Published in final edited form as:

Tetrahedron. 2009 June 27; 65(26): 5074–5083. doi:10.1016/j.tet.2009.03.096.

A new approach to carbon-carbon bond formation: Development of aerobic Pd-catalyzed reductive coupling reactions of organometallic reagents and styrenes

Keith M. Gligorich^a, Yasumasa Iwai^b, Sarah A. Cummings^c, and Matthew S. Sigman^{a,*}

^a Department of Chemistry, University of Utah, 315 South 1400 East Salt Lake City, UT 84112, USA

^b Kyorin Pharmaceutical Co., Ltd., 1848 Nogi, Nogi-machi, Shimotuga-gun, Tochigi-ken, 329-0114, Japan

^c Department of Chemistry, University of Nevada, Reno, Reno NV 89557, USA

Abstract

Alkenes are attractive starting materials for organic synthesis and the development of new selective functionalization reactions are desired. Previously, our laboratory discovered a unique Pd-catalyzed hydroalkoxylation reaction of styrenes containing a phenol. Based upon deuterium labeling experiments, a mechanism involving an aerobic alcohol oxidation coupled to alkene functionalization was proposed. These results inspired the development of a new Pd-catalyzed reductive coupling reaction of alkenes and organometallic reagents that generates a new carbon-carbon bond. Optimization of the conditions for the coupling of both organostannanes and organoboronic esters is described and the initial scope of the transformation is presented. Additionally, several mechanistic experiments are outlined and support the rationale for the development of the reaction based upon coupling alcohol oxidation to alkene functionalization.

Keywords

Catalysis; Cross-Coupling; Molecular Oxygen; Palladium; Mechanism

1. Introduction

Alkenes are attractive starting materials for organic synthesis because they can be readily converted to a wide range of functional groups.ⁱ However, the utility of many alkene functionalization reactions is limited because of poor regioselectivity of the transformation leading to a mixture of products. One strategy to overcome this challenge is the use of metal catalysts to control the selectivity of the functionalization. For example, Pd catalysts have been successfully employed in the Wacker reaction, which selectively oxidizes an alkene to a methyl ketone.ⁱⁱ Previously, our group has developed more effective catalyst systems for the Wacker oxidation.ⁱⁱⁱ As part of this ongoing effort, we were interested in applying these and related catalyst systems to the discovery of new types of selective alkene functionalization reactions. As a result, we discovered a unique Pd^{II}-catalyzed hydroalkoxylation reaction of alkenes

*Corresponding author. Tel.: +1-801-585-0774; fax: +1-801-581-8433; e-mail: sigman@chem.utah.edu (M. S. Sigman).

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

containing a phenol.^{iv} For example, vinyl phenol (**1**) is converted to ether **2** in 72% yield using catalytic Pd[(–)-sparteine]Cl₂ and CuCl₂ (Equation 1).

Pd-Catalyzed Hydroalkoxylation of Vinylphenols

(1)

While there have been numerous reports of metal-catalyzed alkene hydroalkoxylation reactions,^v there were no examples that employed Pd^{II} salts.^{vi} This is most likely due to facile β-hydride elimination after initial oxypalladation, which would lead to Wacker oxidation products.ⁱⁱ We initially hypothesized that the phenolic substrate allowed for competitive protonation of the Pd-carbon bond formed after initial oxypalladation of the alkene with the alcoholic substrate.^{iv} In order to test this hypothesis and probe the origin of the hydrogen atom incorporated into the alkene framework, we believed that conducting the reaction with CH₃CH₂OD as the solvent should result in the incorporation of one deuterium atom into the product at the site of Pd-carbon bond protonation.^v However, subjecting vinyl phenol **3** to the reaction conditions with CH₃CH₂OD as the solvent produced the unlabeled ether product **2** (Figure 1, A). This result rules out the plausibility of a Brønsted acid based mechanism. To further investigate the origin of the hydrogen atom incorporated into the product, a similar reaction was performed with CD₃CD₂OD as the solvent. This led to the formation of isotopomers **4a** and **4b** in a 2.5 to 1 ratio, which contain one deuterium atom incorporated into the alkene framework. This result suggests that the hydrogen atom originates from the alkyl chain of ethanol rather than the acidic proton.

Based upon these results, we propose a mechanism wherein the Pd^{II} catalyst **A** initially oxidizes the alcoholic solvent to generate the Pd-hydride intermediate **B** (Figure 1, B). Coordination of the alkene produces the cationic complex **C**. Based upon the formation of isotopomers **4a** and **4b**, we propose that the alkene inserts into the Pd-hydride at both the α- and β-position of the styrene yielding **D** and **D'**. Since only the benzylic addition product is obtained, we propose that intermediate **D'** proceeds to product *via* formation of an *ortho*-quinone methide intermediate with concomitant reduction of Pd^{II} to Pd⁰ and generation of **E**.^{vii} Ethanol subsequently reacts with the quinone methide intermediate to liberate the ether product and the Pd⁰ species **F**, which is reoxidized by CuCl₂ or O₂.^{ii,viii}

While the deuterium labeling experiments suggest a unique alcohol oxidation coupled alkene functionalization process, the scope of the reaction is limited to substrates that contain a phenol. Therefore, our laboratory was interested in taking advantage of this distinctive mechanistic motif in the realm of new reaction discovery. Specifically, we wanted to develop a Pd^{II}-catalyzed reductive coupling reaction, which employs alkenes that do not contain a phenol in combination with an organometallic reagent to generate a new carbon-carbon and carbon-hydrogen bond under aerobic conditions. Herein, we present the development of an aerobic

reductive coupling reaction of alkenes with both organostannanes and organoboronic esters as well as experiments that showcase the unique mechanism.

2. Approach

We were interested in developing a reductive coupling reaction of alkenes and organometallic reagents that utilizes an alcohol oxidation to initiate the catalysis and generate a Pd-hydride. Mechanistically, this type of transformation differs from Pd⁰-catalyzed cross-coupling wherein the catalyst initially oxidatively adds an electrophilic organic compound, which generally contains a carbon-halogen bond (R–X), that yields the oxidized species R–Pd^{II}–X (Figure 2, A).ⁱⁱⁱ A potential limitation of Pd⁰-catalyzed cross-coupling reactions is the requirement of a substrate that is capable of oxidizing Pd⁰ to Pd^{II}. Unconventional routes to access the requisite R–Pd^{II}–X intermediate from starting materials that circumvent the need to oxidize Pd⁰ to Pd^{II} will increase the versatility and scope of cross-coupling reactions.

Based upon the deuterium labeling experiments performed on the alkene hydroalkoxylation reaction,^{iv} we hypothesized the catalytic R–Pd^{II}–X intermediate could be generated from an alkene (Figure 2, B and C).^{ix} Specifically, oxidation of the alcoholic solvent with Pd^{II} catalyst **A** will lead to the formation of Pd^{II}-hydride **B**. Coordination and insertion of the alkene into the Pd^{II}-hydride yields the Pd^{II}-alkyl intermediate **D** (or **D'**), which resembles the R–Pd^{II}–X species formed *via* oxidative addition of an organic electrophile.ⁱⁱ Transmetalation to form **E** and subsequent reductive elimination generates the reductive coupling product as well as the reduced catalyst **F**. Aerobic oxidation of Pd⁰ to Pd^{II} completes the catalytic cycle.^{ii,viii} The sp²-hybridized carbon atoms of the alkene will be transformed to sp³ atoms, which can be difficult to access with traditional cross-coupling because of facile β-hydride elimination.^x

Initially, we anticipated the formation of undesired byproducts arising from the oxidative Heck reaction^{xi} and homocoupling of the organometallic reagent,^{xii} which are proposed to originate from initial transmetalation of the Pd^{II} catalyst (Figure 2, D). The nature of the catalyst, solvent, and coupling partners were thought to have a significant impact on the formation of these byproducts by modulating the relative rate of transmetalation compared to alcohol oxidation/alkene insertion. Therefore, we initially decided to employ the Pd[(–)-sparteine]Cl₂ catalyst because of its ability to readily oxidize alcohols and alkenes.^{iiib, xiii}

Previously, our laboratory has shown that exposing a simple styrene substrate to the alkene hydroalkoxylation reaction conditions with ethanol as the solvent leads to the acetal product **6** (Figure 3, A).^{xiv} Since the proposed mechanism of acetal formation involves initial nucleophilic addition of the alcohol to the metal bound alkene, we thought a less nucleophilic secondary alcohol, such as isopropanol (IPA), would not readily undergo acetal formation. However, performing the reaction with IPA as the solvent unexpectedly produced the hydroalkoxylation product **8**^{xv} along with the Wacker oxidation product **7**, which most likely originates from an H₂O₂ mediated pathway (Figure 3, B).^{xvi} Further investigation of these results demonstrates that the hydroalkoxylation product **8** forms *via* initial hydrochlorination of the alkene followed by nucleophilic substitution with the alcohol.^{xv} Interestingly, decreasing the amount of CuCl₂ slows the formation of the hydroalkoxylation product. Thus, we believed that IPA would be an effective solvent and hydride source for the reductive coupling reaction as long as the concentration of CuCl₂ was low enough to prevent formation of **8**.

In addition to the solvent, the nature of the coupling partners should play an important role in the outcome of the reaction. Therefore, styrene derivatives were selected because of the inability of the olefin to isomerize.^{xvii} Previously, our laboratory has found styrenes to be excellent model substrates for the development of new reactions and catalyst systems. Information garnered from the use of styrene substrates can subsequently be employed to expand the scope of these systems to include a wide variety of alkenes.ⁱⁱⁱ Furthermore, the

second coupling partner needed to readily undergo transmetalation and had to be stable to the alcoholic solvent and O₂ atmosphere. Many organometallic reagents require a base to facilitate transmetalation with Pd^{II},^{ix} but the presence of exogenous base has been found to affect the rate of alcohol oxidation.^{xiii} Therefore, PhSnBu₃ (**9a**) was initially selected as the organometallic coupling partner because it should be stable under the reaction conditions and does not require base to facilitate transmetalation.^{xviii}

3. Results and discussion

3.1. Organostannanes optimization and scope

Exposure of 4-methylstyrene (**5a**) and PhSnBu₃ (**9a**) to a solution of catalytic Pd[(–)-sparteine]Cl₂ and CuCl₂ in IPA under an O₂ atmosphere led to the desired hydroarylation product **10a** in 23% GC yield as a >25:1 mixture of regioisomers (Equation 2).^{ix, xix} As expected, a significant amount of the oxidative Heck product **11** was formed (18% GC yield), which is proposed to originate from initial transmetalation of the Pd^{II} catalyst.^{xid} Interestingly, the diarylation product **12**, which is the addition of two aryl groups across the alkene, was formed in 20% GC yield. The diarylation product is believed to originate from the same Pd^{II}-alkyl intermediate that leads to the Heck product. However, instead of undergoing β-hydride elimination, the Pd^{II}-alkyl species reacts with another equivalent of the organostannane and subsequent reductive elimination generates the product. While diarylation of alkynes and norbornene have been previously reported, this is the first example of a diarylation reaction of a styrene derivative.^{xx} This unique transformation is currently under further investigation in our laboratory. Additionally, the oxidative homocoupling product **13**^{xii} was formed in 9% GC yield and the Wacker oxidation product **7**^{14–16} was generated in 3% GC yield.

Since the major byproducts originate from either the oxidative Heck or diarylation reactions, we focused our attention on minimizing the formation of these compounds. Based upon the

proposed mechanism, a decrease in the relative rate of initial transmetalation compared to alcohol oxidation/alkene insertion was desired to improve the selectivity for the reductive coupling product. Previously, the addition of Cu salts to Pd⁰-catalyzed Stille couplings had been shown to facilitate transmetalation.^{xviii} Therefore, CuCl₂ was removed from the catalytic conditions leading to a decrease in conversion, which was attributed to catalyst decomposition (Table 1, entry 2). However, the ratio of **10a** to **11** improved to 2.4:1 and, thus, Cu-free conditions were pursued. However, without CuCl₂ to promote catalyst regeneration, we needed to identify an additive to help stabilize the catalyst. Previously our laboratory conducted mechanistic studies on the aerobic oxidation of alcohols with Pd[(–)-sparteine]Cl₂, which demonstrated a significant rate enhancement and improved catalyst stability when exogenous (–)-sparteine was used.^{xiii} Based upon these data, 40 mol% exogenous (–)-sparteine was evaluated and led to an increase in selectivity for the hydroarylation product compared to Heck with a ~28:1 ratio in low conversion (entry 3). Since the aerobic oxidation of alcohols with Pd[(–)-sparteine]Cl₂ is normally conducted at elevated temperatures,^{xiii} the reaction was performed at 60 °C, which led to 63% conversion of **5a** and a 45% GC yield of the hydroarylation product (entry 4).

Considering only 63% conversion of the substrate was observed, a time course analysis of the reaction was performed (Figure 4, A). A significant retardation of the rate was observed as the reaction progressed, suggesting either catalyst decomposition or inhibition. Previously, Waymouth and co-workers^{xxi} and Stahl and co-workers^{xxii} have demonstrated that ligands commonly employed in Pd oxidase catalysis can be consumed via oxidation. Therefore, we hypothesized that a possible inhibitor could originate from oxidation of (–)-sparteine. In the past, (–)-sparteine-*N*-oxide (**14a** and **b**) has been synthesized by treating (–)-sparteine with H₂O₂, which is the product of O₂ reduction (Figure 4, B).^{xxiii} To test our hypothesis, two experiments were performed with added 20 mol% (–)-sparteine-*N*-oxide at two different concentrations of (–)-sparteine. With both sets of conditions, a comparable decrease in the conversion of **5a** was observed (Table 1, compare entries 4–6). These results suggest that (–)-disproportionate H₂O₂ reduce the amount of (–)-sparteine-*N*-oxide generated during the catalysis. Previously, MnO₂ has been shown to disproportionate H₂O₂.^{xxiv} Excitingly, use of 75 mol% MnO₂ led to **10a** in 81% GC yield at >99% conversion (entry 7). Interestingly, addition of MnO₂ and (–)-sparteine-*N*-oxide led to similar conversion and GC yield compared to the absence of MnO₂ (entry 8). It should be noted that the reaction does not effectively proceed without the addition of (–)-sparteine even in the presence of MnO₂.

To test our hypothesis that MnO₂ was reducing the amount of (–)-sparteine-*N*-oxide, two reductive coupling reactions were performed using the optimal catalytic conditions except one reaction did not contain MnO₂ (Table 1, entries 4 and 7). After completion of the reaction, the crude mixtures were analyzed by ESI-MS. Both (–)-sparteine-*N*-oxide and (–)-sparteine were observed and the ratio of the respective peak heights were measured. However, the peak heights are dependent on ionization potential and do not directly reflect the absolute quantity of each species in the mixture. The ratio of peak heights of (–)-sparteine-*N*-oxide to (–)-sparteine was found to be 0.50 for the reaction performed with 75 mol% MnO₂ compared to 0.64 for the MnO₂ free conditions, which is an approximate 28% difference. These data support our hypothesis that MnO₂ disproportionates H₂O₂ and reduces the amount of (–)-sparteine-*N*-oxide generated during the catalysis.

Attempts to scale the reaction from 0.2 to 1 mmol led to inconsistent conversion and GC yields of **10a**. For example, the reductive coupling reaction performed on 0.2 mmol scale produced **10a** in 81% GC yield (Table 2, entry 1). However, conducting the same reaction on 1 mmol scale produced **10a** in only 24% GC yield (entry 2). This discrepancy led us to question if there is not enough O₂ present in the liquid phase and causes catalyst decomposition. Previously, Stahl and co-workers have found that a large liquid to gas surface area is required to achieve

effective mass transport of O₂ into solution in the Pd^{II}-catalyzed aerobic oxidation of alcohols with DMSO, which could be a problem in this case.^{xxv} Additionally, the solubility of O₂ in isopropanol may be decreased at 60 °C.^{xxvi}

In order to test our hypothesis, the pressure of O₂ was increased from balloon (~1.1 atm) to 25 psi (1.7 atm), and this led to a significant improvement of the GC yield of **12a** on 1 mmol scale (Table 2, entry 3). Even with the increased O₂ pressure, MnO₂ was still required to achieve effective catalysis (compare entries 3 and 4). The optimization studies demonstrate that ligand oxidation can inhibit the catalysis and efficient mass transport of O₂ is required to prevent catalyst decomposition.^{xxvii} Even with the improved catalytic conditions, a large diameter flask is still required to obtain acceptable yields of the reductive coupling product. Since this is a triphasic reaction, vigorous stirring is also essential to ensure a sufficient dispersion of MnO₂ and efficient mass transport of O₂.

After identifying suitable catalytic conditions, the initial scope of the Pd^{II}-catalyzed reductive coupling of arylstannanes and styrenes was explored. This methodology can be utilized to access a variety of diarylmethine containing compounds, which are prevalent in biologically active small molecules.^{xxviii} Many of these compounds would be difficult to selectively synthesize using other types of hydroarylation methodologies.^{xxix} Notably, all of the reactions are highly regioselective (>25:1) for addition of the arene to the α -carbon of the styrene. A variety of arylstannanes were competent coupling partners where the steric and electronic nature did not have a significant impact upon the yield of the reaction (Figure 5). In contrast to many previously reported Lewis acid-catalyzed hydroarylation reactions,^{xxix} substrates that contain acid sensitive functional groups can be employed. The scope of the reaction was not limited to arylstannanes, but vinylstannanes were utilized to perform an overall hydrovinylation reaction.^{xxx} Under these conditions, simple alkenes do not lead to appreciable yields of the desired product because of alkene isomerization.^{xvii} Additionally, all of the products were generated with <5% ee even though a chiral ligand was employed.

3.2. Organoboronic esters optimization and scope

In addition to the use of organostannanes, we were interested in expanding the scope of the reductive coupling reaction to include organoboronic acids or esters. Boronic acids are highly attractive coupling partners because of the low toxicity of the byproducts and excellent functional group compatibility.^{xxxii} However, the mechanism of transmetalation is proposed to be more complex as compared to organostannanes. For example, an exogenous base is typically required to activate the organoboronic acid or ester (**A**), which yields intermediate **B** (Figure 6, A).^{xxxii} The activated species then reacts with R-Pd^{II}-X via a proposed four-membered transition state **C**. Integrating an exogenous base to facilitate transmetalation of an organoboronic acid or ester into the reductive coupling reaction was thought to be a significant challenge. The reason for this was based upon the proposed mechanism for the aerobic Pd-catalyzed oxidation of alcohols wherein exogenous base has been shown to accelerate the rate of alcohol oxidation.^{xiii} The proposed mechanism entails initial coordination of the alcohol to the active catalyst **D**, which leads to species **E**. Subsequent deprotonation of the bound alcohol by an exogenous base produces Pd-alkoxide **F**, which undergoes β -hydride elimination to generate Pd-hydride **G**. Specifically, the rate limiting step of the Pd[(–)-sparteine]Cl₂ catalyzed oxidation of alcohols with low concentrations of exogenous base was found to be deprotonation of intermediate **E**.^{xiii} However, when an exogenous base is employed, an acceleration of the rate of the reaction is observed, which is attributed to a change to β -hydride elimination of **F** as the rate limiting step.

With this additional requirement in mind, we attempted to identify catalytic conditions for the reductive coupling of styrenes and organoboronic acids. Initially, we evaluated PhB(OH)₂ (**BA**) with the conditions developed for organostannanes.^{ix} This led to the desired product

10a in poor yield.^{xxxiii} During the course of the reaction, a black precipitate was observed, which suggested decomposition of the Pd catalyst. Therefore, we decided to evaluate different ligands, which should better stabilize the catalyst. Previously, our group has shown that the use of *N*-heterocyclic carbene (NHC) ligands led to highly active catalyst systems for the aerobic oxidation of alcohols.^{xiid} In this case, the [Pd(**SiPr**)Cl₂]₂ catalyst was employed to couple **5a** and **BA** in combination with exogenous (–)-sparteine and *t*BuOK, which led to the desired product **10a** in 8% GC yield (Figure 7). Even with the use of an NHC ligand, catalyst decomposition was observed. This led us to question if the acidity of the boronic acid was inhibiting the reaction or was causing catalyst decomposition.

To test our hypothesis, we evaluated the pinacol derived phenyl boronic ester (**PE**) under the same conditions. This led to a higher yield of the desired product and through further optimization it was found that the use of 2.5 equivalents of **PE** produced **10a** in 64% GC yield. Even though the yield was significantly improved, the reaction required 24 h, which led us to question if the large size of **PE** was reducing the rate of the reaction. Therefore, both the propanediol (**PD**) and the ethylene glycol (**EG**) derived boronic esters were evaluated. Interestingly, **PD** yielded the desired product in 32% GC yield, but the use of 3 equivalents of **EG** generated **10a** in 91% GC yield.

After identifying the optimal boronic ester derivative for the reductive coupling reaction, the nature of the exogenous base was evaluated. Initially, a significant number of nitrogen containing bases were tested, but all of the bases, except (–)-sparteine, did not lead to effective catalysis. However, without (–)-sparteine, only 2% conversion of **5a** was measured and suggests that (–)-sparteine is playing an important role in the reaction (Table 3, entry 1). Therefore, we optimized the concentration of (–)-sparteine and found 6 mol% produced the highest yield of the desired product. Interestingly, removal of *t*BuOK led to >99% conversion of **5a** and 78% GC yield of **10a** (entry 3). The lower selectivity for the reductive coupling product suggests that both bases are required to achieve higher yields. Based upon these results, we evaluated higher concentrations of *t*BuOK, which decreased the yield of **10a** (entries 4 and 5). After identifying the optimal concentration of *t*BuOK, we questioned if other inorganic bases would be more effective. Therefore, we evaluated five different inorganic bases, which led to lower yields of **10a** compared to *t*BuOK (entries 6–10). The optimization studies showcase the importance of the nature of the boronic ester derivative and that both (–)-sparteine and *t*BuOK are required to achieve optimal yields of the reductive coupling product.

Using the optimized catalytic conditions, the scope of the reductive coupling of boronic ester derivatives was investigated. All of the diarylmethine containing compounds synthesized with this method had >25:1 selectivity. The electronic nature of the styrene did not significantly impact the yield of the transformation (Figure 8). However, electron donating groups on the arylboronic ester reduced the rate of the reaction leading to lower yields. Acid sensitive functional groups, such as an acetal, are stable under the conditions and are readily removed during workup. Unfortunately, under these conditions vinylboronic ester derivatives did not undergo reductive coupling. Additionally, straight chain alkenes rapidly isomerizes.^{xvii} Finally, considering that the chiral substance (–)-sparteine is employed, the enantioselectivity was measured for several reductive coupling products revealing less than 5% ee using either boronic ester derivatives or organostannanes.

3.3. Mechanistic studies

After exploring the initial scope of the reductive coupling reaction of styrenes with both organostannanes and organoboronic esters, we had several mechanistic questions. The first question we addressed was where does the hydrogen atom incorporated into the alkene framework originate from? This was explored utilizing two isotopic labeling experiments similar to those used for the alkene hydroalkoxylation reaction (Figure 1, A).^{iv} The reductive

coupling of **5a** and **9a** was performed with $(\text{CH}_3)_2\text{CH}(\text{OD})$ as the solvent (Figure 9).^{ix} As expected, no deuterium was incorporated into the product **10a**, which rules out the involvement of acidic protons in the catalysis. In contrast, employment of $(\text{CH}_3)_2\text{CD}(\text{OH})$ as the solvent led to three hydroarylation products, which were quantified by ^1H NMR and GC/MS. Isotopomers **16a** and **16b** account for 70% and 22% of the isolated products respectively and the remaining 8% is the unlabeled product **10a**.

The labeling studies support our original mechanistic proposal wherein oxidation of the alcoholic solvent initiates the catalysis and yields the Pd^{II} -hydride intermediate **B** (Figure 2, C). The formation of two isotopomers suggests that the alkene inserts into the Pd^{II} -hydride species at both the α - and β -position. This leads to intermediates **D** and **D'**, which equilibrate *via* β -hydride elimination. However, when $(\text{CH}_3)_2\text{CD}(\text{OH})$ is employed as the solvent, deuterium is incorporated into the styrene during the course of the reaction, which suggests that the alkene can dissociate from **C**. This process implies that the Pd^{II} -deuteride can exchange with the alkene substrate *via* an insertion/ β -hydride elimination pathway to generate a Pd^{II} -hydride intermediate. This may account for the formation of 8% of the hydroarylation product, which does not contain any deuterium.

Since the deuterium labeling studies support the formation of both intermediates **D** and **D'**, this led to the next mechanistic question of why is the regioselectivity >25:1 for substitution of the arene at the benzylic position of the styrene? The high regioselectivity suggests that only **D** leads to product even though both isomers are proposed to form. To account for this observation, we thought intermediate **D**, which is a $\text{Pd}^{\text{II}}\text{-}\eta^1\text{-alkyl}$ species, can be stabilized by converting to a $\text{Pd}^{\text{II}}\text{-}\eta^3\text{-}\pi\text{-benzyl}$ intermediate when using a styrenyl substrate.^{xxxiv} To test our hypothesis, we believed a conjugated diene substrate would lead to a similar $\text{Pd}^{\text{II}}\text{-}\eta^1\text{-alkyl}$ intermediate that can be stabilized *via* a possible $\text{Pd}^{\text{II}}\text{-}\eta^3\text{-}\pi\text{-allyl}$ species (Figure 10). Reaction of diene **17** with vinylstannane **9f** yields the reductive coupling product in 40% yield as a single regioisomer and 1:1 mixture of diastereomers.

The deuterium labeling experiments suggest the possible formation of a well defined $\text{Pd}^{\text{II}}[(-)\text{-sparteine}](\text{H})\text{X}$ intermediate **B** (Figure 2). Since the bidentate ligand $(-)\text{-sparteine}$ is employed, this causes the hydride and anionic ligand to be *cis* to each other, which is the required geometry for the complex to undergo reductive elimination to generate $\text{Pd}^0[(-)\text{-sparteine}]$. To the best of our knowledge, there are no known isolated *cis*- $\text{Pd}^{\text{II}}\text{-(H)X}$ complexes, which can be attributed to facile reductive elimination of HX .^{xxxv} This led to the question does the ligand, $(-)\text{-sparteine}$, in combination with the polar alcoholic solvent facilitate chloride dissociation to generate a cationic Pd^{II} -hydride intermediate, which does not readily undergo reductive elimination?^{xxiii} To investigate this question, we attempted to synthesize and characterize a cationic $\text{Pd}^{\text{II}}[(-)\text{-sparteine}](\text{H})(\text{X})$ complex.

A variety of strategies have been previously reported to access *trans*- Pd^{II} -hydrides and we believed the use of a non-coordinating counterion, such as triflate, would help prevent reductive elimination of HX .^{xxxv} However, attempts to synthesize $\text{Pd}^{\text{II}}[(-)\text{-sparteine}](\text{H})(\text{OTf})$ using a variety of different reported methods to access *trans*- Pd^{II} -hydrides led to the formation of a black precipitate.^{xxxvi} These results suggest that the Pd^{II} -hydride may have been generated, but underwent reductive elimination to yield a Pd^0 complex, which decomposed. Since the initial attempts did not employ a polar alcoholic solvent, we decided to attempt to synthesize the desired complex *via* an alcohol oxidation.^{xxxv} Therefore, the $\text{Pd}^{\text{II}}[(-)\text{-sparteine}](\text{OTf})_2$ complex (**20**) was synthesized by treatment of $\text{Pd}^{\text{II}}[(-)\text{-sparteine}]\text{Cl}_2$ with two equivalents of AgOTf . The $\text{Pd}^{\text{II}}[(-)\text{-sparteine}](\text{OTf})_2$ complex was subsequently dissolved in isopropanol, which unfortunately led to the formation of a black precipitate (Figure 11, A).

The formation of a black precipitate in all of our attempts suggests that the $\text{Pd}^{\text{II}}[(-)\text{-sparteine}](\text{H})(\text{X})$ complex is not stable and undergoes facile reductive elimination to generate $\text{Pd}^0[(-)\text{-sparteine}]$ and HX . This led to the question how does the reductive coupling reaction progress effectively if the proposed catalytic intermediate **B** readily undergoes reductive elimination (Figure 2, C)? One of the key differences between the stoichiometric studies we performed and the catalytic conditions is the presence of an alkene. Previously, it has been shown that cationic Pd^{II} -hydride species, which are not stable, can be trapped by reacting with conjugated dienes.^{xxxvii} Based upon this report, we dissolved the $\text{Pd}^{\text{II}}[(-)\text{-sparteine}](\text{OTf})_2$ complex (**20**) in an isopropanol solution that contained 10 equivalents of styrene (Figure 11, B). The desired $[(-)\text{-sparteine}]\text{Pd}^{\text{II}}\text{-}\eta^3\text{-}\pi\text{-benzyl}(\text{OTf})$ complex (**21**) was generated and characterized by ESI-HRMS. Unfortunately, attempts to isolate the complex led to the formation of a black precipitate and ^1H and ^{13}C NMR analysis of the complex generated *in situ* reveals the presence of multiple unidentifiable species.

The generation of complex **21** supports our mechanistic hypothesis and suggests that the unstable Pd^{II} -hydride intermediate **B**, which is generated during the catalysis, undergoes competitive alkene insertion instead of reductive elimination of HX . This proposal led to the question of how efficient is the alcohol oxidation compared to alkene functionalization? To investigate this question, a time course analysis of the reductive coupling of styrene **5a** and organoboronic ester **15a** was conducted with *sec*-butanol as the solvent (Table 4).^{xxxiii} The higher molecular weight alcohol allows for quantification of the amount of ketone product being formed by GC. The GC yields of the oxidized alcohol product butan-2-one (**22**) and the reductive coupling product **10a** as well as the percent of **5a** remaining were measured over time. At 6 h or about 50% conversion of **5a**, the GC yield of **10a** and **22** are similar, which indicates that oxidation of one alcohol yields one product. These data suggest that the Pd^{II} -hydride species undergoes faster alkene insertion than reductive elimination.^{xxxviii} However, as more of the alkene substrate is consumed, reductive elimination or other processes become competitive.

During the optimization studies conducted on the reductive coupling of organoboronic esters, it was found that three equivalents of the arylboronic ester derivative were required to achieve acceptable yields. This observation led to another question we wanted to investigate, which is why are multiple equivalents of the transmetalating agent required for organoboronic esters, but not for organostannanes? In both cases, the transmetalation agent can undergo oxidative homocoupling. However, arylboronic esters can be oxidized to the respective phenol derivatives by H_2O_2 generated *in situ*.^{xiid} We initially hypothesized that the excess boronic ester may be oxidized under the catalytic conditions. Therefore, as the reaction progressed, the fate of the boronic ester was investigated. At 6 h, approximately two equivalents of **15a** were consumed (Table 4). Interestingly, at 14 h, a 139% GC yield of phenol (**23**) was measured, which supports our hypothesis that the excess **15a** required is oxidized by H_2O_2 . Additionally, oxidative homocoupling of **15a** converts approximately 0.28 equivalents of **15a** to biphenyl (**13**). The time course highlights the undesired side reactions that lead to the requirement of multiple equivalents of organoboronic esters. Typically organostannanes are more oxidatively stable to H_2O_2 , which allows for lower quantities to be employed. However, the excess boronic ester scavenges H_2O_2 , which potentially prevents oxidation of the exogenous $(-)\text{-sparteine}$ that would inhibit the catalysis as observed with the use of organostannanes.

Possible Role of (-)-sparteine

(3)

The last mechanistic question we wanted to address originated from the optimization studies. Specifically, why is (-)-sparteine required to achieve catalysis considering other amines such as 2,2'-bipyridine, TMEDA, and TEA are not viable? One of our initial hypotheses was that (-)-sparteine was responsible for breaking up the dimeric $[Pd^{II}(SiPr)Cl_2]_2$ catalyst. To investigate the plausibility of our proposal, we dissolved $[Pd^{II}(SiPr)Cl_2]_2$ and two equivalents of (-)-sparteine in 1,2-dichloroethane (DCE) and heated the mixture to reflux (Equation 3). After 2 h, the solution was analyzed by ESI-MS and one major Pd species was observed [$m/z (M+H)^+ = 801.3$]. The molecular weight corresponds to the $Pd^{II}[(-)\text{-sparteine}](SiPr)Cl_2$ complex (**24**). We propose that the NHC ligand is *trans* to the monodentate (-)-sparteine ligand based upon the *trans* geometry of previously reported $Pd^{II}(NHC)(pyridine)Cl_2$ complexes.^{xxxix} However, attempts to isolate complex **24** were unsuccessful, but instead $[Pd^{II}(SiPr)Cl_2]_2$ and free (-)-sparteine were obtained. This suggests that complex **24** is in equilibrium with the dimer and (-)-sparteine. Under these conditions, $Pd^{II}[(-)\text{-sparteine}]Cl_2$ was not detected by ESI-MS. These data suggest the possibility of the role of (-)-sparteine is to break up the dimer or the free nitrogen of complex **24** may act as an intramolecular base.^{xiii}

4. Conclusion

Based upon mechanistic insight garnered from the study of the hydroalkoxylation reaction of vinyl phenols, we were able to design and development a fundamentally new reductive cross-coupling reaction of styrenes and organometallic reagents. This transformation is proposed to proceed by initial oxidation of the alcoholic solvent followed by alkene insertion to yield a Pd^{II} -alkyl species, which subsequently undergoes transmetalation with either an organostannane or an organoboronic ester to ultimately generate a new carbon-carbon bond. Overall, this process rapidly yields a valuable diarylmethine core structure *via* a sp^3 - sp^2 cross-coupling in high regioselectivity, which is proposed to arise from stabilization *via* a Pd^{II} - η^3 - π -benzyl complex. One interesting aspect of this transformation is the use of O_2 as a terminal oxidant in what is an overall formal reduction of the alkene. This unique mode of catalysis is currently being investigated in our laboratories in the development of new hydrofunctionalization reactions as well as applications to asymmetric catalysis.

5. Experimental section

5.1. General considerations

Isopropanol was dried by refluxing over calcium oxide for 12 h followed by fractional distillation. $Pd[(-)\text{-sparteine}]Cl_2$ was synthesized according to a previously reported procedure.^{xi} (-)-sparteine was prepared from (-)-sparteine sulfate pentahydrate according to a previously reported procedure.^{xlii} HRMS were obtained with either an ESI or APCI source with a Waters TOF. GC separations were performed with an HP6890 GC with a flame ionization detector equipped with a DB-5 column using a 50:1 split. *While our laboratory has*

not encountered any problems, great caution should be taken when heating flammable solvents and adding solid metals to a flammable solution in the presence of O₂.

5.2. General reductive coupling procedure of alkenes and organostannanes

The procedure and characterization data for the synthesis of compounds **10a–j** has been previously reported.^{ix} The following general procedure was used to synthesize compounds **10a–j**: A three-way joint was fitted to the side arm of an oven dried 100 mL thick-wall glass pressure vessel equipped with a stir bar. An O₂ tank was connected to the three-way joint and O₂ was flowed through the vessel. To the vessel, was added 65.2 mg of MnO₂ (0.750 mmol, 0.750 equiv.), 4.30 mL of isopropanol, 200 µL of a 2.00 M solution of (–)-sparteine (0.400 mmol, 0.400 equiv.) in isopropanol, 1.00 mmol of the alkene (1.00 equiv.), and 1.50 mmol of the organostannane (1.50 equiv.). The vessel was sealed, pressurized to 25 psi, evacuated *via* water aspiration, and re-pressurized to 25 psi O₂. This procedure was repeated three times. The vessel was sealed and the mixture was stirred **vigorously** for ca. 20 min at room temperature at 25 psi O₂. The vessel was opened and O₂ was flowed through the vessel. To the stirred mixture, was added 10.3 mg of Pd[(–)-sparteine]Cl₂ (0.0250 mmol, 0.0250 equiv.). The vessel was immediately pressurized to 25 psi O₂ and was sealed. The three-way joint was removed and the reaction mixture was stirred **vigorously** for 5 min at room temperature. The mixture was then heated to 60 °C in an oil bath and was stirred **vigorously** for 18 h. The vessel was removed from the oil bath, cooled to room temperature, and the pressure released. To the reaction mixture, was added 5.00 mL of a 1.00 M solution of aqueous NaOH and was stirred for 1 h.^{xlii} The mixture was filtered through Whatman filter paper, rinsed with ca. 10.0 mL of Et₂O, and was transferred to a separatory funnel. The aqueous layer was extracted three times with 20.0 mL of Et₂O, all of the organic extracts were combined, washed with 40.0 mL of brine, and dried over MgSO₄. The mixture was filtered and the solvent was removed *in vacuo*. The product was purified *via* flash chromatography.

5.3. General reductive coupling procedure of alkenes and organoboronic esters

The procedure and characterization data for the synthesis of compounds 10k-r has been previously reported.^{xxxiii} The following general procedure was used to synthesize compounds 10k-r: To an oven dried 100 mL Schlenk flask equipped with a stir bar, was added 4.3 mg of [Pd(SiPr)Cl₂]₂ (0.0038 mmol, 0.0076 equiv.), 300 µL of a 100 mM solution of (–)-sparteine (0.030 mmol, 0.060 equiv.) in isopropanol, and 7.4 mL of isopropanol. A dried water condenser and a three-way joint fitted with a balloon of O₂ were installed on the flask. The flask was evacuated *via* water aspiration and refilled with oxygen three times and the mixture was stirred vigorously for ca. 20 minutes at room temperature under an O₂ atmosphere. To the mixture, was added 1.0 mL of a 500 mM solution of the alkene (0.50 mmol, 1.0 equiv.) in isopropanol, 1.0 mL of a 1.5 M solution of the organoboronic ester (1.5 mmol, 3.0 equiv.) in isopropanol, and 300 µL of a 100 mM solution of potassium *tert*-butoxide (0.030 mmol, 0.060 equiv.) in isopropanol. The mixture was then heated to 55 °C and was stirred vigorously for 24 hours. The reaction mixture was cooled to room temperature. The mixture was concentrated under reduced pressure. To the residue, was added 10 mL of water and was extracted two times with 10 mL of hexanes. To the combined organic extracts, was added 1.0 g of magnesium sulfate and 1.00 g of silica. The mixture was stirred at room temperature for 10 minutes, filtered, washed with hexanes, and concentrated under reduced pressure to yield a colorless oil. The product was purified *via* flash chromatography.

5.4. Synthesis of Pd[(–)-sparteine](OTf)₂ (**20**)

To a flame dried 100 mL round bottom flask equipped with a stir bar under a nitrogen atmosphere, was added 618 mg of Pd[(–)-sparteine]Cl₂ (1.50 mmol, 1.00 equiv.) and 60.0 mL of CH₂Cl₂. The orange solution was stirred for 5 min and 771 mg of silver triflate (3.00 mmol,

2.00 equiv.) was added. The cloudy orange solution was stirred for 1 h and the precipitate was removed by filtering the solution through Celite rinsing with CH_2Cl_2 . The solution was concentrated *in vacuo* to approximately 10 mL and ca. 10 mL of hexanes were added until the solution turned cloudy. The solvent was removed *in vacuo* to yield an orange solid, which was rinsed with hexanes and the residual solvent was removed by applying a vacuum to the solid. Yield: 76% (730 mg); orange solid mp: 120–123 °C (decomposition); IR 3140, 2941, 2870, 1453, 1271, 1224, 1161, 1025, 982, 625, 576; HRMS (ESI/APCI) m/z (M-OTf)⁺ calcd.: 489.0646 obsd.: 489.1531.

5.5. Attempted hydride synthesis *via* isopropanol and Pd[(-)-sparteine](OTf)₂

To a flame dried 5 mL round bottom flask equipped with a stir bar under a nitrogen atmosphere, was added, 3.2 mg of Pd[(-)-sparteine](OTf)₂ (0.0050 mmol, 1.0 equiv.) and 500 μL of isopropanol. The orange mixture was stirred for 10 min and a black precipitate began to form. The mixture was diluted by adding 1 μL to 1 mL of isopropanol. The solution was infused into an ESI-MS instrument and no identifiable Pd complexes were observed.

5.6. Synthesis of the Pd^{II}- η^3 - π -benzyl complex from Pd[(-)-sparteine](OTf)₂ (21)

To a flame dried 5 mL round bottom flask equipped with a stir bar under a nitrogen atmosphere, was added, 5.2 mg of styrene (0.050 mmol, 10 equiv.) and 500 μL of isopropanol. Next, 3.2 mg of Pd[(-)-sparteine](OTf)₂ (0.0050 mmol, 1.0 equiv.) was added and the orange mixture was stirred for 10 min. The mixture was diluted by adding 0.5 μL to 1 mL of isopropanol. The solution was infused into the (APCI/ESI)-HRMS instrument. HRMS (ESI/APCI) m/z (M)⁺ for ¹⁰⁶Pd calcd.: 445.1835 obsd.: 445.1841. Unfortunately, attempts to isolate the complex result in the formation of black precipitate. Additional attempts to employ (CD₃)₂CD(OD) as the solvent to characterize the complex by ¹H and ¹³C NMR indicated the presence of multiple species, which could not be identified.

Acknowledgments

This work was supported by the National Institutes of Health (Grant NIGMS RO1 GM3540). M.S.S. thanks the Dreyfus Foundation (Teacher-Scholar) and Pfizer for their support. K.M.G. thanks Sanofi-Aventis for a graduate research fellowship. Y. I. thanks Kyorin Co., Ltd. for financial support. We would like to thank Dr. Jim Muller for assistance with the ESI-MS experiments. We are grateful to Johnson Matthey for the gift of various Pd salts.

References and notes

- i. Beller M, Seayad J, Tillack A, Jiao H. *Angew Chem, Int Ed* 2004;43:3368–3398.
- ii. (a) Tsuji, J. *Palladium Reagents and Catalysts*. John Wiley & Sons Inc; Hoboken, NJ: 2004. (b) Stahl SS. *Angew Chem, Int Ed* 2004;43:3400–3420. (c) Cornell CN, Sigman MS. *Inorg Chem* 2007;46:1903–1909. [PubMed: 17348721]
- iii. (a) Cornell CN, Sigman MS. *J Am Chem Soc* 2005;127:2796–2797. [PubMed: 15740083] (b) Cornell CN, Sigman MS. *Org Lett* 2006;8:4117–4120. [PubMed: 16928088]
- iv. (a) Gligorich KM, Schultz MJ, Sigman MS. *J Am Chem Soc* 2006;128:2794–2795. [PubMed: 16506746] (b) Zhang Y, Sigman MS. *Org Lett* 2006;8:5557–5560. [PubMed: 17107071] For an example of a Pd^{II}-catalyzed coupled alcohol oxidation/alkene hydrogenation, see: (c) Tsuchiya Y, Hamashima Y, Sodeoka M. *Org Lett* 2006;8:4851–4854. [PubMed: 17020319]
- v. For examples of metal catalyzed alkene hydroalkoxylation reactions, see: (a) Qian H, Han X, Widenhoefer RA. *J Am Chem Soc* 2004;126:9536–9537. [PubMed: 15291546] (b) Yang CG, Reich NW, Shi Z, He C. *Org Lett* 2005;7:4553–4556. [PubMed: 16209477] (c) Coulombel L, Favier I, Dunach E. *Chem Commun* 2005:2286–2288. (d) Yang CG, He C. *J Am Chem Soc* 2005;127:6966–6967. [PubMed: 15884936]
- vi. For an example of a Pd(0)-catalyzed hydroalkoxylation, see Matsukawa Y, Mizukado J, Quan H, Tamura M, Sekiya A. *Angew Chem, Int Ed* 2005;44:1128–1130.

- vii. (a) For a review of quinone methides in synthesis, see: Van De Water RW, Pettus TRR. *Tetrahedron* 2002;58:5367–5405. [PubMed: 19079773] (b) For the use of stoichiometric Pd(II)/Cu(II) to generate a quinone methide in the elegant synthesis of carpanone, see: Chapman OL, Engel MR, Springer JP, Clardy JC. *J Am Chem Soc* 1971;93:6696–6698.
- viii. (a) Stahl SS. *Science* 2005;309:1824–1826. [PubMed: 16166508] (b) Gligorich KM, Sigman MS. *Angew Chem, Int Ed* 2006;45:6612–6615.
- ix. Gligorich KM, Cummings SA, Sigman MS. *J Am Chem Soc* 2007;129:14193–14195. [PubMed: 17963397]
- x. Netherton, MR.; Fu, GC. *Top Organomet Chem. Vol. 14.* Springer Verlag; Berlin: 2005. Palladium-Catalyzed Cross-Coupling Reactions of Unactivated Alkyl Electrophiles with Organometallic Compounds; p. 85-108.
- xi. For selected examples of the oxidative Heck reaction, see: (a) Hirabayashi K, Ando JI, Nishihara Y, Mori A, Hiyama T. *Synlett* 1999:99–101. (b) Andappan MMS, Nilsson P, Larhed M. *Chem Commun* 2004:218–219. (c) Delcamp JH, Brucks AP, White MC. *J Am Chem Soc* 2008;130:11270–11271. [PubMed: 18671350] For a mechanistic study of the oxidative Heck reaction, see: (d) Enquist PA, Nilsson P, Sjöberg P, Larhed M. *J Org Chem* 2006;71:8779–8786. [PubMed: 17081006]
- xii. For selected examples of Pd^{II}-catalyzed homocoupling of organometallic reagents, see: (a) Alcaraz L, Taylor RJK. *Synlett* 1997:791–792. (b) Smith KA, Campi EM, Jackson WR, Marcuccio S, Naeslund CGM, Deacon GB. *Synlett* 1997:131–132. (c) Yoshida H, Yamaryo Y, Ohshita J, Kunai A. *Tetrahedron Lett* 2003;44:1541–1544. For a mechanistic study of Pd^{II}-catalyzed homocoupling of organoboronic acids, see: (d) Adamo C, Amatore C, Ciofini I, Jutand A, Lakmini H. *J Am Chem Soc* 2006;128:6829–6836. [PubMed: 16719463]
- xiii. (a) Mueller JA, Sigman MS. *J Am Chem Soc* 2003;125:7005–7013. [PubMed: 12783555] (b) Mueller JA, Goller CP, Sigman MS. *J Am Chem Soc* 2004;126:9724–9734. [PubMed: 15291576] (c) Mueller JA, Cowell A, Chandler BD, Sigman MS. *J Am Chem Soc* 2005;127:14817–14824. [PubMed: 16231935] (d) Sigman MS, Jensen DR. *Acc Chem Res* 2006;39:221–229. [PubMed: 16548511]
- xiv. Balija AM, Stowers KJ, Schultz MJ, Sigman MS. *Org Lett* 2006;8:1121–1124. [PubMed: 16524283]
- xv. Podhajsky SM, Sigman MS. *Organometallics* 2007;26:5680–5686. [PubMed: 19779575]
- xvi. Nishimura T, Kakiuchi N, Onoue T, Ohe K, Uemura S. *Perkin Trans 1* 2000:1915–1918.
- xvii. Sen A, Lai TW. *Inorg Chem* 1984;23:3257–3258.
- xviii. (a) For a review of the Stille reaction, see: Espinet P, Echavarren AM. *Angew Chem, Int Ed* 2004;43:4704–4734. (b) Shirakawa E, Nakao Y, Murota Y, Hiyama T. *J Organomet Chem* 2003;670:132–136.
- xix. (a) For a Rh-catalyzed hydroarylation reaction of vinyl pyridines, see: Lautens M, Roy A, Fukuoka K, Fagnou K, Martin-Matute B. *J Am Chem Soc* 2001;123:5358–5359. [PubMed: 11457403] (b) For an example of Pd^{II}-catalyzed hydroarylation reaction of a Michael acceptors, see: Ohe T, Wakita T, Motofusa S-i, Cho CS, Ohe K, Uemura S. *Bull Chem Soc Jpn* 2000;73:2149–2155.
- xx. (a) Oda H, Morishita M, Fugami K, Sano H, Kosugi M. *Chem Lett* 1996:811–812. (b) Fugami K, Hagiwara S, Oda H, Kosugi M. *Synlett* 1998:477–478.
- xxi. Conley NR, Labios LA, Pearson DM, McCrory CCL, Waymouth RM. *Organometallics* 2007;26:5447–5453.
- xxii. Konnick MM, Stahl SS. *J Am Chem Soc* 2008;130:5753–5762. [PubMed: 18393426]
- xxiii. Boczon W, Pieczonka G, Wiewiorowski M. *Tetrahedron* 1977;33:2565–2570.
- xxiv. Larson EJ, Pecoraro VL. *J Am Chem Soc* 1991;113:7809–7810.
- xxv. Steinhoff BA, Stahl SS. *J Am Chem Soc* 2006;128:4348–4355. [PubMed: 16569011]
- xxvi. Fischer K, Wilken M. *J Chem Thermodyn* 2001;33:1285–1308.
- xxvii. Iwasawa T, Tokunaga M, Obora Y, Tsuji Y. *J Am Chem Soc* 2004;126:6554–6555. [PubMed: 15161274]
- xxviii. (a) Barda DA, Wang ZQ, Britton TC, Henry SS, Jagdmann GE, Coleman DS, Johnson MP, Andis SL, Schoepp DD. *Bioorg Med Chem Lett* 2004;14:3099–3102. (b) Moriconi A, Cesta MC, Cervellera MN, Aramini A, Coniglio S, Colagioia S, Beccari AR, Bizzarri C, Cavicchia MR, Locati M, Galliera E, Di Benedetto P, Vigilante P, Bertini R, Allegretti M. *J Med Chem* 2007;50:3984–4002. [PubMed: 17444444]

17665889] (c) Liang H, Wu X, Yalowich JC, Hasinoff BB. *Mol Pharmacol* 2008;73:686–696. [PubMed: 18045852]

- xxix. For selected examples of alkene hydroarylation reactions, see: (a) Youn So W, Pastine Stefan J, Sames D. *Org Lett* 2004;6:581–584. [PubMed: 14961628] (b) Nevado C, Echavarren AM. *Synthesis* 2005:167–182. (c) Anderson LL, Arnold J, Bergman RG. *J Am Chem Soc* 2005;127:14542–14543. [PubMed: 16231885] (d) Han X, Widenhoefer RA. *Org Lett* 2006;8:3801–3804. [PubMed: 16898821] (e) Lapis AAM, Da Silveira Neto BA, Scholten JD, Nachtigall FM, Eberlin MN, Dupont J. *Tetrahedron Lett* 2006;47:6775–6779. (f) Rueping M, Nachtsheim BJ, Scheidt T. *Org Lett* 2006;8:3717–3719. [PubMed: 16898800] (g) Sun G, Sun H, Wang Z, Zhou MM. *Synlett* 2008:1096–1100.
- xxx. For a review of the hydrovinylation reaction, see: RajanBabu TV. *Chem Rev* 2003;103:2845–2860. [PubMed: 12914483]
- xxxi. (a) Nicolaou KC, Bulger PG, Sarlah D. *Angew Chem, Int Ed* 2005;44:4442–4489. (b) Kotha S, Lahiri K, Kashinath D. *Tetrahedron* 2002;58:9633–9695.
- xxxii. (a) Chemler SR, Trauner D, Danishefsky SJ. *Angew Chem, Int Ed* 2001;40:4544–4568. (b) Miyaura N. *J Organomet Chem* 2002;653:54–57.
- xxxiii. Iwai Y, Gligorich KM, Sigman MS. *Angew Chem, Int Ed* 2008;47:3219–3222.
- xxxiv. Johns AM, Utsunomiya M, Incarvito CD, Hartwig JF. *J Am Chem Soc* 2006;128:1828–1839. [PubMed: 16464081]
- xxxv. Grushin VV. *Chem Rev* 1996;96:2011–2033. [PubMed: 11848819]
- xxxvi. (a) Konnick MM, Gandhi BA, Guzei IA, Stahl SS. *Angew Chem, Int Ed* 2006;45:2790–2793. (b) Johns AM, Tye JW, Hartwig JF. *J Am Chem Soc* 2006;128:16010–16011. [PubMed: 17165734]
- xxxvii. Mabbott DJ, Maitlis PM. *J Chem Soc, Dalton Trans* 1976:2156–2160.
- xxxviii. Hills ID, Fu GC. *J Am Chem Soc* 2004;126:13178–13179. [PubMed: 15479044]
- xxxix. O'Brien CJ, Kantchev EAB, Valente C, Hadei N, Chass GA, Lough A, Hopkinson AC, Organ MG. *Chem--Eur J* 2006;12:4743–4748.
- xl. Mandal SK, Sigman MS. *J Org Chem* 2003;68:7535–7537. [PubMed: 12968915]
- xli. Mueller JA, Jensen DR, Sigman MS. *J Am Chem Soc* 2002;124:8202–8203. [PubMed: 12105896]
- xlii. Renaud P, Lacote E, Quaranta L. *Tetrahedron Lett* 1998;39:2123–2126.

(A) Deuterium Labeling Experiments **(B) Proposed Mechanism****Alcohol Oxidation** **Alkene Insertion** **Quinone Methide** **Figure 1.**

(A) Deuterium labeling experiments. (B) Proposed mechanism of the alkene hydroalkoxylation reactions involves coupling an alcohol oxidation to alkene functionalization.

(A) Pd⁰-Catalyzed Cross-Coupling **(B) Pd^{II}-Catalyzed Reductive Cross-Coupling Reaction** **(C) Mechanistic Proposal****Alcohol Oxidation** **Alkene Insertion** **Transmetalation** **(D) Competitive Oxidative Heck Pathway** **Figure 2.**

(A) Traditional Pd⁰-catalyzed cross-coupling with an organic oxidant. (B) Proposed aerobic Pd^{II}-catalyzed reductive coupling reaction and (C) mechanistic hypothesis. (D) Competitive oxidative Heck pathway.

(A) Acetal Formation with Ethanol **(B) Hydroalkoxylation With Isopropanol *via* Hydrochlorination** **Figure 3.**

(A) Exposing styrene **5a** to the alkene hydroalkoxylation conditions with ethanol leads to the formation of the acetal **6**. (B) Employing IPA as the solvent with similar reaction conditions unexpectedly produced the hydroalkoxylation product **8**.

(A) Time Course Analysis of the Reductive Coupling Reaction **(B) Possible Inhibitor: (-)-sparteine-*N*-oxide** **Figure 4.**

(A) Time course analysis of the reductive coupling reaction. (B) The compound (-)-sparteine-*N*-oxide can be synthesized using H₂O₂ and may inhibit the catalysis.

Figure 5.
The initial scope of the reductive coupling reaction of styrenes and organostannanes.

(A) Base Facilitated Transmetalation with Boronic Esters **(B) Base Modulates Rate of Alcohol Oxidation** **Figure 6.**

(A) A base is typically required to facilitate transmetalation of boronic esters *via* a proposed four-member transition state. (B) The proposed mechanism of the Pd-catalyzed aerobic oxidation of alcohols where exogenous base can modulate the rate.

Figure 8.

The initial scope of the reductive coupling reaction of styrenes and ethylene glycol derived boronic ester derivatives.

Deuterium Labeling Experiments **Figure 9.**Deuterium labeling experiments on the reductive coupling of **5a** and PhSnBu_3

Figure 10. Reductive coupling of a diene and **9f**, which proceeds *via* the possible Pd^{II}- η^3 - π -allyl intermediate **19**.

(A) Attempted Pd^{II}-Hydride *via* Alcohol Oxidation **(B) Synthesis of the Pd^{II}- π -Benzyl Complex** **Figure 11.**

(A) Attempted synthesis of a Pd^{II}-hydride complex *via* alcohol oxidation. (B) Synthesis of Pd^{II}- η^3 - π -benzyl complex 21.

Table 1

Optimization for the hydroarylation product **10a**, which led to the discovery of a possible inhibitor.

Entry ^a	X	Y	Temp.	Conv. (%) ^b	10a (%) ^c	10a : 11 ^d
1 ^e	0	0	rt	85	23	1.3 : 1
2	0	0	rt	67	23	2.4 : 1
3	40	0	rt	40	17	28 : 1
4	40	0	60 °C	63	45	27 : 1
5 ^f	20	0	60 °C	37	30	12 : 1
6 ^f	40	0	60 °C	30	22	7.4 : 1
7	40	75	60 °C	>99	81	35 : 1
8 ^f	40	75	60 °C	26	19	7.7 : 1

^aReaction performed on a 0.2 mmol scale.

^bPercent conversion measured by GC using an internal standard.

^cGC yield.

^dRatio of GC yields.

^e7.5 mol% CuCl₂ was added.

^f20 mol% (-)-sparteine-N -oxide was added.

Table 2

Optimization for the reductive coupling product on 1 mmol scale.

Entry	Scale ^a	Y	O ₂	Conv. (%) ^b	10a (%) ^c	10a : 11 ^d
1	0.2	75	balloon	>99	81	35 : 1
2	1.0	0	balloon	40	24	16 : 1
3 ^e	1.0	0	25 psi	63	46	26 : 1
4 ^e	1.0	75	25 psi	94	86	22 : 1

^a Scale in mmol.

^b Percent conversion measured by GC using an internal standard.

^c GC yield.

^d Ratio of GC yields.

^e Reaction was performed in a sealed thick-wall glass pressure vessel.

Table 3

Optimization of the exogenous base for the reductive coupling of **5a** and **EG**.

Entry	X (mol%)	Base	Conv. (%) ^a	10a (%) ^b	10a : 11 ^c
1	6	<i>t</i> BuOK	>99	91	>30 : 1
2 ^d	6	<i>t</i> BuOK	2	1	4.3 : 1
3	0	-	>99	78	23 : 1
4	15	<i>t</i> BuOK	86	76	>30 : 1
5	25	<i>t</i> BuOK	56	49	>30 : 1
6	6	Cs ₂ CO ₃	>99	85	>30 : 1
7	6	K ₂ CO ₃	>99	85	>30 : 1
8	6	KHCO ₃	87	73	17 : 1
9	6	Na ₂ CO ₃	87	75	24 : 1
10	6	CsF	82	74	>30 : 1

^a Percent conversion measured by GC using an internal standard.

^b GC yield.

^c Ratio of GC yields.

^d No (-)-sparteine was added.

Table 4

Time course analysis of the reductive coupling of **5a** and **15a**.

Time (h)	5a (%) ^a	15a (%) ^a	10a (%) ^b	22 (%) ^b	13 (%) ^b	23 (%) ^b
6	47	98	46	47	12	86
14	3	<1	78	112	14	139

^aPercent remaining measured by GC using an internal standard.

^bGC yield measured using an internal standard.