T. Rovis and J. B. Johnson

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Transition-Metal Catalysis

More than Bystanders: The Effect of Olefins on Transition-Metal-Catalyzed Cross-Coupling Reactions

*Jeffrey B. Johnson and Tomislav Rovis**

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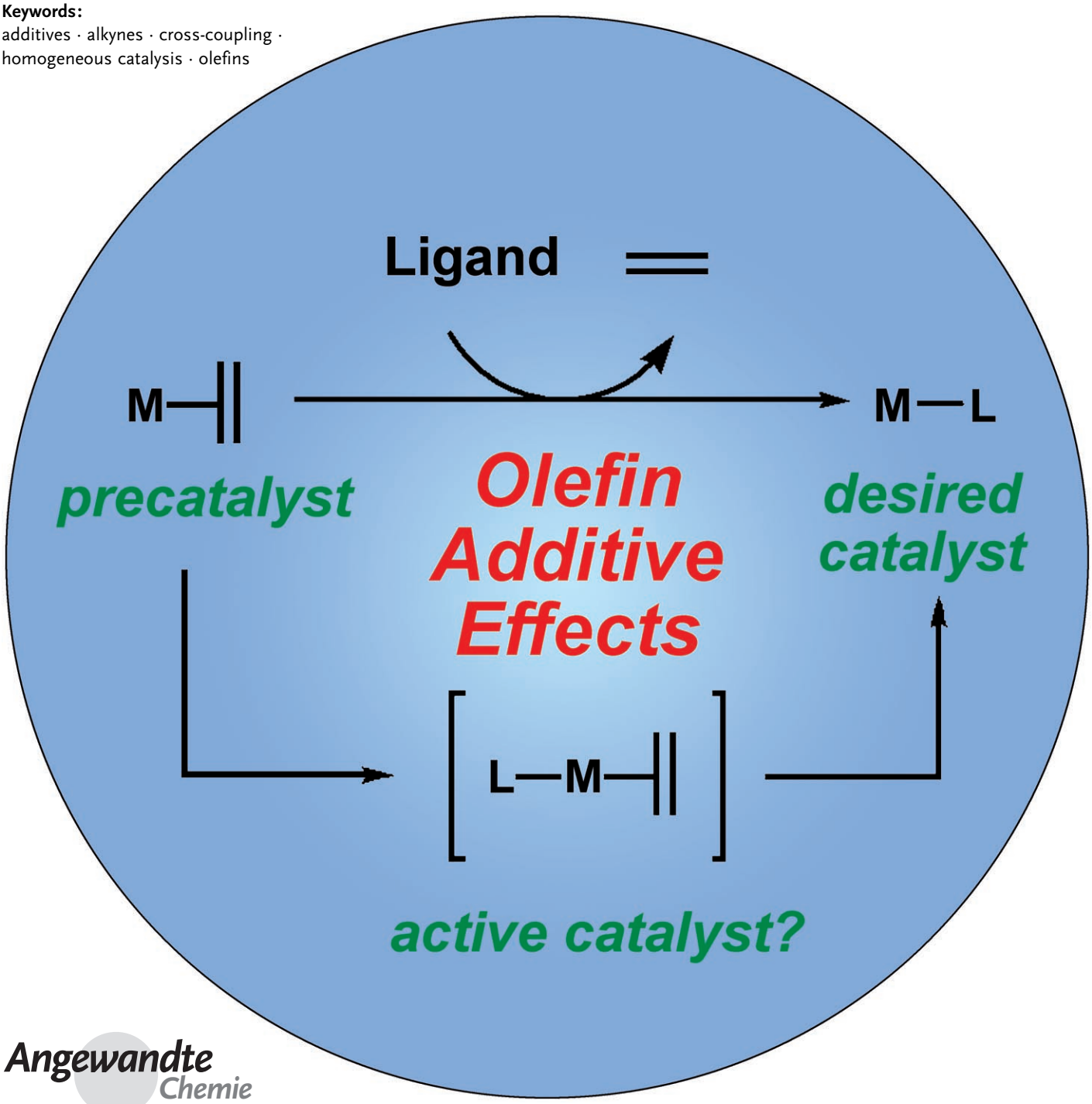

Olefins and alkynes are ubiquitous in transition-metal catalysis, whether introduced by the substrate, the catalyst, or as an additive. Whereas the impact of metals and ligands is relatively well understood, the effects of olefins in these reactions are generally underappreciated, even though numerous examples of olefins influencing the outcome of a reaction, through increased activity, stability, or selectivity, have been reported. This Review provides an overview of the interaction of olefins with transition metals and documents examples of olefins influencing the outcome of catalytic reactions, in particular cross-coupling reactions. It should thus provide a basis for the improved understanding and further utilization of olefin and alkyne effects in transition-metal-catalyzed reactions.

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1. Introduction

The power of transition-metal chemistry lies in the ability to tune reactivity with innumerable ligand and metal combinations. In addition to the innate properties of a given transition metal, ligand characteristics, such as steric and electronic characteristics, have a profound influence upon the nature of the reactive species and dictate the course of a reaction. Within the realm of transition-metal cross-coupling catalysis, dramatic effects have been observed on reaction efficiency and selectivity with relatively subtle changes in ligand properties. The steric and electronic properties of traditional ligands, most notably phosphines, can be readily tuned to achieve the desired reactivity. Other significant ligands include halides, the widely ranging effects of which have been recently reviewed,[1] as well as noncoordinating counterions.[2] An additional facet of transition-metal catalysis is the attenuation of reactivity with the inclusion of exogenous additives.[3] Each component of a given catalyst system offers a means of modification and the promise of new reactivity.

The impact of olefins on transition-metal catalysis is much less appreciated, despite their prevalence in such reactions, particularly from catalyst precursors such as $[Pd(dba)_2]$, $[Ni(cod)_2]$, and $[Rh(cod)Cl]_2$. These species contain one or more olefins that are generally dissociated in solution when combined with another ligand. The presence of these olefins often has a distinct impact on the reactivity. In addition to differing catalyst precursors, it has become an increasingly common practice to utilize olefins and alkynes as exogenous additives to manipulate reactivity. In carbon–carbon bond-forming cross-coupling methodology, olefin and alkyne additives have been reported to increase reaction efficiency, improve selectivity, and dictate new reaction mechanisms.

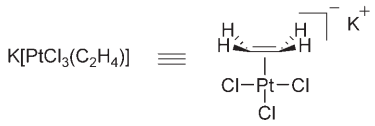
This Review provides a compilation of the effects of olefins and alkynes observed in transition-metal catalysis with a focus on the use of these species as cocatalysts in carbon–carbon bond-forming cross-coupling reactions. Section 2 describes the nature of metal–olefin complexes and the influence of olefin coordination on the electronic structure of the metal center. Section 3 briefly summarizes basic organometallic transformations, including oxidative addition, transmetalation, and reductive elimination, and Section 4 outlines the influence of olefins on these processes. Section 5 provides numerous examples of the effect of olefins on catalytic reactions. Although this section includes examples in which the olefins are contained within the substrates as well as alteration of catalyst precursors that contain olefins, the primary focus is on reactions that utilize exogenously added olefin and alkyne cocatalysts. Finally, Section 6 addresses the development of enantioenriched heteroatom-containing olefin and bisolefin ligands and their use in catalysis. Throughout, emphasis is given to the difference in reactivity in the presence and absence of the unsaturated species and modification of reactivity on the basis of the nature of the olefin, as well as to the rationale for the observed results. It is hoped that this Review will serve as a compilation of the numerous reports of the impact of olefins on carbon–carbon bond-forming cross-coupling reactions and function as a basis for the improved understanding and utilization of these effects in the development of such reactions.

2. Transition-Metal–Olefin Complexes

Transition-metal complexes with olefins have been known for nearly two hundred years; they were first prepared by Zeise in 1827 by the dehydration of EtOH with $K_2[PtCl_4]$.[4,5] When the structure of Zeise's salt $K[PtCl_3(C_2H_4)]\cdot H_2O$ was

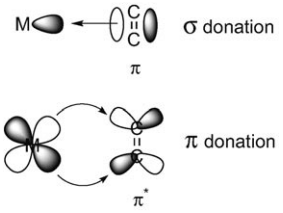
[*] Dr. J. B. Johnson, Prof. T. Rovis
Department of Chemistry
Colorado State University
Fort Collins, CO 80523 (USA)
Fax: (+1) 970-491-1801
E-mail: rovis@lamar.colostate.edu

finally elucidated in the 1950s,[6] it proved to be representative of olefin coordination to transition metals. Bonding of the metal center to both carbon atoms of ethylene results in an increase in the length of the C–C bond and bending of the C–H bonds away from the metal (Scheme 1). This change in



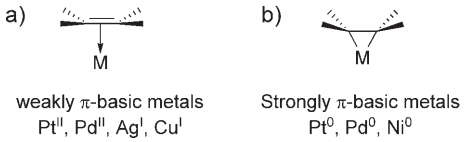
Scheme 1. Geometry of Zeise's salt, $K[PtCl_3(C_2H_4)]$.

geometry is most commonly described by the model of Dewar, Chatt, and Duncanson,[7] who proposed synergistic olefin-to-metal σ donation and metal-to-olefin π donation. The σ donation occurs from the highest occupied molecular orbital (HOMO) of the olefin, the C=C π electrons, to an empty orbital on the metal center, if available. Concurrent π backdonation occurs from an occupied metal d orbital to the lowest unoccupied molecular orbital (LUMO) of the olefin, the vacant π^* orbital. This backbonding weakens and lengthens the C–C bond and simultaneously results in a partial rehybridization of the carbon centers (Scheme 2).



Scheme 2. Schematic representation of donor–acceptor model for transition-metal–olefin complexes.

In general, the strength of the metal–olefin bond, which in turn relates to the length of the carbon–carbon bond, is dictated by the efficiency of the π backbonding. A weakly π-basic metal, such as Pt^{II} in Zeise's salt, provides minimal backbonding, and the resulting carbon–carbon bond length (1.375 Å) varies relatively little from that of free ethylene (1.337 Å).[5d] This complex can be represented as a simple π complex of the olefin and metal (Scheme 3a) and is typical



Scheme 3. Different binding modes in transition-metal–olefin complexes according to electronic characteristics of the metal center.

of olefin complexes from metals in high oxidation states. At the other extreme, coordination of an electron-deficient olefin with a strongly π-basic metal maximizes backbonding. In the Pt^0 complex $[Pt(PPh_3)_2(C_2CN_4)]$, the carbon–carbon bond of the olefin is extensively lengthened and can be best represented by a metallacyclopropane structure (Scheme 3b). Most transition-metal–olefin complexes lie between these two extremes.

Although computational quantification of the electronic effects of olefin coordination depends greatly upon a given metal–olefin combination and the level of theory utilized for calculation,[8,9] it is generally accepted that coordination of an olefin results in the removal of electron density from the metal center. This is particularly the case for π-basic metals with strong backbonding.

2.1. Trans Effects of Olefins

An important characteristic of any transition-metal ligand is its *trans* effect, defined as "the effect of a coordinated group on the rate of substitution reaction of ligands *trans* to itself."[10] The *trans* effect is a combination of the σ donation from ligand to metal and the π acceptance from metal to ligand. Olefins are generally quite weak σ donors, but excellent π acceptors, as outlined above. Taken in tandem, these characteristics give olefins a strong *trans* effect, thereby significantly weakening the metal–ligand bond of the substituent *trans* to the olefin. Although typically quantified for

Jeffrey Johnson was born and raised in Grand Forks, North Dakota, and received his BA in chemistry in 2000 from Gustavus Adolphus College. He earned his PhD in 2004 under the direction of Prof. Charles P. Casey from the University of Wisconsin-Madison, where he was an ACS Division of Organic Chemistry Fellow. As an NIH Postdoctoral Fellow at Colorado State University under the direction of Prof. Tomislav Rovis, he studied the catalytic desymmetrization of cyclic carboxylic anhydrides. He began his independent career in 2007 at Hope College in Holland, Michigan.

Tomislav Rovis was born in Zagreb in the former Yugoslavia but was largely raised in Southern Ontario, Canada. After his undergraduate studies at the University of Toronto, he earned his PhD there in 1998 under the direction of Mark Lautens. From 1998 to 2000, he was an NSERC postdoctoral fellow at Harvard University with David A. Evans. In 2000, he began his independent career at Colorado State University (CSU) and was promoted in 2005. He has been named a GlaxoSmithKline Scholar, Amgen Young Investigator, Lilly Grantee, Sloan Fellow, and Monfort Professor at CSU.

square-planar complexes, studies have shown that the sequence of ligand *trans* effects remains similar in octahedral complexes.[11]

As the *trans* effect of an olefin ligand is dominated by its capability for π acceptance, stronger *trans* effects are observed for more-electron-deficient olefins.

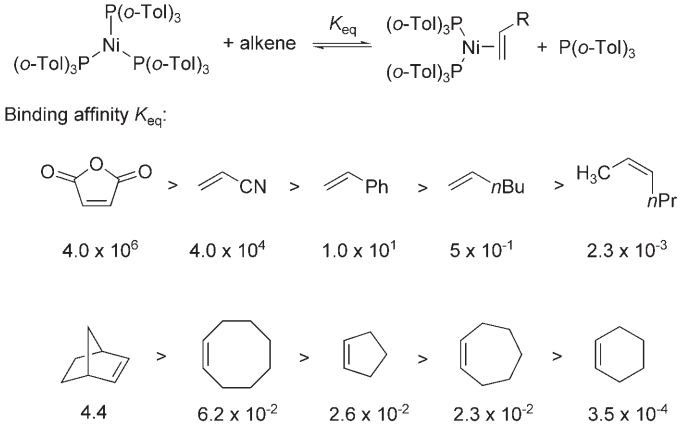
2.2. Additional Considerations: Binding Strength of Olefin Coordination

In addition to the electronic nature of the olefin, other factors must be taken into account to assess the strength of metal–olefin coordination, as stability is also a function of olefin structure. Coordination complexes are successively less stable with additional olefin substitution, and *cis* olefins generally bind more tightly than the respective *trans* isomers, presumably because of steric factors.[12] In addition, strained olefins such as norbornene bind particularly well to metal centers owing to the relief of ring strain upon carbon rehybridization and reduction of steric hindrance. These effects are illustrated below by the binding constants determined for a wide variety of transition-metal–olefin complexes.

2.2.1. Late-Transition Metal–Olefin Complexes

A significant number of studies have examined the effect of variables such as metal oxidation state, number of d electrons, and ligand properties on the strength of olefin binding to late transition metals.

Tolman studied the impact of olefin electronics on the binding strength (Scheme 4).[12b,13] Electron-deficient olefins

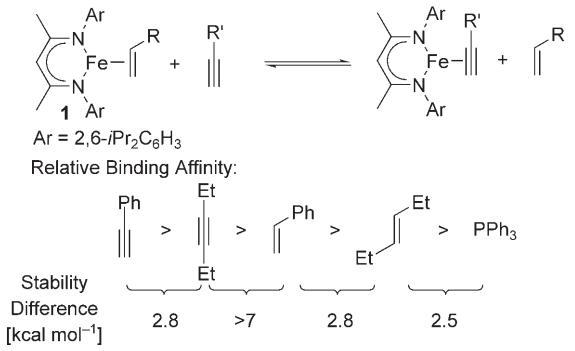


Scheme 4. Binding affinities of substituted and cyclic olefins to a Ni^0 complex. *o*-Tol = *ortho*-tolyl.

are bound more tightly than their electron-rich counterparts in metal complexes such as $[Ni^0\{P(o\text{-}Tol)_3\}_3]$, because of the predominance of π-backbonding from the metal.

Further studies by Tolman illustrate the impact of olefin strain energy on the strength of olefin coordination.[12c] A series of cyclic olefins were added to a solution of $[Ni^0\{P(o\text{-}Tol)_3\}_3]$; the corresponding equilibrium constants indicate that stronger metal–olefin binding occurs in olefins with greater strain energy (Scheme 4). This increased bond strength is due to the relief of ring strain experienced upon rehybridization of the carbon atoms of the olefin when π-backbonding occurs.

Holland and co-workers recently reported a study of the binding affinity of olefins and alkynes to low-coordinate Fe^I (Scheme 5).[14] Through a series of competitive binding

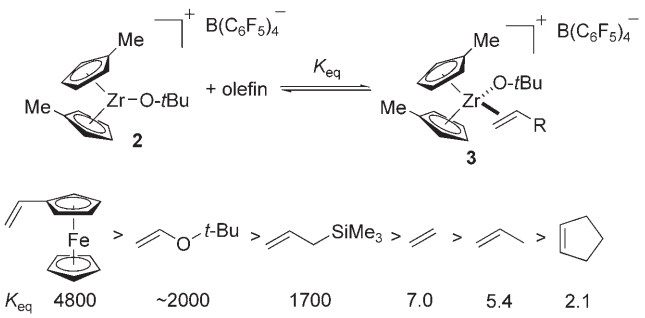


Scheme 5. Binding affinities of olefins and alkynes to a neutral Fe^I complex.

studies between similar olefins and alkynes, the authors determined that olefins bind more tightly to a Fe^I β-diketiminate complex than common ligands such as PPh_3, and alkynes in turn bind significantly more tightly than related olefins. The relative stability of the iron complexes is shown in Scheme 5. As expected, terminal olefins and alkynes form more-stable complexes than internal analogues.

2.2.2. Early-Transition-Metal–Olefin Complexes

Stoebenau and Jordan,[15] among others,[16] determined the binding constants of various olefins to early transition metals. The equilibrium constants for the binding of a series of olefins to cationic Zr^{IV} species **2** are provided in Scheme 6. In this case involving a d^0 metal, bonding is dominated by σ donation from the olefin. Thus, more-electron-rich olefins bind more tightly than electron-deficient olefins. In addition, substitution that stabilizes the partial cationic nature of the inner olefin carbon atom also increases the binding affinity. These



Scheme 6. Equilibrium constants of olefin coordination to a d^0 Zr^{IV} complex.

results are also consistent with binding dependence on the steric nature of the olefin.

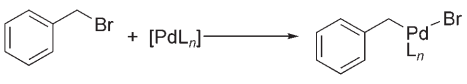
3. Organometallic Transformations

In the field of catalysis, there are several transformations that are common to the catalytic cycle of nearly every cross-coupling reaction: oxidative addition, transmetalation, and reductive elimination. In light of the importance of these steps, the nature of each is briefly examined below, particularly with regard to the influence of olefins and alkynes on the process.

3.1. Oxidative Addition

Oxidative addition, a component of the vast majority of cross-coupling catalytic cycles, is relatively well understood.[5e] There are numerous mechanisms for oxidative addition, and each has different optimum characteristics of the metal center.[5d] Several factors impact the efficiency of the oxidative addition process, including metal coordination and electronic characteristics, and these are readily altered through the judicious choice of ligands.

The impact of the electronic nature of substrates, including organohalides, ligands, and metals, in the oxidative addition process has been thoroughly explored. In numerous examples, aryl halides containing electron-deficient substituents undergo oxidative addition more rapidly than those containing electron-donating functionality. Although quantitative effects of metal properties are difficult to determine because of the innumerable ligand–metal combinations and different reaction mechanisms, several general trends have emerged. It is well understood that an increase in the electron density at the metal center generally results in more rapid oxidative addition (Scheme 7).[17] Ligands play a significant role in determining the electronic nature of the metal center: strongly electron-donating ligands favor oxidative addition.



Relative Rates:

$[Pd(PEt_3)_3]$ > $[Pd(PPh_3)_4]$ > $[Pd(PPh_3)_3CO]$

Scheme 7. Relative rates of oxidative addition of Pd^0 complexes to benzyl bromide.

Metal centers in lower oxidation states typically undergo more-facile reactions than their counterparts in high oxidation states, and the propensity to undergo oxidative addition increases down the periodic table (1st row < 2nd row < 3rd row), as 3rd row metals better stabilize higher oxidation states.[17] For the same ligand environment, the relative propensity of d^8 metals to undergo oxidative addition increases with increasing size and decreasing oxidation state of the metal center (Scheme 8).[17b]

Order of Activity for d^8 metals:

$Os^0 > Ru^0 > Fe^0$, $Ir^I > Rh^I > Co^I$, $Pt^{II} > Pd^{II} >> Ni^{II}$, Au^{III}

Scheme 8. Relative reactivity of d^8 metals in oxidative addition of H_2.

Olefin binding to a transition-metal center, particularly a late transition metal, is dominated by π-backbonding effects (see Section 2). As such, olefin binding generally demonstrates a net withdrawal of electron density from the metal center; thus, the coordination of one or more olefins generally reduces the reactivity of a metal center for oxidative addition.[5]

3.2. Transmetalation

Of the three basic steps of a common cross-coupling catalytic cycle, transmetalation is the least understood process. Numerous detailed kinetics studies have provided insight into specific mechanisms.[18] No clear overarching themes are consistent in all situations, but several discrete mechanisms have been identified. Although the relative transmetalation rate of substituents is understood in terms of hybridization[19] and electronic nature,[20] few quantitative studies have been performed examining the impact of the electronic nature of the metal center on the rate of transmetalation. For most transmetalation mechanisms, it is believed that an open coordination site is required, thus resulting in rate inhibition in the presence of excess ligand or when the substrate contains an olefin or alkyne.[21]

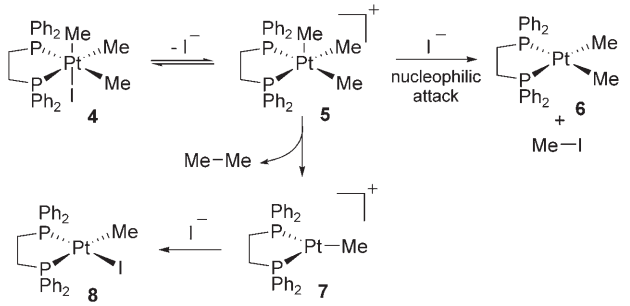
3.3. Reductive Elimination

As the reverse reaction of oxidative addition, reductive elimination has also been extremely well studied.[5,22] In contrast to oxidative addition, reductive elimination is typically facilitated by more-electron-deficient complexes and by systems containing bulky, sterically encumbering ligands.

Factors that greatly impact the rate of reductive elimination from a metal complex include electron density and coordination number.[5d,e] Greater positive charge on the metal center typically results in acceleration of reductive elimination. Thus, metals in higher oxidation states, including d^8 metals Ni^{II}, Pd^{II}, and Au^{III} and d^6 metals Pt^{IV}, Pd^{IV}, Ir^{III}, and Rh^{III}, undergo rapid reductive elimination. Also, oxidation of a metal center is a means of facilitating the elimination process.

The extent of ligand coordination also impacts the rate of reductive elimination. It has been observed that reductive elimination typically proceeds more rapidly from three- and five-coordinate metal centers relative to corresponding four- and six- coordinate centers.[23,24] This difference in rate, particularly with five-coordinate species, is generally attributed to the configurationally labile structures.[25] Thus, ligand

association or dissociation is commonly observed prior to reductive elimination from typical square-planar and octahedral complexes. The change in ligand environment may also serve a second purpose: dissociation of an electron-rich ligand simultaneously decreases the coordination number and the electron density of a metal center, thus accelerating elimination. This concept has been demonstrated by Goldberg and co-workers with the trimethylplatinum(IV) complex **4** (Scheme 9).[26] This species is stable until the dissociation of



Scheme 9. Dissociative mechanism of reductive elimination.

iodide. The resulting five-coordinate cation **5** then undergoes reductive elimination (with competing nucleophilic attack of iodide) to release ethane and platinum(II) complex **7**, which adds iodide to give the final product **8**. In a similar fashion, association of an electron-deficient ligand to a four-coordinate square-planar complex accelerates reductive elimination by simultaneously decreasing electron density at the metal center and altering the complex geometry by generating a five-coordinate species. Several examples of such reactivity with olefin ligands are provided below.

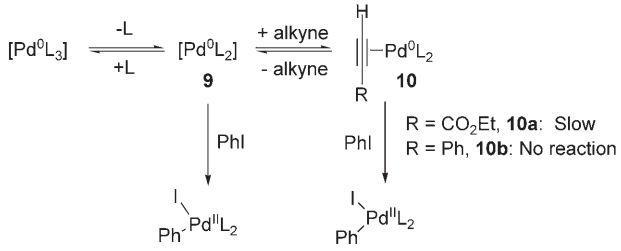
4. Additives to Stoichiometric Reactions

The effect of olefins on transition-metal-mediated reactions has become better understood through the detailed study of stoichiometric reactions. Summarized within this section are results from a number of such studies and discussion of the impact of olefins on basic organometallic transformations. Several examples also illustrate the influence of olefins upon product selectivity.

4.1. Olefin Effects on Oxidative Addition

An olefin ligand in a transition-metal complex influences oxidative addition by both altering the electronic nature and increasing the coordination number of a metal center. For oxidative insertion into a substrate, the metal center must be coordinatively unsaturated. Thus, oxidative addition is often preceded by ligand dissociation. Olefin ligands are generally quite labile, and thus easily dissociate to promote oxidative addition relative to more tightly bound ligands. In the presence of excess olefin, however, such as when this is utilized as a substrate, oxidative addition may suffer from severe inhibition because of the difficulty in achieving the coordinatively unsaturated complex.

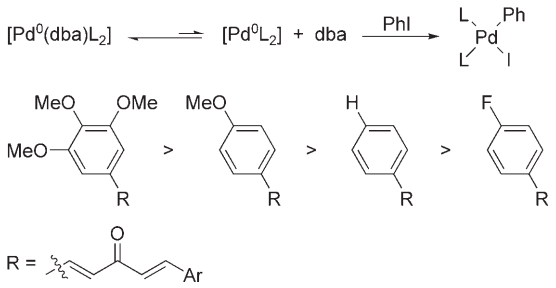
Amatore, Jutand, and co-workers have described the detailed mechanistic study of the oxidative addition of PhI to Pd^0 complexes.[27] The mechanism of oxidative addition of PhI to $[Pd(PPh_3)_4]$ has been established to proceed through two successive dissociation events to form $[Pd^0(PPh_3)_2]$ (**9**), which inserts into the carbon–iodide bond (Scheme 10). In the



Scheme 10. Mechanism for oxidative addition of PhI to $[Pd(PPh_3)_2]$.

presence of exogenous olefin or alkyne, this reaction is considerably slowed or completely hindered as result of olefin or alkyne coordination (to form **10**). Propiolate species **10a** is still active for oxidative addition, whereas the phenylacetylene analogue **10b** is inactive.

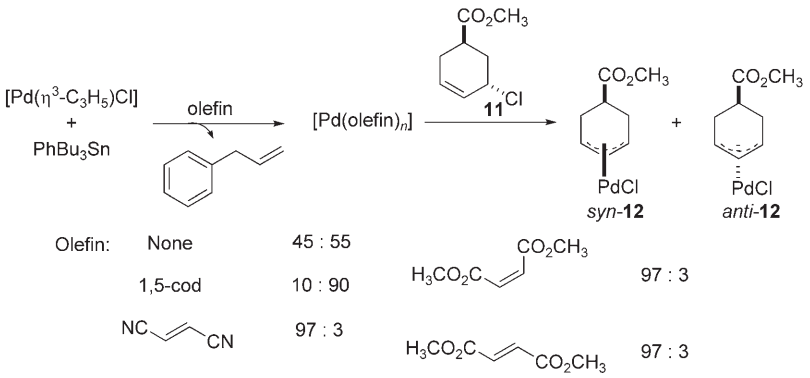
As the lability of an olefin ligand is related to the strength of coordination with the metal, differing ligand electronic characteristics may result in a more active metal center while preserving the structural scaffold. In a series of stoichiometric studies, Jutand, Fairlamb, and co-workers examined the reactivity of Pd^0 complexes generated by addition of PPh_3 to a series of $[Pd(dba)_2]$ or $[Pd_2(dba)_3]$ complexes with variable and symmetrical aryl substitution on dba (dba = dibenzylideneacetone; Scheme 11).[28] They observed that



Scheme 11. Relative reaction rate for oxidative addition of substituted $[Pd(dba)_2]$ complexes. L = PPh_3.

oxidative addition occurs more rapidly with electron-rich dba analogues, as electron density limits π-backbonding from the metal center, thus providing weaker and more labile coordination. Furthermore, complexes generated from $[Pd_2(dba)_3]$ are more active than their $[Pd(dba)_2]$ counterparts becuase of the lower concentration of olefin relative to palladium.

Ligated olefins may alter the typical course of reactivity. Kurosawa et al. reported that the stereochemistry of oxidative addition of Pd^0 and Pt^0 compounds to *trans*-5-methoxycarbonyl-2-cyclohexenylchloride (**11**) is altered by the presence of different olefin additives (Scheme 12).[29] A Pd^0–olefin complex, formed by reaction of [Pd(π-allyl)Cl] with $PhBu_3Sn$ in the presence of selected olefins, reacts by oxidative addition to allyl chloride **11** to provide the resulting [Pd(π-allyl)] complex **12**. In the absence of exogenous olefins, a 45:55 ratio of *syn*:*anti* products is isolated. In the presence of norbornene or cyclooctadiene (cod; 2 equiv relative to Pd), the *anti* product is formed preferentially (*syn*:*anti* = 1:9). When the additive is changed to a strongly electron-deficient olefin such as maleic anhydride, dimethylmaleate, dimethyl fumarate, or fumaronitrile, the *syn* complex is obtained in greater than 19:1 selectively. The authors propose that the use of more-electron-rich metal sources results in the *syn* product from direct nucleophilic displacement of the leaving group. In the presence of electron-deficient olefins, which withdraw electron density from the metal center, the formation of the π-allyl complex occurs by insertion into the carbon–chlorine bond. The variation in product distribution in these experiments clearly demonstrates the effect of exogenous olefin on oxidative addition. Further details of the structure of ligand–metal complexes and effects upon substitution can be found in reference [126].



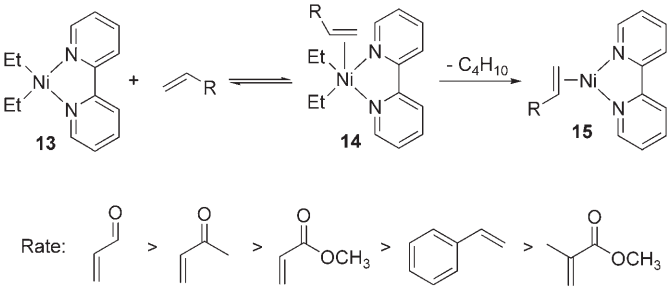
Scheme 12. Stereoselectivity of the oxidative addition of [Pd(olefin)$_n$] complexes with *trans*-5-methoxycarbonyl-2-cyclohexenyl chloride (**11**).

4.2. Olefin Effects on Reductive Elimination

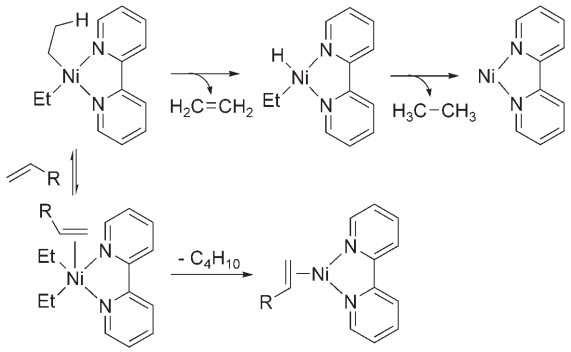
Yamamoto et al. reported a detailed study in 1971 on the impact of olefin additives on reductive elimination in the acceleration of the thermal decomposition of [Ni(bipy)(dialkyl)] complexes (bipy = bipyridine).[30] In the absence of an exogenous olefin, [Ni(bipy)Et_2] (**13**) decomposes by β-hydride elimination to release ethane and ethene as the primary products only with significant heating. Addition of an olefin significantly increases the rate of decomposition, which then occurs at room temperature. Decomposition provides nickel–olefin complex **15** and releases butane, formed by reductive elimination from **14** (Scheme 13). Electron-deficient monosubstituted olefins provide the greatest rate acceleration, and both electronic and steric factors impact relative reactivity.

Additional studies by Yamamoto and co-workers indicate that this acceleration process occurs through an associative mechanism, and accordingly they propose a pentavalent Ni^{II} intermediate.[31] Coordination of an electron-deficient olefin results in reduced electron density at the metal center, subsequently facilitating reductive elimination (Scheme 14). In these experiments with olefin additives, the reductive coupling product, butane, was obtained exclusively. There is no evidence for the formation of ethane and ethene, the products of a β-hydride elimination/reductive elimination sequence. It is believed that the coordination of olefins fills the vacant coordination sites required for β-hydride elimination to occur, thus inhibiting this process (Scheme 14).

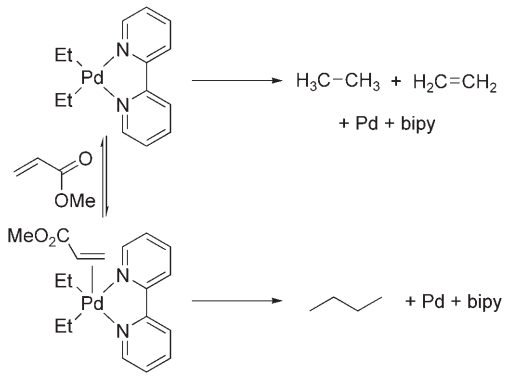
In a related example, Sustmann and Lau reported a distinct change in product composition with the presence or absence of methyl acrylate.[32] In the absence of an additive, thermolysis of [Ni(bipy)Et_2] yields not only butane, the coupling product, but also ethane and ethene.[33] In contrast, thermolysis of the analogous Pd complex [Pd(bipy)Et_2] yields the disproportionation products ethane and ethene (Scheme 15). When thermolyzed in the presence of methyl acrylate, however, [Pd(bipy)Et_2] decomposes to give exclusively butane. The use of more



Scheme 13. Associative pathway for facilitation of reductive elimination from a dialkyl nickel complex by coordination of electron-deficient olefins.



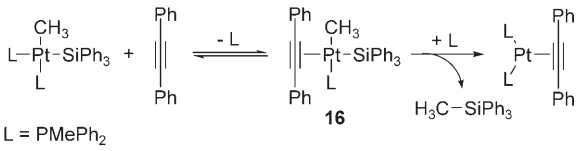
Scheme 14. Competitive pathways for reductive elimination and β-hydride elimination.



Scheme 15. The effect of methyl acrylate on the decomposition pathway of a dialkyl Pd(bipy) complex.

electron-deficient olefins, such as maleic anhydride, leads to a mixture of disproportionation and cross-coupling products. The authors propose an associative cross-coupling mechanism, in which coordination of methyl acrylate to the metal center serves both to induce reductive elimination and to prevent β-hydride elimination through occupation of a vacant coordination site. There are also numerous similar reports of olefin and alkyne assisted reductive elimination, primarily through an associative pathway.[34–38]

Ozawa et al. reported a similar olefin-accelerated reductive elimination from *cis*-[PtMe(SiPh$_3$)(PMePh$_2$)$_2$].[39] Instead of an associative mechanism, however, the authors suggest that the predominate reaction pathway proceeds through phosphine dissociation (formation of **16**), which is followed by reductive elimination (Scheme 16).

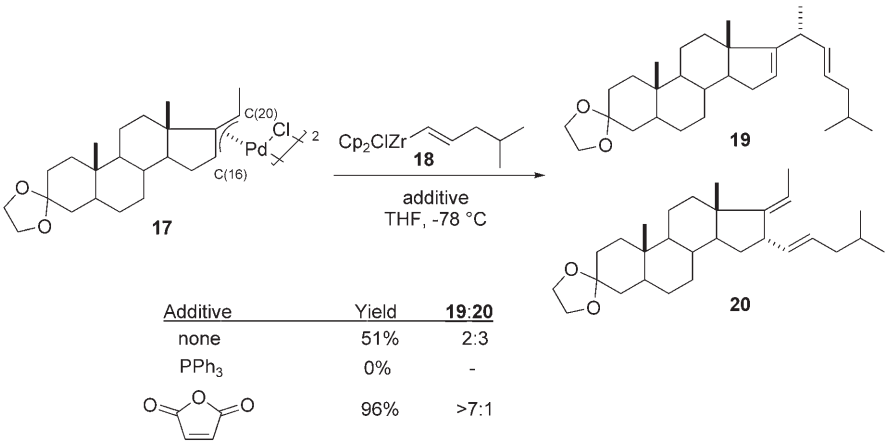


Scheme 16. Dissociative pathway for reductive elimination from a Pt^{II} complex.

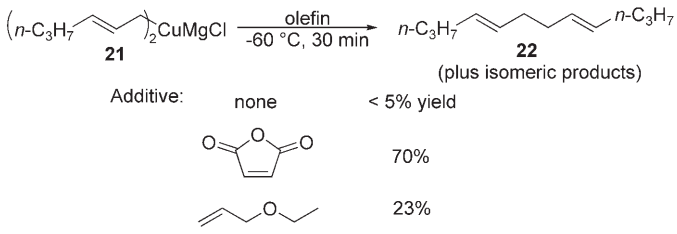
4.3. Olefin Effects on Product Selectivity

Schwartz and co-workers studied the coupling of preformed (π-allylic)palladium complexes with organozirconium species as a new route for steroid synthesis. They observed that the regiochemistry of the coupling product could be controlled, and the reaction accelerated, with the use of exogenous olefins (Scheme 17).[40] At room temperature, the coupling of palladium complex **17** and zirconium complex **18** is quite slow and is completely inhibited by addition of PPh$_3$. In the presence of maleic anhydride, however, the reaction proceeds to completion within 5 minutes, even at −78 °C. Furthermore, the regiochemistry of this coupling is influenced by exogenous olefins. In the absence of ligands, coupling products **19** and **20**, formed by reaction at the C(20) and C(16) carbons, respectively, were obtained in a 2:3 ratio (51 % yield) in addition to the reduction products. In the presence of maleic anhydride, the C(20) coupling product (**19**) was obtained in 96 % yield with greater than 7:1 selectivity.

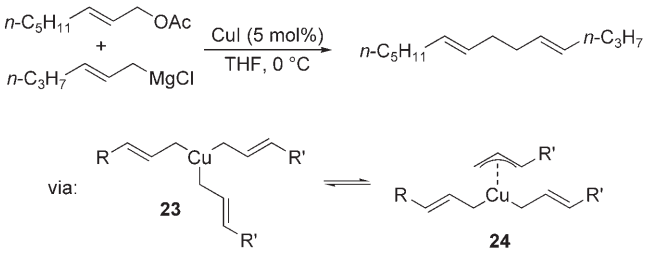
In examining copper-catalyzed coupling reactions of an allylic ester and a magnesium diallyl cuprate, Karlström and Bäckvall described the impact of olefin additives on product formation (Scheme 18).[41] Addition of either maleic anhydride or allyl ethyl ether results in significantly faster, and higher yielding, reductive elimination of **22** from diallylcuprate **21**. Ultimately, these control experiments were used to support a proposed triallyl Cu^{III} intermediate **23** and related isomers (**24**) in the catalytic coupling of allylic acetate and allylic Grignard reagent (Scheme 19).



Scheme 17. Additive effects in the coupling of π-allyl palladium complexes with organozirconium species.



Scheme 18. Acceleration of reductive elimination from a Cu^{I} species in the presence of olefinic additives.



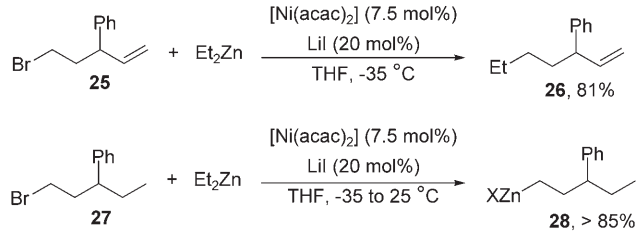
Scheme 19. Copper-catalyzed coupling of allylic esters and Grignard reagents with the proposed Cu^{III} intermediate.

5. Additives to Transition-Metal-Catalyzed Reactions

There have been numerous reports, particularly in recent years, of transition-metal-catalyzed reactions being greatly influenced by the presence of an olefin or alkyne. In some cases, the olefin functionality is contained within the substrate, and reaction is observed only when such unsaturation is present. This concept is taken further with the development of olefin-directed transition-metal-catalyzed reactions, for which the regiochemistry of a reaction is dictated by the tethered olefin. This section deals with reactions using exogenous olefins, in either stoichiometric or catalytic amounts, to control reactivity.

5.1. Olefin-Containing Substrates

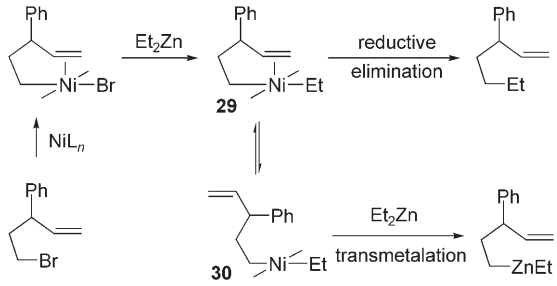
In the course of developing the Ni-catalyzed cross-coupling between sp^3 carbon centers, Knochel and co-workers observed that unsaturated primary alkyl bromide **25** undergoes facile coupling with diethylzinc to form **26**, whereas saturated alkyl bromide **27** fails to undergo similar coupling, providing only transmetalated product **28** upon warming (Scheme 20).[42] The authors attribute this phenomenon to an



Scheme 20. Ni-catalyzed reaction of Et_2Zn and alkyl bromides with and without olefin units.

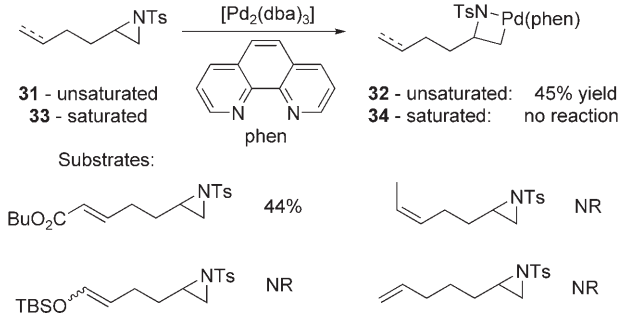
olefin-facilitated reductive elimination from Ni^{II}–dialkyl intermediate **29** (Scheme 21). If coordination of the olefin does not occur (**30**), or the olefin is not present, the dialkyl species proceeds through a transmetalation process.

Ney and Wolfe recently described their efforts toward the preparation of azapalladacyclobutanes by reaction of a palladium precursor with an aziridine.[43] In the course of these studies, they observed that, with a metal complex formed from $[Pd_2(dba)_3]$ and 1,10-phenanthroline, formation



Scheme 21. Associative pathway for facilitation of reductive elimination by coordination of an electron-deficient olefin to metal center.

of the desired metallacycle only occurs in a substrate containing a pendant olefin (Scheme 22). In the absence of other additives, addition to aziridine **31** produces palladium



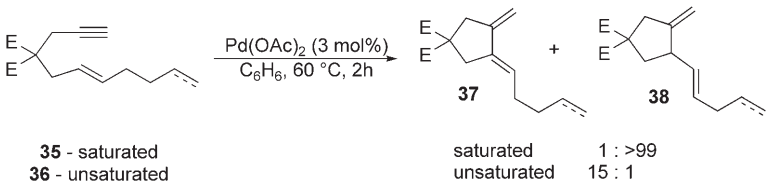
Scheme 22. Effect of pendant olefins on the formation of azapalladacyclobutanes. NR: no reaction.

complex **32**, which was isolated as an air-stable solid. No reaction, however, was observed under the same conditions with aziridine **33**. It should be noted that this reaction is not general, as product yields are very sensitive to tether length and both olefin geometry and electronic characteristics.

5.2. Substrate Directing Effects

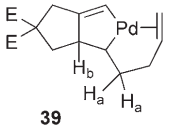
As olefins have been identified as good ligands in numerous transition-metal-catalyzed reactions, it is anticipated that they may also serve to direct regiochemistry or reactivity between similar functional groups. This concept has been thoroughly reviewed for other functional groups, such as alcohols, amines, and carbonyls,[44] but olefin-directed effects, particularly in the context of transition-metal-catalyzed cross-coupling, have received relatively little attention.

An early example of olefin directing effects was reported by Trost et al. in 1991.[45] The authors hypothesized that, a tethered olefin could direct β-hydride elimination in the Pd-catalyzed cycloisomerization of enynes and provide additional control over the product diene. Enynes **35** and **36** were used for comparison; the best regioselectivity was observed for $Pd(OAc)_2$ (Scheme 23). With 3 mol% $Pd(OAc)_2$, unsaturated enyne **36** was converted into conjugated cyclic diene **37** with 15:1 selectivity, whereas saturated enyne **35** selectively yields regioisomer **38**. The selectivity of elimination in the

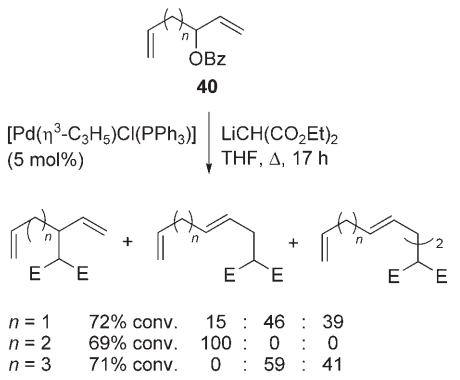


Scheme 23. Effect of pendant olefin unit on the chemoselectivity of β-hydride elimination. E = CO_2Me.

presence of the tethered olefin is attributed to intermediate **39**, in which olefin coordination constrains the geometry of the tether. This geometry precludes β-hydride elimination with H_a, leading to elimination with H_b.

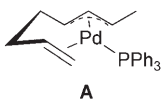


Krafft et al. reported the use of tethered terminal olefins to direct the regiochemistry of the palladium-catalyzed addition of malonate nucleophiles to allylic esters.[46] The impact of the tethered olefin is immediately evident on the [Pd(π-allyl)Cl(PPh_3)]-catalyzed addition of lithium malonate to allylic acetates with varying tether lengths. The results of these experiments clearly demonstrate the directing effect imparted by the olefin unit of species **40** (Scheme 24). With the correct tether length, the olefin directs the nucleophile selectively to the internal carbon atom of the

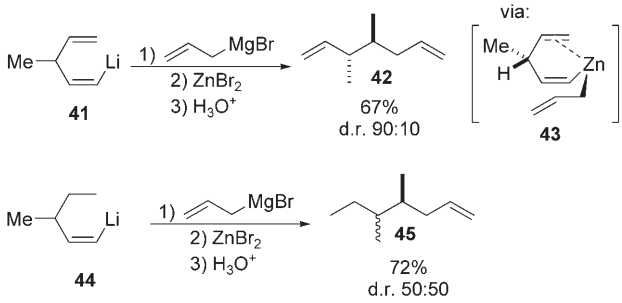


Scheme 24. Regioselective addition to π-allyl intermediates.

intermediate π-allyl species, overcoming steric bias. It is notable that, in the presence of excess PPh_3, all previously observed selectivity is lost, presumably because of the preferential coordination to palladium of PPh_3 relative to the terminal olefin. The authors propose that the selectivity is due to the changes in ring strain that occur upon nucleophilic attack on a proposed chairlike palladium allylene intermediate (**A**).

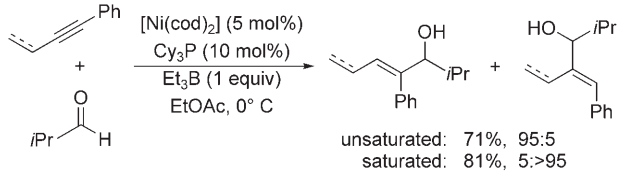


Marek et al. observed direction by a pendant olefin in the zinc-mediated coupling of vinyllithium and allyl Grignard reagents (Scheme 25).[47] The reaction of diene **41** with allyl magnesium bromide led to dimethylheptadiene **42** in 67% yield in a 90:10 ratio of diastereomers favoring the *anti* product. The authors speculate that the diastereoselectivity results from coordination of the pendant olefin (intermediate **43**, Scheme 25) prior to formation of the carbon–carbon bond. This conclusion was supported by the results of the coupling of allyl magnesium bromide with the terminally saturated vinyllithium **44**. In this case, no diastereoselectivity was observed in the corresponding product **45**. Similar directing effects attributed to π coordination in aryl groups have also been reported.[47,48]



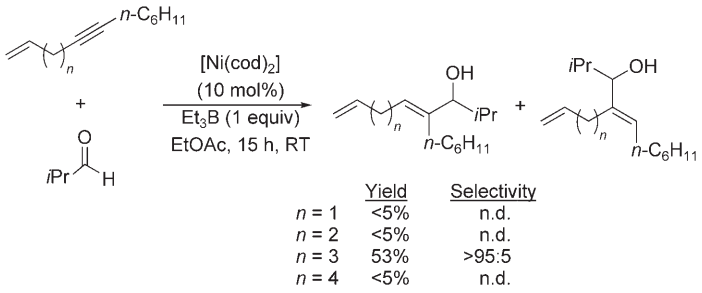
Scheme 25. Regioselective addition to π-allyl zinc intermediates.

Jamison and co-workers observed that tethered olefins can direct the regioselectivity of the nickel-catalyzed addition of aldehydes to alkynes. Initial work focused on the addition of aldehydes to conjugated enynes.[49] In these reactions, [Ni(cod)$_2$] facilitates the addition of aldehydes to form allylic alcohols with a regioselectivity of over 95:5 for addition to the distal carbon atom of the alkyne. The impact of this reaction was most obvious upon comparison with the analogous substrate lacking the directing olefin (Scheme 26).



Scheme 26. Regioselective addition of conjugated alkynes to aldehydes. Cy = cyclohexyl.

Regioselectivity can also be attained from nonconjugated olefins. A brief survey of tether lengths in the [Ni(cod)$_2$]-catalyzed (10 mol%) addition of alkynes to *i*PrCHO suggests that the inclusion of three methylene units between the terminal olefin and the internal alkyne is optimum for regioselectivity and, in fact, necessary for reactivity (Scheme 27).[50] The lack of reactivity for all substrates without the correct tether length indicates that in the absence of phosphine, the olefin must serve as a ligand to activate the metal center for reaction. This transformation is quite general for alkyl aldehydes and enynes, including those containing heteroatom tethers. Yields near 60% are typical for this transformation, and in all cases, selectivity greater than 95:5 is

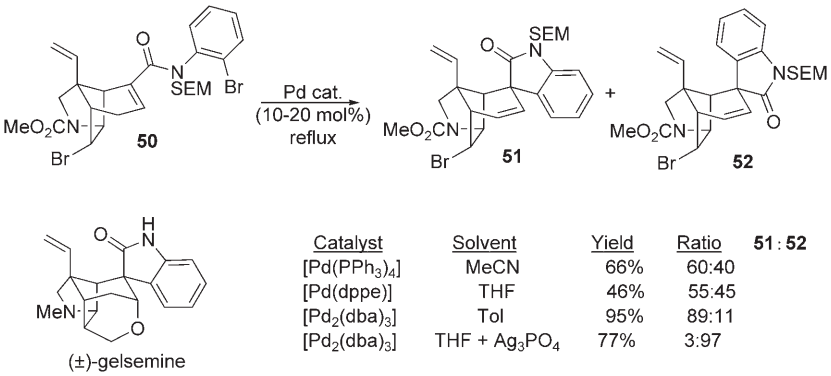


Scheme 27. Regioselective addition of enynes to aldehydes. n.d. = not determined.

observed for addition of the aldehyde on the alkyne carbon atom distal to the tethered olefin.

In an equally interesting result, Jamison and co-workers reported the complete reversal of regioselectivity upon addition of 20 mol% tricyclopentylphosphine (Cyp_3P).[51] Under these conditions, nearly complete (>95:5) selectivity is observed for aldehyde addition to the alkyne carbon atom proximal to the tethered olefin (Scheme 28). The authors attribute these two distinct, regioselective reactions to a reversal of reaction sequence in the presence of Cyp_3P (Scheme 29). In the absence of phosphine, the olefin and alkyne ligated Ni intermediate reacts first with the aldehyde to form intermediate **46**, which then reacts with Et_3B to form product **47** and close the catalytic cycle. In the presence of phosphine, the first reaction is with Et_3B to form intermediate **48**, which then reacts with aldehyde to form **49**. Montgomery and co-workers previously described detailed evidence for a similar deviation of mechanism in the presence of phosphines.[52]

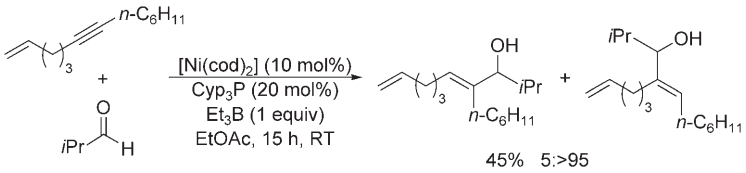
Olefin directing effects have also been utilized in the synthesis of significantly more complicated molecules, such as (±)-gelsemine by Overman and co-workers (Scheme 30).[53] The authors planned to generate the spiro-fused oxindole fragment by an intramolecular Heck reaction of aryl bromide **50**. As well as the potential complications because of the number of pendant functionalities, facial differentiation of the olefin also posed an obstacle: insertion from the α face leads to desired spirooxindole **51**, whereas insertion from the β face leads to undesired epimer **52**.



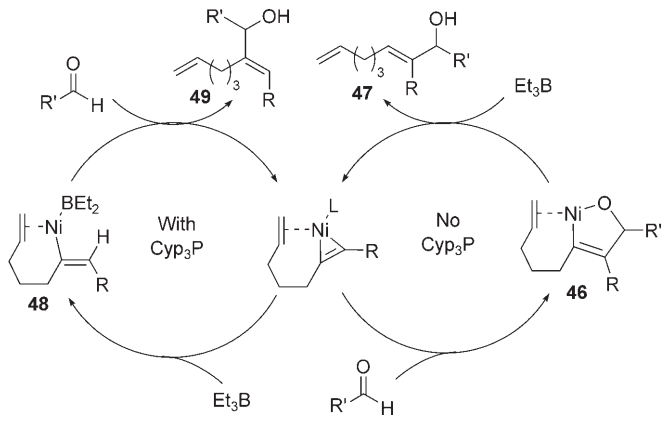
Scheme 30. Heck reaction in Overman's approach to (±)-gelsemine. SEM = (2-trimethylsilylethoxy)methyl, dppe = bis(diphenylphosphanyl)ethane.

Initial attempts using $[Pd(PPh_3)_4]$ led to unsatisfactory ratios of products **51** and **52**, typically around 3:2. The best selectivity for desired oxindole **51** was obtained by using $[Pd_2(dba)_3]$ in the absence of other ligands, which presumably allows coordination of palladium to the olefin to guide the reaction pathway. The proposed reactive intermediate **53** is depicted in Scheme 31a. However, attempts to utilize "ligandless" conditions, by using Ag_3PO_4 as an additive to extract the halide ion from the metal center after the oxidative addition, provide excellent selectivity, albeit for the undesired product (Scheme 31b). The authors propose that, in the absence of the halide, the more electrophilic cationic palladium center is stabilized by coordination to both the desired and the distant terminal olefin units (intermediate **54**), thus directing insertion to the β face. The authors make no mention of attempting to control the regiochemistry of the "ligandless" reaction by masking the second olefin unit.

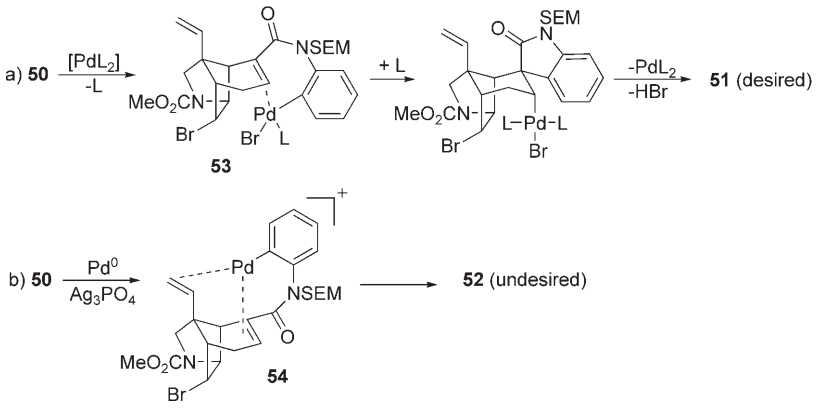
An example of the directing effects of olefins in the $ZnBr_2$-catalyzed insertion of aldehydes into silacyclopropanes was reported by Franz and Woerpel in 2000 (Scheme 32).[54] The insertion of butanal into silacyclopropane **55** proceeded in 70% yield with nearly complete control of regioselectivity (>99:1) and moderate diastereoselectivity of resulting heterocycle **56**. When the corresponding α,β-unsaturated aldehyde is used, a reversal of regioselectivity is observed: the regioisomeric silacyclopentane **57** was obtained in 60% yield



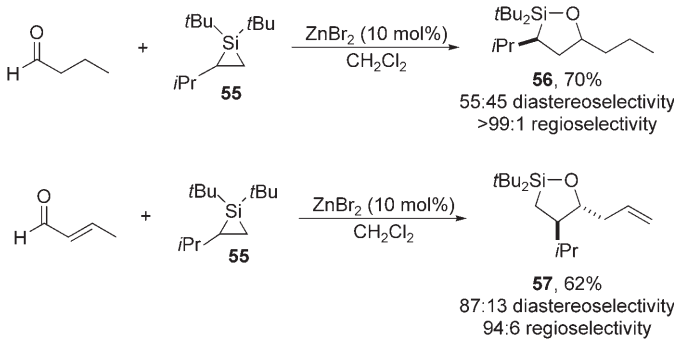
Scheme 28. Reversal of regioselectivity with addition of Cyp_3P.



Scheme 29. Mechanistic cycles in the presence and absence of Cyp_3P.



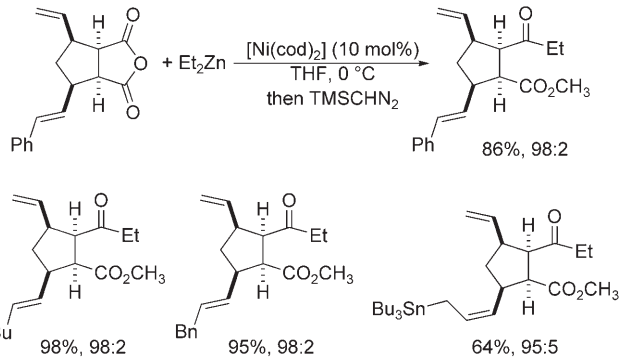
Scheme 31. The influence of Pd coordination to an olefin unit on event the reaction in Scheme 30. a) Formation of the desired isomer **51**; b) under "ligandless"conditions undesired isomer **52** is formed.



Scheme 32. Reversal of regiochemistry in aldehyde insertion into silacyclopropanes.

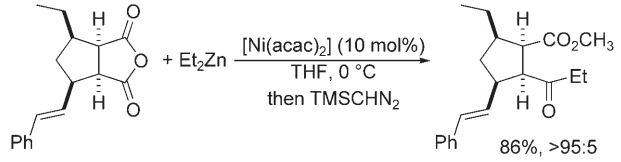
with a regioselectivity of 94:6 and a diastereoselectivity of 87:13. The authors suggest a different reaction pathway for unsaturated substrates, but have yet to propose mechanistic alternatives.

Rovis and co-workers have also explored reactions using previously developed anhydride alkylation chemistry to provide directing effects of olefins.[55] In earlier work, qualitative results suggested that styrene plays an intimate role in the nickel-catalyzed cross-coupling of carboxylic anhydrides with diethylzinc reagents.[127] Several cyclic anhydrides containing both a terminal and a substituted olefin were subjected to alkylation conditions with Et_2Zn using $[Ni(cod)_2]$ (10 mol%) as a catalyst; high selectivity was observed for alkylation of the carbonyl carbon atom proximal to the terminal olefin (Scheme 33). Variation of the substitution on the disubstituted olefin has only minor impact on the selectivity of the alkylation, which proceeds smoothly with a significant number of alkyl, aryl, and heteroatom substituents.



Scheme 33. Yields and regioselectivities for the alkylation of anhydrides directed by proximity to a terminal olefin. TMS = trimethylsilyl.

If the terminal olefin is selectively reduced, this alkylation protocol results in the selective formation of the complementary ketoacid, that is, the carbonyl carbon atom proximal to the disubstituted olefin is alkylated (Scheme 34). It appears that, in the absence of a terminal olefin, disubstituted olefins are capable of directing the alkylation. The highest regioselectivities for these reactions are obtained with the use of 10 mol% $[Ni(acac)_2]$. Although results vary with olefin substitution, typical selectivities are in excess of 95:5 and yields are above 85%.

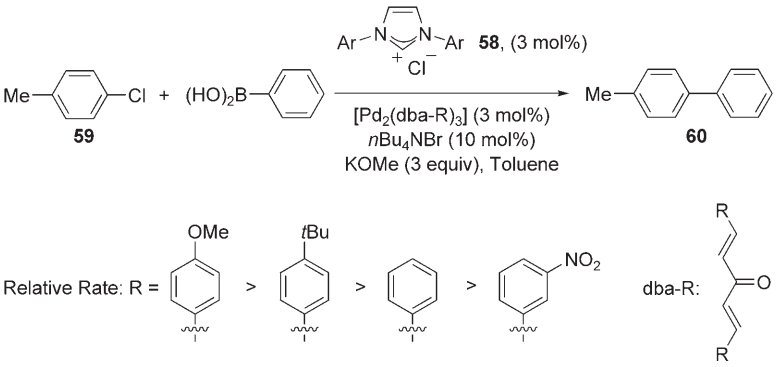


Scheme 34. Direction of alkylation by an internal olefin in the absence of a terminal olefin.

5.3. Catalysis by Preformed Olefin-Containing Complexes

Several detailed studies on cross-coupling reactions with olefin-containing catalyst precursors have quantitatively investigated the effect of altering the electronic nature of the olefin. Most of these efforts focused on the effects of changing the nature of palladium catalysts used in Suzuki–Miyaura coupling, typically with $[Pd_2(dba)_3]$ precursors. Mechanistic studies by Amatore and Jutand[56,27] indicate that the rate-limiting process in this coupling is the dissociation of dba to form a low-valent "Pd^0L_n" complex, which then undergoes oxidative addition with an organohalide.

Fairlamb et al. hypothesized that, by changing the electronic character of the coordinated olefin, they could tune the reactivity of the palladium catalyst by changing the rate of dba dissociation.[57] Thus, the authors prepared a series of substituted $[Pd(dba\text{-}R)_2]$ and $[Pd_2(dba\text{-}R)_3]$ complexes with methoxy, *tert*-butyl, dimethoxy, nitro, or trifluoromethyl substitution on the dba ligands (Scheme 35). Each catalyst precursor (3 mol% Pd), in the presence of the N-heterocyclic carbene formed from **58** (3 mol%), was tested for reactivity in the Suzuki–Miyaura coupling of 4-chlorotoluene (**59**) with phenyl boronic acid to produce biaryl **60**. The greatest

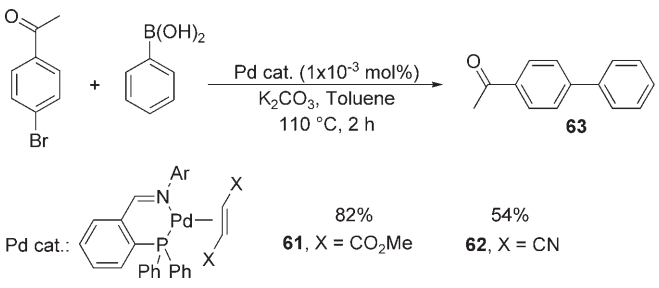


Scheme 35. The influence of dba substitution on the rate of Pd-catalyzed Suzuki–Miyaura coupling of 4-chlorotoluene and phenyl boronic acid. Ar = 2,6-iPr$_2$C$_6$H$_3$.

conversion over a 24-hour period was observed for the precursor with the most-electron-rich ligand (methoxy-substituted dba), whereas the lowest conversion was observed for the precursor with the most-electron-deficient ligand. The rate of coupling can be altered by over an order of magnitude for a constant catalyst framework. The authors attribute the change in catalytic activity to the strength of the palladium–olefin coordination. Electron-deficient ligands are known to enhance π-backbonding from the metal center, thus strengthening the Pd–olefin bond and reducing the equilibrium concentration of the unsaturated palladium complex.

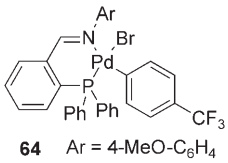
Unlike effects proposed for Negishi-type cross-coupling processes, the presence of olefins appears to have a greater influence on the oxidative-addition step rather than the reductive-elimination step of the catalytic cycle.

In related work, Scrivanti and co-workers provided evidence that olefins not only affect the rate of oxidative addition through formation of an active palladium species, but may also play a role in stabilization of the catalyst.[58] With a palladium(0) complex formed from an iminophosphine ligand and an olefin, very low catalyst loading (down to 1×10^{-3} mol% Pd) could be used to effect the coupling of 4-bromoacetophenone with phenylboronic acid in toluene at 110 °C (Scheme 36). By comparing reactions with methyl fumarate (**61**) and fumaronitrile (**62**) complexes, Scrivanti and co-workers could confirm the conclusion of Fairlanb et al. regarding the electronic nature of olefin ligands: They obtained yields of 82% and 54%, respectively, for the cross-coupling product **63** after 2 hours.



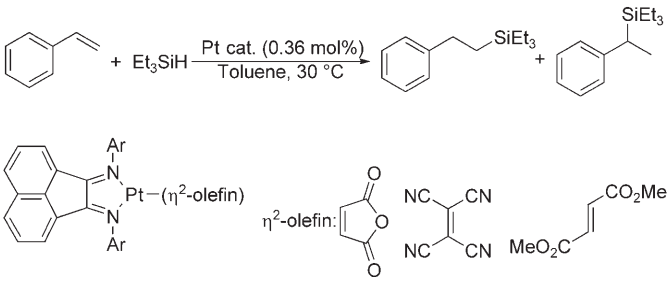
Scheme 36. Yields of cross-coupling product obtained with various olefin-substituted Pd catalysts. Ar = 4-MeOC$_6$H$_4$.

While studying catalytic activity, Scrivanti and co-workers observed that the electron-deficient olefin has a dual role. Assuming that a "naked" (iminophosphine)Pd species should show superior catalytic activity to olefin-containing complexes, they isolated Pd^{II} complex **64** and used it for catalysis in the complete absence of olefins. Surprisingly, a significant decrease in catalytic activity was observed, which they attributed to relatively rapid decomposition of the catalyst. More evidence was provided for this conclusion by a control experiment in which catalysts were subjected to typical reaction conditions but without the aryl bromide. At 90 °C, rapid decomposition of the methyl fumarate complex **61** was observed, whereas complex **62** is much more resistant to decomposition under identical conditions because of the strongly π-accepting fumaronitrile ligand. Thus, the olefin plays dual, conflicting roles in Suzuki–Miyaura coupling. It must dissociate to form the active palladium(0) species for oxidative addition, but simultaneously must stabilize the palladium(0) intermediates to prevent the formation of metallic palladium black.



64 Ar = 4-MeO-C$_6$H$_4$

Elsevier and co-workers investigated the effect of various olefin electronic characteristics on platinum-catalyzed hydrosilylation.[59] Bisimine platinum complexes with maleic anhydride, dimethyl fumarate, and tetracyanoethylene were synthesized and tested for their efficiency in catalyzing the hydrosilylation of styrene with triethylsilane (Scheme 37).

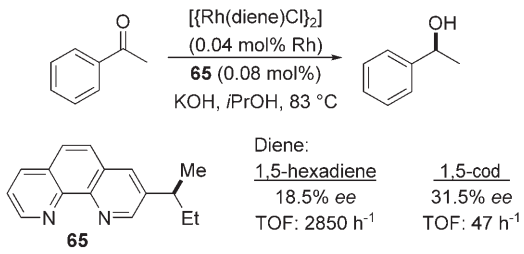


Scheme 37. Olefin-containing catalysts used for Pt-catalyzed hydrosilylation of styrene. Ar = 4-MeOC$_6$H$_4$.

The authors observed that, whereas the substitution on the bisimine ligand results in little change in catalytic activity, alteration of the olefin leads to significantly different results. Complexes containing maleic anhydride show higher initial reactivity, but decompose relatively quickly. In contrast, complexes formed with dimethyl fumarate react relatively slowly, but display no evidence for catalyst decomposition after 6 hours. The authors correlate these observations with the relative stability of the platinum–olefin complexes. The fumarate complexes that are more stable during synthesis are also more resistant to catalyst decomposition. The authors also speculate that the bisimine ligand may be more labile

than previously believed and that the olefin imparts the greatest influence on the reactive center during catalysis.

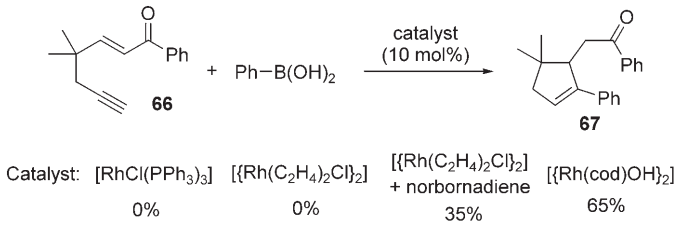
Diene ligands on preformed rhodium species have been shown to influence both catalyst reactivity and enantioselectivity. Gladiali et al. observed that cod-containing rhodium precatalysts behave differently in solution than analogous 1,5-hexadiene complexes.[60] When used in conjunction with optically active phenanthroline **65**, either species catalyzes the transfer hydrogenation of acetophenone (Scheme 38).



Scheme 38. Rhodium-catalyzed transfer hydrogenation of acetophenone. acac = acetylacetonate.

The rhodium-1,5-hexadiene species displays significantly more activity but with less selectivity than its cod analogue. The authors suggest numerous catalytically active intermediates, and the equilibria between these species, impacted by the binding strength of the diene, provide the variations in turnover frequency and enantioselectivity.

Chen and Lee recently reported a Rh-catalyzed transformation that illustrates the underappreciated influence of olefins.[61] In the presence of $[\{Rh(C_2H_4)_2Cl\}_2]$ and base, no reaction was observed between 1,5-enyne **66** and phenyl boronic acid. However, when norbornadiene was added to the catalyst precursor $[\{Rh(C_2H_4)_2Cl\}_2]$, cyclization product **67** was observed in 35% yield (Scheme 39). A rhodium catalyst containing a nonvolatile olefin, such as $[\{Rh(cod)OH\}_2]$, results in formation of **67** in 65% yield. The authors rationalize these results on the basis of the intermediacy of a rhodium–olefin species necessary for the desired transformation. This conclusion is further supported by the lack of reactivity observed with Wilkinson's catalyst.

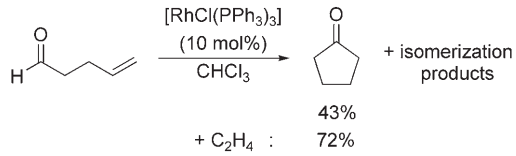


Scheme 39. The cyclization of enynes with olefin-containing Rh catalysts.

5.4. Exogenous Additives to Catalytic Reactions

Numerous examples have been reported in which the addition of exogenous olefins or alkynes has profound effects on catalytic activity, particularly with transition-metal-catalyzed cross-coupling reactions. In some cases the presence of the additive simply increases previously observed reactivity, whereas in others the additive is intimately responsible for the progress of the transformation. Olefin and alkyne additives are proposed to play different roles depending on the reaction: olefins may facilitate reductive elimination, assist in the formation of more-active catalytic intermediates for oxidative addition processes, and inhibit catalyst decomposition pathways, among other functions.

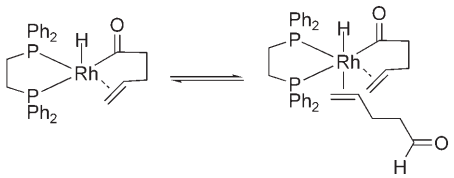
In an early example of the impact of an exogenous olefin on a transition-metal-catalyzed process, Miller and co-workers reported that rhodium-catalyzed cyclization of 4-pentenal proceeds more cleanly in ethylene-saturated chloroform (Scheme 40).[62] In the presence of 10 mol% of $[RhCl(PPh_3)_3]$, 4-pentenal was slowly consumed, and the desired cyclopentanone represented only 43% of the converted enal. In contrast, the use of ethylene-saturated chloroform increases the reaction rate and increases the fraction of desired product up to 72% of the converted enal. The authors suggest that the increased catalytic efficiency is a result of labile coordination of ethylene, which precedes decarbonylation of the intermediate acylhydride rhodium complex, one possible catalyst decomposition route.



Scheme 40. Rhodium-catalyzed cyclization of enals facilitated by ethylene.

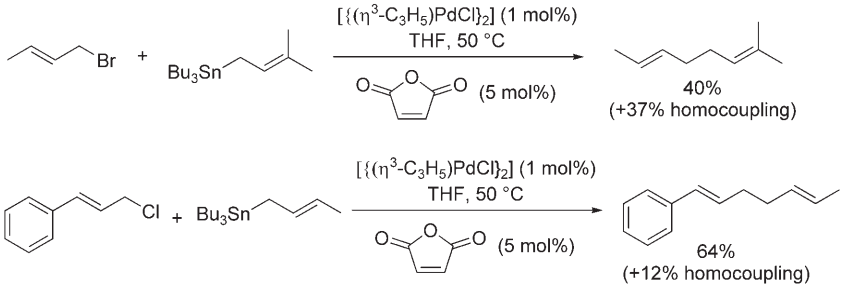
Fairlie and Bosnich report that in the same cycloisomerization of 4-pentenal to cyclopentanone, in this case catalyzed by $[Rh(dppe)]^+$ (dppe = bisdiphenylphosphinoethane), greater catalyst turnover numbers are attainable with increased substrate concentrations despite initial rate inhibition.[63] The authors attribute these observations to coordination of the substrate olefin to the active rhodium intermediate (Scheme 41). This coordination prevents decarbonylation, the most common decomposition pathway, as an open coordination site is required for this process, but also inhibits catalyst turnover, as there is competition for the sites required for cyclization.

In the investigation of the stoichiometric cross-coupling reaction of allyl palladium complexes with allyl tin reagents, Gollaszewski and Schwartz observed that no desired product



Scheme 41. Proposed intermediate of Pd-catalyzed cycloisomerization of 4-pentenal.

is formed: the only isolated species is a bis(η^3-allyl)palladium complex.[64] In the presence of an electron-deficient olefin, maleic anhydride, high yields of the corresponding 1,5-dienes are obtained. This information was used in the development of a palladium- catalyzed cross-coupling of allylic bromides and chlorides with allyl tin reagents using maleic anhydride as a cocatalyst. In the presence of (η^3-allyl)palladium chloride dimer (1 mol%), the coupling of a series of allyl chlorides and bromides with trialkylallyl tin reagents proceeds in moderate yields (Scheme 42). In all cases, the addition of 5 mol% of

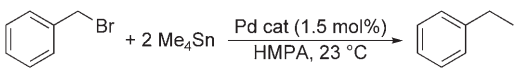


Scheme 42. Palladium-catalyzed coupling of allyl halides with allyl stannanes facilitated by maleic anhydride.

maleic anhydride is necessary for reactivity and produces the *E*-configured cross-coupling products. By-products, primarily homocoupling products from either reagent, are also isolated in variable yields. On the basis of the evidence provided by the stoichiometric experiments, the authors propose that maleic anhydride is required for the facilitation of reductive elimination from the bisallyl palladium species and closing of the catalytic cycle.

Sustmann et al. reported an early example of the use of additive olefins to dictate product selectivity. In earlier work (see Scheme 15), the authors reported the influence of olefins on the reductive elimination from a diethylpalladium complex similar to that proposed by Stille as an intermediate in the cross-coupling of aryl halides with organotin reagents.[32,65] Therefore, Sustmann et al. used olefin adducts to examine the palladium-catalyzed cross-coupling of alkyl bromides with tetramethylstannane.[66]

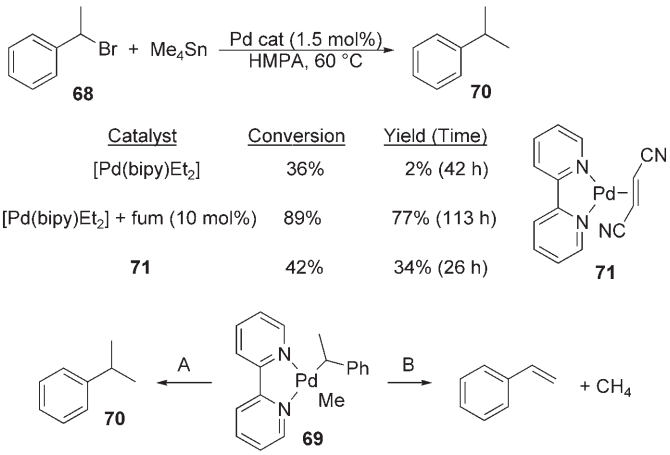
The coupling of benzyl bromide with tetramethylstannane (2 equiv), catalyzed by [Pd(bipy)Et$_2$] (1.5 mol%) in HMPA, proceeds in excellent yields and selectively forms ethylbenzene (Scheme 43). Upon reaction in the presence of catalytic fumaronitrile (3 equiv relative to Pd) or with [Pd(bipy)(fumaronitrile)] (1.5 mol%), a slight, qualitative retardation of the reaction rate is observed. Under these conditions, the coupling product is isolated in high yield. However, with substrates containing β-hydrogen atoms, for example alkyl bromide **68**, significantly different reactivity is observed (Scheme 44). When [Pd(bipy)Et$_2$] is used as the



Scheme 43. Palladium-catalyzed coupling of benzyl bromide with tetramethylstannane. HMPA = hexamethylphosphoramide.

catalyst, only 36% conversion of the alkyl bromide is observed. The primary product of this reaction is styrene, presumably formed from β-hydride elimination from proposed dialkyl palladium intermediate **69** (path B in Scheme 44). The presence of fumaronitrile, however, has significant impact on the reaction.[67] With addition of 5 mol% fumaronitrile, the conversion increased to 72% over 66 hours and gave isopropylbenzene (**70**) from the cross-coupling of the alkyl bromide and tetramethylstannane as the primary product (61% yield) (path A in Scheme 44,). The use of fumaronitrile-containing catalyst **71** led to very similar results, yielding the cross-coupling product in 34% yield after 26 hours.

These examples provide significant insight into the effect of electron-deficient olefins on the behavior of dialkyl palladium complexes. The authors propose that the coordination of fumaronitrile to the palladium dialkyl intermediate precludes the availability of an open coordination site on palladium required for β-hydride elimination. It is further speculated that the electron-deficient nature of the olefin removes electron density from the metal center, thus facilitating reductive elimination of the sp^3-hybridized alkyl substituents. Acceleration of this event effectively limits the



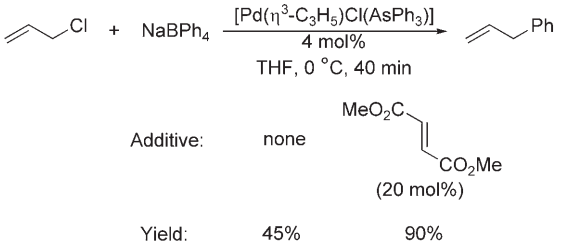
Scheme 44. Palladium-catalyzed coupling of 1-bromo-1-phenylethane (**68**) with tetramethylstannane and two possible reaction pathways for the proposed dialkyl palladium intermediate **69** (A: reductive elimination; B: β-hydride elimination).

lifetime of the dialkyl intermediate and reduces the time in which β-hydride elimination can occur.

Kurosawa et al. observed that the nature of the allylic chloride substrates has a distinct impact on the efficiency of Pd-mediated cross-coupling reaction of allyl halides.[68] Further investigation indicated that reductive elimination is promoted by the allylic chloride, and the relative ease of olefin coordination to a Pd^{II} intermediate relates directly to the rate of reductive elimination. To follow up on these initial observations, Kurosawa et al. investigated the effects of a series of exogenous olefin ligands on the efficiency of the catalytic cross-coupling of various allylic chlorides with

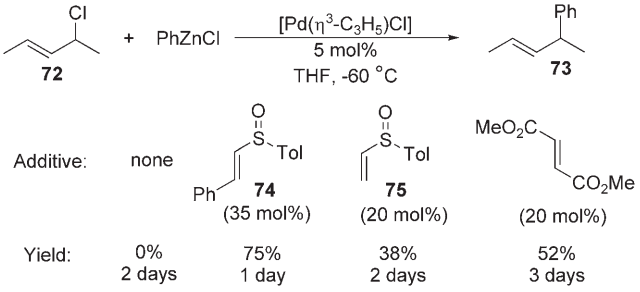
boron, zinc, and tin nucleophiles.[69] In each case, qualitative rate data suggests that the presence of the olefin results in more-facile coupling and catalyst turnover.

The coupling of allyl chloride with sodium tetraphenylborate catalyzed by $[Pd(\eta^3\text{-}C_3H_5)Cl(AsPh_3)]$ proceeded to 45% completion after 40 minutes in the absence of exogenous olefin, but provided the coupling product in 90% yield after 40 minutes in the presence of a catalytic amount of dimethyl fumarate (Scheme 45). Likewise, the reaction of



Scheme 45. Increase in catalytic activity with addition of dimethyl fumarate in the cross-coupling of allyl chloride with tetraphenylborate.

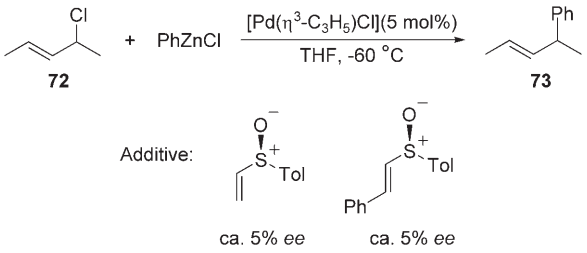
allylic chloride **72** with PhZnCl in the presence of $[Pd(\eta^3\text{-}C_3H_5)Cl]$ as a catalyst failed in the absence of an olefinic additive, but produced the desired coupling product **73** in the presence of a vinyl sulfoxide or dimethyl fumarate (Scheme 46).



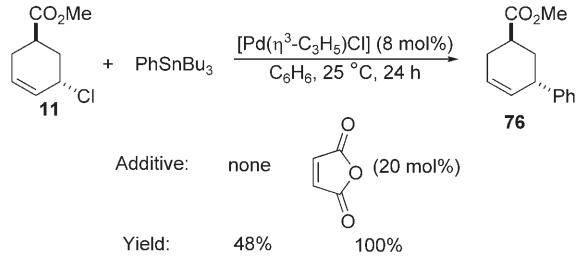
Scheme 46. Increase in catalytic activity with addition of dimethyl fumarate or vinyl sulfoxides in cross-coupling of allylic chloride and phenyl zinc chloride.

On the basis of the probable intimate role of the olefinic additives, Kurosawa et al. attempted to induce asymmetry in the coupling product by using (*R*)-(+)-tolylvinylsulfoxide and (*R*)-(+)-tolylstyrylsulfoxide. Unfortunately, the corresponding phenyl adduct was obtained with less than 5% *ee* in each case (Scheme 47).

Kurosawa et al. also examined the coupling of *trans*-5-methoxycarbonyl-2-cyclohexenyl chloride (**11**) with tributylphenylstannane (Scheme 48).[69] Again, a significant difference was observed with the inclusion of an olefin, in this case maleic anhydride. In the absence of olefin, 48% of the desired coupling product **76** was obtained after 24 hours. In the presence of maleic anhydride, however, the desired product is obtained in quantitative yield.

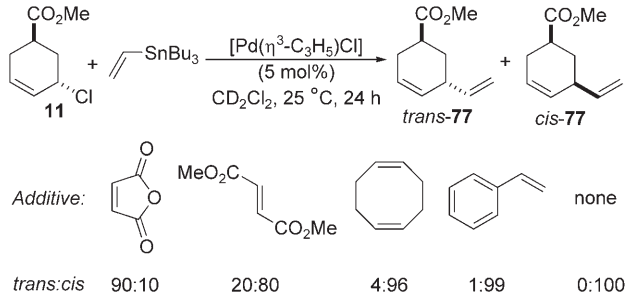


Scheme 47. Use of enantioenriched sulfoxides as additives in the Pd-catalyzed coupling in Scheme 46.



Scheme 48. Addition of maleic anhydride results in faster reaction and higher product yields in coupling of allyl chloride **11** with phenyltributyltin.

Further insight into this reaction was obtained with the use of **11** and tributylvinylstannane. In the absence of an olefinic additive, only the *cis* coupling product was obtained. The ratio of *cis* to *trans* products changes with additives and culminates in a nearly complete reversal of selectivity with the use of maleic anhydride (Scheme 49). The authors attribute

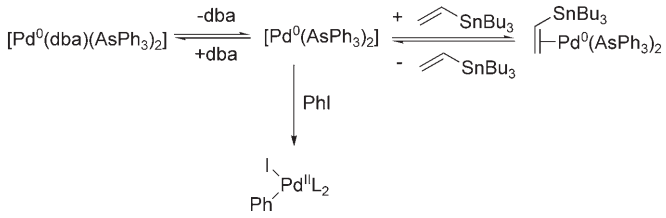


Scheme 49. Variation in *trans*:*cis* product ratio of **77** with the use of various olefinic additives.

this effect to the stereochemically different pathways of the Pd^0 intermediate in the oxidative addition. In previous work, the authors observed that $[Pd(PPh_3)_4]$ undergoes oxidative addition with *anti* selectivity, whereas oxidative addition with $[Pd(\text{maleic anhydride})_n]$ has *syn* selectivity (see Scheme 12).[29]

A number of palladium catalyzed cross-coupling reactions, including Stille and Heck reactions, are initiated by oxidative addition of an aryl halide to a Pd^0 complex. Amatore, Jutand, and co-workers, in studying these reactions, observed that when the nucleophile contains an olefin, such as a vinyl stannane or a terminal olefin, it may also participate in the oxidative addition step.

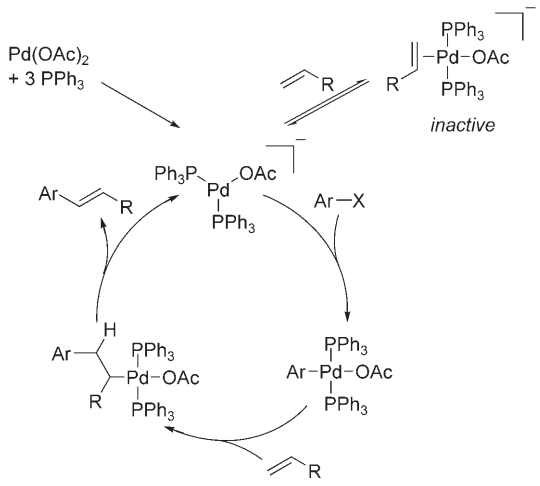
A common efficient catalyst precursor in Stille reactions, the combination of $[Pd(dba)_2]$ and $AsPh_3$, forms the active species for oxidative addition: solvated $[Pd(AsPh_3)_2]$.[70] This species, however, is formed in only trace concentrations in equilibrium with the inactive dba-coordinated complex (Scheme 50). The coupling partner tributylvinylstannane



Scheme 50. Formation of the active palladium species and inhibition by excess vinyl stannane.

may also coordinate the Pd center, further decreasing the concentration of the active species available for oxidative addition. Thus, somewhat counterintuitively, the rate of Stille coupling may be significantly decreased by increased concentrations of the nucleophile.

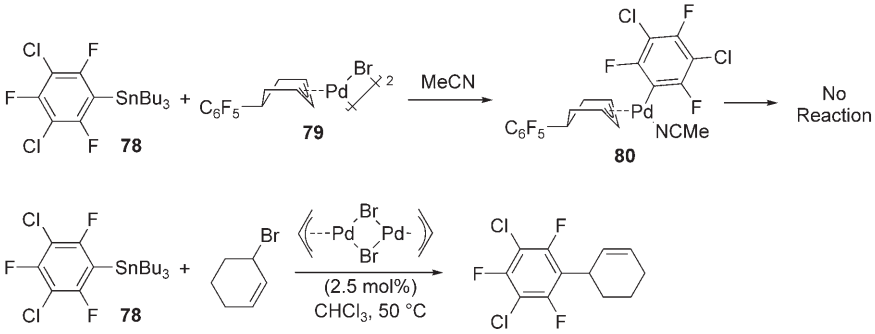
Similar effects have been observed in Heck couplings with $[Pd(dba)_2]$ or $Pd(OAc)_2$ and PPh_3 as the catalyst.[71,72] In each case, the low-coordinate Pd^0 species, $[Pd(PPh_3)_2]$ or $[Pd(PPh_3)_2(OAc)]^-$, respectively, are the most active species for oxidative addition with phenyl halide. Coordination compounds formed by complexation of the substrate are generally inactive toward this reaction, and thus are not in the active catalytic cycle. Like in the Stille reaction, excess olefin substrate may inhibit oxidative addition, as it simultaneously accelerates olefin insertion. The catalytic cycle of the Heck reaction, including the participation of the olefin as both an inhibitor and substrate, is shown in Scheme 51.



Scheme 51. Simplified catalytic cycle of Heck reaction depicting inactive species formed by early olefin complexation.

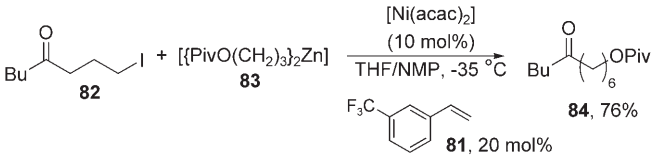
Amatore, Jutand, and co-workers have recently explored the effect of alkynes on the rate of the processes within the palladium-catalyzed Sonogashira reaction of terminal alkynes with phenyl iodide.[73] Under catalytic conditions, it appears that terminal alkynes play a dual role, both as an inhibitor of oxidative addition and as a substrate in the carbopalladation step. Under catalytic conditions, increasing concentrations of alkyne decelerate oxidative addition and increase the rate of carbopalladation. The authors propose that these interactions increase the overall efficiency of the catalytic cycle by bringing the rates of each step closer to one another.

Espinet and co-workers report an intriguing example of the impact of substrate olefins on the Pd-catalyzed cross-coupling of allyl halides and aryl stannanes.[74] Both the stoichiometric and catalytic reactions are illustrated in Scheme 52. Addition of a stoichiometric amount of a tributylaryl stannane **78** to a solution of $Pd(\eta^3\text{-allyl})$ complex **79** in acetonitrile resulted in the formation of palladium complex **80**, but there was no evidence of a cross-coupling product. Only under catalytic conditions with an excess of electron-deficient olefin, such as a typical allyl halide substrate or benzoquinone, was the cross-coupling product observed. With this example, Espinet and co-workers presented a detailed study of a reaction that proceeds catalytically but not stoichiometrically.



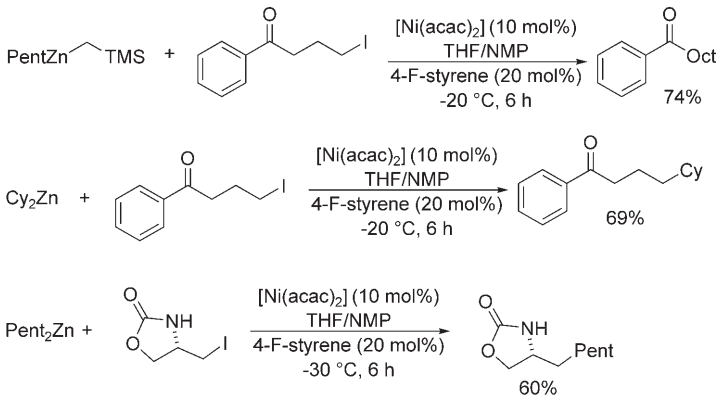
Scheme 52. Stoichiometric and catalytic cross-coupling of aryl stannane **78**.

In earlier work (see Scheme 20),[42] Knochel and co-workers observed the nickel-catalyzed cross-coupling of primary alkyl bromides with diethylzinc, but only when the halide contained unsaturation. To extend the utility of this reaction, Knochel and co-workers explored the use of exogenous olefins to duplicate the effect observed with unsaturated alkyl bromides.[75] Thus, a series of electron-deficient styrenes and arenes were investigated as possible additives. Criteria for optimal additives included the suppression of halide–zinc exchange products and increased reaction rate. In the presence of *meta*-trifluoromethylstyrene (**81**), the cross-coupling of iodoalkane **82** with the diorganozinc compound **83** catalyzed by 10 mol% $[Ni(acac)_2]$ proceeded with 76% yield and no observed iodide–zinc exchange product (Scheme 53).



Scheme 53. Ni-catalyzed cross-coupling of a primary alkyl iodide with a diorganozinc reagent in the presence of a styryl additive. Piv = pivaloyl.

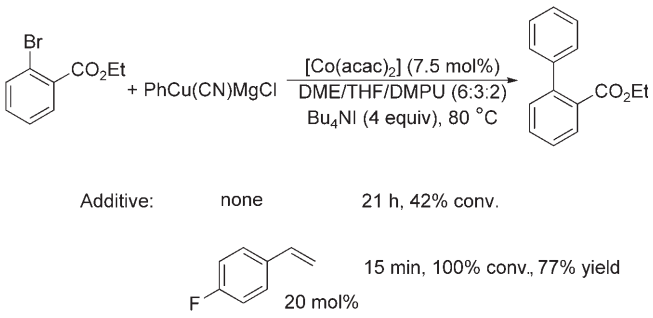
This new methodology has been utilized for a wide variety of couplings, including highly functionalized aryl- and alkylzinc halide reagents with primary alkyl iodides and bromides. Functional group tolerance on the diorganozinc reagent includes halide-, ester-, and nitrile-substituted aryl groups, as well as *tert*-butyl esters and ketones, and the alkyl iodide functionality may include esters, ketones, thioethers, and amides. With the use of a second additive, Bu_4NI, the reaction scope is further increased to include more-reactive secondary dialkyl zinc reagents, including mixed zinc reagents such as $RZnCH_2TMS$.[76] These more-hindered zinc reagents selectively transfer the R substituent, thus alleviating the need for two equivalents of R in forming the dialkyl zinc species. Some examples of the current reaction scope are illustrated in Scheme 54. It should be noted that Knochel and co-workers



Scheme 54. Scope of Ni-catalyzed cross-coupling of primary alkyl iodides with diorganozinc reagents in the presence of a styryl additive. Pent = n-C_5H_{11}, Oct = n-C_8H_{17}.

report a similar cross-coupling of benzylic and alkyl zinc halides with alkenyl or aryl triflates catalyzed by $[Pd(dba)_2]$ and diphenylphosphinoferrocene (dppf).[76a] This reaction, however, does not require additional exogenous olefin beyond that liberated from the catalyst precursor upon coordination of dppf.

Knochel and co-workers reported the related cobalt-catalyzed cross-coupling of aryl copper reagents with aryl halides.[77] Reaction of ethyl 2-bromobenzoate with a phenylcopper reagent, generated from PhMgCl and CuCN·2 LiCl, in the presence of $[Co(acac)_2]$ as a catalyst produces limited coupling product. In the presence of the additives Bu_4NI (4 equiv) and 4-fluorostyrene (20 mol%), however, complete conversion was obtained in approximately 15 minutes (Scheme 55). This reaction has since been extended to the coupling of *ortho*-haloaryl ketones and ester substrates,

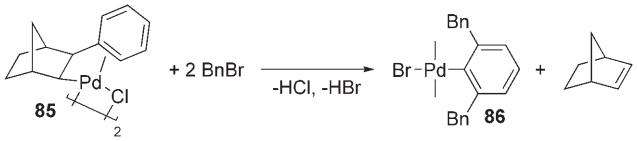


Scheme 55. Co-catalyzed cross-coupling of *ortho*-ester-substituted aryl halides with aryl copper reagents.

including aryl bromides, chlorides, fluorides, and tosylates. Nucleophile scope currently includes a variety of polyfunctionalized aryl copper reagents. The authors provide no further rationale for the role of the styrene in these reactions.

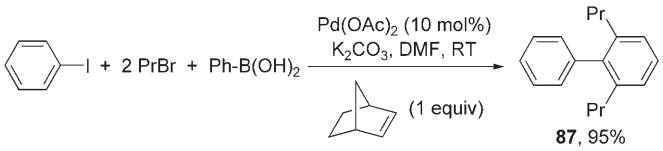
Catellani et al. used exogenous olefin additives to facilitate the sequential aryl alkylation and Suzuki-type coupling of aryl iodides, alkyl bromides, and aryl boronic acids.[78] In these reactions, however, the norbornene additive is proposed to function through a significantly different mode of reactivity from that typically suggested for exogenous olefins. In early work, Catellani and Fagnola observed that the arylnorbornylchloropalladium complex **85** reacts with an alkylating agent, presumably via palladacylces, to produce the corresponding *ortho*-dialkylated arylpalladium complex **86** with the regeneration of norbornene (Scheme 56). Subsequent Heck or Suzuki coupling with this aryl palladium complex results in the formation of disubstituted styrenes or biaryls, respectively.

Catellani et al. reasoned that these reactions could be combined into a catalytic process, as both palladium and norbornene are regenerated. This goal was realized in the development of a one-pot procedure combining phenyl iodide, two equivalents of propylbromide, and phenyl boronic acid in the presence of a catalytic amount of $Pd(OAc)_2$ and a stoichiometric amount of norbornene.[79] The desired dipropylbi-



Scheme 56. Alkylation of (arylnorbornyl)chloropalladium complex **85** with release of norbornene.

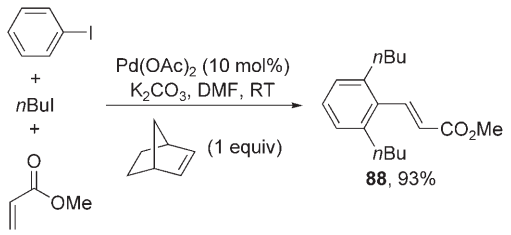
phenyl product **87** was obtained in 95% yield (Scheme 57). Although the reaction can be run with catalytic amounts of norbornene, one equivalent relative to the aryl iodide is often used for optimal yields. The catalytic cycle can also be closed by reaction of the aryl palladium complex with methyl acrylate to provide exclusively the *trans* isomer of the



Scheme 57. Sequential bisalkylation and Suzuki coupling of iodobenzene.

corresponding 2,6-disubstituted styrene derivative **88** in 93% yield (Scheme 58).[80]

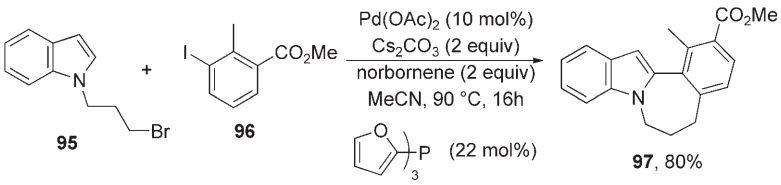
The authors propose that norbornene is required for formation of the palladacycles necessary for aryl functionalization and suggect the catalytic cycle shown in Scheme 59.[81] After oxidative addition of a Pd^0 species into the aryl iodide, insertion of norbornene forms complex **89**. This species is proposed to undergo a second reductive elimination into an aryl C–H bond to form a transient Pd^{IV} intermediate, which loses HI to produce Pd^{II} palladacycle intermediate **90**. This intermediate undergoes oxidative addition with the primary alkyl iodide, again forming a Pd^{IV} intermediate (**91**), followed by reductive elimination of alkyl and aryl substituents to form intermediate **92**. The activation/functionalization of the aryl C–H bond is repeated to give intermediate **93**, which undergoes β-alkyl elimination to release norbornene and form arylpalladium complex **94**. The cycle is closed with either Suzuki or Heck coupling to regenerate the palladium(0) complex.



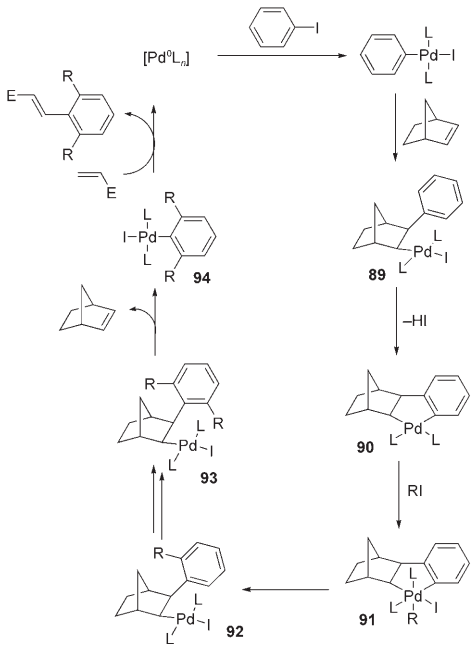
Scheme 58. Pd-catalyzed bisalkylation and Heck coupling of iodobenzene.

Lautens and co-workers recently utilized the chemistry developed by Catellani et al. in a palladium-catalyzed alkylation/arylation sequence.[82] Subjecting bromoalkyl indole **95** and substituted aryliodide **96** to $Pd(OAc)_2$ and trifurylphosphine resulted in the formation of seven-membered ring annulated indole **97** in 80% yield (Scheme 60). It is of note that the authors used *ortho*-substituted aryl iodides to prevent the second alkylation that is observed with unsubstituted iodobenzene.

Kambe and co-workers recently reported several examples of nickel- and palladium-catalyzed cross-coupling of alkyl halides with Grignard reagents in the presence of diene or tetraene additives. In each case, the presence of the additive results in the selective production of the coupling product, whereas reaction in the absence of additive leads to a series of alkane and olefin by-products. In the initial



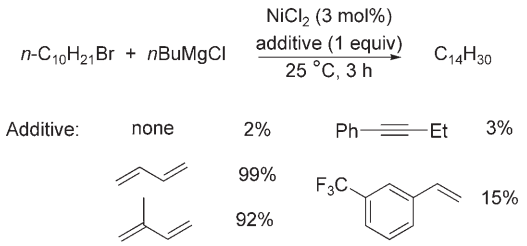
Scheme 60. Formation of annulated indoles by a Pd-catalyzed tandem alkylation/arylation reaction.



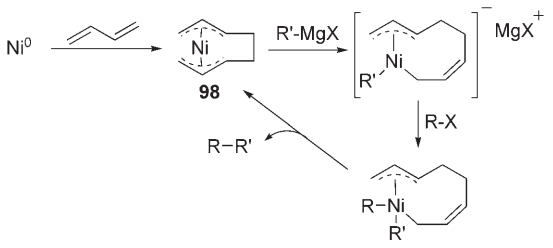
Scheme 59. Proposed catalytic cycle of Pd-catalyzed sequential bisalkylation and Heck coupling of aryl iodides facilitated by norbornene.

communications, the authors describe the cross-coupling of several primary alkyl chlorides, bromides, and tosylates with alkyl and aryl Grignard reagents catalyzed by Ni^{II} precursors.[83] A series of additives were examined in the reaction of *n*-decylbromide, *n*-butylmagnesium chloride, and $NiCl_2$, as the parent reaction provides only 2% of the desired coupling product as well as 49% decane and 27% decene. The use of 1,3-butadiene provides the most startling increase in reactivity and leads to 99% of the desired linear alkane (Scheme 61). Although isoprene is also an efficient additive, other common additives, such as phenyl-1-butyne and *meta*-trifluoromethylstyrene, provide little increase in reaction efficiency. To explain the difference in reactivity, the authors propose an intermediary bis(π-allyl)nickel species **98** as the reactive intermediate (Scheme 62). Subsequent nucleophilic addition of the Grignard reagent and displacement of the alkyl halide produces a Ni^{IV} intermediate, which undergoes reductive elimination to form the product and close the catalytic cycle.

Similar effects are observed in the Pd-catalyzed coupling of primary bromides and tosylates with Grignard reagents.[84] With $[Pd(acac)_2]$ in the absence of a diene, the coupling of phenyl magnesium bromide and heptyltosylate proceeds in



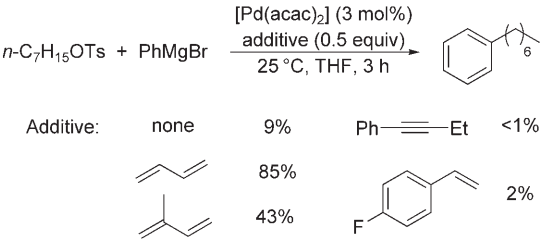
Scheme 61. Effects of olefin additives on the yields of the Ni-catalyzed cross-coupling of alkyl bromides with alkyl Grignard reagents.



Scheme 62. Proposed intermediate of the Ni-catalyzed allylation reaction in Scheme 61.

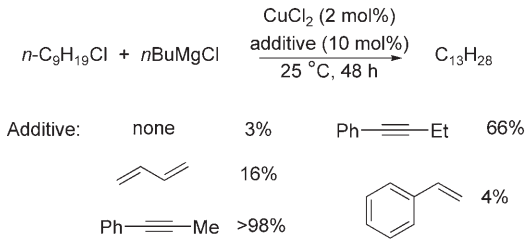
less than 10% yield; the disproportionation products heptane and heptene are the major products. Addition of 1,3-butadiene again has a profound effect on the reaction, resulting in the successful cross-coupling of the aforementioned reagents in 85% yield (Scheme 63).

Most recently, Kambe and co-workers reported the Cu-catalyzed variant of the coupling of primary alkyl halides with Grignard reagents.[85] Several additives were screened in the reaction of *n*-$C_9H_{19}Cl$, *n*BuMgCl, and $CuCl_2$ (Scheme 64). Much like in previous cases, an additive is necessary for reactivity. In this reaction, however, dienes are ineffective activators, whereas alkynes effectively promote coupling. Furthermore,



Scheme 63. The effects of additives in the Pd-catalyzed cross-coupling of alkyl tosylates with aryl Grignard reagents.

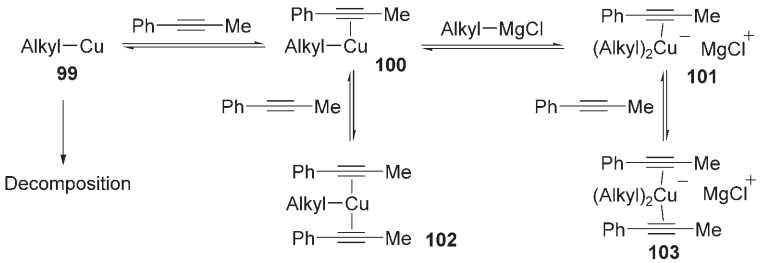
Kambe and co-workers describe several direct competition experiments that illustrate the unique reactivity of alkyl halides: chloride < fluoride < bromide. Rudimentary kinetic results suggest that whereas alkyne is necessary for the promotion of the cross-coupling, excess alkyne inhibits the reaction. The authors proposed the reaction pathway shown in Scheme 65. Under very low alkyne concentrations, unstable Cu^I species **99** is the predominant species and undergoes decomposition more rapidly than it promotes coupling. Only



Scheme 64. Additive effects in the Cu-catalyzed coupling of alkyl halides with alkyl Grignard reagents.

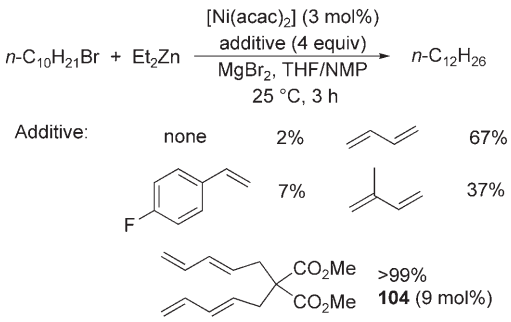
in the presence of alkyne can the proposed catalytically active species **100** and **101** form. The presence of excess alkyne drives the reaction equilibria toward inactive bisalkyne species **102** and **103**. Thus, only with moderate amounts of alkyne (e.g., 10 mol%) does the reaction proceed efficiently.

Kambe and co-workers have also utilized nickel catalysts for the coupling of alkyl halides with diorganozinc reagents. The use of $NiCl_2$ (3 mol%) in the presence of excess $MgBr_2$ catalyzes the cross-coupling of decyl bromide with diethylzinc only in the presence of 1,3,8,10-tetraene **104** efficiently



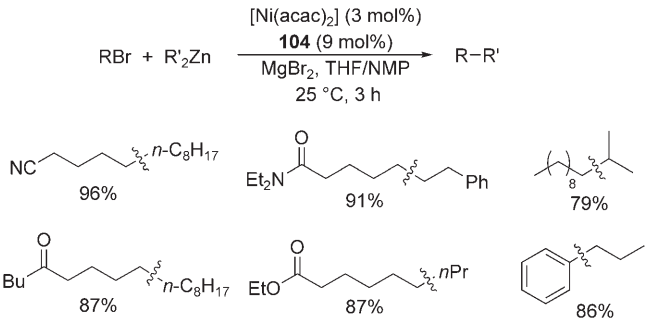
Scheme 65. Reaction pathway of Cu-catalyzed coupling of alkyl halides and Grignard reagents promoted by alkynes.

(Scheme 66).[86] A 3:1 ratio of **104**:$NiCl_2$ provides the optimal reaction rates. The dienes used in previous examples proved quite ineffective in this case in facilitating the cross-coupling reaction; the desired products were obtained in very modest yields. Only slight product formation is observed in the complete absence of polyene. This methodology has been extended to incorporate functionality into the alkyl halide, including amides, ketones, and esters as well as the organozinc reagent, including aryl and secondary alkyl nucleophiles



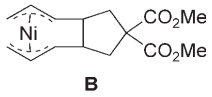
Scheme 66. Ni-catalyzed cross-coupling of primary alkyl bromides with diorganozinc reagents with diene and tetraene additives.

(Scheme 67). The authors attribute the increased activity of this system to the ease of formation of the active bis(π-allyl) species from the tetraene (**B**) relative to two separate dienes.



Scheme 67. Reaction scope of the Ni-catalyzed cross-coupling in Scheme 66 in the presence of tetraene **104**.

The nickel-catalyzed alkylation of aldehydes with trialkyl boranes, as reported by Hirano, Yorimitsu, and Oshima, utilizes an exogenous olefin to increase the yield and efficiency of the transformation.[87] In the absence of additives, the addition of triethylborane to benzaldehyde in the presence of $[Ni(cod)_2]$ and tBu_3P proceeds sluggishly, providing only 45% of the desired secondary alcohol after 24 hours (Scheme 68). The addition of allyl-Cp* (5-allyl-1,2,3,4,5-pentamethyl-1,3-cyclopentadiene) dramatically increases the efficiency of reaction. With 10 mol% allyl-Cp*, the reaction is complete after 24 hours,



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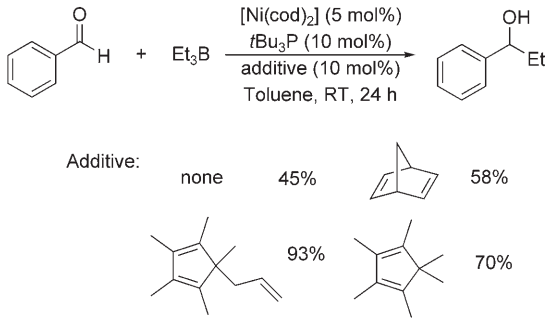
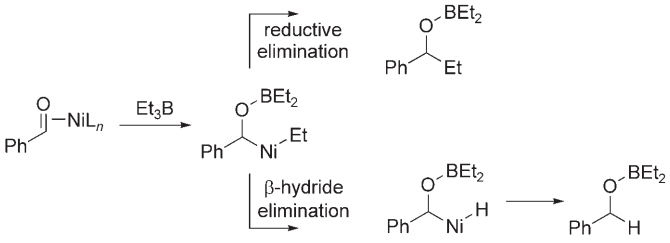


Scheme 68. Alkylation of aldehydes by triethylborane catalyzed by $[Ni(cod)_2]/tBu_3P$ in the presence of olefins.

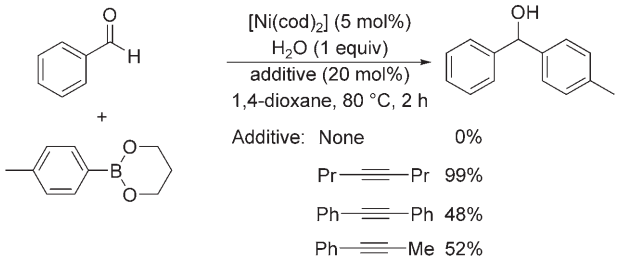
even at 0 °C, and gives the desired product in 93% yield. The scope of this reaction includes a number of aryl and alkyl aldehydes. Inexplicably, however, changing the nucleophile from Et_3B to nBu_3B led to nearly complete lack of reactivity (a difficulty addressed with use of Cs_2CO_3, presumably a different means of alleviating potential side reactions).

Although the authors do not explicitly speculate on the role of the allyl-Cp* additive, they propose an intermediate alkoxy(ethyl)nickel species, which is capable of undergoing β-hydride elimination to form unwanted aldehyde reduction products (Scheme 69). In the presence of additives, this reaction pathway is not observed. Coordination of allyl-Cp* may inhibit β-hydride elimination while facilitating reductive elimination. It is of note, however, that the reduction product dominates when organoboranes with secondary alkyl groups are used.



Scheme 69. Proposed mechanistic pathways for Ni-catalyzed conversion of aldehydes.

Also in the context of nucleophilic additions to aldehydes, Shirakawa and co-workers observed that cocatalytic alkyne, as well as the catalyst $[Ni(cod)_2]$ and one equivalent H_2O, is required for the facile addition of organoboronic esters to aldehydes (Scheme 70).[88] In the absence of alkyne, no

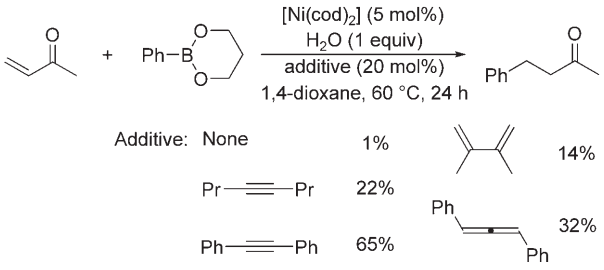


Scheme 70. Ni-catalyzed addition of aryl boronic esters to aromatic aldehydes in the presence of various additives.

coupling product is observed. The reaction scope currently includes a series of aryl and alkyl aldehydes, as well as aryl and styryl boronic esters. The system exhibits significant functional group tolerance, including ketones, esters, and trifluoromethyl substituents.

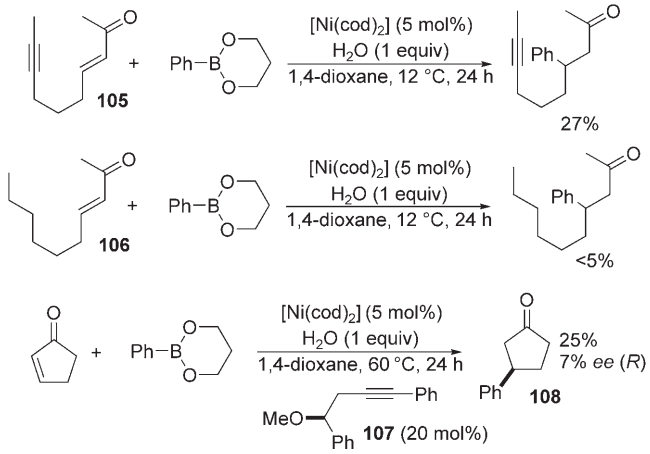
In an extension of this work, Shirakawa, Yasuhara, and Hayashi reported the Ni-catalyzed conjugate addition of aryl boron reagents to α,β-unsaturated ketones (Scheme 71).[89] As before, the authors note that an additive, in addition to one equivalent H_2O, is necessary for reactivity, as only 1% of the desired product is obtained in the absence of such a promotor. The authors include a screen of other possible activators, including allenes, dienes, and phosphines, and note that the optimal results are obtained with diphenylacetylene.

Of particular interest are the studies of the nature of the participation of the alkyne in the reaction. Significant conversion is observed with an alkyne-containing substrate such as **105**, indicating that the alkyne can be included in the substrate rather than being limited to an exogenous acetylene (Scheme 72). In contrast, the same reaction with a substrate without the pendant alkyne group (**106**) gives less than 5%



Scheme 71. Ni-catalyzed addition of aryl boronic esters to α,β-unsaturated ketones in the presence of various additives.

yield. Of arguably more interest, the authors rationalized that, if the alkyne is intimately involved in the carbon–carbon



Scheme 72. Ni-catalyzed addition of aryl boronic esters to enones in the presence or absence of additives.

bond-forming event, the use of optically active alkyne **107** should induce asymmetric addition. In fact, the reaction of a phenyl boronic ester with 2-cyclopentenone provides (*R*)-3-phenylcyclopentanone **108**, but in only 7% *ee* and 25% yield.

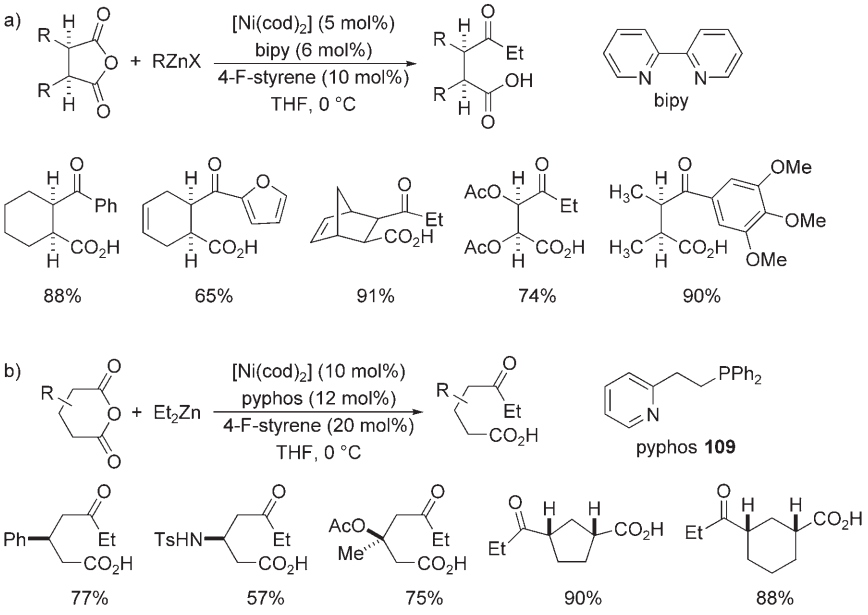
Although the authors provide no specific mechanistic rationale for the effect of exogenous alkynes on the reaction, they note that the activity of alkyne and diene ligands relative to phosphine ligands suggests these species may not act as conventional ligands. One possibility is their reaction with Ni^0 in an oxidative cyclization to form a Ni^{II}–metalacycle, which is responsible for subsequent reactivity.

Rovis and co-workers have investigated the nickel-catalyzed alkylation of *meso* cyclic carboxylic anhydrides by diorganozinc nucleophiles. What has resulted is the development of a very general cross-coupling methodology: succinic anhydride (Scheme 73a) and glutaric anhydride (Scheme 73b) are suitable substrates with bipy and pyphos (**109**), respectively, for a wide variety of diorganozinc compounds and organozinc halides.[90] The catalytic cycle, as confirmed by kinetic studies, is shown in Scheme 74.[91]

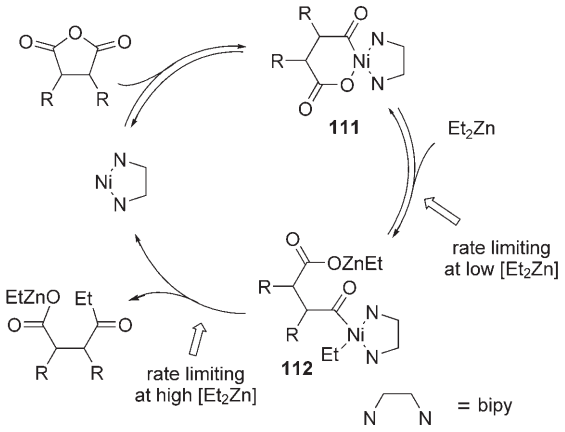
Following the precedent of Knochel and others in Ni-catalyzed cross-coupling reactions, electron-deficient olefinic additives are used to facilitate the reaction. In the absence of an additive, the coupling of *cis*-cyclohexanedicarboxylic anhydride **110** with diethylzinc, catalyzed by $[Ni(cod)_2]$ (5 mol%) and bipy (6 mol%), provides a 76% yield of the desired ketoacid after approximately 20 hours (Scheme 75). In contrast, the presence of 4-fluorostyrene significantly accelerates the reaction, which fully consumes the anhydride in approximately 30 minutes. The use of 4-trifluoromethylstyrene as an additive leads to complete reaction within 5 minutes.

Although the short reaction times were initially attributed to facilitation of reductive elimination by the proposed acylethylnickel intermediate **112**, detailed kinetic studies revealed that the presence of 4-fluorostyrene has no effect on the initial rate of alkylation of anhydride **110** under similar conditions to those described above.[91] At approximately 20% consumption of anhydride **110** (three turnovers), the rates with and without 4-fluorostyrene are identical within experimental error, suggesting that styrene is not involved in the rate-limiting step of catalysis. At longer reaction times, however, reactions run in the presence of 4-fluorostyrene proceed to completion in approximately 30 minutes, whereas significant rate retardation is observed in the absence of styrene (Figure 1). These results suggest that the primary role of styrene in this system is the stabilization of the catalyst, which effectively inhibits catalyst decomposition and increases overall reactivity.

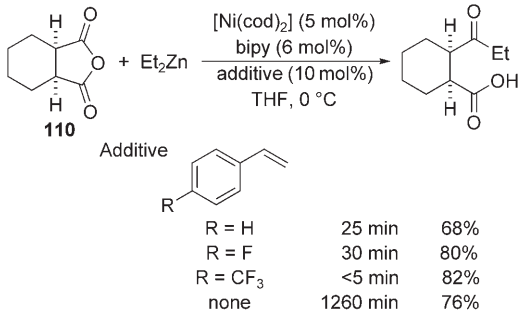
These conclusions, however, are in contrast to those observed in the development of an asymmetric variant of the



Scheme 73. Ni-catalyzed cross-coupling of a) succinic anhydrides with diorganozinc or organozinc halide reagents, and b) glutaric anhydrides with diethylzinc in the presence of 4-fluorostyrene.



Scheme 74. Catalytic cycle of [Ni(cod)$_2$]–bipy-catalyzed cross-coupling of succinic anhydrides with diethylzinc.



Scheme 75. Ni-catalyzed cross-coupling of *cis*-cyclohexanedicarboxylic anhydride (**110**) with diethylzinc in the presence of various styrene additives.

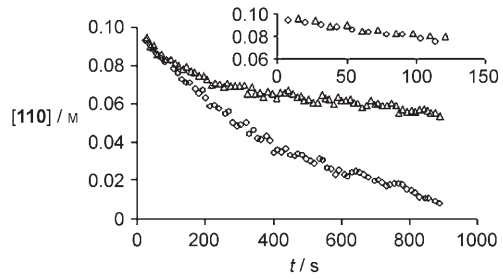


Figure 1. The concentration of succinic anhydride **110** versus time during Ni-catalyzed cross-coupling with diethylzinc in the presence (○) and absence (◇) of 4-fluorostyrene (see Scheme 74).

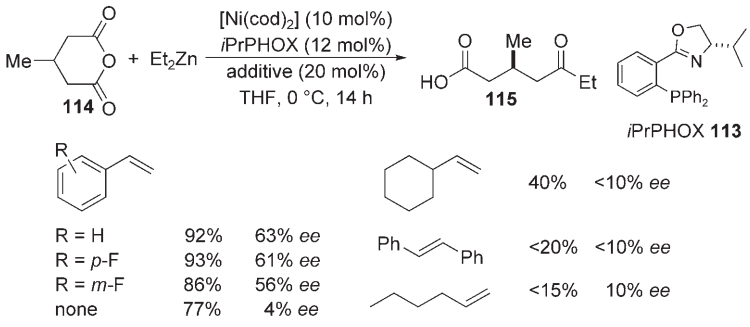
alkylation. In the presence of [Ni(cod)$_2$] and isopropyl(phosphinophenyl)oxazoline **113** (*i*PrPHOX), the alkylation of 4-methylglutaric anhydride (**114**) with Et_2Zn proceeds with 77% yield and 4% *ee*. In the presence of styrene, however, the enantioselectivity increases to 63% *ee*, and the yield improves to 92%. Furthermore, a screen of several olefin additives, including a number of styrene derivatives, indicates that the nature of the additive impacts the enantioselectivity of the reaction (Scheme 76). These results provide a clear indication that in the Ni-*i*PrPHOX-catalyzed system, styrene plays an intimate role in the enantioselectivity-determining event.[91]

Kinetic study of this system, including investigation of the effects of styrene, revealed that oxidative addition limits catalyst turnover under typical reaction conditions. It was also observed that competing catalytic cycles are operative in this reaction (Scheme 77): a slower, less-selective cycle in the absence of styrene (**119–121**), and a faster, more-selective cycle in its presence (**116–118**). Although these results appear to be contradictory to earlier results that indicate that "naked" metal centers promote faster oxidative addition, the exact nature of the active species is currently under investigation. It is hypothesized that a three-coordinate nickel species is active in the oxidative addition. Thus, 1,5-cyclooctadiene, a bisolefin, must dissociate prior to reaction, whereas monodentate styrene coordination does not inhibit oxidative addition.

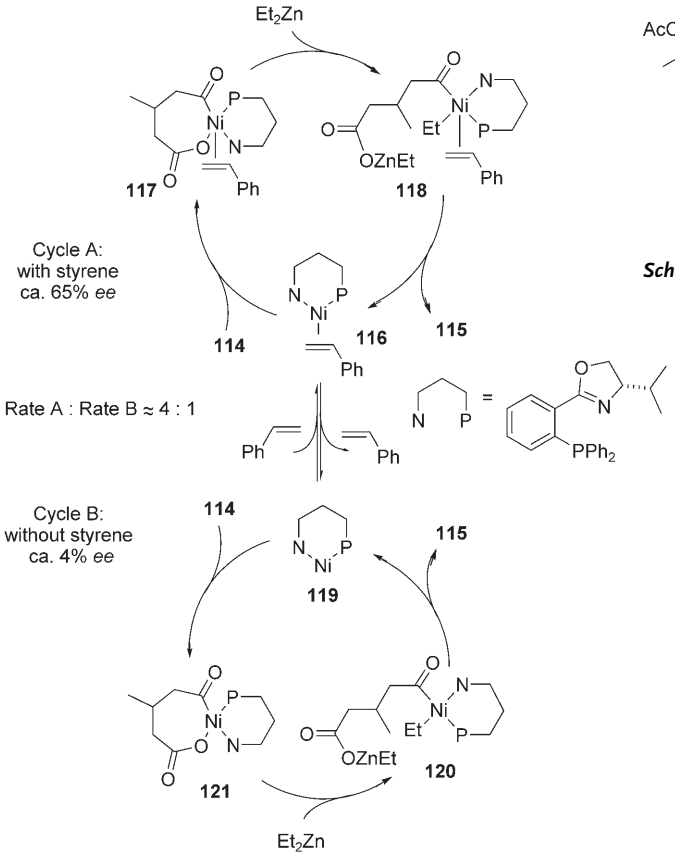
Furthermore, Bercot and Rovis reported that the presence of styrene also influences enantioselectivity in the palladium-catalyzed coupling of organozinc reagents with succinic anhydrides.[92] In the absence of styrene additives, the alkylation of anhydride **122** with Me_2Zn catalyzed by Pd(OAc)$_2$ and (*R*,*S*)-JOSIPHOS (**123**) proceeds with 78% yield and 64% *ee* (Scheme 78). In the presence of 4-fluorostyrene (25 mol%), however, the reaction proceeds with 80% yield and 90% *ee*. Although a dramatic increase in enantioselectivity is observed with Me_2Zn, similar phenomena are not observed with the use of Et_2Zn or Ph_2Zn.

In related work, Zhang and Rovis reported the nickel-catalyzed cross-coupling of acid fluorides with diorganozinc reagents (Scheme 79).[93] This protocol proceeds with a variety of aromatic and aliphatic acid fluorides and is tolerant of numerous functional groups, including olefins, ethers, esters, and imides. In the presence of [Ni(cod)$_2$], pyphos (**109**), and 4-fluorostyrene, the coupling of benzoyl fluoride (**125**) with Ph_2Zn proceeds in approximately 3 minutes with 97% yield. The impact of the styrenyl additive is illustrated by the reaction run in its absence, which produces benzophenone in only 18% yield after 16 hours.

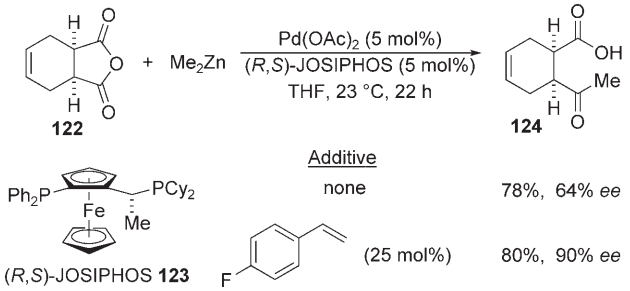
Ohe et al. recently utilized ruthenium species to catalyze the [1,5]-metallotropic shift of polyynes to form dienes (Scheme 80).[94] In the presence of [{RuCl$_2$(CO)$_3$}$_2$], diacetoxytriyne **126** rearranges to dienediyne **127** in 55% yield through a proposed [1,5]-metallotropic shift from a carbene



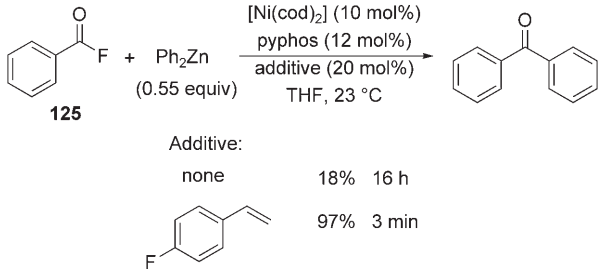
Scheme 76. Effect of additives on the enantioselectivity of Ni-catalyzed cross-coupling of glutaric anhydride (**114**) with diethylzinc.



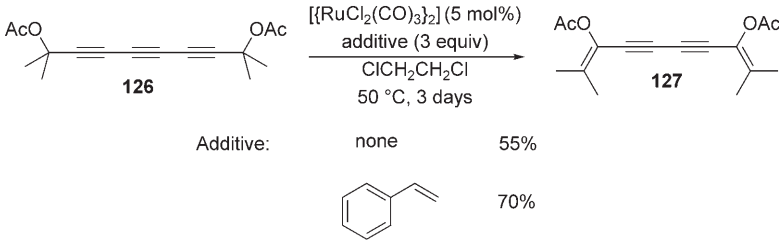
Scheme 77. Catalytic cycles of the [Ni(cod)$_2$]–*i*PrPHOX-catalyzed alkylation of cyclic anhydrides in the presence and absence of styrene.



Scheme 78. Effect of 4-fluorostyrene on the enantioselectivity of Pd-catalyzed cross-coupling of succinic anhydride (**122**) with dimethylzinc.



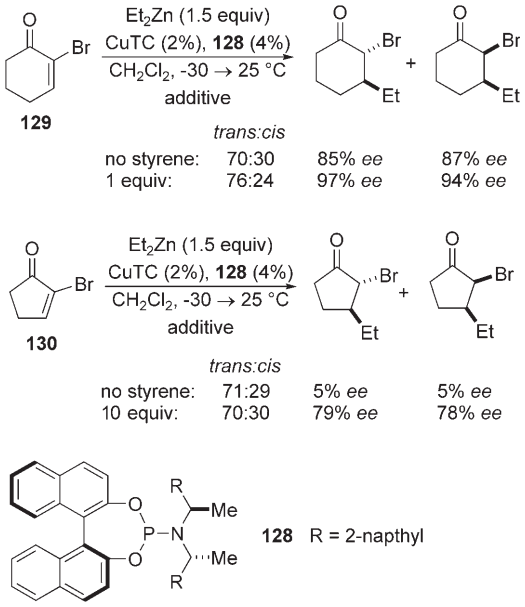
Scheme 79. Ni-catalyzed coupling of acyl fluorides with diorganozinc reagents.



Scheme 80. Ru-catalyzed isomerization of diacetoxypolyynes.

intermediate. The authors note that the yield of this rearrangement product can be increased to 70% with the inclusion of 3 equivalents of styrene, although they provide no rationale for this increase.

In recent work, Li and Alexakis observed a dramatic effect of styrene on the enantioselectivity of conjugate additions to α-halo enones catalyzed by CuTC (TC = thiophene carboxylate) in the presence of phosphoramidite ligand **128** (Scheme 81).[95] In the absence of styrene, the addition of



Scheme 81. Cu-catalyzed asymmetric conjugate addition of Et$_2$Zn to α-halo enones.

diethylzinc to bromoenone **129** occurs in a 70:30 ratio of diastereomers, whereby the dominant *trans* isomer is formed in 85% *ee*. In the presence of one equivalent of styrene, the diastereomeric ratio increases to 76:24 and the enantioselectivity increases to 97% *ee*. Similar increases are observed for several related substrates, the most dramatic of which is observed with bromocyclopentenone **130**. In the absence of styrene, the *trans* diastereomer is formed nearly racemically (5% *ee*), but upon addition of 10 equivalents of styrene, the *trans* diastereomer is produced in 79% *ee*. The authors attribute this profound effect to the inhibition of radical processes, which produce racemic product, by styrene.

Benzoquinone, and related oxidizing species, have also been used to promote reactivity in several catalytic sys-

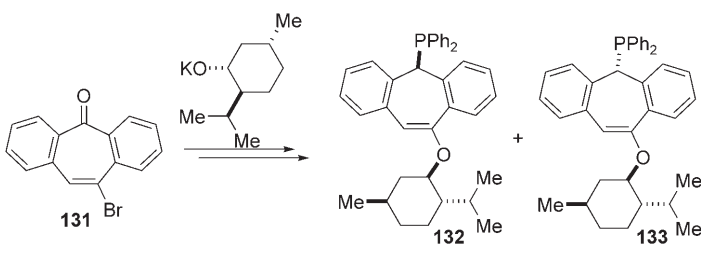
tems.[96–98] The role of such additives can be attributed to either the facilitation of reductive elimination or the stabilization of catalytic intermediates.[99] The impact of benzoquinone on reductive elimination may be twofold: coordination of the electron-deficient olefins may result in an acceleration of reductive elimination as described previously, or oxidation of an M^0 species to an M^{II} species may serve to shift the equilibrium of a reaction with reversible reductive elimination. In many cases, the role of the benzoquinone as a promoter or oxidant has not been thoroughly deconvoluted and will not be further addressed herein.

6. Asymmetric Ligands with One or Two Olefin Units

Given the body of precedent concerning the influence of olefins as ligands in at least portions of catalytic cycles,[100,101] it is perhaps not surprising to observe the development of olefin-based chiral ligands. Although the use of olefins as ligands in transition-metal-catalyzed reactions has been commonplace for many decades, particularly in the form of catalyst precursors such as $[Ni(cod)_2]$ and $[\{Rh(cod)Cl\}_2]$, it is only recently that asymmetric ligands, both in the form of heteroatom-containing olefins and bisolefin ligands, have appeared. This section focuses on the use of asymmetric η^2-olefin and η^4-diene ligands in transition-metal catalysis.[102–104]

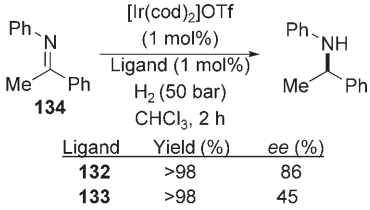
6.1. Phosphino-Olefin Ligands

Although examples of phosphine-olefin species as ligands for transition-metal complexes have been known for over 30 years,[105] only recently have these species been used as a scaffold for asymmetric ligands. In 2004, Grützmacher and co-workers reported the development of enantiomerically pure ligands **132** and **133** based on the "tropp" (5-phosphanyl-5*H*-dibenzo[*a*,*d*]cycloheptene) framework (Scheme 82).[128] These ligands are derived in several steps from cycloheptanone **131** and the appropriate potassium mentholate salt, and the corresponding diastereomers are separated by chromatography. The use of ligand **132** in conjunction with an iridium precatalyst results in the direct hydrogenation of imine **134** in greater than 98% conversion and 86% enantioselectivity. In contrast, use of the mismatched ligand (**133**) provides the product in comparably high yield but only 45% *ee* (Scheme 83). Attempts with analogous rhodium precursors failed to produce the desired hydrogenation product.



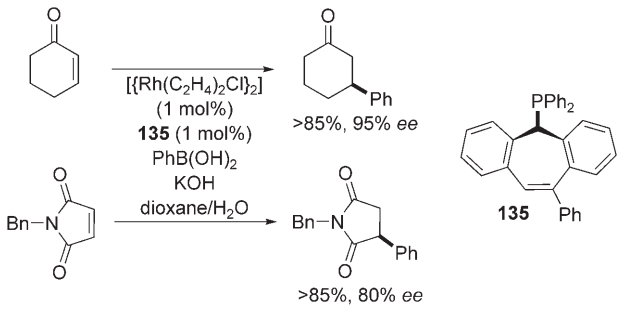
Scheme 82. Synthesis of chiral phosphine-olefin ligands with the "tropp" framework.

Grützmacher and co-workers recently developed an additional ligand based on the tropp framework, phenyl-substituted species **135** (Scheme 84).[129] The complex of this ligand with $[\{Rh(C_2H_4)_2Cl\}_2]$ has proven to be an active and selective catalyst for the addition of phenylboronic acid to 2-cyclohexenone and *N*-benzylmaleimide, providing the 1,4-addition products in 95% and 80% *ee*, respectively.



Ligand	Yield (%)	*ee* (%)
132	>98	86
133	>98	45

Scheme 83. Asymmetric hydrogenation of imines with phosphine-olefin ligands **132** and **133**.

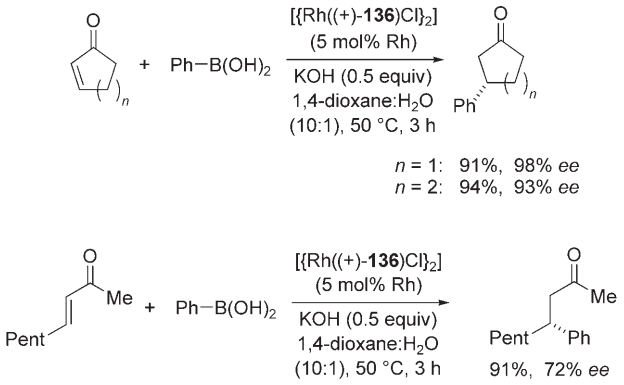


Scheme 84. 1,4-Addition using **135**, a second generation "tropp"-based phosphine-olefin ligand.

Concurrently with Grützmacher's development of the enantiomerically pure tropp ligands, Hayashi and co-workers reported the development of chiral phosphine-olefin ligands based on a norbornene framework (**136**).[106] These ligands are prepared from racemic bromoalcohol **137**, and the enantiomers are separated by using chiral HPLC [Eq. (1)]. The

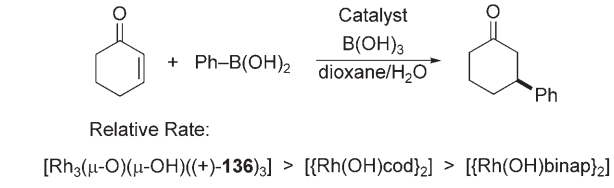
(1)

authors demonstrate the utility of these ligands in the rhodium-catalyzed addition of aryl boronic acids to a series of α,β-unsaturated ketones and esters, which is achieved with excellent yields and selectivities, particularly with cyclic species (Scheme 85).[107] Hayashi and co-workers also report a series of kinetic experiments on the 1,4-addition of phenyl boronic acid to 2-cyclohexenone. These studies indicate that



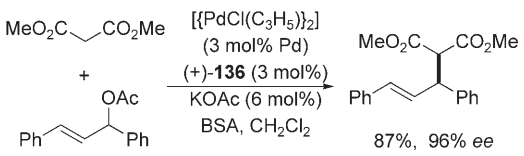
Scheme 85. Rh-catalyzed 1,4-addition of boronic acids to unsaturated ketones in the presence of ligand (+)-**136**.

catalyst turnover occurs much more rapidly with the rhodium complex of ligand **136** than with analogous rhodium–binap or rhodium–cod complexes (Scheme 86).[108]

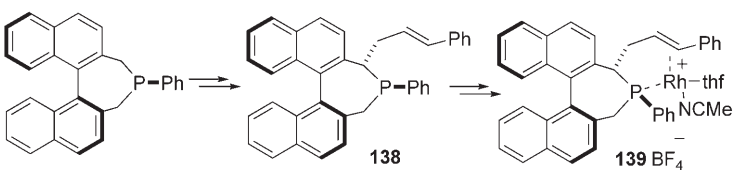


Scheme 86. Relative rate of 1,4-addition of boronic acids to cyclohexenone with various rhodium catalysts.

Hayashi and co-workers also reported the use of norbornene-based phosphine-olefin ligand **136** in the palladium-catalyzed allylic alkylation of 1,3-diphenyl-2-propenyl acetate.[109] The allylic alkylation with [{PdCl(η^3-C_3H_5)}$_2$] and ligand **136** in the presence of dimethyl malonate, BSA [*N*,*O*-bis(trimethylsilyl)acetamide], and KOAc proceeds with 87% yield and 96% *ee* (Scheme 87).

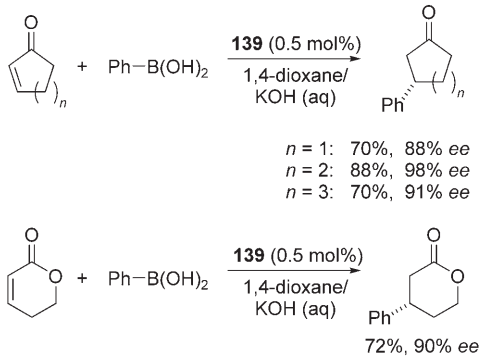


Scheme 87. Pd-catalyzed allylic alkylation using phosphine-olefin ligand **136**.



Scheme 88. Synthesis of binaphthyl-based phosphine-olefin complex **139**.

Similar asymmetric catalysis of conjugate addition was achieved by Widhalm and co-workers with phosphine-olefin ligand **138**, which is prepared in three steps from a chiral monodentate bis(naphthyl)phosphepine.[110] With preformed catalyst **139**, formed from reaction of **138** with [{Rh-(C_2H_4)$_2$Cl}$_2$] and subsequent halide abstraction with $AgBF_4$ (Scheme 88), the 1,4-addition of aryl boronic acids to a series of cyclic enones and enoates proceeds in excellent yield and selectivity (Scheme 89). All nucleophilic 1,4-additions to 2-cyclohexenone provide high selectivities.



Scheme 89. Rh-catalyzed 1,4-addition using phosphine-olefin ligand **138**.

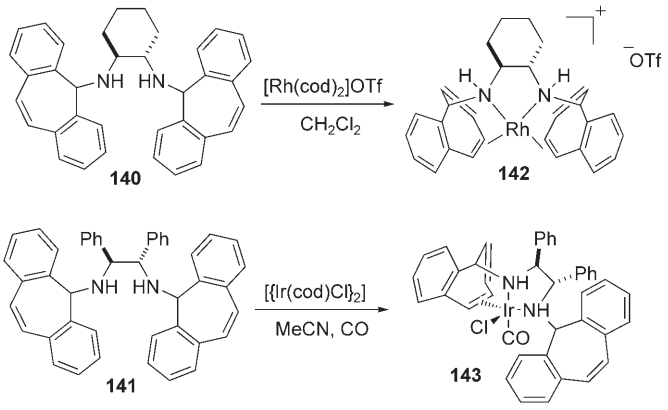
6.2. Amino-Olefin Ligands

Despite the extensive use of amine ligands in transition-metal catalysis, the use of chelating amine-olefin ligands remains quite rare.[111,112] Only recently have Grützmacher and co-workers disclosed the development of optically active amino-olefin ligands such as **140** and **141**.[113] These ligands behave as tetradentate species when complexed with Rh^I and as tridentate species (coordinated through both nitrogen atoms and one double bond) when complexed with Ir^I under a CO atmosphere (Scheme 90). Whereas Rh complex **142** displays no catalytic behavior under typical transfer hydrogenation conditions (*i*PrOH, 10 mol% KO*t*Bu, 80 °C), Ir complex **143** efficiently reduces acetophenone in excellent yield and with 82% *ee* (Scheme 91).

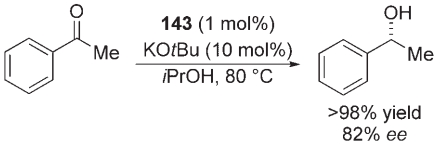
6.3. Chiral Diene ligands

Whereas bisolefin ligands have been long utilized in transition-metal catalysis, asymmetric diene ligands have emerged only within the last several years. The groups of Hayashi and Carreira independently reported enantiomerically pure dienes in 2003 and 2004, respectively, and these species have continued to serve as frameworks for the development of new ligands. This section focuses on the use of asymmetric dienes in transition-metal catalysis.

Hayashi and co-workers reported the development of a number of diene ligands

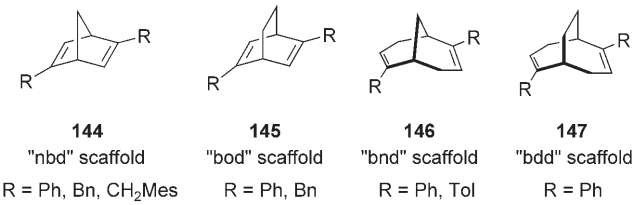


Scheme 90. Synthesis of rhodium and iridium complexes with amino-olefin ligands (back aryl rings omitted for clarity).



Scheme 91. Asymmetric hydrogenation of acetophenone using Ir–ligand complex **143**.

based on 1,4-cyclohexadiene and 1,5-cyclooctadiene frameworks. The enantiomerically enriched species can be accessed from the corresponding diketones and subsequent resolution of diastereomers or separation by chiral HPLC. Several examples of these species, as well as their nomenclature, are provided in Scheme 92.

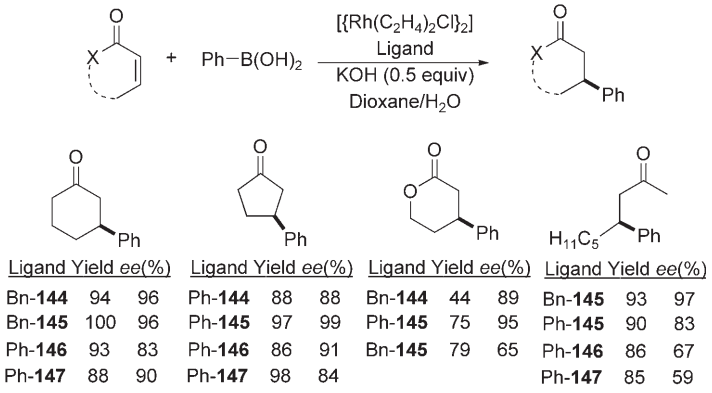


Scheme 92. Chiral dienes developed by Hayashi and co-workers, and therir nomenclature. nbd = bicyclo[2.2.1]hepta-2,5-diene (norbornadiene), bod = bicyclo[2.2.2]octa-2,5-diene, bnd = bicyclo[3.3.1]nona-2,6-diene, bdd = bicyclo[3.3.2]deca-2,6-diene.

Most of the catalysis performed with these chiral diene ligands has focused on rhodium-catalyzed addition to α,β-unsaturated carbonyl species.[114] Although the reactions are generally run in the presence of KOH in a 10:1 mixture of dioxane and water with 3 mol% rhodium and ligand, catalyst loadings can be as low as 0.005 mol%. The 1,4-addition of phenyl boronic acid to unsaturated ketones, esters, aldehydes, and Weinreb amides typically proceeds with excellent yields and enantioselectivities near or above 90%. A survey of various diene scaffolds is shown in Scheme 93. High yields and enantioselectivities are accessible with numerous functionalities in the carbonyl compound (Scheme 94). Although the examples shown in Scheme 94 are relatively limited, most additions occur in similar selectivity with a variety of substrate substitution and aryl boronic acids or boroxines.

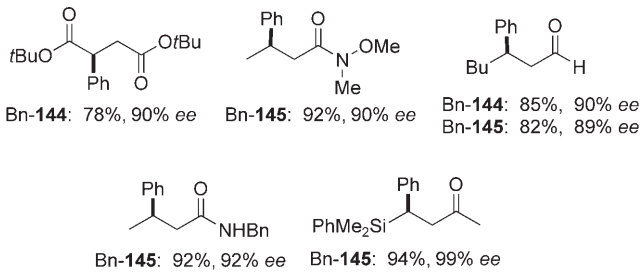
Hayashi and co-workers also utilized these chiral dienes for the asymmetric addition of boronic acids to aryl imines (Scheme 95). Imines with electron-deficient substitution, such as *N*-tosyl or *N*-4-nitrobenzenesulfonyl species, react efficiently with aryl boronic acids to produce the corresponding chiral amines in excellent yields and enantioselectivities.[115] Although it is generally less efficient than the use of aryl boronic acids, dimethylzinc is also a suitable nucleophile for the rhodium-catalyzed addition.[116]

The phosphine-free reaction conditions obtained with the use of chiral dienes can also be utilized in cyclization

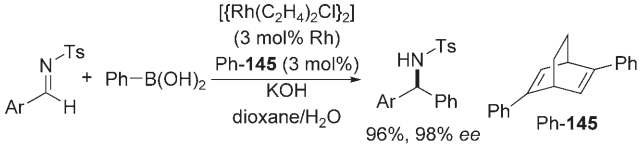


Ligand	Yield	*ee*(%)	Ligand	Yield	*ee*(%)	Ligand	Yield	*ee*(%)	Ligand	Yield	*ee*(%)
Bn-**144**	94	96	Ph-**144**	88	88	Bn-**144**	44	89	Bn-**145**	93	97
Bn-**145**	100	96	Ph-**145**	97	99	Ph-**145**	75	95	Ph-**145**	90	83
Ph-**146**	93	83	Ph-**146**	86	91	Bn-**145**	79	65	Ph-**146**	86	67
Ph-**147**	88	90	Ph-**147**	98	84				Ph-**147**	85	59

Scheme 93. Asymmetric Rh-catalyzed 1,4-addition of phenyl boronic acid to unsaturated esters and ketones in the presence of the Hayashi diene ligands.

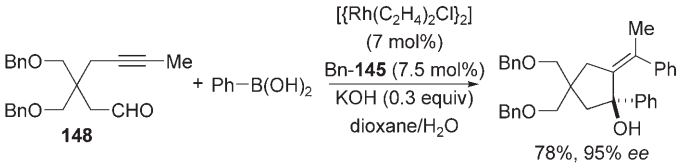


Scheme 94. Scope of products from Rh-catalyzed conjugate addition.

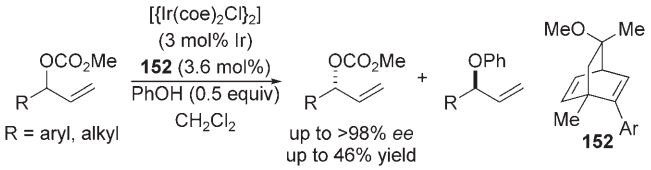


Scheme 95. Asymmetric 1,2-addition to *N*-tosyl imines. Ar = *p*-ClC$_6$H$_4$.

reactions. Hayashi and co-workers recently reported the use of dienes in the cyclization of alkynals (Scheme 96).[130] Early experiments using 1,5-cyclooctadiene showed that phosphine-free conditions are required for an efficient reaction. When



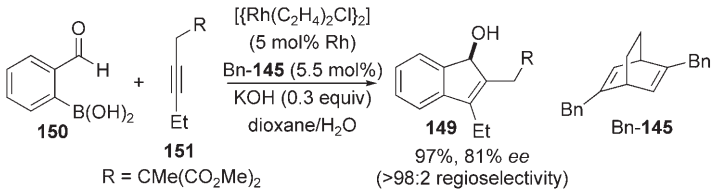
Scheme 96. Rh-catalyzed cyclization of alkynals using chiral diene ligands.



Scheme 99. Ir-catalyzed kinetic resolution of allylic carbonates. coe = cyclooctene.

asymmetric ligand Bn-**145** is used in conjunction with [{Rh-$(C_2H_4)_2Cl\}_2$], alkynal **148** and phenyl boronic acid cyclize to generate the corresponding *exo*-cyclopentene in good yield and with an enantioselectivity greater than 90%.

Similarly, the rhodium-catalyzed cyclization of alkynes with *ortho*-carbonylated aryl boronic acids proceeds with excellent yields in the absence of exogenous phosphine. This reaction was rendered asymmetric by using Bn-**145**. Under these conditions, indenol **149** is obtained in 97% yield and 81% *ee* from boronic acid **150** and alkyne **151** (Scheme 97).



Scheme 97. Formation of indenols from carbonylated arylboronic acids and alkynes.

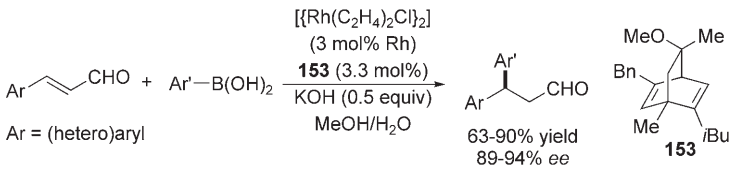
In 2004, Carreira and co-workers reported a series of chiral diene ligands readily constructed from (−)-carvone.[117] The use of the inexpensive enantiomerically pure starting material allows preparation of the chiral dienes without resolution or separation by HPLC. Further development has resulted in catalysts with additional substitution, including *i*Bu and alkenyl groups. A series of examples are shown in Scheme 98.

Carreira and co-workers first used these ligands in the iridium-catalyzed kinetic resolution of allylic carbonates (Scheme 99). For a series of aryl- and alkyl-substituted allylic carbonates in the presence of ligand **152** and [{Ir(coe)$_2$Cl}$_2$], one enantiomer is etherified with phenol more rapidly than the other. From this kinetic resolution, unreacted allylic carbonate was recovered in 28–46% yield and with 84–98% *ee*. Unfortunately, no k_{rel} values were reported for these reactions.

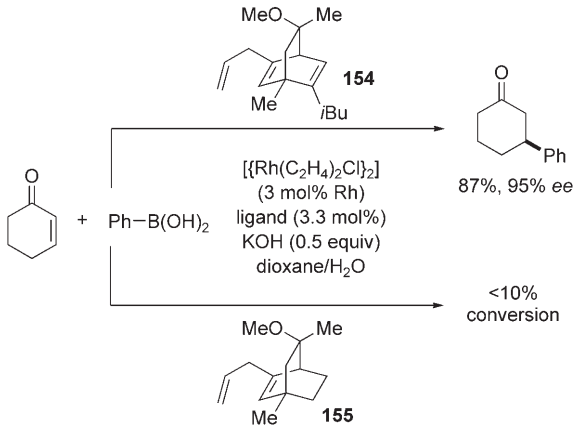
These diene ligands have also proven amenable to the catalysis of 1,4-additions of boronic acids to α,β-unsaturated acceptors.[131] This addition, catalyzed by [{Rh$(C_2H_4)_2Cl\}_2$] and a chiral diene, provides adducts of esters, ketones, and amides in good yields and excellent selectivities. Notably, the rhodium-catalyzed reaction, when performed with ligand **153** (*i*Bu/Bn), enables the addition of aryl boronic acids to aryl- and heteroaromatic-substituted unsaturated aldehydes and ketones in excellent selectivities (Scheme 100).

In their report of the rhodium-catalyzed 1,4-additions, Carreira and co-workers also mentioned a series of experiments that clarified the influence of various structural components of the diene ligands. The addition of phenyl boronic acid to 2-cyclohexenone was used for comparison. When the addition was performed with the use of ligand **154**, which contains an additional allylic substituent, the product is obtained in 87% yield and 95% *ee* (Scheme 101). With the partially hydrogenated ligand **155** the same reaction results in less than 10% conversion into the desired addition product. This result indicates that the structurally rigid bisolefin framework is required for reactivity.

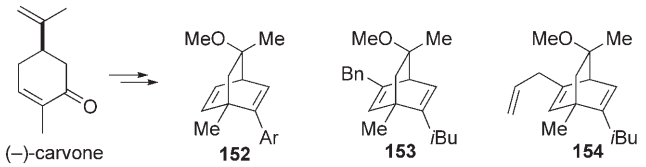
Mikami and co-workers recently described the synergistic use of Carreria's chiral dienes with chiral



Scheme 100. Rh-catalyzed 1,4-addition of boronic acids (Ar′ = various aryl groups) to Michael acceptors.

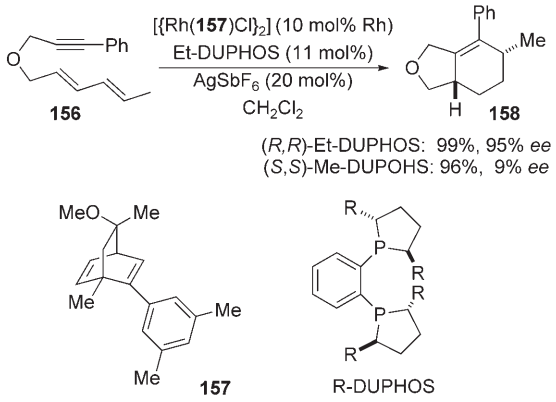


Scheme 101. Influence of rigid diene framework on the asymmetric 1,4-addition of phenyl boronic acid to cyclohexenone.



Scheme 98. Chiral diene ligands derived from (−)-carvone.

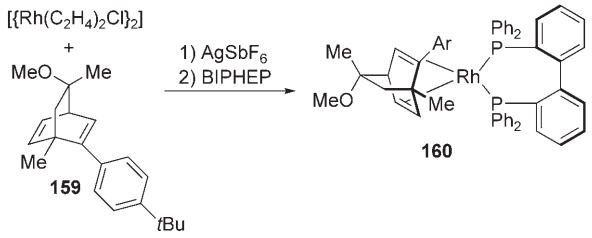
bisphosphines in a rhodium-catalyzed [4+2] cycloaddition (Scheme 102).[118] The tethered dieneyne **156** in the presence of diene species [{Rh(**157**)Cl}$_2$], (*R*,*R*)-Et-DUPHOS, and



Scheme 102. Asymmetric [4+2] cycloaddition catalyzed by phosphine-(diene)rhodium complexes.

$AgSbF_6$ provides the desired cyclohexadiene **158** in 99% yield and 95% *ee*. The use of a mismatched diene–phosphine pair provides the product in a similarly high yield but with only 9% *ee*.

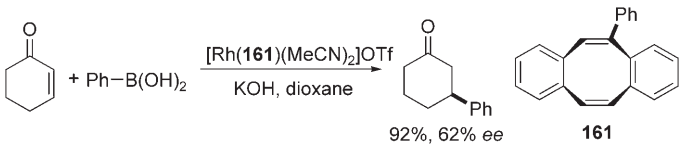
Chiral dienes have also been used in the resolution of an atropisomerically chiral biphenyl bisphosphine. Faller and Wilt reported the use of Carreira's diene **159** in the resolution of BIPHEP (Scheme 103), which undergoes racemization



Scheme 103. Use of chiral dienes for resolution of configurationally unstable phosphine BIPHEP ((biphenyl-2,2′-diyl)bis(diphenylphosphine)).

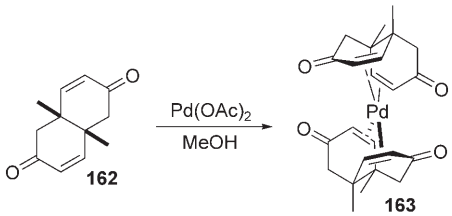
slowly at room temperature.[119] After chloride abstraction from [{Rh(**159**)Cl}$_2$] with $AgSbF_6$, addition of racemic BIPHEP leads to the formation of a single diastereomer of the corresponding rhodium complex **160**. Unfortunately, attempts to use this species in asymmetric catalysis proved unsuccessful; the most promising result was the hydroboration of styrene with only 12% *ee*.

In addition to their work with heteroatom-containing olefin ligands, Grützmacher and co-workers have also reported chiral cyclooctadiene derivative **161** prepared by ring expansion of the corresponding cycloheptenone and resolution of diastereomeric Rh–diamine complexes.[120] Although the parent hydrocarbon has served in many coordination compounds,[121] no previous reports exist for the resolution of the chiral product and its use in catalysis. The enantioenriched cationic rhodium–diene complex [Rh(**161**)-(MeCN)$_2$]$^+$ was tested for catalytic activity in both hydrogenation and 1,4-addition reactions. Attempts to reduce activated olefins resulted in very little desired product. The asymmetric addition of phenyl boronic acid to 2-cyclohexenone proceeds with 92% yield and 62% *ee* (Scheme 104).



Scheme 104. Use of cyclooctadiene ligand **161** in 1,4-addition.

Trauner and co-workers recently reported the use of enantiomerically pure C_2-symmetric rigid olefin **162** in the formation of a palladium bisdiene complex (Scheme 105).[122]



Scheme 105. Formation of a stable Pd^0 complex with chiral diene **162**.

Although this complex displays exceptional stability for a Pd^0 species, it has been used for enyne cyclization at high temperatures. Unfortunately, no asymmetric induction was observed in the cycloisomerization product.

The development of chiral diene ligands promises to provide new means of providing asymmetric influence in reactions that best proceed under "ligandless" conditions,[123] such as enyne cyclizations, or those unsuitable for phosphines.[124] Despite the numerous recent successes in this area, it may be fair to suggest that these studies remain in their infancy, and the best may be yet to come.

7. Summary and Outlook

In this review, we have attempted to compile reports of the use of olefin and alkyne additives to control transition-metal-catalyzed reactions. Olefins and alkynes have been observed to exert significant impact on a reaction, whether present as a substrate, ligand, or additive. We believe that these effects are far-reaching and are present in numerous systems in which the impact of such unsaturation has not yet been identified. Indeed, in many cases these differences manifest themselves in optimal precatalysts; [Pd(dba)$_2$] with four equivalents of PPh_3 behaves differently from [Pd-(PPh_3)$_4$]; [Ni(cod)$_2$] with a ligand is not identical to NiX_2 in the presence of a reducing agent and the same ligand. As such, we suspect that there are many more examples of this behavior than we have described herein.[125]

It has also become readily apparent that although the use of olefin and alkyne additives is quite widespread, there is a current lack of understanding of their mode of action in transition-metal catalysis. Olefins are a ubiquitous, yet underappreciated, facet of these reactions. With better understanding, such ligands may be used to tune reactivity, control catalyst function, and even impart asymmetry. It is our hope that this compilation stimulates interest in this area, serving to prompt further studies to investigate the role of these species as well as encourage the use of exogenous additives to further improve control of catalytic activity.

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