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Recent advancements and challenges of palladium^{II}-catalyzed oxidation reactions with molecular oxygen as the sole oxidant

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Abstract

During the past 10 years there have been significant advances in Pd^{II}-catalyzed oxidation reactions where the use of ligands has led to the development of catalytic systems capable of achieving high turnover numbers, which employ molecular oxygen as the sole stoichiometric oxidant. This Feature article will highlight some of the recent developments in direct molecular oxygen-coupled Pd^{II}-catalyzed oxidation reactions with an emphasis on enhanced catalytic systems and new reactions. Additionally, limitations of current catalytic systems, such as ligand oxidation, are presented and their implications for the development of new reactions are discussed.

Introduction

Oxidation reactions are essential for both functional group manipulation and heteroatom incorporation in the synthesis of biologically relevant compounds. Additionally, newly discovered and significantly improved oxidative processes can have a direct effect on the approaches to and execution of targeted syntheses. Therefore, the development of selective, practical oxidation reactions is a continuing challenge facing chemists in both academia and industry.[1] Recently, this has been reinforced by the *Technology Vision 2020* report published by the Council for Chemical Research. A key consideration in developing oxidation reactions is selection of the stoichiometric oxidant where versatility, expense, and environmental impact need to be addressed. An attractive approach is the use of metal-catalyzed oxidations coupled to a practical terminal oxidant such as molecular oxygen.[2]

In this regard, Pd^{II} catalysts are highly attractive for applications in homogenous catalytic oxidation.[3] This is in part due to their ability to effectively use molecular oxygen as a terminal oxidant and the relatively predictable organometallic reaction manifolds, which can be accessed. The catalysis can be broken down into two distinct half reactions, wherein the first half is oxidation and/or functionalization of the organic substrate, which occurs independently of the catalyst regeneration step (Scheme 1).[4] Molecular oxygen can be used as the terminal oxidant in combination with two equivalents of a Brønsted acid to regenerate the active catalyst with concomitant formation of hydrogen peroxide. These transformations have been termed "oxidase" type reactions because they are inspired by enzyme oxidases wherein substrate oxidation does not occur by oxygen atom transfer.[3a] A powerful aspect of the oxidase type manifold is the ability to develop a wide variety of new catalytic oxidation reactions, which can be coupled to the reduction of molecular oxygen. It should be noted that the reactions need not undergo a "dehydrogenation" process as illustrated in Scheme 1 and is showcased within this Feature article as an emerging area of research for palladium oxidase type processes.

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During the past decade, there have been significant advances in the development of new palladium oxidase reactions and improved catalytic systems with increased turnover numbers. The use of “oxidatively stable” ligands and mechanistic studies of palladium oxidase reactions have both played key roles in these advances by providing insight on how to improve the catalysis. In 2004, Stahl published a comprehensive review of direct molecular oxygen-coupled palladium oxidase reactions, which highlights many of the key advances in catalyst systems and mechanistic understanding.[3a] Since the publication of Stahl’s review, there have been many notable improvements in catalytic systems for known reactions, innovative oxidase processes have been developed, and new mechanistic studies have been performed that are relevant to the field of palladium oxidase catalysis. This feature article is not a comprehensive review of palladium oxidase reactions, but instead will highlight recent important advancements and developments in palladium oxidase catalysis with an emphasis on improved catalytic systems, mechanistic studies, and the development of novel reactions. Specific case studies are presented that showcase both important improvements and current limitations of palladium oxidase reactions, which illustrate the challenges of developing new more efficient direct molecular oxygen-coupled processes.

Alcohol oxidation

The area of Pd^{II}-catalyzed aerobic alcohol oxidations has received a significant amount of attention because the majority of known alcohol oxidation processes require high loadings of toxic metals or are impractical on a large scale.[1,5] Pd^{II}-catalyzed aerobic alcohol oxidations overcome many of these limitations because of the mild reaction conditions, including low catalyst loadings, and the non-toxicity of the byproducts.[3a] However, the first Pd^{II}-catalyzed aerobic alcohol oxidations required co-catalysts, such as Cu^{II} salts, which limited their overall practicality.[6] Blackburn and Schwartz reported the first co-catalyst free direct O_2 coupled Pd^{II}-catalyzed aerobic oxidation of alcohols in 1977.[7] Since that time, numerous systems employing ligands have been developed, which have helped to overcome the need for high pressures of O_2, excessive catalyst loadings, elevated temperatures, and the use of toxic solvents. For example, Sheldon and co-workers disclosed the first aerobic Pd^{II}-catalyzed alcohol oxidation in an aqueous solution, which employs the water-soluble ligand PhenS (1) in combination with $Pd^{II}(OAc)_2$ under 100 bar of air (Fig. 1).[8] More recently, the $Pd^{II}(OAc)_2$–TEA system developed by the Sigman laboratory can oxidize a wide range of alcohols at room temperature under 1 atmosphere of O_2.[9] The use of the Pd^{II}(I*i*Pr)$(OAc)_2(H_2O)$ complex (2), which employs the *N*-heterocyclic carbene (NHC) ligand I*i*Pr with catalytic amounts of an acid, allows for the oxidation of a variety of primary and secondary alcohols under an air atmosphere.9b,c›10 In 2001, the Stoltz11a and Sigman[11b] groups independently disclosed an enantioselective oxidative kinetic resolution of secondary alcohols using the Pd[(−)-sparteine]Cl_2 catalyst with an exogenous base achieving k_{rel} values of up to 47.[12]

The development of ligand-modulated catalytic systems, which do not require the use of a co-catalyst, greatly simplified the catalysis and has allowed for the elucidation of the mechanistic features of these reactions. A significant number of mechanistic studies have been performed by the Sigman,[9c] Stahl,[13] and Stoltz[14] groups. Information garnered from these studies has led to a generally accepted mechanistic proposal for the oxidation illustrated in Fig. 2. The alcoholic substrate initially coordinates to the $L_nPd^{II}X_2$ catalyst (**A**) to generate intermediate **B**. An exogenous base can facilitate deprotonation of the alcohol to yield the Pd^{II}-alkoxide intermediate **C**. Alternatively, an intramolecular deprotonation *via* a 6-membered transition state is proposed when an acetate counter-ion is employed.[9c] Subsequent β-hydride elimination generates the Pd^{II}-hydride intermediate **D**, which undergoes reductive elimination to yield the Pd^0 species **E**. Reoxidation with O_2 and two equivalents of HX completes the cycle.

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Since 2004, many of the advancements in Pd^{II}-catalyzed aerobic alcohol oxidations have been the development of new ligands[15] and improvements to existing catalytic systems.[16] Numerous mechanistic studies have also been conducted, which have uncovered specific details about the role of ligands in the catalysis.[9c,17] Other mechanistic investigations have shed light on some of the current limitations of alcohol oxidations. One such example was disclosed by Stahl and co-workers on the mechanism of the $Pd^{II}(OAc)_2$–DMSO catalyst system.[13a] Initial experiments suggested that at high catalyst concentrations, the rate limiting step was oxidation of Pd^0 to Pd^{II}, which is unusual considering that the Pd^0 intermediate would be the resting state, and this situation would likely result in the precipitation of the catalyst. However, a recent study of this system showcases one of the major limitations of Pd oxidase catalysis, which is efficient mass transport of O_2 into the liquid phase.[13d] By monitoring the amount of O_2 consumed during the course of the reaction, the authors discovered that there were not sufficient amounts of O_2 present in solution in their initial studies, which significantly influenced the kinetics of the reaction. The issue of inefficient O_2 mass transport can typically be solved through using larger diameter reaction flasks to increase the surface area of the liquid phase, increasing the stir rate, and/or the use of elevated pressures of O_2. Also, O_2 solubility is dependent on the nature of the solvent and temperature, and these issues should be addressed when developing new methodologies.[18]

Besides mass transport, another important limitation of alcohol oxidation was characterized by Waymouth and co-workers.[19] The authors were interested in developing a new catalyst system capable of achieving high turnover numbers under ambient pressures of air at room temperature. Their catalyst design was based upon a previously reported mechanistic study of the $Pd(IiPr)(OAc)_2(H_2O)$ catalyst system by our laboratory, which indicated that the monodentate NHC ligand facilitated rapid binding of the alcohol and increased the rate of β-hydride elimination, while the acetate ligands led to facile intramolecular deprotonation to form the Pd^{II}-alkoxide intermediate.[20] The authors hypothesized that a Pd^{II} complex with a bidentate ligand containing both a triflate and an acetate counter-ion would also increase the rates of alcohol binding, deprotonation, and β-hydride elimination by providing a readily accessible open coordination site in combination with an intramolecular base.[19]

Thus, they synthesized the dimeric pre-catalyst **5** by combining a $L_nPd^{II}(OAc)_2$ salt with a dicationic $L_nPd^{II}(OTf)_2$ complex. However, subjecting 2-heptanol (**4**) to the reaction conditions with the Pd^{II} pre-catalyst **5** led to only a 36% yield of 2-heptanone (**6**) (Fig. 3). A time course analysis of the transformation was performed and indicated a fast initial rate followed by a significant decrease over time, which accounted for the diminished yield. One possible explanation for this observation is decomposition of the catalyst during the course of the reaction. However, no precipitation of Pd metal was observed, which rules out slow reoxidation of Pd^0. Analysis of the mixture after completion of the reaction indicated the presence of complex **9**, which was found to be catalytically inactive. The authors propose that the Pd^{II}-hydroperoxide **7** is converted to the Pd^{II}-alkoxide **8** and subsequent oxidation by O_2 generates complex **9** under the catalytic conditions. The complex was also independently synthesized and crystallized by subjecting the pre-catalyst to aqueous hydrogen peroxide.

Recently, Stahl and co-workers disclosed another example of how a ligand, in this case the NHC ligand IMes, can be oxidized to the alkoxide by a Pd^{II}-hydroperoxide species.[21] These results illustrate a common misconception that the “oxidatively stable” ligands, such as those depicted in Fig. 1, routinely employed in aerobic alcohol oxidations are inert to oxidation by reactive species formed during the catalysis. In reality, many ligands can be oxidized and identification of new oxidatively stable ligands may facilitate the development of the next generation of aerobic alcohol oxidation systems capable of higher turnover numbers.

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In addition to the reports discussed above on the general oxidation of alcohols, significant advances have been made in expanding the scope and mechanistic understanding of the Pd^{II}-catalyzed aerobic oxidative kinetic resolution of secondary alcohols. For example, O'Brien, Stoltz and co-workers recently reported the first example of a room temperature Pd^{II}-catalyzed oxidative kinetic resolution of a variety of secondary alcohols using the Pd[(−)-sparteine]Br_2 catalyst with exogenous (−)-sparteine and Cs_2CO_3 (Table 1, conditions A).[22] Both benzylic (11–13) and aliphatic (**15**) secondary alcohols can be resolved with k_{rel} values comparable to the Pd[(−)-sparteine]Cl_2 catalyst at elevated temperatures.[11,23] Also, the reactions can be performed under an air atmosphere with negligible differences in enantioselectivity and k_{rel} values compared to one atmosphere of O_2. The milder reaction conditions will be advantageous for the resolution of substrates, which are not stable at higher temperatures.

The design of the more reactive catalyst system was based upon structural data obtained from X-ray crystallographic analyses of a series of Pd^{II} complexes.[22] The studies revealed that the bromide counter-ion deviated 14° out of the square plane in the Pd[(−)-sparteine]Br_2 complex compared to 9.9° for the chloride ion in the Pd[(−)-sparteine]Cl_2 complex. Stoltz and co-workers hypothesized that the greater deflection of the bromide counter-ion will lead to a more active and selective catalyst. This hypothesis is supported by a study performed by our laboratory, which found that approximately 35% of the chloride ion is dissociated from the Pd[(−)-sparteine]Cl_2 complex under catalytic conditions and this may in part account for the observed enantioselectivity.[24] However, O'Brien, Stoltz, and co-workers found that the Pd[(−)-sparteine]Br_2 catalyst decomposed under the reaction conditions at elevated temperatures, which suggests this complex is significantly less stable compared to the chloride catalyst.

One of the major limitations of the Pd[(−)-sparteine]Cl_2-catalyzed oxidative kinetic resolution is access to (+)-sparteine, the other enantiomer of the ligand. Interestingly, other chiral diamine ligands do not effectively induce asymmetry and this suggests the unique structure of (−)-sparteine is critical for a successful resolution. Stoltz and co-workers have recently developed a model for enantioselectivity based upon X-ray structures of Pd^{II} complexes with different enantiomerically enriched alkoxides and sparteine derivatives.[25] They propose the C_1 symmetry of the ligand is required to induce a diastereoselective chloride substitution that ultimately leads to faster oxidation of the *R* enantiomer.

In addition to the X-ray structural studies conducted by Stoltz and co-workers, our laboratory has kinetically investigated the origin of enantioselectivity and found the concentration of (−)-sparteine·HCl, which is formed during the deprotonation step, influences the observed k_{rel} values.[24] A mathematical model was derived that predicts the k_{rel} values at different concentrations of (−)-sparteine·HCl. Together, the kinetic studies suggest the origin of enantioselectivity is a competition between the different enantiomers of the alcohol for an active Pd^{II} catalyst and a balance of kinetic reprotonation of the alkoxide by (−)-sparteine·HCl and β-hydride elimination.

All of the mechanistic studies indicate that (−)-sparteine is uniquely suited for the Pd^{II} -catalyzed oxidative kinetic resolution of secondary alcohols. However, in order to increase the utility of this methodology other ligands need to be identified to access the other enantiomer of the alcohol. Recently, Shi and co-workers reported the use of an axially chiral bidentate NHC ligand to achieve an oxidative kinetic resolution.[26] Unfortunately, the scope is limited to only benzylic and allylic alcohols and modest k_{rel} values are achieved for the majority of substrates.

O'Brien, Stoltz, and co-workers have reported a room temperature oxidative kinetic resolution that employs ligand **10**,[22] which has been shown to be a (+)-sparteine mimic and can be accessed in three synthetic steps from (−)-cytisine (Table 1, conditions B).[27] The catalyst can

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resolve a variety of benzylic (**11, 12**), allylic (**16**) and aliphatic (**17, 18**) substrates with k_{rel} values comparable to those of (−)-sparteine with either an O_2 or air atmosphere.[22] The use of ligand **10** or (−)-sparteine enables rapid access to both enantiomers of the alcohol, thus overcoming one of the greatest limitations to $\mathrm{Pd^{II}}$-catalyzed oxidative kinetic resolutions of secondary alcohols. The utility of this methodology was showcased by the Stoltz laboratory in the synthesis of a variety of natural products including the formal synthesis of both antipodes of amurensinine.[28] The mechanistic studies performed on the $\mathrm{Pd^{II}}$-catalyzed aerobic alcohol oxidations have led to the development of new more efficient catalyst systems for aerobic oxidations of alcohols and illustrate the challenges the next generation of oxidation reactions will need to overcome.

Oxidative Heck

The Heck cross-coupling reaction of an aryl halide and an alkene has been widely employed in natural product and pharmaceutical synthesis.[29] The proposed mechanism involves oxidative addition of an aryl halide to the $\mathrm{Pd^0}$ catalyst resulting in a $\mathrm{Pd^{II}}$-aryl species, which further reacts with the alkene to generate the product.[30] A potential limitation is that this sequence requires the use of an organic oxidant, which is incorporated into the product, and the use of a $\mathrm{Pd^0}$ catalyst is not compatible with certain types of alkene substrates.[31]

To further expand the scope and utility of the Heck reaction, an oxidative version that utilizes a Pd catalyst and an organometallic reagent as the aryl source would overcome some of the limitations of the traditional reaction conditions.[3a] The proposed mechanism is similar to the original Heck reaction, except that the $\mathrm{Pd^{II}}$-aryl species **B** is accessed via transmetalation of an organometallic reagent with the $\mathrm{Pd^{II}}$ catalyst **A** (Fig. 4).[32] The alkene coordinates to **B** leading to intermediate **C**, which undergoes migratory insertion to produce the $\mathrm{Pd^{II}}$-alkyl **D**. Subsequent β-hydride elimination generates the alkene bound $\mathrm{Pd^{II}}$-hydride complex **E**. Alkene dissociation leads to **F** and reductive elimination of HX yields the $\mathrm{Pd^0}$ intermediate **G**, which is reoxidized by molecular oxygen to complete the catalytic cycle.

In 1968, a seminal report by Heck demonstrated that PhHgCl underwent transmetalation with catalytic $\mathrm{Pd^{II}}$ to yield a $\mathrm{Pd^{II}}$-aryl species, which subsequently reacts with an alkene to generate the desired oxidative Heck product.[33] Almost 25 years after this report, a more practical catalytic version was disclosed by Cho and Uemura, which required the use of acetic acid as the solvent.[34] Since that time, there have been numerous reports of oxidative Heck reactions with organoboronic acids,[35] organotrifluoroborates,[36] organosilanols,[37] organostannanes,[38] and organophosphonic acids[39] that utilize mild reaction conditions and a variety of oxidants, including $\mathrm{Cu^{II}}$ salts and O_2. In 2004, Larhed and co-workers published the first ligand-modulated oxidative Heck reaction of aryl boronic acid derivatives and electron deficient alkenes with O_2 as the sole stoichiometric oxidant.[40]

This publication has led to the discovery of improved ligand-modulated oxidative Heck catalytic systems, which can be performed at room temperature under an air atmosphere and have greatly expanded the alkene scope.[41] The use of ligands has also led to the first reported catalytic asymmetric oxidative Heck reaction with organoboronic acids.[42] Asymmetric Heck reactions with $\mathrm{Pd^0}$ have been documented in the literature,[43] but the identification of oxidatively stable chiral ligands, which effectively induce asymmetry, has been challenging for the $\mathrm{Pd^{II}}$-catalyzed variant.[3a] For example, Mikami and co-workers found the flexible phosphine ligand (*S,S*)-chiraphos (**21**) in combination with $\mathrm{Pd(OAc)_2}$ under an O_2 atmosphere generated the desired oxidative Heck product **22** (Fig. 5A).[42] However, only the tri-substituted alkene **19** and the electron deficient organoboronic acid **20** were competent coupling partners under these conditions. Besides the limited scope, the modest yields and poor enantioselectivity greatly diminish the utility of this methodology.

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In 2007, Jung and co-workers reported another example of an enantioselective oxidative Heck reaction catalyzed by the oxazoline containing complex **24** at room temperature under an O_2 atmosphere (Fig. 5B).[44] A variety of organoboronic acids can be used in combination with two different alkenes (**23**) to yield the product (**25**) in good yields and modest enantiomeric excesses. The authors utilized the preformed ligand–Pd^{II} complex **24** because attempts to generate the complex *in situ* by addition of the free ligand and $Pd(OAc)_2$ resulted in diminished enantioselectivity and this suggests that complex formation is slow in DMF.

Gelman and co-workers recently disclosed the use of (R)-BINAP (**28**) and (R)-MeOBiphep (**29**) in combination with $Pd^{II}(OAc)_2$ and stoichiometric $Cu^{II}(OAc)_2$ as the terminal oxidant (Table 2).[45] The scope of the transformation was investigated by coupling a variety of organoboronic acids (**26a–g**) with dihydrofuran (**27**). The results suggest (R)-MeOBiphep (**29**) is the best ligand for the reaction, and electron neutral (**26a**) and electron deficient (**26b** and **c**) organoboronic acids are competent coupling partners. However, the steric nature of the organoboronic acid seems to have more of an influence on enantioselectivity (**26d–g**). Even though the ligand should be stable under the O_2-free conditions, only modest enantioselectivity is observed, showcasing the difficulty of achieving an effective asymmetric catalytic system.[46]

The enantiodetermining step of the asymmetric Heck reaction is proposed to be migratory insertion of the Pd^{II} bound alkene complex **C** to generate the Pd^{II}-alkyl species **D** (Fig. 4). Thus, if the bidentate ligand dissociates from complex **C**, this could possibly explain the modest enantioselectivity observed in these reactions. All of the asymmetric Heck reactions utilize DMF as the solvent, which may partially displace the chiral ligand from Pd. This hypothesis is supported by a mechanistic study performed by Larhed and co-workers on the oxidative Heck coupling of the organoboronic acid **26d** with alkene **31** to generate **33** with the use of the dmphen ligand (**32**) and $Pd(OAc)_2$ in MeCN (Fig. 6).[32] After completion of the reaction, the mixture was diluted with MeCN and infused into an electrospray ionization–mass spectrometer (ESI-MS). Only positively charged species can be detected by this method. Interestingly, intermediates **A–E** were identified and further characterized by MS/MS and these data support the proposed mechanism of the oxidative Heck reaction. For example, species **A** contains one bidentate and one monodentate dmphen ligand and intermediate **B** is coordinated by two MeCN ligands, which causes the dmphen ligand to bind in a monodentate manner. The authors propose that these intermediates can undergo transmetalation with organoboronic acid **26d** to yield the Pd^{II}-aryl species **C** and **D**. Alkene coordination generates species **E**, and subsequent migratory insertion and β-hydride elimination generate the Pd^{II}-hydride **F**, which is not detected because of the propensity of these intermediates to undergo reductive elimination to form Pd^0 and HX.[47] The identification of species that have both mono- and bidentate dmphen ligands provides evidence that the ligand can dissociate from the complex in polar coordinating solvents and could account for the difficulty in achieving an effective asymmetric reaction.

During the past 10 years, there have been numerous reports detailing the development of more efficient ligand-modulated oxidative Heck reactions that can be performed under an air atmosphere at room temperature. However, the asymmetric oxidative Heck reaction still suffers from many limitations and mechanistic studies suggest that the identification of different reaction conditions, which do not promote ligand dissociation, is required. The future of oxidative Heck chemistry may be the discovery of more robust systems for asymmetric catalysis and the possibility of eliminating the need for an oxidant through the use of a hydride acceptor, which has been recently reported.[48]

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Oxidative homocoupling of organometallic reagents

In addition to the Heck reaction, Pd^0 is employed in the cross-coupling of aryl halides and organometallic reagents, which is commonly referred to as the Stille (organostannanes) or Suzuki (organoboronic acids) reaction, and is one of the most widely utilized Pd-catalyzed methodologies.[49] The proposed mechanism involves oxidative addition of an aryl halide to a Pd^0 catalyst that yields a Pd^{II}-aryl species, which undergoes subsequent transmetalation of the organometallic reagent and reductive elimination generates a new carbon– carbon bond. In addition to the Pd^0-catalyzed pathway, there is an oxidative version of this reaction that yields symmetrical biaryls, which is a common byproduct of the oxidative Heck reaction.[49b] In this case, the catalysis is similar to the proposed mechanism of the oxidative Heck reaction except that intermediate **B** undergoes another transmetalation of an organometallic reagent followed by reductive elimination to yield the biaryl and the Pd^0 intermediate **G** (Fig. 4).

In 1968, Davidson and Triggs reported the first stoichiometric version of the homocoupling of an organometallic reagent.[50] Since that time, there have been numerous examples of this transformation as a byproduct in Suzuki cross-coupling reactions with organoboronic acids.[51] This has led to the development of catalytic systems for the efficient homocoupling of organometallic reagents, which utilize a variety of ligands and oxidants including O_2 and Cu^{II} salts.[52] As expected, homocoupling of the transmetalation reagent is one of the main byproducts observed in the oxidative Heck reaction described above.[35–38]

Even though there have been numerous reports on the development of the oxidative homocoupling of a variety of organometallic reagents, very little is known about the precise mechanistic details of the catalysis.[52] An initial mechanistic proposal for the homocoupling of organoboronic acids was similar to the Suzuki cross-coupling reaction, which involved oxidative addition of the carbon–boron bond to Pd^0 followed by transmetalation and reductive elimination.52a,c Almost 10 years after this hypothesis, Adamo and co-workers investigated this possibility using both kinetic and computational analysis.[53] Initially, they subjected catalytic $Pd^0(PPh)_4$ to an aryl boronic acid derivative and there was no reaction. However, if the same reaction was performed in the presence of O_2, the expected homocoupling product was obtained, which ruled out the oxidative addition pathway initially proposed.52a,c

The authors hypothesized that O_2 could initially react with the $Pd^0(PPh)_4$ catalyst (**A**) to generate the Pd^{II}-η^2-peroxo species **B** to initiate the catalytic cycle (Fig. 7A).[53] In a stoichiometric experiment, both $Pd^0(PPh)_4$ and O_2 were combined and complex **B** was isolated. Subsequent detailed kinetic and NMR studies were conducted with this catalytically active complex to probe the plausibility of it being a true intermediate in the reaction. Interestingly, a second order dependence on the concentration of $ArB(OH)_2$ was measured and in combination with ^1H and ^{31}P NMR studies, the authors propose a fast equilibrium of initial binding of $ArB(OH)_2$ to the oxygen of the Pd^{II}-η^2-peroxo species **B** to generate intermediate **C**. Initial binding of $ArB(OH)_2$ is proposed to activate this intermediate for transmetalation with a second equivalent of $ArB(OH)_2$ to produce intermediate **D**. Addition of H_2O to **D** leads to the Pd^{II}-hydroxide species **E**, which undergoes *cis–trans* isomerization to generate **F**.

Interestingly, complex **F** was independently isolated and subjected to another equivalent of $ArB(OH)_2$. The reaction was monitored by ^{31}P NMR and the trans-Pd^{II}-biaryl species **G** was observed. To complete the catalytic cycle, intermediate **G** isomerizes to the cis-Pd^{II}-biaryl complex **H**, and reductive elimination liberates the product and forms **A**. The detailed mechanistic analysis demonstrates the complexity of the oxidative homocoupling of organoboronic acids where the use of O_2 leads to an intermediate that is believed to be involved in the initial transmetalation step.

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Another issue of utilizing ArB$(OH)_2$ in the presence of O_2 and a Pd^{II} catalyst is the formation of the undesired ArOH byproduct. Adamo and co-workers investigated the origin of the phenol, and they found ArB$(OH)_2$ to be stable after extended exposure to O_2 without Pd. However, in the presence of a Pd-catalyst, the phenol was formed and the authors propose that H_2O_2 generated during the catalysis can react with the organoboronic acid to generate the phenol (Fig. 7B). This mechanistic proposal has broad implications for all palladium oxidase reactions that utilize O_2 and organoboronic derivatives. For example, H_2O_2 can oxidize both phosphine and amine ligands under the catalytic conditions,[19,54] but excess organoboronic acid can sequester the free H_2O_2. This may explain why phosphine ligands can be used in the oxidative Heck and homocoupling reactions with boronic acid derivatives and demonstrates the importance of mechanistic studies.

Wacker oxidation

In addition to aerobic alcohol oxidation and oxidative carbon-carbon bond forming reactions, one of the first examples of the use of molecular oxygen as the terminal oxidant in a Pd-catalyzed oxidation reaction was reported in 1959 by Smidt and co-workers.[55] The authors disclosed the oxidation of ethylene to acetyl aldehyde using a Pd^{II} catalyst in combination with Cu salts under an aerobic atmosphere. This seminal report led to the development of the Wacker oxidation, which is one of the most widely used palladium oxidase type transformations and has played a key role in the development of all Pd^{II}-catalyzed aerobic oxidation reactions. In recent years, there have been a significant number of reviews on the current progress of the Wacker reaction and, thus, will not be comprehensively reviewed in this article.[56] However, one important aspect of the recent advances in the Wacker oxidation is the development of direct molecular oxygen-coupled catalytic systems, which eliminate the need for co-catalysts by employing ligands to stabilize the Pd^0 intermediates.[57]

One of the first examples of a co-catalyst free direct molecular oxygen-coupled Wacker oxidation was reported in 1998 by Sheldon and co-workers.[58] The catalytic system employed the water-soluble ligand PhenS (**1**) in combination with 30 bar of air at 100 °C. In 2006, Kaneda and co-workers disclosed a direct molecular oxygen-coupled Wacker oxidation that utilized a mixed dimethylacetamide (DMA)–H_2O solvent system at 80 °C and 6 atm of molecular oxygen.[59] Interestingly, dimethylformamide (DMF), which is a common solvent employed in the Wacker reaction, did not lead to appreciable yields of the methyl ketone under these conditions.[56] The authors hypothesize that DMA potentially acts as a ligand to prevent catalyst decomposition and Pd^0 may have a more negative redox potential in DMA compared to other solvents leading to a more stable catalytic system.

Both of these co-catalyst free aerobic Wacker oxidations require the use of high pressures of molecular oxygen or air as the terminal oxidant, which limits the overall applicability of the methodology. In 2006, Cornell and Sigman reported the first example of a co-catalyst free aerobic Wacker oxidation at balloon pressures of molecular oxygen or air.[57] The catalytic system employs the ligand (−)-sparteine and a DMA–H_2O solvent system at 70 °C (Fig. 8). A variety of terminal alkenes can be selectively oxidized to the methyl ketone product and the catalyst exhibits excellent functional group tolerance for the presence of unprotected alcohols (**35b, e**, and **f**) and acid sensitive protecting groups (**35d**). An exciting aspect of this system is that the ligand (−)-sparteine in combination with DMA prevents alkene isomerization, which is a common side reaction in Wacker oxidations.[60] This is showcased by oxidation of alkene **34f**, which contains a homoallylic chiral center, to the methyl ketone **35f** without racemization. The use of a ligand in this case increases the practicality and synthetic utility of the Wacker oxidation.

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New palladium oxidase reactions

Dialkoxylation of vinylphenols: a surprising Cu-effect

Recently, several novel Pd^{II}-catalyzed oxidase based reactions have been reported in the literature. Out of these transformations, there have been only a few examples of asymmetric processes.[61] Previously, many oxidase reactions typically required a stoichiometric oxidant, such as a Cu-salt or benzoquinone to aid in the regeneration of the active Pd^{II} catalyst.[49b] Unfortunately, these oxidants have the potential to displace chiral ligands from Pd and their use has been a limiting factor in the development of asymmetric oxidase based transformations, which is highlighted by the enantioselective oxidative Heck reaction that requires one equivalent of $Cu(OAc)_2$ presented in Table 2. However, as demonstrated in this Feature article, replacing these stiochiometric oxidants with molecular oxygen has been accomplished with the use of ligands. Even with the widespread employment of ligands on Pd, there are still surprisingly few asymmetric oxidase based reactions.

An example of an asymmetric oxidase reaction was recently reported by our laboratory.[62] Specifically, the detrimental effect of a co-oxidant was highlighted while developing an asymmetric dialkoxylation reaction of styrenes containing a phenol (Table 3). Treatment of the substrate **36a** with catalytic Pd^{II}(MeCN)$_2$Cl$_2$, 20 mol% $CuCl_2$, and the quinoline oxazoline based ligand **37a** in methanol led to the desired difunctionalized product in 88% GC yield and only 10% ee (Table 3, entry 1). Further optimization of the reaction conditions revealed a profound effect that $CuCl_2$ has on the reaction. For example, as the concentration of $CuCl_2$ is reduced, the ee of the product significantly increases. This is exemplified by completely removing $CuCl_2$ from the reaction conditions, which led to the desired product in 67% GC yield and 82% ee (entry 5). These data suggest that the ligand is exchanging between $CuCl_2$ and the Pd catalyst and showcases the potential problems of utilizing co-oxidants.

After optimization of the reaction conditions, the scope of the transformation was investigated. The electronic nature of the aryl ring (**38a–c**) does not significantly affect the yield or the ee (Fig. 9A). Furthermore, other alcohols, such as ethanol or ethylene glycol, are competent nucleophiles and produce the desired products **38e** and **38f**, respectively. In addition to exploring the scope, the mechanism of the unique dialkoxylation reaction was investigated. The proposed mechanism involves initial coordination of the alkene to the active catalyst **A**, which produces **B** (Fig. 9**B**). Oxypalladation by the alcoholic nucleophile yields **C**, which undergoes formation of an *o*-quinone methide intermediate leading to **D** and the desired product. Aerobic oxidation of **E** leads to the active catalyst. The enantiodetermining step of the reaction is proposed to be oxypalladation of the metal-bound alkene with the alcoholic solvent. This is a rare example of an inter-molecular asymmetric oxypalladation reaction, which is most likely due to facile β-hydride elimination of the Pd^{II}-alkyl intermediate resulting in racemization of the chiral center. This led to the question, why is asymmetric induction observed in this case? To address this, the authors turned to a previous mechanistic study on the dialkoxylation reaction reported by Schultz and Sigman, which demonstrated that there is no β-hydride elimination after initial oxypalladation.[62a] This result suggests that formation of the *o*-quinone methide intermediate may be faster than β-hydride elimination, thus preventing racemization in this case. This transformation exemplifies the recent advances in palladium oxidase catalysis and the impact of eliminating the need for a co-oxidant.

Reductive coupling of styrenes and organometallic reagents

In addition to the dialkoxylation of styrenes discussed above, our laboratory discovered a unique hydroalkoxylation reaction of vinyl phenols, which is the addition of one alcohol to the alkene.[63] Deuterium labeling experiments suggest a mechanism wherein oxidation of the alcoholic solvent generates a Pd^{II}-hydride intermediate, which reacts with the alkene to

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generate a Pd^{II}-alkyl intermediate. Based upon this mechanistic hypothesis, a new reductive coupling reaction of styrenes and organometallic reagents was developed, which generates a new carbon–carbon bond (Fig. 10).[64] In this case, the active catalyst **A** initially oxidizes the alcoholic solvent to generate the Pd^{II}-hydride intermediate **B** and alkene coordination leads to **C**. The alkene subsequently inserts into the hydride yielding the Pd^{II}-alkyl species **D**, which undergoes transmetalation with an organometallic reagent producing **E**. Reductive elimination liberates the product and the Pd^0 species **F**, which is reoxidized to the active catalyst **A** by O_2.

Optimization of the reaction conditions for the reductive coupling of styrene **39a** and $PhSnBu_3$ (**40a**) was a significant challenge due to a variety of undesired pathways, which lead to the formation of the oxidative Heck and oxidative homocoupling products. In addition to these undesired pathways, a time course analysis of the reaction revealed a fast initial rate, but at 20 h only 63% conversion of styrene **39a** was measured (Table 4, entry 1). This suggested the possible formation of an inhibitor. Since both Waymouth and co-workers,19 and Konnick and Stahl [21] had previously observed ligand oxidation, it was hypothesized that (−)-sparteine could be oxidized to (−)-sparteine-*N*-oxide (**43a** and **b**) illustrated in Fig. 11A.[65] To test this hypothesis a reductive coupling reaction was performed with exogenous (−)-sparteine-*N*-oxide, which led to only 30% conversion of **39a** and 22% GC yield (Table 4, entry 2).[64a] Therefore an additive needed to be identified to disproportionate H_2O_2 to reduce the formation of the inhibitor (−)-sparteine-*N*-oxide. Previously, MnO_2 has been shown to disportionate H_2O_2 (Fig. 11B).[66] Addition of 75 mol% MnO_2 to the reductive coupling reaction produced the desired product **41a** in 81% GC yield (Table 4, entry 3). As a control both (−)-sparteine-*N*-oxide and MnO_2 were evaluated and led to only a 19% GC yield of **41a**, which further supports the detrimental effect of (−)-sparteine-*N*-oxide on the catalysis (entry 4).

The plausibility of MnO_2 reducing the amount of (−)-sparteine-*N*-oxide generated during the course of the reaction was further investigated. Two reductive coupling reactions were conducted using the optimized conditions where one did not employ MnO_2. Both reaction mixtures were analyzed by ESI-MS for the presence of (−)-sparteine-*N*-oxide. The ratio of the peak heights of (−)-sparteine to (−)-sparteine-*N*-oxide was found to be 0.50 for the reaction performed with 75 mol% MnO_2 compared to 0.64 for the reaction performed without MnO_2. Even though the peak heights do not correlate to the absolute concentration of each species, there is an approximate 28% difference. These data further support the role of MnO_2 in the catalysis is to disproportionate H_2O_2.

After optimization of the reaction conditions for the reductive coupling product, the scope of the transformation was explored (Fig. 12). The electronic nature of the arylstannane does not significantly affect the yield (**41a–c**) and acid sensitive functional groups are stable under the reaction conditions (**41c** and **d**). Additionally, vinylstannanes were competent coupling partners leading to **41e** and **f**.

The scope of the reductive coupling reaction was recently expanded to include organoboronic ester derivatives.[64b] However, optimization studies demonstrated that 3 equivalents of the ethylene glycol derived organoboronic ester **44a** were required in addition to catalytic [Pd(S*i*Pr)Cl_2]$_2$, (−)-sparteine, and *t*BuOK (Fig. 13). A time course analysis of the reaction mixture was conducted with *sec*-BuOH as the solvent to identify all of the undesired byproducts that account for the requirement of excess **44a**. At 14 h, < 1% of **44a** remained and a 78% GC yield of the desired reductive coupling product **41a** was measured. Additionally, 112% GC yield of the oxidized alcohol product butan-2-one (**46**) was measured and suggests that not every oxidized alcohol is converted to the desired product. Furthermore, a 14% GC yield of the oxidative homocoupling product **47** and a 139% GC yield of phenol (**48**) were measured.

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The formation of the phenol suggests that the organoboronic ester is sequestering the H_2O_2 generated during the catalysis, which is supported by Adamo and co-workers' observations.[53] These results indicate that the use of boron containing organometallic reagents in palladium oxidase catalysis may allow for the use of less oxidatively stable ligands. Furthermore, the identification of new more efficient additives besides MnO_2 to disproportionate H_2O_2 generated *in situ* will be a continuing challenge in the pursuit of new palladium oxidase reactions.

Conclusions

As described in this Feature article, significant progress has been reported in oxidation catalysis over the last decade by utilizing Pd^{II} and molecular oxygen as the sole stoichiometric oxidant. We have highlighted this progress in the areas of alcohol oxidation, oxypalladation processes, and carbon– carbon bond forming reactions. Many of these catalytic systems were developed based upon information garnered from detailed mechanistic studies, which illustrate the complexity of coupling molecular oxygen to catalyst regeneration. An underlying theme of this article was to illustrate the issues associated with using molecular oxygen in oxidation catalysis wherein the production of hydrogen peroxide can lead to consumption of the ligand and substrates. This aspect will certainly be addressed in the design of improved and new reactions. Another key development in Pd^{II}-catalyzed oxidation reactions using molecular oxygen is generating new reaction manifolds, which extend the scope of these reactions from being mainly associated with dehydrogenation processes (alcohol oxidation, oxidative Heck, *etc*.). Our lab has been particularly interested in this area and has reported an alkene dialkoxylation reaction and a reductive coupling of alkenes with organometallic reagents. The latter reaction is especially interesting to us in that a formal reduction of the alkene occurs under oxidative conditions. Future work in our lab and others will be to continue to reveal new ligand classes for Pd-catalyzed aerobic oxidations in the context of new reaction discovery.

Biographies

Keith M. Gligorich

Keith M. Gligorich was born in Munster, IN, on 9 March 1982. He obtained a BS degree from Butler University in Indianapolis, Indiana, in 2004 (working with Prof. Meng-Chih Su and Prof. Geoffrey C. Hoops). He traveled to Taiwan in 2004 to work with collaborators at the Institute of Atomic and Molecular Sciences Academia Sinica, Taipei, Taiwan. In the fall of 2004, he began his graduate studies at the University of Utah (under the direction of Prof. Matthew S. Sigman). His thesis work has focused on the development of aerobic palladium-catalyzed alkene functionalization reactions. He is currently a postdoctoral fellow at the Huntsman Cancer Institute, Salt Lake City, UT (Prof. Bryan E. Welm) investigating new small molecules for the treatment of breast cancer.

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Matt Sigman

Matt Sigman was born in Los Angeles, CA, and received a BS in chemistry from Sonoma State University in 1992 before obtaining his PhD at Washington State University with Prof. Bruce Eaton in 1996. He then moved to Harvard University to complete an NIH postdoctoral stint with Prof. Eric Jacobsen. In 1999, he joined the faculty of the University of Utah where his research group has focused on the development of new synthetic methodology and new oxidation reactions using practical terminal oxidants.

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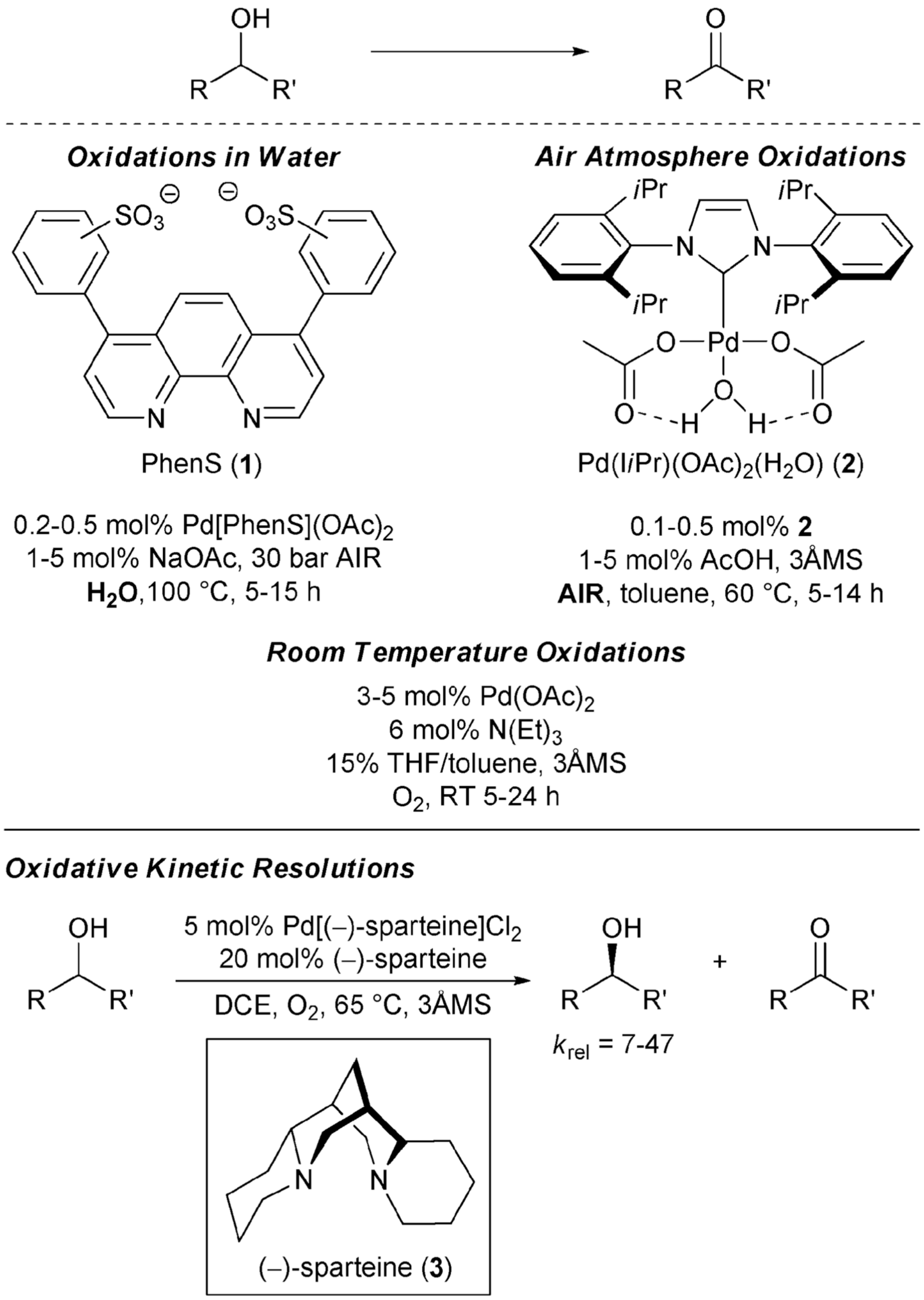

Fig. 1.

Examples of catalyst systems for the aerobic oxidation of alcohols.

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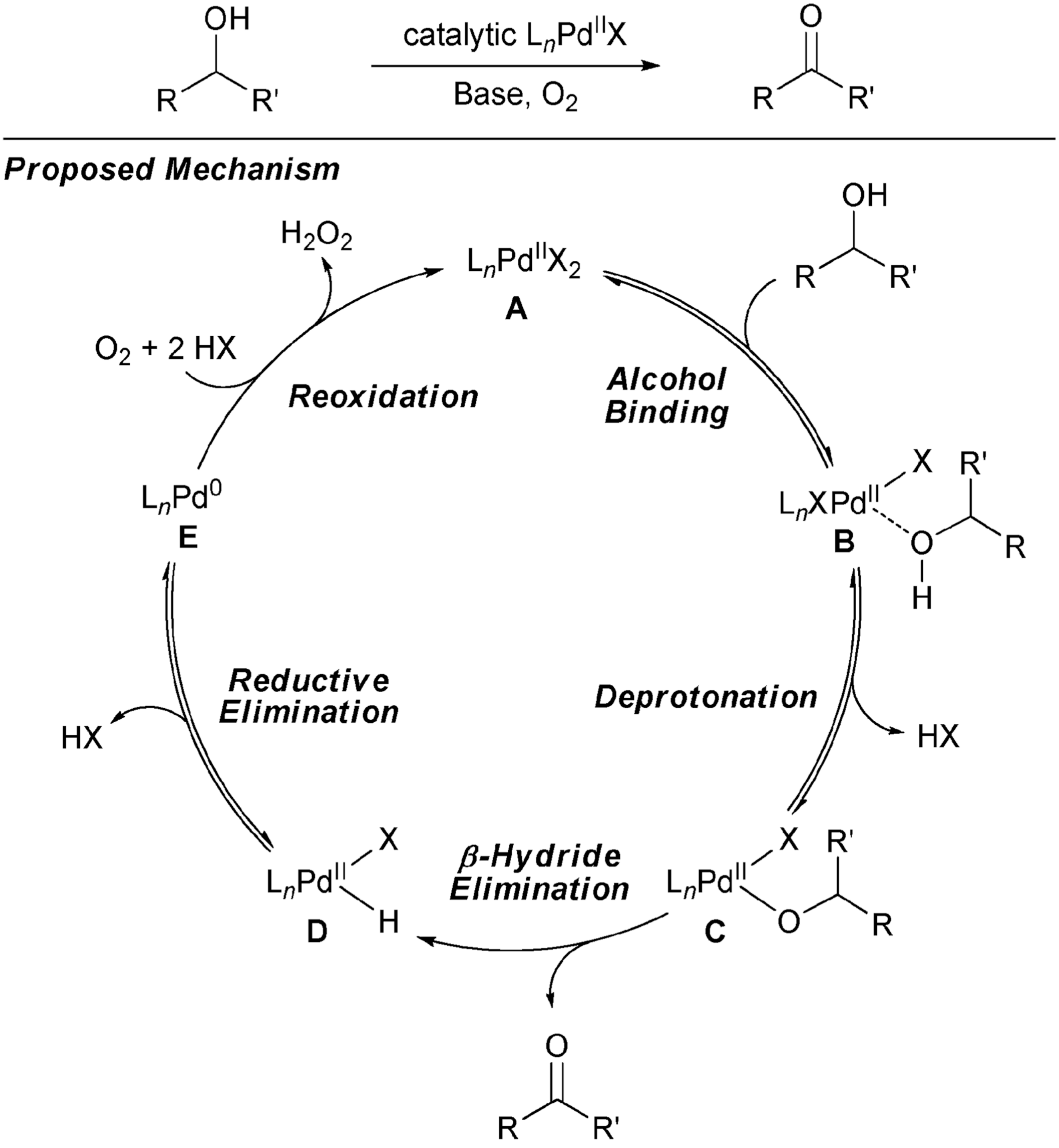

Fig. 2.

The generally accepted mechanism of the aerobic Pd^{II}-catalyzed oxidation of alcohols.

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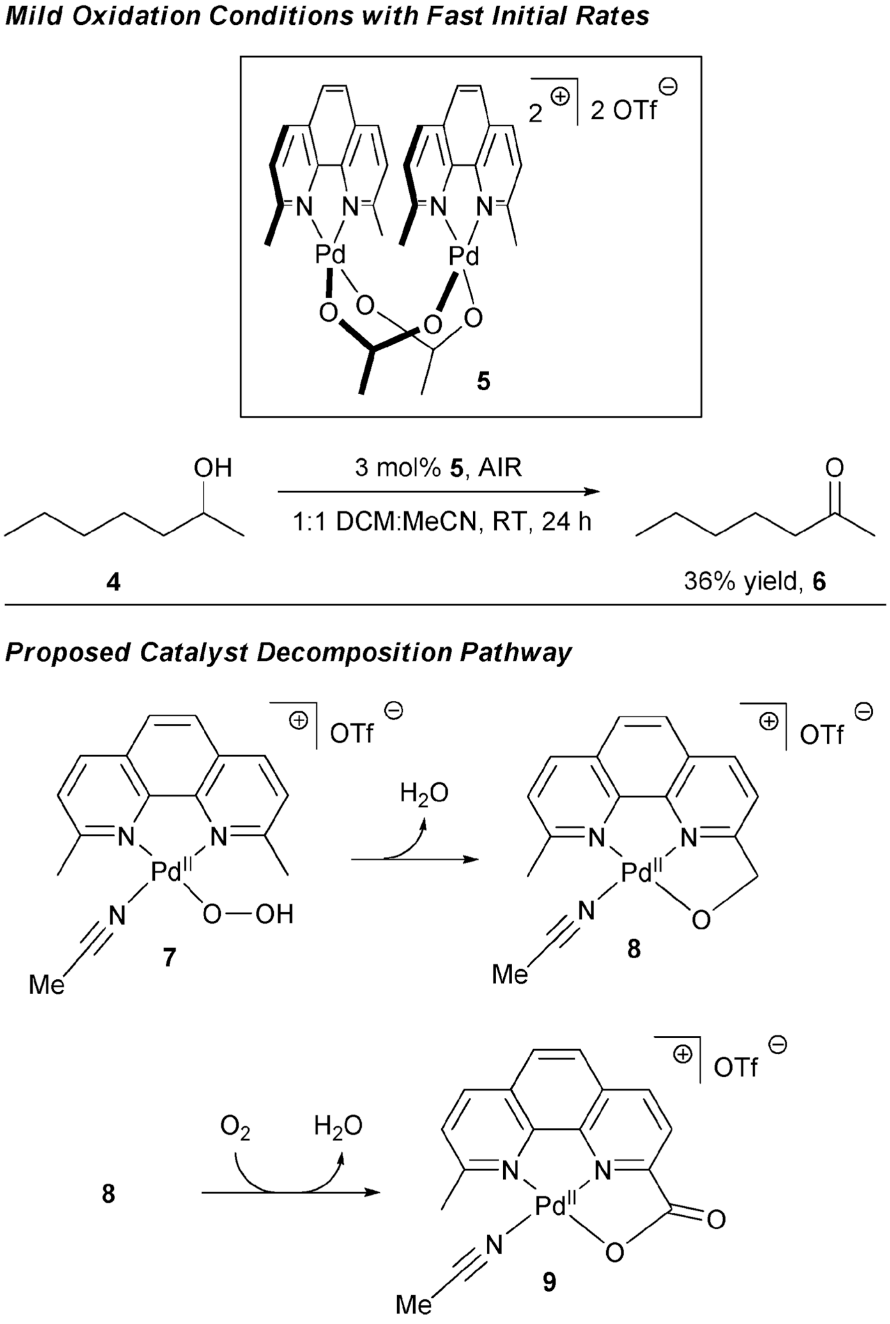

Fig. 3.

Development of a new catalyst system for the aerobic oxidation of alcohol by Waymouth and co-workers demonstrates how oxidation of the ligand can be a significant problem.

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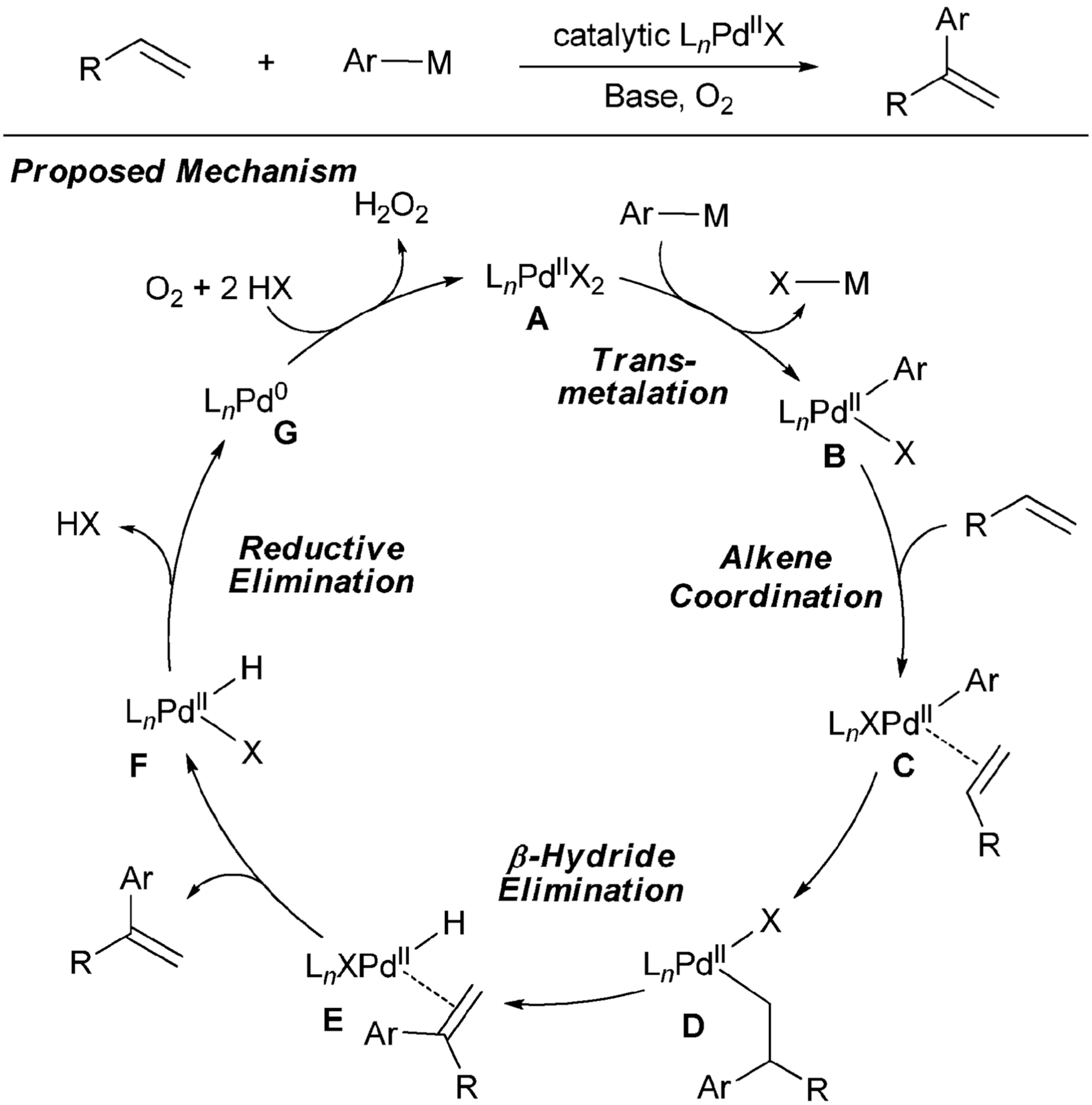

Fig. 4.

Proposed mechanism of the Pd^{II}-catalyzed oxidative Heck reaction.

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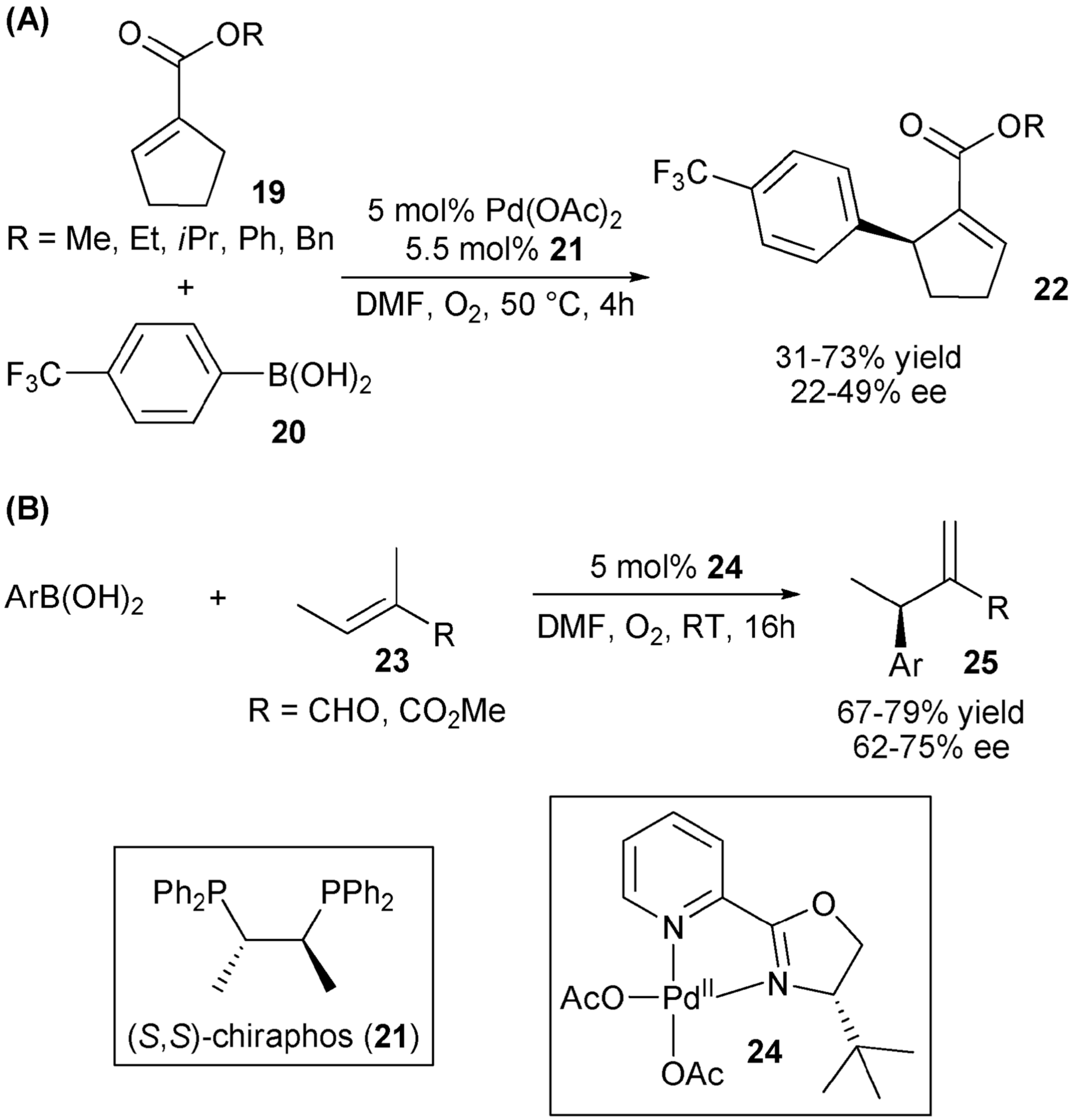

Fig. 5.

(A) One of the first examples of an asymmetric oxidative Heck reaction with the (*S S*)-chiraphos (**21**) ligand disclosed by Mikami and co-workers. (**B**) Jung and co-workers' asymmetric oxidative Heck reaction with complex **24**.

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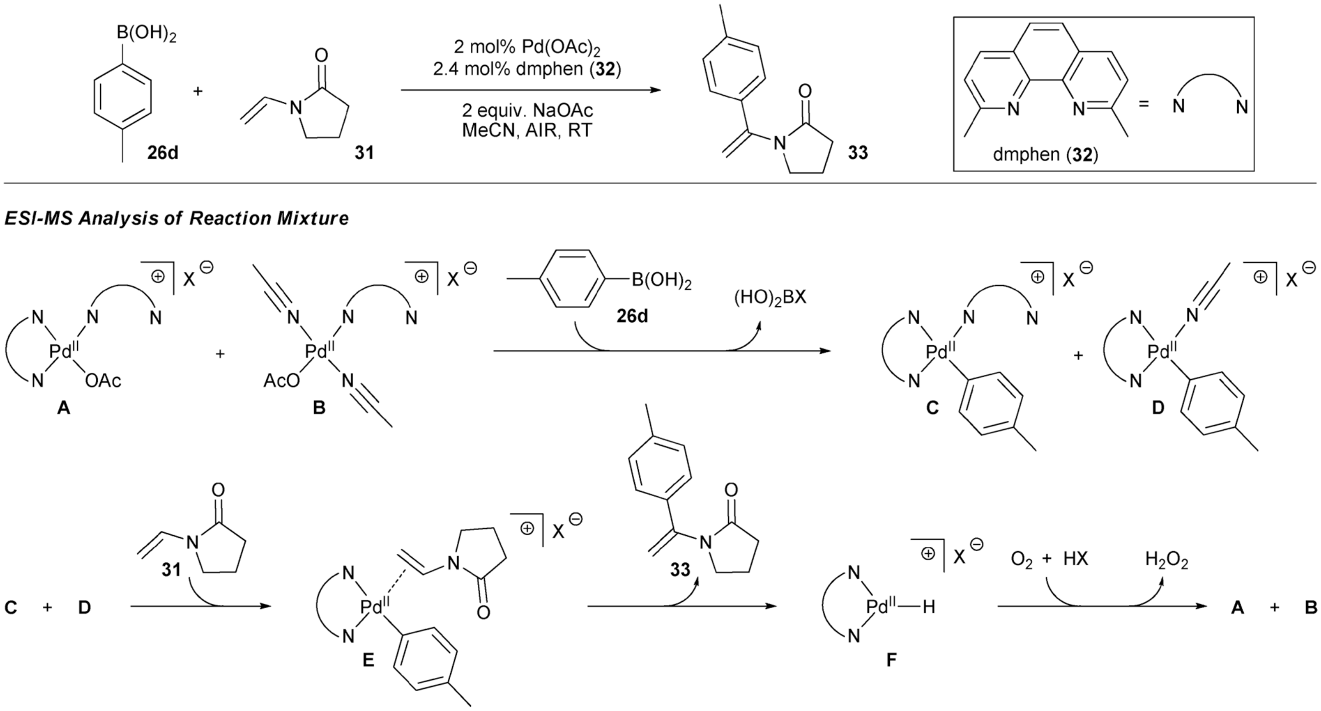

Fig. 6.

Larhed and co-workers investigated the mechanism of the oxidative Heck coupling of **26d** and **33** by identifying intermediates **A–E** by ESI-MS.

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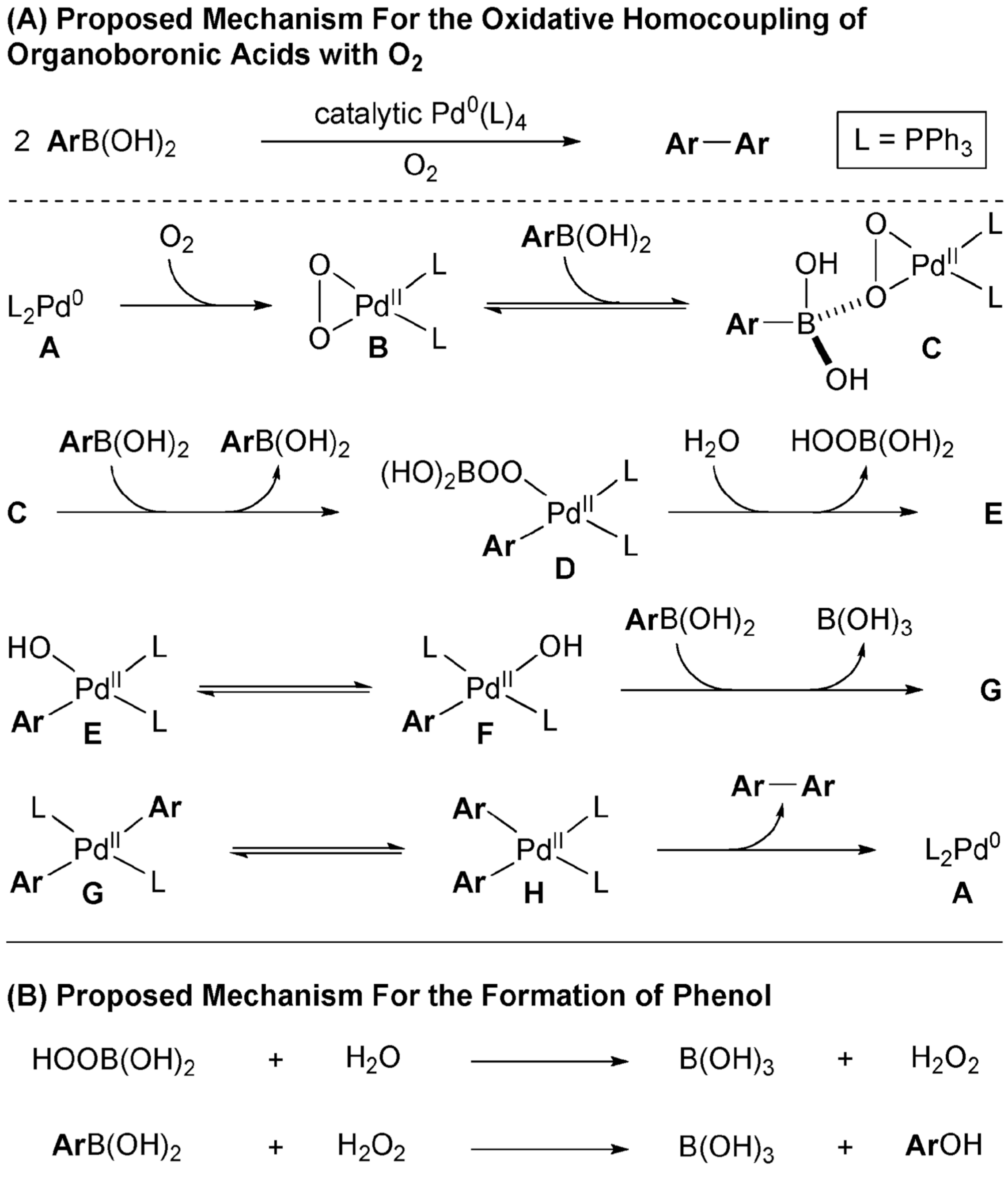

Fig. 7.

(A) The proposed mechanism for the Pd^{II}-oxidative homocoupling of organoboronic acids with O_2 as the terminal oxidant and (B) the proposed mechanism for the formation of phenol.

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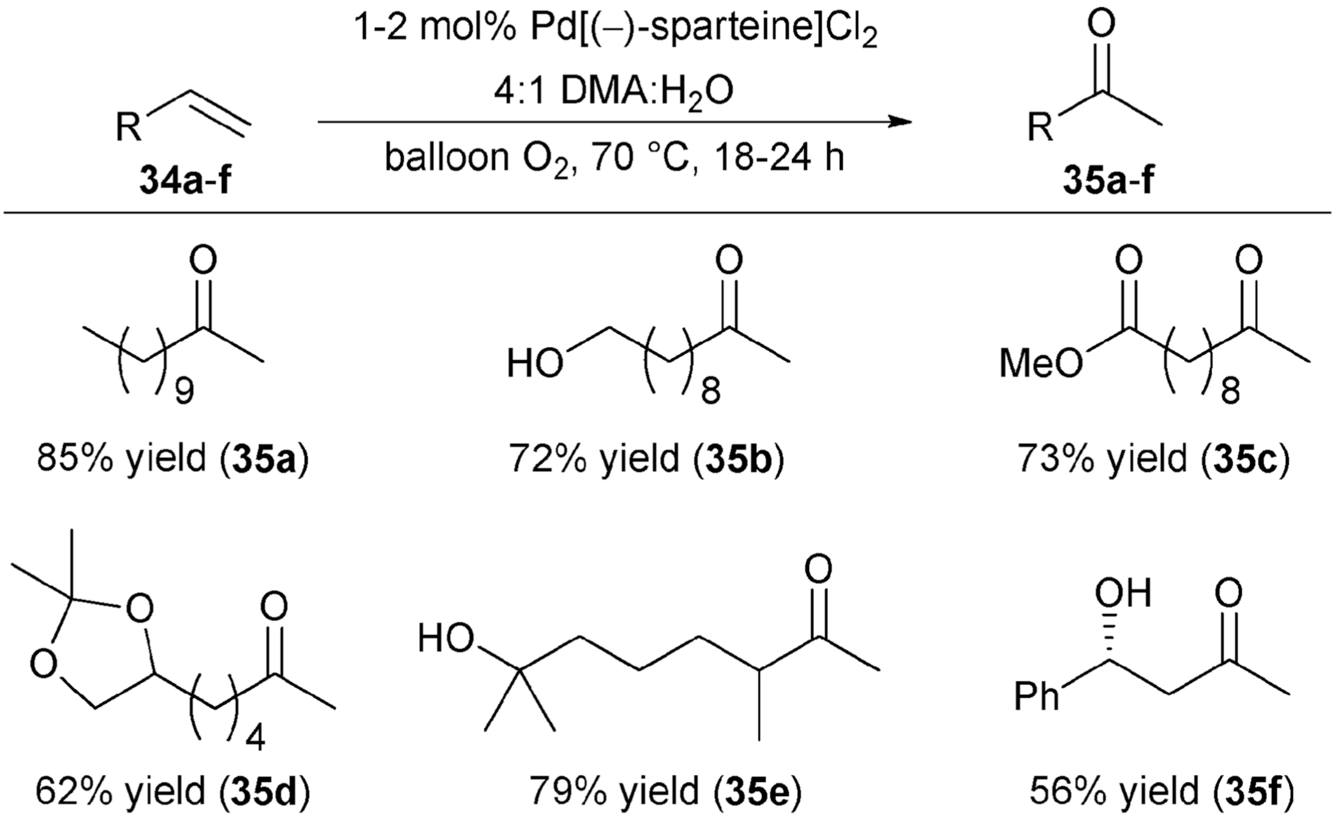

Fig. 8.
The first example of a balloon pressure direct molecular oxygen-coupled Wacker oxidation disclosed by Cornell and Sigman.

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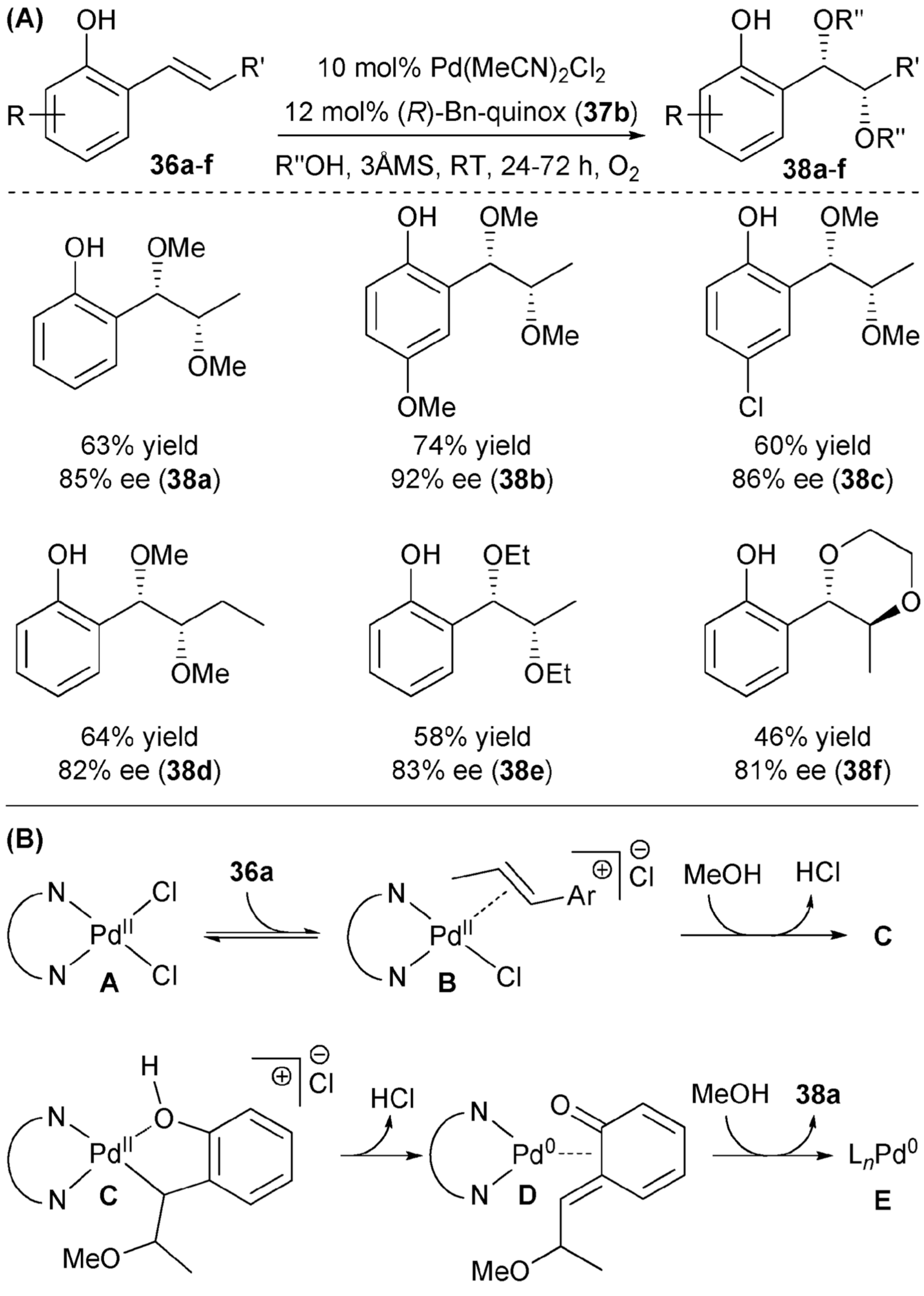

Fig. 9.

(A) Selected scope and (**B**) proposed mechanism of the asymmetric dialkoxylation reaction of styrenes containing a phenol.

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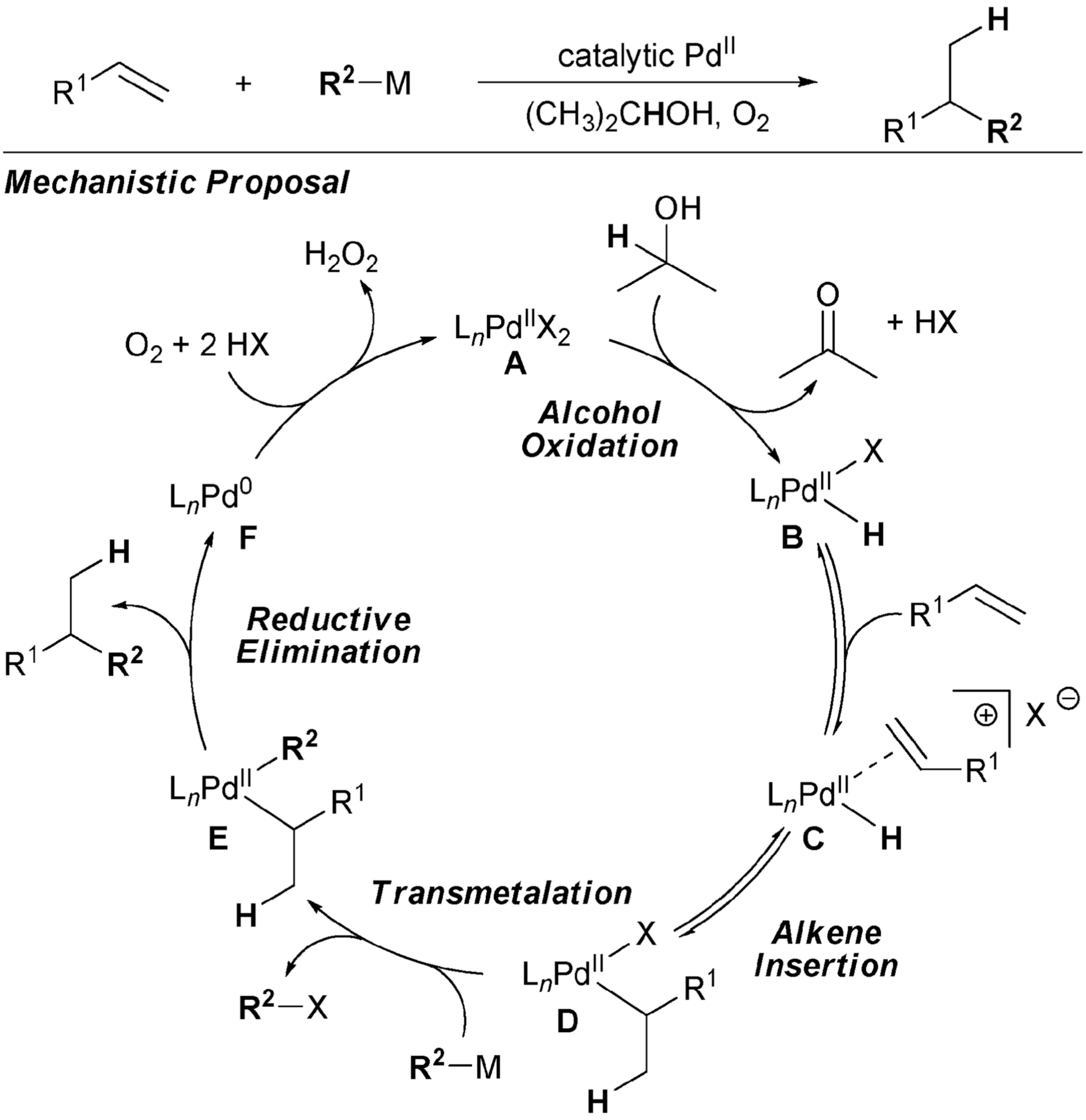

Fig. 10.

The proposed mechanism of the aerobic reductive coupling reaction of styrenes and organometallic reagents.

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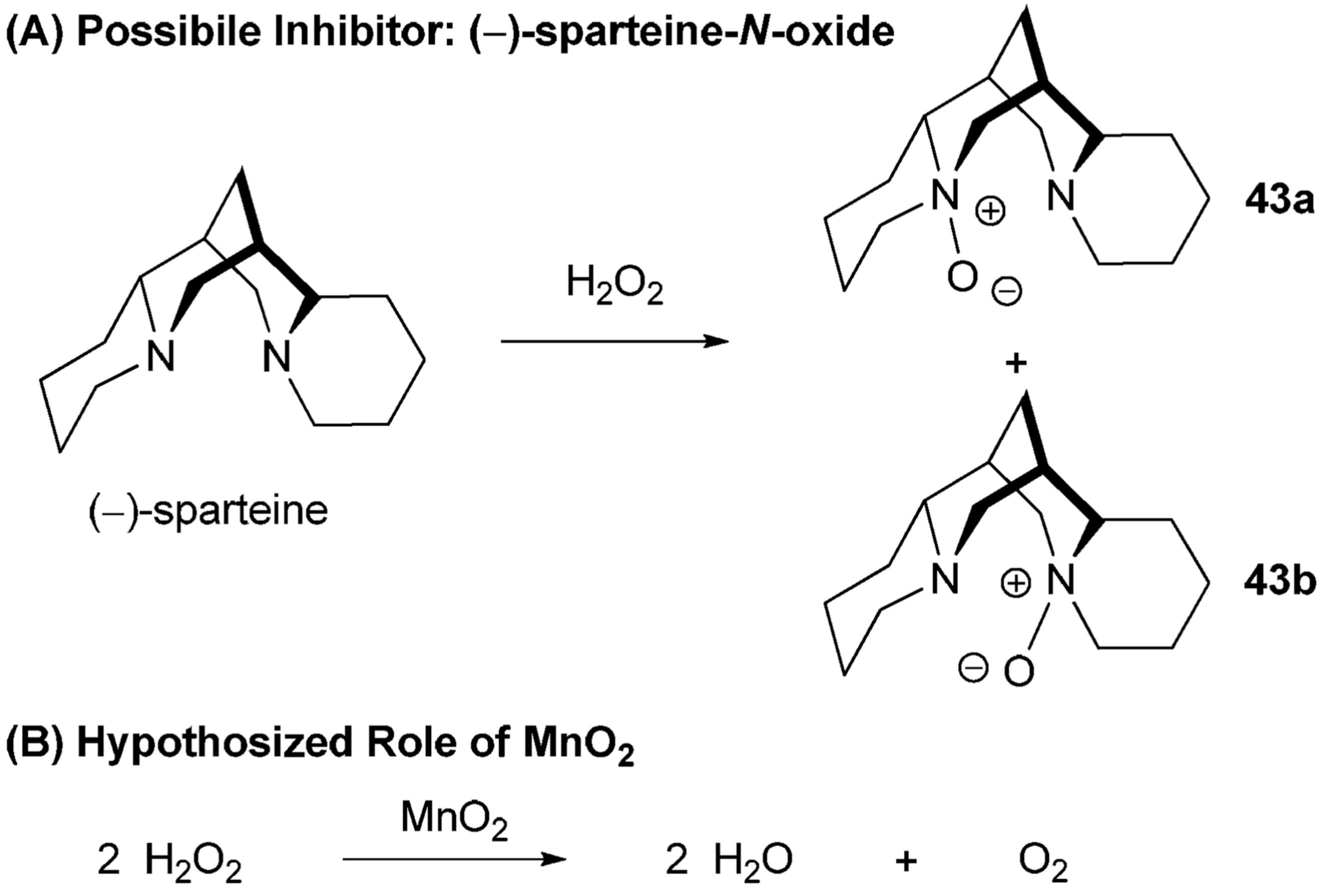

(A) Possibile Inhibitor: (–)-sparteine-*N*-oxide

(B) Hypothosized Role of MnO_2

Fig. 11.

(A) Oxidation of (−)-sparteine by hydrogen peroxide leads to (−)-sparteine-*N*-oxide (**43a** and **b**). (B) The hypothesized role of MnO_2 in the catalysis is to disproportionate H_2O_2.

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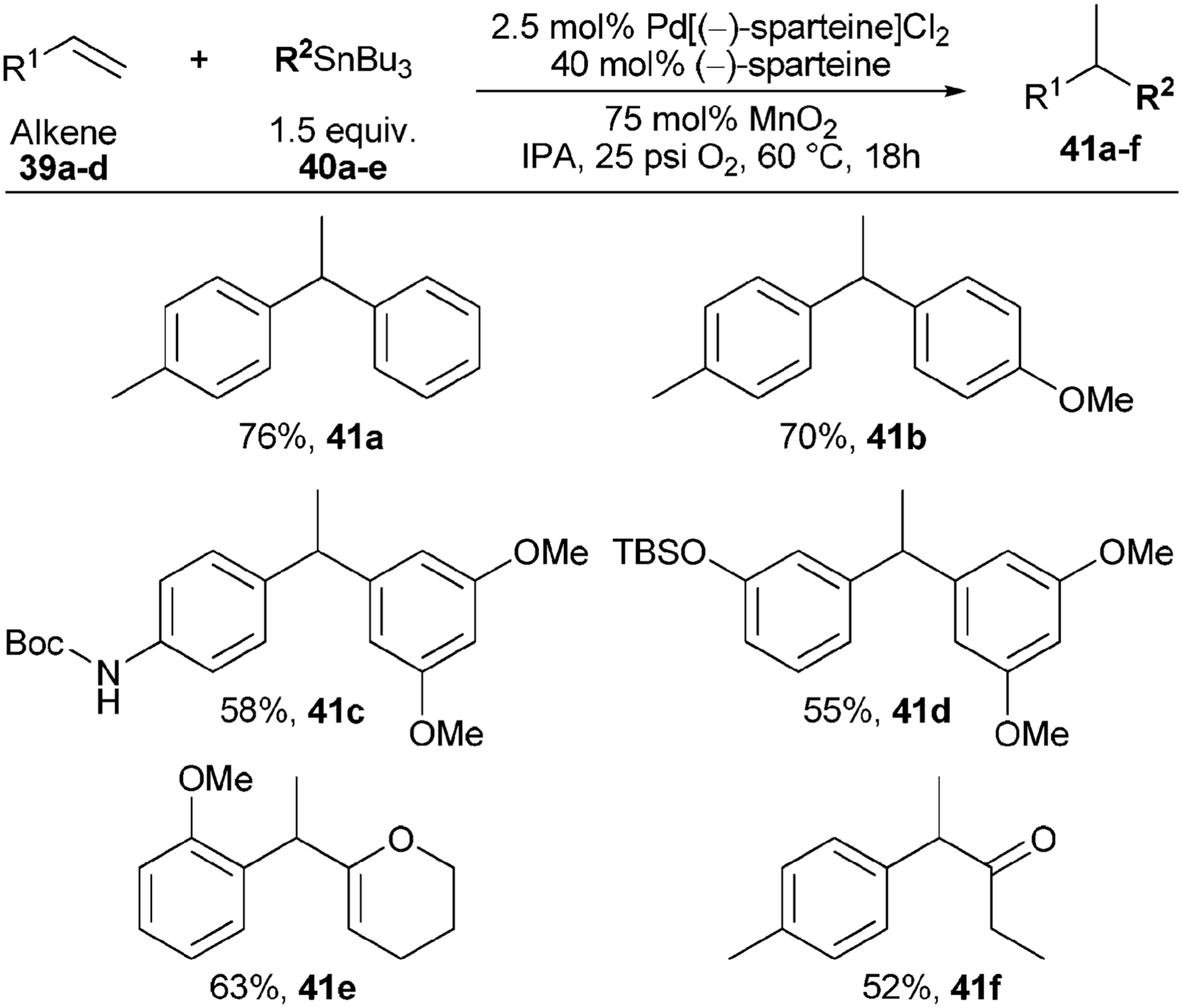

Fig. 12.

Selected scope of the reductive coupling reaction of styrenes and organostannanes.

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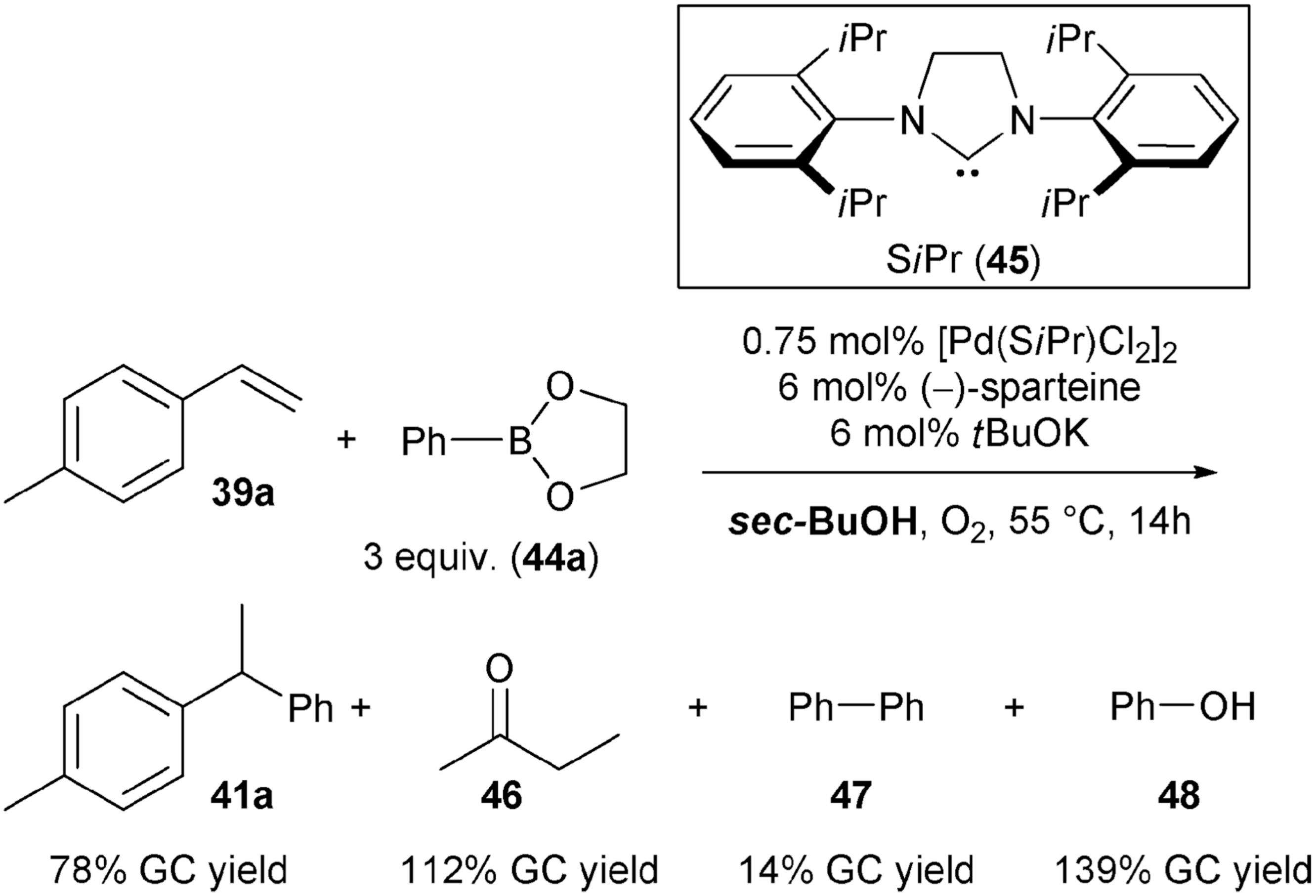

Fig. 13.

The reductive coupling of **39a** with **44a** was performed with sec-BuOH as the solvent in order to investigate why 3 equivalents of **44a** are required.

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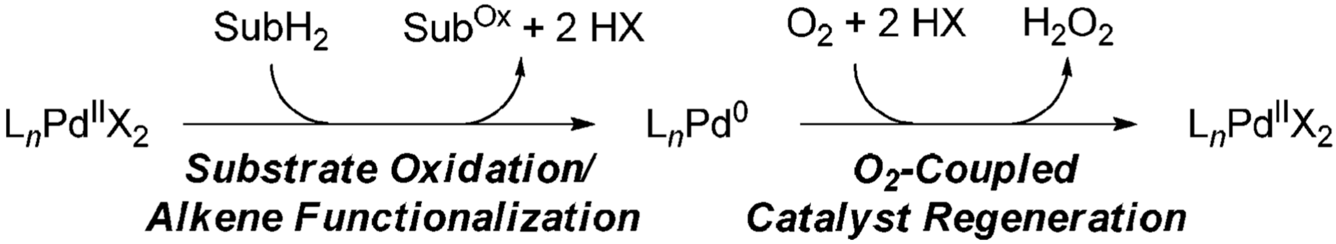

Scheme 1.

Palladium oxidase catalysis can be separated into two half reactions: (1) substrate ($SubH_2$) oxidation, which yields the oxidized product (Sub^{Ox}) and (2) O_2-coupled catalyst regeneration.

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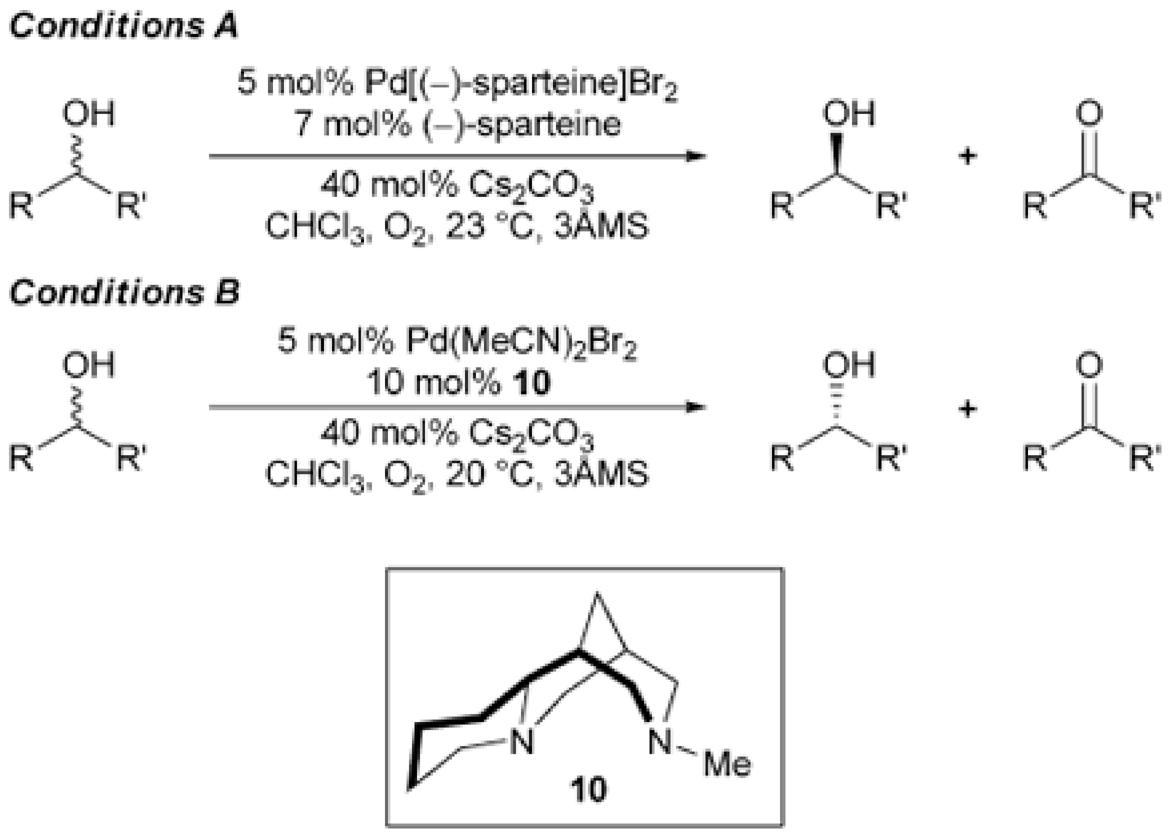
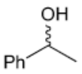
Table 1

Oxidative kinetic resolution of secondary alcohols disclosed by Stoltz, O’Brien and co-workers, which employs either (−)-sparteine or **10** to access both enantiomers



Entry	Alcohol[a]	Cond.	*t*/h	Conv. (%)[b]	ee (%)[c]	k_{rel}
1	 **11**	A	4	56	96 (*S*)	28
2		B	30	58	97 (*R*)	25

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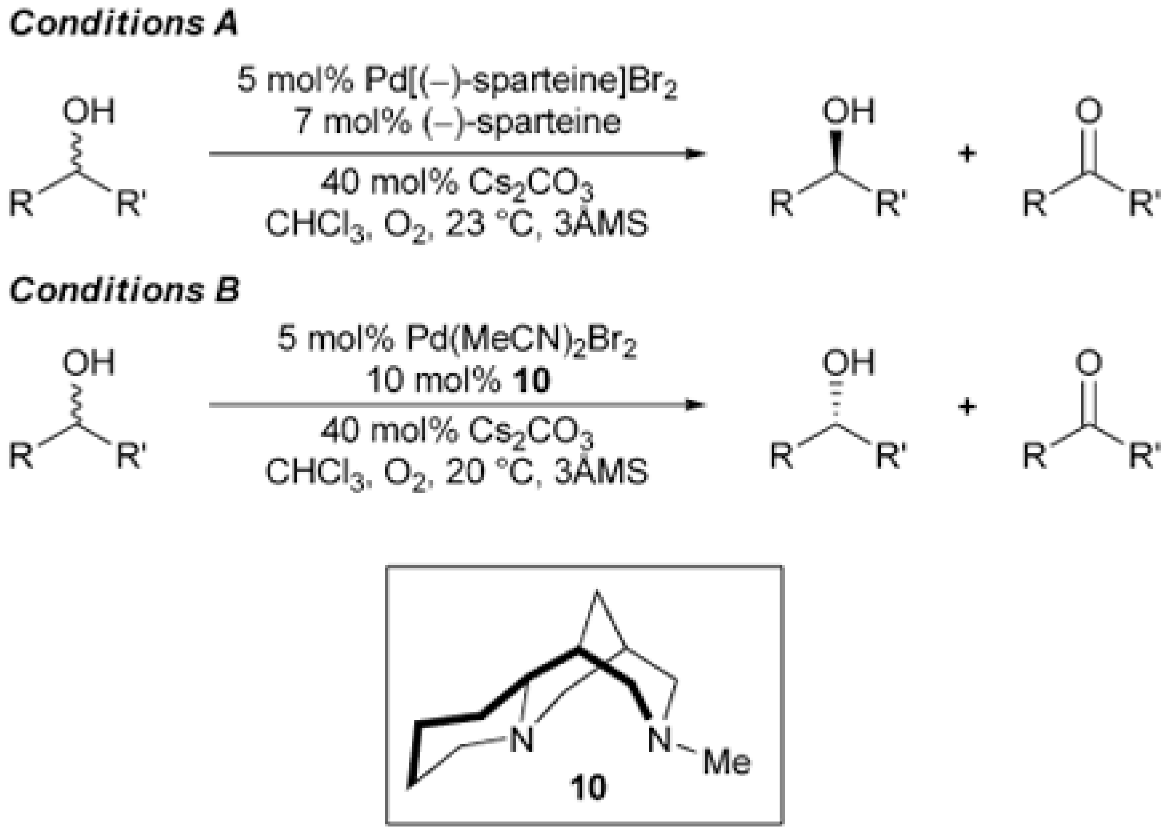
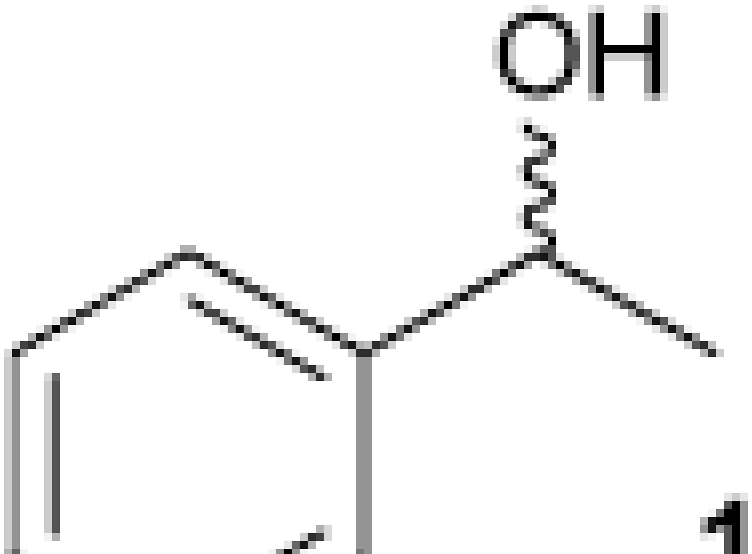


Entry	Alcohol[a]	Cond.	*t*/h	Conv. (%)[b]	ee (%)[c]	k_{rel}
3		A	4	59	95 (*S*)	17
4		B	30	60	98 (*R*)	19

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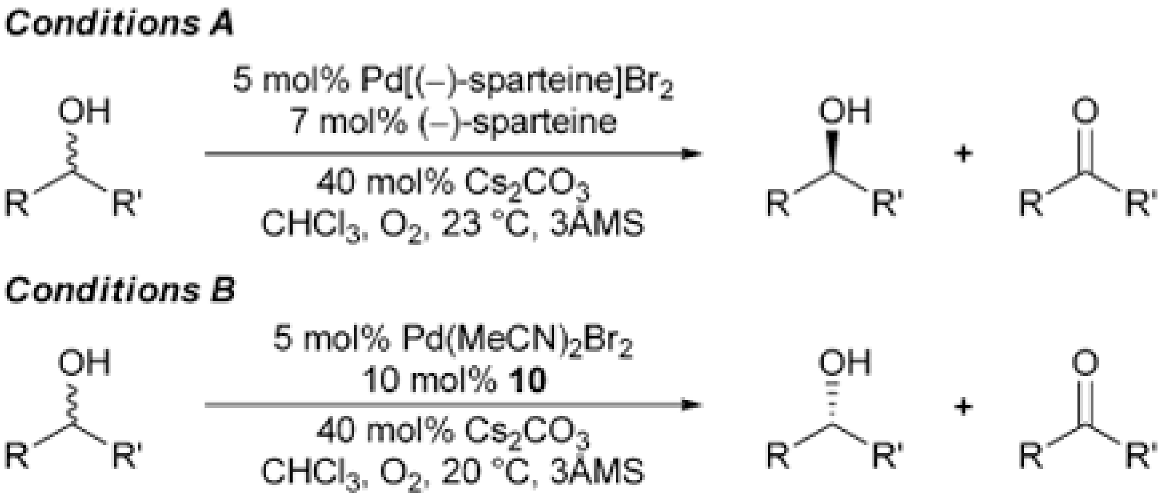
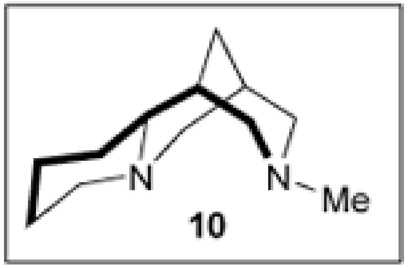
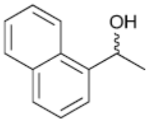
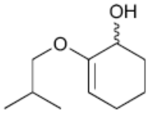




10

Entry	Alcohol[a]	Cond.	t/h	Conv. (%)[b]	ee (%)[c]	k_{rel}
5	 **13**	A	24	60	93 (*S*)	14
6	 **14**	A	48	62	97 (*S*)	16

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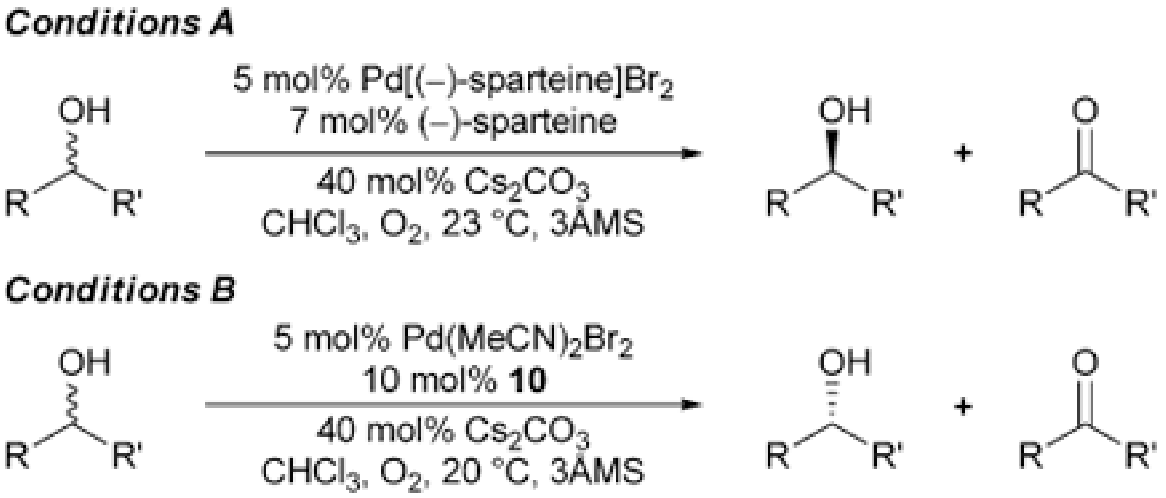
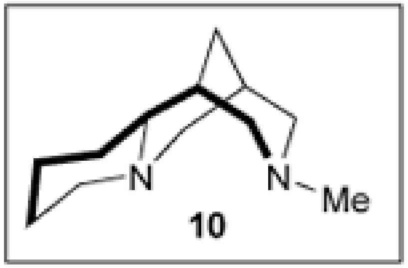
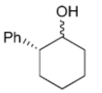
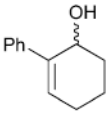
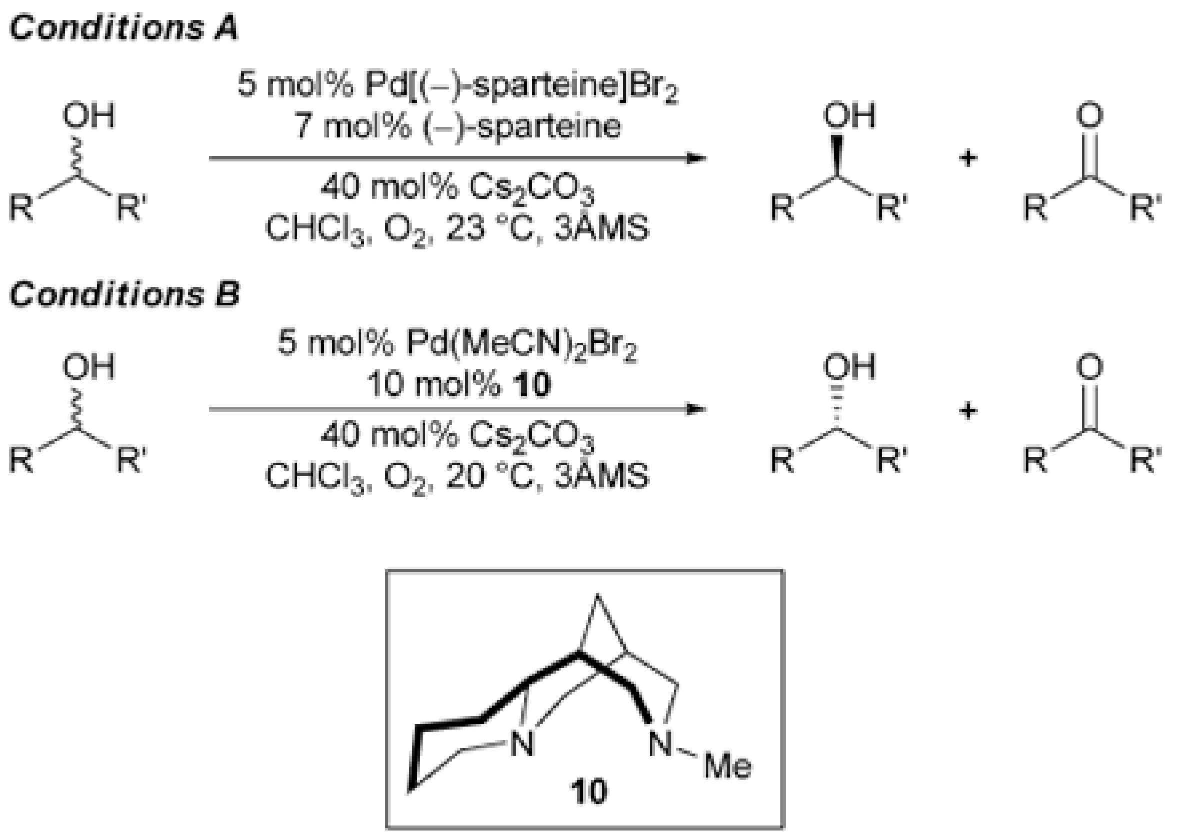
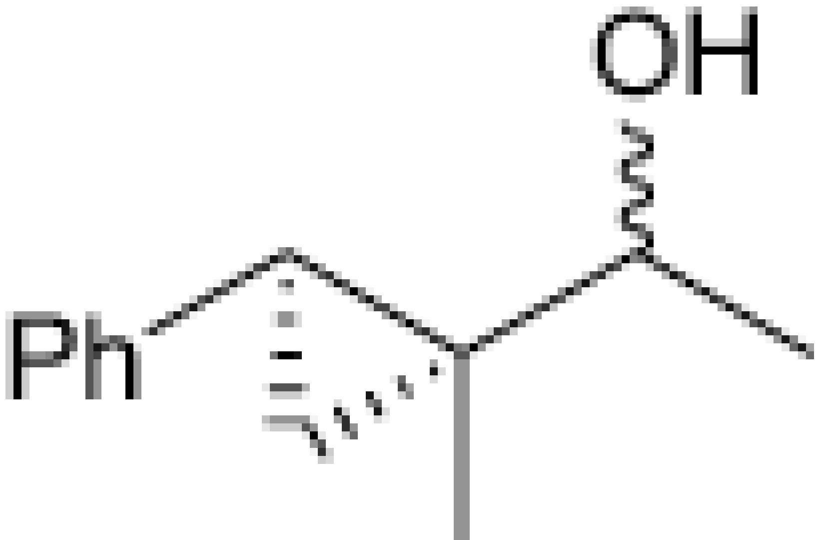




10

Entry	Alcohol[a]	Cond.	*t*/h	Conv. (%)[b]	ee (%)[c]	k_{rel}
7	 **15**	A	49	58	91 (*S*)	15
8	 **16**	B	46	57	91 (*R*)	17



Entry	Alcohol[a]	Cond.	t/h	Conv. (%)[b]	ee (%)[c]	k_{rel}
9	 **17**	B	32	59	90 (*R*)	13

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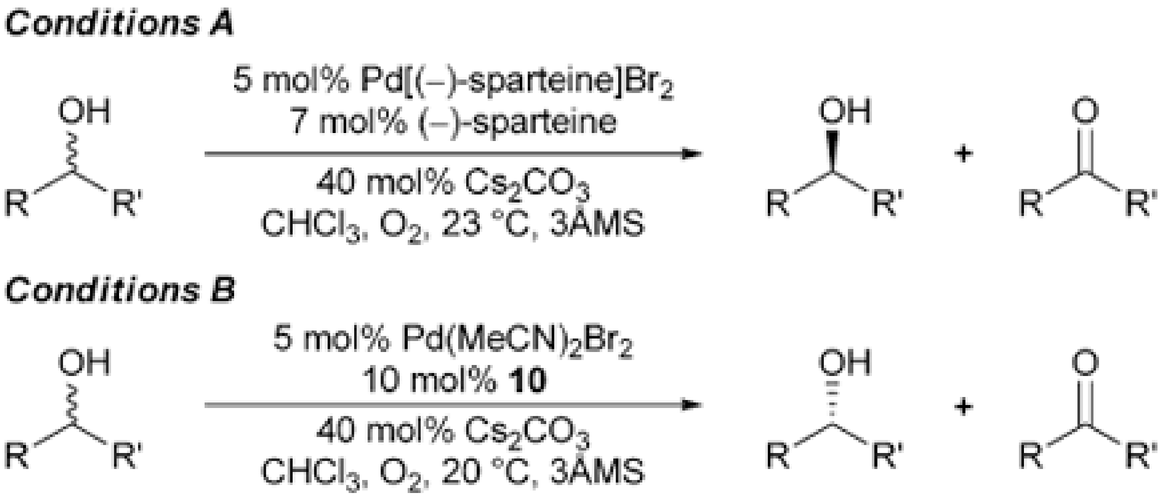
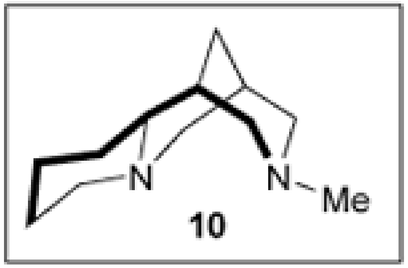
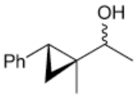




10

Entry	Alcohol[a]	Cond.	*t*/h	Conv. (%)[b]	ee (%)[c]	k_{rel}
10	 **18**	B	35	62	90 (*R*)	10

[a] Racemic starting alcohol shown.

[b] Determined by GC or ^{1}H NMR methods.

[c] Determined by chiral GC or HPLC methods and the major enantiomer of the product is shown in parentheses.

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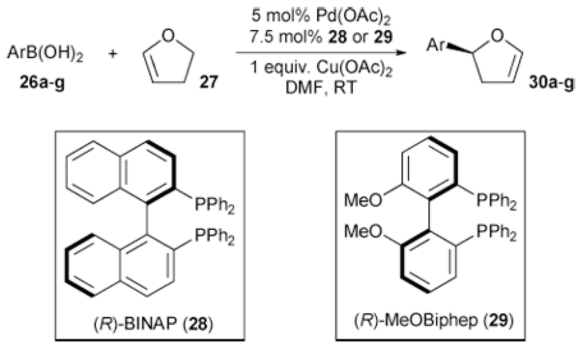
Table 2

Scope of the enantioselective oxidative Heck reaction of aryl boronic acids and dihydrofuran



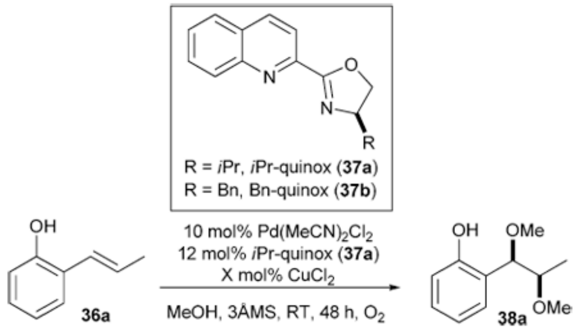
Entry	Ar		(*R*)-BINAP, 28		(*R*)-MeOBiphep, 29	
			Yield[a] (%)	ee[b] (%)	Yield[a] (%)	ee[b] (%)
1	C_6H_5	**26a**	71	57	67	82
2	*p*-FC_6H_4	**26b**	47	42	46	75
3	*p*-$(F_3C)C_6H_4$	**26c**	32	56	37	78
4	*p*-MeC_6H_4	**26d**	51	43	48	63
5	*m*-MeC_6H_4	**26e**	42	60	47	76
6	*o*-MeC_6H_4	**26f**	35	17	36	< 1
7	1-Naphthyl	**26g**	78	21	74	4

[a] Average isolated yield of two experiments.

[b] The ee was determined by HPLC equipped with a chiral stationary phase or by ^{1}H NMR.

Table 3

The observed detrimental effect of $Cu^{II}Cl_2$ on the ee of the Pd^{II}-catalyzed dialkoxylation of styrenes containing a phenol reported by Zhang and Sigman



Entry	$CuCl_2$/mol%	Yield[a] (%)	ee[b] (%)
1	20	88	10
2	10	81	26
3	5	78	59
4	2.5	80	72
5	0	67	82

[a] GC yield measured using an internal standard.

[b] Determined by GC equipped with achiral stationary phase.

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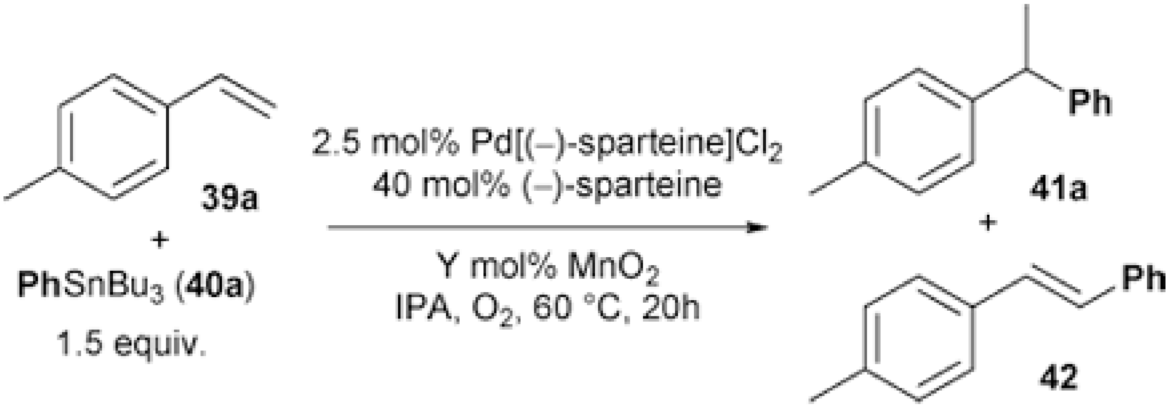
Table 4

Optimization of the reaction conditions for the reductive coupling product **41a** led to the identification of a possible inhibitor



Entry	MnO_2/mol%	Conv.[a] (%)	41a[b] (%)	41a : 42[c]
1	0	63	45	27 : 1
2[d]	0	30	22	7.4 : 1
3	75	>99	81	35 : 1
4[d]	75	26	19	7.7 : 1

[a] Percent conversion measured by GC using an internal standard.

[b] GC yield.

[c] Ratio of GC yields.

[d] 20 mol% (−)-sparteine-*N*-oxide was added.