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Palladium(II)-Catalyzed Alkene Functionalization via Nucleopalladation: Stereochemical Pathways and Enantioselective Catalytic Applications

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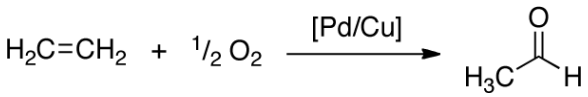
1. Introduction

The development of catalytic reactions of alkenes transformed the chemical industry in the mid-20[th] century. Representative reactions included hydrogenation, oxidation, hydroformylation, oligomerization and polymerization. In 1959, researchers at Wacker Chemie developed a Pd-catalyzed method for the aerobic oxidative coupling of ethylene and water to produce acetaldehyde (eq 1, Scheme 1).[1,2,3] This reaction represented the starting point for the development of numerous other Pd-catalyzed reactions in subsequent decades, ranging from alkene and diene oxidation reactions to cross-coupling reactions of aryl halides.



(1)

The stoichiometric oxidation of ethylene by aqueous Pd^{II} salts had been known since the 19[th] century;[4] however, the industrial Wacker Process owes its success to the recognition that the oxidized catalyst could be regenerated by molecular oxygen in the presence of cocatalytic $CuCl_2$ (Scheme 1). The reaction proceeds through a β-hydroxyethyl-Pd^{II} intermediate that forms via the net addition of hydroxide and Pd across the C–C double bond of ethylene. This seemingly straightforward "hydroxypalladation" step has been the subject of extensive mechanistic research and controversy over the past five decades. A major focus of this debate has centered on whether the reaction proceeds by a *cis*-hydroxypalladation pathway, involving migration of a coordinated water or hydroxide to the ethylene molecule (eq 2), or a *trans*-hydroxypalladation pathway, involving nucleophilic attack of exogenous water or hydroxide on the coordinated ethylene molecule (eq 3). The current mechanistic understanding of the hydroxypalladation step in the Wacker Process is the subject of an excellent recent review by Keith and Henry.[3]

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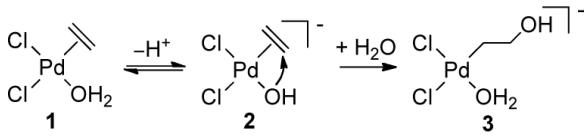

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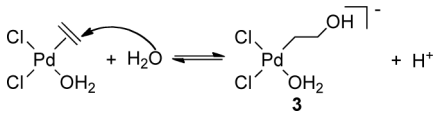

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Soon after the discovery of the Wacker process, a number of research groups demonstrated that Pd^{II} could facilitate the addition of several different nucleophiles to alkenes, and a variety of oxidative and non-oxidative C–O, C–N, and C–C bond-forming transformations have been developed, including intra- and intermolecular reactions.[5] The Pd^{II}-alkyl intermediate formed in the nucleopalladation step can participate in a number of subsequent transformations (e.g., see Scheme 2). Such opportunities, together with the broad functional-group compatibility and air- and moisture-tolerance of the Pd^{II}-catalysts, enable the preparation of important organic building blocks as well as useful hetero- and carbocyclic molecules.

Nucleopalladation of an alkene often generates a new stereogenic center, and the synthetic utility of the catalytic reactions is enhanced significantly if the stereochemical course of C–Nu bond formation can be controlled. Enantioselective Pd^{II}-catalyzed functionalization of alkenes has experienced considerably less success than have many other classes of enantioselective transformations, despite the extensive history of the Wacker process and related oxidation reactions. The former reactions face several challenges. Phosphine ligands, which have been highly successful in other enantioselective processes, are often incompatible with the oxidants used in these reactions (such as O_2), and their σ-donating ability can attenuate the electrophilicity and/or oxidizing ability of the Pd^{II} salts. A mechanistic basis for the difficulty in achieving effective enantioselective catalysis is that nucleopalladation reactions are capable of proceeding by two stereochemically different pathways: *cis*- or *trans*-nucleopalladation (Scheme 3). Experimental results obtained over the past 40 years, especially in the last decade, demonstrate that the energy barriers associated with these different pathways can be very similar, in some cases similar enough that both pathways operate in parallel. This mechanistic scenario can increase the difficulty of achieving high levels of enantioinduction.

In the present review, we summarize recent progress in two synergistic areas: (1) mechanistic studies of the stereochemical pathway of nucleopalladation reactions of alkenes (i.e., *cis*- vs. *trans*-nucleopalladation) under catalytically relevant reaction conditions and (2) advances in the development of enantioselective Pd-catalyzed reactions that proceed via nucleopalladation of an alkene substrate. The results summarized in the first portion of this review highlight the mechanistic complexity of these reactions and illustrate how subtle changes to the catalyst, substrate, and/or the reaction conditions can alter the stereochemical course of the reaction. Despite the challenges associated with enantioselective Pd^{II}-catalyzed reactions of alkenes, important progress has been made over the past 10–15 years. These advances are surveyed in the second portion of this review. The comprehensive coverage of this review begins with results from the late 1990s and early 2000s, when several important

advances were made, including the first examples of highly enantioselective reactions proceeding via nucleopalladation[6,7,8,9] and the development of ligand-supported Pd-catalysts for aerobic Wacker-type cyclization reactions.[10,11] It is hoped that the collective presentation of mechanistic insights and empirical reaction-discovery efforts in this review will provide a foundation for accelerated progress in this important field.

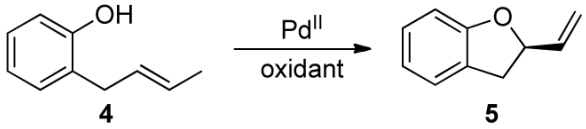
2. Mechanistic Studies of Nucleopalladation

2.1. Oxypalladation

The Wacker Process, involving the oxidation of ethylene to acetaldehyde, is the most prominent example of a catalytic reaction that proceeds via oxypalladation of an alkene. Studies probing the mechanism of this reaction have spanned five decades. The recent review by Keith and Henry[3] provides a thorough presentation of this work, and only a brief discussion will be included here. Stereochemical analysis of the oxypalladation step in the Wacker Process is complicated because the product of the reaction, acetaldehyde, is achiral. Nevertheless, Henry provided strong kinetic arguments supporting a *cis*-hydroxypalladation pathway.[12] His argument was based on determination of the rate law for the reaction and careful kinetic analysis, which revealed that nucleophilic attack of external hydroxide on a Pd^{II}-coordinated ethylene molecule would require a bimolecular reaction to proceed faster than diffusion. Subsequently, a number of groups, including those of Stille,[13] Bäckvall and Åkermark,[14] and others[15] designed studies to probe the stereochemistry of oxypalladation of alkenes. These studies employed modified reaction conditions (e.g., reactions carried out in the presence of carbon monoxide, high [Cl^-], and/or high [$CuCl_2$]) that lead to the formation of products amenable to stereochemical analysis. Most of these studies provided clear evidence for *trans*-hydroxypalladation of the alkene. During the same time period, studies of stoichiometric aminopalladation and carbopalladation reactions also were shown to proceed via *trans* addition of an amine or carbon nucleophile to a coordinated alkene.[16,17] The clarity and elegance of these experiments had a profound impact on the field, to the extent that early evidence for *cis*-hydroxypalladation of ethylene in the Wacker reaction seemed to be overlooked. The term “Wacker-type reaction” was often used a synonym for *trans*-nucleopalladation of an alkene, and such nomenclature has even been used in the recent literature.[18] Later work by Henry and co-workers, however, provided convincing evidence that the reaction conditions used in stereochemical studies by other groups caused a switch in the stereochemical outcome of the reaction. For example, they showed that oxypalladation proceeds by *cis* addition at low [Cl^-] (relevant to the industrial reaction conditions) and *trans* attack at high [Cl^-].[19] Computational studies by Goddard, Oxgaard, and co-workers provided added support for this change in mechanism and highlighted additional mechanistic features of the *cis*-hydroxypalladation pathway.[20] Meanwhile, recent experimental[21] and computational efforts[22] have provided renewed support for *trans*-hydroxypalladation, including a *trans*-hydroxypalladation pathway involving a three-water hydrogen-bond bridged chain.[21] Overall, the extensive mechanistic studies of oxypalladation reactions related to the Wacker process have highlighted the extreme sensitivity of the stereochemical course of the reaction to the identity of the catalyst, substrate, and/or the reaction conditions.

2.1.1. Phenol Cyclization—The oxidative cyclization of *ortho*-allyl phenols for the synthesis of dihydrobenzofurans was first reported in 1975 by Hosokawa and co-workers (eq 4).[23] Following this initial report, a number of chiral catalysts were developed for enantioselective catalysis (see section 3.1). Intrigued by the high levels of stereocontrol demonstrated for this cyclization, Hayashi and co-workers employed a stereospecifically deuterated substrate to probe the mechanism of oxypalladation (Scheme 4).[24] Phenol *cis*-3-*d*-**6** was subjected to $Pd(MeCN)_4(BF_4)_2$, chiral ligand **7a**, and the oxidant, benzoquinone

(BQ, 4 equiv), in methanol (Scheme 4). Analysis of the reaction mixture revealed four regioisomeric dihydrobenzofuran derivatives **8**, *cis*-2-*d*-**9**, *cis*-2-*d*-**10**, and 2-*d*-**11** in a ratio of 16/46/29/9. All of the products are consistent with a *cis*-oxypalladation pathway.



4 **5**

(4)

Analysis of the proposed reaction mechanism provides a basis for the formation of oxidative cyclization products **8**–**11** (Scheme 5). Oxypalladation involving alkene insertion into the phenol oxygen–Pd bond (*cis*-oxypalladation) forms Pd-alkyl intermediate **A**. The *syn*-facial relationship of the Pd and deuterium leads to β-deuteride elimination, a step that has been shown to proceed in a *cis* fashion.[25] The resulting Pd(D)(alkene) complex **B** furnishes dihydrobenzofuran **8** upon alkene dissociation. The lack of a deuterium atom at C3 provides direct evidence for cis-oxypalladation. Alternatively, alkene **8** can re-insert into the Pd-deuteride to form Pd–alkyl intermediate **C**, which can undergo β-hydride elimination to give regioisomer *cis*-2-*d*-**9**. Analogously, alkene reinsertion of **D** and subsequent β-hydride elimination generates isomer *cis*-2-*d*-**10**. The lack of products containing a deuterium atom at C3 implies that a *trans*-aminopalladation pathway is not operable under these reaction conditions.

As was observed in mechanistic studies of the Wacker reaction,[3] the mechanism of phenol cyclization appears to change from *cis*- to *trans*-oxypalladation under high [Cl^-] reaction conditions (Scheme 6). Cyclization of *cis*-3-*d*-**6** with a $Pd(MeCN)_2Cl_2/Na_2CO_3$/LiCl/BQ catalyst system in THF (in the absence of chiral ligand **7a**), provided a mixture of **8**, *cis*-2-*d*-**9**, *cis*-2-*d*-**10**, and 3-*d*-**12** in a 6/5/7/82 ratio. While the presence of small amounts of **8**, *cis*-2-d-**9**, and *cis*-2-*d*-**10** indicates that a *cis*-aminopalladation pathway is operable, formation of 3-*d*-**12** as the major product is consistent with *trans*-oxypalladation as the major reaction pathway (Scheme 7). These results clearly demonstrate that a single substrate can undergo both *cis*- and *trans*-nucleopalladation under different reaction conditions. In light of this work and previous mechanistic studies of the Wacker reaction,[3] it is tempting to suggest that a general correlation between [Cl^-] and nucleopalladation mechanism exists; however, as will be described in various sections below, the effect of [Cl^-] on the nucleopalladation mechanism is not consistent for all substrates/reaction conditions.

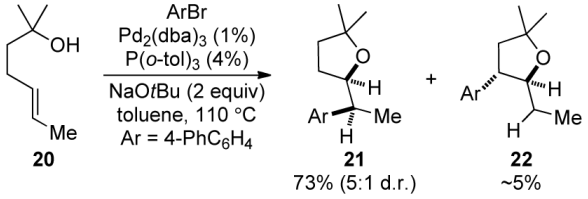
2.1.2. Carboxylic Acid Cyclization—Stoltz and co-workers probed the stereochemical pathway of a similar oxypalladation reaction using a carboxylic acid substrate with a catalytic system capable of direct dioxygen-coupled turnover.[26] Subjecting carboxylic acid *trans*-3-*d*-**13** to $(py)_2Pd(TFA)_2$, pyridine, Na_2CO_3, and 3Å molecular sieves (3Å M.S.) under one atmosphere of O_2 in toluene provided **14** as the exclusive product in 30% yield (Scheme 8). By a similar analysis as that described for *cis*-3-*d*-**6** (Scheme 5), loss of deuterium indicates that carboxylic acid cyclization occurs by a *trans*-oxypalladation pathway.

2.1.3. Alcohol Cyclization—In contrast to carboxylic acid substrate *cis*-3-*d*-**13**, Stoltz and co-workers observed *cis*-oxypalladation in the cyclization of the corresponding primary alcohol *trans-3-d*-**15**.[26] Under identical conditions, *trans-3-d*-**15** underwent cyclization to provide 3-*d*-**16** along with alkene isomer 3-*d*-**17** in a 4:1 ratio and 91% overall yield (Scheme 9). Products derived from *cis*-addition were also formed when the bidentate ligand bipyridine was employed (Scheme 9).

Although the reasons for the change in product distribution between the primary alcohol and carboxylic acid substrates remain unclear, the authors suggest that geometrical constraints, pK_a differences, or the variation in nucleophilicity between an acid and an alcohol all influence the reaction mechanism. These results highlight the principle that seemingly small changes to the substrate or reaction conditions can result in a change in the oxypalladation pathway.

Further evidence for a *cis*-oxypalladation reaction mechanism during alcohol cyclization has been furnished by Wolfe and co-workers, who have developed a class of alkene difunctionalization reactions that are initiated by oxidative addition of aryl bromides by Pd^0 catalysts (Scheme 10).[27] The resulting Pd^{II}-aryl species **18** then undergoes intramolecular oxypalladation to give Pd-alkyl **19**, followed by reductive elimination to form a new C–C bond.

Preliminary studies of the oxypalladation step focused on the stereochemical relationship of the nucleophilic oxygen atom and the aryl substituent.[28] Tertiary alcohols bearing internal alkenes underwent alkoxyarylation to generate furans in which the aryl substituent and nucleophilic oxygen added to the alkene in a *cis* fashion (i.e., **21**, eq 5), as was demonstrated by the reaction of *trans*-alkene **20** with 4-bromobiphenyl (eq 5). A trace amount of the regioisomeric product **22** was also observed.



(5)

The authors proposed that the modest diastereoselectivity observed for the formation of **21** could be the result of competing *cis*- and *trans*-oxypalladation, or alternatively, the diastereomeric mixture could form by isomerization steps that occur after oxypalladation.[29] In order to distinguish between these two possibilities, deuterated tertiary alcohol 5-*d*-**23** was subjected to catalytic $Pd_2(dba)_3$/P(*o*-tol)$_3$ and NaO*t*Bu (Scheme 11). The reaction yielded diastereomers **24** and **25** in a 79:17 mixture and trace quantities of regioisomeric side product **26**. Alkene isomer 6-*d*-**27** reacted in a similar fashion (Scheme 11). The major diastereomers (**24** and **28**) appear to arise from *cis*-oxypalladation. The minor diastereomers (**25** and **29**) are formed with significant quantities of deuterium scrambling, an observation that cannot be readily explained by invoking a *trans*-oxypalladation reaction mechanism. The authors proposed an alternative pathway that accounts for the formation of the minor diastereomers and the regioisomeric product **26** (Scheme 12).

As illustrated in Scheme 12, all products in the alkoxyarylation of 5-*d*-**23** are proposed to arise from a *cis*-oxypalladation pathway. Upon formation of Pd-alkyl intermediate **30**, reductive elimination forms the major product **24**. Alternatively, σ-bond rotation, followed by β-deuteride elimination and alkene reinsertion generates intermediate **31**, which accounts for the formation of deuterium scrambled products. From **31**, successive σ -bond rotation, β -hydride elimination, reinsertion, and C–C reductive elimination leads to the minor diastereomer **25**. Intermediate **31** also provides a mechanistic hypothesis for the formation of **26**, as a similar pathway can be invoked for the formation of this product. Together, these deuterium scrambling studies provide support for an exclusive *cis*-aminopalladation

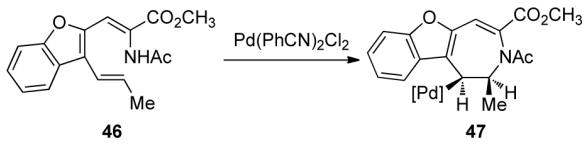
pathway, with the minor diastereomers **25** and **29** arising from an isomerization pathway rather than *trans*-aminopalladation.

Wolfe and co-workers also explored the stereochemical course of an intramolecular alkoxyarylation reaction of unsaturated alcohols (Scheme 13).[18a] For these transformations, the stereochemistry of oxypalladation was controlled by the identity of the phosphine ligand. Reactions employing monodentate phosphines such as PCy_3 or $P[(p\text{-}MeO)C_6H_4]_3$ led to products arising from alkene insertion into a Pd–O bond (*cis*-oxypalladation). In contrast, the use of catalysts with chelating ligands (±)-BINAP or 1,2-bis(diphenylphosphino)benzene (DPP-benzene) afforded products attributed to *trans*-oxypalladation.

The authors proposed a rationale that accounts for the apparent change in oxypalladation mechanism between mono- and bidentate phosphine ligands. The *cis*-oxypalladation product **33**, was observed when monophosphine ligands were employed in the cyclization of *trans*-alkene **32**, was proposed to occur by the pathway illustrated in Scheme 14a. Pd-alkene complex **38** could form by oxidative addition of aryl bromide **32**, followed by alkene coordination. This 16-electron intermediate is then proposed to form Pd-alkoxide **39**, resulting from alcohol deprotonation by NaO*t*Bu and anionic ligand exchange. Alkene insertion into the Pd–O bond furnishes **40**, which undergoes C–C reductive elimination to provide the product **33**. Alternatively, a model for the observation of the *trans*-oxypalladation product when bidentate phosphine ligands are employed is shown in Scheme 14b. In this case, 18-electron complex **41** is proposed to form by oxidative addition of the aryl bromide followed by alkene coordination. Backside nucleophilic attack then generates Pd-alkyl intermediate **43**. The transition from *cis*- to *trans*-oxypalladation in the presence of bidentate phosphine ligands was attributed to the notion that Pd-alkoxide formation, the step required for a *cis* process to occur, would likely be disfavored because proposed complex **41** (direct evidence was not obtained) is coordinatively saturated and, therefore, unable to react with the pendant oxygen (i.e., step **38** to **39** in the *cis*-oxypalladation pathway). Instead, *trans*-oxypalladation of **41** would presumably yield Pd-alkyl intermediate **43**. Subsequent C–C reductive elimination would then afford *trans*-addition product **34**.

2.2. Aminopalladation

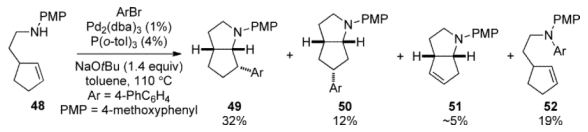
Early fundamental studies of aminopalladation reactions by Åkermark, Bäckvall, Zetterberg, and Hegedus[16b,30,31] demonstrated that discrete Pd-alkene complexes react with amine nucleophiles to generate C–N bonds (for example, Scheme 15).[32] Evidence for *trans* attack of the coordinated alkene was provided by formation of cyclometalated Pd-alkyl intermediate **44**,[16b] whose stereochemistry was established by NMR spectroscopic studies or by reduction with $LiAlD_4$ to form stereospecifically deuterated product **45** (Scheme 15).[31a] Later, a report by Taniguchi and co-workers showed that enamide **46** underwent aminopalladation to furnish isolable Pd-alkyl intermediate **47** (eq 6).[33] The *anti* relationship between Pd and the β -hydrogen precludes β -hydride elimination from occurring, and the product stereochemistry supports a *cis*-aminopalladation mechanism. These early studies, which established a foundation for future investigations of alkene amination, were based upon stoichiometric reactions and therefore the insights do not necessarily apply to catalytic systems. Mechanistic studies aimed at elucidating the stereochemical course of catalytic aminopalladation reactions remained sparse until 2004. In the last 6 years, however, a number of research groups have provided valuable mechanistic insights into catalytic transformations. These studies have dramatically increased the current understanding of factors that influence the course of aminopalladation.



46 47

(6)

2.2.1. Aminoarylation—Analogous to the alkoxyarylation of alkenes (see section 2.1.3), Wolfe and co-workers have developed methods for the synthesis of pyrrolidines from γ-(*N*-arylamino) alkenes and aryl halides. For example, cyclization of **48** in the presence of 4-bromobiphenyl and catalytic $Pd_2(dba)_3$/P(*o*-tolyl)$_3$ generated a mixture of four products (**49**–**52**, eq 7).[34] The authors provided a *cis*-aminopalladation reaction pathway that accounts for all of the observed products (Scheme 16). Following oxidative addition of the aryl bromide to form a Pd(Ar)Br species, Pd–N bond formation provides **53**. Alkene insertion into the Pd–N bond generates Pd-alkyl intermediate **54**, which forms product **49** by reductive elimination or **50** by a β -hydride elimination, alkene reinsertion, reductive elimination pathway. The observation of *N*–arylated product **52** lends further support to the presence of Pd–N intermediate **53**, which presumably undergoes C–N reductive elimination instead of alkene insertion.

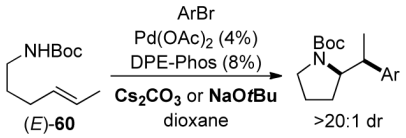


48 **49** 32% **50** 12% **51** ~5% **52** 19%

(7)

Wolfe and co-workers obtained additional support that aminoarylation proceeds via a *cis*-aminopalladation pathway by studying the bicyclization of **57** (Scheme 17).[18a] The reaction of **57** catalyzed by $Pd_2(dba)_3$/PCy_3•HBF_4 afforded *cis*-addition product **58** exclusively, likely in a manner analogous to that described for the similar alkoxyarylation substrate (Scheme 13). Whereas the alcohol substrate **35** undergoes predominately *trans*-oxypalladation with the $Pd_2(dba)_3$/(±)-BINAP catalyst, the reaction of the aniline substrate with the BINAP catalyst resulted in a 1:1 mixture of *cis*- and *trans*-addition products. The authors suggest that the ability of the more acidic oxygen atom to be deprotonated by exogenous base leads to a higher rate of *trans*-oxypalladation, whereas the less acidic aniline favors coordination to Pd prior to deprotonation, leading to significantly lower levels of *trans* attack.

Additional studies were performed to elucidate the effect of the base on the mechanism of aminopalladation.[35] Cyclization of substrates (*E*)-**60** and (*Z*)-**60** bearing a Boc-protected amine and a disubstituted alkene formed the pyrrolidine products with high diastereoselectivity (eqs 8 and 9). Irrespective of the identity of the base (Cs_2CO_3 or NaO*t*Bu), the product stereochemistry was indicative of *cis*-aminopalladation. This result was confirmed through the use of stereospecifically deuterated **61**, which underwent aminoarylation to provide a single diastereomer resulting from *cis*-aminopalladation (eq 10). The absence of side products resulting from deuterium scrambling provided additional support that the reaction proceeds through the proposed *cis*-aminopalladation pathway and indicates that the strength of the exogenous base has little effect on the mechanism in this reaction.



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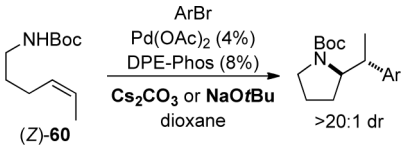

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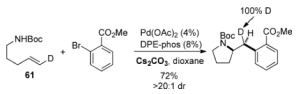
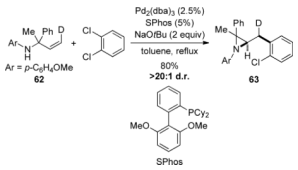


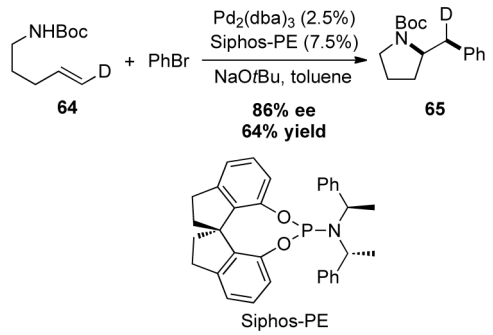
(10)

The synthesis of aziridines by intramolecular aminoarylation of allyl amines was recently reported by Hayashi, Yorimitsu, and Oshima.[36] The authors proposed that the transformation proceeds by oxidative addition of an aryl halide, followed by intramolecular aminopalladation and C–C reductive elimination (Scheme 18). Deuterated substrate **62** bearing an aniline nucleophile was employed as a stereochemical probe (eq 11). Following further derivatization of aziridine product **63** (derivatizations not shown), the nitrogen and aryl chloride were shown to exist in a stereochemical configuration indicative of *cis* addition to the alkene, in agreement with the conclusions made by Wolfe and co-workers for aminoarylation in the presence of a monodentate phosphine ligand.



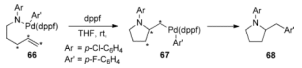
(11)

Until recently, no mechanistic studies had been reported for enantioselective Pd^{II}-catalyzed amination reactions. Future studies of this type will undoubtedly provide information regarding the mechanistic requirements of a successful enantioselective reaction. To this end, Mai and Wolfe disclosed an enantioselective aminoarylation reaction using the chiral phosphoramidate ligand Siphos-PE (see section 4.5 for a description of the enantioselective methodology) and examined the course of aminopalladation in this transformation.[37] Deuterated substrate **64** provided a probe for analysis of the reaction stereochemistry in the presence of the chiral ligand (eq 12). Cyclization of **64** under the optimal reaction conditions yielded pyrrolidine **65**, whose stereochemical composition indicated a *cis*-aminopalladation mechanism. This outcome further supports the observation that aminoarylation proceeds by *cis*-addition in the presence of a monodentate ligand and establishes that this reaction pathway is amenable to enantiocontrol.



(12)

Wolfe and co-workers recently reported a detailed investigation of stoichiometric aminopalladation from aryl Pd-amido complexes.[38] Immediately upon forming Pd-amido **66** at room temperature, a new species was identified via NMR spectroscopy, which then converted to the pyrrolidine product **68** (eq 13). Following ^{13}C labeling of the substrate and analysis by ^{13}C and ^{31}P NMR spectroscopy (* indicates ^{13}C enriched atoms; eq 13), the identity of the intermediate Pd species was proposed to be Pd-alkyl **67**, which forms via aminopalladation of the alkene. Through the use of deuterated complex **69**, this stoichiometric transformation was shown to proceed via *cis*-aminopalladation (eq 14). These studies provide a rare example of direct observation of alkene insertion into a Pd–N.[39]



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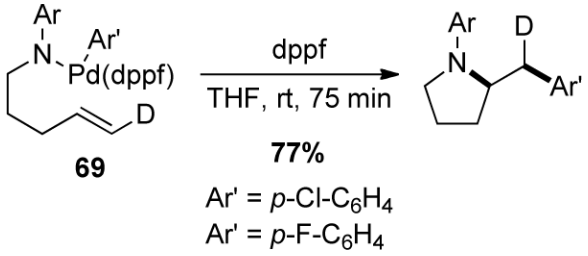
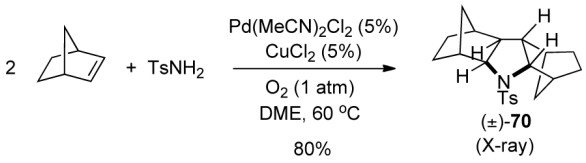


(14)

2.2.2. Wacker-Type Oxidative Amination—The amination reactions discussed above were initiated by oxidative addition of an aryl halide to Pd^0 and terminated by C–C reductive elimination. The aminopalladation step in these transformations presumably occurs from an electron-rich Pd^{II} complex bearing aryl and phosphine ligands. In contrast, Wacker-type oxidative aminations are catalyzed by electrophilic Pd^{II} species, and proceed by an aminopalladation/β-hydride elimination sequence. Despite these important differences, it appears that oxidative amination also proceeds through a predominantly *cis*-aminopalladation pathway, although evidence has also been obtained for a *trans*-addition pathway.

In studies of aerobic Pd^{II}-catalyzed *inter*molecular oxidative amination of alkenes, Stahl and co-workers found that the reaction between norbornene and *para*-toluene sulfonamide

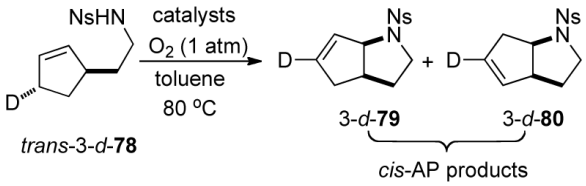
($TsNH_2$) in 1,2-dimethyoxyethane (DME) formed C_2-symmetrical pyrrolidine **70** in good yield (eq 15).[40] Complex **70** arose from the oxidative coupling of the sulfonamide nucleophile with two equivalents of norbornene. Crystallographic characterization of **70** revealed that both equivalents of norbornene underwent *cis*-difunctionalization on the *exo* face of the alkene. The authors proposed that this product arises from *cis*-aminopalladation of norbornene, intermolecular alkene insertion into the Pd-alkyl bond, and C–N reductive elimination (Scheme 19, top). A pathway involving two sequential *cis*-aminopalladation steps, followed by C–C reductive elimination is also possible (Scheme 19, bottom).[41]



(15)

Liu and Stahl performed mechanistic studies of intramolecular aminopalladation with a series of common oxidative amination catalyst systems.[42] Stereospecifically deuterated substrate *trans*-3-*d*-**71** provided a mechanistic probe for determining the stereochemistry of aminopalladation (Scheme 20). As shown in path A, *cis*-aminopalladation generates Pd-alkyl species **72** in which the metal and nitrogen exist in a *syn*-facial arrangement. This intermediate is then positioned for *syn* β-hydride elimination, leading to 3-*d*-**75**. Alkene reinsertion into the Pd-hydride would afford alkene 3-*d*-**74**. Alternatively, the formation of non-deuterium-labelled product **76** and deuterium-scrambled product **77** would result from attack of the amide *trans* to a Pd-coordinated alkene (Scheme 20B). In this case, the Pd-alkyl intermediate formed by aminopalladation has Pd *syn* with respect to the deuterium, leading to β-deuteride elimination. By this analysis, products that do not contain a deuterium in the 3-position arise from a *trans*-aminopalladation pathway.

Subjecting *trans*-3-*d*-**71** to various catalyst systems provided 3-*d*-**74** and 3-*d*-**75**, products indicative of *cis*-aminopalladation, in all but one instance (Table 1). The only exception occurred with reactions that employed an *N*-heterocyclic carbene (NHC) ligand and included benzoic acid (BzOH) as an additive. In this case, a mixture of *cis*- and *trans*-aminopalladation products was observed. Use of a more acidic nosyl (Ns) nitrogen nucleophile **78** afforded *cis*-aminopalladation products 3-*d*-**79** and 3-*d*-**80** exclusively for all catalyst systems, including the NHC/BzOH catalyst (eq 16).



(16)

A systematic study of additive effects provided further insight into the origin of the aminopalladation mechanism for the NHC-$Pd(TFA)_2$ catalyzed cyclization of tosyl substrate *trans*-3-*d*-**71**. Replacement of BzOH with NaOAc or Na_2CO_3 led to products derived exclusively from *cis*-aminopalladation (Figure 1), a result that suggests that under basic conditions aminopalladation occurs by alkene insertion into a Pd–N bond (i.e., *cis*-aminopalladation). These data indicate that exogenous base may facilitate *cis*-

aminopalladation by deprotonating the nitrogen nucleophile, either prior to or immediately following nitrogen complexation to Pd (eq 17).

(17)

The stereochemistry of aminopalladation was also investigated under high [Cl^-] conditions (Scheme 21). Oxidative cyclization of *trans*-3-*d*-**71** with a catalyst system consisting of $Pd(MeCN)_2Cl_2$, BQ, Na_2CO_3, and LiCl in THF gave 3-*d*-**74**, 3-*d*-**75**, 2-*d*-**81** and *trans*-2-*d*-**77** in a ratio of 37/49/6/8 (78% overall yield), in addition to a small amount of alkene isomerized starting material. Major products 3-*d*-**74** and 3-*d*-**75** indicated that the reaction proceeds by *cis*-aminopalladation. The presence of *trans*-2-*d*-**77** and 2-*d*-**81** (the latter was proposed to form by isomerisation of *trans*-2-*d*-**77**) was attributed to a *trans*-aminopalladation pathway. The predominance of *cis*-addition products contrasts the observations made by Hayashi for *ortho*-allyl phenol substrates, which demonstrated that *trans*-oxypalladation is operative under identical conditions (Scheme 6).[24] While the differences in the stereochemical outcome of these transformations are not entirely clear, the results highlight that the identity of the substrate can directly influence the reaction mechanism.

Liu and Stahl also investigated the cyclization of substrate *trans*-3-*d*-**82** bearing a more acidic tosyl-substituted carboxamide nucleophile (Table 2). This substrate cyclized to afford a mixture of *cis*- and *trans*-aminopalladation products. The authors propose that both reaction pathways may proceed via a Pd–N bond; however, because the weakly-basic anion resulting from nitrogen deprotonation is more stable, ionization of the Pd–N bond would be facilitated. Alternatively, the more acidic nitrogen nucleophile may undergo deprotonation in solution, followed by *trans* attack of the alkene. Exclusive formation of *trans*-aminopalladation products with the $Pd(OAc)_2$/DMSO catalyst system supports this hypothesis. A pK_a analysis suggests that acetate is basic enough to deprotonate the substrate in DMSO. The high polarity of DMSO should facilitate anionic *trans* attack by solvation of the deprotonated imide anion. Together with the observations made by Stoltz and co-workers for a substrate consisting of a carboxylic acid nucleophile (Section 2.1.2), these data indicate that more acidic nucleophiles possess an increased propensity to undergo *trans*-aminopalladation.

To date, no examples of enantioselective *inter*molecular aminopalladation have been reported; however, the insights gained from mechanistic studies could provide a basis for future catalyst design. To this end, Stahl and co-workers provided preliminary evidence for a *cis*-aminopalladation pathway in an aerobic intermolecular oxidative amination using phthalimide as the nucleophile (Scheme 22).[43] The reaction of **87** and phthalimide catalyzed by $Pd(OAc)_2$ in 1,2-dichloroethane (DCE) led to (*Z*)-**88** as the exclusive oxidative amination product in 20% yield. Oxidative amination product (*E*)-**88**, expected to form by a pathway that proceeds through a *trans*-aminopalladation/β-hydride elimination pathway, was not observed. The authors therefore concluded that (*Z*)-**88** arose by a *cis*-aminopalladation/*syn* β-hydride elimination sequence. These results with the relatively acidic nucleophile phthalimide are somewhat unexpected when considering that the increased nitrogen acidity of tosyl-substituted carboxamide substrate **82** appeared to favor a *trans*-aminopalladation pathway (Table 2). Future work will be necessary to ascertain whether this mechanistic observation can be extended to intermolecular transformations that proceed with more synthetically viable yields.

An alternative hypothesis for the exclusive formation of (*Z*)-**88** by a *trans*-aminopalladation mechanism could not be excluded: the product of *trans* aminopalladation, (*E*)-**88**, may be

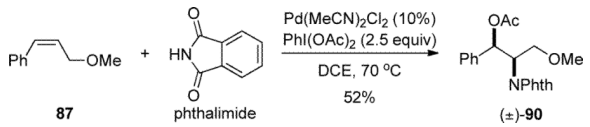
formed and then rapidly consumed by a pathway involving rapid alkene reinsertion into the Pd–H bond, followed by σ-bond rotation and β-hydride elimination to form the observed product (*Z*)-**88** (Scheme 23).[44] This *trans*-aminopalladation pathway requires that (*Z*)-**88** is the more thermodynamically stable product.

Very recently, Hartwig and co-workers studied the intermolecular insertion of alkenes into Pd-amide species.[39] Various Pd-amide complexes were prepared and exposed to ethylene or octene (Scheme 24). The reactions generated enamine products in high yields in less than 2 hours at −10 °C via an aminopalladation/β-hydride elimination reaction sequence. Electronic variation of the nitrogen nucleophile revealed that complexes bearing electron-rich amides reacted more rapidly than electron-poor amides (Scheme 24).

The stereochemistry of ethylene aminopalladation was studied by analyzing the composition of products formed in the reaction of Pd-amide complex **89** with *cis*-ethylene-d_2. As shown in Scheme 25, products resulting from *cis*-aminopalladation were formed exclusively. This experiment was performed with the diphenylamine complex; it remains to be seen if nitrogen nucleophiles bearing more electron withdrawing substituents also proceed by *cis*-aminopalladation in analogous transformations.

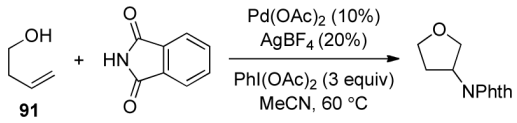
2.2.3. Alkene Difunctionalization—In recent years, a number of novel Pd-catalyzed intramolecular alkene difunctionalization reactions have been reported, and the stereochemical arrangement of the two newly incorporated functionalities has been used as a basis for mechanistic proposals. These transformations have been shown to occur with very high diastereoselectivities, providing products in which the two new functional groups exist in either a *trans*- or *cis*-relationship. Recent examples of aminohalogenation,[45] aminoacetoxylation,[46] aminofluorination,[47] and acetoxyvinylation[48] afforded products featuring *trans*-substituted functional groups, whereas diamination[49] yielded *cis* products (Scheme 26). As illustrated in Scheme 27, *trans* and *cis* products could arise from either *cis*- or *trans*-aminopalladation pathways, depending on the stereochemistry of the reductive elimination step. While the authors in most cases have proposed a mechanism involving *trans*-aminopalladation, these hypotheses were often based upon assumptions regarding the stereochemistry of the reductive elimination step, and were not experimentally validated. Described below are mechanistic studies aimed at elucidating the stereochemical course of aminopalladation in alkene difunctionalization reactions.

Evidence for an intermolecular amination that proceeds by a *cis*-aminopalladation pathway was provided by Stahl and coworkers in their studies of the intermolecular aminoacetoxylation of alkenes.[43] The $Pd(MeCN)_2Cl_2$ catalyzed reaction of (*Z*)-alkene **87** and phthalimide in the presence of $PhI(OAc)_2$[50] afforded *anti*-addition product **90** (eq 18). The authors used their analysis of the oxidative amination of **87**, shown above, (Scheme 22) to suggest that the mechanism of addition involves *cis*-aminopalladation of the alkene followed by oxidation to a Pd^{IV} intermediate and S_N2-type nucleophilic attack of acetate on the Pd^{IV}-alkyl species (Scheme 28).[51] These mechanistic conclusions assume that using $PhI(OAc)_2$ as the oxidant, rather than O_2, (Scheme 22) does not alter the aminopalladation pathway.



(18)

Desai and Sanford reported a similar aminoacetoxylation reaction of 3-alken-1-ols (eq 19) that also appears to proceed by a *cis*-addition pathway.[52] The intermolecular oxidative amination of alkene **92** with molecular oxygen in place of $PhI(OAc)_2$ was used as a stereochemical probe (Scheme 29, analogous to Scheme 22). Although the reaction only proceeded in 3% yield, observation of (*Z*)-**93** as the major product provided circumstantial evidence for a *cis*-aminopalladation mechanism. Further work will be required to provide support for this pathway in a more catalytically relevant transformation.



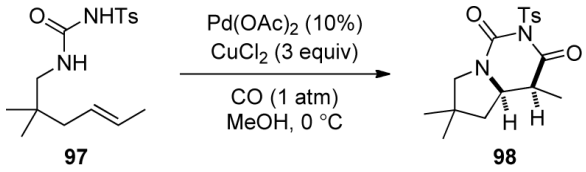
(19)

Perhaps the most relevant investigation of the aminopalladation mechanism for an alkene difunctionalization reaction was provided by Michael and co-workers, who recently reported Pd^{II}-catalyzed alkene diamination and aminoarylation reactions that are promoted by *N*-fluorobenzenesulfonimide (NFBS).[53,54] Both transformations are catalyzed by $Pd(TFA)_2$, and are proposed to commence by aminopalladation, followed by divergent trapping of the Pd-alkyl intermediate (Scheme 30). In non-aromatic solvents, diamination products were observed, while in the presence of aromatic solvents, aminoarylation products were observed, presumably by an aryl C–H activation/reductive elimination mechanism.

Studies of the stereochemistry of aminopalladation for these reactions were performed by analysis of the structure of stable Pd-alkyl intermediates.[55] The Pd-alkyl intermediate **95** formed by aminopalladation of alkenyl amide **94**, and **95** was trapped by addition of bipyridine (bpy), affording (bpy)Pd(alkyl) complex **96**. The structure of **96** was confirmed by X-ray crystallographic analysis (Scheme 31). This reaction sequence allowed for the study of the stereochemistry of the aminopalladation step directly by ^1H NMR spectroscopic analysis of the corresponding deuterated complex **96**. The results of this study revealed that Pd and nitrogen had added in a *trans* fashion. The authors attributed the preference for *trans*-aminopalladation to the identity of the nitrogen nucleophile. Previous mechanistic studies of aminopalladation reactions involving sulfonamide or phthalimide nucleophiles, which are more acidic than acetamides, support a *cis*-aminopalladation pathway.

These results, together with the observations made by Liu and Stahl in the Wacker-type oxidative amination of sulfonamides, suggest that nitrogen nucleophiles with substantially enhanced acidity (i.e., *N*-tosylcarboxamides) or reduced acidity (i.e., amides) favor a *trans*-aminopalladation pathway, but substrates bearing nitrogen nucleophiles with intermediate acidity (i.e., sulfonamides) favor *cis*-aminopalladation. These results reflect the interplay between substrate nucleophilicity (prior to deprotonation) and acidity.

2.2.4. Aminocarbonylation—In 1988, Tamaru and co-workers obtained products derived from *trans*-aminopalladation in a catalytic aminocarbonylation reaction.[56] Tosyl urea **97** cyclized to afford exclusively bicyclic product **98** by an aminopalladation/carbonylation reaction mechanism (eq 20). Because carbonylation of a Pd–C bond is known to proceed with retention of configuration, the stereochemical arrangement of **98** provided direct insight into the stereochemical course of aminopalladation. Structural determination revealed that the nitrogen and carbonyl added to the alkene in a *trans* fashion, indicating that the reaction proceeds by backside attack of a Pd-coordinated alkene. These results are consistent with previous observations that nucleopalladation reactions performed in the presence of CO occur by *trans* attack.[13]



97 98

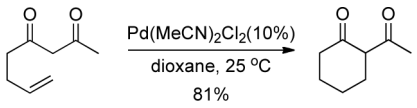
(20)

2.2.5. Rearrangement of Allylic Imidates—The Pd^{II}-catalyzed rearrangement of allylic imidates for the synthesis of allylic amines was first reported in the early 1980s,[57] and has been amenable to highly enantioselective catalysis (see section 4.1). Although the net transformation constitutes a net [3,3]-sigmatropic rearrangement, the reaction has been proposed to proceed through a Pd^{II}-catalyzed "cyclization-induced rearrangement," involving aminopalladation to form Pd-alkyl intermediate **99** and then fragmentation to generate the allylic amine product (Scheme 32).[57c]

Recently, Bergman and Overman performed experimental and computational studies that provided further insight into the rearrangement of allylic trichloroacetimidates.[58] They found that a mixture of allylic imidate **100** and the chiral catalyst COP–Cl (refer to section 4.1 for a more detailed description) yielded a new species, identified as Pd-imidate **101** (Scheme 33). The authors proposed that the imidate dissociates to yield a Pd^{II}-alkene adduct that undergoes *trans*-nucleophilic attack by the imidate nitrogen. A relatively low calculated transition-state barrier (~10 kcal/mol) provided the basis for support of a *trans*-aminopalladation pathway, although the *cis*-aminopalladation pathway was never explicitly investigated.

2.3. Carbopalladation

2.3.1. Hydroalkylation—Widenhoefer and co-workers have reported Pd-catalyzed intramolecular hydroalkylation reactions of alkenyl β-dicarbonyl compounds.[59] The reaction employs β-diketone substrates bearing a pendant alkene that, upon exposure to Pd^{II} salts, undergoes non-oxidative addition of the enolic C–H bond across the alkene (eq 21).

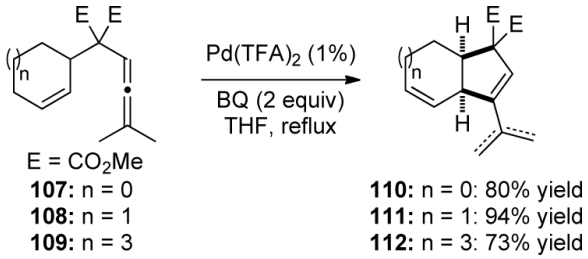


(21)

To gain insight into the key carbopalladation step of these reactions, stereospecifically deuterated substrate (*E*)-7,8-d_2-**102** was synthesized and used as a stereochemical probe (Scheme 34).[60] *Trans*-carbopalladation of the alkene would form the Pd-alkyl intermediate **104**. With the assumption that protonolysis of the Pd–C bond proceeds with retention of configuration, cyclohexyl product *cis*-3,4-d_2-**103** would be generated. Alternatively, a *cis*-carbopalladation pathway would be initiated by formation of the Pd–enol-carbon bond (**105**), followed by alkene insertion and protonolysis of the Pd–C. In this pathway, the expected product would be *trans*-3,4-d_2-**106**. The researchers found that subjecting (*E*)-7,8-d_2-**102** to catalytic $Pd(MeCN)_2Cl_2$ in dioxane resulted in the formation of *cis*-3,4-d_2-**103** (Scheme 34). This result indicates that hydroalkylation proceeded by a *trans*-carbopalladation mechanism.

2.3.2. Addition of Allene Nucleophiles—Allenes are also capable of participating in alkene nucleopalladation transformations. Bäckvall and co-workers have shown that allenes

such at **107** undergo an oxidative cyclization in the presence of catalytic amounts of $Pd(TFA)_2$ and 2 equiv of BQ to furnish highly unsaturated bicyclic products (eq 22 and 23).[61] The size of the alkene-containing ring affects the reaction outcome; while the five-, six- and eight-membered ring substrates (**107**, **108**, and **109**, respectively; eq 22) cyclized to afford *cis* products, *trans*-fused ring **114** was observed as the only product in the reaction of seven-membered ring substrate **113** (eq 23). Intrigued by this divergent reactivity, the researchers investigated the cyclization of stereospecifically deuterated substrate analogues.



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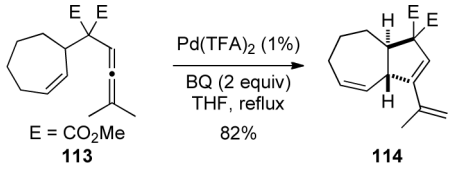
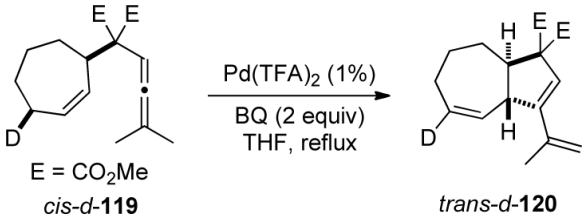


(23)

Cyclization of the stereochemical probe *trans-d*-**115** with $Pd(TFA)_2$/BQ afforded *cis-d*-**116** as the only product (Scheme 35). The absence of deuterium loss or scrambling suggested that the reaction is initiated by allene addition to Pd, generating the Pd–C(sp^2) species **117**. Subsequent *cis*-alkene insertion then yields Pd-alkyl **118**, with the Pd positioned *anti* with respect to the deuterium and *syn* with respect to the β-hydrogen. This stereochemical arrangement positions Pd for β-hydride elimination rather than β-deuteride elimination, resulting in the formation of *cis-d*-**116** and the absence of deuterium scrambled products. Retention of deuterium was also observed for the cyclization of *cis-d*-**119**, suggesting that for the seven-membered ring substrate, the *cis*-carbopalladation mechanism is also operative (eq 24).

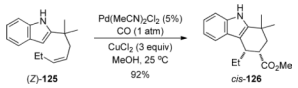


(24)

2.3.3. Annulation of Indoles—Stoltz and co-workers developed an aerobic oxidative cyclization of indoles with pendant alkenes that generate fused five-membered carbocycles (Scheme 36).[62] Insight into the mechanism of this transformation was obtained by analyzing the reaction of indole **121**. Upon exposure to the standard reaction conditions, **121** generated tricyclic indole **122** as a single diastereomer (Scheme 36). The stereochemical relationship

of the indole and the methylene-benzyl ether substituent provided a direct probe of the carbopalladation mechanism. The stereochemistry of **122** suggests that the reaction is initiated by C–H activation of the indole to form intermediate **123**, followed by alkene insertion (*cis*-carbopalladation) to provide Pd-alkyl **124**. The requirement that Pd and the β-hydrogen be positioned in a *syn*-facial arrangement for β-hydride elimination implicates Pd-alkyl **124** as the immediate product of carbopalladation.

Liu and Widenhoefer have described the reactions of other indole substrates that undergo intramolecular arylation/alkoxycarbonylation to afford densely functionalized products (eqs 25 and 26).[63] These reactions proceed under one atmosphere of CO and with 3 equivalents of $CuCl_2$. The $CuCl_2$ is proposed to act as the stoichiometric oxidant to regenerate Pd^{II} from Pd^0. Stereospecific conversion of (*Z*)-**125** into *cis*-**126** indicated that the indole and CO added in a *trans*-fashion across the pendant alkene (eq 25). Because α-migratory insertion of CO into Pd–C bonds occurs with retention of configuration,[64] the formation of *cis*-**126** is indicative of *trans* attack by the indole onto a Pd-alkene complex (*trans*-carbopalladation) (Scheme 37). This proposal was further supported by the exclusive formation of *trans*-**128** from (*E*)-**127**.



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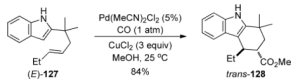
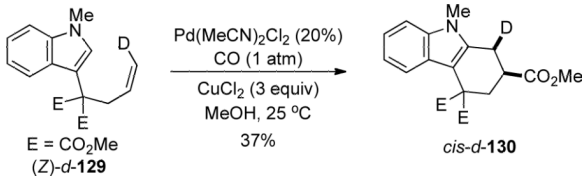


(26)

The authors confirmed that *trans*-carbopalladation was the operative reaction pathway by investigating the cyclization of stereospecifically deuterated substrates (*Z*)-*d*-**129** and (*E*)-*d*-**129** (eqs 27 and 28). The substrate (*Z*)-**129** generated *cis*-*d*-**130** exclusively, and (*E*)-*d*-**129** formed *trans*-*d*-**130**. In the reaction of (*Z*)-*d*-**129**, Pd-alkene complex formation followed by *trans*-carbopalladation affords a Pd-alkyl intermediate *syn*-facial with respect to the deuterium (analogous to Scheme 36). Subsequent α-migratory insertion of CO with retention of configuration forms *cis*-*d*-**126**.



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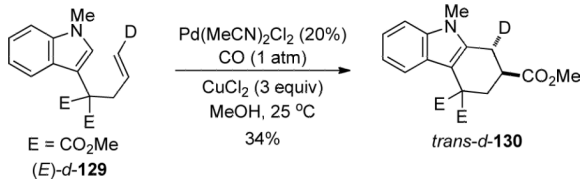
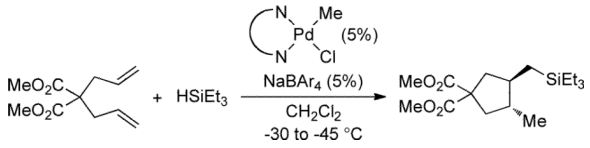


The observation of a *trans*-carbopalladation pathway differs from the indole annulation reaction developed by Stoltz (Scheme 36). These results could be attributed to the presence of high [Cl^-] as a result of the superstoichiometric quantities of $CuCl_2$, as has been discussed previously, or the presence of CO, which could occupy a coordination site and disfavor the formation of the bidentate alkene-indole complex (i.e., **123**, Scheme 36) required for *cis*-carbopalladation, reminiscent of early work by Stille and co-workers in the oxycarbonylation of alkenes, which was shown to proceed via a *trans*-oxypalladation mechanism.[13]

2.3.4. Hydrosilylation/Cyclization—Widenhoefer and co-workers have developed a Pd^{II}-catalyzed hydrosilylation/cyclization reaction for the synthesis of silylated cyclopentane derivatives.[65] 1,6-Substituted dienes react to afford hydrosilylated cyclopentene derivatives in the presence of a stoichiometric silane and a Pd^{II} precursor (eq 29). Perch and Widenhoefer performed studies with stoichiometric Pd complexes to explore the mechanism of this transformation.[66] At −62 °C, Pd-silyl complex **131** reacted with 1,6-diene **132** in high yield to form the hydrosilylation product, Pd-alkyl **133** (Scheme 38). Upon warming to −41 °C, alkene insertion occurred in less than 2 hours to form carbopalladation product **134**. Although the course of the reaction may differ under catalytic reaction conditions, these stoichiometric studies provide strong support for a *cis*-carbopalladation reaction mechanism involving alkene insertion into a Pd–C(sp^3) bond, analogous to the Heck reaction.



(29)

2.4. Summary of Mechanistic Studies

The presentation above highlights the dramatic growth in mechanistic understanding of nucleopalladation reactions in synthetically useful transformations. Many reactions that were once assumed to proceed by a *trans*-nucleopalladation mechanism actually proceed by olefin insertion into the Pd-nucleophile bond. In fact, *cis*-nucleopalladation appears to be the favored reaction pathway in the majority of Pd^{II}-catalyzed alkene functionalization reactions. Perhaps the most important lesson provided by the many studies over the last 10 years is that minor alterations in substrate, catalyst, or reaction conditions can change the stereochemical course of nucleopalladation.

The development of enantioselective reactions is a prominent goal for many catalytic transformations. Enantioselective Pd^{II}-catalyzed alkene functionalization represents a particularly difficult class of reactions to develop, because the stereochemical ambiguity of the nucleopalladation step presents an additional challenge. The remainder of this review focuses on alkene nucleopalladation reactions for which enantioselective catalysis has been achieved. Although in some cases very high levels of stereocontrol are demonstrated, these reactions often proceed with only moderate enantioselectivities. Determining whether or not the difficulties associated with enantioselective nucleopalladation are a direct result of an inability to control *cis*/*trans* nucleopalladation selectivity remains as a challenge for future mechanistic studies.

3. Enantioselective Reactions Involving Oxypalladation

3.1. Phenol Cyclization

In 1978, Hosokawa, Murahashi, and co-workers reported the first example of an enantioselective Pd-catalyzed alkene functionalization.[67] This pioneering work described the oxidative C-O bond-forming cyclization of *ortho*-allyl phenols such as **135** (Scheme 39) and established phenol cyclization as a benchmark reaction for the identification of new enantioselective Pd^{II} catalysts.[68] In this report, a catalyst system consisting of the chiral alkene β-pinene, $Pd(OAc)_2$, and stoichiometric $Cu(OAc)_2 \cdot H_2O$ provided low levels of asymmetric induction (12% ee) in the oxidative cyclization of **135** under one atmosphere of O_2 in MeOH.[67] Similar enantioselectivities were obtained when a preformed π -allyl Pd-acetate dimer **136** was used as the pre-catalyst with catalytic quantities of $Cu(OAc)_2$ and O_2 as the stoichiometric oxidant.[69] Mechanistic studies established that the reaction rate and enantioselectivity were strongly dependent on [Cu] and provided strong evidence for a bimetallic Pd/Cu catalyst. Although the exact nature of the active catalyst could not be unambiguously established, the authors propose a bimetallic acetate-bridged complex consisting of a β-pinene-ligated Pd center (**137**, Scheme 39).69b,c

Cyclization of various *para*-substituted phenols revealed a relationship between the electronic effect of the substrate nucleophile and the reaction enantioselectivity (Scheme 40).69c Phenols containing electron-donating substituents (R = OMe or Me) proceeded with appreciable levels of asymmetric induction (up to 26% ee for R = OMe), whereas only trace levels of enantioinduction were observed with substrates containing electron-withdrawing substituents (R = Cl, COMe). The authors suggested that this strong electronic dependence indicates a mechanistic transition between *cis*- and *trans*-oxypalladation; however, no other evidence for such a mechanistic transition was provided.

Following the initial work of Hosokawa and Murahashi, nearly twenty years passed before new reports of enantioselective Pd^{II}-catalyzed alkene functionalization began to appear. In 1997, Uozumi, Hayashi and co-workers showed that a novel binaphthyl derived bisoxazoline ligand (**7**, BOXAX) was a highly effective ligand for the enantioselective cyclization of *ortho*-allyl phenol (Scheme 41).[6] The combination of $Pd(TFA)_2$, **7a**, and BQ in MeOH catalyzed the cyclization of tetrasubstituted alkene **138** in 96% ee and good yield. Bisoxazolines **139** and **140a** and other ligands derived from the binaphthyl framework provided poor stereocontrol and minimal reactivity. The quantity of the oxidant had a significant impact on the reaction efficiency; decreasing from four equivalents of BQ to one dramatically reduced the reaction yield (from 72% to 43%), although enantioselectivity was unaffected. Despite the limited substrate scope, this report demonstrated for the first time that excellent enantioselectivities and yields could be achieved for Pd^{II}-catalyzed alkene functionalization.

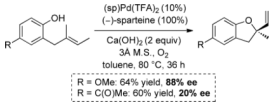
Reaction rates in the oxidative phenol cyclization were strongly dependent on the identity of the Pd source. Pd salts bearing less coordinating anionic ligands afforded improved catalysts. For example, $Pd(OAc)_2$ led to a decrease in reactivity and enantioselectivity when compared to $Pd(TFA)_2$ (54 and 96% ee respectively). Subsequent studies revealed that cationic Pd precursors generated more reactive catalysts and enabled reaction times to be decreased from one day to one hour.[70] With $Pd(MeCN)_4(BF_4)_2$, the catalyst loading could be reduced from 10% to 2% without loss of yield or enantioselectivity.

Although BOXAX ligand **7a** was highly effective for the enantioselective cyclization of phenol **138**, the scope of successful reactions was limited to oxygen addition onto tetrasubstituted alkenes. For example, cyclization of trisubstituted alkene **142** occurred with only 9% ee (Scheme 42). This limitation was overcome through the use of ligands with

achiral oxazoline moieties and steric bulk at the 3,3'-position of the binaphthyl ring.[71] A complex generated from $Pd(MeCN)_4(BF_4)_2$ and the 3,3'-COOMe ligand **139** catalyzed the cyclization of trisubstituted alkene **142** in 90% yield and 88% enantioselectivity (Scheme 42). This ligand was ineffective for tetrasubstituted alkenes, affording nearly racemic product in low yield (Scheme 41).

Zhang and co-workers have developed a unique class of axially chiral bisoxazoline and tetraoxazoline ligands that afford high levels of enantioselectivity for *ortho*-allyl phenol cyclization.[72] In solution these ligands exhibit free rotation around the biaryl bond, but upon complexation to Pd^{II} only one diastereomeric complex is formed (Scheme 43a). Use of ligands **143a** and **144a** and conditions previously optimized for the BOXAX-ligated Pd catalysts enabled the cyclization of tri- and tetrasubstituted alkenes in >90% ee (Scheme 43b). Identification of an appropriate Pd precursor was vital for the success of this reaction: the use of $Pd(TFA)_2$ and $Pd(OAc)_2$ was optimal, while $PdCl_2$, $Pd(MeCN)_2Cl_2$ and $Pd(MeCN)_4(BF_4)_2$ resulted in decreased yields and stereoselectivity.

Stoltz and co-workers demonstrated the first example of a successful enantioselective *aerobic*[73] Pd-catalyzed oxidative cyclization.[11,26,74] These efforts were built upon studies by the Sigman[75] and Stoltz[76] groups who identified the C_1-symmetric natural product (−)-sparteine as an effective chiral ligand for the aerobic oxidative kinetic resolution of secondary alcohols. For the cyclization of phenol **142**, various Pd sources in conjunction (−)-sparteine were analyzed under one atmosphere of molecular oxygen (Scheme 44). The combination of a preformed (−)-sparteine/$Pd(TFA)_2$ complex and excess (−)-sparteine provided good yields and enantioselectivity. Chloride and bromide anionic ligands resulted in poor stereocontrol and $Pd(OAc)_2$ displayed low reactivity. The best results were obtained with 3Å M.S.[77] and $Ca(OH)_2$ (2 equiv). This reaction suffers from low reaction rates, high catalyst and ligand loading, and the lack of a readily accessible (+)-sparteine derivative.[78] As was observed by Hosokawa and Murahashi, electron-withdrawing substituents *para* to the nucleophile dramatically decrease the yield (eq 30). Despite these limitations, the demonstration of an enantioselective alkene functionalization that uses molecular oxygen as the sole oxidant represents a vital step towards the goal of environmentally benign methods for the synthesis of enantioenriched small molecules from feedstock hydrocarbons.[73]



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Bisoxazolines, chiral bidentate amines, bisphosphines, and other common chiral ligands were ineffective for the oxidative cyclization of phenol **142** under aerobic conditions (Scheme 45). The poor results obtained with these ligands highlights the difficulties associated with the discovery of catalysts for enantioselective aerobic alkene functionalization and the unique nature of (−)-sparteine as a chiral ligand.

The Pd-alkyl intermediate generated by oxypalladation of *ortho*-allyl phenols can be efficiently trapped by methyl acrylate or CO (Scheme 46). Tietze and co-workers designed phenol substrates that were unable to undergo β-hydride elimination and studied their cyclization in the presence of methyl acrylate.[79,80] Using the $Pd(TFA)_2$/BOXAX **7b**/BQ catalytic system, phenol **145** afforded dihydrobenzopyran **146** in 97% ee and 84% yield over a 3.5-day reaction time (Scheme 47). This transformation was applied to the asymmetric synthesis of α-tocopherol, a member of the Vitamin-E class of molecules.[79]

Similar phenol substrates also cyclized in the presence of CO and MeOH, resulting in carbonylation of the Pd-alkyl intermediate (Scheme 48).[80,81] In agreement with the case for the alkoxy alkylation reaction, oxycarbonylation of phenol **147** provided the corresponding six-membered ring with excellent stereocontrol (>95% ee). These two transformations (Schemes 47 and 48) represent rare examples of enantioselective Pd^{II}-catalyzed alkene functionalization that do not form five-membered rings.

Sasai and co-workers investigated the cyclization of geraniol derived *ortho*-allylic phenol **148** in their attempts to develop an asymmetric synthesis of the benzopyran natural product (−)-cordiachromene (Scheme 49).[82] They discovered that a catalyst mixture consisting of $Pd(TFA)_2$/**149a** and 4 equivalents of BQ afforded six-membered ring **150** in 55% yield and 54% ee. The six- membered ring was formed preferentially to the five-membered ring, a feature observed in other oxycyclization reactions that employ this ligand class. Mechanistic studies to establish the stereochemical course of the oxypalladation reaction have not been done, but the formation of 6-endo cyclization products seems to provide circumstantial support for a *trans*-oxypalladation pathway. Conformational considerations suggest that 6-endo cyclization via alkene insertion into a Pd–O bond (i.e., *cis*-oxypalladation) will be disfavored.

A non-oxidative *inter*molecular addition of phenols to alkenes was recently disclosed by Overman and co-workers.[83] Phenol nucleophiles were shown to add with high regio- and stereoselectivity to trichloroacetamide derivatives of (*Z*)-2-alken-1-ols (i.e., (*Z*)-**151**, Scheme 50). Cobalt oxazoline palladacyle COP-OAc (described in more detail in Sections 4.1 and 4.2) was found to catalyze the addition of a variety of phenols, including phenols bearing electron-withdrawing groups and halogen substituents, with good enantioselectivities (≥90%) and yield (>85%). The use of electron rich *p*-methoxyphenol resulted in reduced yield, but high enantioselectivity was retained. In all cases, regioselectivity was excellent; only the branched allylic ether products were observed. A drawback of the COP-OAc catalyst was the requirement for (*Z*)-alkenes. With the corresponding (*E*)-alkenes, a substantial portion of the reagent underwent [3,3] sigmatropic rearrangement to form allylic trichloroacetamides (i.e., (*E*)-**151**, Scheme 51; the enantioselective rearrangement of allylic trichloroacetamides is described in Section #).

The undesirable reactivity of (*E*)-allylic trichloroacetimidates as substrates was overcome through the use of a novel cobalt oxazoline palladacycle that was ineffective in catalyzing the undesired [3,3] sigmatropic rearrangement.[84] Replacement of the bridging acetate ligand of COP-OAc with a di-μ-amidate bridge afforded COP-$NHCOCCl_3$, which yielded allylic trichloroacetamide side product **152** in only 8% yield. In the presence of phenol (5 equiv), the desired allylic aryl ether **153** could be formed with high chemo- and stereoselectivity (Scheme 51).

3.2. Carboxylic Acid Nucleophiles

Analogous to the addition of phenols to (*Z*)-allylic trichloroacetimidates (Scheme 51), Overman and co-workers demonstrated that carboxylic acids are also effective nucleophiles (Scheme 52).[8586] Cobalt oxazline palladacycles COP-OAc was found to be highly effective, catalyzing the addition of carboxylic acids in excellent yields and enantioselectivities. Various acetimidate-functionalized (*Z*)-allylic alcohols reacted with excellent regio- and stereoselectivities and high yields (Scheme 52). The presence of a primary alcohol, acetate, or silyl ether was not detrimental to reaction performance. Aliphatic and aryl carboxylic acids were effective nucleophiles (Scheme 52). Electron-rich aryl carboxylic acids furnished products with excellent yields and enantioselectivities, while highly acidic carboxylic acids resulted in decreased yields. For example, use of 4–nitrobenzoic acid furnished the corresponding allylic ester in 94% ee and 60% yield.

3.3. Alcohol Nucleophiles

Alcohols are an attractive class of nucleophiles for alkene functionalization, however, primary and secondary alcohols often undergo facile oxidation to the corresponding aldehyde or ketone derivatives in the presence of Pd^{II} catalysts.[87] The development of catalysts that promote effective alkoxypalladation of alkenes therefore requires good chemoselectivity. Alternatively, the problem of alcohol oxidation can be avoided by employing tertiary alcohols, for which formation of the carbonyl compounds is not possible.

3.3.1. Addition of Alcohols to Unactivated Alkenes—The use of oxygen nucleophiles other than phenol for an enantioselective Pd^{II}-catalyzed alkene functionalization was first reported in 2001 by Sasai and co-workers.[9] Enantioselective desymmetrization of a primary diol with $Pd(TFA)_2$ and the novel spirocyclic bis(isoxazoline) ligand **149a** (referred to as the SPRIX class of ligands)[88] afforded the cyclic ether product in 70% ee (Scheme 53). As with the phenol substrate in Scheme 49, the reaction proceeds via an endo cyclization pathway to afford the 6-membered heterocycle. This reaction did not proceed with BOXAX **7a**, bisoxazoline **141a**, or BINAP. The identity of the anionic ligand and solvent were both vital to the success of the reaction: $Pd(OAc)_2$, $Pd(MeCN)_4(BF_4)_2$, $PdCl_2$, or $PdCl_2$/AgOTF instead of $Pd(TFA)_2$ resulted in lower yields. Low enantioselectivities, ranging from 27–39%, were observed if CH_3CN, MeOH, THF, or toluene were used instead of CH_2Cl_2. This demonstration marks an important departure from phenolic substrates, but high catalyst loading (15% $Pd(TFA)_2$ and 18% **149a**) and modest stereoselectivity leave room for future improvement. Four equivalents of BQ were also required; a $Cu(OAc)_2/O_2$ oxidant system provided a decrease in reactivity and enantioselectivity.

The $Pd(TFA)_2$/SPRIX catalyst system was applied to an alkoxy alkylative desymmetrization reaction initiated by oxypalladation of an alkene, followed by trapping of the Pd-alkyl intermediate by a pendant alkene (Scheme 54).[9] This reaction gave high levels of enantioselectivity (up to 97% ee) with 20 mol % Pd. Subsequent reports investigated the use of spiro bis(isoxazole) **154**[89] and hybrid spiro (isoxazole-isoxazoline) **155** ligands.[90] Although **154** was not as effective as the SPRIX ligand class, hybrid spiro (isoxazole-isoxazoline) ligands **155** were more promising, affording a catalyst with increased reactivity without compromising enantiocontrol (Scheme 54).

Kapitán and Gracza reported that primary alcohols undergo intramolecular oxycarbonylation with moderate levels of enantioinduction.[91] In the presence of $Pd(OAc)_2$ and bisoxazoline ligand **156a**, a racemic diol underwent cyclization with 62% ee (Scheme 55). The bicyclic product was presumably formed by trapping a Pd-acyl intermediate with the pendant alcohol.[92] Screening of other bisoxazoline ligands did not provide improved results and the use of the BOXAX or SPRIX ligand class was not reported.

The use of β-dicarbonyl nucleophiles as substrates in enantioselective cyclization were recently reported by Sasai and coworkers.[93,94] Such nucleophiles, which can readily form an enol structure, cyclized in the presence of a $Pd(TFA)_2$/SPRIX **149a** catalyst to furnish 6-*endo-trig* products (Scheme 56). The SPRIX ligand appears to be uniquely successful in this reaction. Bisoxazoline **141d**, BOXAX **7a**, and BINAP all provided complex reaction mixtures, whereas (–)-sparteine generated a racemic product in 14% yield. Interestingly, substrates containing a pendant alkene dramatically improved the reaction performance. For example, enol **157a** afforded the bicyclic product in 80% yield and 81% ee, while the corresponding *n*-Bu derivative **157b** cyclized in 60% yield and 51% ee (Scheme 56).

Very few examples of enantioselective *inter*molecular nucleopalladation reactions exist, and in all cases carefully designed substrates that rapidly trap the Pd-alkyl intermediate are

required. Hosokawa and co-workers have developed an enantioselective coupling of allylic alcohols and vinyl ethers that proceeds via initial asymmetric oxypalladation, followed by intramolecular trapping of Pd-alkyl intermediate by a pendant alkene (Scheme 57).[95] Building upon previously reported conditions for the non-enantioselective transformation,[96] a combination of $Pd(OAc)_2$, bisoxazoline **140b**, $Cu(OAc)_2$, and catechol was employed with molecular oxygen as the stoichiometric oxidant, resulting in good yield and moderate enantioselectivity. Removing catechol from the reaction mixture decreased enantioselectivity, an observation attributed to competitive binding of the chiral ligand to copper in the absence of catechol. Furthermore, $Cu(OAc)_2$/catechol was required for good catalytic activity, but their removal did not affect enantioselectivity Based on these results, the authors proposed the binuclear catalyst **158** consisting of a catechol-ligated copper center and bisoxazoline ligated Pd.

3.3.2. Addition of Alcohols to ortho-Vinyl Phenols—Sigman and co-workers have recently developed an enantioselective aerobic oxidative difunctionalization of *ortho*-vinyl phenols.[97] Mechanistic studies support a reaction pathway involving oxypalladation followed by formation of an *ortho*-quinone methide intermediate (Scheme 58).[98,99] Various bidentate nitrogen ligands were screened in conjunction with $Pd(MeCN)_2Cl_2$ in MeOH using molecular oxygen as the stoichiometric oxidant. Although (–)-sparteine and bisoxazoline ligands **7a**, **140a**, and **141b** gave low yields and trace levels of stereoinduction, C_1-symmetrical quinoline oxazoline ligands **160** provided good reactivity and enantioselectivities (Scheme 59). The corresponding pyridine oxazoline **159a**-Pd complex exhibited poor catalytic activity.

Alkene difunctionalization of *ortho*-vinyl phenols can also be initiated by an intramolecular oxypalladation.[100] The proposed *ortho*-quinone methide intermediate can then be trapped by a wide variety of exogenous nucleophiles including alcohols, water, sodium azide, indoles, and pyrroles. These reactions proceed with excellent enantioselectivities and moderate to excellent diastereoselectivities (Scheme 60). The cyclization of primary alcohols to form five- and six-membered rings was shown to also proceed with high chemoselectivity. This method was applied to the synthesis of a small library of 3-substituted indoles whose biological activity against a luminal-type breast cancer cell line was evaluated.[100b]

3.4. Oxypalladation Reactions With Water as the Nucleophile

Enantioselective alkene functionalization reactions that use water as the nucleophile represent an attractive route to enantioenriched alcohols. Extensive investigation of the Wacker reaction has revealed that the reaction can either provide traditional ketone products or can undergo hydroxy-chlorination to generate chlorohydrin products, depending on the reaction conditions (Scheme 61).[14a,101] Studies by Henry and co-workers have demonstrated that $PdCl_3(py)^-$ species provide chlorohydrin products, even at relatively low [Cl^-] (Scheme 61).[102] The researchers then evaluated the ability of chiral ligands to control the stereochemistry of this process. The use of chiral monodentate amines as chiral analogues to pyridine resulted in low enantioselectivities (~10% ee);[103] however, phosphine ligands provided improved stereocontrol. For example, a $Pd(MeCN)_2Cl_2$/tol-BINAP catalyst in a H_2O/THF (1:2) solvent system with $CuCl_2$ and LiCl yielded the chlorohydrin product in 56% ee and 55% yield (Scheme 62). Methyl vinyl ketone and allyl phenyl ether underwent hydroxy-chlorination with higher stereocontrol (82 and 80% ee, respectively) than the alkyl olefin substrate.

Henry and co-workers also investigated the use of chiral bimetallic catalysts in the enantioselective chlorohydrin reaction.[104] These catalysts were formed by treatment of triketones with $Pd(MeCN)_4(BF_4)_2$, followed by addition of chiral bidentate phosphine,

amine, or oxazoline ligands (Figure 2). Bisphosphine ligands BINAP, **161**, DIOP, and bisoxazoline **155b** provided good yields and >85% ee. Unfunctionalized alkenes, methyl acrylate, allyl ethers, and styrenes, reacted in the presence of phosphine ligated catalysts with excellent stereocontrol. Alkenes with alcohols, carboxylic acids, esters, and aldehydes were not effective substrates (Scheme 63).

4. Enantioselective Reactions Involving Aminopalladation

4.1. Rearrangement of Allylic Imidates

The emergence of catalysts capable of enantioselective C–O bond formation coincided with Pd^{II}-catalysts for the enantioselective C–N bond-forming allylic imidate rearrangement pioneered by Overman and co-workers. This work was recently the subject of two reviews;[105] therefore, only a brief discussion of milestone developments will be presented here. As discussed in section 2.2.5, the reaction is proposed to proceed via aminopalladation to form Pd-alkyl intermediate **99**, followed by rapid collapse to generate the allylic amide product and re-form the Pd^{II}-catalyst (Scheme 32).

The first example of an enantioselective Pd^{II}-catalyzed allylic imidate rearrangement was reported by Overman and Zipp in 1997.[7] Through a series of systematic studies, they arrived at the dicationic complex **163**, consisting of a proline-derived chiral diamine ligand, for the asymmetric rearrangement of allylic imidate **162**. (Scheme 64). This reaction proceeded with moderate enantioselectivity and yield (Scheme 64).[106] Soon after, Hollis and Overman reported that planar chiral ferrocenyl palladacycles catalyzed the rearrangement of **162** in nearly quantitative yields, although again with only moderate enantioselectivity. The use of ferrocenyl oxazoline catalyst **165** provided a dramatic increase in enantioselectivity, allowing the cyclization to occur in >90% ee.[8] This catalyst was synthesized in situ by anionic ligand exchange between the AgTFA and the corresponding Pd chloride. One limitation of these catalysts was that only *N*-aryl imidates were suitable substrates. Allylic trichloroacetimidates, which would provide direct access to the free amines following facile deprotection,[107] were unreactive.

The enantioselective rearrangement of allylic trichloroacetimidates was demonstrated in 2003 by Anderson and Overman using planar chiral catalyst **166a** (COP–Cl) (Scheme 65).[108] The COP ligand class features planar chiral cobaltocene and chiral oxazoline moieties and is proposed to bind to Pd in a bidentate manner by aryl C–H activation of the cyclopentyl ring. These transformations proceed with excellent enantiocontrol and yields over a wide range of substrates.

4.2. Non-Oxidative Cyclization of *N*-Tosyl Carboxamides

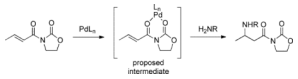
In 1997, Overman and co-workers reported enantioselective intramolecular allylic substitution reactions of *N*-tosyl carbamates, amides, and ureas using catalysts developed for the allylic imidate rearrangement.[109] These reactions differ from most Pd-catalyzed allylic substitution reactions in that Pd remains in the +2 oxidation state throughout the catalytic cycle.[110] These non-oxidative transformations are proposed to proceed via an aminopalladation/β-acetate elimination sequence to provide heterocyclic products. A simple catalyst system consisting of ferrocenyl oxazoline palladacyle **165**, generated in-situ by anionic ligand exchange between a Pd-iodide pre-catalyst and AgTFA, promoted the high-yielding cyclization of (*Z*)-allylic *N*-tosyl carboxamides **167** with excellent stereocontrol (Scheme 66). These reactions require nucleophiles with acidic N–H protons. For example, aniline derived carboxamides were unreactive. Interestingly, the analogous (*E*)-alkene did not react efficiently, converting in only 65% ee and 22% yield after 4 days.

Further studies revealed that COP-catalysts provided excellent yields and enantioselectivities without requiring pre-activation with silver salts.[111] Although the chloride **166a** or the hexafluoroacetylacetonate (hfacac) **166b** catalyst reacted slowly, the corresponding acetate bridged dimer **166c** provided the oxazolidinone in quantitative yield in only 4.5 hours (Scheme 67). Reaction optimization revealed that the addition of 15% acetic acid in dichloromethane provided a 19% ee increase. With optimized catalyst conditions (1% **166c**, 20% acetic acid in CH_2Cl_2, 29 h at 0 °C), the product was obtained in 95% ee and 97% yield.

4.3. Hydroamination

Few examples of enantioselective Pd^{II}-catalyzed hydroamination of alkenes exist, these reports have been limited to styrenes and α,β-unsaturated carbonyl compounds. It is unlikely that either substrate class react via aminopalladation of the alkene. Hartwig and co-workers provided the first example of an enantioselective Pd^{II}-catalyzed hydroamination in 2000, demonstrating that BINAP ligated $Pd(OTf)_2$ catalyzes the hydroamination of 4-trifluoromethyl styrene with aniline in 81% ee (Scheme 68).[112] Mechanistic studies by Nettekoven and Hartwig support a mechanism that involves alkene insertion into a palladium hydride to form an η^3-benzyl intermediate and subsequent external nucleophilic attack of the π-allyl species (Scheme 69).[113] Reports by the Hii[114] and Lin[115] groups demonstrated slightly improved results by employing dicationic palladium catalysts.

A number of research groups have reported the enantioselective conjugate addition of nitrogen nucleophiles to α,β-unsaturated carboxamides, a Michael-type transformation that represents a formal hydroamination process (eq 31).[116,117,118] Because the reaction appears to proceed by a Lewis-acid catalyzed mechanism,[119] as opposed to a nucleopalladation mechanism, further discussion of this reaction is not included here; however, the interested reader is directed to recent reviews detailing this topic.[120]



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4.4. Aminocarbonylation

The early examples of enantioselective aminopalladation described by Overman and co-workers featured non-oxidative transformations. The requirement for oxidants presents an additional challenge, because successful enantioselective catalysts must be stable to the oxidizing reaction conditions. The first report of an *oxidative* Pd^{II}-catalyzed enantioselective alkene amination was the aminocarbonylation reaction reported by Sasai and co-workers using the versatile SPRIX ligand (Scheme 70).[121] This cyclization presumably occurs via aminopalladation, then carbonylation of the resulting Pd-alkyl intermediate.[122] Initial efforts using $Pd(TFA)_2$, SPRIX ligand **149b**, and BQ (4 equiv) under one atmosphere of CO afforded moderate enantioselectivities (<65% ee). The reaction did not proceed with BINAP, BOXAX **7a** or bisoxazoline **141b**. Aminocarbonylation favored the formation of five-membered rings, which differs from the 6-endo cyclization products formed with alcohol nucleophiles and SPRIX-ligated catalysts. The mechanistic origin of this difference has not been elucidated.

Additional studies showed that tosyl urea-derived substrates cyclized under similar reaction conditions with moderate enantioselectivity (Scheme 71). In this case, trapping of the Pd-acyl by a pendant nitrogen nucleophile provided bicyclic 5,6-dihydrouracil derivative **170** with 54% ee. Reaction optimization identified conditions for the cyclization of tosyl urea

169 with increased levels of enantioselectivity.[123] Using cationic $Pd(MeCN)_4(BF_4)_2$ and the bulkier SPRIX catalyst **149a** provided the product in 94% yield and 66% ee. Lowering the ligand loading to a Pd:ligand ratio of 1.1:1 allowed the reaction to be performed at −40 °C, which resulted in an increase to 88% ee, although the reaction required 7 days to reach completion.

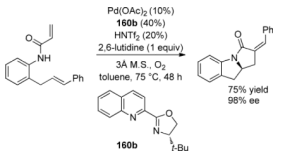
Gracza and co-workers have developed an aminocarbonylation reaction that results in kinetic resolution of amino alcohol substrates.[124] Sulfonamide **171** undergoes intramolecular aminopalladation and carbonylation, followed by trapping of the Pd-acyl intermediate by a pendant alcohol moiety to yield the bicyclic pyrrolidine lactone **172** (Scheme 72). While chiral phosphine and pyridine bisoxazoline ligands provided low yields and enantioselectivity, bisoxazoline ligands resulted in higher levels of enantiocontrol. Despite attempts at reaction optimization, yields of this reaction were low and could only be increased at the expense of enantioselectivity.

4.5. Aminovinylation

In 2006, Yang and co-workers reported the first aerobic oxidative enantioselective C–N bond-forming transformation.[125] Their studies focused on the aminovinylation of *N*-acyl-anilide substrate **174** (Scheme 73). The reaction employed the catalyst system developed by Stoltz for aerobic oxidative phenol cyclization: $Pd(TFA)_2$/(−)-sparteine in toluene with molecular oxygen as the oxidant. A variety of alternative chiral nitrogenous ligands were examined, but none provided the bicyclic product with appreciable enantioselectivities. As was observed for phenol cyclization, 3Å M.S. led to an increase in both yield and enantioselectivity. For unknown reasons, the addition of *N*,*N*-diisopropylethylamine (DIPEA, 2 equiv) provided a further increase in yield and enantioselectivity. With these optimized conditions, the cyclization occurred in 75% yield and with 86% enantiomeric excess, and catalyst loading could be decreased to 10% without any loss in yield.

Stahl and co-workers investigated the application of *N*-heterocyclic carbenes (NHC) as chiral ligands in the enantioselective aerobic oxidative bicyclization of the substrate reported by Yang (**174**).[126] Achiral NHC ligands had been successfully utilized in aerobic alcohol oxidation,[127] *ortho*-allyl phenol cyclization,[128] and aerobic oxidative amination,[129,130] however application of chiral NHCs in enantioselective Pd^{II}-catalyzed reactions had been unexplored. Scarborough and Stahl developed a novel class of NHCs bearing seven-membered rings (7-NHC)[131] and applied these ligands to the aminovinylation of **174** (Scheme 74). While 7-NHC **175** gave products with moderate levels of enantioselectivity, the bicyclic products were formed in only 35% yield. The chiral, cyclometalated five-membered NHC complex **176**[132] catalyzed the reaction in similar yield, though without asymmetric induction.

Recently, Yang and co-workers reported that the use of quinox ligands led to a more effective catalyst for the enantioselective aerobic oxidative aminovinylation of **174**.[133] For example, use of *tert*-Bu-oxazoline ligand **160b** in conjunction with $Pd(MeCN)_2(OTf)_2$ (generated by the addition of AgOTf to $Pd(MeCN)_2Cl_2$) led to the cyclization of amide **174** in 62% yield with 93% ee. Although similar pyridine and quinoline oxazoline ligands (**159a, 179, 177, and 178**) generated active catalysts, all did so with low levels of stereocontrol (Scheme 75). Bisoxazoline **141c**, pyridine bisoxazoline **173b**, and (−)-sparteine ligated catalysts provided poor yields. Additional reaction optimization led to increased yield and excellent enantioselectivity with quinoline oxazoline ligand **160b** (75% yield, 98% ee, eq 32).



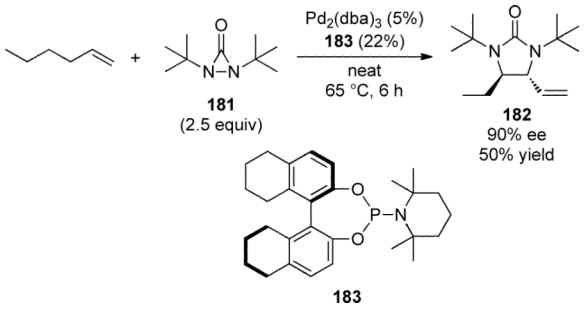
(32)

4.6. Aminoarylation

An enantioselective non-oxidative aminoarylation of alkenyl sulfonamides and aryl and vinyl halides was recently reported by Mai and Wolfe.[37] A ligand screen revealed that monodentate chiral phosphoramidite ligands provided good levels of enantioselectivity, whereas bidentate phosphine ligands were ineffective (Scheme 76). A $Pd_2(dba)_3$/Siphos-PE catalyst was effective for enantioselective aminopalladation/cross-coupling of N-(boc)-pent-4-enylamine **180** and a variety of aryl bromides and iodides and vinyl bromides (Scheme 77). These reactions proceeded in moderate yield and good enantioselectivity, and could be performed on a 1.0 mmol scale. This transformation represents the only successful application of monodentate chiral ligands to an enantioselective alkene nucleopalladation reaction.

4.7. Diamination with Di-*tert*-butyldiaziridinone

In 2008, Shi and co-workers disclosed an enantioselective Pd^0-catalyzed oxidative diamination of terminal alkenes that employs di-*tert*-butyldiaziridinone **181** as both the nitrogen nucleophile and the stoichiometric oxidant (eq 33).[134,135] This transformation evolved from earlier work by the same group involving diamination of conjugated dienes and trienes.[136] The proposed reaction pathway involves oxidative addition of the diaziridinone, followed by subsequent allylic and homoallylic C-H activation steps to form a diene (Scheme 78). Insertion of a carbon-carbon double bond of the diene into the Pd–N bond furnishes a π-allyl–Pd^{II}–amidate intermediate, which then undergoes reductive elimination to provide the diamination product and regenerate the Pd^0-catalyst.[137]



(33)

The enantioselective diamination proceeded with high levels of diastereo- and enantioselectivity in the presence of phosphoramidite ligand **183** (Scheme 79). The reaction was performed as a neat solution and employed 2.5 equiv of di-*tert*-butyldiaziridonone **181**. Substrates bearing internal alkenes and nitrogen or oxygen functional groups were tolerated, providing access to a variety of cyclic ureas with high levels of enantiocontrol. Thus far, the diaziridinone is limited to the di-*tert*-butyl derivative.[138]

4.8. Wacker-Type Oxidative Amination

The enantioselective aminations described to this point have all required substrates containing activated alkenes or pendant functionalities that intercept the Pd^{II}-alkyl aminopalladation intermediate. Wacker-type oxidative amination reactions terminate by β-hydride elimination and therefore can be applied to the amination of simple internal alkenes. Stahl and co-workers investigated the use of 7-NHC ligands in the enantioselective oxidative amination of *ortho*-allyl tosylanilide **184** (Scheme 80).[126] Although this marked the first report of an attempted enantioselective oxidative amination, the product was recovered in low yield and only 9% ee.

Very recently, improved results for the oxidative amination of *ortho*-allyl tosylanilides were reported.[139] Zhang and co-workers showed that pyridine bisoxazoline **173a**, axially chiral phenyl tetraoxazoline **144a**, and pyridine oxazoline **159b** were ineffective in the cyclization of **185**, but quinoline oxazoline ligands **160** afforded slightly increased levels of enantioselectivity and high yields (Scheme 81). Following reduction of the reaction temperature to 0 °C, the reaction proceeded with 69% ee and 94% yield, albeit with a reaction time of 5 days.

5. Enantioselective Reactions Involving Carbopalladation

Various approaches have been developed as a means of generating carbon nucleophiles for enantioselective alkene functionalization. While the most common method involves transmetallation of a metal-C(sp^2) species, carbon nucleophiles have been formed by C–H activation, hydrosilylation, or nucleopalladation by an exogenous nucleophile.

5.1. Fujiwara-Moritani Cross-Coupling

The pioneering example of enantioselective Pd^{II}-catalyzed C–C bond formation was disclosed in 1999 by Mikami and co-workers.[140] The enantioselective Fujiwara-Moritani cross-coupling of benzene and cyclic vinyl nitrile **186** with $Pd(OAc)_2$, sulfamide oxazoline ligand **187**, and the stoichiometric oxidant *tert*-butyl peroxybenzoate furnished the desired product in low yields and moderate stereocontrol (Scheme 82). Interestingly, the complex formed by a mixture of 1:1 $Pd(OAc)_2$:**187** revealed the coordination of two ligands to each Pd center. Addition of excess $Pd(OAc)_2$ was required for this complex to become catalytically competent, presumably due to the necessity of ligand exchange to form a 1:1 Pd:ligand complex.

Oestrich and co-workers expanded upon the work of the Stoltz group in the development of the enantioselective aerobic oxidative cyclization of indole **188** (Scheme 83).62a,[141,142] This reaction has been shown to proceed via indole C–H activation, insertion of the pendant alkene and β-hydride elimination.[62] Stoltz and co-workers highlighted the utility of ethyl nicotinate as an achiral ligand. Oestrich and co-workers therefore investigated the effectiveness of ethyl nicotinate derived pyridine oxazoline ligands **189** for the oxidative cyclization of **188** with $Pd(OAc)_2$ and BQ (Scheme 83). While ester substitution appeared to provide a modest increase in yield, it did so at the cost of stereocontrol. As was observed by Mikami, the use of $PhCO_3$-*t*Bu was also an effective oxidant; however, enantioselectivities above 50% were not achieved.

5.2. Oxidative Heck Reaction

The enantioselective oxidative coupling of aryl boronic acids and alkenes (the oxidative Heck reaction, Scheme 84) was first reported in 2005 by Mikami and co-workers.[143] Use of $Pd(OAc)_2$ and the chiral bisphosphine ligand, Chiraphos, in DMF under one atmosphere of molecular oxygen enabled the coupling of *para*-trifluoromethyl phenylboronic acid **190** with

cyclic vinyl ester **191** to occur in 46% ee and 73% yield (Scheme 85). Other chiral bisphosphine ligands, as well as bisoxazolines **140b** and **141a** and pyridine oxazoline **159a**, led to decreased enantioselectivity and yield. A solvent screen indicated that MeOH, toluene, THF, and DMSO all provided higher levels of enantioselectivity compared to DMF, but with reduced yields.

Gelman and co-workers demonstrated the use of chiral phosphine ligands in the enantioselective oxidative Heck cross-coupling of aryl boronic acids and 2,3-dihydrofuran (Scheme 86).[144] In this instance, the use of atropisomeric bisphosphines in conjunction with Cu^{II} salts as the stoichiometric oxidant was required. Chiraphos and bisoxazoline **140b** generated inactive catalysts. The presence of molecular oxygen imparted a negative effect on the reaction yield, perhaps due to oxidation of the phosphine ligand. With (*R*)-MeOBiphep as the chiral ligand, enantiomeric excess as high as 83% was achieved, although the yields were typically moderate.

In contrast to Pd^{II}-catalyzed oxygenation and amination reactions, only one example of an enantioselective intramolecular C–C bond-forming reaction has been reported. An intramolecular enantioselective oxidative Heck cyclization for the synthesis of enantioenriched heterocycles was disclosed by Akiyama and Mikami (Scheme 87).[145] Substrate **192**, an aryl boronic acid linked to a trisubstituted alkene by a sulfonamide tether, was shown to cyclize in the presence of a Chiraphos-ligated Pd_2dba_3 or $Pd(OAc)_2$ catalyst. Good enantioselectivity and yield was achieved, although the products were formed as a mixture of the alkene and the corresponding saturated compound. With optimized conditions (Pd_2dba_3, 25 °C), the heterocyclic product was obtained with 91% total yield (51% of alkene, 40% alkane) in 86% ee. Unfortunately, the substrate scope was quite limited, as other sulfonamide and ether linkages resulted in low asymmetric induction.

Jung and co-workers described the enantioselective oxidative Heck coupling of acyclic alkenes in 2007.[146] Aryl boronic acids were coupled with α,β-unsaturated aldehydes in DMF, catalyzed by a $Pd(OAc)_2$/pyridine oxazoline catalyst (Scheme 88). Although the reaction occurred in the presence of bisoxazoline **141a** and pyridine oxazoline **173c**, stereocontrol was poor. Use of *tert*-butyl pyridine oxazoline **159c** provided higher levels of enantioselectivity. The preformed $Pd(OAc)_2$/pyridine oxazoline complex **193** enabled the reaction to proceed in up to 75% ee.

Jung and co-workers recently reported the application of a Pd^{II} complex with a novel tridentate NHC-amidate-alkoxide ligand to the oxidative Heck cross-coupling of acyclic alkenes (Scheme 89).[147] In preliminary reports, dimeric complex **194** was shown to catalyze the aerobic oxidative arylation of unsaturated aldehydes and esters with excellent enantioselectivity (>90% ee), but modest yields. The stereoselectivities are the highest to date for an enantioselective Heck reaction and suggest that this ligand class holds promise for other Pd^{II}-catalyzed alkene functionalizations.

5.3. Conjugate Addition to α,β-Unsaturated Carbonyls

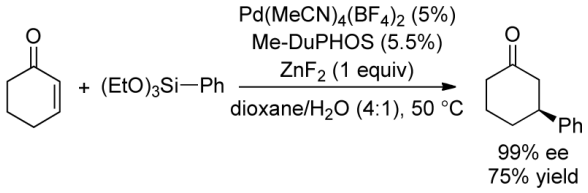
The C–C bond-forming transformations discussed to this point have involved alkene insertion into a preformed Pd–C(sp^2) bond, followed by β-hydride elimination to generate an alkene and regeneration of the reduced metal by a stoichiometric oxidant (Scheme 90a). Alternatively, the carbopalladation intermediate can undergo protonolysis, resulting in an alkene hydroarylation process (Scheme 90b). Reactions of this type have been successfully applied in conjugate additions to α,β-unsaturated carbonyls. A noteworthy challenge for these transformations is the avoidance of β -hydride elimination products. It should be noted that the conjugate addition of carbon nucleophiles to α,β-unsaturated carbonyls represents the only Pd^{II}-catalyzed alkene functionalization that proceeds with high stereoselectivity and

yields with phosphine-ligated catalysts. This presumably reflects the fact that the reactions are non-oxidative, and therefore problems associated with ligand oxidation are avoided. It should be noted that a number of other transition-metals are highly effective catalysts for enantioselective conjugate additions to α,β-unsaturated carbonyls.[148]

The use of Pd^{II}-catalysts for the enantioselective 1,4-addition of aryl and alkenyl bismuths, trifluoroborates, and boronic acids to α,β-unsaturated ketones has received limited attention following the first reports in 2004 and 2005 by Miyaura and co-workers. They initially demonstrated that triarylbismuths react with cyclic enones to yield 1,4-addition products with excellent enantioselectivities and yields in the presence of cationic $[(L)Pd(PhCN)_2](SbF_6)_2$ complexes and the bisphosphine ligand Dipamp (Scheme 91).[149] Bisphosphite **195** and the bisphosphine ligands Chiraphos and Norphos provided either poor yield or low enantioselectivity. Paramount to the success of the Dipamp catalyst system was the use of $Cu(BF_4)_2$ as a stoichiometric additive. The copper salt was proposed to perform anionic ligand exchange with the $[(L)Pd(PhCN)_2]^{2+}$ catalyst to afford a cationic tetrafluoroborate Pd^{II} species, in addition to reoxidizing any reduced Pd that had formed due to reductive biaryl side product formation. An initial investigation of the substrate scope indicated that acyclic enones also underwent arylation with high yields and enantioselectivities, although these results were decreased with an aldehyde derivative (Scheme 91).

By employing the same bisphosphine Pd^{II} catalysts, conjugate addition to enones could be performed with potassium aryltrifluoroborates and aryl trifluorosilicates with similar results (Scheme 92).[150,151] The Pd-Dipamp complex was shown to be most effective for cyclic enones, while a Chiraphos-ligated complex provided better results for acyclic enones. Use of potassium aryltrifluoroborates appeared to provide the best yields and enantioselectivities and did not require the use of a stoichiometric additive; $Cu(BF_4)_2{\bullet}6H_2O$ and ZnF_2 were required for the bismuth and trifluorosilicate coupling partners, respectively.

Bisphosphine ligands were also effective for the enantioselective 1,4-addition of aryl boronic acids[152] and arylsiloxanes to α,β-unsaturated ketones.[153] With a very simple $Pd(TFA)_2$/Me-DuPhos catalyst in aqueous THF, Minnard and co-workers showed that a variety of aryl boronic acids and α,β-unsaturated ketones were coupled with good yields and excellent enantioselectivity (Scheme 93). Aldehydes and esters were less successful coupling partners. Similar results could be obtained for the conjugate addition of arylsiloxanes by using $Pd(MeCN)_4(BF_4)_2$ and ZnF2 as a stoichiometric additive (eq 34).



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5.4. Hydrosilylation/Cyclization

Widenhoefer and co-workers have developed a Pd^{II}-catalyzed hydrosilylation/cyclization reaction that has proven highly amenable to enantioselective catalysis.[65] These reactions provide access to functionalized carbocycles from 1,6- and 1,7-dienes (Scheme 94). Based upon preliminary reports highlighting the use of 1,10-phenanthroline-ligated Pd catalysts,[154] chiral bidentate nitrogenous ligands were explored for their effectiveness in the enantioselective reaction of 1,6-diene **196**.[155] The active catalyst was pre-formed by the reaction of (ligand)Pd(Me)Cl with $NaBAr_4$ [Ar = 3,5-$C_6H_3(CF_3)_2$]. Both bisoxazoline and

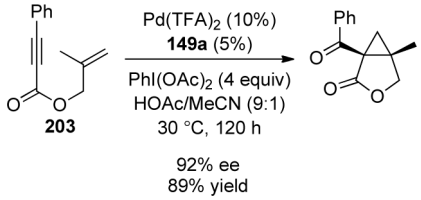
pyridine oxazoline ligands provided high enantio- and diastereocontrol, however the use of pyridine oxazolines resulted in higher yields (Scheme 94). With pyridine oxazoline **159a**, the reaction proceeded in 87% ee, 82% yield and >35:1 dr.

Despite the high yields and stereoselectivities achieved for these C–C bond-forming reactions, the resulting triethylsilanes could not be readily cleaved to form oxygenated products (i.e., **197** to **198**; Scheme 95). Pei and Widenhoefer therefore examined various silanes that could be removed efficiently under mild conditions. Initial efforts focused on pentamethyldisiloxane ($HSiMe_2OTMS$) as an alternative silane.[156] Stereocontrol of hydrosilylation/carbocyclization using this silane was slightly decreased (from 91% ee to 82% ee), but cleavage of the resulting silylated carbocycle **197** using KF and an excess of peracetic acid provided the alcohol in 92% yield (Scheme 95). Alternatively, the use of $HSiMe_2OTBDPS$ generated much higher enantioselectivities, however with decreased yields for oxidative cleavage.[157] Benzhydryldimethylsilane ($HSiMe_2CHPh_2$) proved to be the most effective silane; hydrosilylation/carbocyclization proceeded with 95% ee and 96% yield, followed by facile oxidation to the corresponding alcohol **198**.[158] This transformation highlights the good yields and selectivities attainable with Pd^{II}-catalyzed alkene functionalization.

5.5. Enyne Cyclization

Alkyne acetoxypalladation provides an alternate route to Pd–C bonds that are poised for carbopalladation of a pendant alkene. This approach has been applied to the synthesis of enantioenriched γ –lactones.[159] The cyclization of enynes such as **199** is proposed to proceed through initial acetoxypalladation of the alkyne, then intramolecular alkene insertion to generate a new stereocenter. β -Acetoxy elimination generates a terminal alkene (Scheme 96).[160] Zhang and Lu screened chiral bidentate nitrogenous ligands in conjunction with $Pd(OAc)_2$ and found that both bisoxazoline **141b** and pyridine oxazoline **159b** provided high levels of enantioselectivity (Scheme 97). The cyclization of **199** was also shown to furnish γ-lactones **200** in 85% ee using the $Pd(TFA)_2$/SPRIX **149a** catalyst under the same conditions (Scheme 98).[161]

The $Pd(TFA)_2$/SPRIX catalyst system was also capable of inducing high levels of enantioselectivity in a mechanistically related Pd^{II}/Pd^{IV}-catalyzed C–C bond-forming reaction.[162] Reports from the labs of Sanford[163] and Tse[164] previously showed that ester-linked enynes such as **201** undergo oxidative C–C bond formation to furnish cyclopropanes when $PhI(OAc)_2$ is used as the stoichiometric oxidant. This reaction is proposed to proceed through a *trans*-acetoxypalladation/alkene insertion mechanism in a similar manner to the work described above (Scheme 99). The authors propose that oxidation of Pd-alkyl intermediate **202** to a Pd^{IV} species induces cyclopropane formation. Sasai and co-workers showed that this reaction could proceed with high levels of stereocontrol with a $Pd(TFA)_2$/SPRIX catalytic system, while (–)-sparteine, bisoxazoline **141c**, and BOXAX **7a** yielded racemic products (Scheme 100). A variety of Pd sources generated active, stereoselective catalysts, but $Pd(TFA)_2$ led to the best combination of enantioselectivity and yield, and further optimization enabled product formation in >90% ee and excellent yields (eq 35).



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6. Dibromination

Henry and co-workers have reported an enantioselective synthesis of vicinal dibromides using mono- or bimetallic catalysts and superstoichiometric quantities of $CuBr_2$ as the bromide source (Scheme 101; Figure 3).[165] The use of bimetallic bisphosphine, diamine, or bisoxazoline ligated catalysts afforded high enantioselectivities for a small class of substrates, including two examples of a disubstituted alkene. Although this transformation was performed in water, only trace quantities of products arising from alkene hydration were observed.

7. Summary and Conclusions

The results summarized in this review highlight numerous important advances that have been made in the development of Pd^{II}-catalyzed methods for alkene functionalization. The mechanistic results challenge prevailing assumptions concerning the stereochemical course of the nucleopalladation reaction. Examples of *cis*-nucleopalladation not only exist, but they appear to be more common than the widely established *trans*-nucleopalladation pathway. Perhaps just as importantly, these recent studies demonstrate that small changes to the catalyst, substrate and/or reaction conditions can alter the pathway of nucleopalladation. Unfortunately, the factors that dictate, and the ability to predict, the preferred pathway remain elusive. In some reactions, more-acidic substrates have been shown to favor *cis*- over *trans*- nucleopalladation, but in other reactions, this trend is reversed. These observations draw attention to the important influence of substrate pK_a and the role of proton-transfer steps in controlling the reaction outcome. Future efforts to gain a clearer understanding into mechanistic aspects of “proton management” could play an important role in further developments in this field. Such insights could be gained from additional studies probing systematic trends in substrate acidity, the role of basic additives, solvent effects on proton transfer steps, and the relationship between these factors and the stereochemical course of the nucleopalladation reaction. Furthermore, only two examples of mechanistic studies have been reported to date with an enantioselective catalyst system.[24,37] The influence of chiral ligands on the preferred nucleopalladation pathway remains to be established.

Despite the challenges associated with controlling the stereochemistry of nucleopalladation, the number of successful enantioselective transformations has expanded significantly over the past decade. Nevertheless, significant challenges must be addressed to expand the synthetic utility of these reactions. Only a small number of reactions proceed with very high enantiomeric excess, and the successful examples generally have been demonstrated for only a small scope of substrates, with limited variation in the identity of the alkene and/or nucleophile. Many chiral ligands appear to have deleterious effects on catalyst activity, resulting in the need for high catalyst loadings and long reaction times, and many of the oxidation reactions require the use of a large excess of undesirable oxidants, such as benzoquinone. The development of enantioselective catalysts with increased reactivity and oxidation reactions compatible with the use of molecular oxygen as the oxidant will have important implications for the practical application of these reactions. Such advances will likely arise from the discovery of new classes of chiral ligands, and the field would benefit from the establishment of a stronger link between the mechanistic investigations and empirical reaction-discovery efforts, including an increased contribution from computational studies.

Acknowledgments

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Biographies

Richard McDonald was born in Strasbourg, France in 1983. He attended UC-Davis, where he received a B.S. degree in Chemistry (2005) and performed research in the laboratory of Prof. Michael D. Toney. He carried out his doctoral work at the University of Wisconsin–Madison under the supervision of Prof. Shannon S. Stahl. His research included the discovery of novel aerobic palladium(II)-catalyzed alkene amination methods for the stereoselective synthesis of 1,2-diamines and 2,5-disubstituted pyrrolidines and the development of enantioselective oxidative amination reactions. He also developed a new synthesis of 1,2- and 1,3-aminoaldehydes and 1,3-alkoxyaldehydes by Rh-catalyzed enantioselective hydroformylation. After receiving his Ph.D. in November of 2010, he began postdoctoral studies in the laboratories of Prof. David R. Liu at Harvard University.

Guosheng Liu studied chemistry at Nanjing University of Science and Technology (1995), and obtained his M.S. degree at Dalian Institute of Physical Chemistry, Chinese Academy of Science (CAS), China (1999) with Prof. Zhuo Zheng. He then moved to the group of Prof. Xiyan Lu at Shanghai Institute of Organic Chemistry, CAS, where he received his Ph.D. in 2002. From 2003 to 2007, he conducted postdoctoral research at Lehigh University with Prof. Li Jia and at University of Wisconsin–Madison with Prof. Shannon S. Stahl. In 2007,

he began his independent career at Shanghai Institute of Organic Chemistry, CAS. His current research interests focus on the development of novel synthetic methodologies and degradable polymer synthesis.

Shannon Stahl is currently Professor of Chemistry at the University of Wisconsin–Madison. His research group specializes in homogeneous catalysis, with an emphasis on the development and study of aerobic oxidation reactions and their applications in organic chemistry. He was an undergraduate at the University of Illinois at Urbana-Champaign (B.S., Chemistry, 1992). Shannon subsequently attended Caltech (Ph.D., Chemistry, 1997), where he was an NSF predoctoral fellow in the laboratory of Prof. John E. Bercaw, and his Ph.D. thesis work focused on mechanistic studies of Pt-catalyed oxidation of methane to methanol (the Shilov system). From 1997–1999, he was an NSF postdoctoral fellow with Prof. Stephen J. Lippard at MIT, and he investigated the mechanism of selective methane oxidation by the enzyme, soluble methane monooxygenase (sMMO). He has been at the University of Wisconsin-Madison since 1999.

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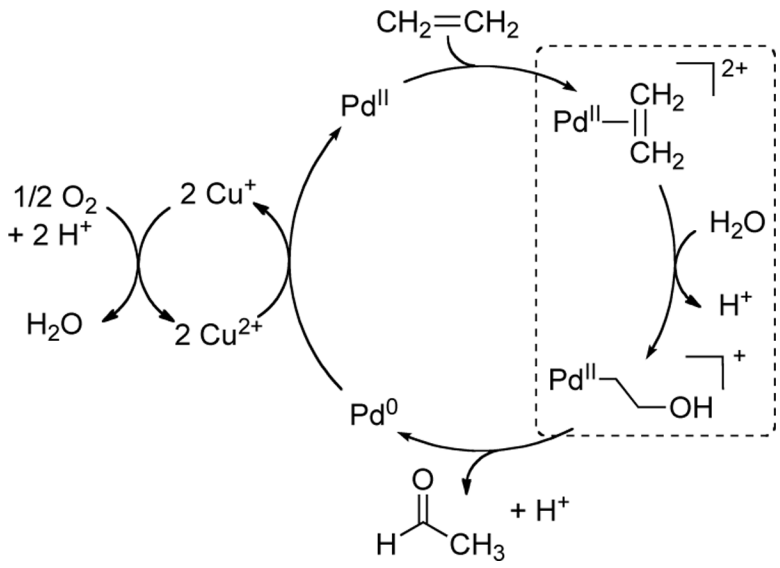
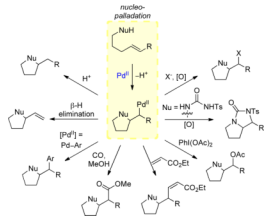
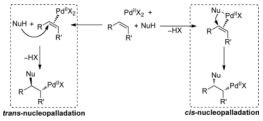


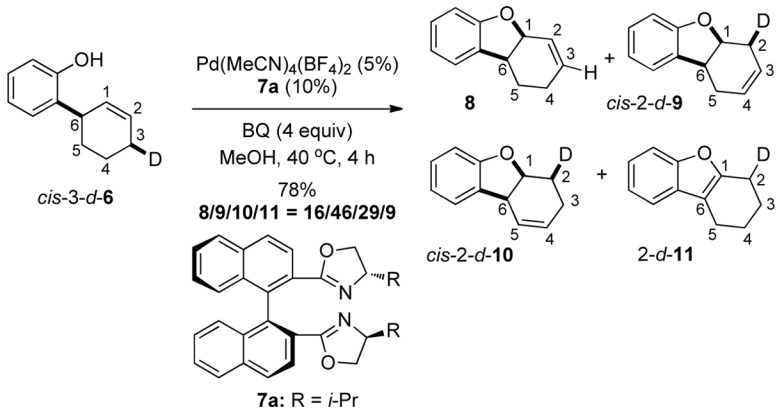
Scheme 1.
The Wacker Reaction.



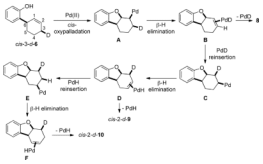
Scheme 2.
Versatility of the Pd^{II}-Alkyl Intermediate Arising from Alkene Nucleopalladation.



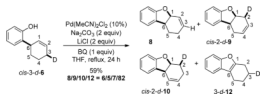
Scheme 3.
Stereochemical Pathways of Nucleopalladation.



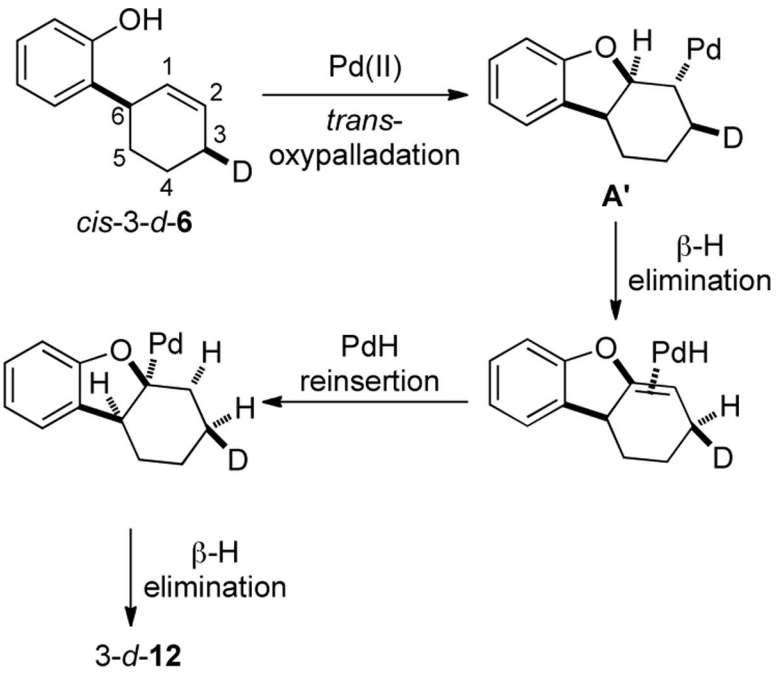
Scheme 4.
Analysis of Phenoxypalladation Stereochemistry Using BOXAX Ligands.



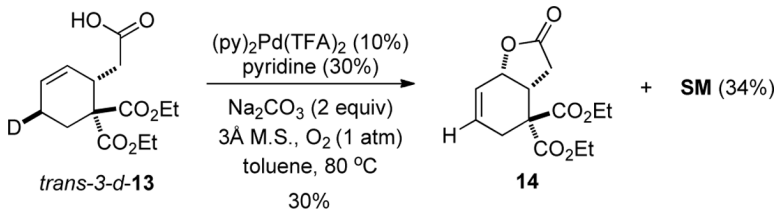
Scheme 5.
Mechanistic Basis for the Observed Products Following Cyclization of *cis*-3-*d*-6.



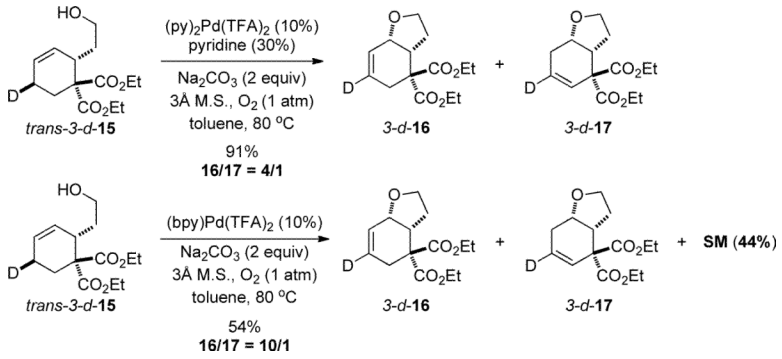
Scheme 6.
Observation of *trans*-Oxypalladation Products at High [Cl^-].



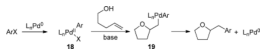
Scheme 7.
Mechanistic Explanation for the Formation of 3-*d*-12.



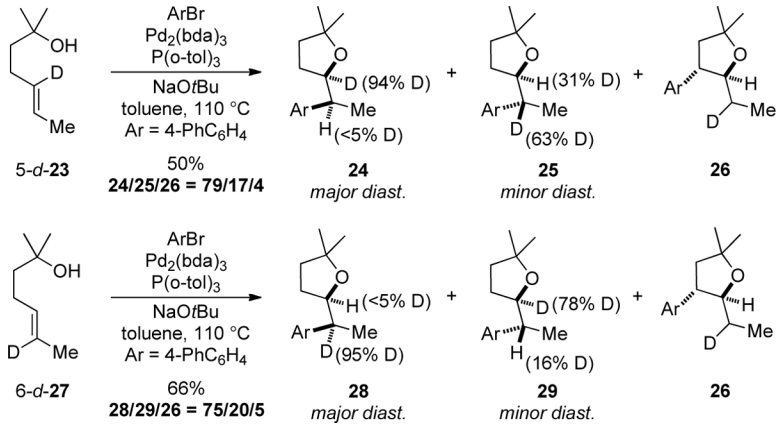
Scheme 8.
Carboxylic Acid Cyclization Proceeds Exclusively via *trans*-Oxypalladation.



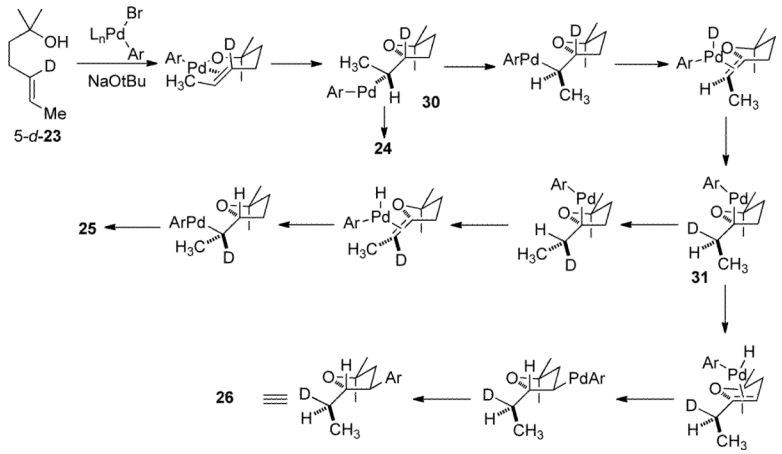
Scheme 9.
Alcohol Cyclization Proceeds Exclusively via *cis*-Oxypalladation.



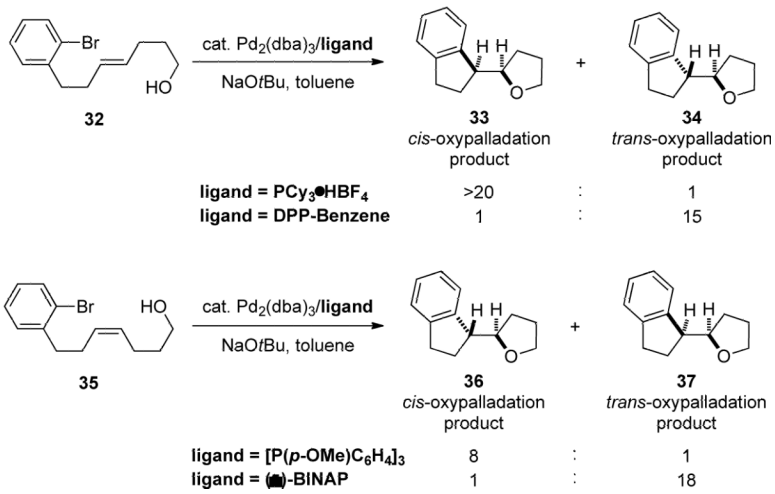
Scheme 10.
Mechanistic Proposal for the Alkoxyarylation of Alkenes.



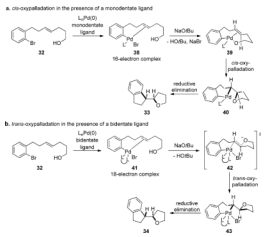
Scheme 11.
Alkoxyarylation of Deuterated Substrates.



Scheme 12.
Mechanistic Explanation for the Formation of 24, 25, and 26.

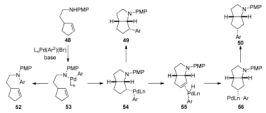


Scheme 13.
Divergent Alkoxyarylation Stereochemical Outcomes by Variation of the Achiral Ligand.

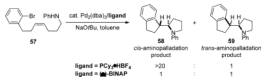


Scheme 14.
Mechanistic Hypothesis for the Formation of 33 and 34.

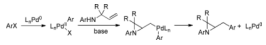
Scheme 15.
Stoichiometric Studies of the Addition of Amine Nucleophiles to Pd-Coordinated Alkenes.



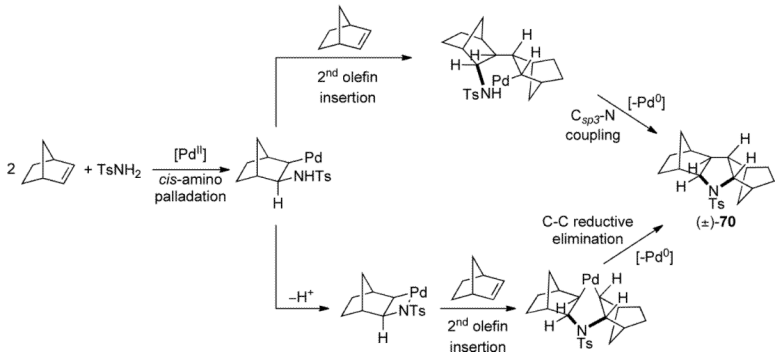
Scheme 16.
Mechanistic Proposal Accounting for the Reaction Outcome in the Aminoarylation of 48.



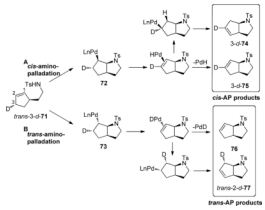
Scheme 17.
Divergent Aminoarylation Stereochemical Outcomes by Variation of the Achiral Ligand.



Scheme 18.
Proposed Mechanism for the Intramolecular Aminoarylation of Allyl Amines.

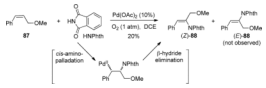


Scheme 19.
Intermolecular Oxidative Amination of Norbornene.

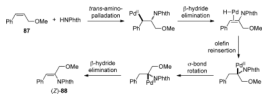


Scheme 20.
Mechanistic Rational for the Formation of Products 74–77.

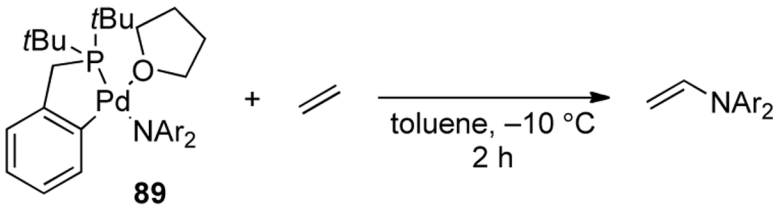
Scheme 21.
Aerobic Oxidative Amination at High [Cl^-].



Scheme 22.
Mechanistic Explanation for the Formation of (*Z*)-88.

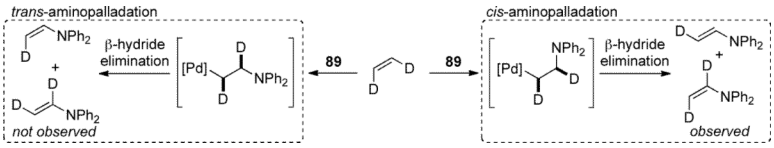


Scheme 23.
Alternative Proposal for the Formation of (*Z*)-88.

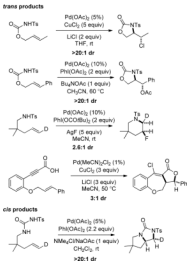


Ar	k_{obs} x 10^3 (s^{-1})
$(3,5\text{-}CF_3)_2C_6H_3$	0.053
p-C_6H_4F	0.79
Ph	0.91
p-C_6H_4Me	4.3
p-C_6H_4OMe	9.6

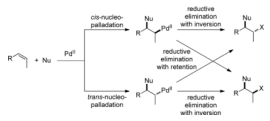
Scheme 24.
Insertion of Ethylene into a Pd-Amide Bond.



Scheme 25.
Stereochemistry of Ethylene Insertion into a Pd-Amide Species.

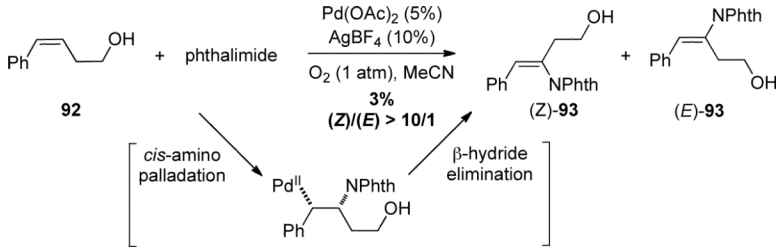


Scheme 26.
Alkene Difunctionalization Reactions.

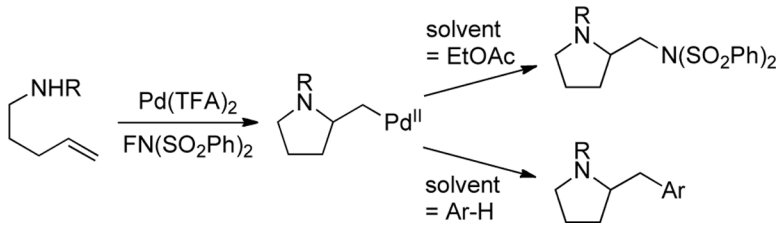


Scheme 27.
Possible Stereochemical Pathways for Alkene Difunctionalization Reactions.

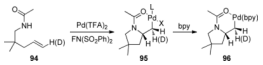
Scheme 28.
Proposed Mechanism for the Intermolecular Aminoacetoxylation of Alkenes.



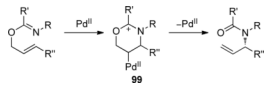
Scheme 29.
Mechanistic Rational for the Formation of (*Z*)-93 via Oxidative Amination of 92.



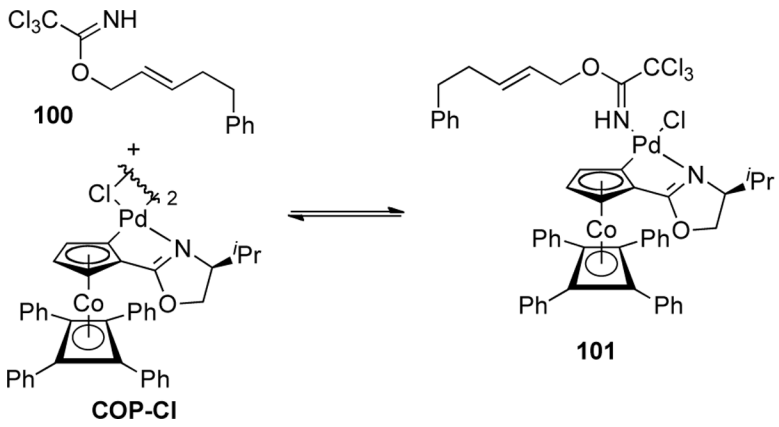
Scheme 30.
Alkene Difunctionalization in the Presence of *N*-Fluorobenzenesulfonimide.



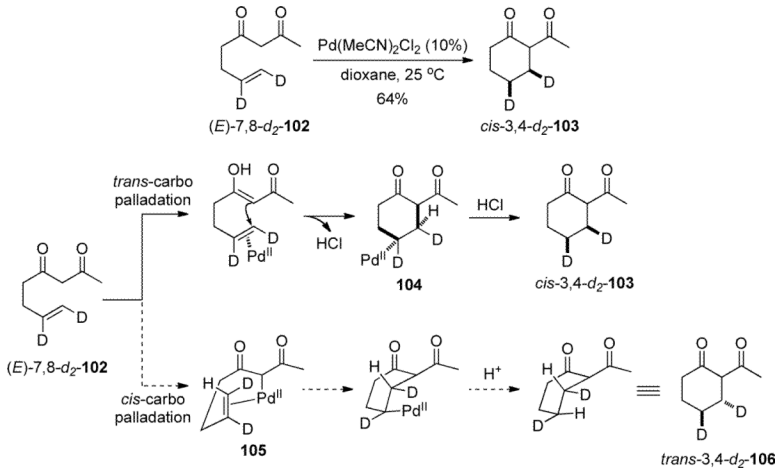
Scheme 31.
Trapping an Aminopalladation Intermediate with Bipyridine.



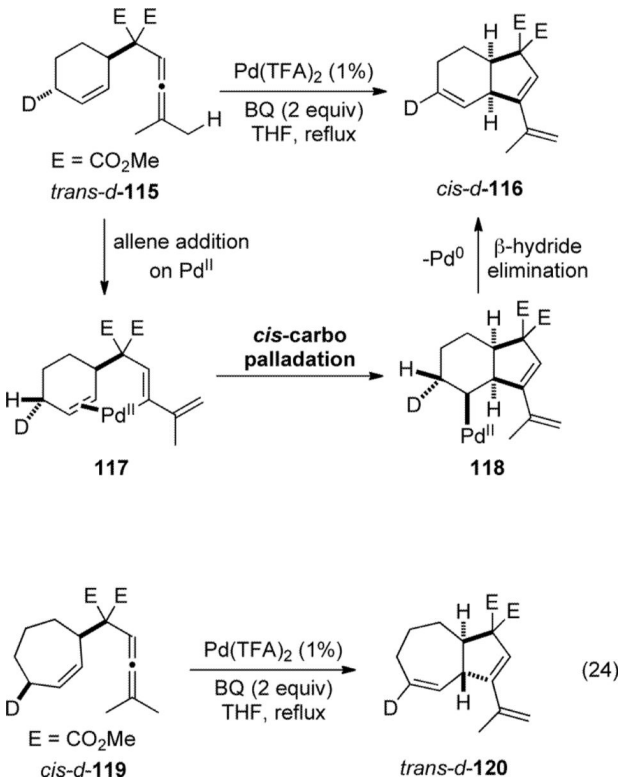
Scheme 32.
Proposed Mechanism for the Rearrangement of Allylic Imidates.



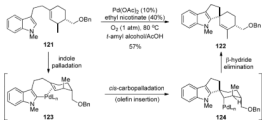
Scheme 33.
Formation of a Pd-Imidate Species.



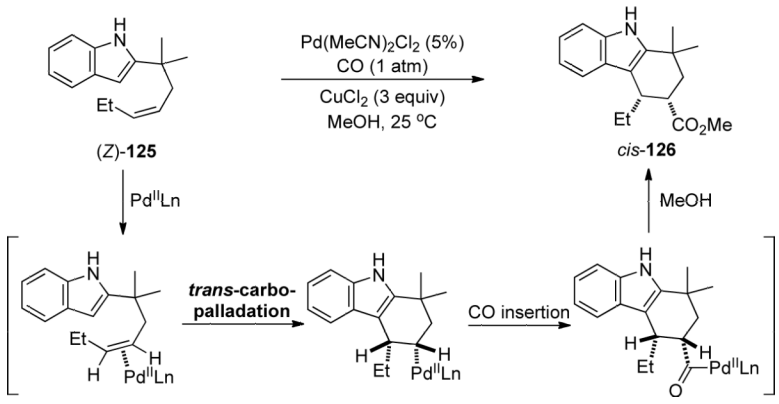
Scheme 34.
Mechanistic Explanation for the Formation of *cis*-3,4-d_2-103.



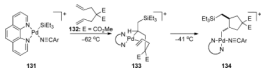
Scheme 35.
Mechanistic Hypothesis for the Formation of *cis-d*-116.



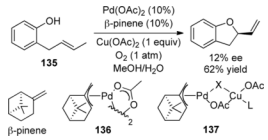
Scheme 36.
Proposed Mechanism for the Oxidative Annulation of Indoles.



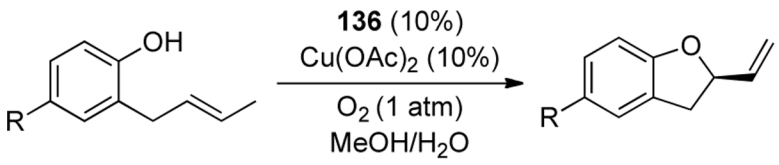
Scheme 37.
Mechanistic Explanation for the Formation of *cis*-126.



Scheme 38.
Evidence for *cis*-Aminopalladation in a Stoichiometric Carbopalladation Reaction.

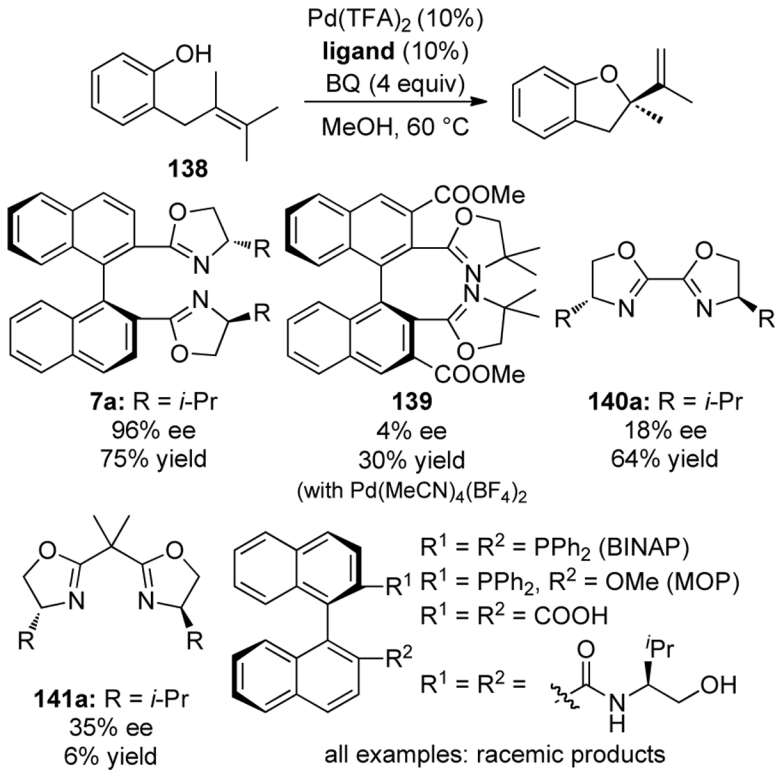


Scheme 39.
Enantioselective Phenol Cyclization Using the Chiral Alkene β-Pinene.



R	yield (%)	ee (%)
OMe	44	26
Me	76	21
H	77	18
Cl	72	6
COMe	74	1.1

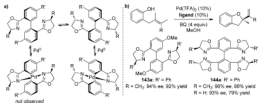
Scheme 40.
The Effect of *para*-Substitution on Yield and Enantioselectivity.



Scheme 41.

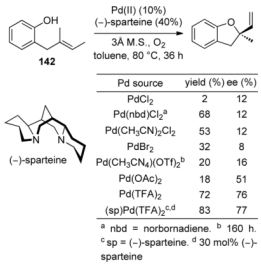
Binaphthyl-Derived Bisoxazoline Ligands (BOXAX) for Enantioselective Oxidative Phenol Cyclization Onto Tetrasubstituted Alkenes.

Scheme 42.
Phenol Cyclization onto Trisubstituted Alkenes.



Scheme 43.

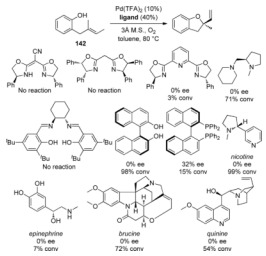
a) Chelation-Induced Axially Chiral Bisoxazoline Ligands and b) Their Application to Enantioselective Phenol Cyclization.



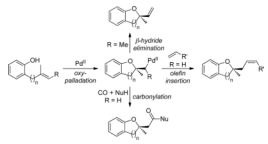
Pd source	yield (%)	ee (%)
$PdCl_2$	2	12
$Pd(nbd)Cl_2$[a]	68	12
$Pd(CH_3CN)_2Cl_2$	53	12
$PdBr_2$	32	8
$Pd(CH_3CN_4)(OTf)_2$[b]	20	16
$Pd(OAc)_2$	18	51
$Pd(TFA)_2$	72	76
(sp)$Pd(TFA)_2$[c,d]	83	77

[a] nbd = norbornadiene. [b] 160 h. [c] sp = (−)-sparteine. [d] 30 mol% (−)-sparteine

Scheme 44.
Aerobic Enantioselective Phenol Cyclization Using (−)-Sparteine.

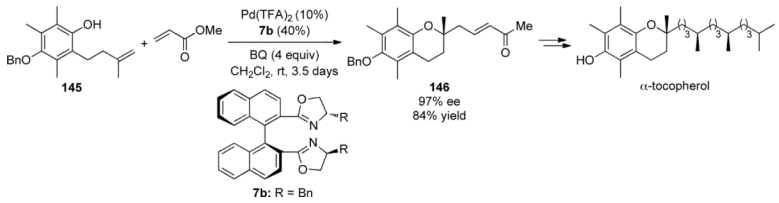


Scheme 45.
Ligand Screen for Aerobic Phenol Cyclization.



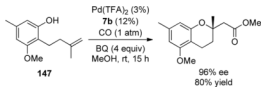
Scheme 46.

Phenol Cyclization Yields Pd-Alkyl Species that Terminate by β-Hydride Elimination or are Trapped by Alkenes or CO.

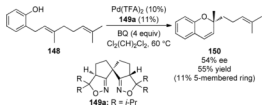


Scheme 47.

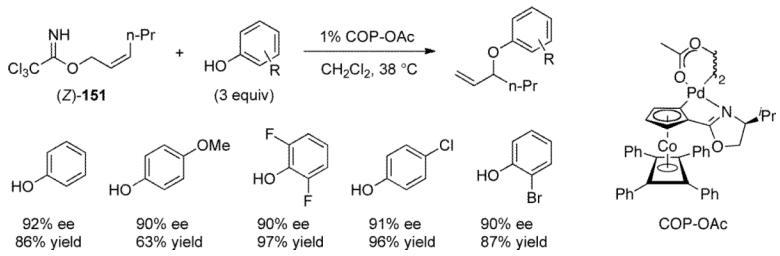
Enantioselective Oxidative Oxycarbonylation as the Key Step in the Asymmetric Total Synthesis of α-Tocopherol.



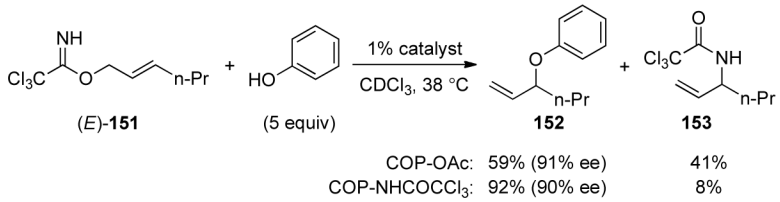
Scheme 48.
Enantioselective Oxidative Oxycarbonylation.



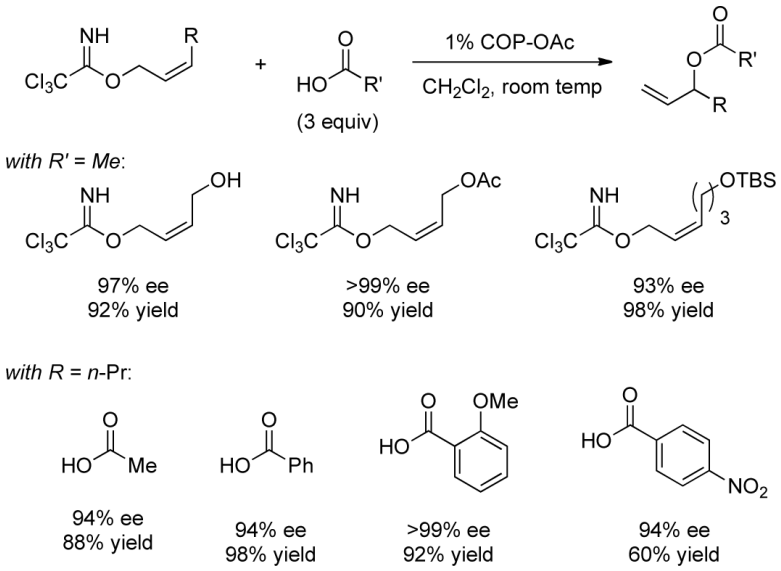
Scheme 49.
Phenol Oxypalladation/β-Hydride Elimination to Afford Six-Membered Rings.



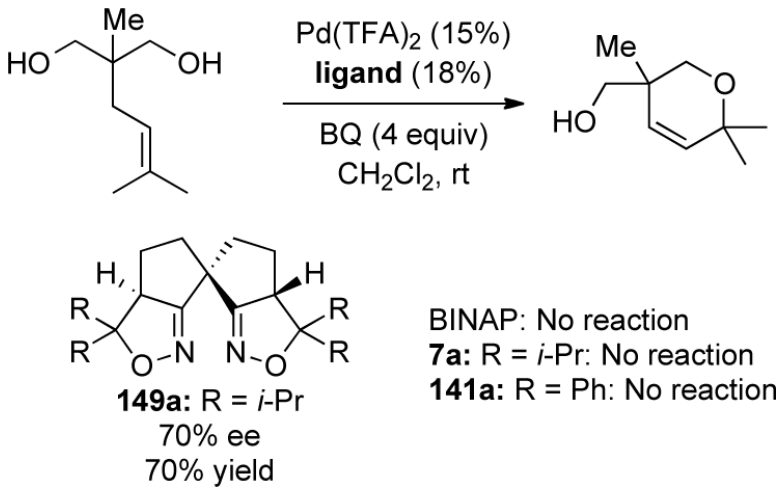
Scheme 50.
Intermolecular Addition of Phenols to (*Z*)-Allylic Trichloroacetimidates.



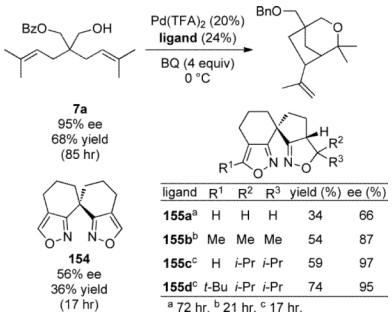
Scheme 51.
Addition of Phenols to (*E*)-Allylic Trichloroacetimidates.



Scheme 52.
Addition of Carboxylic Acids to (Z)-Allylic Trichloroacetimidates.



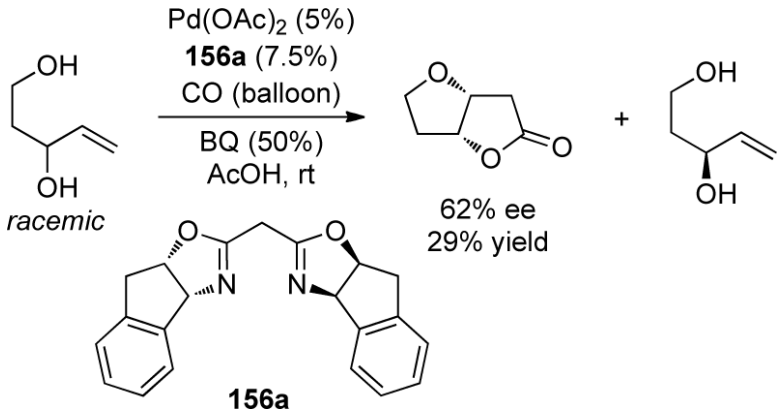
Scheme 53.
Enantioselective Oxidative Cyclization of Primary Alcohols.



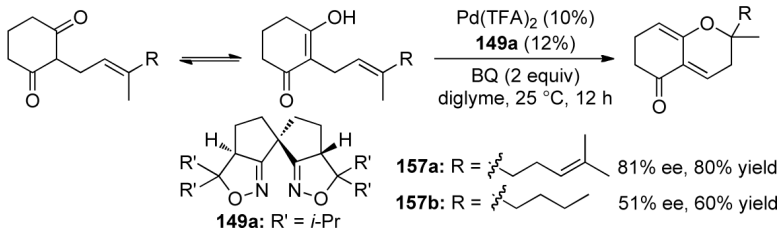
ligand	R^1	R^2	R^3	yield (%)	ee (%)
155a[a]	H	H	H	34	66
155b[b]	Me	Me	Me	54	87
155c[c]	H	*i*-Pr	*i*-Pr	59	97
155d[c]	*t*-Bu	*i*-Pr	*i*-Pr	74	95

[a] 72 hr. [b] 21 hr. [c] 17 hr.

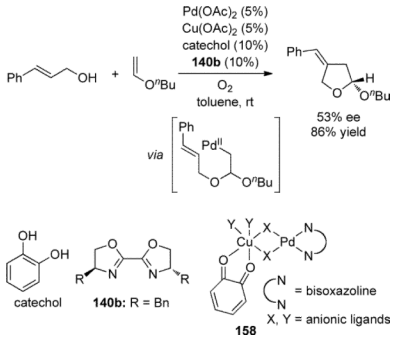
Scheme 54.
Alkoxy Alkylation of Primary Alcohols.



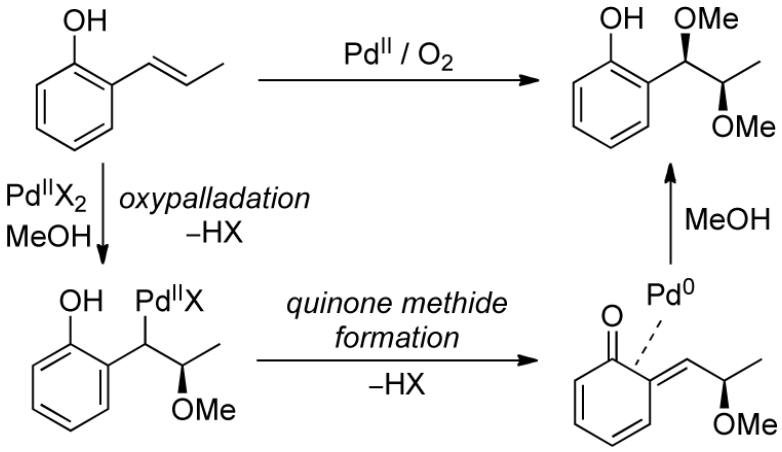
Scheme 55.
Intramolecular Oxycarbonylation of Primary Alcohols.



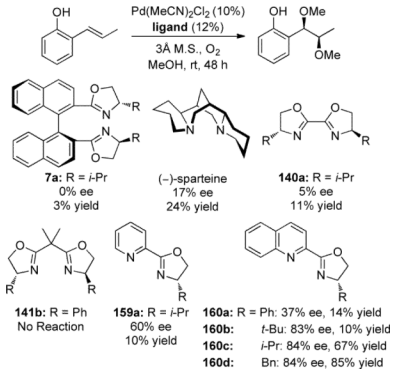
Scheme 56.
Cyclization of β-Dicarbonyl Nucleophiles.



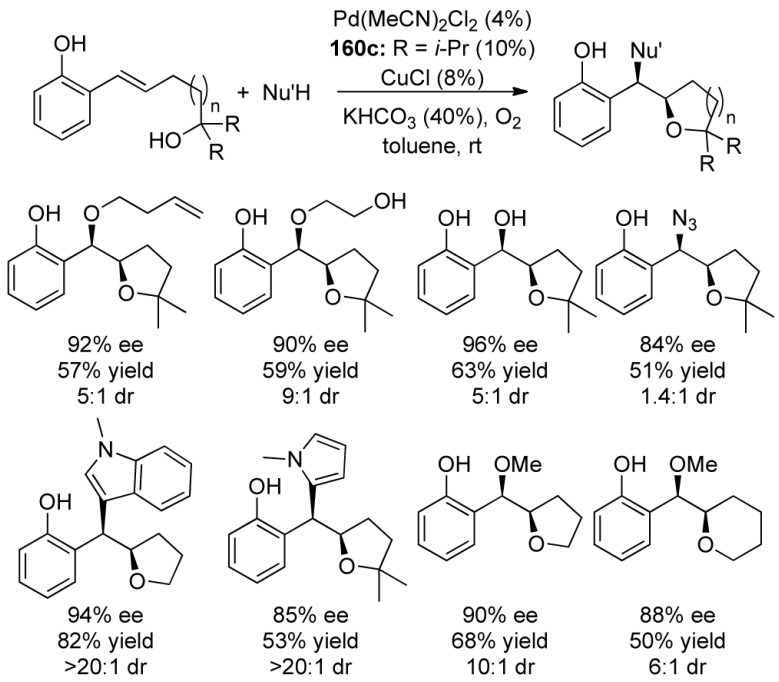
Scheme 57.
Intermolecular Alkoxyvinylation of Vinyl Ethers.



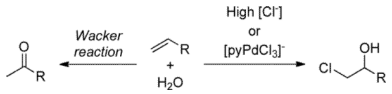
Scheme 58.
Difunctionalization of *ortho*-Vinyl Phenols via a Quinine Methide Intermediate.



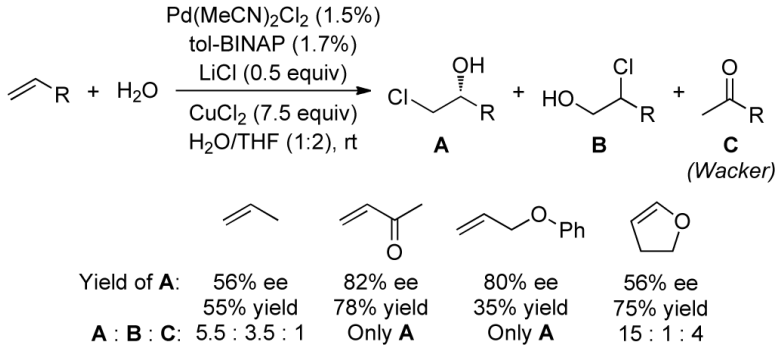
Scheme 59.
Intermolecular Dialkoxylation of *ortho*-Vinyl Phenols.



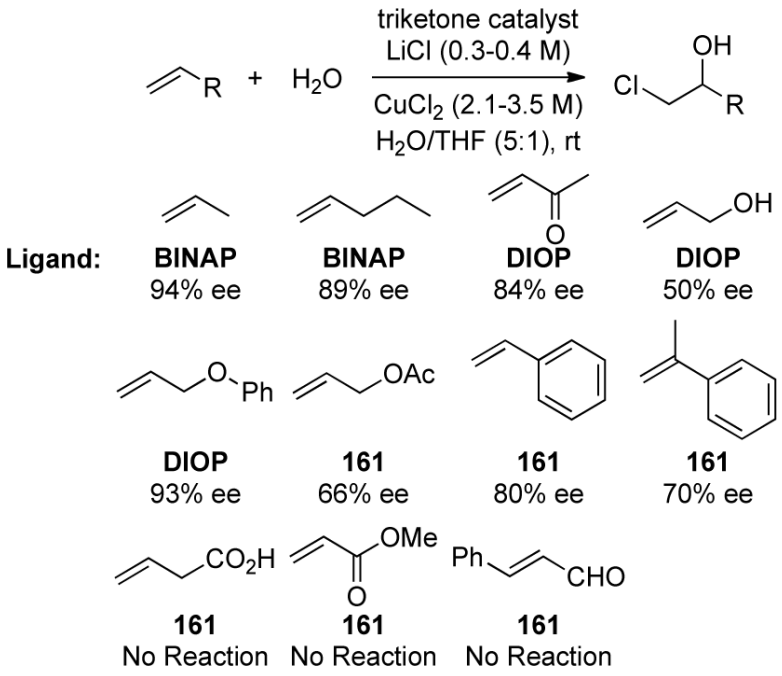
Scheme 60.
Intramolecular Difunctionalization of *ortho*-Vinyl Phenols.



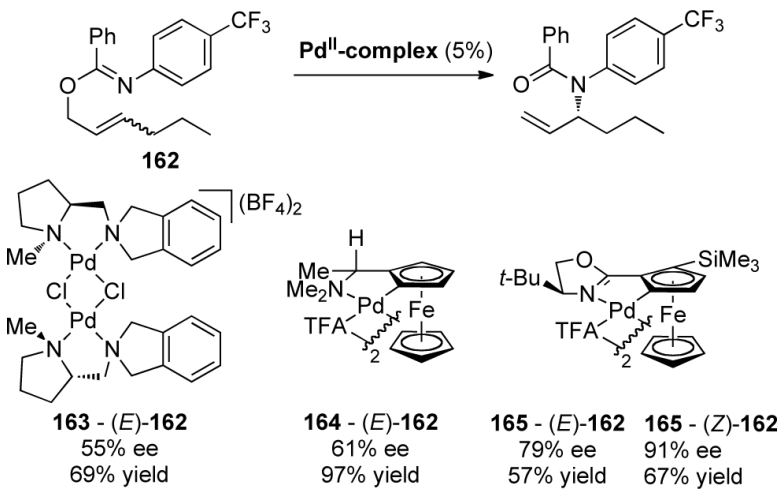
Scheme 61.
Synthesis of Traditional Wacker Products or Chlorohydrin Derivatives.



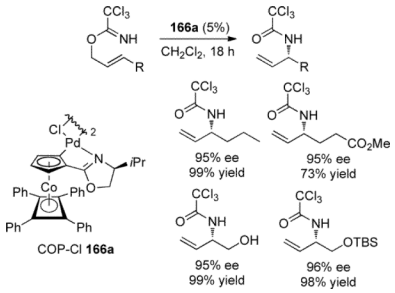
Scheme 62.
Hydroxy-Chlorination Using Monometallic Catalysts.



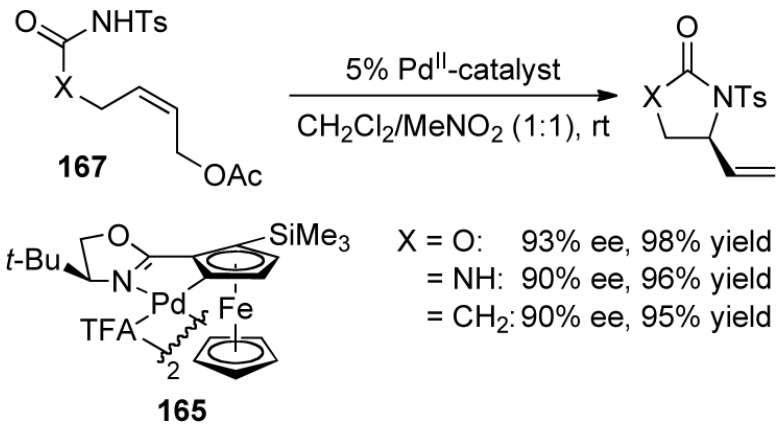
Scheme 63.
Hydroxy-Chlorination Using Bimetallic Catalysts.



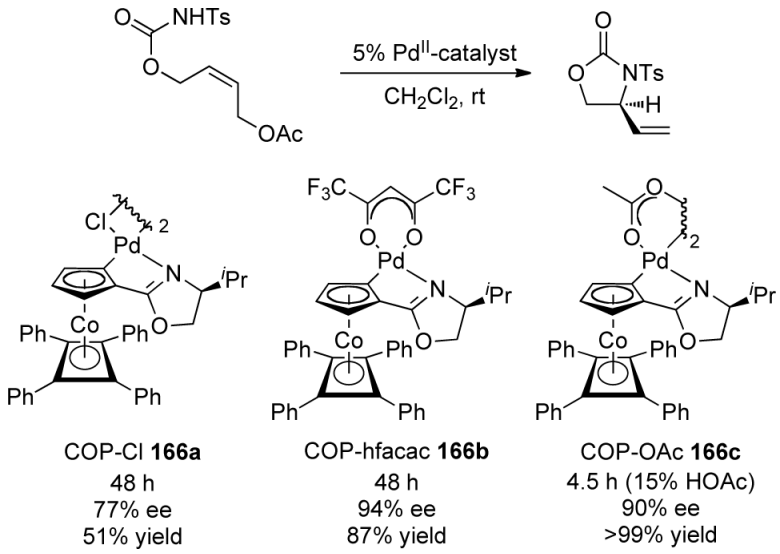
Scheme 64.
The First Pd^{II}-Catalyzed Enantioselective Allylic Imidate Rearrangement.



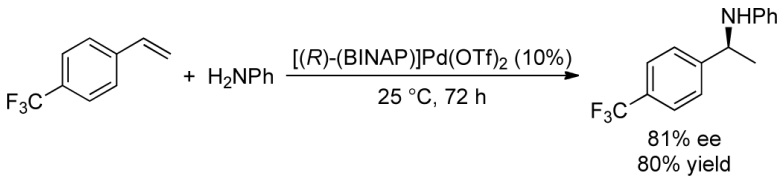
Scheme 65.
Enantioselective Allylic Trichloroacetimidate Rearrangement.



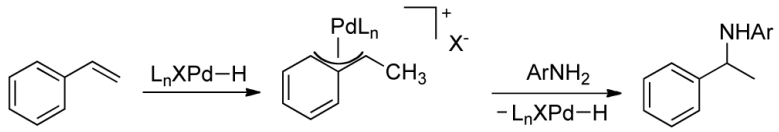
Scheme 66.
Intramolecular C–N Bond-Forming Allylic Substitution.



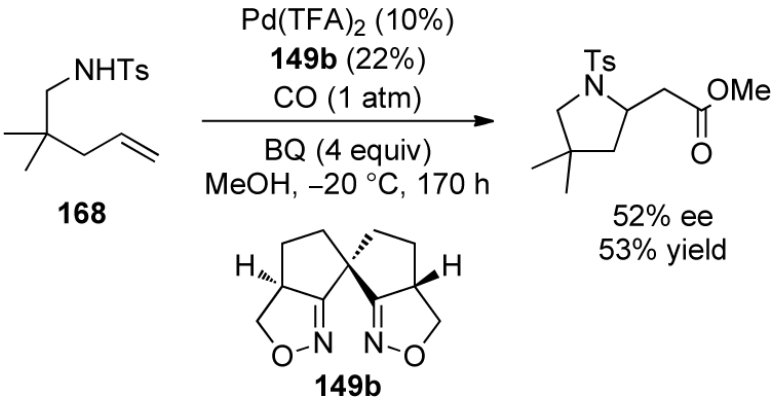
Scheme 67.
COP–X Catalyzed Enantioselective Aminopalladation/β-Hydride Elimination.



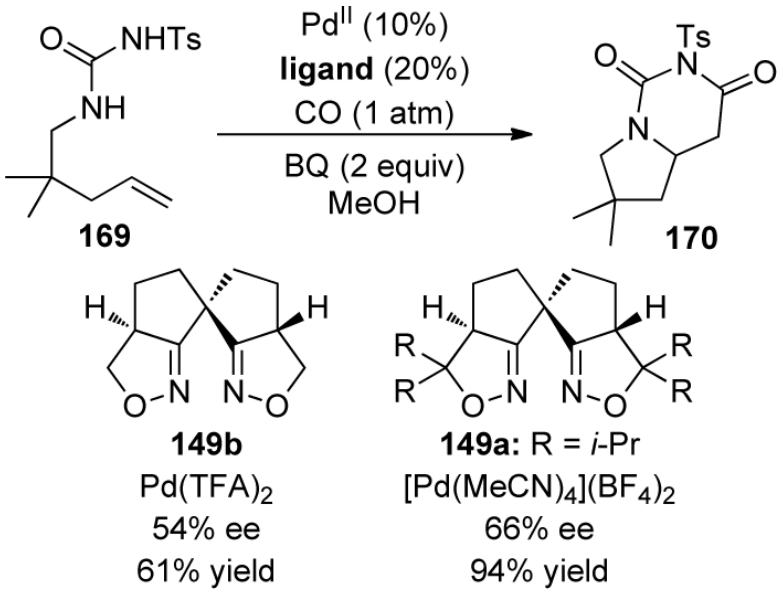
Scheme 68.
Enantioselective Hydroamination of Styrenes



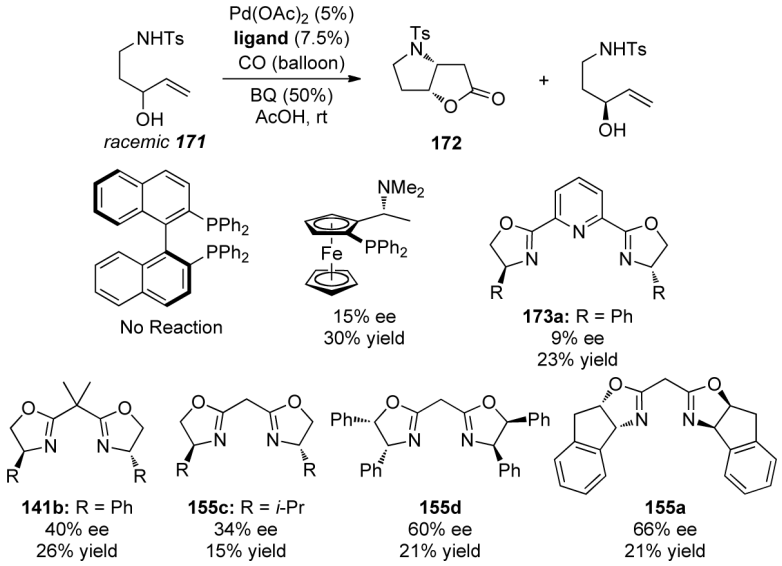
Scheme 69.
Proposed Mechanism for Styrene Hydroamination.



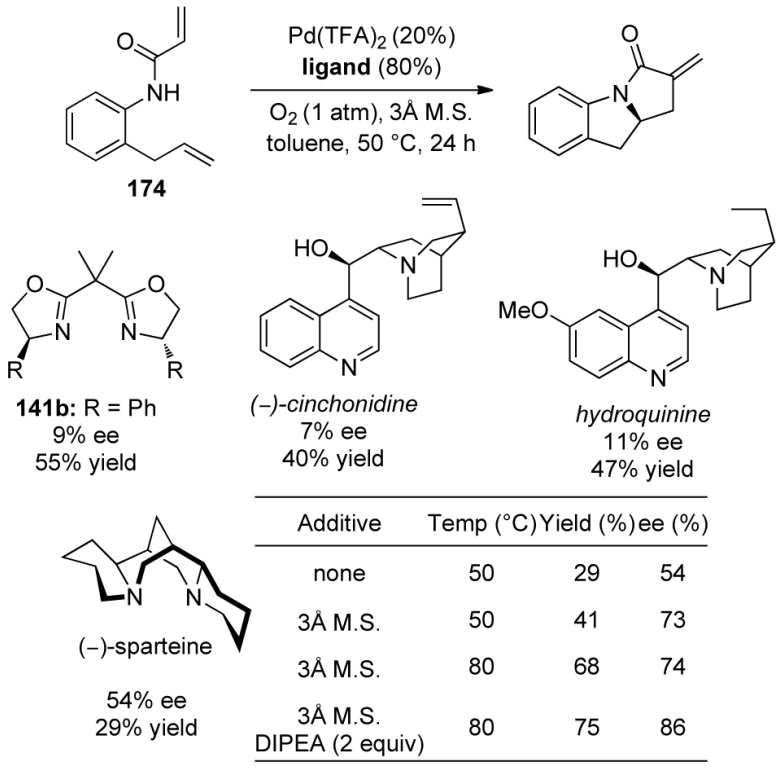
Scheme 70.
Aminocarbonylation of Sulfonamides.



Scheme 71.
Aminocarbonylation of *N*-Tosyl Ureas.

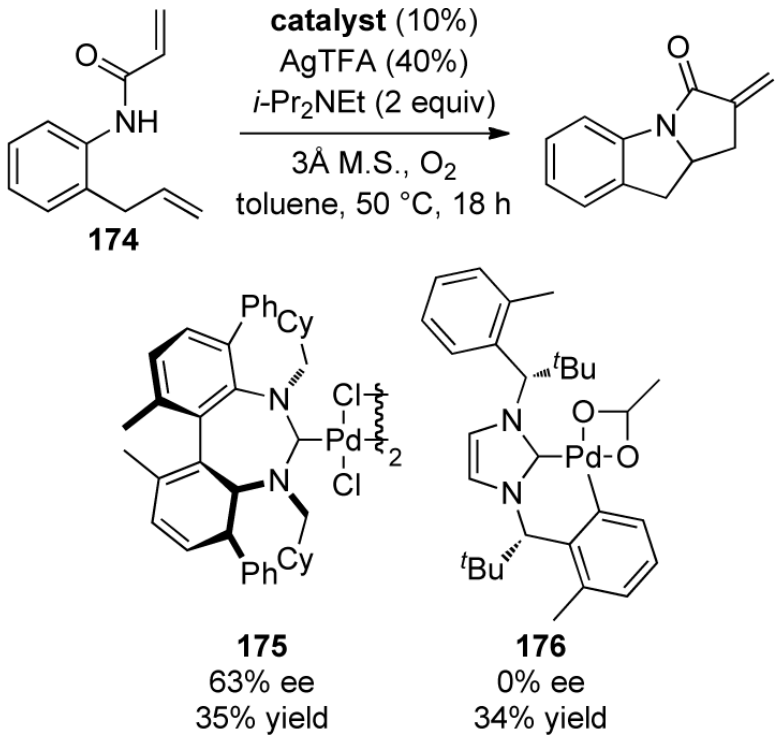


Scheme 72.
Aminocarbonylation of Amino Alcohols.

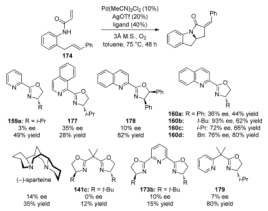


Additive	Temp (°C)	Yield (%)	ee (%)
none	50	29	54
3Å M.S.	50	41	73
3Å M.S.	80	68	74
3Å M.S. DIPEA (2 equiv)	80	75	86

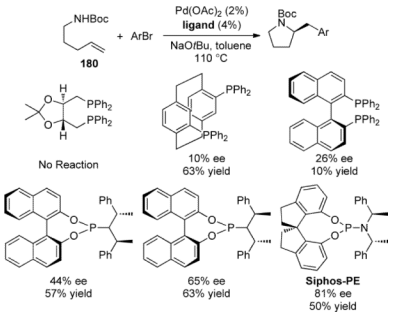
Scheme 73.
Aerobic Oxidative Aminovinylation.



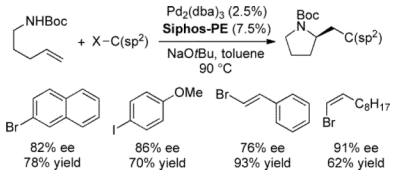
Scheme 74.
Aerobic Oxidative Aminovinylation with Chiral Pd^{II}-NHC Complexes.



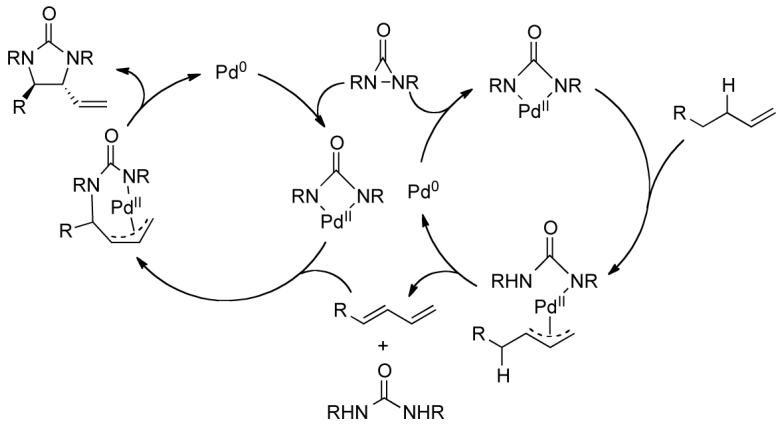
Scheme 75.
Ligand Screen for Aerobic Oxidative Aminovinylation.



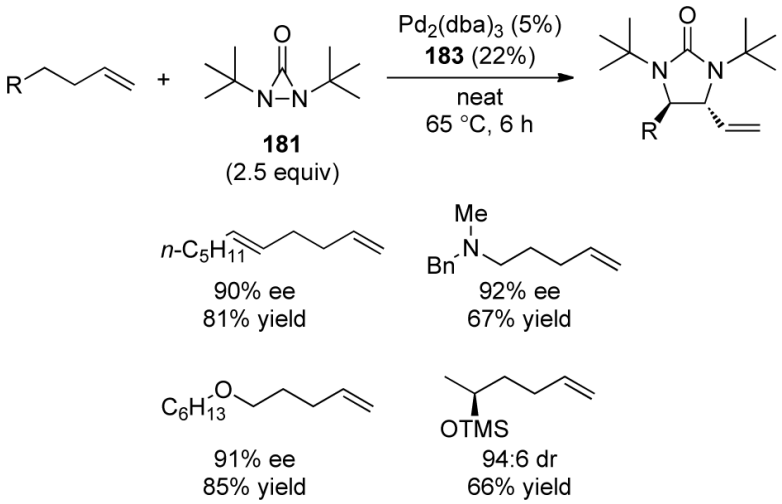
Scheme 76.
Screen of Chiral Phosphine Ligands.



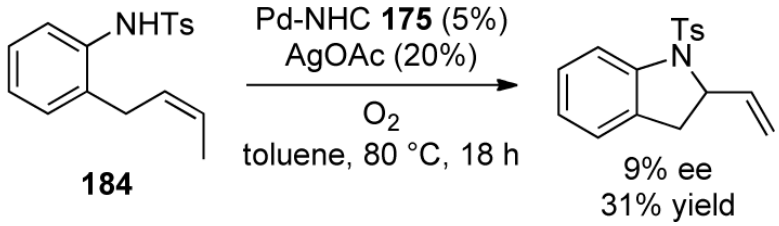
Scheme 77.
Enantioselective Aminoarylation with Aryl and Vinyl Halides.



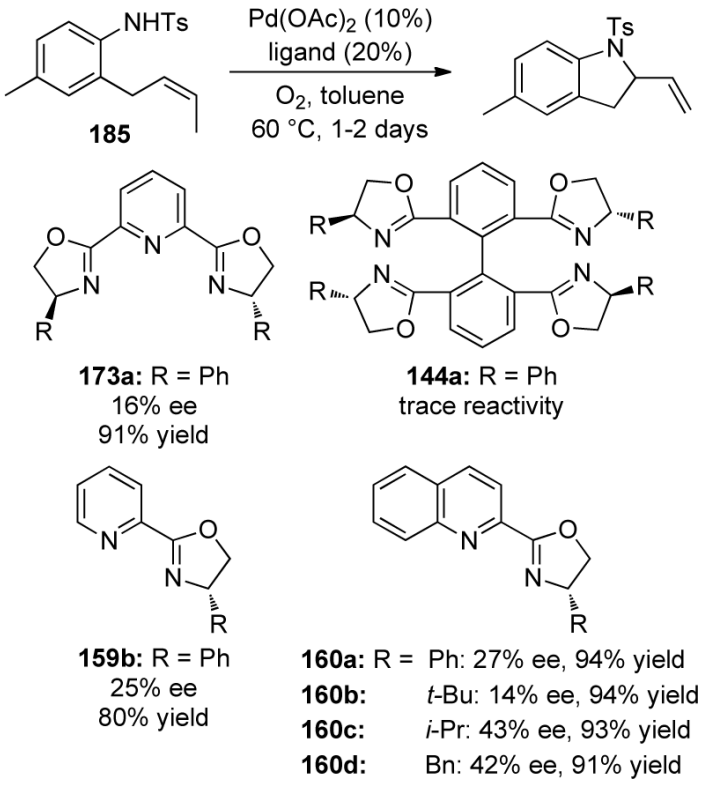
Scheme 78.
Proposed Mechanism for Alkene Diamination with Di-*tert*-butyldiaziridinone.



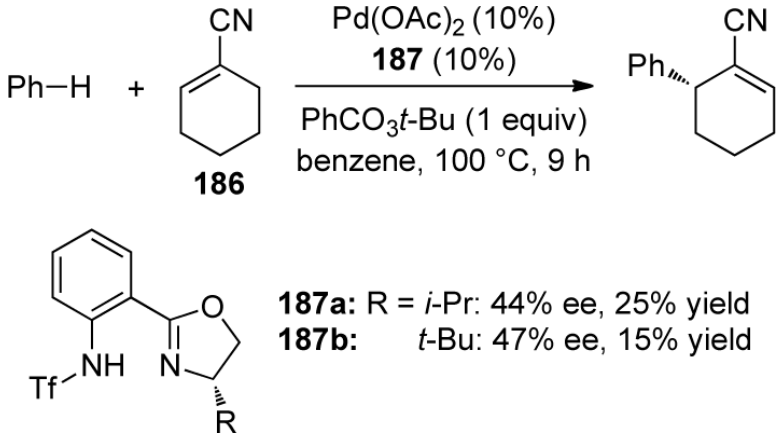
Scheme 79.
Pd^0-Catalyzed Diamination of Terminal Alkenes.



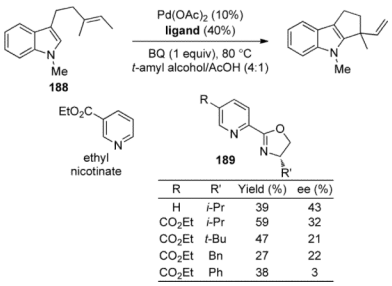
Scheme 80.
Aerobic Oxidative Amination with Chiral Pd^{II}-NHC Complexes.



Scheme 81.
Aerobic Oxidative Amination of *ortho*-Allyl Tosylanilides.

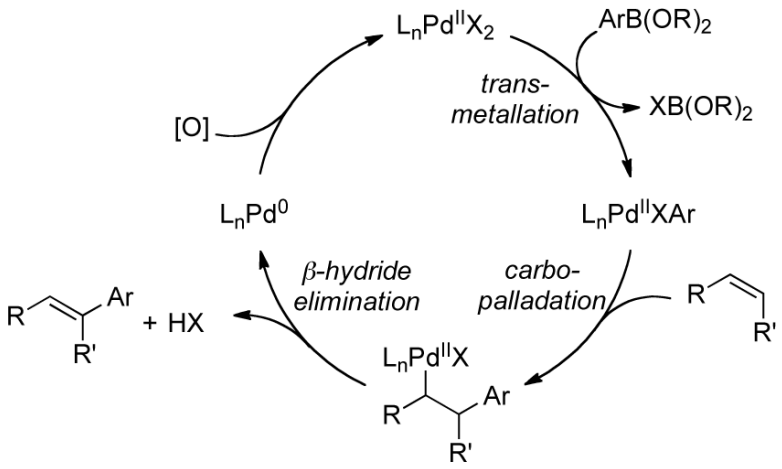


Scheme 82.
Enantioselective Fujiwara-Moritani Cross-Coupling.

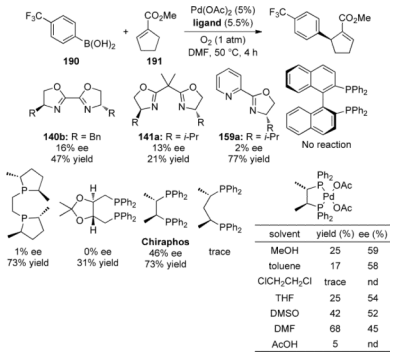


R	R'	Yield (%)	ee (%)
H	*i*-Pr	39	43
CO_2Et	*i*-Pr	59	32
CO_2Et	*t*-Bu	47	21
CO_2Et	Bn	27	22
CO_2Et	Ph	38	3

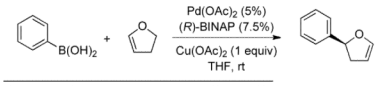
Scheme 83.
Aerobic Oxidative Annulation of Indoles.



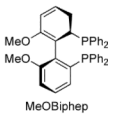
Scheme 84.
General Mechanism for the Oxidative Heck Reaction.



Scheme 85.
Aerobic Oxidative Heck Cross-Coupling of Aryl Boronic Acids and α,β-Unsaturated Esters.



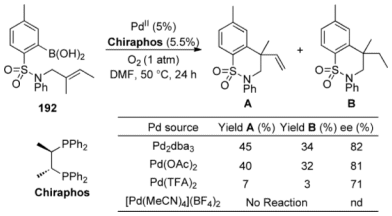
Oxidant 1	Oxidant 2	Base	Yield (%)	ee (%)
$Cu(OAc)_2$	air	K_2CO_3	34	41
$Cu(OAc)_2$	air	none	33	43
none	air	K_2CO_3	17	nd
$Cu(OAc)_2$	none	K_2CO_3	46	57
$Cu(OAc)_2$	none	none	69	57
$Cu(OAc)_2$[a]	none	none	67	83



MeOBiphep

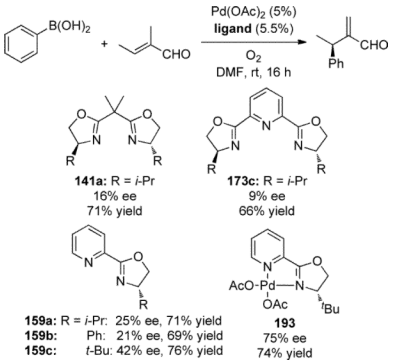
Scheme 86.

Aerobic Oxidative Heck Cross-Coupling of an Aryl Boronic Acid and Vinyl Ether.
[a]With MeOBiphep



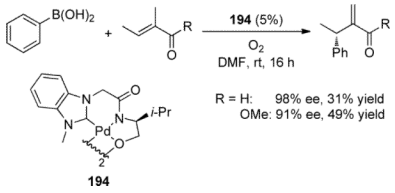
Pd source	Yield **A** (%)	Yield **B** (%)	ee (%)
Pd_2dba_3	45	34	82
$Pd(OAc)_2$	40	32	81
$Pd(TFA)_2$	7	3	71
$[Pd(MeCN)_4](BF_4)_2$	No Reaction		nd

Scheme 87.
Intramolecular Aerobic Oxidative Heck Reaction.

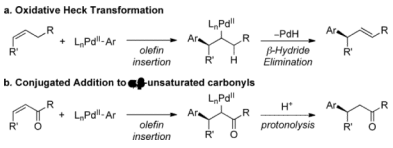


Scheme 88.

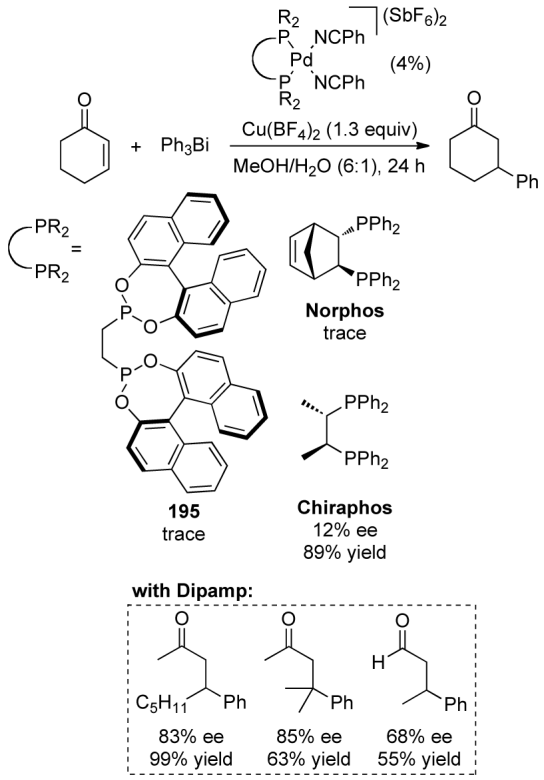
Aerobic Oxidative Heck Cross-Coupling of Phenyl Boronic Acids and α,β-Unsaturated Aldehydes.



Scheme 89.
Tridentate NHC-Amidate-Alkoxide Ligands in Aerobic Oxidative Heck Cross-Coupling.

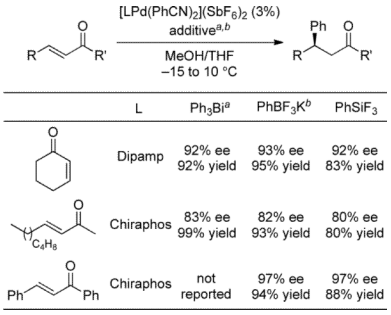


Scheme 90.
Pd^{II}-Catalyzed Arylation of Alkenes.



Scheme 91.

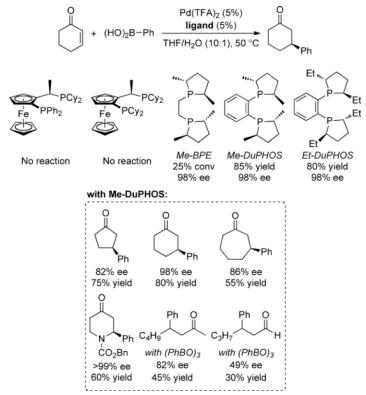
1,4-Addition of Triarylbismuths to α,β-Unsaturated Carbonyls.



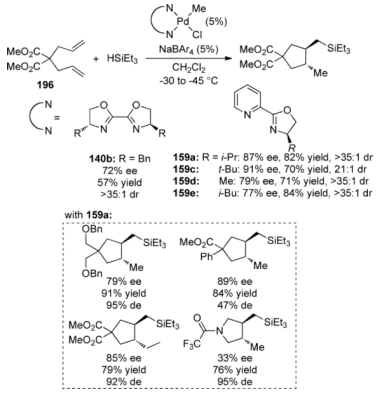
Scheme 92.

Conjugate Addition of Triarylbismuths, Aryl Potassium Trifluoroborates, and Aryl Trifluorosilicates to Enones.

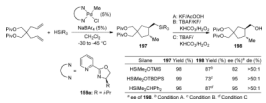
[a]$Cu(BF_4)_2 \cdot 6H_2O$ (0.76 equiv relative to enone). [b]ZnF_2 (1 equiv).



Scheme 93.
Conjugate Addition of Aryl Boronic Acids to Enones.



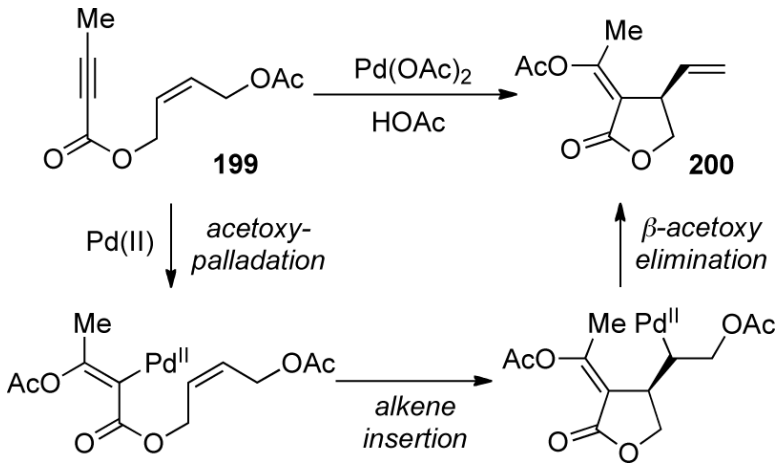
Scheme 94.
Hydrosilylation/Cyclization of 1,6-Dienes.



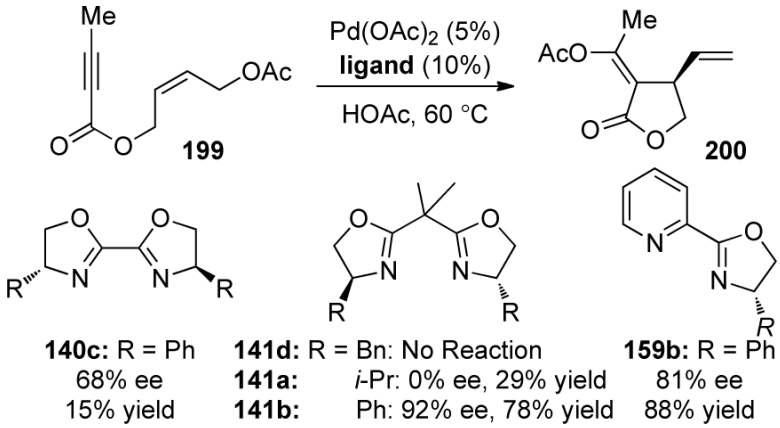
Silane	197 Yield (%)	198 Yield (%)	ee (%)[a]	de (%)
$HSiMe_2OTMS$	98	87[b]	82	>50:1
$HSiMe_2OTBDPS$	99	73[c]	95	>50:1
$HSiMe_2CHPh_2$	96	87[c]	95	>50:1

[a] ee of 198. [b] Condition A. [c] Condition B. [d] Condition C

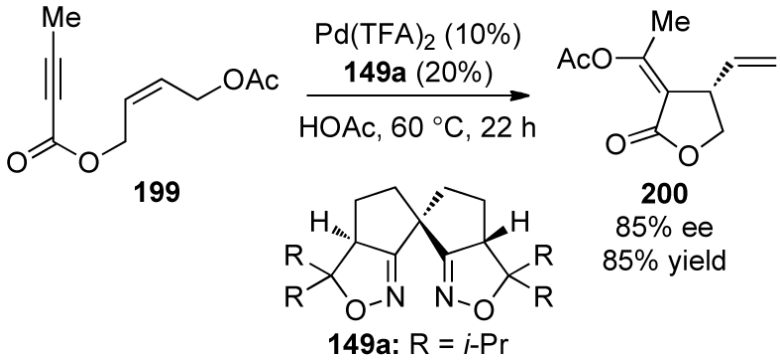
Scheme 95.
Hydrosilylation/Cyclization Using Various Silanes.



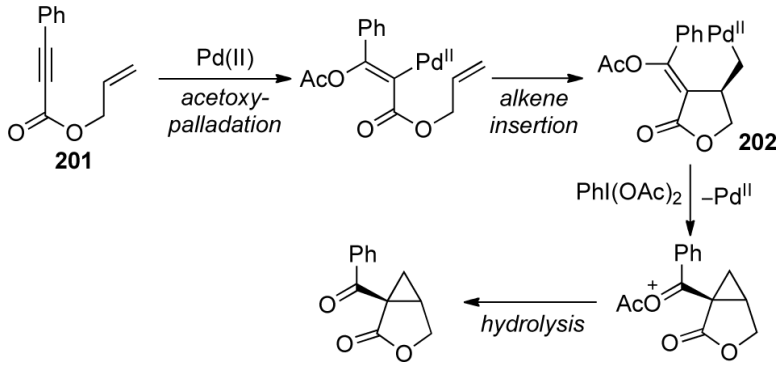
Scheme 96.
Proposed Mechanism for Acetoxylation/Cyclization.



Scheme 97.
Chiral Ligand Screen for Enantioselective Carbocyclization.

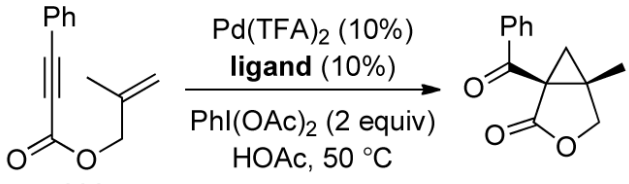


Scheme 98.
Acetoxylation/Cyclization with the $Pd(TFA)_2$/SPRIX Catalyst.

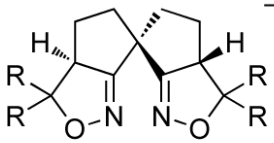


Scheme 99.

Proposed Mechanism for the Synthesis of Cyclopropanes via Oxidative Cyclization of Enynes.



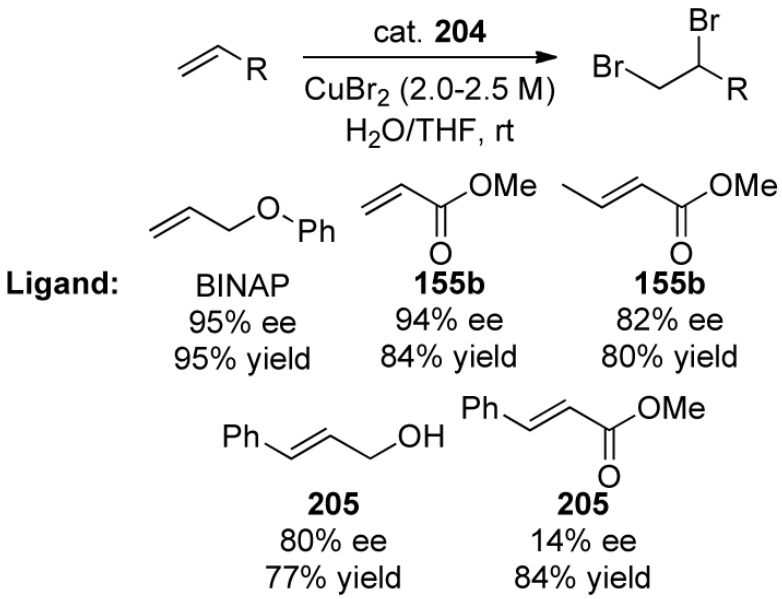
(–)-sparteine: 87% yield, 0% ee
bisoxazoline **141c**: 39% yield, 2% ee
BOXAX **7a**: 71% yield, 4% ee
SPRIX **149a**: 80% yield, 45% ee



149a: R = *i*-Pr

Pd catalyst	Yield (%)	ee (%)
[**149a**]$PdCl_2$	59	58
[**149a**]$Pd(OAc)_2$	72	52
[**149a**]$Pd(TFA)_2$	79	56
$Pd(hfacac)_2$ + **149a**	79	39
$[Pd(MeCN)_4](BF_4)_2$ + **149a**	67	69

Scheme 100.
Ligand Screen for the Oxidative Cyclization of Enynes.



Scheme 101.
Dibromination Using Bimetallic Catalysts.

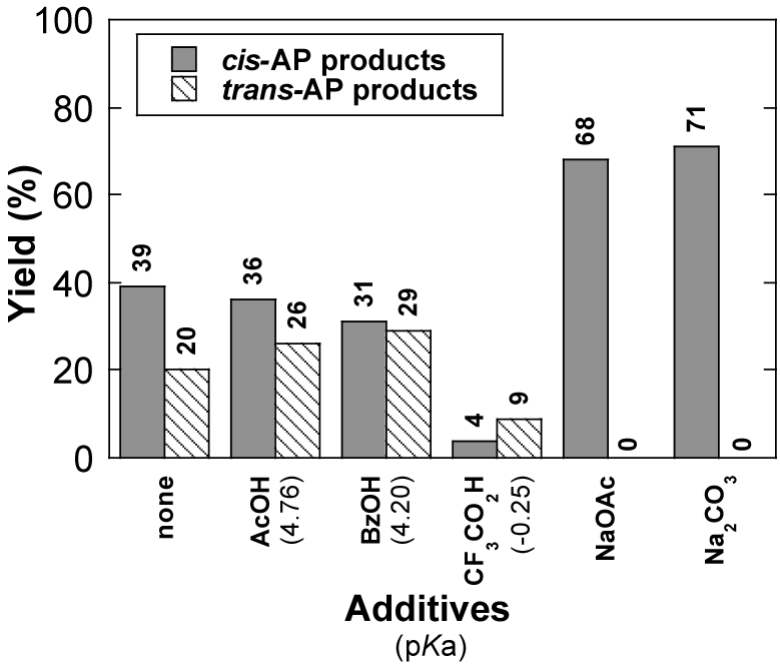


Figure 1.

Catalyst: (IMes)Pd(O_2CCF_3)$_2$(OH_2). Na_2CO_3 (2 equiv), AcOH (0.2 equiv), BzOH (0.2 equiv), *p*-$NO_2C_6H_4CO_2H$ (0.2 equiv), trifluoroacetic acid (1 equiv). The pK_a value of additives (in parentheses) was determined in H_2O.

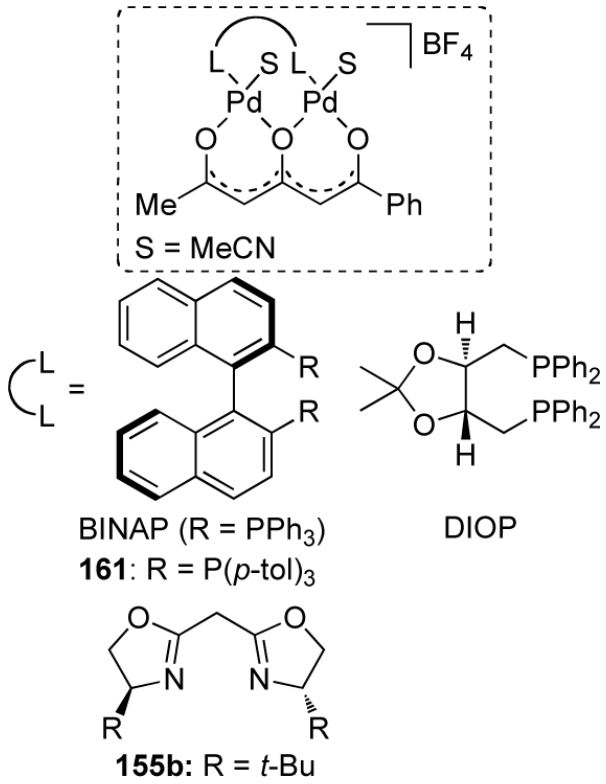


Figure 2.
Bimetallic Pd^{II}-Catalysts for Hydroxy-Chlorination of Alkenes.

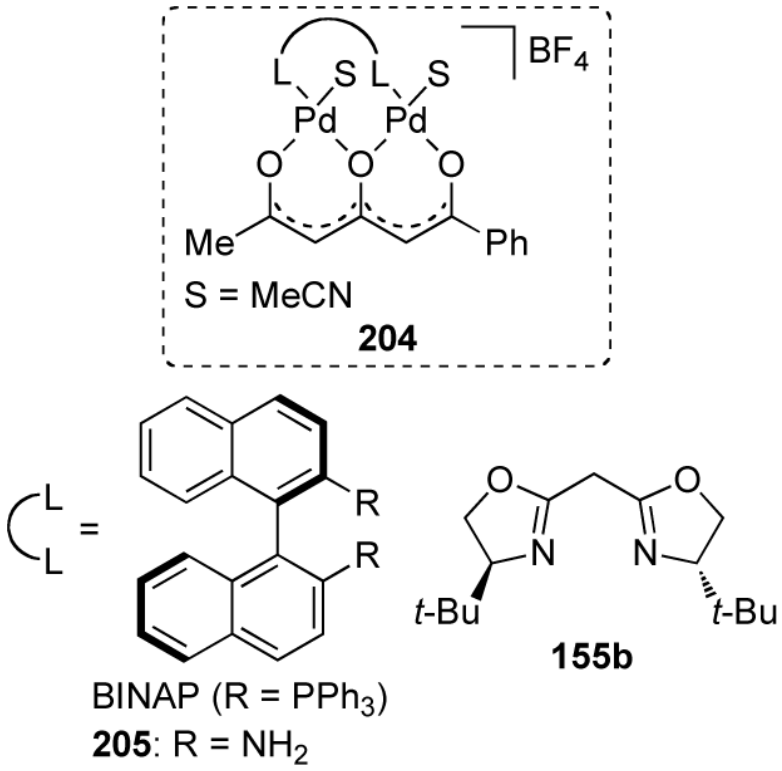
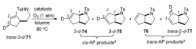


Figure 3.
Bimetallic Pd^{II}-Catalysts for Dibromination of Alkenes.

Table 1

Stereochemical Outcome for the Oxidative Amination of *trans*-3-*d*-71 Under Different Catalyst Systems.



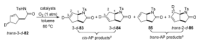
		product ratio	
catalysts	**yield (%)**	***cis*-AP 3-*d*-74+3-*d*-75**	***trans*-AP 76+*trans*-2-*d*-77**
$Pd(OAc)_2$/DMSO	70	100	0
$Pd(OAc)_2$/py	84	100	0
$Pd(TFA)_2$/py	85	100	0
$Pd(TFA)_2$/(−)-sparteine[b]	37	100	0
$Pd(IMes(TFA)_2$/BzOH	60	51	49

[a] AP = aminopalladation.

[b] 10% Pd

Table 2

Stereochemical Analysis of the Aerobic Oxidative Amination of Tosyl-Carboxamide *trans*-3-*d*-82.



		product ratio	
catalysts	**yield (%)**	***cis*-AP 3-*d*-83+3-*d*-84**	***trans*-AP 85+*trans*-2-*d*-86**
$Pd(IMes(TFA)_2/Na_2CO_3$	34	67	33
$Pd(OAc)_2$/py	47	89	11
$Pd(TFA)_2$/py	83	84	16
$Pd(IMes(TFA)_2$/BzOH	74	54	46
$Pd(OAc)_2$/DMSO	73	0	100

[a] AP = aminopalladation.