane with a triflate involves a pentacoordinate silicate intermediate which is generated by nucleophilic attack of a fluoride ion to an organosilicon compound. The retention of configuration in THF at low temperature is ascribed to a fluoride ion-assisted cyclic four-centered transition state, whereas at higher temperatures or in HMPA-THF, the fluoride bridge is cleaved and a back-side attack of the Pd-complex occurs, leading to inversion (Figure 133).

Crudden and coworkers reported the Pd-catalyzed cross-coupling of chiral secondary alkylboronic esters with aryl iodides.⁴⁶⁴ The chiral boronic esters were synthesized by Rh-catalyzed hydroboration of alkenes with excellent enantiomeric ratios. A subsequent cross-coupling with aryl iodides in the presence of 0.08 equiv Pd₂(dba)₃ and 1.0 equiv Ag₂O afforded coupling products in high yields and with retention of configuration (Figure 134). The Deng group⁴⁶⁵ and the Gevorgyan group⁴⁶⁶ also reported a Pd-catalyzed cross-coupling of chiral cyclopropylboronic acids with aryl iodides and aryl bromides, producing the corresponding cross-coupling products in high yields and with retention of configuration. Interestingly, the primary alkylboron remains intact under the reaction conditions.

While the enantioenriched 1-arylethylboronic esters underwent cross-coupling with retention of configuration, an inversion of configuration was observed in the case of Pd-catalyzed cross-coupling between α -(acetyl amino)benzylboronic esters and aryl bromides (Figure 135).⁴⁶⁷ Presumably, due to the strong intramolecular coordination of the carbonyl group to boron, the Pd-complex cannot attack from the same side of boron via p-orbital overlap (TS2). Alternatively, a backside attack on the carbon center of α -(acetyl amino)benzylboronic esters (TS1) leads to the inversion of configuration in the final product (Scheme 62). β -hydride elimination is not an issue in these substrates.

Campos and coworkers reported a reagent-controlled enantioselective α -arylation of *N*-Boc-pyrrolidines (Figure 136). The enantioenriched zinc reagent was prepared *in situ* via deprotonation of *N*-Boc pyrrolidine by *s*-BuLi and (–)-sparteine followed by treatment with zinc chloride at –78 °C. The reagent was then cross-coupled at room temperature with aryl halides in the presence of 5 mol% Pd(OAc)₂ and 6 mol% *t*-Bu₃P-HBF₄ in MTBE, affording high yield and enantioselectivities of the α -arylated products.⁴⁶⁸ The high degree of stereoselectivity of the cross-coupled product suggests that the secondary zinc reagents are configurationally stable under the reaction conditions and undergo facile transmetalation with the Pd-species. Since numerous biologically active molecules contain *N*-protected pyrrolidines in their backbone, this methodology can offer a concise and practical route for their synthesis. An illustrative example is the synthesis of a glucokinase activator (Scheme 63).⁴⁶⁹ Recently, Knochel and coworkers reported a Pd-catalyzed diastereoselective Negishi coupling with substituted cycloalkylzinc reagents.⁴⁷⁰

8.3. Catalyst-Controlled Enantioselective Cross-Coupling Reactions

Catalyst-controlled enantioselective cross-coupling is the most powerful technique to afford optically active cross-coupled products, as it requires only substoichiometric chiral ligands.

⁴⁷¹ In 1982, Kumada and coworkers reported the asymmetric cross-coupling of secondary alkyl Grignard reagents with organic halides catalyzed by chiral ferrocenyl-phosphine complexes of Ni and Pd.⁴⁷² It was observed that the ferrocene planar chirality was a dominant factor over the chiral carbon center attached to one of the cyclopentyl rings, and a dimethylamino group vicinal to the chiral carbon center was required to achieve high degrees of enantioselectivity (Scheme 64). Mechanistically, it is speculated that the ferrocenyl metal complex undergoes oxidative addition to the alkenyl halide to generate a tetracoordinated complex **143** (Scheme 65). When the Grignard reagent approaches, the dimethylamino group dissociates from metal center and coordinates with the magnesium atom of the Grignard reagent to form the diastereomeric intermediate **144**. This coordination occurs selectively with one of the enantiomers of the racemic Grignard reagent, and facile transmetalation occurs to form the diorganonickel- or Pd-intermediate **145**. The stereoselectivity of the reaction is determined at the transmetalation step, and coordination with the pendant dimethylamino group is influential.

In 1986, the Kellogg group designed, developed, and synthesized a series of chiral, macrocyclic sulfide- and sulfide/alkylamine-containing ligands for Ni-catalyzed cross-coupling reactions with Grignard reagents (Scheme 66).⁴⁷³ After ligand evaluation, it was observed that an L-cysteine-derived tetradentate ligand provided moderate yield (50%) with 46% enantiomeric excess of the cross-coupled product between vinyl bromide and 1-phenyl-1-chloroethane (Scheme 66). The square planar geometry provided by this ligand at the Ni(0) and diorganonickel intermediates was found to be crucial for effective asymmetric induction, as the open chain analogue of the ligand afforded only 8% ee of the same product.

Shibasaki and coworkers developed an intramolecular asymmetric Suzuki-Miyaura cross-coupling reaction to construct cyclopentane derivatives (Scheme 67).⁴⁷⁴ Prochiral 9-BBN derivatives of vinyl triflates were prepared by hydroboration of the corresponding alkenes and subsequently cross-coupled in the presence of Pd₂(dba)₃·CHCl₃, (*S*)-(*R*)-BPPFOAc and K₂CO₃ in THF at 40 °C. The product was isolated after the subsequent oxidative work-up and benzoylation in overall 58% yield with 28% ee.

In 2001, Lemaire reported an asymmetric Kumada-Corriu coupling of 1-phenylethylmagnesium chloride with vinyl bromide in the presence of NiCl₂ and quinphos ligand (Scheme 68).⁴⁷⁵ A satisfactory enantiomeric excess was obtained (85%) at 0 °C along with a moderate yield (50%) of the cross-coupling product.

In 2004, Aoyama also reported the Pd-catalyzed asymmetric cross-coupling of 1-phenylethylmagnesium and (*E*)-β-bromostyrene using an *N*-Ar axially chiral ligand (Figure 137). Interestingly, this protocol offered the chemoselective cross-coupling of vinyl bromides in the presence of aryl halides.⁴⁷⁶

From the above examples, it is quite evident that asymmetric induction in cross-coupling is very difficult and, in most cases, moderate to good enantiomeric excess of the cross-coupled products was observed. Recently, Fu and coworkers developed a series of Ni-catalyzed enantioselective cross-coupling reactions between alkyl organometallics and different types of secondary electrophiles using chiral nitrogen-based ligands. In a mechanistic study, Vicic and coworkers illustrated that Ni-catalyzed cross-couplings proceed in a stereoconvergent manner instead of through a kinetic resolution. Therefore, the oxidative addition of alkyl halides most likely occurs through a radical pathway and a planar radical intermediate has been proposed.^{20,21} The stereochemistry of the cross-coupling product can then be determined by the configuration of the ligand used. In 2005, the Fu group reported the enantioselective Negishi coupling of benzylic halides in the presence 10 mol% NiBr₂·diglyme and 13 mol% (*S*)-(*i*-Pr)-Pybox in DMA at 0 °C (Figure 138).⁴⁷⁷ The high

yields and excellent enantioselectivity of the cross-coupled products are noteworthy. In the same year, they also reported an enantioselective Negishi coupling of secondary α -bromo amides in the presence of 10 mol% $\text{NiCl}_2 \cdot \text{glyme}$ and 13 mol% (*R*)-(*i*-Pr)-Pybox in DMI/THF at 0 °C.⁴⁷⁸

The Fu group also reported a Ni-catalyzed enantioselective cross-coupling of secondary allylic chlorides and primary alkylzinc bromides. Consiglio and coworkers have previously reported Ni-catalyzed, asymmetric Kumada-Corriu couplings with cyclic allyl phenyl ethers, but the yields and enantioselectivities were poor.⁴⁷⁹ Furthermore, the substrate scope was limited to cyclic allyl phenyl ethers to avoid regioselectivity issues. Using Fu's conditions high yields and excellent regio- and enantioselectivities were obtained using (*S*)- BnCH_2 -Pybox as a chiral ligand (Figure 139).⁴⁸⁰ As a showcase, this methodology has been applied to the formal synthesis of fluvirucine **A**₁, where excellent regio-, diastereo-, and enantioselectivity have been achieved (Scheme 69).

In 2008, the Fu group demonstrated the stereoconvergent, enantioselective alkyl-alkyl Suzuki cross-coupling of unactivated homobenzylic halides catalyzed by Ni-complexes. It was hypothesized that the chiral Ni-complex should differentiate between the alkyl groups of benzylCH_2 and alkyl groups attached to secondary bromides. Therefore, proper placement of the aryl groups was found to be important for chiral induction, as deviation from the homobenzylic position produced low enantioselectivity. During this study it was noted that when an ether is present in the electrophile, low enantioselectivity was observed (Figure 140).⁴⁸¹ It was therefore hypothesized that, the Ni-complex might coordinate with the oxygen of the ether moiety. Using this concept, the protocol was extended into the asymmetric alkyl-alkyl cross-coupling of acylated halohydrins under slightly modified reaction conditions, where a simple phenyl-substituted diamine ligand was used in place of the electron-deficient (*m*- CF_3 - C_6H_4) substitution on the diamine ligand.⁴⁸²

8.4. Conclusion

In conclusion, enantioselective cross-coupling reactions with different electrophiles and alkyl organometallics have been demonstrated and more attention is being devoted to this field. Recent advancements using Fu's conditions are noteworthy. However, sparse mechanistic information has been reported on these reactions which may be limiting the extension to broader reaction classes.

9. Applications of Alkyl Organometallic Reagents in Total Synthesis

In recent years, alkyl organometallics have been used extensively in the total synthesis of complex natural products. High functional group tolerance, mild coupling conditions, and the ability to utilize novel disconnections have made cross-coupling a mainstream fragment coupling technology. The application of cross-coupling reactions in total synthesis has been extensively reviewed by Danishefsky²³¹ and Nicolaou²³² in 2001 and 2005, respectively. In this final section of the review, representative examples of alkyl boron, alkyl zinc, and alkyl magnesium compounds used in total synthesis will be covered in chronological order starting from 2001 to 2010.

9.1. Total Synthesis with Alkylboron Reagents

In 2002, Mandal reported the total synthesis of (–)-ebelactone **A** using a Suzuki-Miyaura cross-coupling (Figure 141a).⁴⁸³ The diastereoselective hydroboration of fragment **146** with Still's hydroboration protocol gave compound **147**.⁴⁸⁴ Late stage cross-coupling was achieved between compound **147** and **148** using catalytic $\text{Pd}(\text{dppf})\text{Cl}_2$ in 70% isolated yield as a single diastereomer. In 2002, Marshall and coworkers utilized a *B*-alkyl Suzuki-Miyaura cross-coupling as a key step in their total synthesis of (–)-callystatin **A** (Figure

141b).⁴⁸⁵ The union of subunits **150** and **151** was achieved in 73% yield using 5 mol% Pd(dppf)Cl₂, AsPh₃, Cs₂CO₃, DMF/H₂O.

In 2005, Sasaki and coworkers reported the total synthesis of marine polyether gymnocin-A⁴⁸⁶ using Suzuki-Miyaura cross-coupling methodology developed in their lab.²⁶⁹ They have reported the synthesis of various natural products containing cyclic ether moieties using their methodology.^{487,488} Since all of them follow the same general concept, we will cover only their synthesis of brevenal (Figure 141c).⁴⁸⁷ Hydroboration of compound **153** followed by reaction with compound **152** in the presence of Cs₂CO₃ and Pd(dppf)Cl₂ gave the desired product in good yield. Successful use of the Suzuki-Miyaura reaction in the late stage of a total synthesis of a molecule of this complexity clearly showcases the high chemoselectivity and mildness of these procedures.

Another elegant example of the late stage use of a Suzuki-Miyaura cross-coupling was demonstrated by Lee and coworkers (Figure 141d). During the total synthesis of kendomycin, cross-coupling between compound **155** and compound **156**, using [Pd(dppf)Cl₂] as the catalyst in a ether/THF/DMF solvent mixture, gave product **157** in excellent yield.⁴⁸⁹ Sequential functional group manipulations transformed intermediate **157** into the natural product. In 2004, Cossy and coworkers reported the total synthesis of (+)-(3'S, 2'R)-zaopatanol using the Suzuki-Miyaura reaction (Figure 141e).⁴⁹⁰ In this case, use of Pd(PPh₃)₂Cl₂ with K₃PO₄ in dioxane at 85 °C gave the desired product in 74% yield.

In 2006, Smith and coworkers reported the total synthesis of the indole diterpenoid (+)-nodulisporic Acid F (Figure 142a).⁴⁹¹ The alkyl side chain was introduced by Suzuki-Miyaura cross-coupling between compound **162** and tether **163**. The reaction of **161** with 9-BBN dimer in toluene gave the corresponding alkyl borane **162**, which reacts smoothly with vinyl bromide **163** to furnish **164** in 69% yield. Dai and coworkers synthesized amphidinolide Y, a 17-membered cytotoxic macrolide (Figure 142b).⁴⁹² The treatment of compound **165** with 9-BBN gives intermediate **166**, which was then subjected to Suzuki-Miyaura cross-coupling to give the desired product in 70% yield. Use of the Aphos ligand^{493,494} gave better results compared to dppf and allowed for the use of lower catalyst loading. In 2008, Roulland reported the synthesis of (+)-oocydine A, a cytotoxic and phytopathogenic compound, by means of the *B*-alkyl Suzuki-Miyaura reaction (Figure 142c).⁴⁹⁵ Utilizing a methodology developed in their laboratory,²⁶⁶ they were able to accomplish the coupling of two highly functionalized fragments, **167** and 9-BBN derivative of **168**. It should be noted that, using 1,1-dichloroalkene **167**, the chloride *trans* to the alkyl chain reacts preferentially, giving the *E*-isomer of **169** in excellent yield and selectivity. Kigoshi and coworkers also achieved the synthesis of haterumalide HA ((+)-oocydine A), a potent cytotoxic marine macrolide, using Suzuki-Miyaura cross-coupling (Figure 142d).⁴⁹⁶ The use of 9-BBN dimer gave better results than 9-BBN under optimized reaction conditions.

In 2009, Williams and coworkers reported a unique use of the *B*-alkyl Suzuki-Miyaura cross-coupling in the total synthesis of 4-hydroxydictyolactone (Figure 142e).⁴⁹⁷ They utilized a cross-coupling protocol to construct a macrocycle from highly functionalized late stage intermediate **173**. During their optimization, they observed a significant influence of the protecting group on the reaction outcome. Interestingly, the use of Pd(PPh₃)₄ instead of the widely used Pd(dppf)Cl₂ gave better results for the Suzuki macrocyclization event.

Mycestericin A, a potent immunosuppressant, was synthesized by Chiba and coworkers (Figure 143a).⁴⁹⁸ The Negishi cross-coupling between lactone **176** and the alkylzinc derivative of **175** gave the product **177** in low yield. This was proposed to be due to the presence of base-sensitive functionalities (lactone and acetyl groups) in compound **176**. In

contrast, the Suzuki-Miyaura cross-coupling led to a 77% yield of the desired product **179**. Jatrophane was efficiently synthesized using a Suzuki-Miyaura cross-coupling (Figure 143b).⁴⁹⁹ Hiersemann and coworkers used 7 mol% Pd(dppf)Cl₂, 20 mol% Ph₃As and Cs₂CO₃ in THF:DMF:H₂O at 80 °C to effect the highly efficient coupling of vinyl iodide **181** with the alkyl borane derived from **180**.

Barrero and coworkers reported the first total synthesis of potent anti-inflammatory (+)-myrrhanol-A in 2009 (Figure 143c).⁵⁰⁰ They used a late stage *B*-alkyl Suzuki-Miyaura cross-coupling to assemble the advanced fragments **183** and **184** to give product **185** in 90% yield as a single regioisomer. Subsequent deprotection of ethers afforded the natural product. Another elegant use of a late stage *B*-alkyl Suzuki-Miyaura cross-coupling was demonstrated by Fürstner and coworkers in their total synthesis of spirastrellolide F methyl ester.^{501,502} Two highly functionalized fragments **186** and **187** were coupled under mild conditions to give key intermediate **188** in a respectable 75% yield.

An alternative version of the *B*-alkyl Suzuki coupling was used by Bonazzi and coworkers in a synthesis of the polyketide anguinomycin (Scheme 70).⁵⁰³ Lithiation of primary iodide **189**, followed by an addition of 9-methoxy-BBN gave the intermediate borate **190**, which was coupled with iodoalkene **191** in high yield (Scheme 70).

Other molecules which have been synthesized using the *B*-alkyl Suzuki-Miyaura cross-coupling are depicted in Figure 144.^{274,504–509}

9.2. Total Synthesis with Alkylzinc Reagents

In 2002, Panek and coworkers reported the total synthesis of oleandolide, the aglycon of the macrolide antibiotic oleandomycin (Scheme 71).⁵¹⁰ The failure of the Suzuki-Miyaura cross-coupling to efficiently provide key intermediate **196** prompted the authors to explore a Negishi cross-coupling. The rationale behind this change was that transmetalation from Zn to Pd is faster than the transmetalation from B to Pd, and a cleaner and faster reaction might be achieved.¹³⁴ Indeed, reaction of alkylzinc **197** with vinyl triflate **195** gave the cross-coupled product **196** in 82% isolated yield.

In 2002, Kibayashi reported an elegant use of the Negishi coupling reaction for the synthesis of (+)-Pumiliotoxins A and B⁵¹¹ from common precursor **198** (Figure 145a). This was the first example of cross-coupling between a highly functionalized homoallylic organozinc such as **199** and a vinyl iodide like **200**. The common intermediate **198** was treated with ZnCl₂ in presence of *t*-BuLi to give the corresponding alkylzinc intermediate **199**. The reaction of intermediate **199** with **200** in the presence of Pd(PPh₃)₄ gave compound **201** in 60% yield. When the same methodology was applied to the synthesis of **204**, it resulted in the formation of the desired coupling product in low yield (28%) together with a complex mixture. The low yield was presumably due to the Lewis acid sensitive acetal group, which could react in the presence of IZnCl generated from the cross-coupling. To overcome this problem, dialkylzinc **202** was cross-coupled with **203** to give 51% yield of the desired product **204**. Sequential functional group manipulations transformed intermediates **201** and **204** into the corresponding natural products.⁵¹¹

In 2003, Morken and coworkers reported the total synthesis of borrelidin, a potent angiogenesis inhibitor with an IC₅₀ of 0.8 nM (Figure 145b).⁵¹² Alkyl iodide **205** was converted to the corresponding alkylzinc *in situ* and subjected to the coupling conditions to give **207** in 58% yield. A similar coupling strategy (coupling between alkyl iodide and vinyl iodide) was used by Altmann and coworkers for the total synthesis of *trans*-epothilone A.⁵¹³ For the total synthesis of hemibrevetoxin B, the coupling of two fragments was accomplished utilizing a Negishi cross-coupling by Holton and coworkers (Figure 145c).⁵¹⁴

The authors observed a significant effect of the method of zinc activation on the reaction outcome. When iodine-zinc exchange was performed through Pd catalysis or Mn/Cu⁵¹⁵ mixed metal catalysis, the yield of **211** was low and variable, whereas when the zinc reagent **210** was prepared following a Rieke zinc protocol,⁹⁸ a high yield of **211** was obtained.

In 2003, Fürstner utilized an acyl Negishi cross-coupling between the highly functionalized alkylzinc derivative of **212** and enantiopure acyl chloride **213**, in the total syntheses of amphidinolides T1, T2, T3 and T4 (Figure 145d).⁵¹⁶ The alkyl iodide **212** was treated with Zn/Cu couple, which was activated with TMSCl immediately prior to use, to give the alkylzinc. The alkylzinc generated *in situ* was treated with acyl chloride **213** in the presence of Pd₂(dba)₃ as catalyst and P(2-furyl)₃ as ligand to give the desired product **214** in modest yield. The reaction was sensitive to the conditions used, *e.g.* only toluene as solvent with DMA as the additive was successful; also, the use of coupling partners other than alkylzincs did not result in the formation of the desired product.

In 2004, Vyvyan and coworkers reported the total synthesis of various aromatic bisabolene natural products via Pd-catalyzed Negishi cross-coupling (Figure 146a).⁵¹⁷ The reaction of *sec*-alkylzinc **216** with aryl bromides **217** and **218**, respectively gave the corresponding products in good yields. Scyphostatin, a powerful and specific inhibitor of neutral sphingomyelinase, has been synthesized by various groups using the Negishi coupling (Figure 146b).^{518–522} One representative example is shown in Figure 146b, where the coupling of vinyl iodide **222** with the alkylzinc generated *in situ* from **221** provided the desired product **223** in 81% yield.

During the total synthesis of brevetoxin B, Yamamoto and coworkers⁵²³ used a Negishi cross-coupling to install the side chain **225** on fragment **224** (Figure 146c). In 2007, Crews and coworkers utilized a Negishi cross-coupling to synthesize the C3-C18 fragment of amphidinolides G and H, where the treatment of compound **227** with alkylzinc **228** in the presence of Pd(PPh₃)₄ gave the coupled product **229** in 92% yield (Figure 146d).⁵²⁴ The same alkylzinc (**228**) was used by Pilli and coworkers in the total synthesis of (–)-delactomycin.⁵²⁵

The total synthesis of (–)-kendomycin, a potential antiosteoporotic agent, was achieved by Panek and coworkers utilizing a Negishi cross-coupling (Figure 146e).⁵²⁶ The reaction of **230** with the alkylzinc derived from **231** in the presence of Pd(PPh₃)₄ gave product **232** in 92% yield. In Paige and coworker's approach towards the synthesis of (*S*)-jamaicamide C, a Negishi reaction was used to introduce the alkyl chain (Figure 146f).⁵²⁷ The reaction of vinyl iodide **233** with alkylzinc gave the product **234** in good yield.

In 2009, Jackson and coworkers used a Negishi cross-coupling as a key step in the synthesis of OF4949-III and K-13 (Figure 147a).⁵²⁸ OF4949-III was synthesized by reaction of compound **235** with alkylzinc **236** to give **237** in 75% yield. This provided the full carbon skeleton of OF4949-III and only a few functional group manipulations were needed to furnish the final product. Impressively, K-13 was synthesized via an intramolecular Negishi cross-coupling of highly functionalized compound **238**, though in this case a lower yield was observed.

Recently, Rainier and coworkers synthesized kapakahines E and F, potent cytotoxic compounds, utilizing a key Negishi cross-coupling (Figure 147b).⁵²⁹ The reaction between 3-iodoindole **240** and well known alkylzinc **241** gave the desired product **242** in 74% yield, effectively completing the synthesis of the kapakahine dimeric tryptophan core. Other molecules which have been synthesized using the Negishi cross-coupling are depicted in Figure 148.

9.3. Total Synthesis with Alkylmagnesium Reagents

In 2002, Danishefsky and coworkers demonstrated the use of a Kumada cross-coupling for synthesis of 17- and 18-membered ring homologues of epothilone B (Figure 149a).⁵³² They successfully coupled **243** and **244**, using Pd(dppf)Cl₂ as catalyst, to give **245** in good yield. In 2003, Fürstner and coworkers demonstrated the first example of Fe-catalyzed cross-coupling between a vinyl triflate **246** and alkyl-MgBr (**247**) during their synthesis of latrunculin B (Figure 149b).⁵³³ The reaction affords the desired product in excellent yield. Furthermore, the reaction is highly stereoselective and proceeds very rapidly under notably mild conditions.

To further demonstrate the utility of Fe-catalyzed cross-coupling, Fürstner and coworkers reported the total synthesis of muscopyridine (Figure 149c).⁵³⁴ Here, compound **251** was functionalized to give **254** in one pot with two different alkyl Grignards. First, **251** was treated with **250** to give intermediate **253** after reaction with more reactive C-OTf bond. Upon completion, 6-heptenylmagnesium bromide was added to the same reaction mixture to give **254** in 80% overall yield. Fürstner also utilized an iron-catalyzed cross-coupling for the total synthesis of the macrocyclic spermidine alkaloid isoconcinotine.⁵³⁵

In 2004, Fürstner and coworkers demonstrated another example of Fe-catalyzed cross-coupling for the synthesis of FTY720 (Figure 149d).⁵³⁶ Here, the coupling of aryl triflate **255** and octyl-MgBr was catalyzed by commercially available Fe(acac)₃ to give the desired product **256** in 84% yield. This reaction showcases the chemoselectivity of Fe-catalyzed reactions toward C-OTf bond in the presence of an ester functionality. In 2005, Mulzer and coworkers demonstrated the use of Pd-catalyzed Kumada cross-coupling in the total synthesis of 15-deoxy-16-(*m*-tolyl)-17,18,19,20-tetranorisocarbacyclin.⁵³⁷

Cahiez and coworkers reported an efficient route for the synthesis of terminal conjugated dienes by coupling of dienol phosphates with Grignard reagents. The methodology was used for the synthesis of *Diparopsis castanea* pheromone. The iron-catalyzed cross-coupling between **257** and alkylMgX (**258**) gave the desired product in 79% yield with excellent stereoselectivity.⁵³⁸ The sex pheromone of female moth, *Bombyx mori*, was synthesized stereospecifically by Ni-catalyzed cross-coupling of vinyl bromide with PrMgBr.⁵³⁹

10.0. Summary and Outlook

As demonstrated in this review, the use of alkylorganometallic reagents in metal-catalyzed cross-coupling has seen a rapid acceleration in the development of catalytic procedures using a wide range of coupling partners, metal catalysts, and diverse organometallics. This is highlighted by the general use of these processes to access key building blocks for synthesis and applications to complex fragment couplings in target synthesis. An especially exciting development is in the area of asymmetric catalysis where methods have been developed to set isolated alkyl chiral centers. Furthermore, recent progress in the use of iron catalysts is noteworthy.

While progress has been considerable over the last decade, in our opinion, there are numerous issues that need to be resolved, including further development of C(sp³)-C(sp³) cross-couplings to cover a broader scope (especially secondary electrophiles), enhanced scope for enantioselective variants, and understanding of the underlying processes. There clearly is a dearth of mechanistic understanding particularly in Ni- and Fe-catalyzed processes. We believe the most important synthetic developments will most likely arise from future mechanistic studies and detailed understanding.

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Biographies



Sigman Biography: Matt Sigman received a B.S. in chemistry from Sonoma State University in 1992 before obtaining his Ph.D. at Washington State University with Professor Bruce Eaton in 1996. He then moved to Harvard University to complete an NIH postdoctoral stint with Professor Eric Jacobsen. In 1999, he joined the faculty of the University of Utah where his research group has focused on the development of new synthetic methodology.



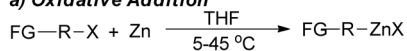
Jana Biography: Ranjan Jana is a native of India. He received his B.Sc. in Chemistry from Midnapur College (West Midnapur, India) in 2000 and M.Sc. in 2002 from Vidyasagar University. After attaining his Ph.D. in Organic Chemistry from the Indian Association for the Cultivation of Science (Kolkata, India) under the direction of Professor B. C. Ranu, Dr. Jana moved to Israel for postdoctoral studies at Bar-Ilan University under the supervision of Professor S. Braverman. He joined the Tunge at the University of Kansas and Center for Environmentally Beneficial Catalysis in 2008. Currently, he is working as a postdoctoral fellow in the Sigman group at the University of Utah and working on the development of small molecules for breast cancer therapy as well as asymmetric catalysis.



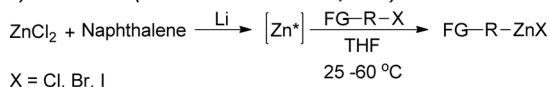
Pathak Biography: Tejas Pathak was born in Baroda, India. In 2003, he received his B.Sc. degree from Maharaja Sayajirao University of Baroda, where he received four gold medals for an excellent academic record. In 2005, he received his M.Sc. degree from the Indian Institute of Technology Madras (IIT-M) under the mentorship of Professor G. Sundarajan. Then, in 2006, he joined the Department of Chemistry at the University of Utah, where he is working in Professor Matthew Sigman's research laboratory. His current research project involves development of Pd-catalyzed asymmetric alkene difunctionalization reactions.



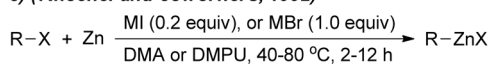
Figure 1.
Cross-Coupling of C(sp³)-Organometallics

a) Oxidative Addition

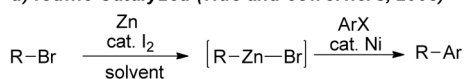
X = I, Br; FG = CH₃, CO₂R, CN, enone, halide, (RCO)₂N, (TMS)₂Si, RNH, NH₂, RCONH, (RO)₃Si, (RO)₂P(O), RS, RS(O), RSO₂, PhCOS; R = alkyl, aryl, benzyl, allyl

b) Rieke Zinc (Rieke and coworkers, 1996)

X = Cl, Br, I

c) (Knochel and coworkers, 1992)

X = Cl, Br, OMs, OTs, OP(O)(OPh)₂; M = Li, Na, Cs

d) Iodine-Catalyzed (Huo and coworkers, 2003)

R = alkyl or functionalized alkyl groups

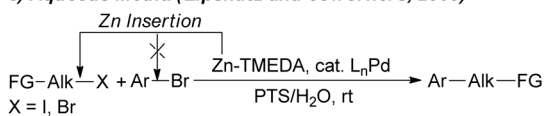
e) Aqueous Media (Lipshutz and coworkers, 2009)

Figure 2.
Standard Methods of Preparation for Alkylzincs Reagents

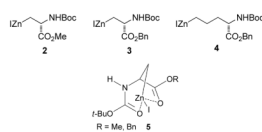


Figure 3.
 α -Amino Acid-Derived Alkylzinc Reagents (Jackson and coworkers, 1998)

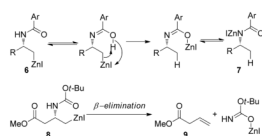


Figure 4.
Decomposition of Amino Acid Derived Alkylzinc Reagents (Jackson and coworkers, 2008)

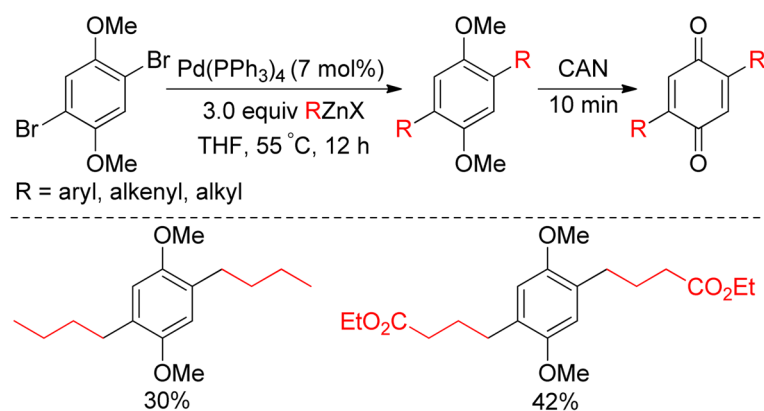


Figure 5. Synthesis of Symmetrical 2,5-dialkyl Benzoquinones via Negishi Coupling (Bäckvall and coworkers, 1998).

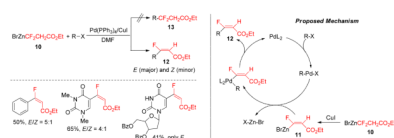


Figure 6.
Negishi Coupling of Ethyl 3-bromo-3,3-difluoropropionate (Qing and coworkers, 2000)

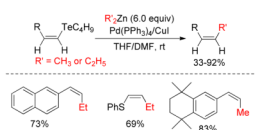


Figure 7.
Negishi Coupling of Unsaturated Organotellurium Compounds (Dabdoub, and coworkers, 2000)

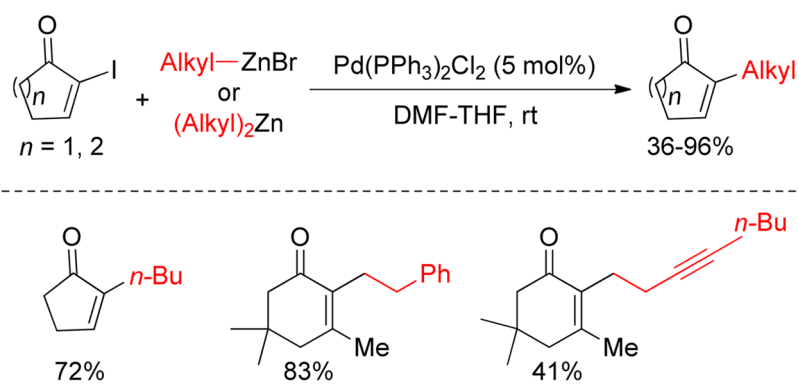


Figure 8.
Negishi Coupling of Cyclic α -Iodoenones (Negishi and coworkers, 2000)

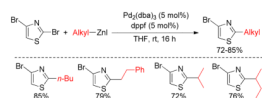


Figure 9.
Regioselective Negishi Coupling of 2,4-Dibromothiazoles (Bach and coworkers, 2002)

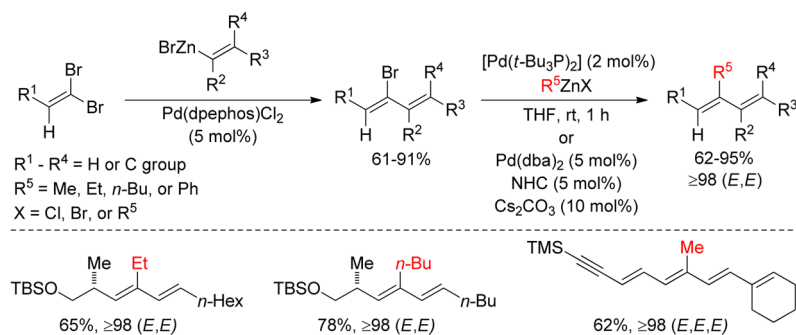
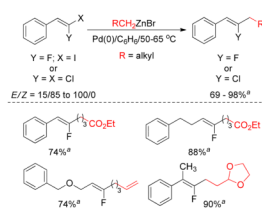


Figure 10.
Stereoselective Negishi Couplings (Negishi and coworkers, 2004)

**Figure 11.**

Negishi Coupling of Dihalalkenes (Wnuk and coworkers, 2006)

^aisolated yields were based on *E*-isomer only.

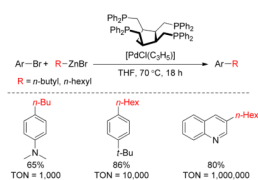


Figure 12.
High TON in Pd(0)-Catalyzed Negishi Couplings (Doucet and coworkers, 2006)

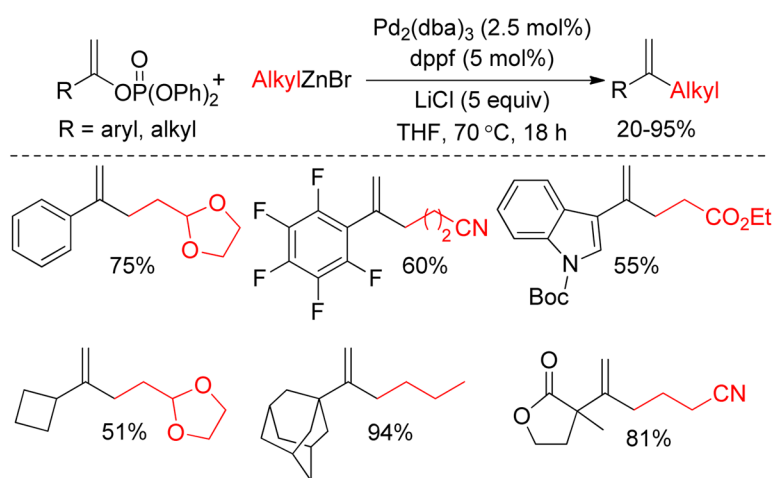


Figure 13.
Negishi Coupling of Alkenyl Phosphates: (Skrydstrup and coworkers, 2007)

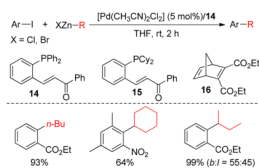


Figure 14.
Negishi Coupling using π -Acceptor Ligands (Lei and coworkers, 2007)

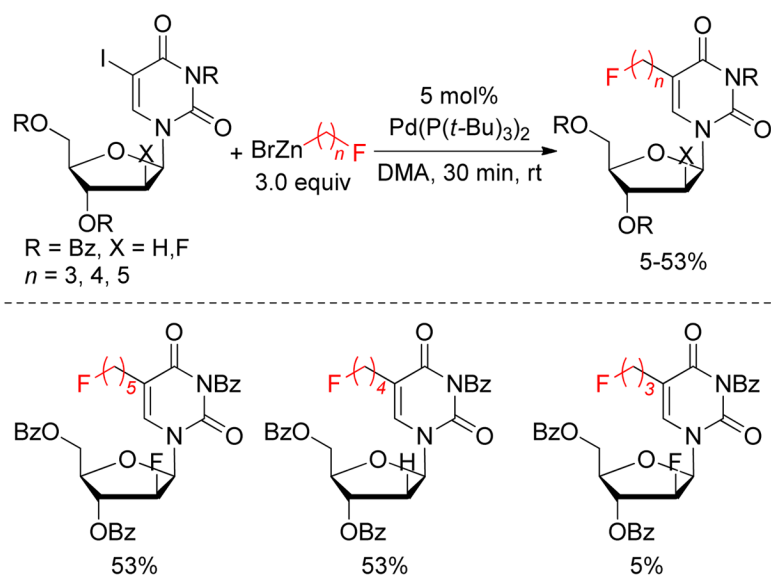


Figure 15.
Negishi Coupling of 5-iodo-pyrimidine Nucleosides (Kung and coworkers, 2008)

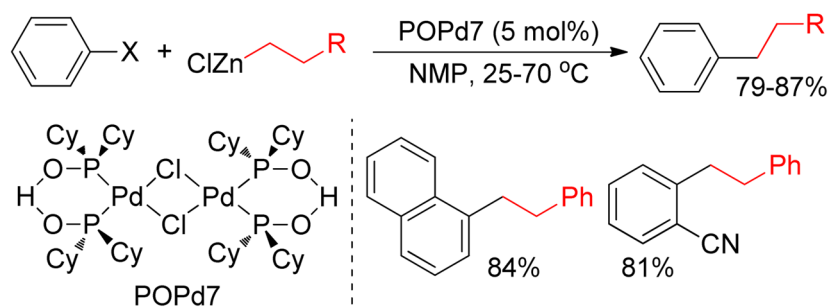


Figure 16.
Pd-phosphinous Acid-Catalyzed Negishi Couplings (Wolf and coworkers, 2008)

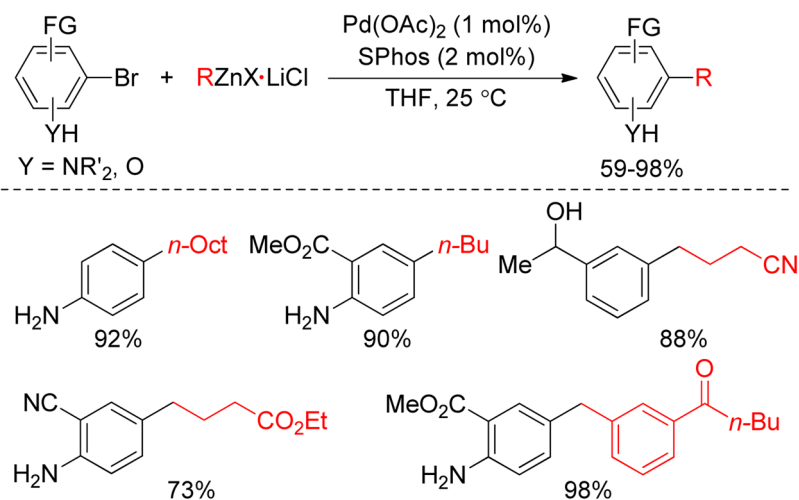
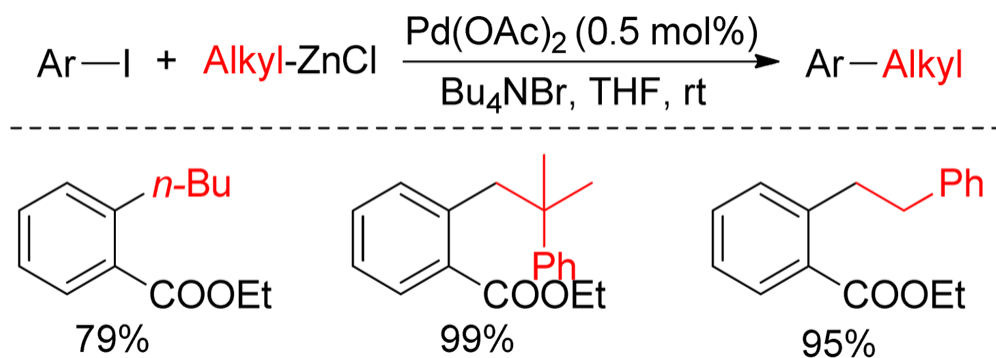


Figure 17.
Negishi Coupling of Aryl Halides Bearing Acidic Protons (Knochel and coworkers, 2008)

**Figure 18.**

Pd-nanoparticle-catalyzed Negishi couplings (Lei and coworkers, 2008)

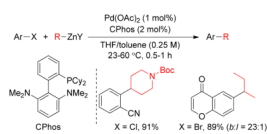


Figure 19.
Negishi Coupling of Secondary Alkylzinc Halides (Buchwald and coworkers, 2009)

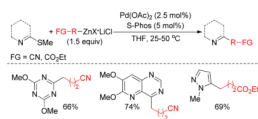


Figure 20.
Negishi Coupling of Thiomethyl-substituted Heterocycles (Knochel and coworkers, 2009)

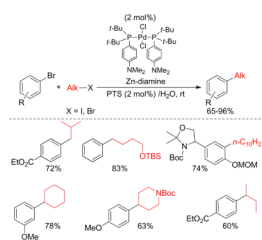


Figure 21.
Negishi Couplings in Aqueous Medium (Lipshutz and coworkers, 2009)

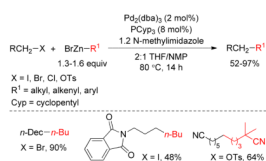


Figure 22.
Negishi Coupling with Unactivated Alkyl Halides and Tosylates (Fu and coworkers, 2003)



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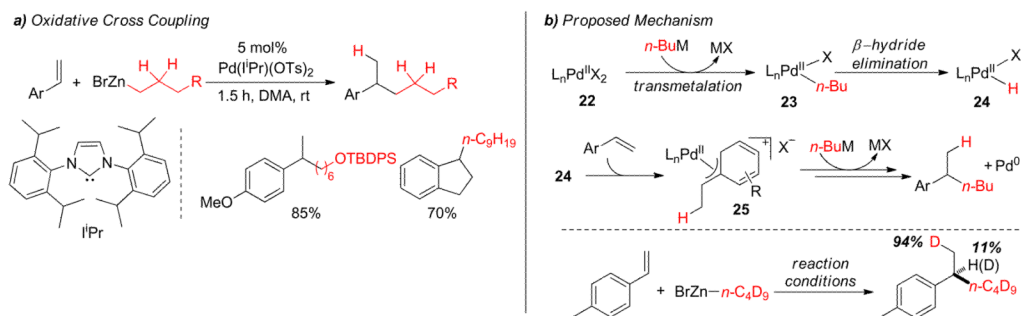


Figure 24.
Oxidative C(sp³)-C(sp³) Coupling (Sigman and coworkers, 2009)

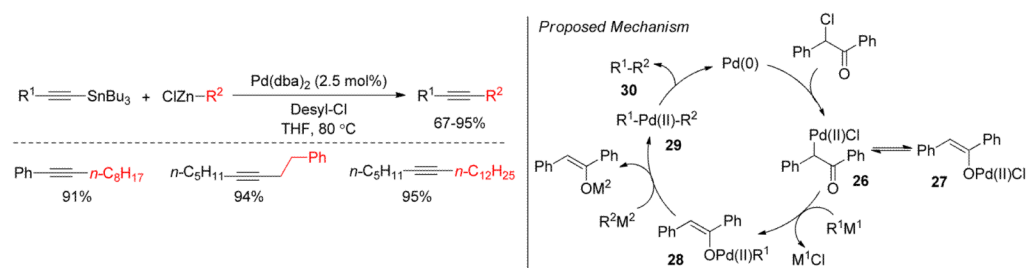


Figure 25.
Oxidative Cross-Coupling through Double Transmetalation (Lei and coworkers, 2006)

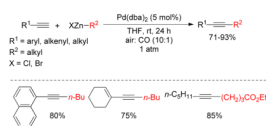


Figure 26.
Oxidative Cross-Coupling with Terminal Alkynes (Lei and coworkers, 2010)

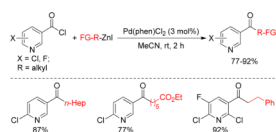


Figure 27.
Formation of Ketones via Negishi Coupling (Ohno and coworkers, 2009)

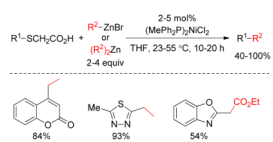


Figure 28.
Negishi Coupling of Thioglycolic Acids (Liebeskind and coworkers, 1999)

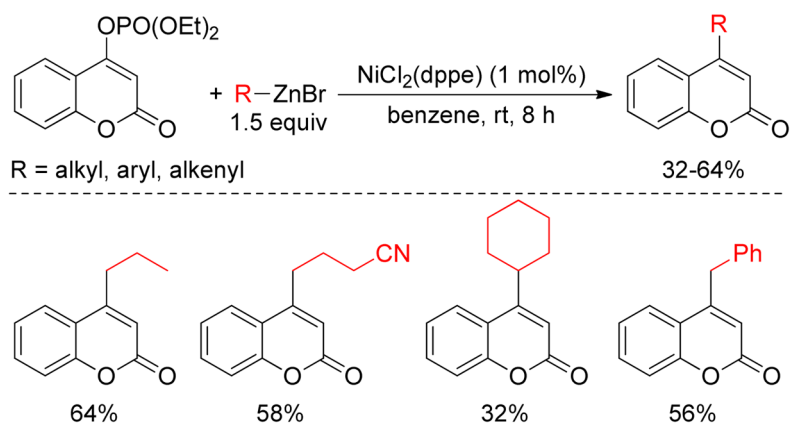


Figure 29.
Negishi Coupling of 4-diethylphosphonoxycoumarins (Yang and coworkers, 2001)



Figure 30.
Negishi Coupling of Amino-heteroaryl Chlorides (Walters, 2005)

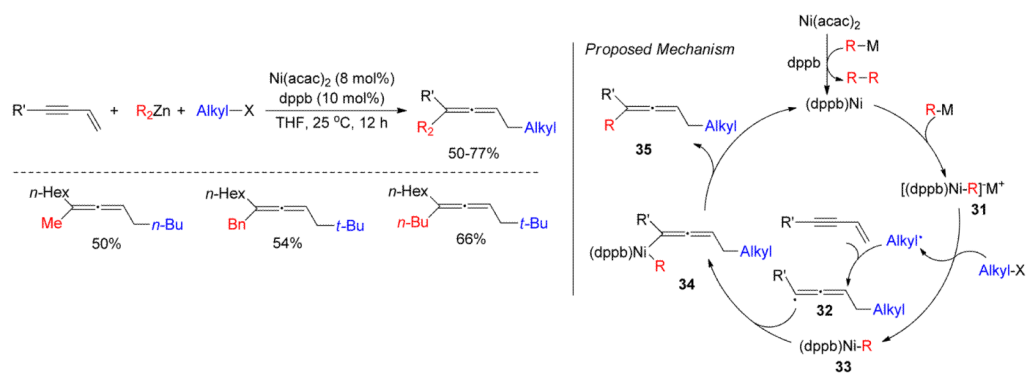


Figure 31.
Ni-Catalyzed Three-Component Coupling (Terao and coworkers, 2009)

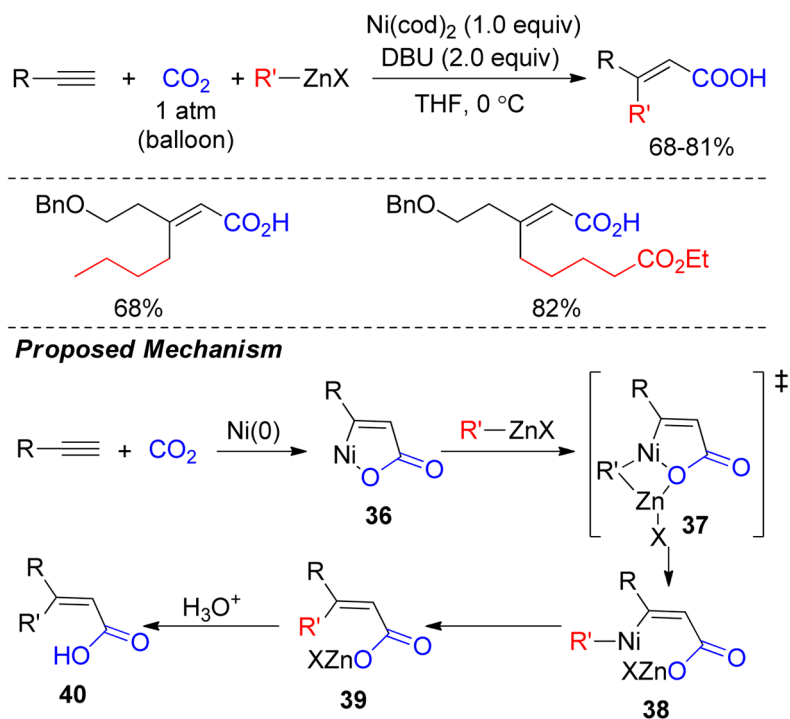


Figure 32.
Alkylative Carboxylation of Alkynes (Mori and coworkers, 2001)

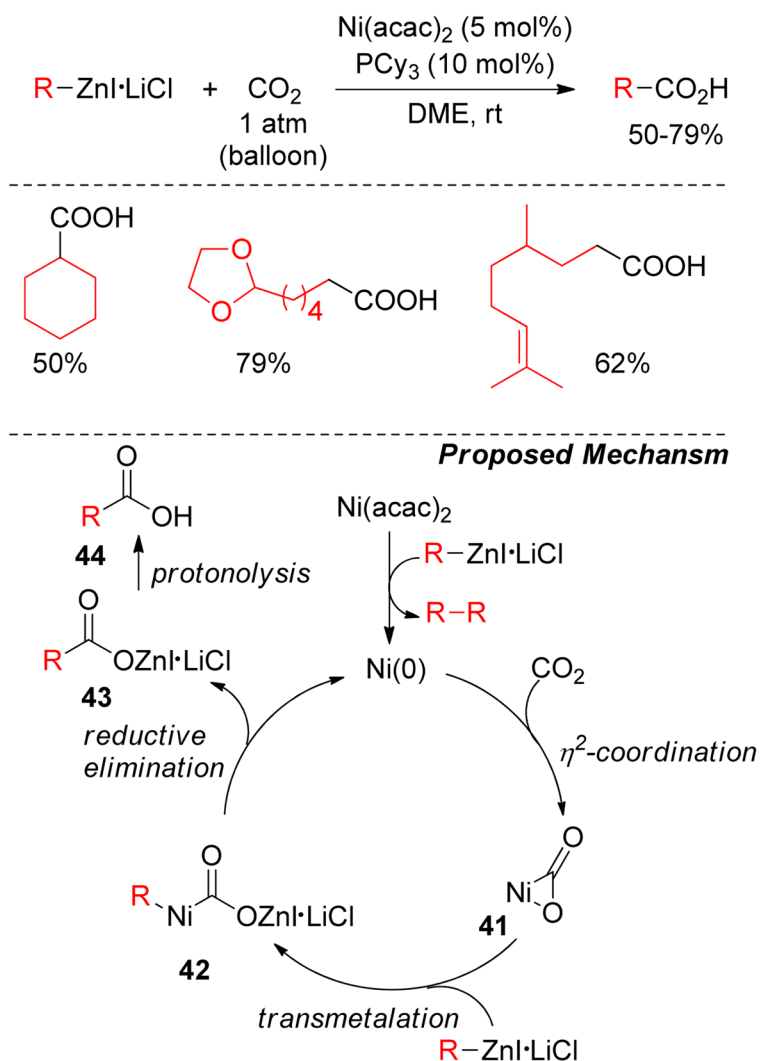


Figure 33.
Carboxylation of Alkylzinc Reagents (Oshima and coworkers, 2008)

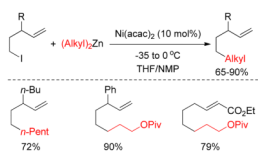


Figure 34.
Substrate-Controlled Alkyl-Alkyl Negishi Coupling (Knochel and coworkers, 1996)

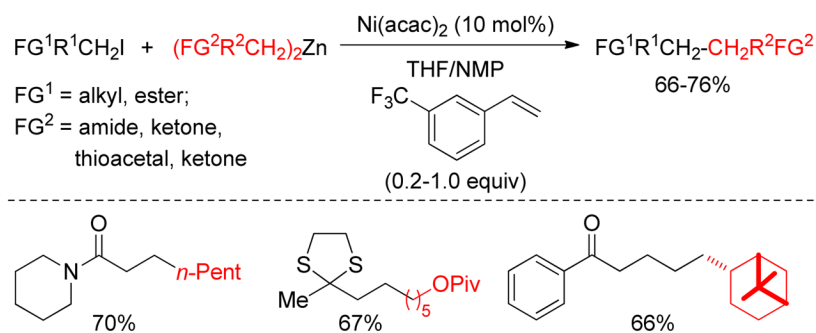
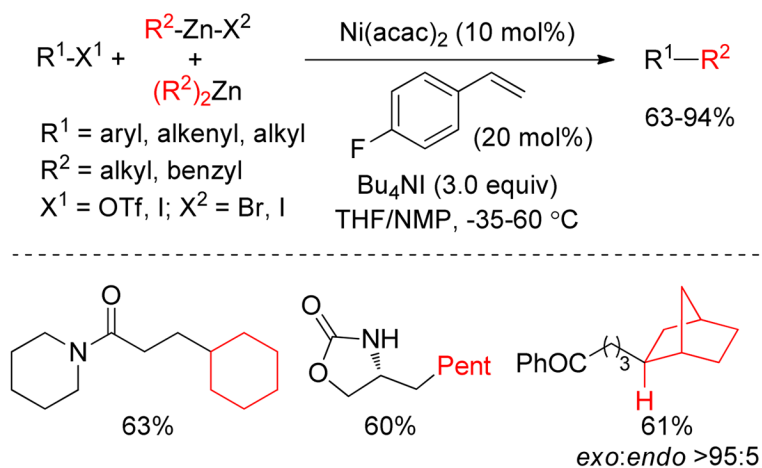


Figure 35.
 Ni-Catalyzed Alkyl-Alkyl Negishi Couplings (Knochel and coworkers, 1998)

**Figure 36.**

Ni-Catalyzed Alkyl-Alkyl Negishi Couplings (Knochel and coworkers, 2002)

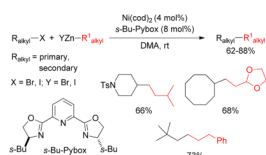


Figure 37.
Negishi Coupling of Secondary Alkyl Halides (Fu and coworkers, 2003)

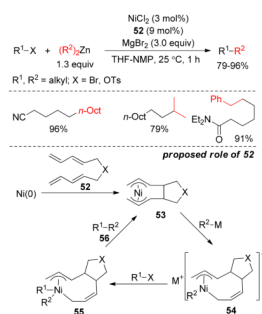


Figure 38.
1,3,8,10-Tetraenes in Negishi Coupling (Kambe and coworkers, 2004)

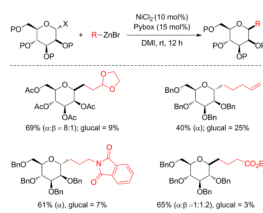


Figure 39.
C1-Alkylation of Glycosides (Gagné and coworkers, 2007)

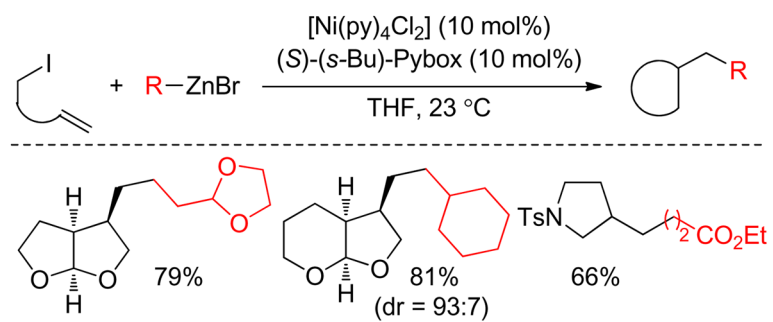


Figure 40.
Ni-Catalyzed Radical Cyclization (Cárdenas and coworkers, 2007)

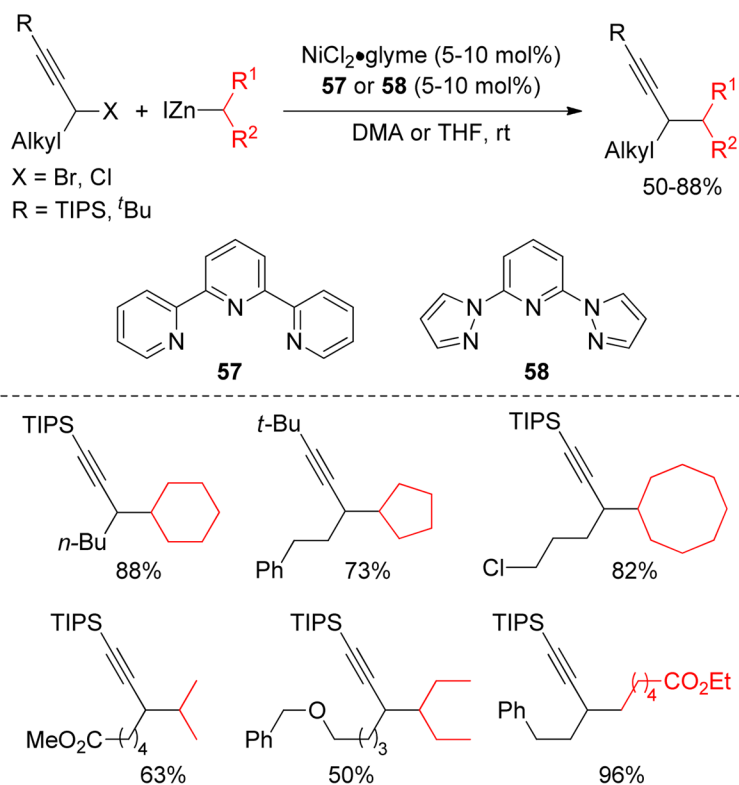


Figure 41.
Secondary-Secondary Negishi Couplings (Fu and coworkers, 2008)

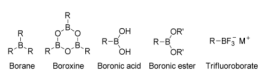
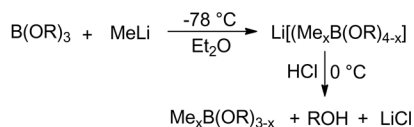
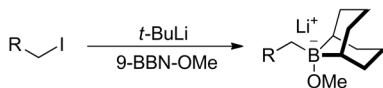
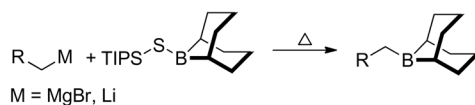
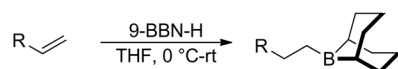
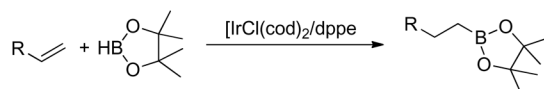
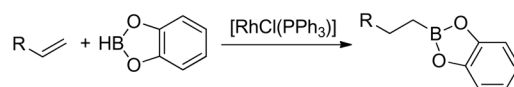
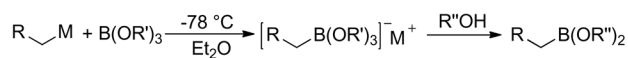
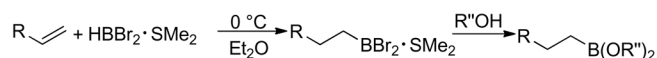


Figure 42.
Various Organoboron Reagents

Brown and coworkers, 1983**Marshall and coworkers, 1998****Soderquist and coworkers, 2000****Brown and coworkers, 1975****Nöth, 1985; Miyaura, 2004****Brown and coworkers, 1983**

M = Li, MgX

R''OH = H₂O, alcohol or diol

M = Li, MgX

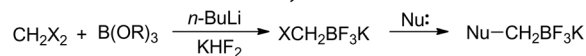
R''OH = H₂O, alcohol or diol**Molander and coworkers, 2006**

Figure 43.
Preparation of Common Alkylboron Reagents

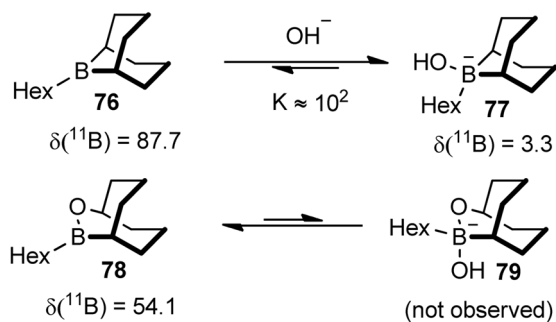
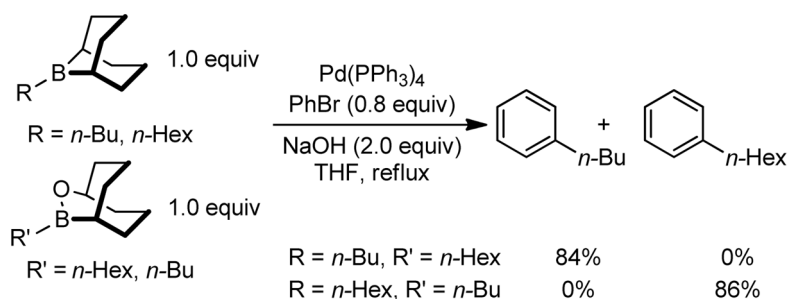


Figure 44.
Rate-Dependence on Boron Derivatives (Soderquist and coworkers, 1998)

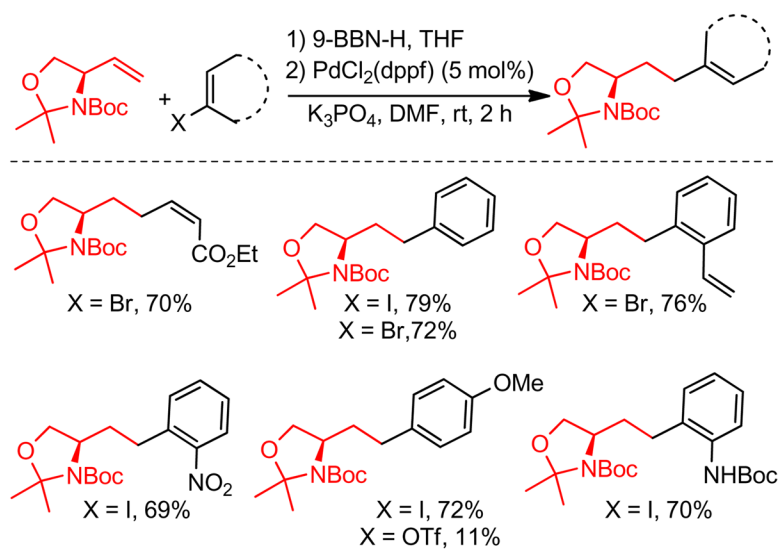


Figure 45.
Suzuki-Miyaura Coupling on Amino Acid Synthons (Taylor and coworkers, 1999)

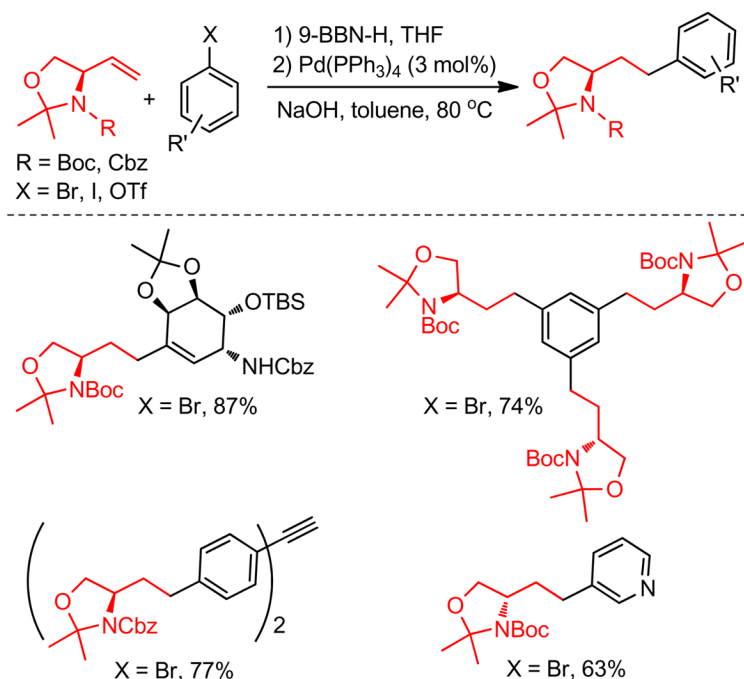


Figure 46. Suzuki-Miyaura Coupling on Amino Acid Synthons (Johnson and coworkers, 2000)

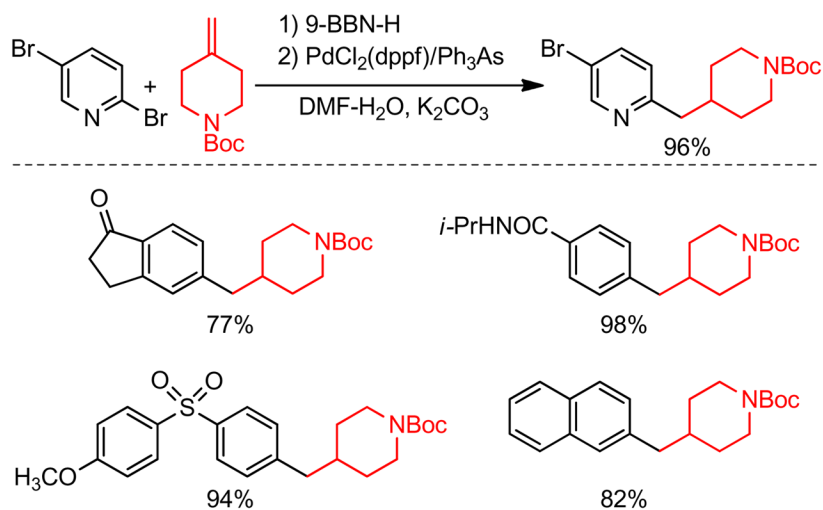


Figure 47.
Cross-Coupling with *N*-Boc-4-methylene Piperidines (Vice and coworkers, 2001)

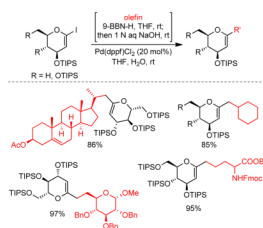


Figure 48.
Suzuki Coupling on C1-iodo-glycals (Tan and coworkers, 2004)

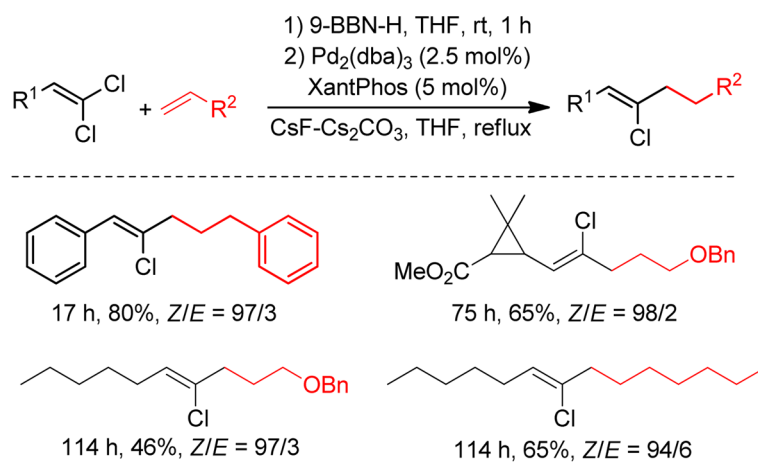


Figure 49.
Suzuki Coupling for Selective Monoalkylations (Roulland and coworkers, 2007)

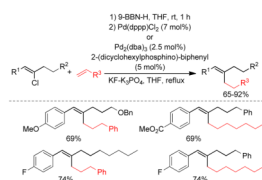


Figure 50.
Suzuki Coupling for the Synthesis of Trisubstituted Olefins (Roulland and coworkers, 2007)

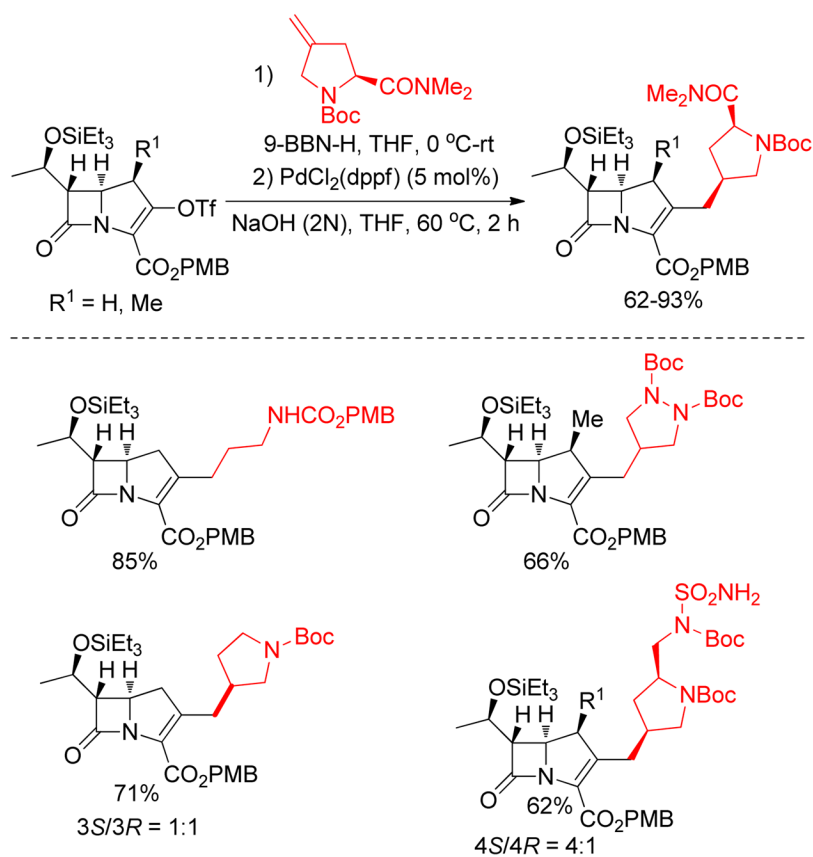


Figure 51.
Suzuki Coupling in Carbapenem Analog Synthesis (Narukawa and coworkers, 1997)

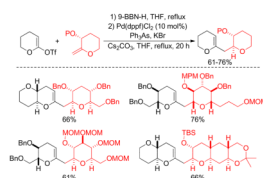


Figure 52.
Suzuki Coupling in Polyether Synthesis (Sasaki and coworkers, 1998)

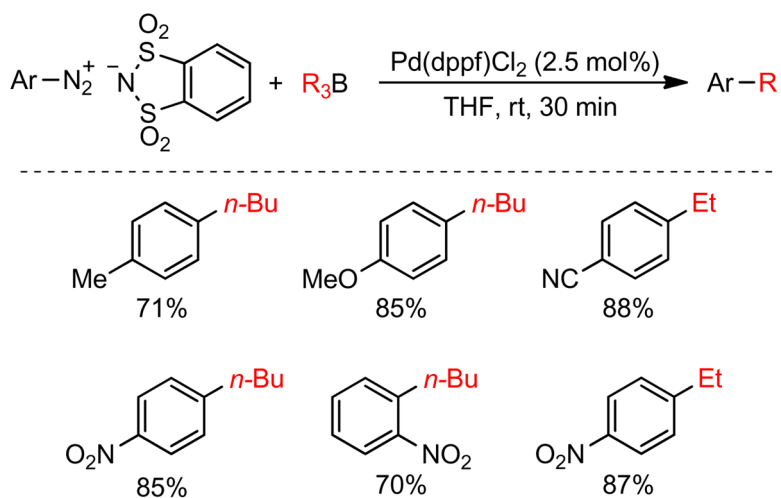


Figure 53. Suzuki Coupling with Arenediazonium *o*-benzenesulfonamides (Dughera and coworkers, 2008)

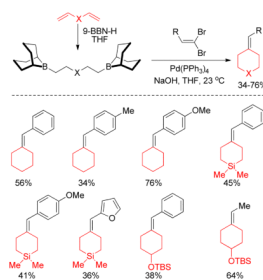


Figure 54. Formation of Six-Membered Rings with Exocyclic Double Bonds (Soderquist and coworkers, 1995)

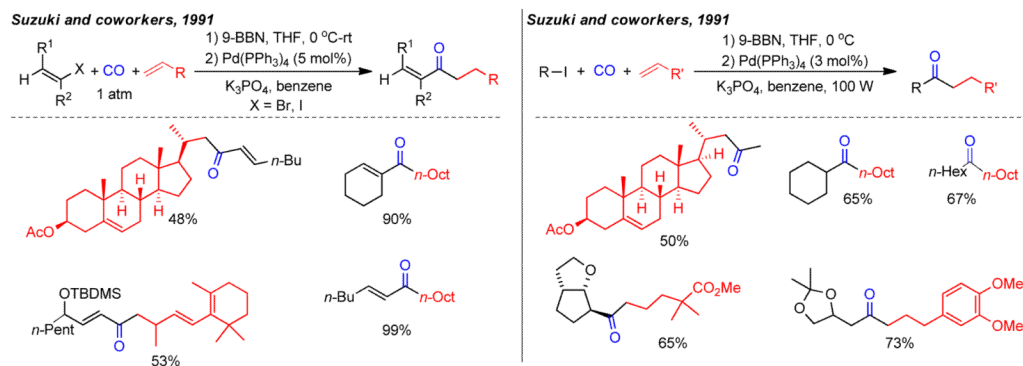


Figure 55.
Carbonylative Suzuki-Miyaura Couplings

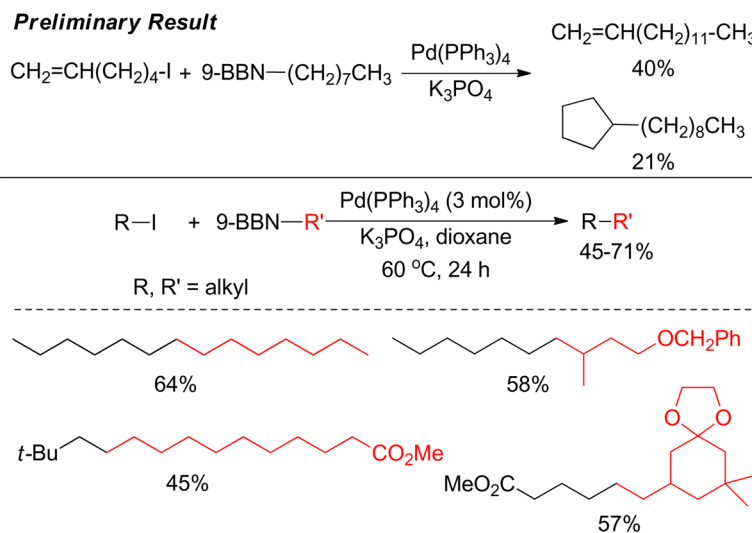
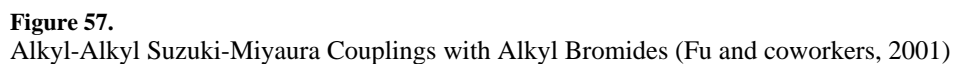


Figure 56.
Radical Oxidative Addition (Suzuki and coworkers, 1992)



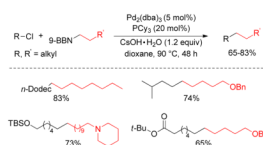


Figure 58.
Alkyl-Alkyl Suzuki-Miyaura Couplings with Alkyl Chlorides (Fu and coworkers, 2002)

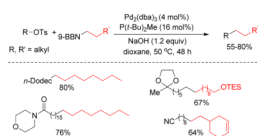
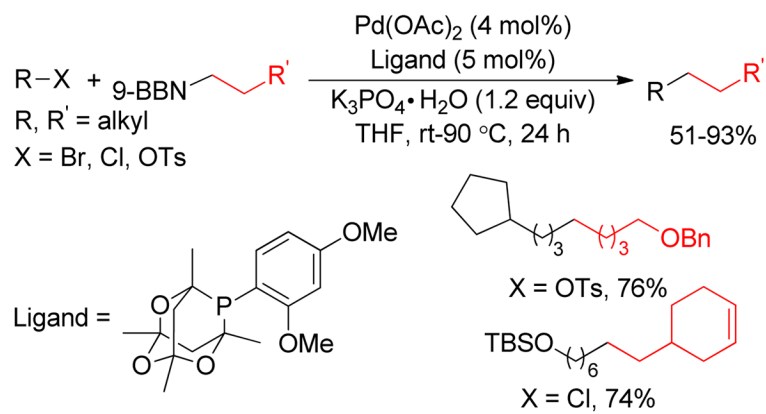


Figure 59.
Alkyl-Alkyl Suzuki Couplings with Alkyl Tosylates (Fu and coworkers, 2002)

**Figure 60.**

Alkyl-alkyl Suzuki-Miyaura Couplings with Alkyl Halides (Capretta and coworkers, 2004)

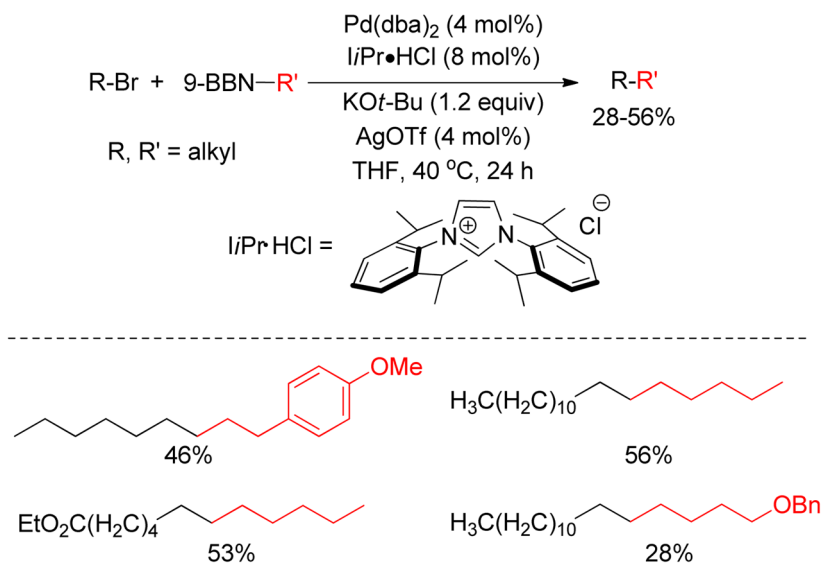


Figure 61.
Alkyl-Alkyl Suzuki Coupling with Alkyl Iodides (Caddick and coworkers, 2004)

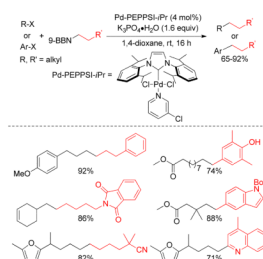


Figure 62.
Alkyl-alkyl Suzuki couplings with alkyl halides (Organ and coworkers, 2008)

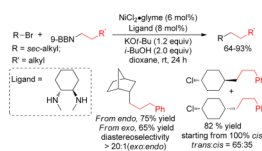


Figure 63.
Alkyl-Alkyl Suzuki-Miyaura Couplings with Secondary Alkyl Bromides (Fu and coworkers, 2007)

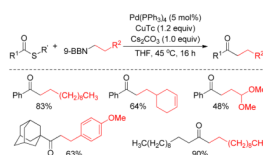


Figure 64.
Formation of Ketones from Thioesters (Liebeskind and coworkers, 2004)

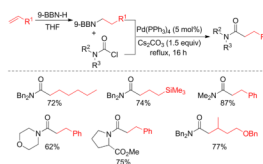


Figure 65.
Formation of Amides from Carbamoyl Chlorides (Takemoto and coworkers, 2007)

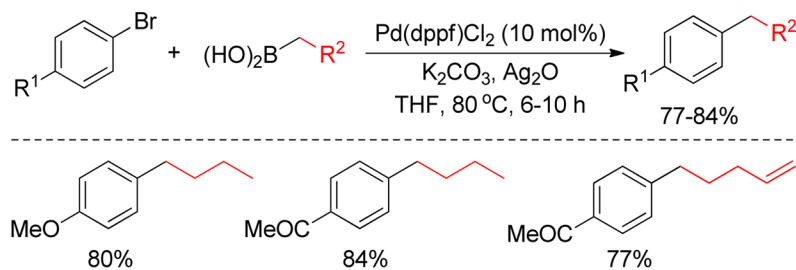


Figure 66.
Suzuki-Miyaura Coupling of Alkylboronic Acids (Falck and coworkers, 2001)

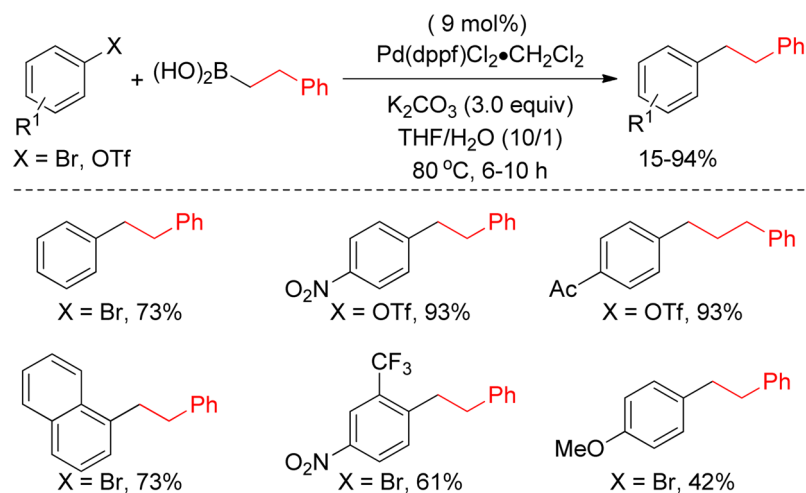


Figure 67. Suzuki Coupling of Phenethylboronic Acids (Molander and coworkers, 2002)

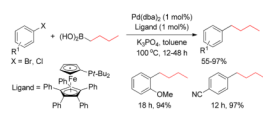


Figure 68.
Suzuki Coupling with Aryl Halides (Hartwig and coworkers, 2002)

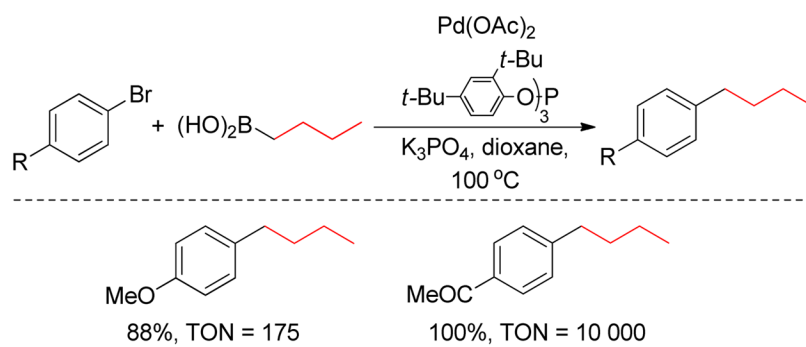


Figure 69.
Suzuki Coupling with Phosphite Ligands (Bedford and coworkers, 2003)

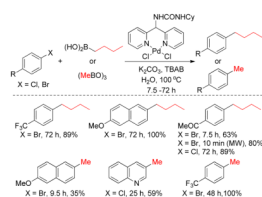


Figure 70.
Suzuki Coupling in Aqueous Medium (Nájera and coworkers, 2004)

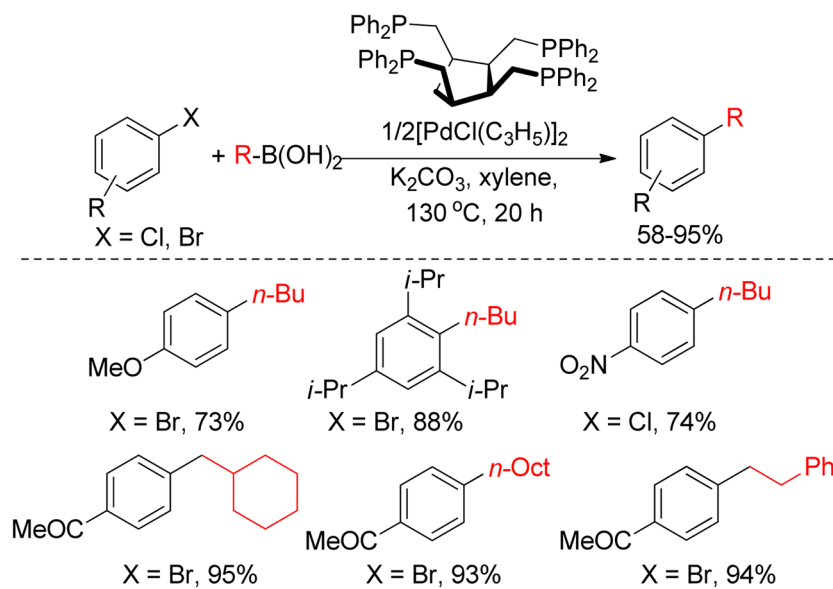


Figure 71.
Suzuki Coupling with Tedicyp Ligand (Doucet and coworkers, 2004)

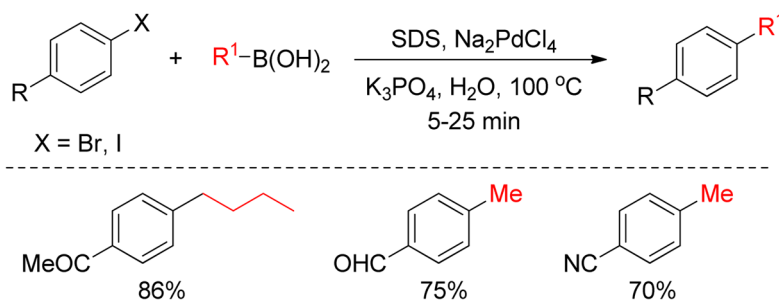


Figure 72.
Pd Nanoparticle-Catalyzed Suzuki Couplings (Ranu and coworkers, 2009)

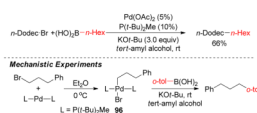


Figure 73.
Alkyl-Alkyl Suzuki Couplings with Alkylboronic Acids (Fu and coworkers, 2002)

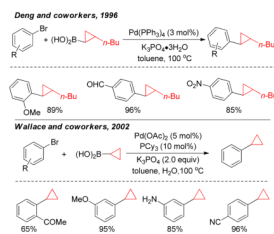


Figure 74.
Suzuki Coupling with Substituted Cyclopropylboronic Acids.

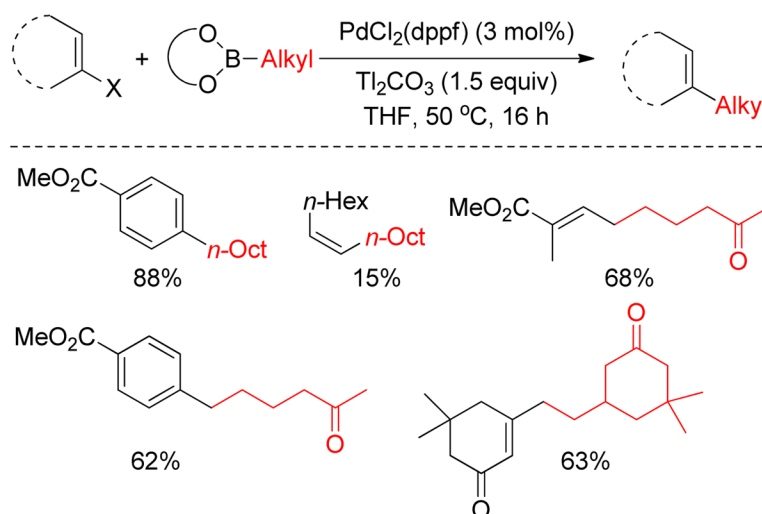


Figure 75.
Suzuki Coupling with Alkylboronic Esters (Suzuki and coworkers, 1989)

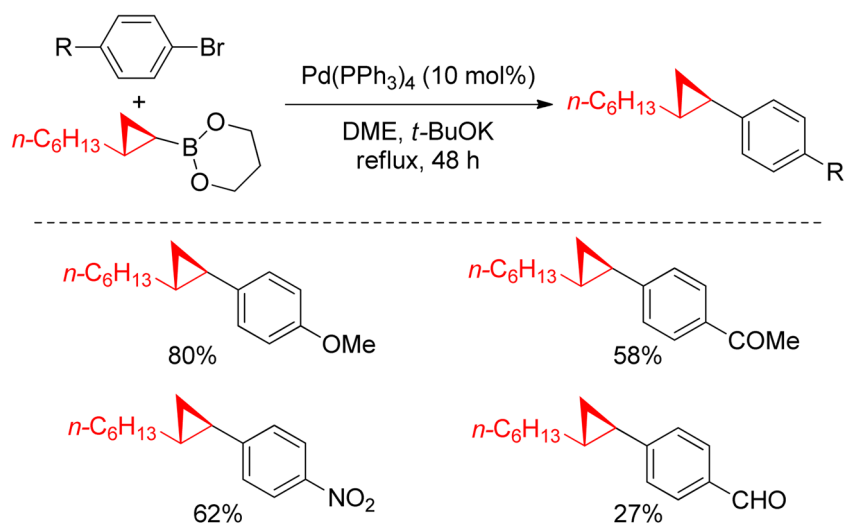


Figure 76.
Suzuki Coupling with Cyclopropylboronic Esters (Marsden and coworkers, 1996)

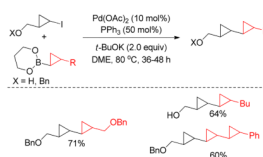


Figure 77.
Suzuki Coupling with Cyclopropylboronic Esters (Charette and coworkers, 1997)

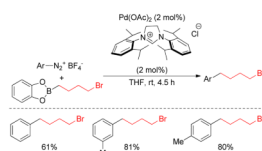


Figure 78.
Suzuki Coupling with Catecholboranes (Andrus and coworkers, 2001)

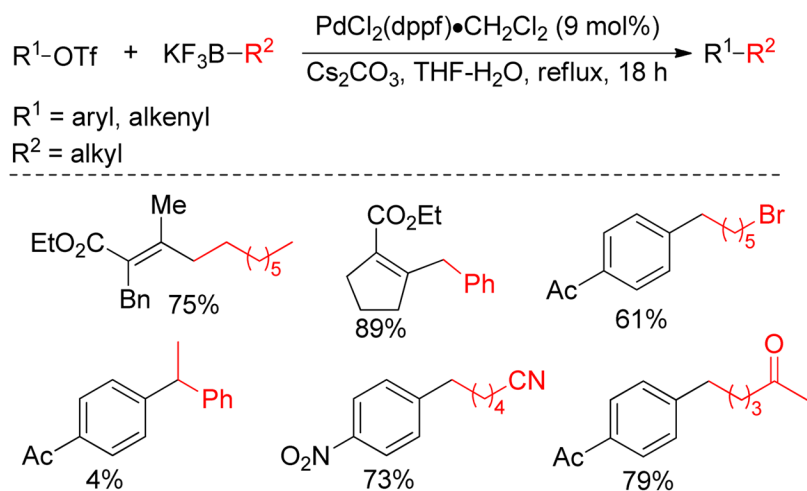


Figure 79. Suzuki Coupling with Alkyl Potassium Trifluoroborates (Molander and coworkers, 2001)

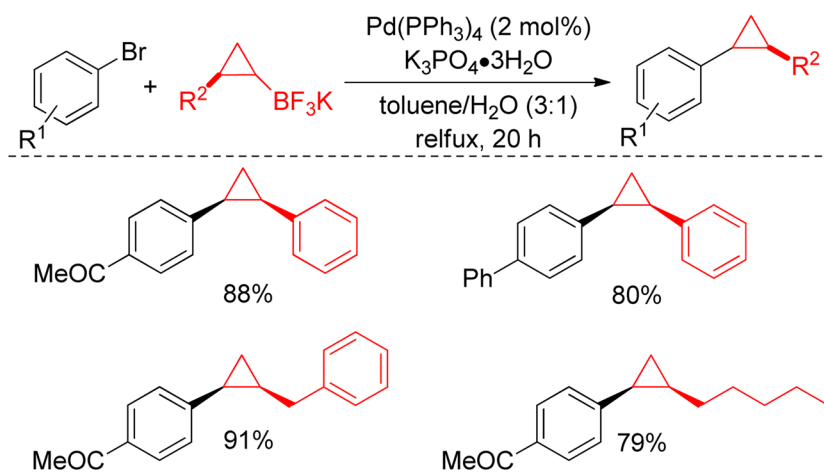


Figure 80.
Suzuki Coupling with Potassium Trifluoroborates (Deng and coworkers, 2004)

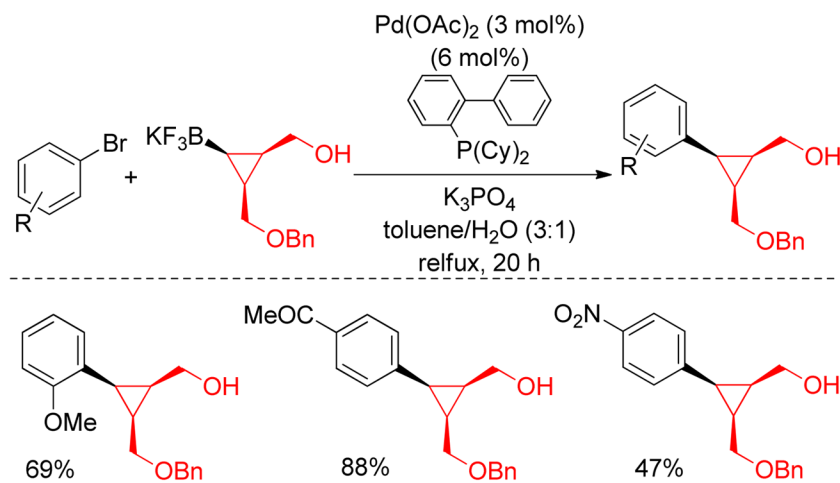


Figure 81. Suzuki Coupling with Substituted Cyclopropyl Potassiumtrifluoroborates (Charette and coworkers, 2005)

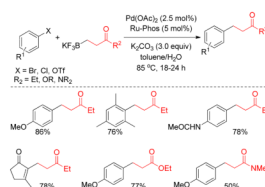


Figure 82.
Suzuki Coupling with Potassium Trifluoroborato-homoenolates (Molander and coworkers, 2008)

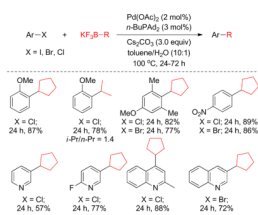


Figure 83. Suzuki Coupling with Secondary Potassiumtrifluoroborates (Molander and coworkers, 2008)

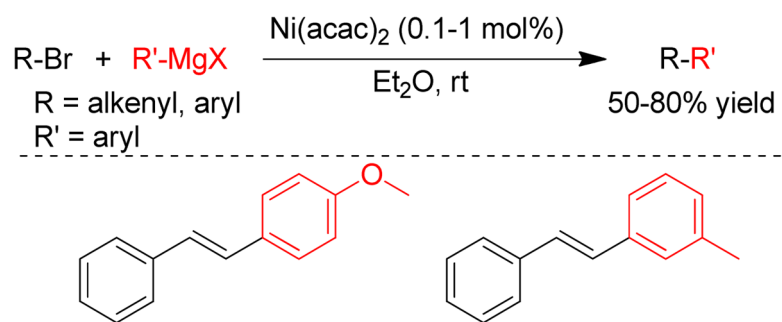


Figure 84.
Seminal Report (Corriu and Masse, 1972)

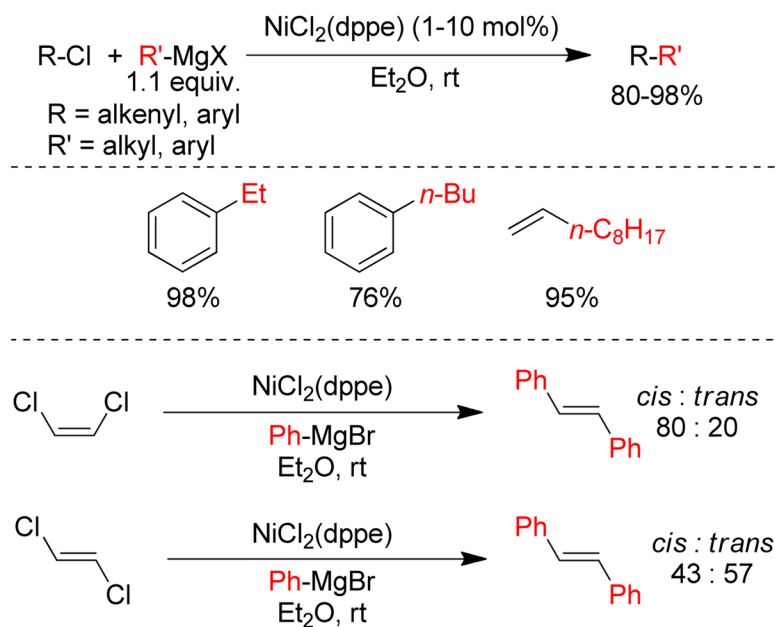
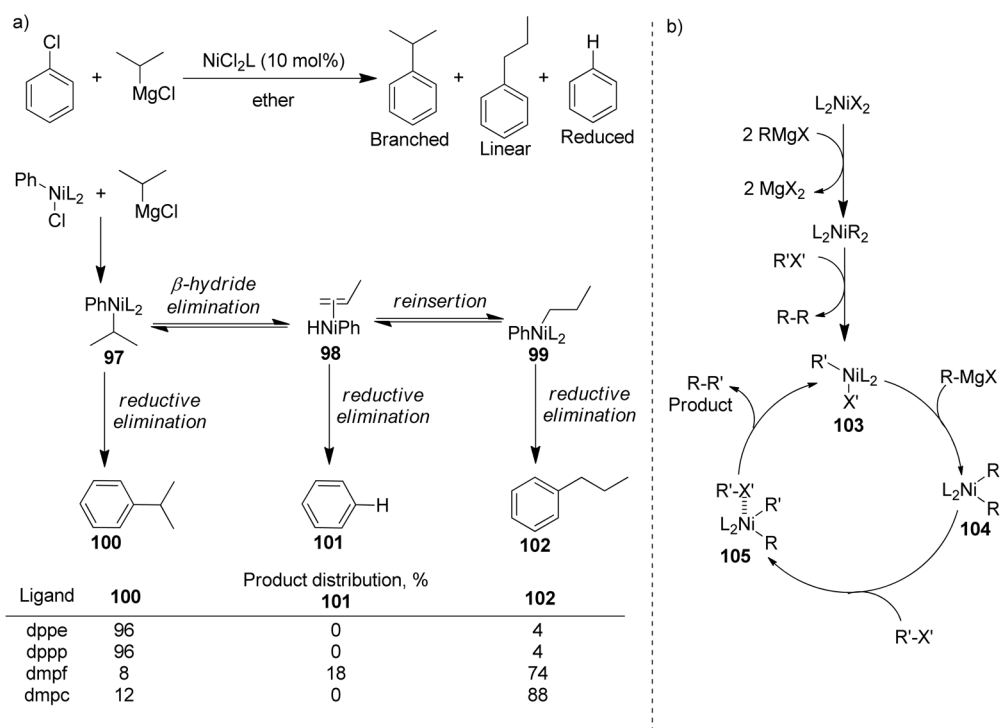


Figure 85.
Seminal report (Kumada and coworkers, 1972)

**Figure 86.**

a) Mechanistic Studies, b) Proposed Mechanism

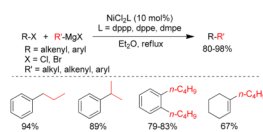


Figure 87.
Cross-Coupling of Aryl and Alkenyl Halides (Kumada and coworkers, 1976)

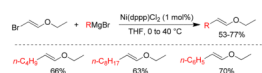


Figure 88.
Cross-Coupling of β -bromovinylethers (Kumada and coworkers, 1976)

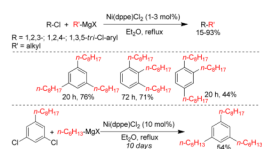


Figure 89.
Trialkylation of Trichlorobenzenes (Tamborski and coworkers, 1983)

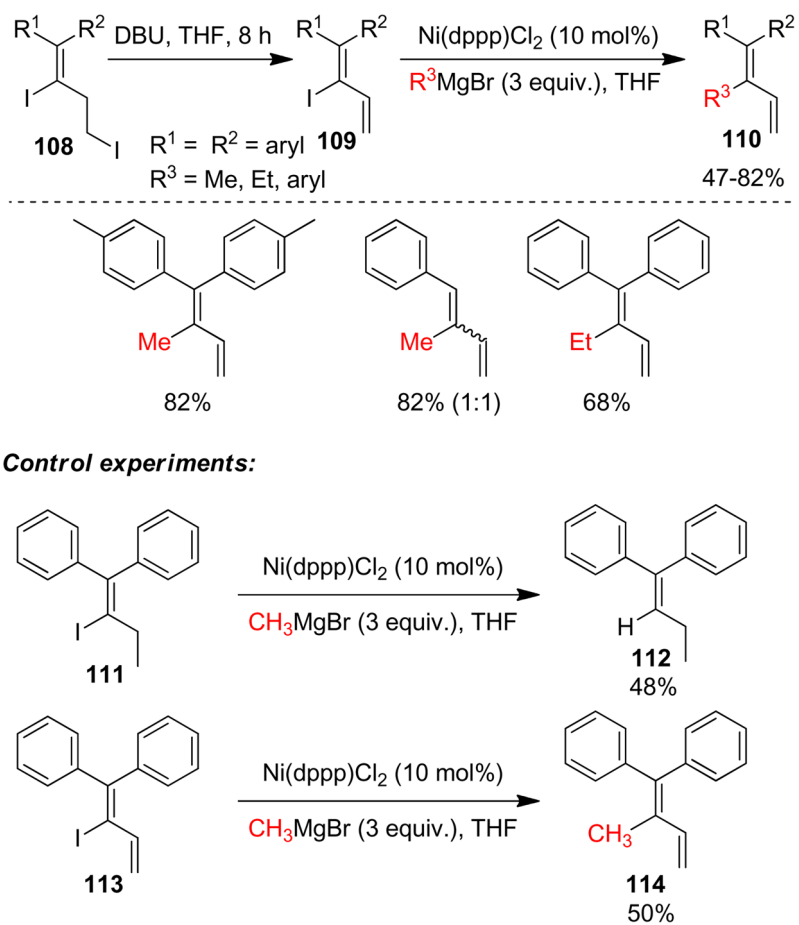


Figure 90.
Synthesis of Multi-substituted 1,3-Butadienes (Shi and Shao, 2005)

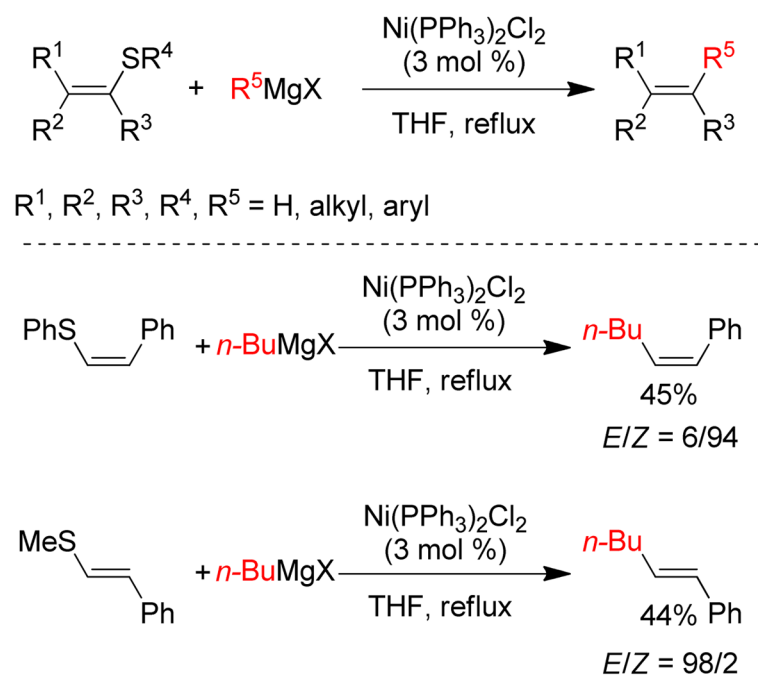


Figure 91.
Alkylation of Organosulfides (Takei and coworkers, 1979)

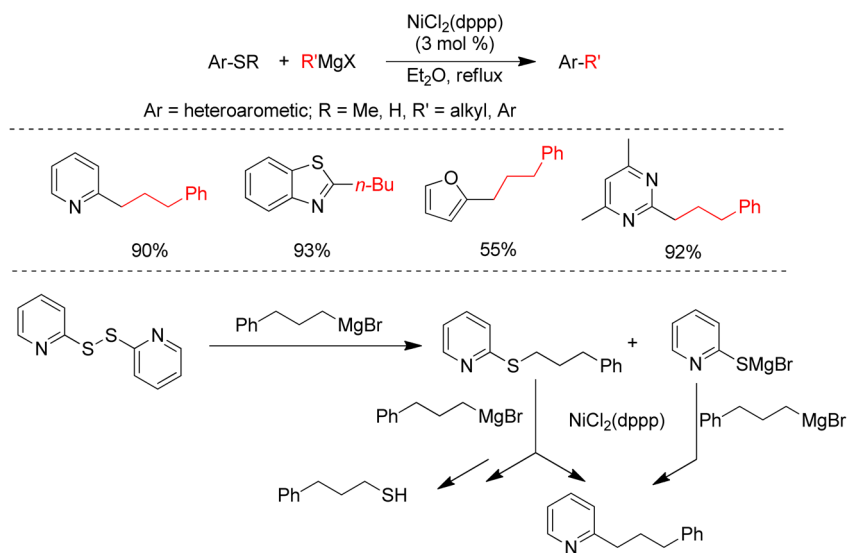


Figure 92.
Scope and Proposed Mechanism (Takei and coworkers, 1979)

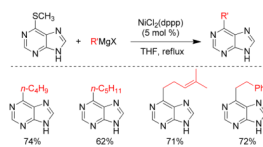


Figure 93.
Synthesis of Substituted Purines (Takei and coworkers, 1985)

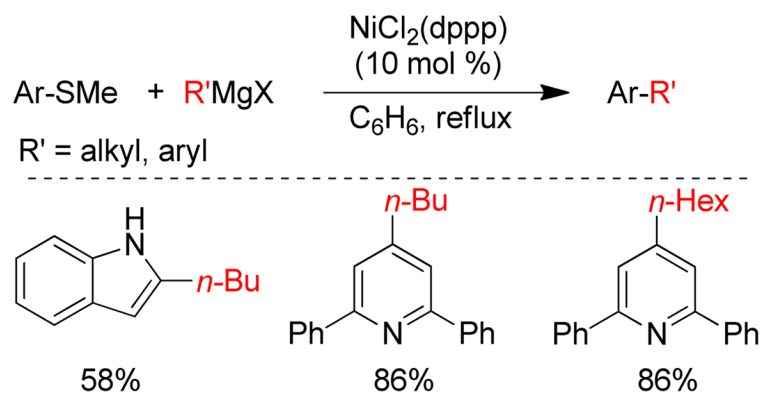


Figure 94. Cross-Coupling of Thioaryls with Grignard reagents (Wenkert and coworkers, 1985)

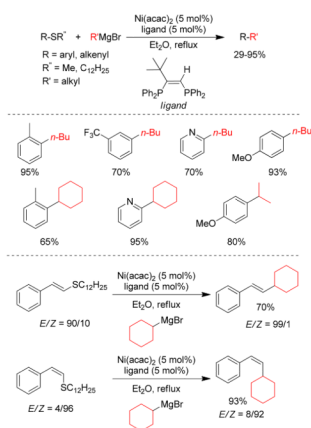


Figure 95.
Cross-Coupling of Sulfides with Alkyl Grignards (Oshima and coworkers, 2008)

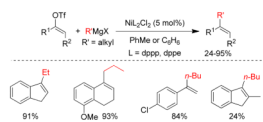


Figure 96.
Cross-Coupling of Vinyl Triflates (Fiaschisi and coworkers, 1999)

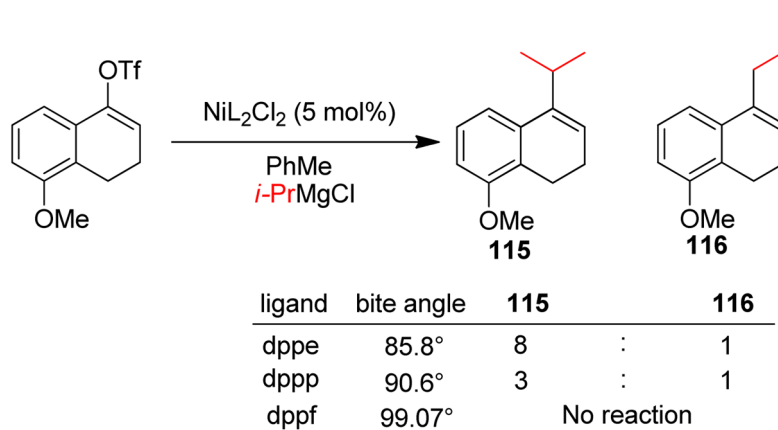


Figure 97.
Effect of Ligand Bite Angle on Product Distribution

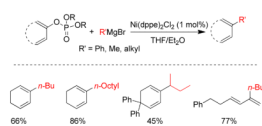


Figure 98.
Synthesis of Substituted Dienes (Bäckvall and coworkers, 1999)

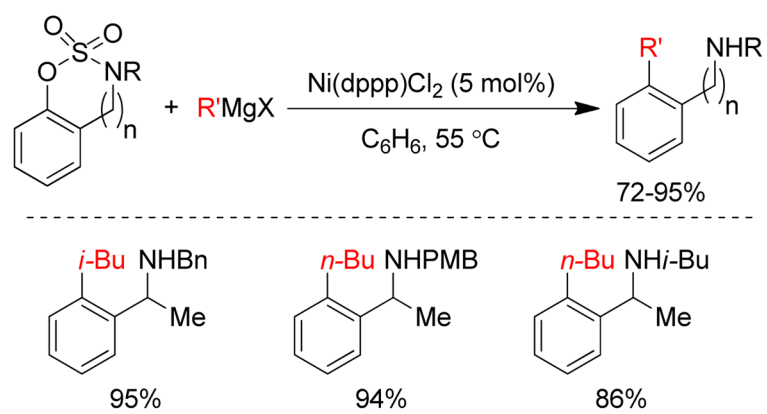


Figure 99.
DuBois and coworkers, 2005

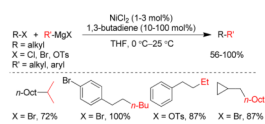


Figure 100.
C(sp³)-C(sp³) Cross-Coupling Reaction (Kambe and coworkers, 2002)

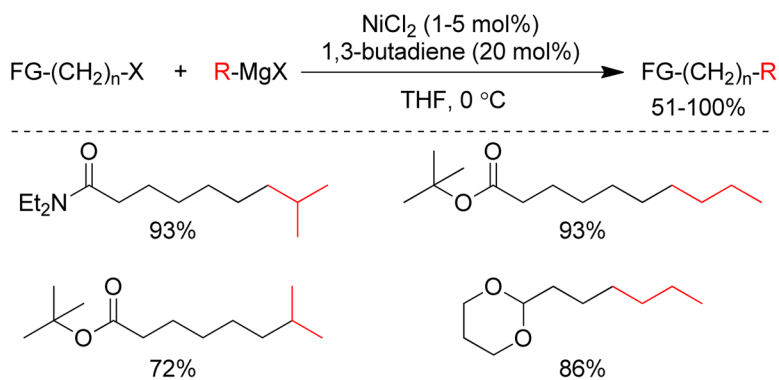


Figure 101.
Scope of Reaction (Kambe and coworkers, 2009)

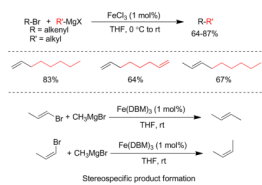


Figure 102.
Seminal Report (Kochi, 1971)

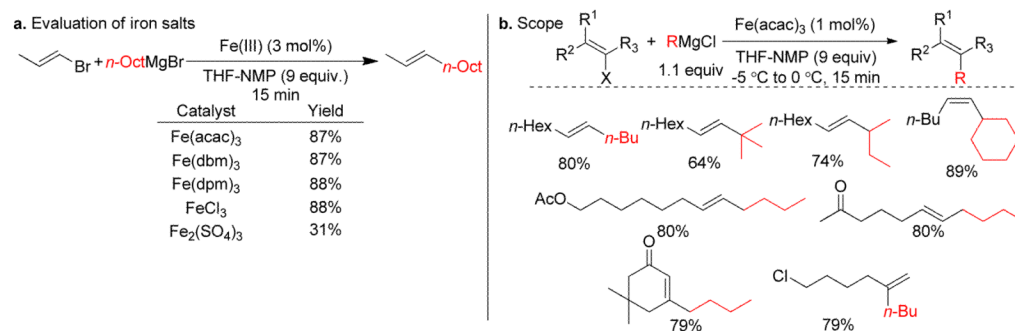


Figure 103.
 Scope (Cahiez and Coworkers, 1998)

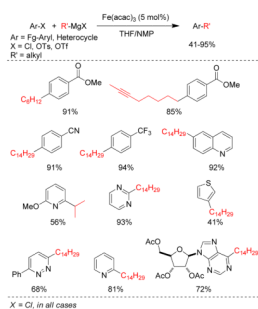


Figure 104.
Scope of Iron-Catalyzed Cross-Coupling (Füerstner and coworkers, 2002)

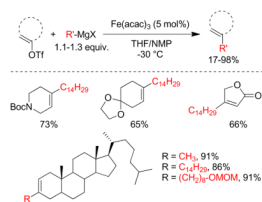


Figure 105.
Cross-Coupling Reaction with Vinyl Triflates (Fürstner and coworkers, 2004)

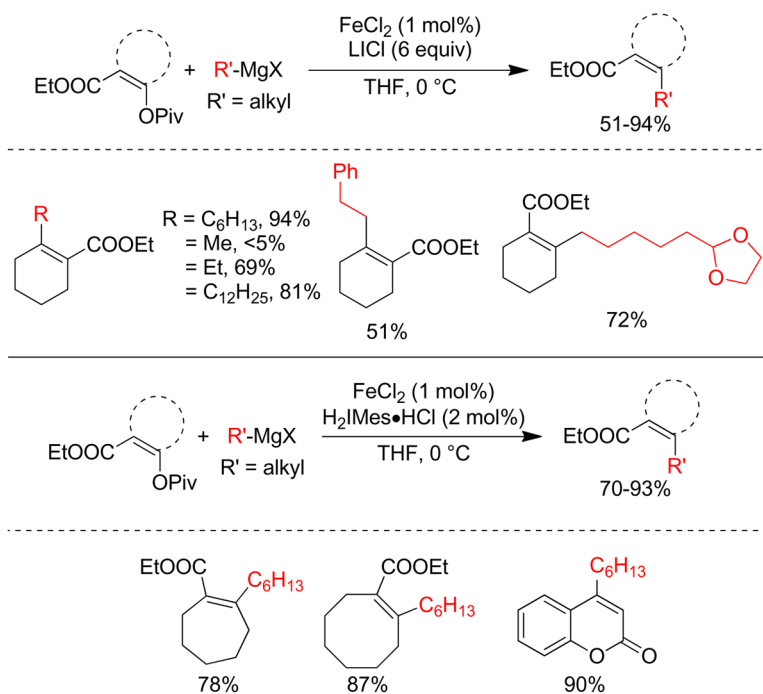


Figure 106.
Cross-Coupling of Alkenyl Carboxylates with Grignard Reagents (Shi and coworkers, 2009)

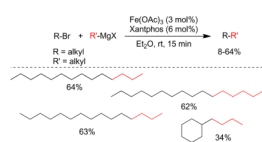


Figure 107.
Iron-catalyzed C(sp³)-C(sp³) Coupling Reaction (Chai and coworkers, 2007)

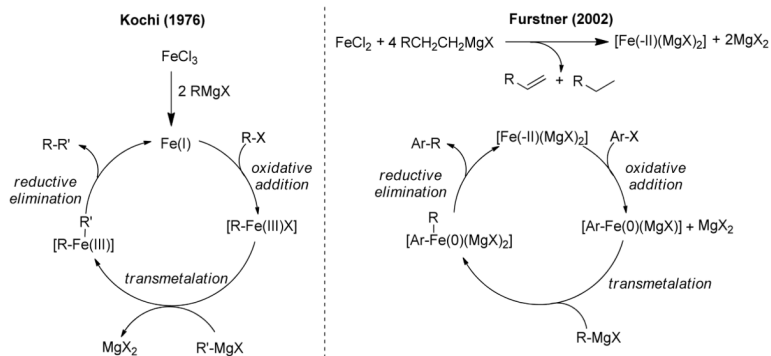


Figure 108.
Proposed Mechanisms

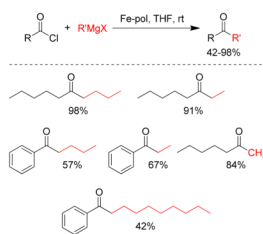


Figure 109.
Polymer Supported Iron Catalyst for Ketone Formation (Taurino and coworkers)

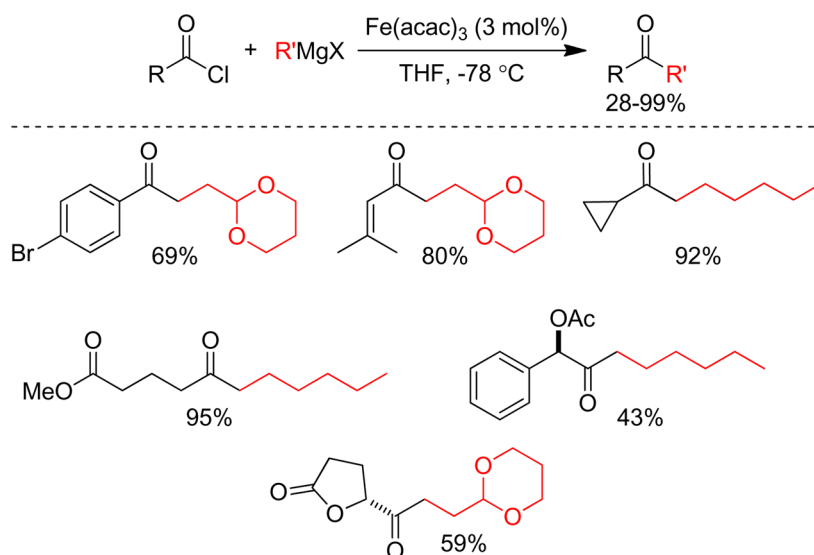


Figure 110.
Cross-Coupling of Acid Chlorides with Grignard Reagents (Fürstner and coworkers, 2004)

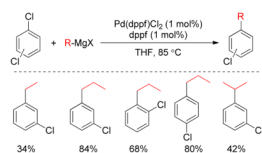


Figure 111.
Selective Monoalkylation of Dichlorobenzene (Katayama and coworkers, 1991)

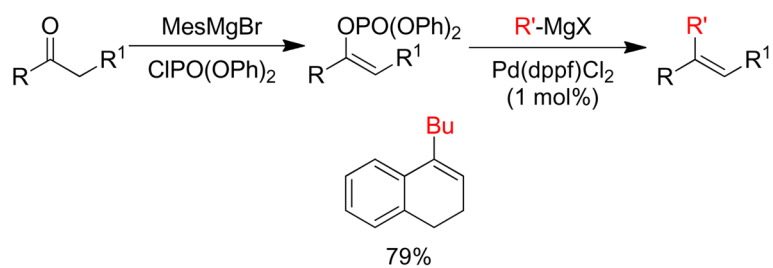


Figure 112.
Cross-coupling Reaction with Enol Phosphonates (Miller, 2002)

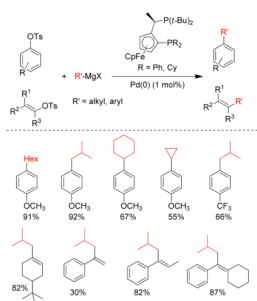


Figure 113.
Cross-Coupling Reaction of Vinyl and Aryl Tosylates (Hartwig and coworkers, 2005)

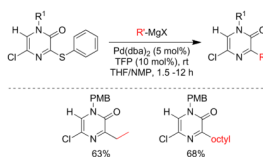


Figure 114.
Synthesis of 2-(1H)-Pyrazinones (Eycken and coworkers, 2009)

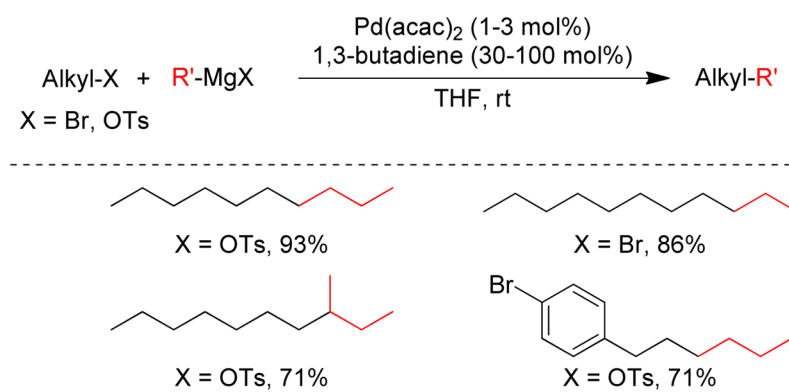


Figure 115.
Pd-Catalyzed C(sp³)-C(sp³) Coupling (Kambe and coworkers, 2003)

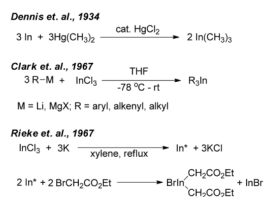


Figure 116.
 Preparation of Indium Reagents

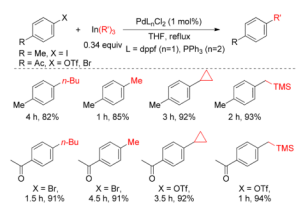


Figure 117.
Cross-Coupling with Aryl Halides (Sarandeses and coworkers, 2001)

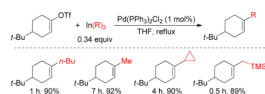


Figure 118.
Cross-Coupling with Alkenyl Triflates (Sarandeses and coworkers, 2001)

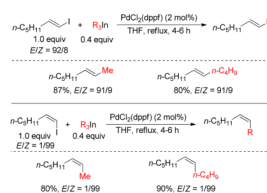


Figure 119.
Stereoselective Cross-Coupling with Iodoalkenes (Sarandeses and coworkers, 2008)

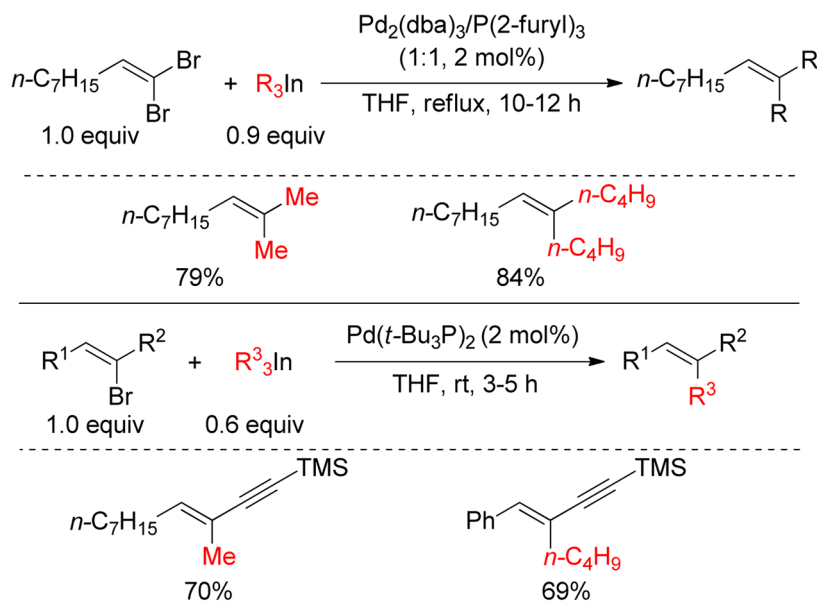


Figure 120.
Cross-Coupling with 1,1-Dibromoalkenes (Sarandeses and coworkers, 2008)

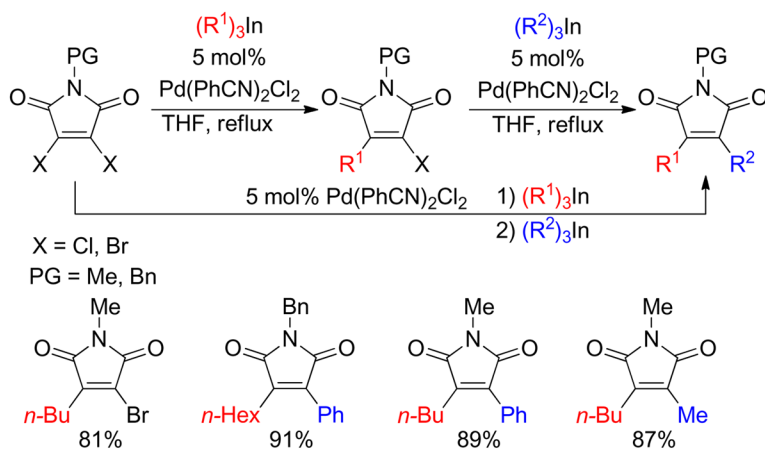


Figure 121.
Cross-Coupling with Maleimides (Sarandeses and coworkers, 2009)

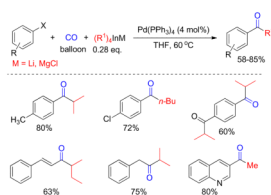


Figure 122.
Carbonylative Cross-Couplings (Lee and coworkers, 2004)

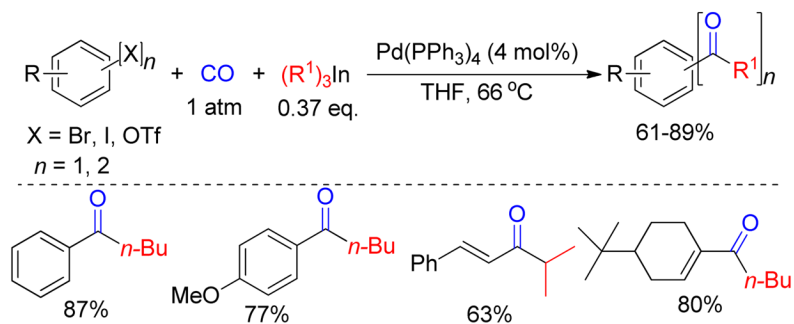


Figure 123.
Carbonylative Cross-Couplings (Lee and coworkers, 2004)

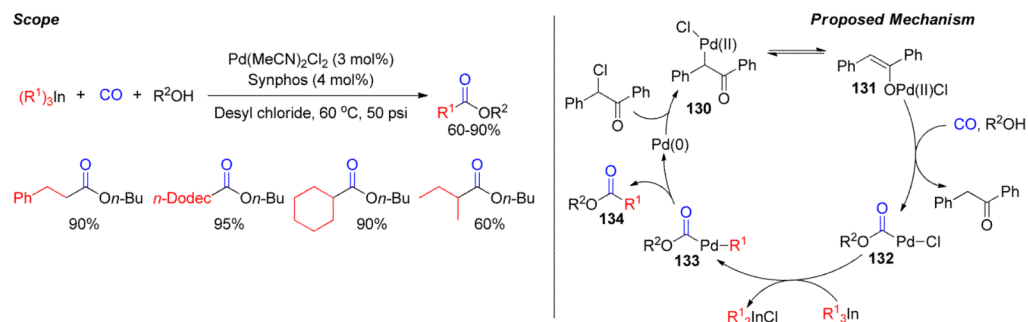
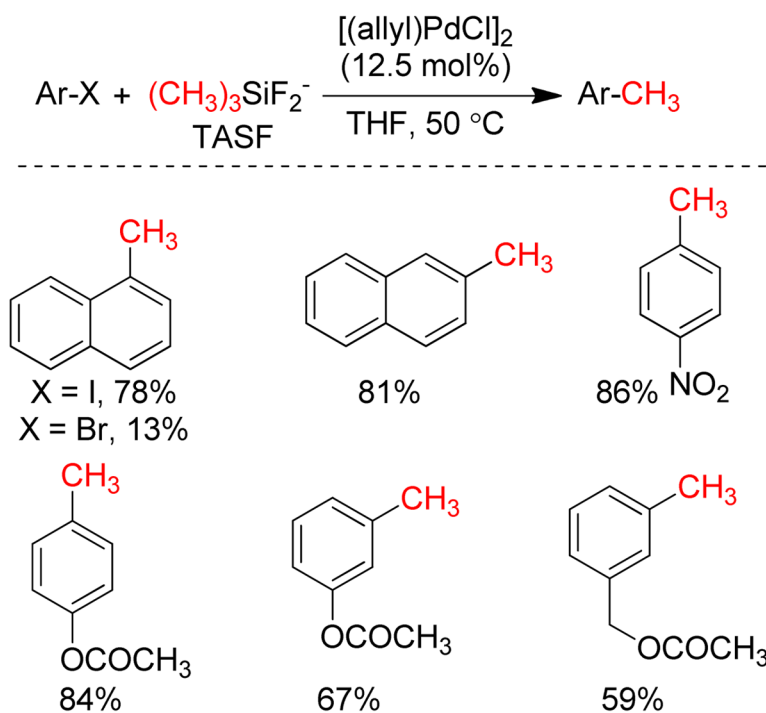


Figure 124.
Oxidative Carbonylative Cross-Couplings (Lei and coworkers, 2008)



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**Figure 126.**

Methylation Reaction of Aryl Halides (Hiyama and coworkers, 1988)

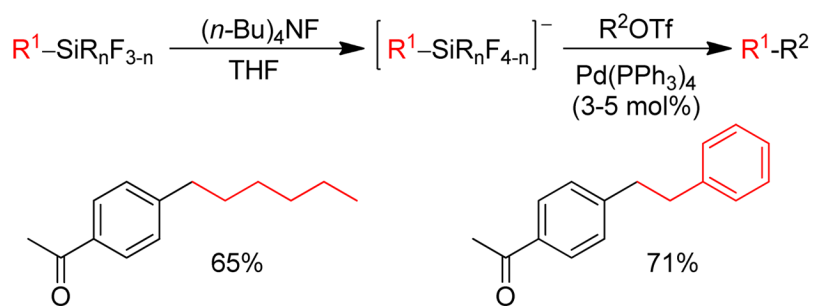


Figure 127.
Cross-Coupling of Aryl Triflate with Alkylsilicon (Hiyama and coworkers, 1990)

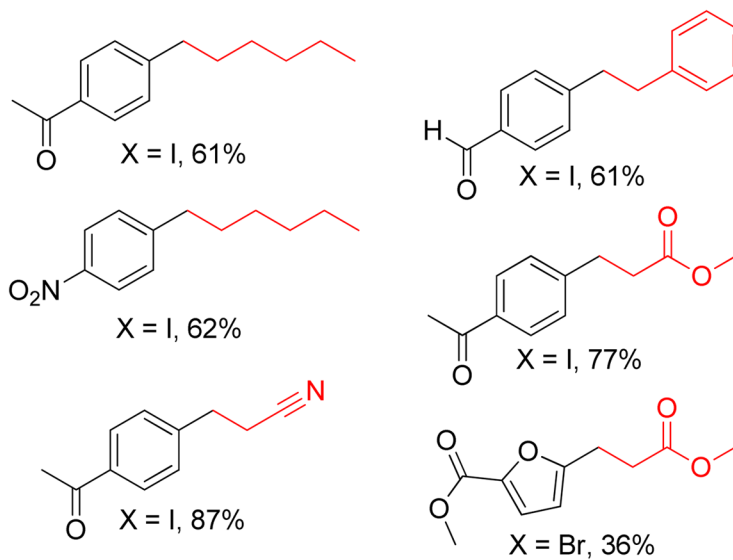
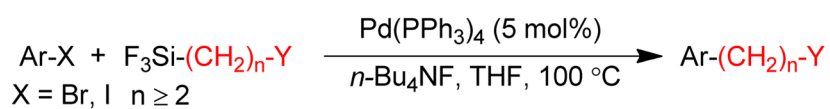


Figure 128.
Cross-Coupling of Aryl halides with Alkylsilicon (Hiyama and coworkers, 1997)

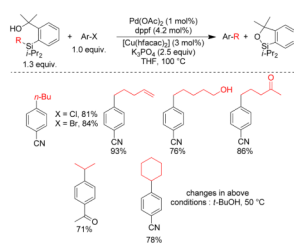
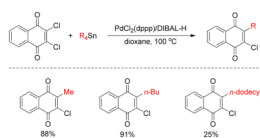


Figure 129.
2-(2-Hydroxyprop-2-yl)phenyl-Substituted Alkylsilanes in Cross-Coupling Reaction.

**Figure 130.**

2-Alkylation of 2,3-Dichloro-1,4-naphthoquinone (Tam and coworkers, 1983)

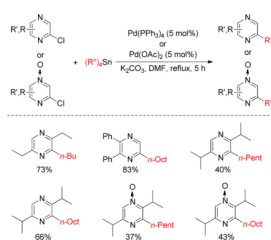


Figure 131.
2-Alkylation of Pyrazines (Ohta and coworkers, 1989)

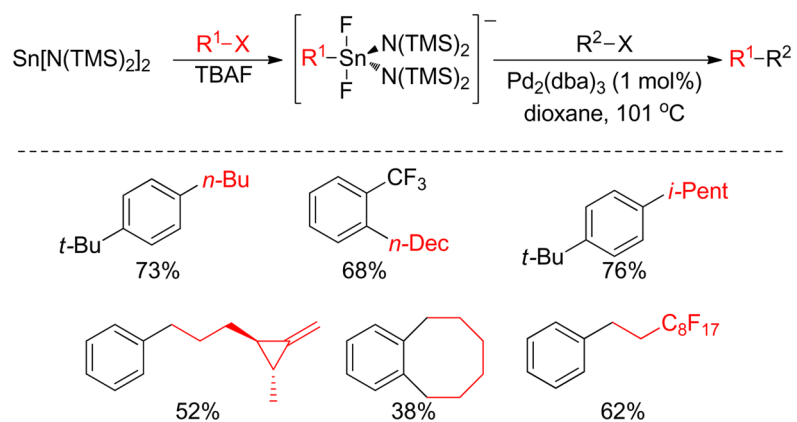


Figure 132.
Stille Coupling of Activated Alkyltin Reagents (Fouquet and coworkers, 2005)

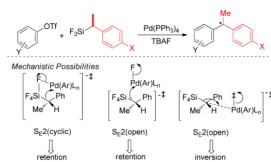


Figure 133.
Hiyama Coupling of Chiral Alkyl Silanes (Hiyama and coworkers, 1990)

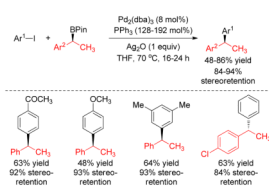


Figure 134.
Suzuki Coupling with Retention of Configuration (Crudden and coworkers, 2009)

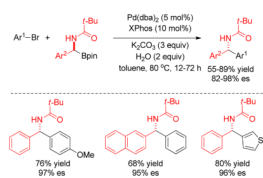


Figure 135.
Suzuki Coupling with Inversion of Configuration (Suginome and coworkers, 2010)

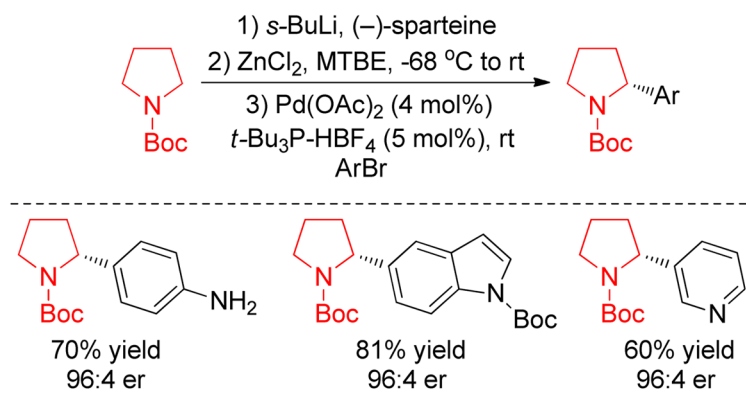


Figure 136.
Negishi Coupling with Chiral Alkylzinc Reagent (Campos and coworkers, 2006)

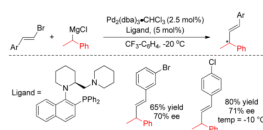


Figure 137.
Asymmetric Kumada Coupling (Aoyama and coworkers, 2004)

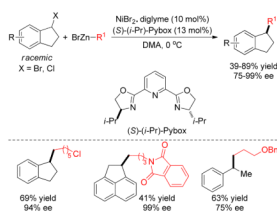


Figure 138.
Asymmetric Negishi coupling with Benzylic Halides (Fu and coworkers, 2005)

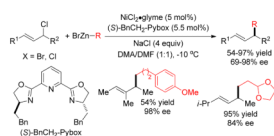


Figure 139.
Asymmetric Negishi Coupling with Allylic Chlorides (Fu and coworkers, 2008)

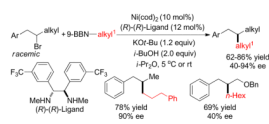


Figure 140.
Asymmetric Suzuki Coupling with Homobenzylic Bromides (Fu and coworkers, 2008)

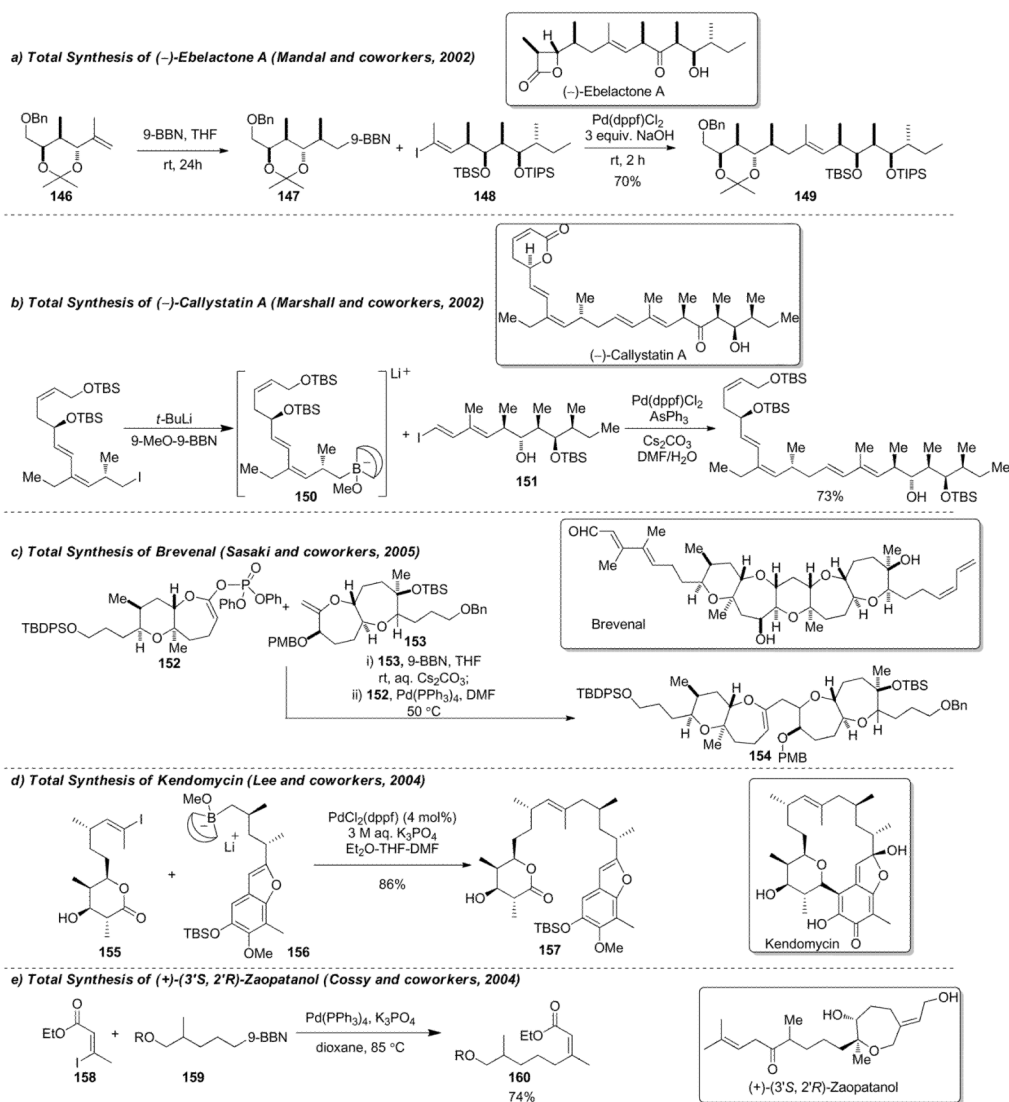


Figure 141.
Total Synthesis using Alkylboron Reagents (2002–2004).

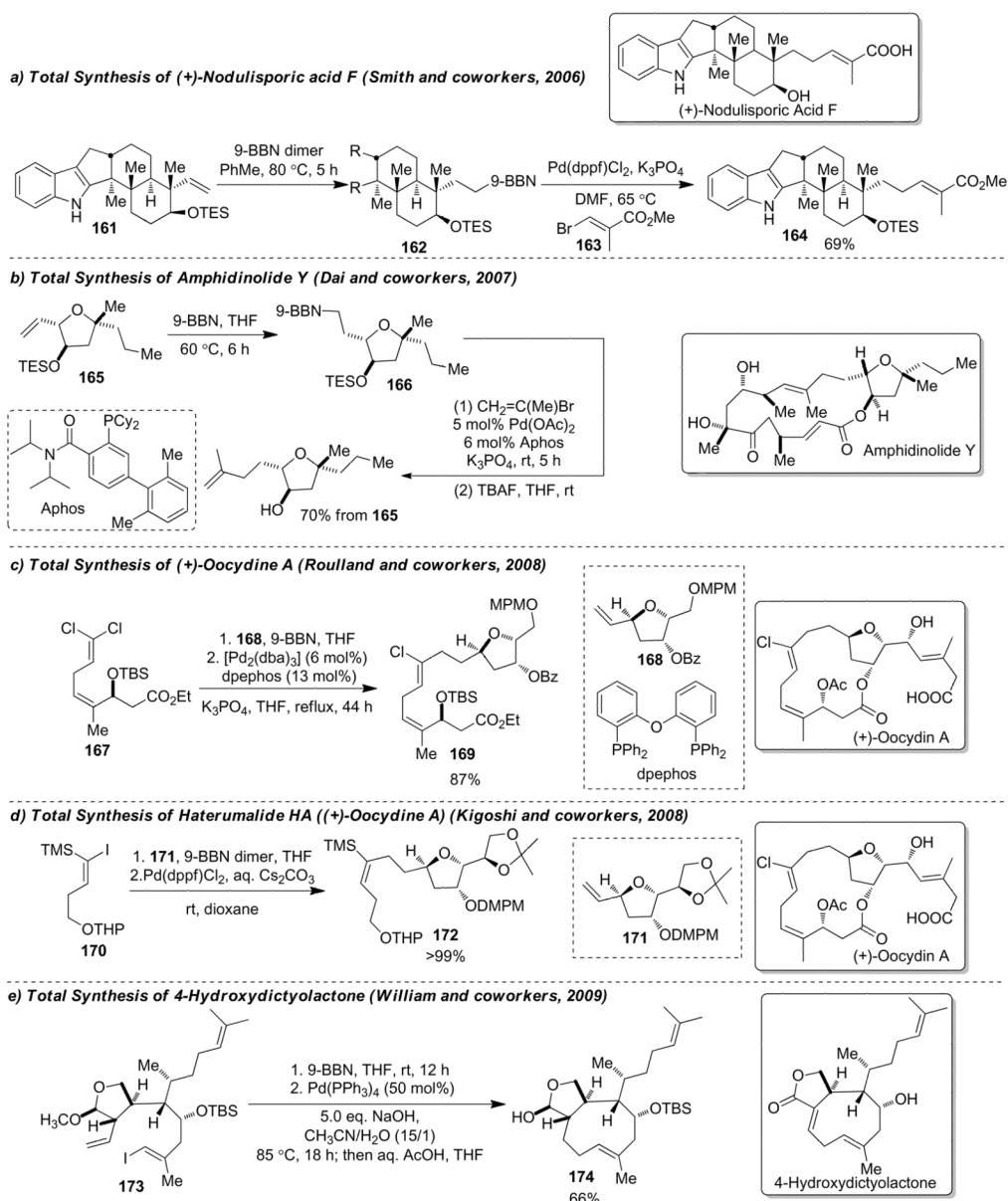


Figure 142.
Total Synthesis using Alkylboron Reagents (2006–2009).

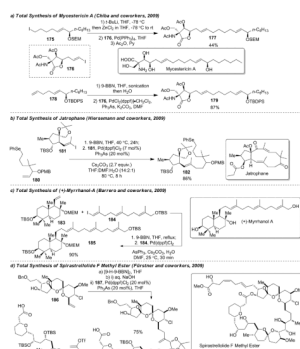


Figure 143.
Total Synthesis Using Alkylboron Reagents (2009)

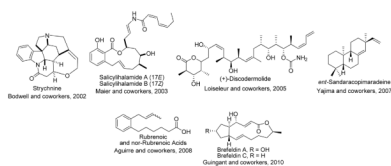
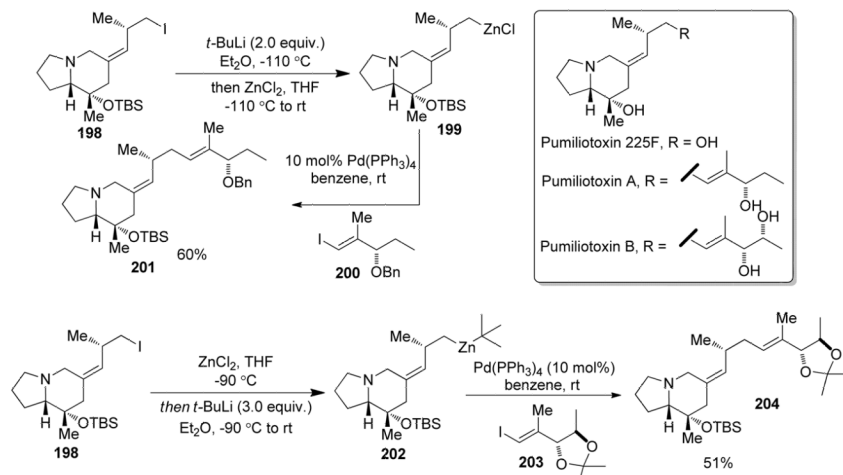
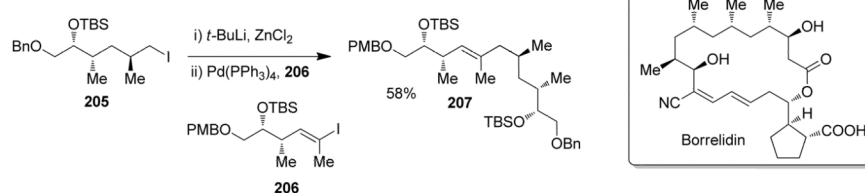


Figure 144.
Application of *B*-alkyl Suzuki-Miyaura Cross-Coupling

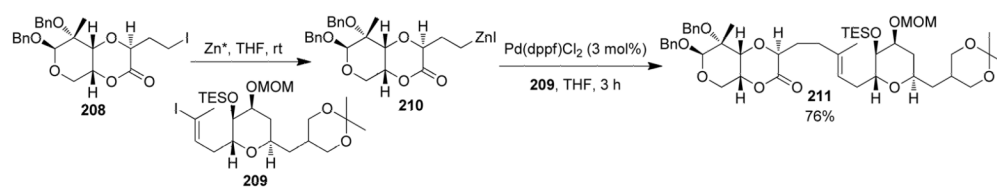
a) Total Synthesis of (+)-Pumiliotoxins A and B (Kibayashi and coworkers, 2002)



b) Total Synthesis of Borrelidin (Morken and coworkers, 2003)



c) **Total Synthesis of Hemibrevetoxin B (Holton and coworkers, 2003)**



d) Total Synthesis of Amphidinolide T1, T2, T3 and T4 (Fürstner and coworkers, 2003)

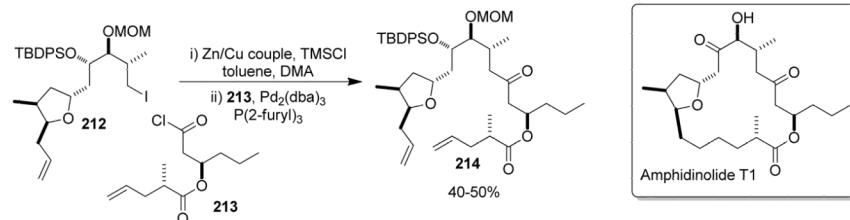
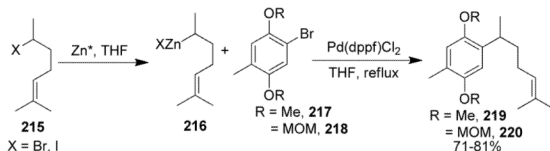
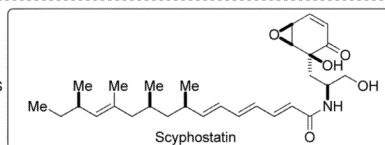


Figure 145.
Total Synthesis using Alkylzinc Reagents (2002–2003).

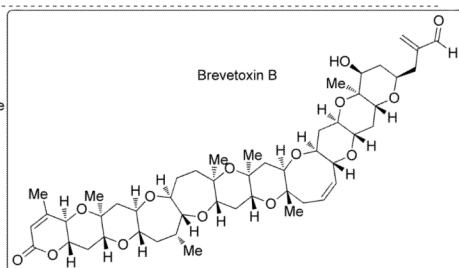
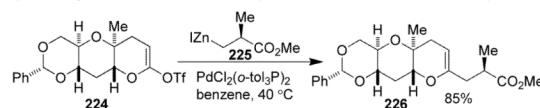
a) Total Synthesis of Various Aromatic Bisabolenes (Vyvyan and coworkers, 2004)



b) Total Synthesis of Scyphostatin (Kato and coworkers, 2004)



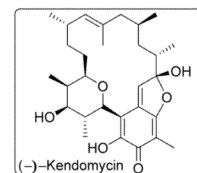
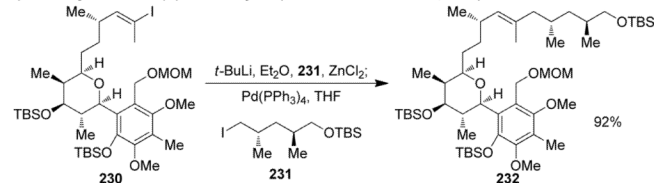
c) Total Synthesis of Brevetoxin B (Yamamoto and coworkers, 2005)



d) Fragments of Amphidinolides G and H (Crews and coworkers, 2007)



e) Total Synthesis of (-)-Kendomycin (Panek and coworkers, 2008)



f) Total Synthesis of (S)-Jamaicamide C (Paige and coworkers, 2009)

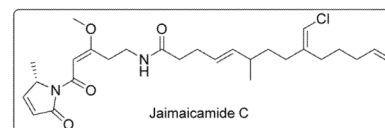
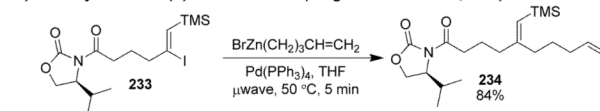
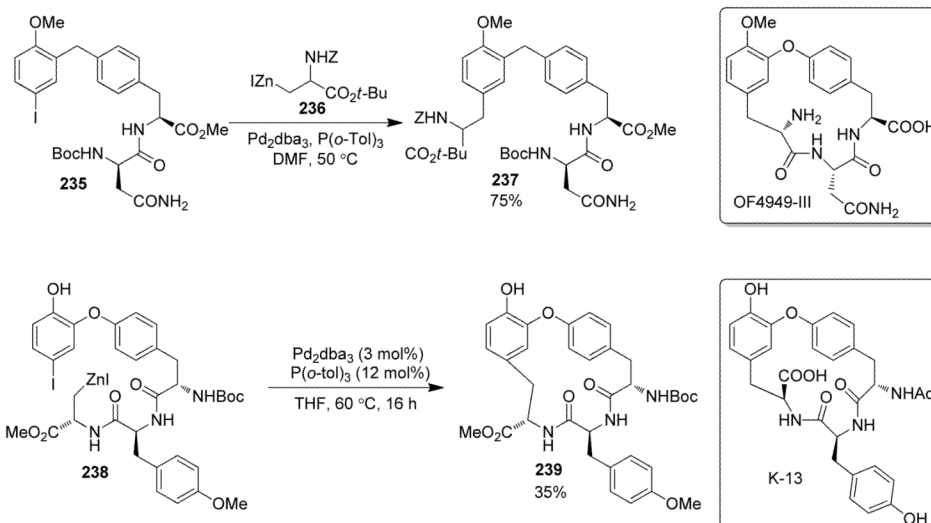


Figure 146.

Total Synthesis using Alkylzinc Reagents (2004–2009).

a) Total Synthesis of OF4949-III and K-13 (Jackson and coworkers, 2009)



b) Total Synthesis of Kapakahine E and F (Rainier and coworkers, 2010)

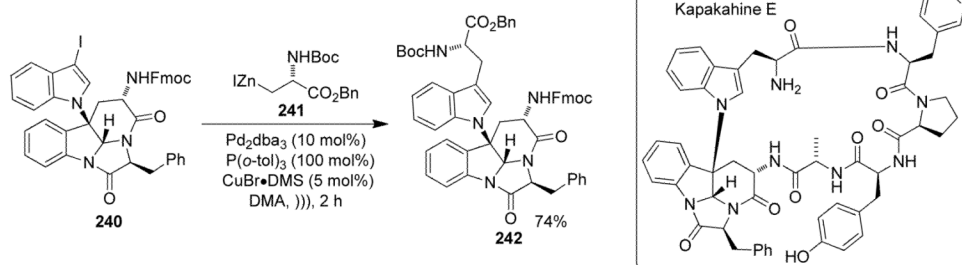


Figure 147.
Total Synthesis using Alkylzinc Reagents (2009–2010).

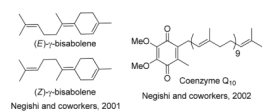


Figure 148.
Application of Negishi Cross-Coupling^{143,530,531}

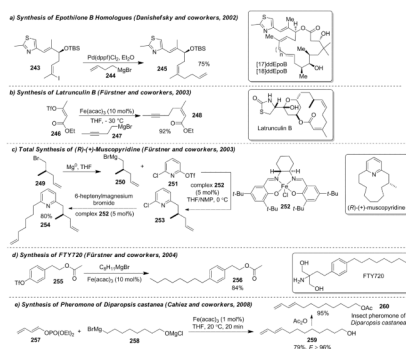
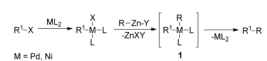


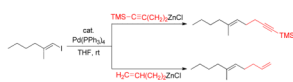
Figure 149.
Total Synthesis using AlkylMg Reagents (2003–2010).



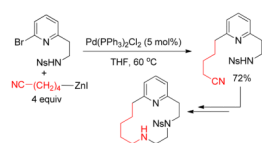
Scheme 1.
Cross-Couplings with Alkylzinc Reagents

**Scheme 2.**

PdCl₂(dppf)-Catalyzed Negishi Coupling (Hayashi and coworkers, 1984)

**Scheme 3.**

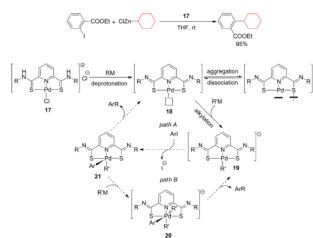
Negishi Coupling with Homoallylic and Homopropargylic Alkylzinc Reagents (Negishi and coworkers, 1980)



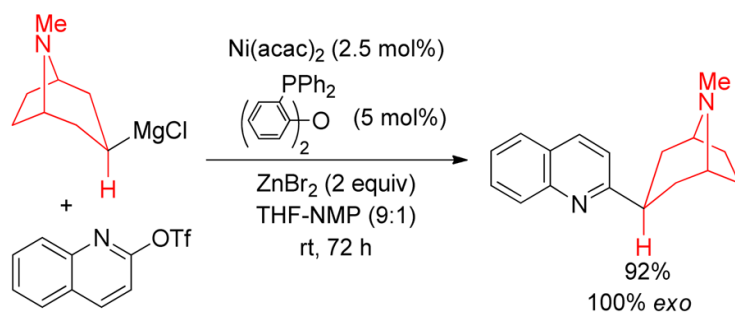
Scheme 4.
Synthesis of Azamacrocycles via Negishi Coupling (Skerlj and coworkers, 2002)

**Scheme 5.**

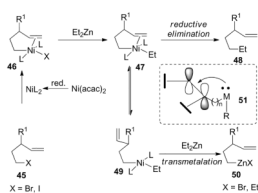
Chemoselective Negishi Coupling of 2-bromo-pyridinylstannanes (Twieg and coworkers, 2008)



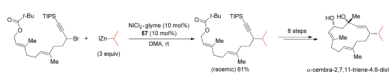
Scheme 6.
Pincer thioimido-Pd complex-Catalyzed Negishi Couplings (Lei and coworkers, 2008)



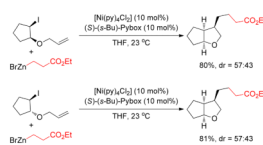
Scheme 7.
Aminoalkylation of Heteroarenes (Knochel and coworkers, 2007)



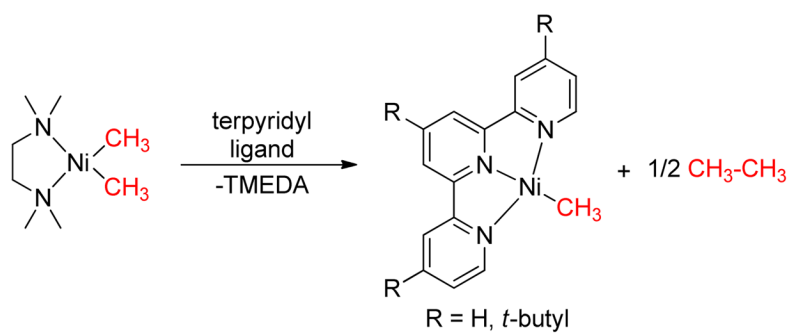
Scheme 8.
Hypothesis for Substrate-Controlled Negishi Coupling (Knochel and coworkers, 1999)

**Scheme 9.**

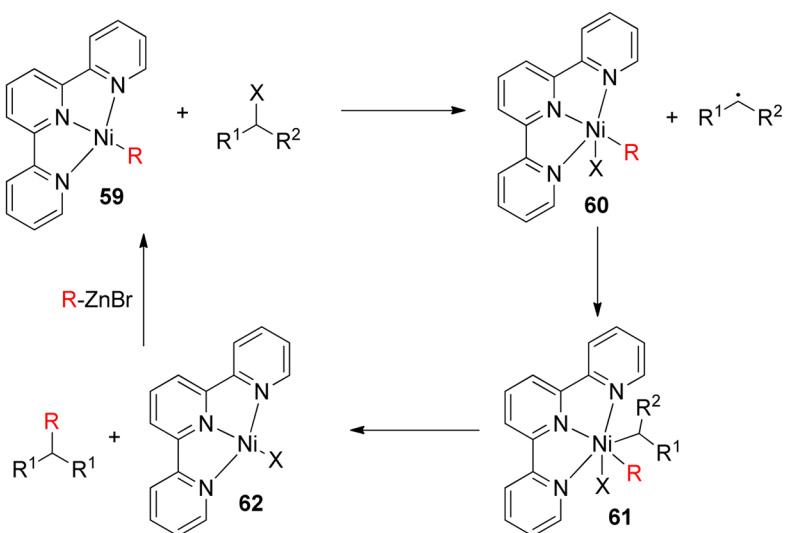
Secondary-Secondary Negishi Coupling in a Formal Total Synthesis of α-cembra-2,7,11-triene-4,6-diol (Fu and coworkers, 2008)

**Scheme 10.**

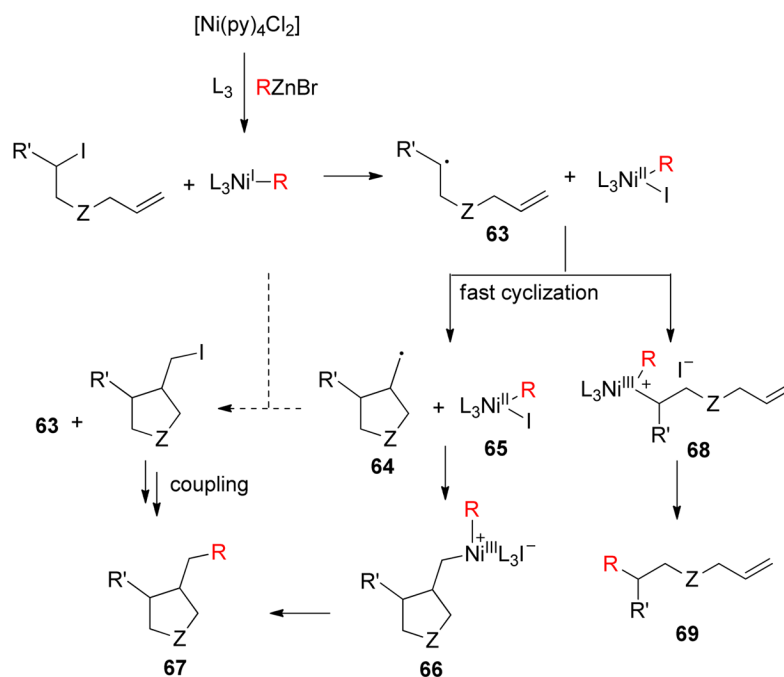
Stereochemistry in Tandem Cyclization-Cross-Couplings (Cárdenas and coworkers, 2007)

**Scheme 11.**

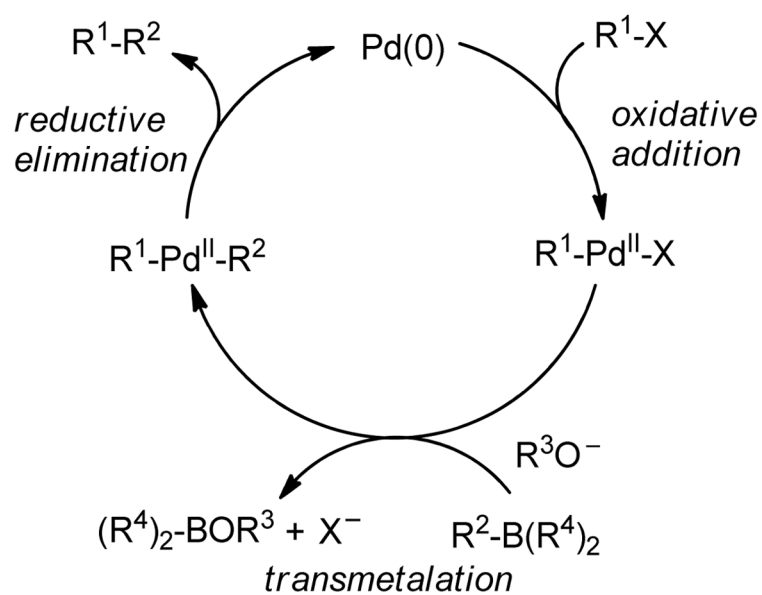
Identification of Mono Methyl Nickel-Complex (Vicic and coworkers, 2005)



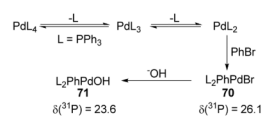
Scheme 12.
Radical Mechanism in Ni-Catalyzed Alkyl-Alkyl Cross-Couplings (Vicic and coworkers, 2006)



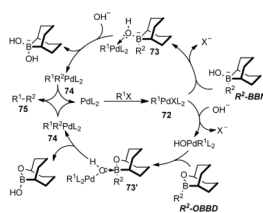
Scheme 13.
Proposed Mechanism for Tandem Radical Cyclization Cross-Coupling (Cárdenas and coworkers, 2007)



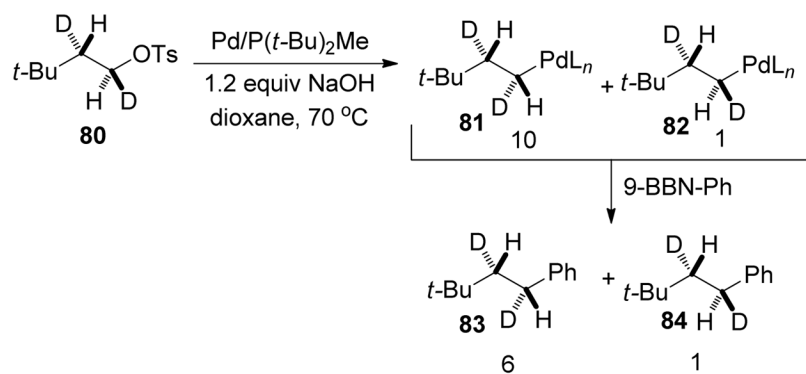
Scheme 14.
Suzuki-Miyaura Catalytic Cycle

**Scheme 15.**

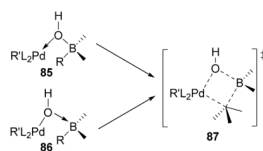
Role of Bases in Suzuki-Miyaura Coupling (Soderquist and coworkers, 1998)



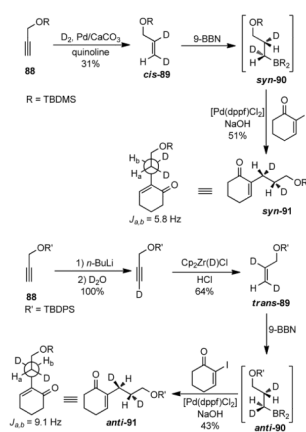
Scheme 16.
Modified Suzuki-Miyaura Catalytic Cycle (Soderquist and coworkers, 1998)

**Scheme 17.**

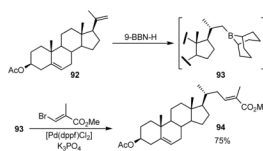
Stereochemistry of the Pd-Catalyzed Oxidative Addition of Alkyl Tosylates (Fu and coworkers, 2002)

**Scheme 18.**

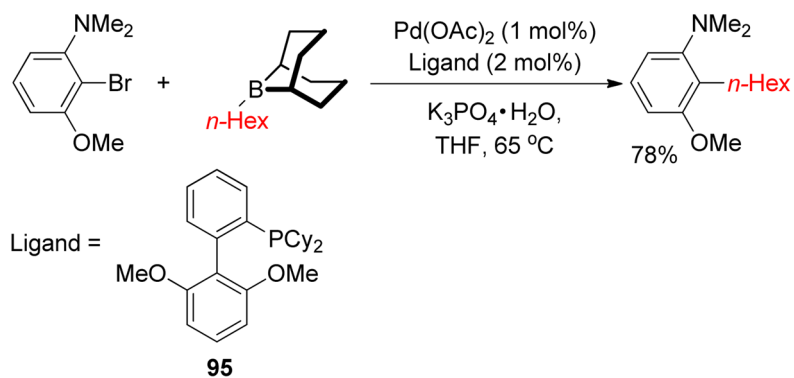
Mechanism of Transmetalation (Soderquist and coworkers, 1998)



Scheme 19.
Stereochemistry in Suzuki-Miyaura Couplings (Woerpel and coworkers, 1998)

**Scheme 20.**

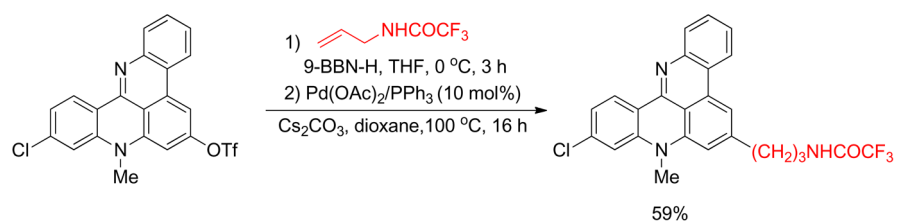
Suzuki-Miyaura Coupling with a Steroidal Moiety (Suzuki and coworkers, 1989)



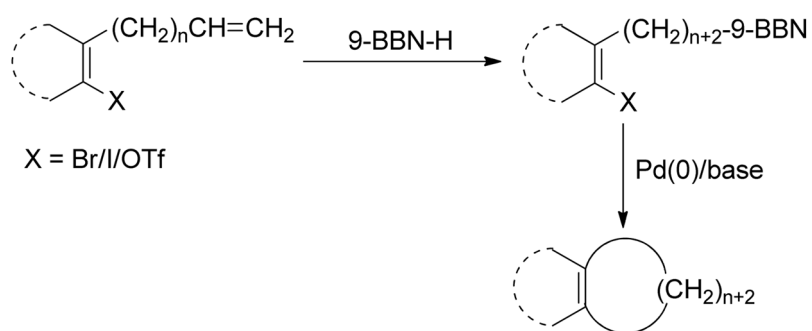
Scheme 21.
Suzuki-Miyaura Coupling with Electron-rich and Sterically Hindered Aryl Bromides
(Buchwald and coworkers, 2004)

**Scheme 22.**

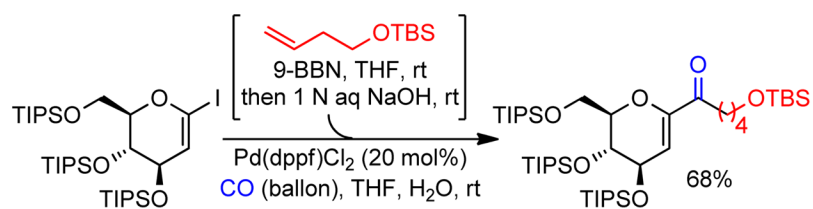
Alkylation of 2-halopurines (Piersanti and coworkers, 2010)

**Scheme 23.**

Suzuki Coupling in Quinoacridine-derivative Synthesis (Stevens and coworkers, 2003)



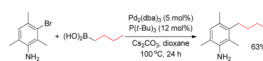
Scheme 24.
Intramolecular Suzuki-Miyaura Couplings

**Scheme 25.**

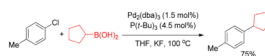
Carbonylative Suzuki Coupling of 2-iodo-glycal (Tan and coworkers, 2004)

**Scheme 26.**

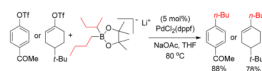
Suzuki Coupling with Chlorobenzylidenelactone (Ma and coworkers, 2006)

**Scheme 27.**

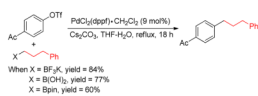
Suzuki Coupling of Hindered Aryl Bromides (Delaude and coworkers, 2007)



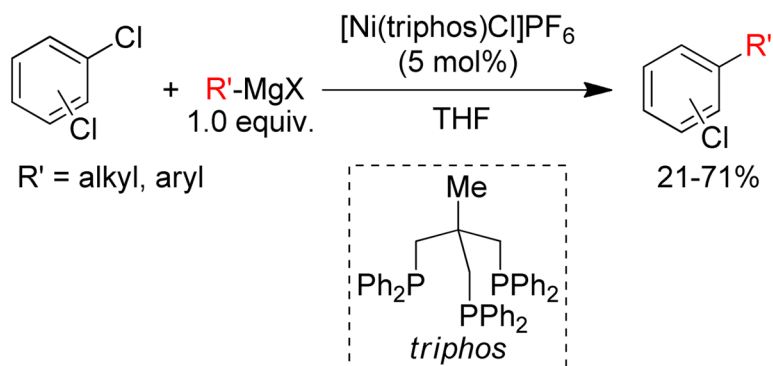
Scheme 28.
Suzuki Coupling with Cyclopentylboronic Acid (Fu and coworkers, 2000)

**Scheme 29.**

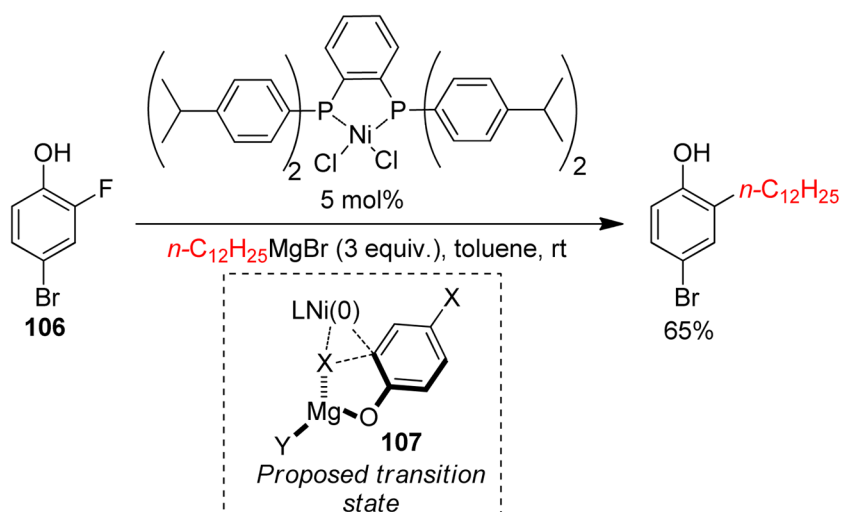
Suzuki Coupling with Mixed Alkylboronic Esters (Falck and coworkers, 2001)

**Scheme 30.**

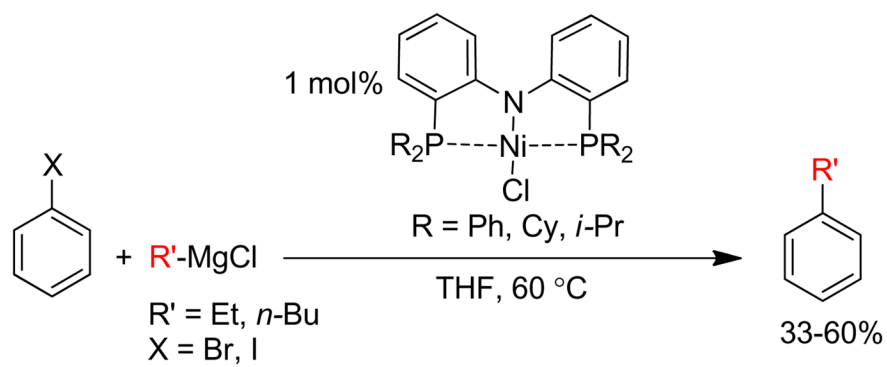
Comparative Study with Boron Derivatives (Molander and coworkers, 2001)

**Scheme 31.**

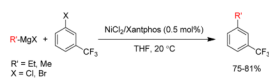
Selective Alkylation of Dichlorobenzene (Tam and coworkers, 1983)



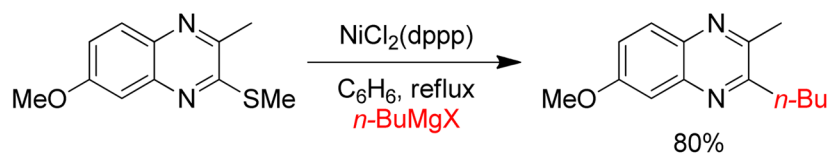
Scheme 32.
Phenol-Directed Alkylation of Halobenzenes (Manabe and coworkers, 2009)

**Scheme 33.**

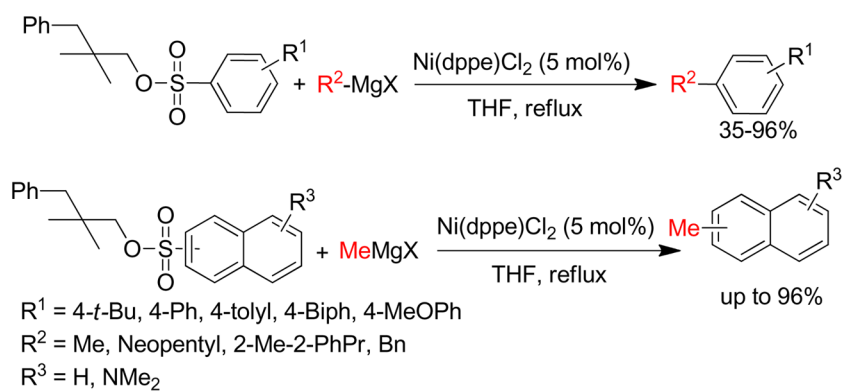
Tridentate Amido Diphosphino Ligand for Ni-Catalyzed Cross-Coupling (Liao and coworkers, 2006)

**Scheme 34.**

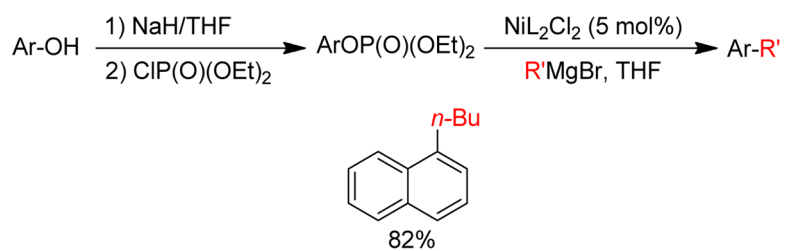
Synthesis of Alkylated Trifluoromethylbenzenes (Saint-Jalmes and Roques, 2006)

**Scheme 35.**

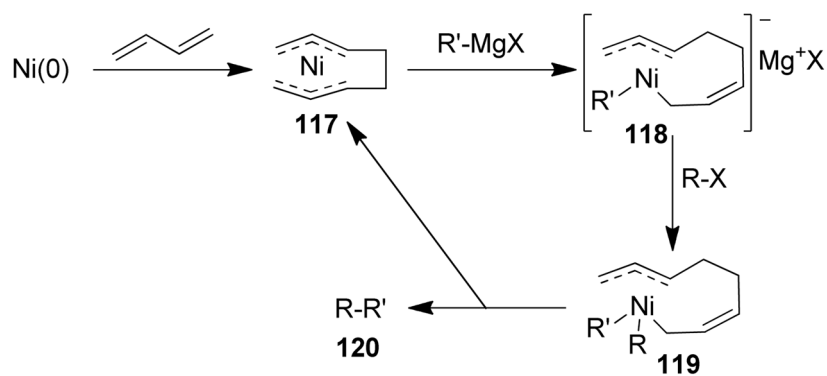
Synthesis of Unsymmetrically Substituted Quinoxaline (Ila and coworkers, 2005)

**Scheme 36.**

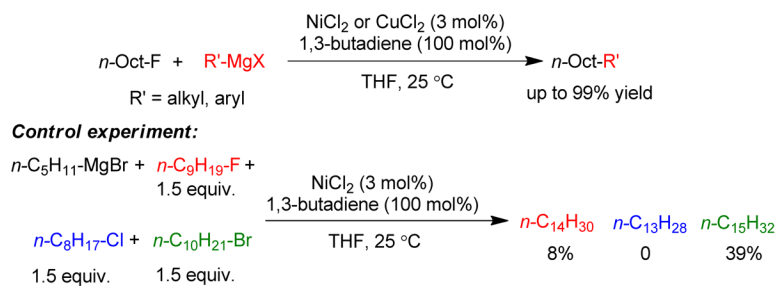
Use of Neopentyl Arenesulfonates in Cross-Coupling (Park and coworkers, 2005)



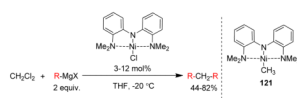
Scheme 37.
Initial Report (Kumada and coworkers, 1981)



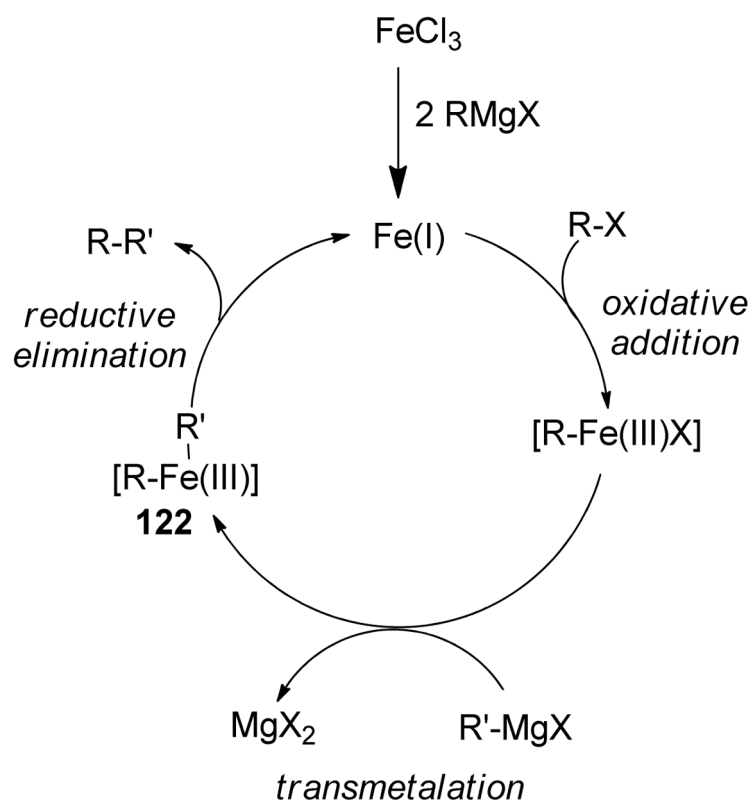
Scheme 38.
Proposed Mechanism (Kambe and coworkers, 2002)

**Scheme 39.**

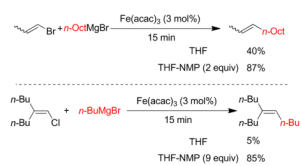
C-F Bond Functionalization (Kambe and coworkers, 2003)

**Scheme 40.**

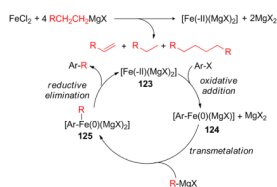
Ni-catalyzed Kumada-Corriu Coupling with a Unique Pincer Amido-*bis*-(amine) Ligand (Hu and coworkers, 2008)



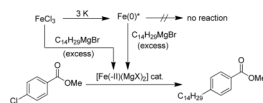
Scheme 41.
Proposed Mechanism (Kochi, 1971)

**Scheme 42.**

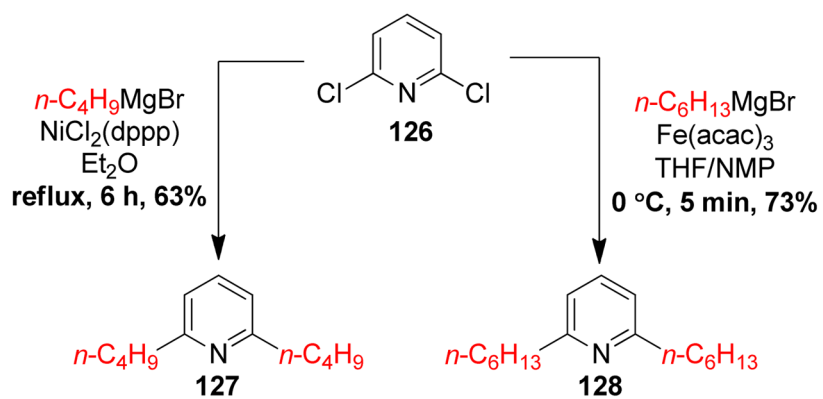
Effect of NMP on Reaction Outcome (Cahiez and coworkers, 1998)



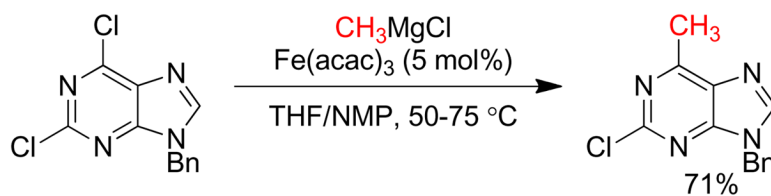
Scheme 43.
Proposed Mechanism (Furstner and coworkers, 2002)



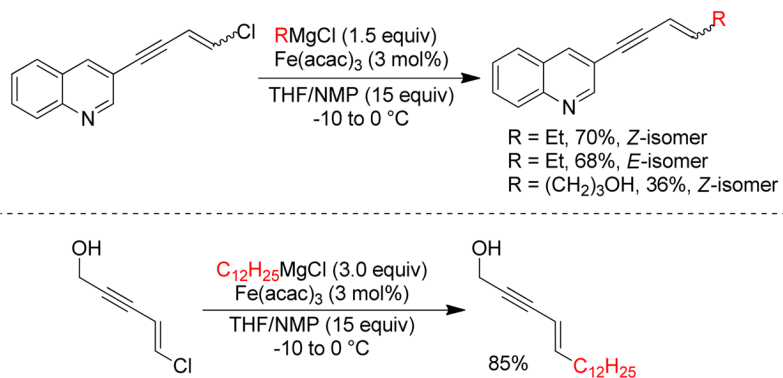
Scheme 44.
Control Experiments (Füstner and coworkers, 2002)

**Scheme 45.**

Superiority of Fe-Catalyzed Reaction over Ni-Catalyzed Reaction (Fürstner and coworkers, 2002)



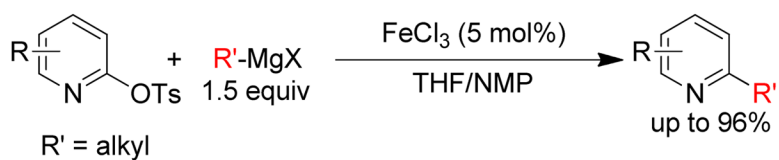
Scheme 46.
Synthesis of 6-Methylpurine Bases (Hocek and coworkers, 2003)

**Scheme 47.**

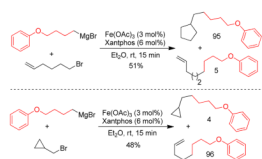
Cross-Coupling of Chloroenynes with Grignard Reagents (Alami and coworkers, 2004)



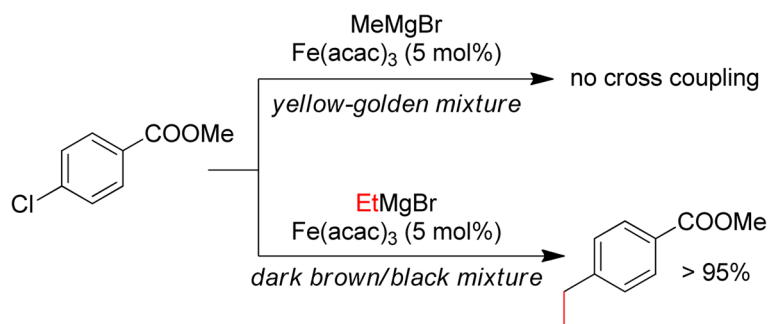
Scheme 48.
Cross-Coupling of Imidoyl Chlorides with Grignard Reagents (Olsson, 2006)

**Scheme 49.**

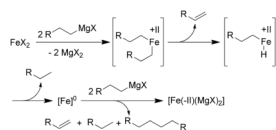
Cross-Coupling of Heteroaromatic Sulfonates with Alkyl Grignards (Skrydstrup and coworkers, 2009)



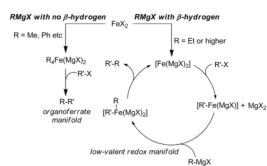
Scheme 50.
Control Experiments (Chai and coworkers, 2007)



Scheme 51.
Different Reactivity for MeMgBr and EtMgBr

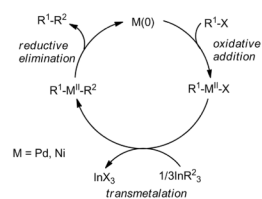
**Scheme 52.**

Proposed Mechanism for Reaction of Grignard Reagents Containing β -hydrogen with FeX_2

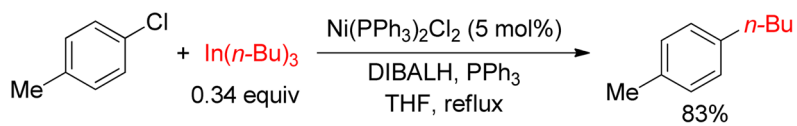


Scheme 53.
Proposed Mechanism for Iron-Catalyzed Cross-Coupling

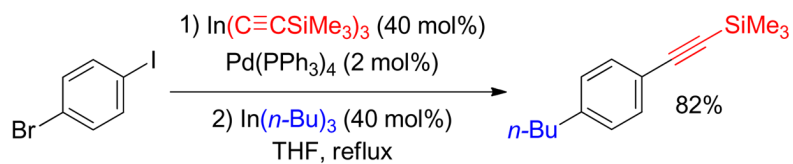
Chem Rev. Author manuscript; available in PMC 2012 March 9.



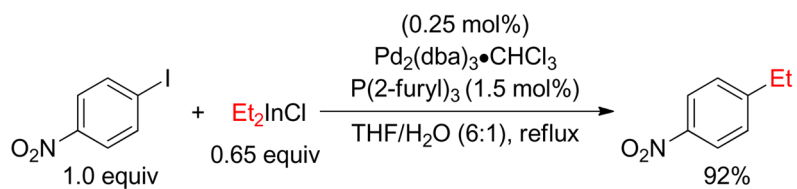
Scheme 55.
Catalytic Cycle for Triorganoindium Reagents

**Scheme 56.**

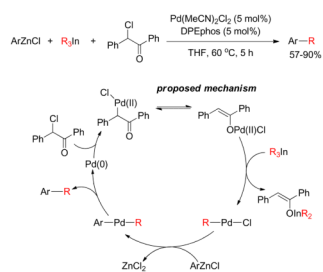
Ni-Catalyzed Cross-Coupling with Aryl Chlorides (Sarandeses and coworkers, 2001)



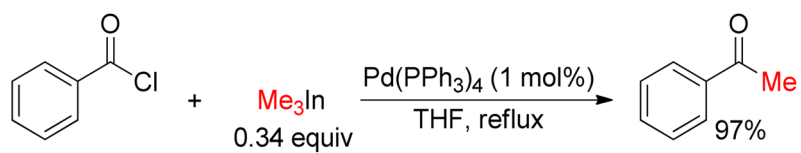
Scheme 57.
Sequential Cross-Coupling (Sarandeses and coworkers, 2002)

**Scheme 58.**

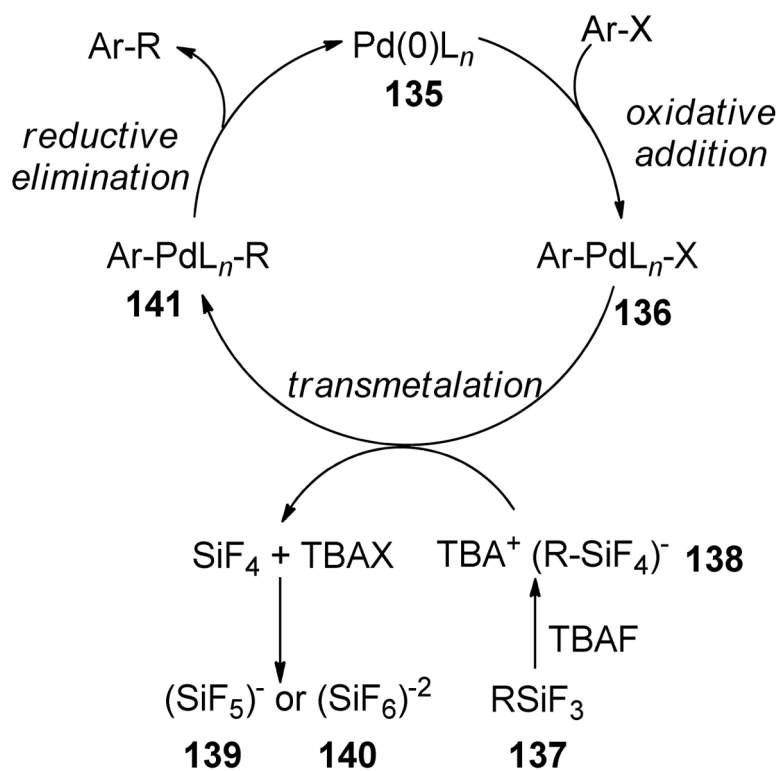
Cross-Coupling in Aqueous Media (Oshima and coworkers, 2001)



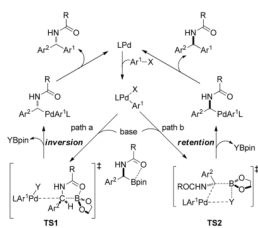
Scheme 59.
Oxidative Cross-Couplings (Lei and coworkers, 2009)

**Scheme 60.**

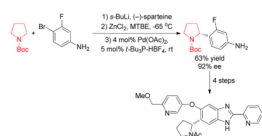
Cross-Coupling with Acid Chlorides (Sarandeses and coworkers, 2001)



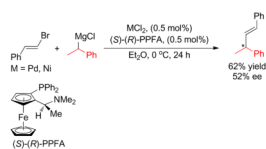
Scheme 61.
Proposed Mechanism (Hiyama and coworkers, 1997)



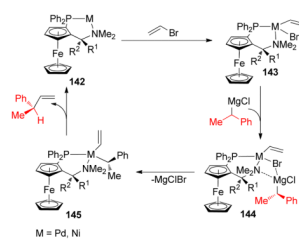
Scheme 62.
Proposed Mechanism for Inversion of Configuration



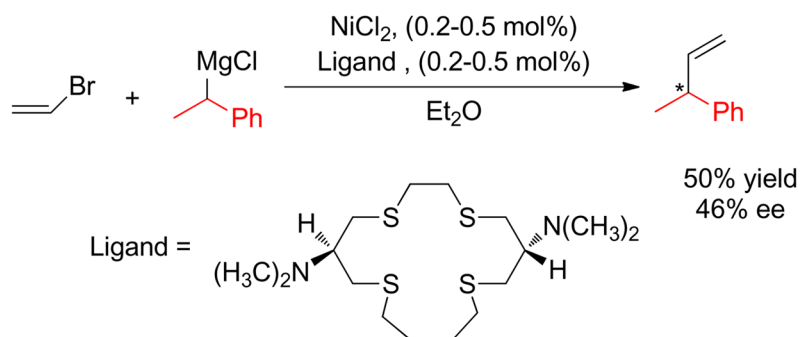
Scheme 63.
Synthesis of Glucokinase Activator (Campos and coworkers, 2008)

**Scheme 64.**

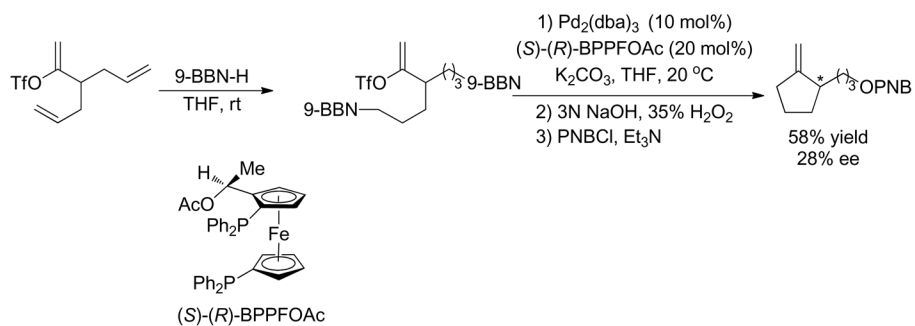
Asymmetric Kumada Coupling with Chiral Ferrocenylphosphine Ligand (Kumada and coworkers, 1982)

**Scheme 65.**

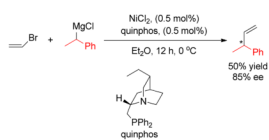
Coordination-Assisted Chiral Induction Model (Kumada and coworkers, 1982)

**Scheme 66.**

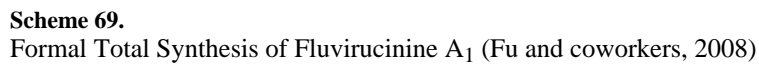
Asymmetric Kumada Coupling with Chiral Sulfide Ligand (Kellogg and coworkers, 1986)

**Scheme 67.**

Asymmetric Synthesis of Cyclopentane Derivatives (Shibasaki and coworkers, 1998)

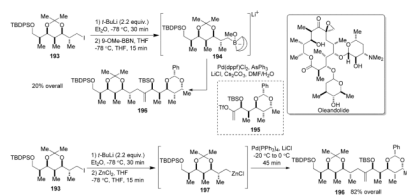
**Scheme 68.**

Asymmetric Kumada Coupling with Quinphos Ligand (Lemaire and coworkers, 2001)





Scheme 70.
Total Synthesis of Anguinomycin (Bonazzi and Coworkers, 2010)

**Scheme 71.**

Total Synthesis of Oleandolide (Panek and coworkers, 2002)

Table 1

Cross-Coupling of Organozinc Reagents with Bromobenzene (Hayashi and coworkers, 1984)

Catalyst	R ^a	Time (h)	Yield (%) ^b		
			<i>sec</i> -BuPh	<i>n</i> -BuPh	Recovered PhBr
PdCl ₂ (dppf)	<i>sec</i> -Bu	20	100	0	0
Pd(PPh ₃) ₄	<i>sec</i> -Bu	24	1	2	78
PdCl ₂ (PPh ₃) ₂	<i>sec</i> -Bu	22	3	3	87
PdCl ₂ (dppp)	<i>sec</i> -Bu	22	13	3	79
NiCl ₂ (PPh ₃) ₂	<i>sec</i> -Bu	22	1	4	59
NiCl ₂ (dppp)	<i>sec</i> -Bu	22	45	7	44
PdCl ₂ (dppf)	<i>n</i> -Bu	22		100	0
PdCl ₂ (PPh ₃) ₂	<i>n</i> -Bu	24		34	13
PdCl ₂ (dppp)	<i>n</i> -Bu	24		66	0
PdCl ₂ (dppb)	<i>n</i> -Bu	21		90	0
NiCl ₂ (PPh ₃) ₂	<i>n</i> -Bu	21		42	22
NiCl ₂ (dppp)	<i>n</i> -Bu	21		3	78

^a 2.0 equiv zinc reagent was used;

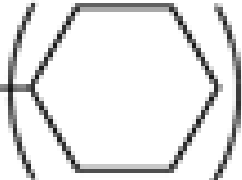
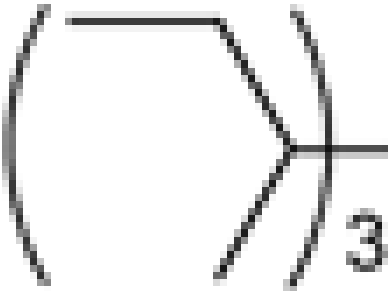
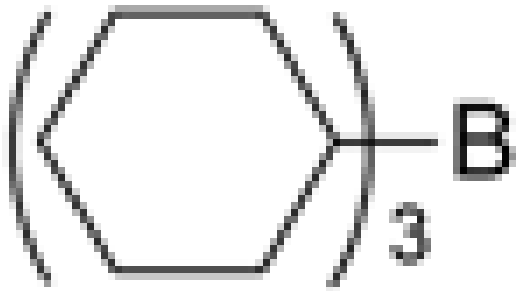
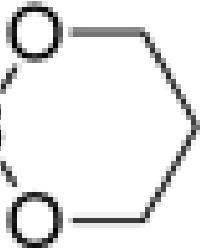
^b GC yields

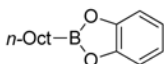
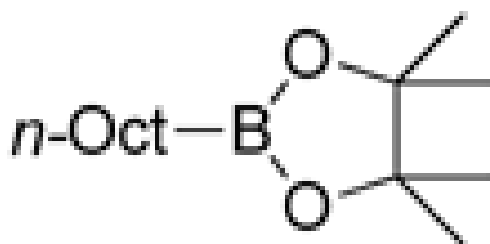
Table 2

Negishi Coupling with Alkylzinc and Alkylmagnesium Reagents (Negishi and coworkers, 1980)

<p>M = Zn, or Mg X = Cl, Br</p>				
Product yield (%)				
Entry	Organometallic reagent	Time (h)	Cross-coupled	De-iodo
1	<i>n</i> -BuZnCl	2	76	2
2	<i>n</i> -BuMgBr	2	25	51
3	<i>sec</i> -BuZnCl	16	68	15
4	<i>sec</i> -BuMgBr	16	40	35
5	H ₂ C=CH(CH ₂) ₂ ZnCl	16	81	tr
6	H ₂ C=CH(CH ₂) ₂ MgBr	16	21	37
7	TMSC≡C(CH ₂) ₂ ZnCl	2	91	tr

Table 3Suzuki Coupling of Iodobenzene with Alkyl Boranes^a

Borane	Base ^b	Solvent	Yield (%)
<i>n</i> -Oct-9-BBN	NaOH	THF/H ₂ O	99
<i>n</i> -Oct—B(Sia) ₂	NaOH	THF/H ₂ O	82
<i>n</i> -Oct—B() ₂	NaOH	THF/H ₂ O	93
(<i>n</i> -Oct) ₃ B	NaOH	THF/H ₂ O	98
	KOH	THF/H ₂ O	40
() ₃ B	KOH	THF/H ₂ O	65
() ₃ B	KOH	THF/H ₂ O	55
<i>n</i> -Oct—B()	NaOH	THF/H ₂ O	1
	TIOH	THF/H ₂ O	75
	Ti ₂ CO ₃	THF	60
	TIOH	benzene/H ₂ O	93

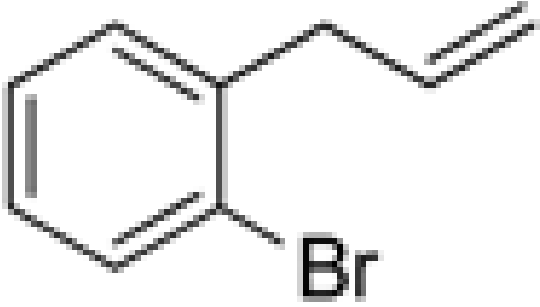
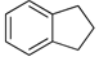
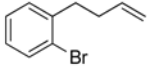
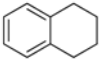
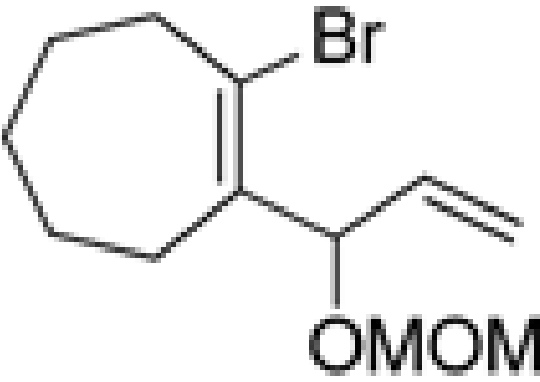
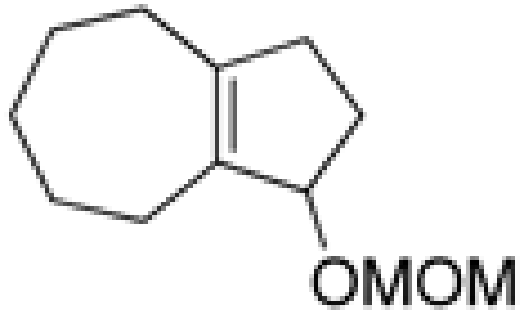
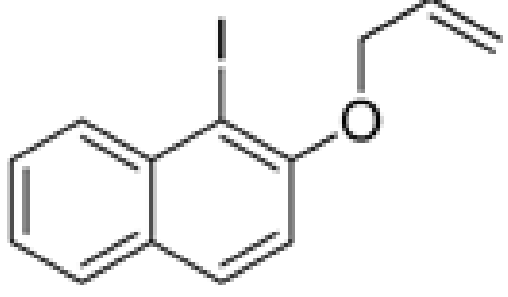
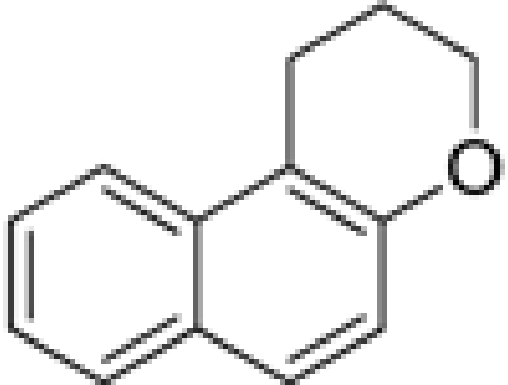
Borane	Base ^b	Solvent	Yield (%)
	KOH	THF/H ₂ O	trace
	TIOH	THF/H ₂ O	41
	Tl ₂ CO ₃	THF	93
	TIOH	THF/H ₂ O	34
	Tl ₂ CO ₃	THF	trace
<i>n</i> -Oct—B(OH) ₂	TIOH	THF/H ₂ O	trace

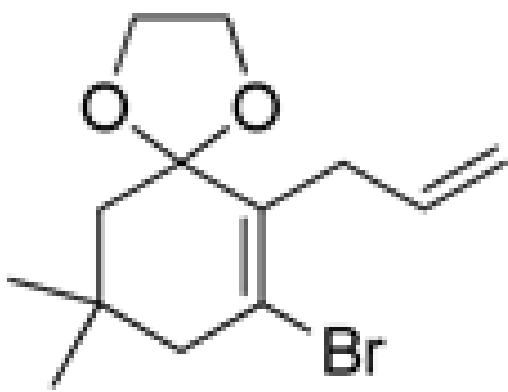
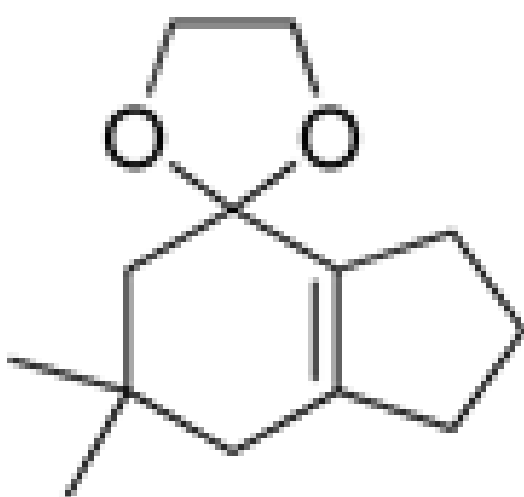
^a 3 mol% PdCl₂(dppf) was used at 50 °C,

^b 3 equiv of NaOH, KOH, TIOH and 1.5 equiv of Tl₂CO₃ were used.

Table 4

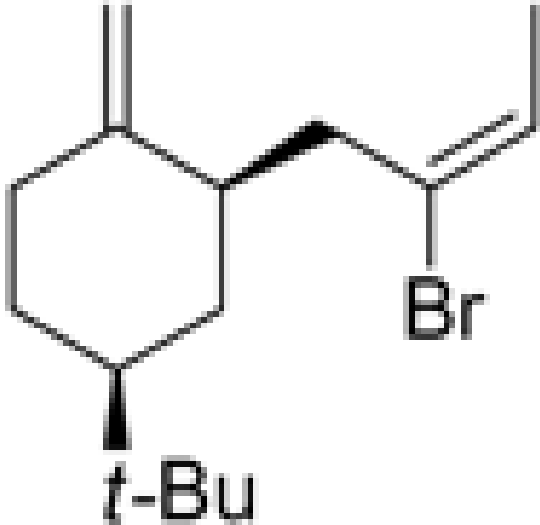
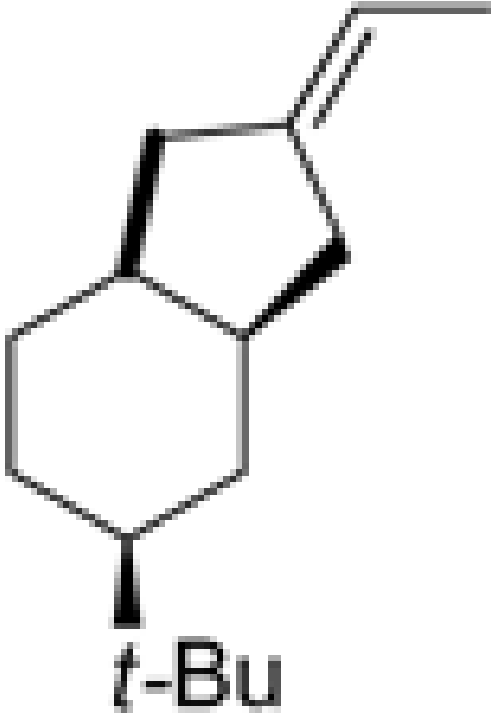
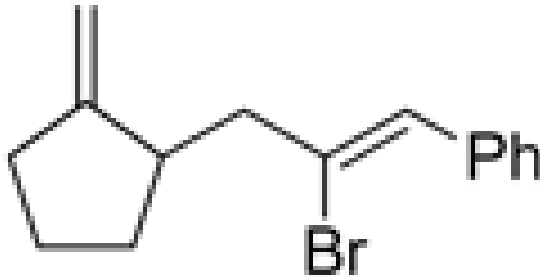
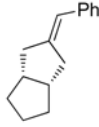
Cyclization of Haloalkenes via Intramolecular Suzuki Coupling (Suzuki and coworkers, 1989)

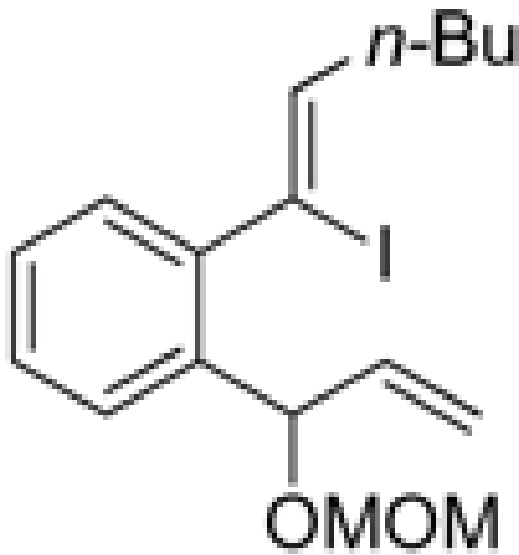
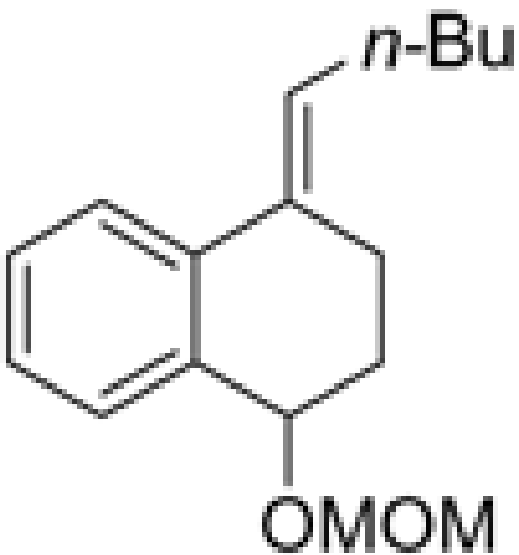
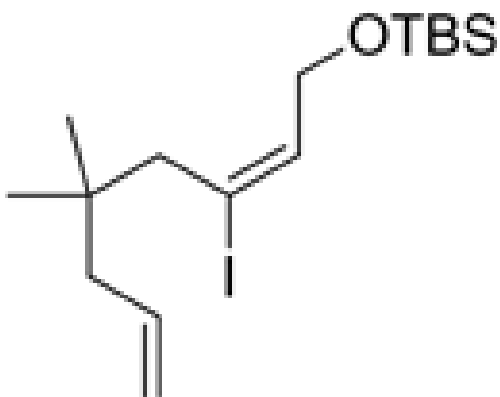
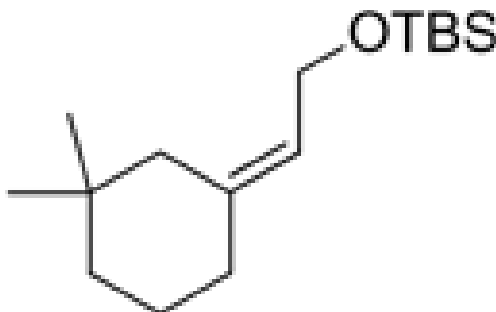
Entry	Haloalkene	Product	Yield (%)
1			86
2			66
3			68
4			70

Entry	Haloalkene	Product	Yield (%)
5			84

^aHydroboration was carried out with 9-BBN-H in THF at 0 °C-rt. for 4 h then cross-coupled intramolecularly in the presence of Pd(dppf)Cl₂ (1.5 mol%) and NaOH (3.0 equiv).

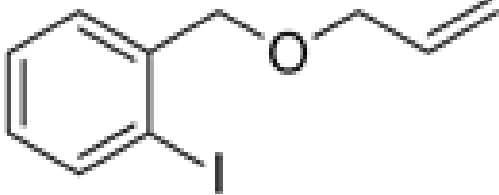
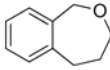
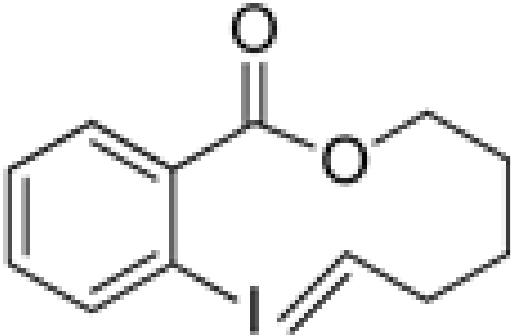
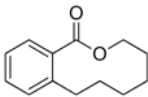
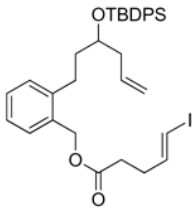
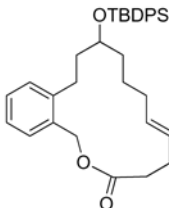
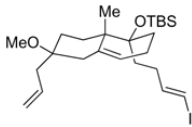
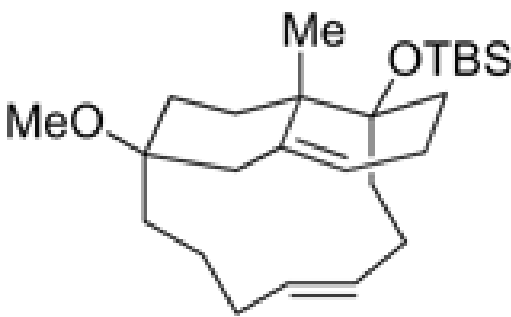
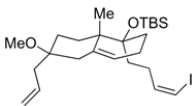
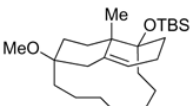
Table 5Synthesis of Exocyclic Alkenes (Suzuki and coworkers, 1992)^a

Entry	Haloalkene	Product	Yield (%)
1			68
2			83

Entry	Haloalkene	Product	Yield (%)
3			51
4			60

^aHydroboration was carried out with 9-BBN-H in THF at 0 °C-rt. for 4 h then cross-coupled intramolecularly in the presence of Pd(dppf)Cl₂ (1.5 mol%) and NaOH (3.0 equiv).

Table 6Macrocyclization via Suzuki-Miyaura Coupling (Danishefsky and coworkers, 2000)^a

Entry	Haloalkene	Product	Yield (%)
1			22
2			23
3			41
4			40, 60 ^b
5			46

^aHydroboration was carried out with 9-BBN-H in THF at 23 °C-rt for 1.5 h then cross-coupled (slow addition for 5 h) intramolecularly in the presence of Pd(dppf)Cl₂ (20 mol%), AsPh₃ (20 mol%), Cs₂CO₃ (3.0 equiv) and H₂O (40 equiv) in THF:DMF (10:1) (0.003 M).

^bH₂O (5 equiv) and preincubation with TIOEt (3 equiv).

Table 7Suzuki Coupling with Alkyl Boron Derivatives^a (Occhiato and coworkers, 2001)

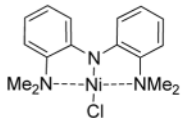
$$\begin{array}{c}
 \text{PG} \\
 | \\
 \text{C}_n\text{H}_{2n-1}\text{N} \\
 | \\
 \text{OTf}
 \end{array}
 + \text{R}^2\text{BX}_2 \xrightarrow[\text{K}_2\text{CO}_3 (3 \text{ equiv}), \text{Ag}_2\text{O} (2 \text{ equiv}), \text{toluene}, 80^\circ\text{C}]{\text{Pd(dppf)Cl}_2 (3 \text{ mol\%})}
 \begin{array}{c}
 \text{PG} \\
 | \\
 \text{C}_n\text{H}_{2n-1}\text{N} \\
 | \\
 \text{R}^2
 \end{array}$$

$n = 1, 2$

Substrate	Boronic acid or ester	Product

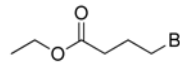
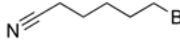
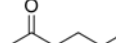

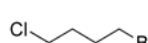
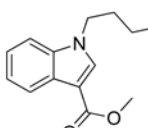
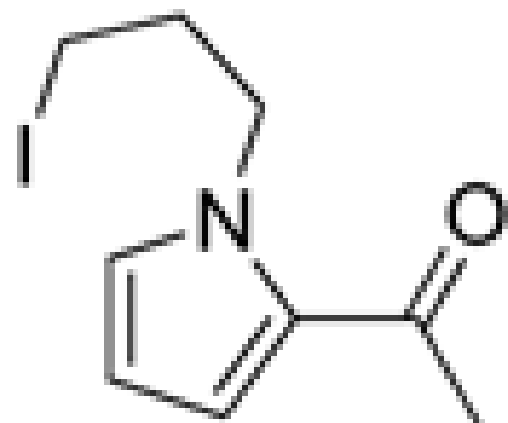
Table 8

Substrate Scope.



$\text{FG}-(\text{CH}_2)_n\text{-X} + \text{R}'\text{-MgCl} \xrightarrow[\text{DMA, -35 } ^\circ\text{C}]{\text{3-9 mol\%}} \text{FG}-(\text{CH}_2)_n\text{-R}'$

1.0 equiv. 56-99%

R-X	R'-MgCl	Yield
	<i>n</i> -Bu	85%
	<i>n</i> -Bu	77%
	<i>n</i> -Pent	60%
	<i>n</i> -Oct	79%
	<i>n</i> -Pent	91%
	<i>n</i> -Bu	91%
	<i>n</i> -Bu	93%

