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Intramolecular Pd-Catalyzed Carboetherification and Carboamination. Influence of Catalyst Structure on Reaction Mechanism and Product Stereochemistry

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Abstract

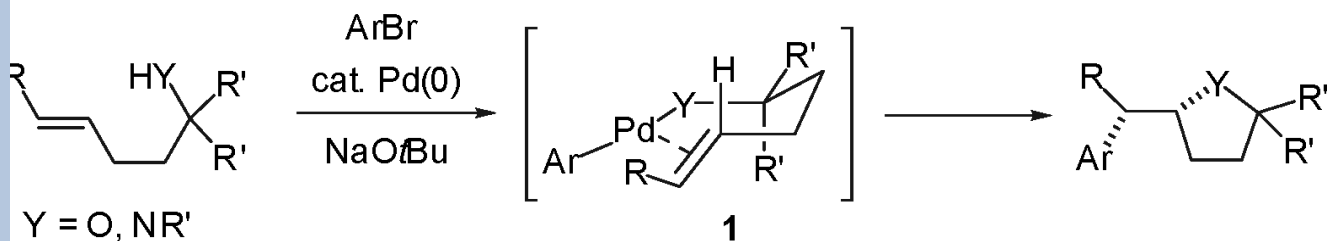
The intramolecular Pd-catalyzed carboetherification of alkenes affords 2-indan-1-yltetrahydrofuran products in moderate to good yield with good to excellent levels of diastereoselectivity. The stereochemical outcome of these reactions is dependent on the structure of the Pd-catalyst. Use of PCy₃ or P[(4-MeO)C₆H₄]₃ as the ligand for Pd leads to *syn*-addition of the arene and the oxygen atom across the double bond, whereas use of (±)-BINAP or DPP-Benzene affords products that result from *anti*-addition. The catalyst-induced change in stereochemistry is likely due to a change in reaction mechanism. Evidence is presented that suggests the *syn*-addition products derive from an unprecedented transannular alkene insertion of an 11-membered Pd(Ar)(OR) complex. In contrast, the *anti*-addition products appear to arise from Wacker-type *anti*-oxypalladation. Studies on analogous Pd-catalyzed intramolecular carboamination reactions, which afford 2-indan-1-ylpyrrolidines that result from *syn*-addition, are also described.

Introduction

A large number of important biologically active molecules and natural products contain subunits comprised of heterocyclic or carbocyclic rings attached by a C-C bond between two stereogenic centers.² Many approaches to the construction of these moieties employ strategies in which one or both stereocenters are generated prior to ring-closure.^{2,3,4} However, a potentially attractive and concise alternate approach would be to form both rings and both stereocenters in a single step via a stereospecific addition across a carbon-carbon double bond.⁵ A strategy that provides access to both possible diastereomers (*syn*-addition or *anti*-addition) from a single starting material should allow for facile preparation of analogs that could be used to optimize biological properties or probe structure/activity relationships. In addition, this strategy would permit construction of the desired product stereoisomer from the starting material with the most easily accessible alkene geometry, which could potentially decrease the length of synthetic sequences and improve overall synthetic efficiency.

We have recently described a stereoselective method for the construction of tetrahydrofurans and pyrrolidines via Pd-catalyzed intermolecular⁶ carboetherification^{7a-b} or carboamination^{7c-d,8} reactions between aryl bromides and γ -hydroxy or -amino alkenes (eq 1). These reactions generate two bonds and up to two stereocenters in one step, and are believed to proceed via intramolecular *syn*-alkene insertion into a Pd(Ar)(YR) complex (e.g. **1**).^{7b,d} We reasoned that this methodology could potentially be employed for the stereoselective construction of heterocycles bearing attached carbocyclic rings (e.g. **4**) by appending the aryl

halide moiety to the unsaturated alcohol or amine, which would lead to the formation of two bonds, two stereocenters, and two rings in a single step (Scheme 1).^{9,10} However, we felt these transformations could be quite challenging, as intermolecular carboetherification reactions of internal olefins are currently limited to substrates bearing tertiary alcohol nucleophiles, and intermolecular carboamination reactions provide complex mixtures of products when acyclic internal alkenes are employed as substrates.⁷



(1)

In addition to the potential synthetic utility and challenges described above, these transformations also posed an interesting mechanistic question. The intramolecular reactions,⁶ if mechanistically analogous to the intermolecular reactions (eq 1), would involve *syn*-alkene insertions of eleven-membered palladacyclic intermediates such as **3** (Scheme 1, Path A). Only one previous report has described transformations that presumably involve macrocyclic palladacycles bearing both Pd-C and Pd-heteroatom bonds,¹¹ and transannular *syn*-alkene insertions of macrocyclic palladacycles bearing internal olefins are unknown. Alternatively, product formation could potentially occur through other mechanistic pathways that have not been previously observed to predominate in carboamination/carboetherification processes.¹² For example, a Wacker-type mechanism (Scheme 1, Path B) could generate products resulting from *anti*-addition across the C-C double bond (**5**).^{9,13} Although *a priori* we could not predict which pathway would predominate, both pathways seemed potentially viable, and we felt it might be possible to influence the mechanistic and stereochemical course of the reactions by varying catalyst structure.^{14,15}

In this paper we describe the first examples of intramolecular carboetherification and carboamination reactions of unsaturated alcohols/amines bearing tethered aryl halides. These reactions afford 2-indan-1-yl tetrahydrofurans and pyrrolidines in good yields with stereoselectivities of up to >20:1. Products resulting from *syn*-addition of the arene and the alcohol/amine across the carbon-carbon double bond are formed when catalysts bearing monodentate phosphines such as PCy₃ or P[(*p*-MeO)C₆H₄]₃ are employed, and likely derive from unprecedented transannular alkene insertions of macrocyclic palladium(aryl)(alkoxide) or palladium(aryl)(amido) complexes (e.g. **3**). In contrast, substrates bearing tethered alcohol nucleophiles provide products resulting from *anti*-addition when catalysts supported by chelating ligands with small bite angles such as (±)-BINAP or DPP-Benzene are used.¹⁶ The experiments described herein suggest that the change in product stereochemistry likely results from a change in reaction mechanism that is influenced by both the structure of the Pd-catalyst and the nature of the tethered heteroatom, and are the first examples of phosphine ligand-control of *syn*- vs. *anti*-oxypalladation pathways in catalytic reactions.

Results

Intramolecular Carboetherification Reactions

In our initial experiments we elected to explore the intramolecular carboetherification of *Z*-alkene **6** bearing a tethered primary alcohol group as we felt that the *Z*-alkene geometry combined with the high nucleophilicity of the unhindered alkoxide (generated *in situ* upon reaction with NaOtBu) would help to facilitate formation of the putative 11-membered palladium(aryl)(alkoxide) complex required for *syn*-alkoxy-palladation. Our previous studies of Pd-catalyzed intermolecular carboetherification reactions demonstrated that the choice of phosphine ligand had a large impact on chemical yield of the desired tetrahydrofuran products.^{7a,17} Thus, our optimization studies focused on variation of this parameter while employing otherwise standard reaction conditions (toluene, NaOtBu, 105 °C).¹⁸

The alcohol substrate was prepared in three steps from commercially available materials¹⁹ and was treated with catalytic amounts of Pd₂(dba)₃/phosphine ligand in the presence of excess NaOtBu (2.0 equiv). As shown in Table 1, we were gratified to find that Pd-catalyzed reactions of **6** proceeded to generate the desired 2-(1-indanyl)tetrahydrofuran as a mixture of two diastereomers (**7** and **8**) in moderate to good yield with stereoselectivities dependent on catalyst structure. Use of a catalyst comprised of Pd₂(dba)₃ and P(*o*-tol)₃ that provided optimal results in intermolecular carboetherification reactions of acyclic internal alkenes^{7b} afforded **7** as the major diastereomer (entry 3), which derives from *syn*-addition of the arene and the alkoxide across the C-C double bond. The major side products observed in this reaction resulted from debromination of the starting material²⁰ or intramolecular Heck-arylation of the alkene. After some experimentation, a mixture of Pd₂(dba)₃ and P[(4-MeO)C₆H₄]₃ was found to provide product **7** in 54% isolated yield with 8:1 diastereoselectivity (entry 1). Use of this catalyst system diminished the competing Heck-arylation, although competing debromination of the substrate was still problematic. X-ray crystallographic analysis of a derivative bearing an aminobiphenyl substituent on the aromatic ring confirmed that the major diastereomer **7** possesses the (1*S**,2*S**)-relative stereochemistry.²¹

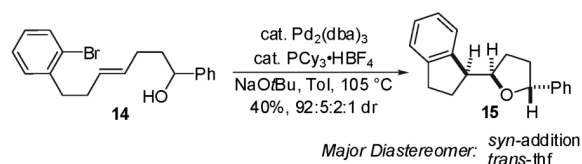
Surprisingly, a complete shift in the stereochemical outcome of this reaction was observed when (±)-BINAP was employed as the ligand (entry 8). Under these conditions, the (1*S**,2*R**)-diastereomer (**8**) was formed as the major product. This substance derives from *anti*-addition of the arene and the alcohol across the double bond, and was obtained in 60% yield and 18:1 dr. Other chelating phosphine ligands with small bite angles (≤ 93°) such as DPPE and DPP-Benzene also provided modest selectivity for the *anti*-addition product.

With optimized reaction conditions in hand, we examined the intramolecular carboetherification of several different alcohol substrates with varying alkene geometries and varying degrees of alcohol substitution. As shown in Scheme 2, the transformations of substrates bearing primary alcohols were found to be stereospecific, and either diastereomer could be selectively obtained from either the *E*- or *Z*-alkene starting materials (**6** or **9**) with the appropriate choice of catalyst. For example, the (1*S**,2*R**)-2-indan-1-yl tetrahydrofuran **8** was generated in 51% yield and >20:1 dr via the Pd/PCy₃-catalyzed *syn*-addition reaction of *E*-alkene substrate **9**,²² and was obtained in 60% yield and 18:1 dr via the Pd/(±)-BINAP catalyzed *anti*-addition of *Z*-alkene substrate **6**. Similarly, the (1*S**,2*S**)-isomer **7** was produced in 56% yield (15:1 dr) from **9** with dpp-benzene as ligand, and 54% yield (8:1 dr) from **6** with the ligand P[(*p*-MeO)C₆H₄]₃.

Substrates **10** and **11** bearing tethered tertiary alcohols were also selectively converted to products of either *syn*- or *anti*-addition depending on catalyst structure (Scheme 3). However, in contrast to reactions of *Z*-alkene primary alcohol **6**, which afforded *syn*-addition product **7** with most catalyst systems, transformations of the analogous tertiary alcohol bearing a *Z*-alkene

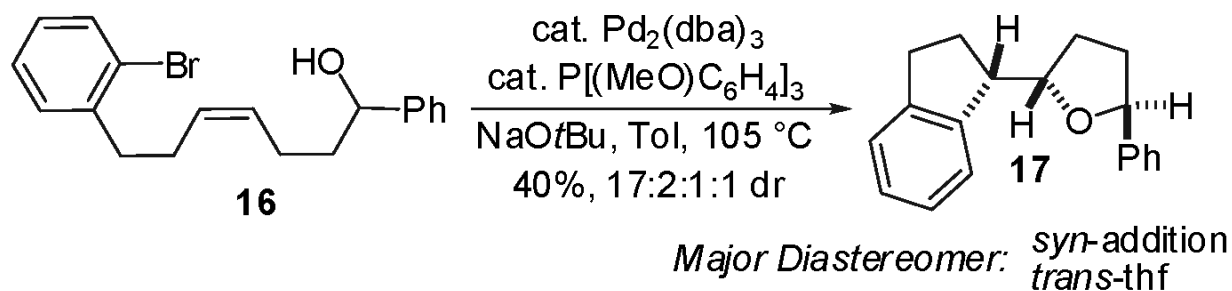
(**11**) gave *anti*-addition product **12** under most conditions examined. After some experimentation, the Pd/PMe₃-HBF₄ catalyzed reaction of **11** was found to provide **13**,²² the product of *syn*-addition across the *Z*-alkene, in 74% yield with 9:1 dr. Use of the ligand PCy₃-HBF₄ for the Pd-catalyzed cyclization of **11** afforded *anti*-addition product **12** in 78% yield and 14:1 dr.²³ Although both diastereomers **12** and **13** could be selectively obtained from either starting material (**10** or **11**), higher yields were obtained with the *Z*-alkene substrate **11**.

In order to examine the possibility of stereoselectively generating products with three stereocenters, the secondary alcohol **14** bearing an *E*-alkene was prepared and subjected to the carboetherification reaction conditions. The best results were obtained with a catalyst comprised of Pd₂(dba)₃/PCy₃-HBF₄, which provided a 40% isolated yield of **15** with 92:5:2:1 selectivity favoring *syn*-addition across the alkene and *trans*-stereochemistry around the tetrahydrofuran ring (eq 2).²⁴ The modest yield can be attributed to the formation of large amounts of side products that derive from reduction of the aryl bromide with concomitant oxidation of the alcohol. Use of (±)-BINAP for this transformation led to complex mixtures of products; only small amounts of the desired tetrahydrofuran derivatives were detected by ¹H NMR analysis of crude reaction mixtures.



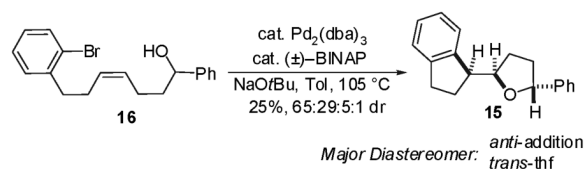
(2)

The cyclization of the corresponding *Z*-alkene **16** proceeded in 40% yield with good selectivity (17:2:1:1 dr)²⁵ for *syn*-addition/*trans*-thf formation (eq 3); the two most prevalent diastereomers both contained *trans*-tetrahydrofuran rings.²⁴ As noted above, competing oxidation/reduction of the substrate was problematic in this system.



(3)

In contrast to the related Pd/BINAP-catalyzed transformation of the *E*-alkene substrate **14**, treatment of **16** with catalytic Pd₂(dba)₃/(±)-BINAP provided **15** as the major diastereomer, which results from *anti*-addition with *trans*-thf formation, albeit in low yield (25%) (eq 4). High selectivity for *anti*-addition was observed (94:6), although *trans*/*cis*-selectivity was modest (ca. 2:1).²⁴ The major side products in this transformation resulted from competing intramolecular Heck-arylation of the starting material.

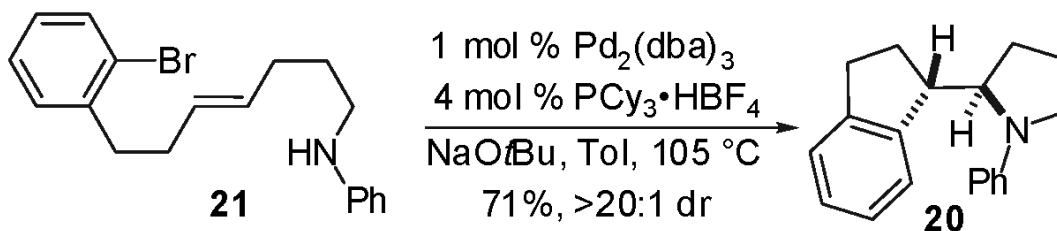


(4)

Intramolecular Pd-Catalyzed Carboamination Reactions

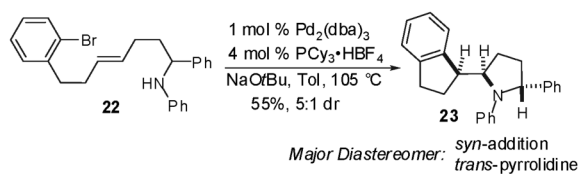
Having demonstrated the feasibility of intramolecular carboetherification reactions, we sought to determine whether or not intramolecular carboamination reactions could also be achieved. Thus, the *Z*-alkene substrate **18** bearing a tethered aniline moiety was prepared and treated with a catalytic amount of Pd₂(dba)₃ and several different phosphine ligands under reaction conditions similar to those described above (Table 2). Interestingly, in contrast to the results obtained in cyclizations of alcohol-containing substrate **6**, all catalysts examined for the cyclization of **18** provided selectivity for formation of (1*S**,2*S**)-stereoisomer **19**, which derives from *syn*-addition across the *Z*-alkene. As observed in the related transformations of substrates bearing alcohol nucleophiles, the major side products formed in these reactions result from debromination of the starting material or intramolecular Heck-arylation. Use of PCy₃·HBF₄ (entry 7) provided the optimal results for this transformation (88% yield, >20:1 dr), and effectively suppressed the formation of both side products.

The intramolecular carboamination reactions also proved to be stereospecific, as *E*-alkene derivative **21** underwent cyclization under optimized conditions to afford (1*S**,2*R**)-diastereomer **20**, the product of *syn*-addition across the *E*-alkene, in 71% yield with >20:1 dr (eq 5). As observed with the analogous alcohol substrates, the chemical yield obtained in the reaction of the *E*-alkene was slightly lower than the yield of the reaction of *Z*-alkene **18**.

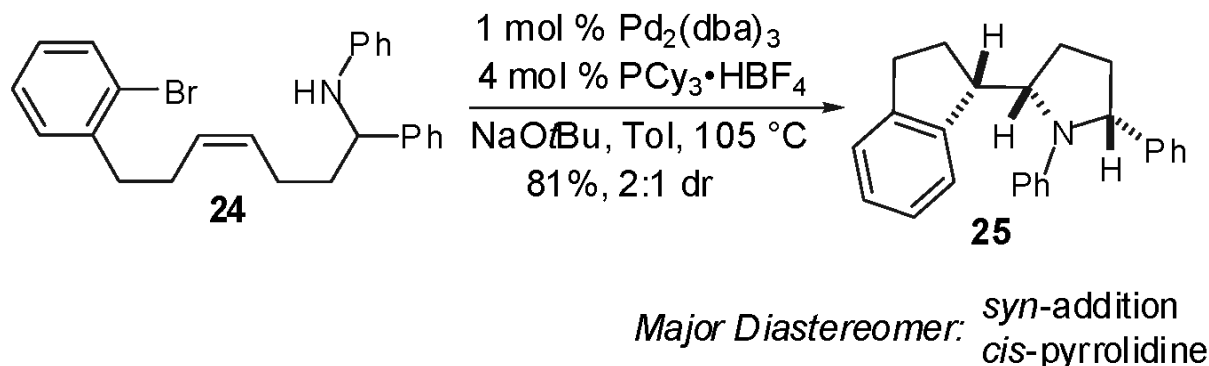


(5)

Reactions involving aniline-bearing substrates that are branched at C-1 proceeded with complete *syn*-selectivity. For example, treatment of **22** with catalytic Pd₂(dba)₃/PCy₃·HBF₄ afforded product **23** in 55% yield and 5:1 diastereoselectivity (eq 6). Interestingly, the major product diastereomer was found to possess 2,5-*trans*-disubstitution around the pyrrolidine ring; the minor diastereomer results from *syn*-addition with *cis*-pyrrolidine formation.²⁴ In contrast, the analogous intermolecular carboamination reactions of γ -(*N*-arylamino)alkenes have been shown to provide generally high selectivity for the formation of 2,5-*cis*-disubstituted pyrrolidine products.^{7c} The reaction of *Z*-alkene **24** proceeded in high yield (81%), but modest diastereoselectivity (2:1 dr) favoring product **25**, which results from *syn*-addition across the alkene with *cis*-stereochemistry around the pyrrolidine ring (eq 7). As seen in the reaction of **22**, both observed diastereomers resulting from the cyclization of **24** derive from *syn*-addition, but differ in their relative stereochemistry about the pyrrolidine ring.²⁴



(6)



(7)

Discussion

Reactivity and Stereoselectivity

The intramolecular palladium-catalyzed carboetherification and carboamination of γ -hydroxy- or γ -aminoalkenes with tethered aryl bromides provides a new, stereoselective means to generate carbocycles bearing attached heterocycles. These reactions effect the conversion of acyclic precursors to bicyclic products with formation of two bonds, two rings, and two stereocenters in a single step. The yields and selectivities are dependent on a number of factors, but under optimal conditions the desired products are obtained in moderate to good yields with good to excellent stereocontrol.

Several trends in reactivity have been observed during the course of these experiments. From the results described above, it appears that the chemical yield is affected by the alkene geometry, the nature of the heteroatom, and the degree of substitution adjacent to the heteroatom. For example, substrates bearing *Z*-alkenes are usually transformed in higher chemical yield than the analogous *E*-alkenes. In addition, reactions involving starting materials with tethered aniline nucleophiles produce higher yields than analogous reactions of alcohol-bearing substrates (with a similar degree of substitution). Finally, in many cases substitution next to the heteroatom decreases chemical yield.

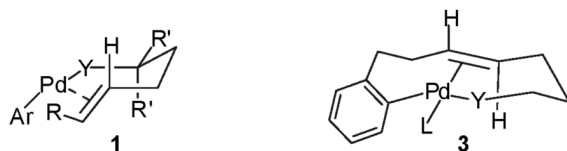
The stereochemical outcome of these reactions is influenced by both the nature of the heteroatom and the catalyst. All substrates containing nitrogen nucleophiles that were examined in these studies are selectively converted to products resulting from *syn*-addition across the double bond. Although the catalyst structure has an effect on the diastereoselectivity of the pyrrolidine-forming reactions, with diastereomeric ratios varying from 1:1 to >20:1, no catalyst examined led to selective formation of the *anti*-addition product. In contrast, primary and tertiary alcohol substrates were transformed to products of *syn*-addition when catalysts bearing electron-rich monodentate ligands such as PCy₃, PMe₃, or P[(MeO)C₆H₄]₃ were

employed, but reactions of these starting materials gave products of *anti*-addition when chelating phosphines with small bite angles (e.g. BINAP, DPP-Benzene, or DPPE; bite angles $\leq 93^\circ$) were used as supporting ligands. Notably, in carboetherification reactions of primary and tertiary alcohols either product diastereomer could be obtained selectively from either starting alkene stereoisomer.

Reactions involving α -substituted alcohols catalyzed by Pd/PCy₃ or P[(MeO)C₆H₄]₃ proceed with good to excellent levels of selectivity for the formation of one of four possible diastereomeric products; the major diastereomer results from *syn*-addition with *trans*-thf formation. However, use of Pd/BINAP with these substrates leads to low yields and modest selectivities. The analogous Pd/PCy₃ catalyzed reactions of α -branched anilines proceed in good yields with very high *syn*-selectivity, but give mixtures of *cis*- and *trans*-pyrrolidine products.

Mechanism of Intramolecular Carboetherification Reactions that Provide *syn*-Addition Products

In our previous studies on intermolecular Pd-catalyzed carboetherification and carboamination reactions we obtained results that were most consistent with a mechanistic pathway involving *syn*-insertion of the alkene moiety into the Pd-heteroatom bond of intermediate Pd(Ar)(OR) or Pd(Ar)(NRR') complexes (e.g. **1**).^{7b,d} Other mechanistic scenarios such as product formation via a Wacker-type *anti*-addition or via intermolecular carbopalladation followed by C-O or C-N bond-forming reductive elimination were ruled out on the basis of the observed product stereochemistry, the side products formed in the reactions, and the high regioselectivity for formation of 5-membered ring products. The fact that *syn*-addition products are also obtained in the intramolecular reactions suggests that a similar mechanism may operate. However, this pathway would necessitate the formation of 11-membered ring intermediates (e.g. **3**), which may be entropically unfavorable, and would require transannular alkene insertion of a macrocyclic palladacycle bearing an internal alkene, which is unprecedented.²⁶ Thus, two plausible mechanisms for the formation of the observed *syn*-addition products of intramolecular reactions merit consideration.



As shown in Scheme 4, oxidative addition of the aryl bromide **26** to the L_nPd(0) species generated *in situ* from Pd₂(dba)₃ and a monodentate phosphine ligand, followed by coordination of the tethered alkene would afford the 16-electron intermediate **27**, a species common to both mechanistic scenarios. This intermediate could potentially be converted to the observed products via a Heck-type 5-exo carbopalladation^{26a} and deprotonation by NaOtBu to provide **28** (Path A), which could undergo nucleophilic displacement of the bromide by the tethered alkoxide to afford **29**.²⁷ An unprecedented sp³-carbon-oxygen bond-forming reductive elimination from Pd(II)-complex **29** (with retention of configuration) would generate the observed product **30**.^{28,29} However, the fact that the cyclizations of secondary alcohol substrates **14** and **16** proceed with good to excellent stereoselectivity for *trans*-tetrahydrofuran formation and *syn*-addition suggests that this pathway is much less likely than the mechanism shown in Path B (see below).³⁰ If the reactions proceed via the mechanism outlined in Path A, the 5-exo carbopalladation event would determine both the *syn/anti*-stereochemistry as well as the stereochemistry around the thf-ring. If the stereochemistry-determining event occurs via intramolecular carbopalladation of intermediate **27** with no communication between the alcohol and the metal, it is unlikely that high selectivity for *trans*-thf formation would be

observed.³¹ In addition, Heck-type side products that would result from slow reductive elimination following the 5-exo carbopalladation are not formed in significant amounts in optimized reactions that lead to *syn*-addition.

In contrast, the mechanistic pathway outlined in Scheme 4, Path B, which is analogous to that proposed for the intermolecular reactions,^{7b,d} can account for both high *syn*-selectivity, and high selectivity for *trans*-thf formation. In this scenario, the 16-electron intermediate **27** could undergo deprotonation followed by associative ligand substitution³² of the alkoxide for the bromide²⁷ to afford eleven-membered palladacycle **31** in which the alkyl group is oriented in a pseudoequatorial position.³³ Formation of the eleven-membered palladacycle **31** is presumably facilitated by complexation of the alkene to the metal, which allows for Pd-O bond formation via an effectively smaller ring.³⁰ Transannular insertion of the alkene into the palladium-oxygen bond would generate **32**, which could undergo C-C bond-forming reductive elimination to form the observed product **30**. Pseudoequatorial orientation of the R-substituent in the transition state for alkene insertion would lead to the observed products bearing *trans*-2,5-disubstituted tetrahydrofuran groups, and should be lower in energy than the related transition state with axial orientation of the R-group due to developing transannular interactions. The side products that comprise the remainder of the mass balance in these reactions result from oxidation of the alcohol with concomitant reduction of the aryl bromide, and are consistent with competing β -hydride elimination of **31** prior to alkene insertion. Although the experiments described in this paper cannot rule out product formation via alkene insertion into the Pd-C bond of macrocycle **31**, literature precedent suggests that alkene insertion into the metal-heteroatom bond of late-metal M(R)(OR) complexes is usually more facile than insertion into the M-C bond.^{7,34,35}

Mechanism of Intramolecular Carboetherification Reactions that Provide *anti*-Addition Products

In contrast to all previously described intermolecular carboetherification reactions of internal alkenes with aryl bromides,^{7a-b,36,37} which provide *syn*-addition products, the intramolecular carboetherifications provide products resulting from *anti*-addition when chelating ligands with small bite angles (e.g. BINAP or DPP-Benzene) are employed. Formation of *anti*-addition products via *syn*-insertion followed by reversible β -hydride elimination/reinsertion/ σ -bond rotation processes that are occasionally observed in the intermolecular transformations^{7b} does not appear to be likely in the intramolecular reactions (Scheme 5), as this pathway would require a 7-endo-hydridopalladation of an aryl(hydrido)palladium alkene complex (**33**), which is energetically unfavorable.³⁸ In addition, side products that would result from reductive elimination of **33** prior to 7-endo-hydridopalladation are not observed; the major side products in reactions that afford *anti*-addition products derive from intramolecular Heck-type reactions (see below).

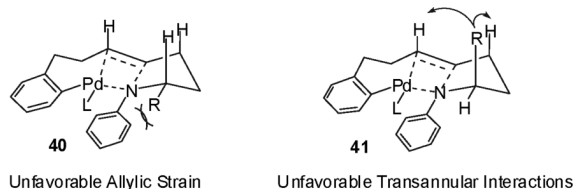
Instead, it appears likely that the change in observed product stereochemistry arises from a fundamental change in the mechanism through which the products are formed. This change can be attributed to the notion that tightly chelating ligands are expected to inhibit the associative ligand substitution process required for palladium-alkoxide formation.³² As outlined in Scheme 6, Path A, oxidative addition of the aryl bromide **26** to a (L-L)Pd(0) complex followed by alkene coordination would generate 18-electron complex **34**. This coordinatively saturated complex could not be converted to a palladium(aryl)(alkoxide) analogous to **31** via an associative ligand substitution process, and it is unlikely that the 11-membered palladacycle **31** would be generated in the absence of alkene coordination, as 11-membered ring formation is entropically unfavorable. Thus, conversion of **34** to **31** is likely to be relatively slow.³⁹ Instead, a mechanistic pathway involving a Wacker-type *anti*-alkoxypalladation may be more accessible in this system than in other carboetherification processes. The *anti*-

alkoxypalladation of **34** via an ordered transition state such as **35** could generate **36**, which would provide *anti*-addition product **37** upon C-C bond-forming reductive elimination. The stereochemistry around the tetrahydrofuran ring would again be dictated by nonbonding interactions in the transition state, with a preference for pseudoequatorial orientation of substituents. However, prior studies have shown that differences in transition state energies for pseudoaxial vs. pseudoequatorial orientation of the α -substituents or the alkene moiety in related Wacker-type cyclizations may be relatively small, as the preference for *trans*-thf formation is often modest in the absence of additional substituents.^{9,37}

Alternatively, the products of *anti*-addition could derive from Heck-type carbopalladation of **34** to generate **38**, followed by C-O bond-forming reductive elimination through an S_N2 mechanism, which would lead to inversion of the C2 stereocenter to provide **37**. Although we cannot rule out product formation via this mechanism, we currently favor the hypothesis involving a Wacker-type pathway, as the sp^3C-O bond-forming reductive elimination required for product formation via Path B is not known to occur from Pd(II) complexes,^{28,29} and would require S_N2 substitution to occur at a hindered secondary carbon atom flanked by an adjacent secondary carbon stereocenter. The fact that Heck-type side products (e.g **39**) are generated in these transformations suggests that complex **38** is kinetically accessible, but mechanistic pathway B cannot account for control of relative stereochemistry around the tetrahydrofuran ring. The observed selectivity for formation of *trans*-disubstituted tetrahydrofuran products in the Pd/BINAP catalyzed reaction of **16** is more consistent with an ordered transition state similar to **35**. Thus, although **38** may be accessible under the reaction conditions, it is not necessarily an intermediate along the pathway between **34** and **37**.

Mechanism and Stereochemistry of Intramolecular Carboamination Reactions

The intramolecular carboamination reactions described above provide products that derive from *syn*-addition of the amine and the arene across the carbon-carbon double bond. It is likely that these transformations proceed via a mechanism similar to that outlined above (Scheme 4) for *syn*-addition reactions of alcohol substrates, which involves an transannular alkene insertion of an 11-membered palladium(aryl)(amido) intermediate through transition state **40** or **41**. However, in reactions of substrates bearing tethered anilines with α -stereocenters, the factors leading to a preference for either *trans*-pyrrolidine stereochemistry (*E*-alkenes) or *cis*-pyrrolidine stereochemistry (*Z*-alkenes) are more complicated than in the related transformations of secondary alcohols, and the origin of the observed stereochemistry is not entirely clear. One possible explanation of these results is that pseudoequatorial orientation of the C1-R-group (**40**) would minimize developing transannular interactions in the transition state,⁴⁰ but could lead to developing $A^{1,3}$ -strain between the Nsp^2 -aryl group and the pseudoequatorial R-substituent.⁴¹ Alternatively, pseudoaxial orientation of the R-group (**41**) may minimize allylic strain at the expense of increased unfavorable transannular interactions. The results of the experiments shown in eq 6-7 are consistent with preferred pseudoequatorial orientation of the substituent when the substrate contains the *E*-alkene geometry, which suggests the energetic effects of the transannular interactions outweigh the effects of $A^{(1,3)}$ -strain for this system. In contrast, there appears to be a slight preference for pseudoaxial orientation with the *Z*-alkene geometry, which implies the transannular interactions may be lessened relative to the degree of allylic strain in this case.⁴²



In contrast to Pd/BINAP or Pd/DPP-Benzene catalyzed reactions of alcohol substrates, which provide good selectivity for products of *anti*-addition, use of BINAP or DPP-Benzene with substrates bearing aniline nucleophiles results in low *syn/anti* stereoselectivity. The differences in the stereochemical outcome of these transformations may be due to the effect of heteroatom nucleophilicity (anionic alkoxide vs. neutral amine) on the rate of *anti*-heteropalladation. In the presence of NaOtBu there is likely a significant equilibrium concentration of highly nucleophilic alkoxides that result from deprotonation of the substrate alcohol.⁴³ In contrast, deprotonation of the less acidic aniline nucleophile would occur to a lesser extent, hence the concentration of anilide anion is likely to be low, which may result in relatively slower rates of Wacker-type addition of the nitrogen nucleophiles. The fact that yields of *anti*-addition products decrease (under identical conditions) with increasing steric bulk of the alcohol nucleophile is consistent with this notion.^{23,44}

Conclusions

In conclusion, we have demonstrated the feasibility of a new strategy for the stereoselective construction of products bearing two attached rings via Pd-catalyzed carboetherification and carboamination reactions. Depending on the structure of the catalyst and the substrate, selectivity for either *syn*-addition or *anti*-addition is observed. The products of *syn*-addition appear to derive from unprecedented transannular alkene insertions of unusual 11-membered Pd(Ar)(YR) intermediates. In contrast, the products of *anti*-addition are consistent with reaction via a different mechanistic pathway that may involve Wacker-type *anti*-heteropalladation of the alkene. These studies represent the first examples of phosphine ligand-control of *syn*-insertion vs. *anti*-addition pathways in catalytic reactions involving olefin oxypalladation, which allows for stereoselective construction of either of two possible product diastereomers from a given alcohol substrate. Further studies on the scope and synthetic applications of this new methodology are currently underway.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment

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References and Notes

1. X-ray structure analysis was performed by Jeff W. Kampf.
2. For examples of heterocycles bearing attached heterocycles, see: a) Bermejo A, Figadere B, Zafra-Polo M-C, Barrachina I, Estornell E, Cortes D. *Nat. Prod. Rep* 2005;22:269–303.303 [PubMed: 15806200] b) Faul MM, Huff BE. *Chem. Rev* 2000;100:2407–2474.2474 [PubMed: 11749289] c) Hoppe R, Scharf H-D. *Synthesis* 1995:1447–1464.1464 d) Koert U. *Angew. Chem., Int. Ed* 1995;34:298–300.300
3. For examples of heterocycles bearing attached carbocycles, see: a) Ukiya M, Akihisa T, Yasukawa K, Kasahara Y, Kimura Y, Koike K, Nikaido T, Takido M. *J. Agric. Food Chem* 2001;49:3187–3197.3197 [PubMed: 11453750] b) Spinella A, Mollo E, Trivellone E, Cimino G. *Tetrahedron* 1997;53:16891–16896.16896 c) Rasmusson GH, Reynolds GF, Steinberg NG, Walton E, Patel GF, Liang T, Cascieri MA, Cheung AH, Brooks JR, Berman C. *J. Med. Chem* 1986;29:2298–2315.2315 [PubMed: 3783591] d) Arthur HR, Ko PDS. *Phytochemistry* 1974;13:2551–2557.2557
4. For representative examples of other strategies that generate attached rings via C-C bond-forming reactions between cyclic precursors, see: a) Lemieux RM, Meyers AI. *J. Am. Chem. Soc*

1998;120:5453–5457.5457b)Lebsack AD, Overman LE, Valentekovich RJ. J. Am. Chem. Soc 2001;123:4851–4852.4852 [PubMed: 11457302]

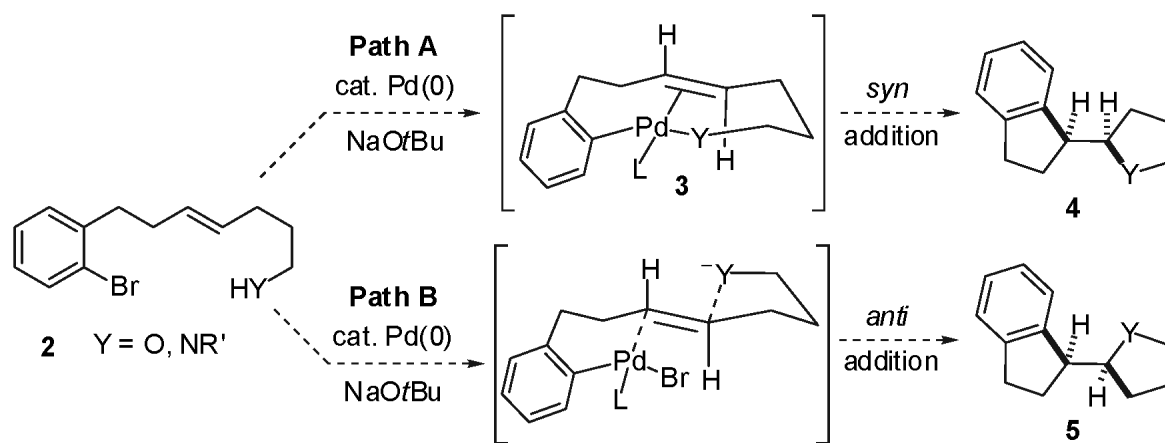
5. a) For attached-ring synthesis via pinacol-terminated Prins cyclizations, which generate two stereocenters and one ring in a single step see:Overman LE, Pennington LD. Can. J. Chem 2000;78:732–738.738b) For attached-ring synthesis via intramolecular 1,3-dipolar cycloaddition followed by Mo-catalyzed ring cleavage, see:Tranmer GK, Tam W. Org. Lett 2002;4:4101–4104.4104 [PubMed: 12423096]c) For attached ring synthesis via Mn(III)-promoted oxidative cyclization reactions of malonates bearing tethered unsaturated alcohols, see:Hulcoop DG, Sheldrake HM, Burton JW. Org. Biomol. Chem 2004;2:965–967.967 [PubMed: 15034618]
6. Both the intermolecular and intramolecular carboetherification/carboamination reactions have an intramolecular component, as the heteroatom is tethered to the alkene in both cases. In this manuscript, the term “intermolecular carboetherification/carboamination” is used to describe the reaction between an aryl bromide and a γ -unsaturated alcohol/amine that are not tethered, whereas the term “intramolecular carboetherification/carboamination” describes reactions in which the γ -unsaturated alcohol/amine are tethered to the aryl bromide.
7. a) Wolfe JP, Rossi MA. J. Am. Chem. Soc 2004;126:1620–1621. [PubMed: 14871078] b) Hay MB, Wolfe JP. J. Am. Chem. Soc 2005;127:16468–16476. [PubMed: 16305233] c) Ney JE, Wolfe JP. Angew. Chem., Int. Ed 2004;43:3605–3608. d) Ney JE, Wolfe JP. J. Am. Chem. Soc 2005;127:8644–8651. [PubMed: 15954769]
8. For recent examples of stoichiometric Cu-promoted carboamination reactions, see:Sherman ES, Chemler SR, Tan TB, Gerlits O. Org. Lett 2004;6:1573–1575.1575 [PubMed: 15128239]
9. Balme has described elegant studies on related intramolecular reactions of alkenes bearing a bromoaryl group tethered to one sp^2 carbon and a malonate derivative tethered to the other. These reactions proceed via Wacker-type *trans*-carbopalladation of intermediate six-membered arylpalladium alkene complexes to afford products resulting from *anti*-addition across the C-C double bond. See:Bruyère D, Bouyssi D, Balme G. Tetrahedron 2004;60:4007–4017.4017
10. For intramolecular *anti*-addition reactions of alkynes bearing an alkyl(bromoaryl) group tethered to one end and an alkyl carboxylic acid to the other see:a)Cavicchioli M, Bouyssi D, Gore J, Balme G. Tetrahedron Lett 1996;37:1429–1432.1432b)Bouyssi D, Balme G. Synlett 2001:1191–1193.1193
11. For examples of Pd-catalyzed N-arylation reactions that likely proceed through macrocyclic palladium(aryl)(amido) complexes, see:Beletskaya IP, Bessmertnykh AG, Averin AD, Denat F, Guillard R. Eur. J. Org. Chem 2005:281–305.305and references cited therein.
12. In our previous studies we have noted that the large majority of products formed in intermolecular carboetherification and carboamination reactions of internal alkenes derive from *syn*-insertion of the alkene into the Pd-heteroatom bond of intermediate Pd(Ar)(OR) or Pd(Ar)(NRR') complexes. See references 4b and 4d.
13. For examples of intramolecular *anti*-carboacetoxylation reactions of alkynes, which proceed through a Wacker-type mechanism, see:Bouyssi D, Balme G. Synlett 2001:1191–1193.1193
14. a) Through a series of deuterium labeling studies, Hayashi has demonstrated that the Pd(II)-catalyzed oxidative cyclization of an *o*-allylphenol derivative proceeds via *anti*-alkoxypalladation in the presence of LiCl, and via *syn*-alkoxypalladation in the absence of LiCl. However, one of the stereocenters formed in these transformations is destroyed by the β -hydride elimination step that terminates the catalytic cycle. Thus, in the absence of labeled substrates both transformations would provide identical products. See:Hayashi T, Yamasaki K, Mimura M, Uozumi Y. J. Am. Chem. Soc 2004;126:3036–3037.3037 [PubMed: 15012118]b) Stoltz has recently described experiments analogous to Hayashi's deuterium labeling studies that provide further evidence for an accessible *syn*-oxypalladation pathway in Wacker-type cyclizations of unsaturated alcohol derivatives. See:Trend RM, Ramtohil YK, Stoltz BM. J. Am. Chem. Soc 2005;127:17778–17788.17788 [PubMed: 16351107]c) For additional studies on the effect of chloride ion concentration on the mechanistic/stereochemical pathway of the Wacker-oxidation, see:Hamed O, Thompson C, Henry PM. J. Org. Chem 1997;62:7082–7083.7083 [PubMed: 11671803]and references cited therein.
15. Previously described Wacker-type cyclizations of alkenes bearing tethered heteroatoms that afford tetrahydrofuran or pyrrolidine products generally proceed via a Pd(II)-Pd(0) catalytic cycle. The mechanism of these transformations involves complexation of the alkene to Pd(II) followed by nucleophilic attack of the tethered heteroatom and β -hydride elimination to generate the heterocyclic

product. The resulting Pd(H)(X) complex undergoes reductive elimination of HX to provide a Pd(0) complex, which is then reoxidized to Pd(II) by an added oxidant. Catalysts employed for these reactions generally contain halide, carboxylate, or amine ligands rather than phosphine ligands. For further details, see: a) reference 14;b)Semmelhack MF, Bodurow C. J. Am. Chem. Soc 1984;106:1496–1498.1498c)Harayama H, Abe A, Sakado T, Kimura M, Fugami K, Tanaka S, Tamaru Y. J. Org. Chem 1997;62:2113–2122.2122 [PubMed: 11671516]

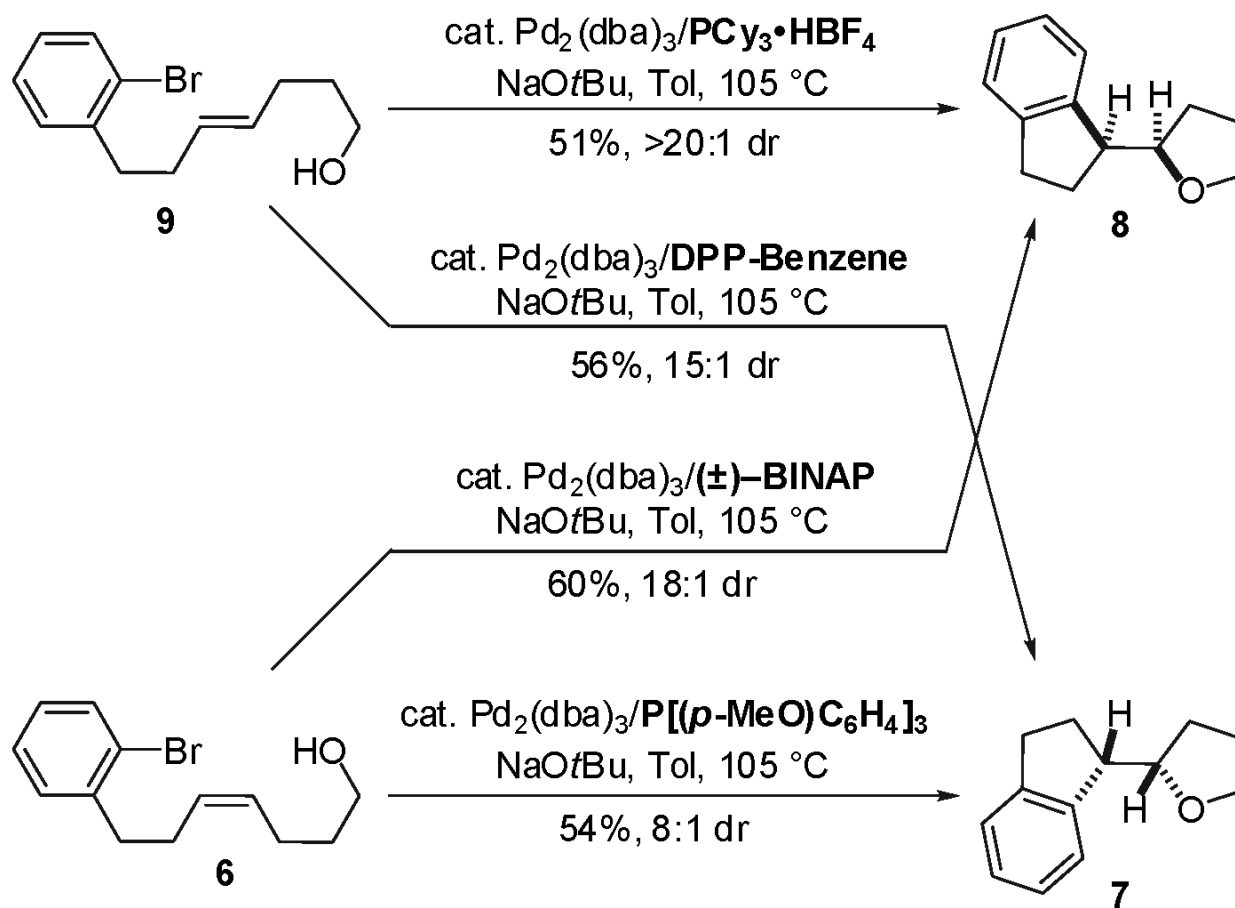
16. (\pm)-BINAP = 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl; Dpp-benzene = 1,2-bis(diphenylphosphino)benzene.
17. Hay MB, Hardin AR, Wolfe JP. J. Org. Chem 2005;70:3099–3107. [PubMed: 15822970]
18. Further optimization experiments revealed that use of bases such as triethylamine and potassium carbonate did not afford the desired cyclization products.
19. Complete details on the synthesis of all substrates is provided in the Supporting Information.
20. Aldehyde products derived from oxidation of the primary alcohol moiety were not observed, but it is likely that these side products are not stable under the reaction conditions.
21. See the Supporting Information for complete details of stereochemical assignments.
22. Basic trialkylphosphine ligands such as tricyclohexylphosphine and trimethylphosphine were employed in the form of their air-stable tetrafluoroborate salts. These ligands (and all other reagents employed in these reactions) were weighed and handled in air. See:Netherton MR, Fu GC. Org. Lett 2001;3:4295–4298.4298 [PubMed: 11784201]
23. The Pd₂(dba)₃/BINAP catalyst system also provided the *anti*-addition product as the major diastereomer, albeit in low yield. Use of BINAP as ligand for the cyclization of **9** gave 35% yield (3:1 dr) of **7**, and the cyclization of **11** proceeded to afford 24% yield (>20:1 dr) of **12** under similar conditions.
24. Only the major product diastereomer is shown in eq 2-4 and 6-7. The structures of the other minor diastereomers are shown in the Supporting Information.
25. The products were isolated in 40% yield as a 17:2:1:1 mixture of diastereomers. However, analysis of the crude reaction mixture indicated that the diastereomers were formed in a 9:2:1:1 ratio, suggesting that partial resolution of the diastereomers occurred upon chromatographic purification.
26. For examples of transannular alkene insertion reactions of intermediates bearing exocyclic alkylpalladium moieties and/or exocyclic alkenes, see:(a)Link JT. Org. React 2002;60:157–534.534 (b) For representative examples, see:a)Hulin B, Newton LS, Cabral S, Walker AJ, Bordner J. Org. Lett 2004;6:4343–4345.4345 [PubMed: 15524479]b)Fox ME, Li C, Marino JP Jr. Overman LE. J. Am. Chem. Soc 1999;121:5467–5480.5480
27. For studies on the formation of Pd(Ar)(OR) and Pd(Ar)(NR₂) complexes, see:a)Yamashita M, Cuevas Vicario JV, Hartwig JF. J. Am. Chem. Soc 2003;125:16347–16360.16360 [PubMed: 14692777]and references cited therein;b)Widenhoefer RA, Buchwald SL. J. Am. Chem. Soc 1998;120:6504–6511.6511 and references cited therein.
28. No examples of sp³ C-O bond-forming reductive elimination from Pd(II) complexes have been previously described. One transformation that may involve sp³ C-N bond-forming reductive elimination from a Pd(II) complex with no *syn*- β -hydrogen atoms has been described by Stahl. See:a) Brice JL, Harang JE, Timokhin VI, Anastasi NR, Stahl SS. J. Am. Chem. Soc 2005;127:2868–2869.2869 [PubMed: 15740119]For examples of related sp³-carbon-heteroatom bond forming reductive elimination from Pd(IV), Pt(IV), and Ni(III), see:b)Lin BL, Clough CR, Hillhouse GL. J. Am. Chem. Soc 2002;124:2890–2891.2891 [PubMed: 11902877]and references cited therein;d) Desai LV, Hull KL, Sanford MS. J. Am. Chem. Soc 2004;126:9542–9543.9543 [PubMed: 15291549] d)Williams BS, Goldberg KI. J. Am. Chem. Soc 2001;123:2576–2587.2587 [PubMed: 11456927]e) Stahl SS, Labinger JA, Bercaw JE. Angew. Chem., Int. Ed 1998;37:2180–2192.2192
29. Although related sp²C-O bond forming reductive elimination is well established, reductive elimination in aryl sp²-systems has been demonstrated to proceed via an addition/elimination mechanism similar to nucleophilic aromatic substitution, which is not an accessible pathway for reductive elimination to form sp³C-O bonds. For details, see reference 27b.
30. Palladium alkoxide formation and alkene 5-exo-insertion into a Pd-O bond appears to be kinetically faster than 5-exo carbopalladation under our optimal reaction conditions. As shown below, treatment of 1-bromo-2-(but-3-enyl)benzene with 2-methylhex-5-en-2-ol with a catalytic amount of Pd₂(dba)

$3/PCy_3$ in the presence of NaOtBu afforded only the 2-benzyltetrahydrofuran derivative. Products derived from 5-exo-Heck cyclization of the aryl bromide were not observed.

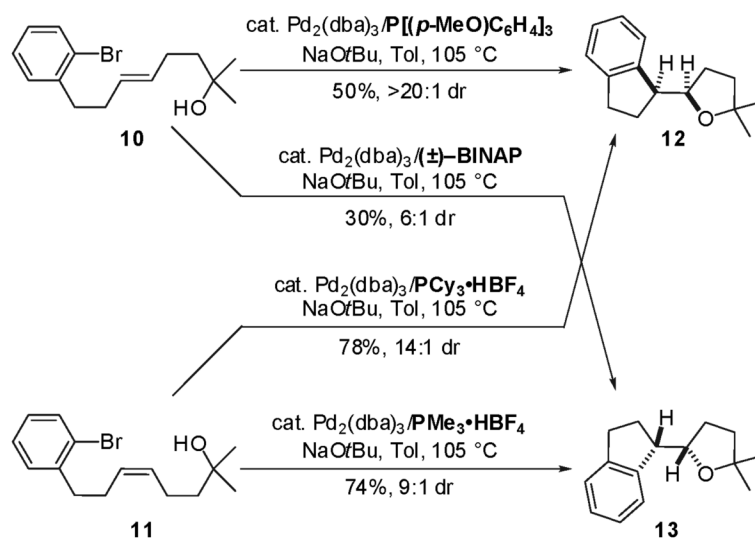
31. A mechanism involving fast and reversible carbopalladation followed by selective Pd-heteroatom bond-formation of one possible diastereomeric intermediate could also account for the high diastereoselectivity. However, reversible carbopalladation reactions have only been observed in complexes lacking β -hydrogen atoms; carbopalladation is believed to be irreversible in most other systems. The fact that oxidized/reduced side products are observed instead of Heck-type side products also suggests this pathway is less plausible than Path B. For lead references on reversible carbopalladation, see:(a)Campora J, Gutierrez-Puebla E, Lopez JA, Monge A, Palma P, del Rio D, Carmona E. *Angew. Chem., Int. Ed* 2001;40:3641–3644.3644b)Catellani M, Frignani F, Rangoni A. *Angew. Chem., Int. Ed* 1997;36:119–122.122
32. The vast majority of ligand substitutions at 16-electron Pd(II) complexes proceed via an associative mechanism. The very rare examples of dissociative ligand substitution at 16-electron Pd(II) complexes involve the extremely bulky, monodentate, and unusually labile ligands tris(2,4,6-trifluoromethylphenyl)phosphine and P(*o*-tol)₃. See:(a)Bartolome C, Espinet P, Martin-Alvarez JM, Villafane F. *Eur. J. Inorg. Chem* 2004:2326–2337.2337(b)Louie J, Hartwig JF. *J. Am. Chem. Soc* 1995;117:11598–11599.11599
33. Although formation of eleven membered rings is usually entropically unfavorable, formation of the eleven-membered palladacycle **31** is presumably facilitated by complexation of the alkene to the metal, which brings the heteroatom closer to the complex.
34. a) Villanueva LA, Abboud KA, Boncella JM. *Organometallics* 1992;11:2963–2965. b) Bryndza HE. *Organometallics* 1985;4:406–408.
35. For other recent examples of *syn*-alkene insertion into late transition metal-heteroatom bonds, see: (a)Helaja J, Göttlich R. *J. Chem. Soc., Chem. Commun* 2002:720–721.721(b)Tsutsui H, Narasaka K. *Chem. Lett* 1999:45–46.46c) reference 28a.
36. Yeh M-CP, Tsao W-C, Tu L-H. *Organometallics* 2005;24:5909–5915.
37. Wacker-type carbonylative carboetherifications described by Semmelhack afford products resulting from *anti*-addition of an oxygen atom and an ester group across an alkene. See reference 15b.
38. 7-Endo carbopalladation reactions are extremely rare, and 7-endo hydridopalladation reactions are unknown. For lead references, see:Gibson SE, Guillo N, Middleton RJ, Thuilliez A, Tozer MJ. *J. Chem. Soc., Perkin Trans. 1* 1997:447–456.456and references cited therein.
39. Conversion of **34** to **31** could occur via dissociation of one arm of the chelating ligand followed by associative substitution of alkoxide for bromide, or by dissociation of the bromide followed by associative ligand substitution. Either of these pathways is likely to be higher in energy than the analogous conversion of **27** to **31**.
40. Dosen-Micovic L, Lorenc L, Mihailovic ML. *Tetrahedron* 1990;46:3659–3666.
41. (a) Hoffmann RW. *Chem. Rev* 1989;89:1841–1860. (b) Hart DJ. *J. Am. Chem. Soc* 1980;102:397–398. (c) Williams RM, Sinclair PJ, Zhai D, Chen D. *J. Am. Chem. Soc* 1988;110:1547–1557.
42. As noted above, our previously described intermolecular carboamination reactions of terminal alkenes have proceeded with high stereoselectivity for the formation of *trans*-2,5-disubstituted *N*-arylpiperidines, which is also consistent with favorable pseudoaxial orientation of a C-1 substituent in the absence of medium-ring transannular interactions. However, the effects of E/Z-alkene geometry on the ratio of *trans/cis*-piperidine formation has not yet been examined in intermolecular transformations. For further details, see reference 7c.
43. The addition of base has been observed to dramatically increase the rate and/or yield of oxidative Wacker-cyclizations of *o*-allylphenol derivatives. See:(a)Trend RM, Ramtohl YK, Ferreira EM, Stoltz BM. *Angew. Chem., Int. Ed* 2003;42:2892–2895.2895(b)Larock RC, Wei L, Hightower TR. *Synlett* 1998:522–524.524
44. The rate and/or yield of Wacker-cyclization reactions that afford tetrahydrofuran products have also been observed to decrease with increasing steric bulk at the C1-position. See:(a)Meulemans TM, Kiers NH, Feringa BL, van Leeuwen PWNM. *Tetrahedron Lett* 1994;35:455–458.458(b)Hosokawa T, Hirata M, Murahashi S. -i. Sonoda A. *Tetrahedron Lett* 1976;17:1821–1824.1824



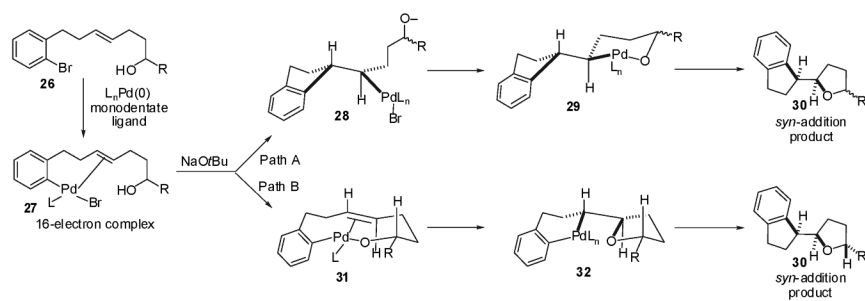
Scheme 1.

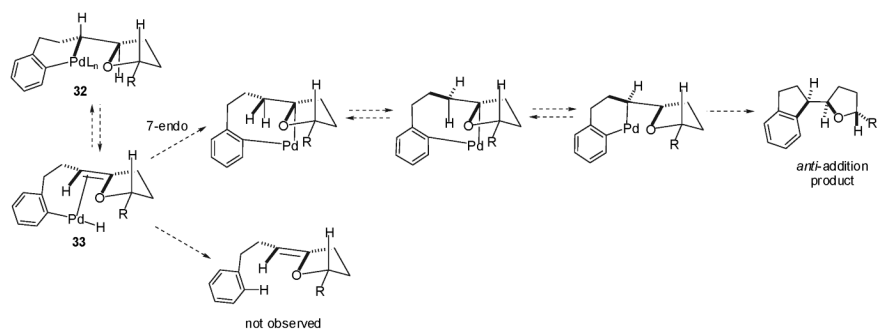
**Scheme 2. a.**

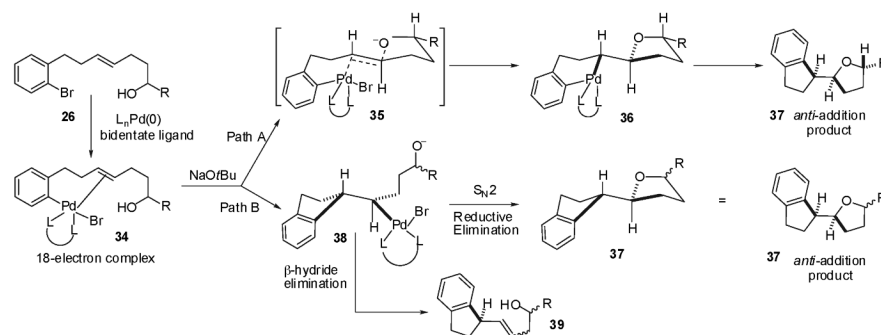
(a) Conditions: 1.0 equiv alcohol substrate, 2.0 equiv NaOtBu , 1 mol % $\text{Pd}_2(\text{dba})_3$, 4 mol % ligand (monophosphines) or 2 mol % ligand (bis-phosphines), toluene (0.1 M), 105 °C, 3-8 h. Diastereoselectivities were determined by GC and/or ^1H NMR analysis.

**Scheme 3.**

(a) Conditions: 1.0 equiv alcohol substrate, 2.0 equiv NaOtBu , 1 mol % $\text{Pd}_2(\text{dba})_3$, 4 mol % ligand (monophosphines) or 2 mol % ligand (bis-phosphines), toluene (0.1 M), 105°C , 3-8 h. Diastereoselectivities were determined by GC and/or ^1H NMR analysis.

**Scheme 4.**

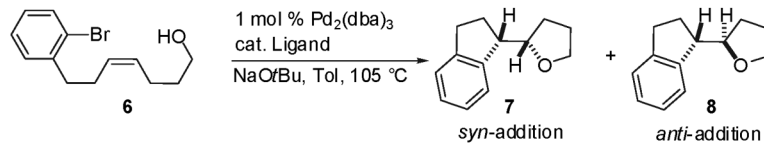
**Scheme 5.**



Scheme 6.

Table 1

(a)



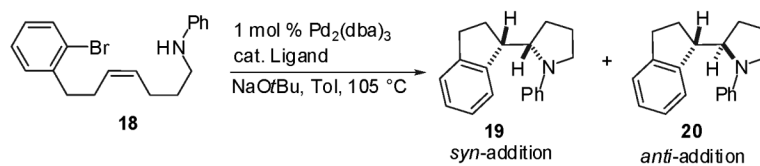
entry	ligand	dr ^(b)	Isolated Yield (7 + 8)
1	P[(<i>p</i> -MeO)C ₆ H ₄] ₃	8:1	54%
2	PPh ₃	5:1	27%
3	P(<i>o</i> -tol) ₃	2:1	35%
4	PCy ₃	2:1	48%
5	DPE-Phos	1:1	49%
6	DPPE	1:2	46%
7	DPP-Benzene	1:2	44%
8	(±)-BINAP	1:18	60%

^(a) Conditions: 1.0 equiv **6**, 2.0 equiv NaOtBu, 1 mol % Pd₂(dba)₃, 4 mol % ligand (monophosphines) or 2 mol % ligand (bis-phosphines), toluene (0.1 M), 105 °C, 3-8 h.

^(b) Diastereoselectivities were determined by GC and/or ¹H NMR analysis of crude reaction mixtures.

Table 2

(a)



<u>entry</u>	<u>ligand</u>	<u>dr^(b)</u>	<u>Isolated Yield (19 + 20)</u>
1	(±)-BINAP	1:1	46%
2	DPE-Phos	15:1	49%
3	DPPE	16:1	54%
4	P(<i>o</i> -tol) ₃	8:1	47%
5	Xantphos	12:1	57%
6	P[(<i>p</i> -MeO)C ₆ H ₄] ₃	13:1	68%
7	PCy ₃ ·HBF ₄	>20:1	88%

(a) Conditions: 1.0 equiv **18**, 2.0 equiv NaOtBu, 1 mol % Pd₂(dba)₃, 4 mol % ligand (monophosphines) or 2 mol % ligand (bis-phosphines), toluene (0.14 M), 105 °C, 3-10 h.

(b) Diastereoselectivities were determined by GC and/or ¹H NMR analysis of crude reaction mixtures.