Palladium-Catalyzed Carboetherification and Carboamination Reactions of γ-Hydroxy- and γ-Aminoalkenes for the Synthesis of Tetrahydrofurans and Pyrrolidines

John P. Wolfe*[a]

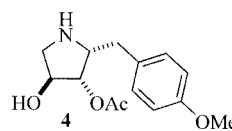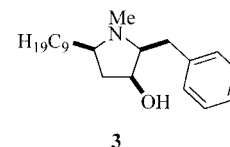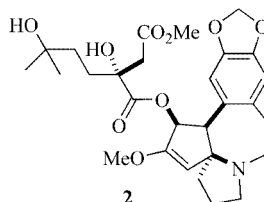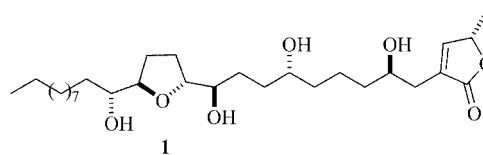Substituted tetrahydrofuran and pyrrolidine moieties are displayed in a wide range of interesting biologically active molecules. The Pd-catalyzed carboetherification or carboamination of γ-hydroxy and γ-aminoalkenes is a powerful tool for the construction of these heterocycles, as it is convergent and can allow access to a variety of analogs from a single γ-hydroxy- or γ-aminoalkene starting material. This microreview describes the current state of this field.
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Introduction

Substituted tetrahydrofuran and pyrrolidine moieties are displayed in a wide range of interesting biologically active molecules. For example, glacin A (**1**) is a member of the annonaceous acetogenins, which are a large family of natural products bearing tetrahydrofuran cores that exhibit a diverse array of biological activities including antitumor, antihelmic, antimalarial, antimicrobial, and antiprotozoal effects.[1] Tetrahydrofurans are also found in several other classes of natural products including polyether ionophores,[2] lignans,[3] and macrodiolides.[4] Many medicinally significant pyrrolidine alkaloids have also been reported,[5] including antileukemia agents such as harringtonine (**2**),[6] antifungal agents such as preussin (**3**)[7] and anisomycin (**4**),[8] and many glycosidase inhibitors such as broussonetine C (**5**).[9] In general, these molecules contain substituents and stereocenters around and/or adjacent to the heterocyclic ring.
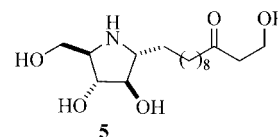
Due to the medicinal importance of molecules such as those described above, there has been a longstanding interest in the stereoselective synthesis of substituted tetrahydrofurans and pyrrolidines; a number of different meth-

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[a] University of Michigan, Department of Chemistry
Ann Arbor, MI 48109-1055, USA
Fax: +1-734-615-3700
E-mail: jpwolfe@umich.edu

John P. Wolfe was born in Greeley, CO, and received his B.A. degree from the University of Colorado, Boulder in 1994. As an undergraduate he conducted research in the laboratories of Professor Gary A. Molander. He received his Ph.D. degree in 1999 from the Massachusetts Institute of Technology under the guidance of Professor Stephen L. Buchwald. Following the completion of his Ph.D. studies, he spent three years as an NIH postdoctoral fellow in the lab of Professor Larry E. Overman at the University of California, Irvine. He joined the faculty at the University of Michigan in July, 2002, where he is currently an Assistant Professor of Chemistry. He is the recipient of a Dreyfus New Faculty Award, a Camille Dreyfus Teacher-Scholar Award, a Research Corporation Innovation Award, a Amgen Young Investigator Award, a Eli Lilly Grantee Award, and a 3M Untenured Faculty Award.

ods have been devised for their preparation.[1,5,10,11] One common strategy for the construction of these moieties involves halo-, seleno-, or oxidative cyclizations of γ-hydroxy- or γ-aminoalkenes in the presence of reagents such as I_2, PhSeCl, or *m*CPBA.[10] These transformations effect ring closure with concomitant generation of a C–X (X = I, SePh, OH) bond adjacent to the ring, and the products of these reactions can be further elaborated using standard methods for C–C bond formation.

Although haloetherifications, haloaminations, and the related reactions described above are well documented and studied, the analogous carboetherification and carboamination reactions that form C–C bonds rather than C–X bonds are relatively rare. However, these reactions are a powerful and convergent tool for heterocycle synthesis, and can allow access to a variety of analogs from a single γ-hydroxy- or γ-aminoalkene starting material. Interestingly, nearly all of the carboetherification and carboamination processes involving γ-hydroxy/aminoalkenes that have been reported to date are catalyzed by Pd complexes,[12] and can be generally divided into two reaction types (Scheme 1). The first type proceeds by outer-sphere oxy- or aminopalladation of PdX_2–alkene complexes to generate products resulting from *anti*-addition across the double bond, and usually employ Pd^{II} catalysts and CO as the source of electrophilic carbon. The second type involves inner-sphere oxy- or aminopalladation of Pd(R)(OR) or Pd(R)(NRR′) complexes to afford *syn*-addition products, and typically utilize Pd^0 catalysts and aryl or alkenyl halides as the electrophilic coupling partners. This microreview will highlight the scope and synthetic utility of both classes of Pd-catalyzed carboetherification and carboamination processes.
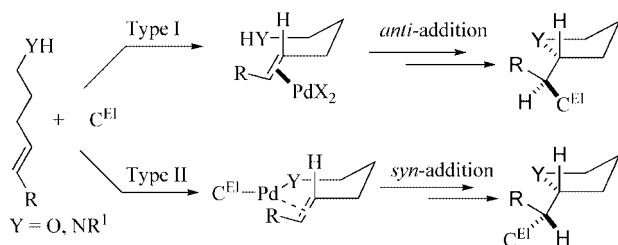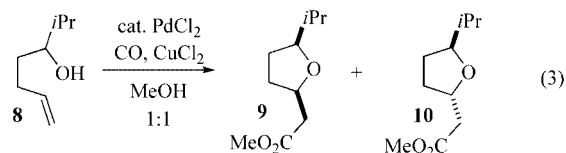

Scheme 1.

Pd^{II}-Catalyzed Carbonylative Cyclizations of γ-Hydroxyalkenes

The first examples of Pd-catalyzed carbonylative carboetherification reactions of γ-hydroxyalkenes were reported by Semmelhack in 1984.[13,14] In a representative example, treatment of the alcohol **6a** with a catalytic amount of $PdCl_2$ and 3.0 equiv. of $CuCl_2$ under CO in methanol afforded tetrahydrofuran **7a** in an 85% yield as a single diastereomer, which results from *anti* addition of the oxygen atom and the ester moiety across the C–C double bond [Equation (1)].[14b] The relative stereochemistry of the 2-, 3- and 5-substituents is controlled by the group at the allylic

position of the double bond. For example, **6a** and **6b** are both transformed to products with a *trans*-relationship between the substituents at the 2 and 3 positions [Equations (1) and (2)].
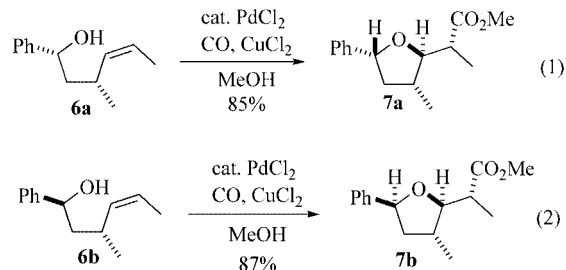
In the absence of a group at the allylic position the reactions typically proceed with low diastereoselectivity. For example, **8** was converted to a 1:1 mixture of tetrahydrofuran stereoisomers **9** and **10** [Equation (3)].[14c] This problem can be circumvented by employing substrates with allylic substituents that can be removed after cyclization.[14c,15]

The Pd-catalyzed alkoxycarbonylation reactions are believed to proceed through coordination of the alkene to Pd^{II} (**11**), followed by nucleophilic attack of the pendant hydroxy group to provide **13** (Scheme 2). This intermediate then undergoes insertion of CO into the Pd–C bond, followed by methanolysis to afford the observed products. The methanolysis step leads to the generation of a catalytically inactive Pd^0 species, which is then reoxidized to Pd^{II} by the Cu^{II} salts present in the reaction mixture.
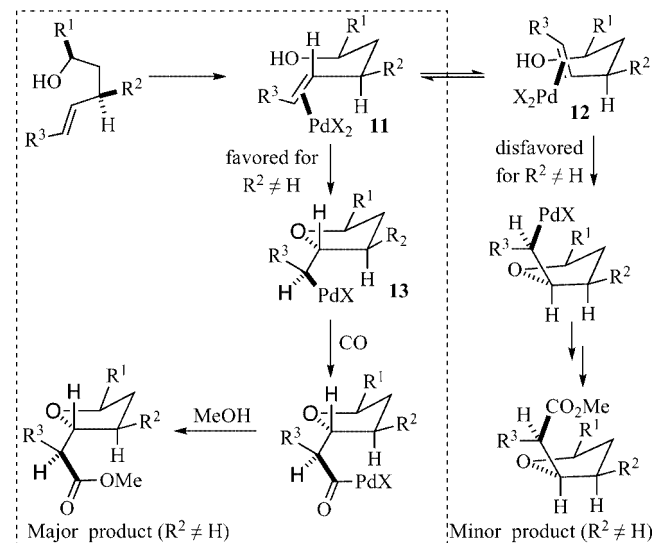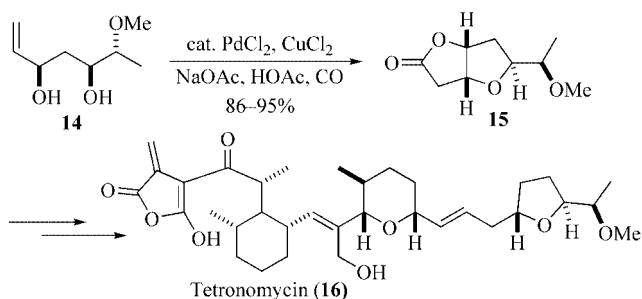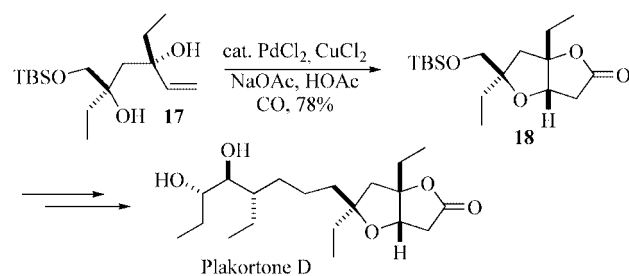

Scheme 2.

As noted above, the stereoselectivity of these reactions is highly dependent on the structure of the substrate. In the absence of a substituent at the allylic position (R^2 ≠ H),

cyclizations via the conformers **11** and **12** appear to proceed with equal facility, which gives rise to mixtures of diastereomeric products. When a bulky group is present at the allylic position, the reaction appears to proceed via the conformer **11**, and good diastereoselectivity is observed.[13,14]

The Pd[II]-catalyzed carbonylative carboetherification reactions have been employed as key transformations in the construction of several natural products. For example, Semmelhack prepared both the tetrahydrofuran and tetrahydropyran cores of tetronomycin (**16**) using this strategy.[15] As shown below, the carbonylative cyclization of **14** provided lactone **15**, which was carried on to the natural product in subsequent steps (Scheme 3). A related strategy was also used for the construction of the heterocyclic core of the plakortone family of natural products via conversion of **17** to **18** (Scheme 4).[16] Similar transformations have been employed in the syntheses of bicyclic lactone natural products excreted by parasitic wasps,[17] and the tetrahydrofuran derivative goniothalesidol.[18]
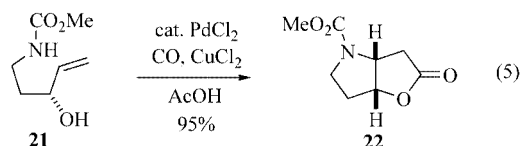

Scheme 3.

Scheme 4.

Pd[II]-Catalyzed Carbonylative Cyclization of γ-Aminoalkenes

Palladium[II]-catalyzed carbonylative cyclizations of γ-aminoalkenes that are analogous to the tetrahydrofuran-forming reactions described above have been extensively studied by Tamaru and Hegedus.[19,20] These transformations are typically conducted using a catalytic amount of PdCl₂ and excess CuCl₂ under CO in methanol, and are most effective with substrates bearing sulfonamide, carbamate, or urea nucleophiles. For example, the *exo*-carbamate **19** was transformed to the pyrrolidine **20** in an 88% yield

using the conditions described above [Equation (4)].[19g] The mechanism of these reactions is believed to be similar to that shown in Scheme 2.
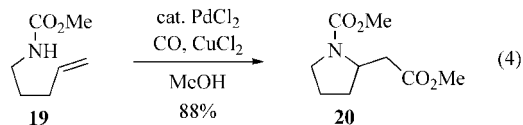
The stereoselectivity of these transformations has not been fully explored. However, substrates bearing a hydroxy group at the allylic position (e.g. **21**) are converted to *cis*-bicyclic pyrrolidines (e.g. **22**) in excellent yield with high diastereoselectivity [Equation (5)].[19d]


Palladium-catalyzed carbonylative carboamination reactions have been employed in the construction of several natural products, including the tropane alkaloid ferruginine (**25**).[21] As shown below (Scheme 5), cyclization of **23** using the carboamination conditions described above provided **24** in a 49% yield, which was converted into the natural product in subsequent steps. The related alkaloid anatoxin-A was prepared using a similar strategy.[22]
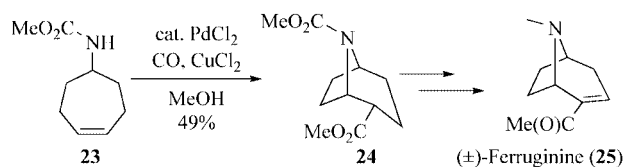
Scheme 5.

Other Pd[II]-Catalyzed Carboamination and Carboetherification Reactions That Afford Tetrahydrofuran or Pyrrolidine Products

Although the vast majority of Pd[II]-catalyzed carboetherification and carboamination reactions employ CO as an electrophilic carbon source, Semmelhack has reported that Pd[II]-catalyzed carboetherifications of γ-unsaturated alcohols can also be executed using activated alkene electrophiles such as styrene, methyl vinyl ketone, or methyl acrylate. As shown below [Equation (6)], treatment of **26a** with methyl vinyl ketone in the presence of 10 mol% Pd(OAc)₂ and 1 equiv. of CuCl in DMF under O₂ provided an 89% yield of **27**, albeit as a 1:1 mixture of diastereomers. However, this transformation is limited to substrates bearing 1,1-disubstituted alkenes; use of substrates bearing terminal alkenes (e.g. **26b**) led to the generation of ketone products [e.g. **28**, Equation (7)].[23]

$$ \text{(6)} $$

26a: R = Me
26b: R = H

$$ \text{(7)} $$
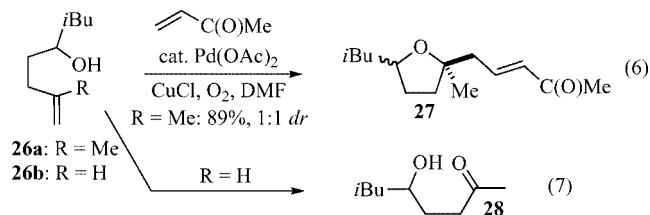
Three recent reports have described Pd^{II}-catalyzed oxidative carboamination reactions that afford pyrrolidine products. Stahl has developed an intermolecular coupling of allyl sulfonamides with alkenes to afford 2,4-disubstituted products in excellent yield with modest diastereoselectivity.[24] As shown below (Scheme 6), treatment of **29** with styrene in the presence of Pd^{II} and Cu^{II} co-catalysts under air provides **30** in a 93% yield with 1.6:1 *dr*. This reaction proceeds through intermolecular aminopalladation of styrene to afford **31**, which undergoes alkene insertion, followed by β-hydride elimination from **32** to generate the product. The methyl acrylate additive serves to stabilize Pd^0 that is formed at the end of the catalytic cycle, and prevents the generation of catalytically inactive palladium black. A related intramolecular reaction was used by Yang for the synthesis of indoline derivatives.[25] As shown in Equation (8), 2-allylaniline derivative **33** was converted to **34** in a 91% yield. Enantioselectivities up to 91% *ee* were obtained when (–)-sparteine was used as a ligand in these reactions. The mechanism of these transformations is analogous to that shown in Scheme 6.
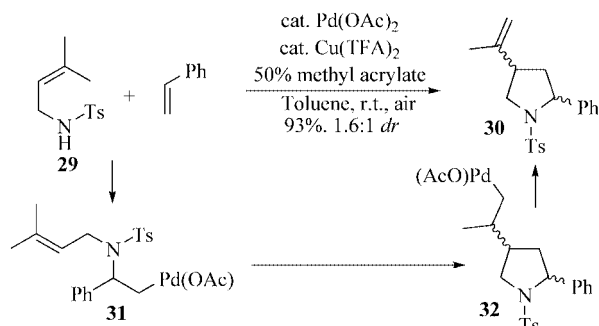
Scheme 6.
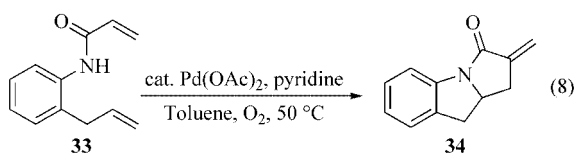
$$ \text{(8)} $$

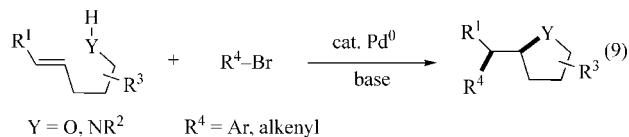## Pd^0-Catalyzed Carboetherification and Carboamination Reactions of γ-Hydroxyalkenes with Aryl/Alkenyl Bromides

Although the Pd^{II}-catalyzed carboetherification and carboamination reactions described above are very useful tools for the construction of tetrahydrofuran and pyrrolidine products, these methods have two significant limitations. In general, the stereoselectivity of reactions that generate polysubstituted heterocyclic rings is low (ca. 1:1), unless the

unsaturated starting material is substituted at the allylic position. In addition, although the carbonylation reactions are very effective for the installation of ester functionality at the C1′ position, the generation of other C–C bonds or installation of alkyl, aryl, or alkenyl groups cannot be achieved except in special cases such as those noted above [Equations (6), (8), and Scheme 6].

Over the past three years, our research group has directed a considerable amount of effort towards the development of new carboetherification and carboamination reactions that circumvent many of the limitations of the transformations described above. Our approach to this problem utilizes palladium complexes generated in situ from mixtures of Pd$_2$(dba)$_3$ or Pd(OAc)$_2$ and phosphane ligands to catalyze reactions of γ-hydroxy- or γ-aminoalkenes with aryl or alkenyl bromides [Equation (9)]. These reactions lead to the formation of a C2–heteroatom bond and a C1′–carbon bond in one step, with generation of up to two stereocenters. In addition, cyclization reactions of substrates bearing substituents at the 1- or 3-position are converted to 2,5- or 2,3-disubstituted heterocycles with good to excellent levels of stereocontrol. The aryl/alkenyl halide coupling partners for these transformations are readily available, which allows for facile synthesis of diverse analogs from a single alcohol or amine substrate. The following sections of this review describe our studies and results in this area.[26]

$$ \text{(9)} $$

Y = O, NR^2 R^4 = Ar, alkenyl

Carboetherification of γ-Hydroxyalkenes with Aryl/Alkenyl Bromides

In initial studies directed towards the development of new Pd-catalyzed carboetherification reactions, we focused on the use of Pd/phosphane complexes for coupling reactions between simple γ-hydroxyalkenes and aryl bromides.[27] After some experimentation, we discovered that mixtures of Pd$_2$(dba)$_3$ and dpe-phos effectively catalyzed the desired transformations, and minimized competing oxidation of the alcohol/reduction of the aryl bromide. In a representative example, 4-penten-1-ol (**35**) was converted to **36** in a 76% yield by treatment with 2-bromonaphthalene, NaOtBu, and catalytic amounts of Pd$_2$(dba)$_3$ and dpe-phos [Equation (10)]. The nature of the phosphane ligand has a large impact on the chemical yield of this transformation; ligands such as dppf, dppe, P(o-tol)$_3$ and PPh$_3$ give poor results with primary alcohol substrates such as **35**.[28]


$$ \text{(10)} $$
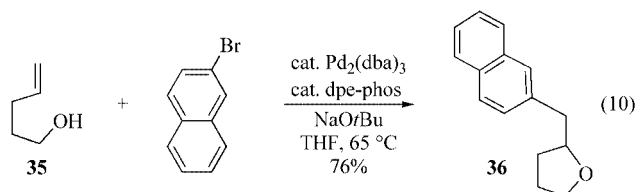
As shown in Table 1, a variety of primary, secondary, and tertiary alcohol substrates are efficiently coupled with a broad array of aryl bromides. In contrast to the carbonylative carboetherification reactions described above, very high stereoselectivity (>20:1 *dr*) for the formation of *trans*-2,5-disubstituted tetrahydrofurans is observed in reactions of secondary alcohol substrates. These transformations are also useful for the conversion of substrates bearing an allylic substituent to 2,3-*trans*-disubstituted products in moderate to good diastereoselectivity, and cycloalkanols bearing a C-2 allyl group are converted to bicyclic products with good to excellent selectivity. However, the conversion of 3-substituted γ-hydroxyalkenes to *cis*-2,4-disubstituted tetrahydrofurans proceeds with lower (ca. 2:1) diastereoselectivity. The reactions are most effective with electron-rich or -neutral aryl bromide coupling partners; reactions of electron-poor aryl bromides proceed in modest yield due to competing *O*-arylation of the alcohol substrate. 1-Bromoalkenes are efficiently coupled with tertiary alcohol substrates, although low yields are obtained in reactions of 1-bromoalkenes with primary or secondary alcohols. Functional groups that are not sensitive to strong base are well tolerated.

Table 1. Carboetherification of terminal alkenes.
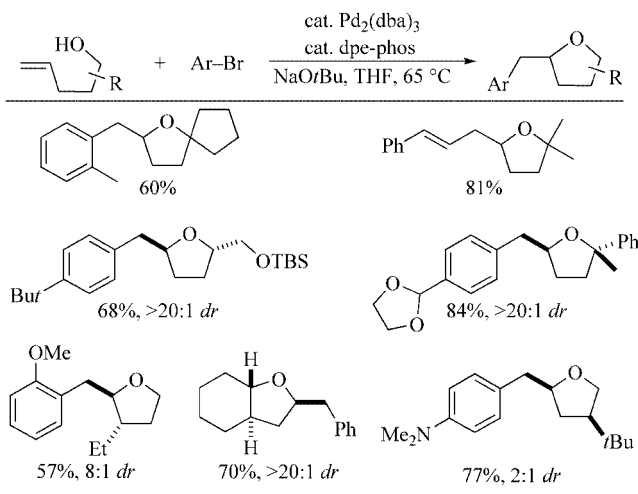
As shown in Table 2, transformations of tertiary alcohol substrates bearing acyclic internal alkenes afford 2,1'-disubstituted tetrahydrofurans in good yield with moderate levels of diastereoselectivity (ca. 3–5:1).[27a,29,30] In contrast, the analogous reactions of cycloalkene substrates provide bicyclic or spirocyclic products with excellent stereocontrol (>20:1). The observed products derive from *syn* addition of the alkene and the aryl unit across the C–C double bond, which is complementary to the *anti* addition stereochemistry that is typically observed in the Pd^II^-catalyzed carbonylative carboetherifications described above. The reactions are stereospecific, and substituted alcohol substrates that contain internal alkenes are converted to polysubstituted tetrahydrofurans in good yield with modest stereocontrol.[31]

Table 2. Carboetherification of internal alkenes.
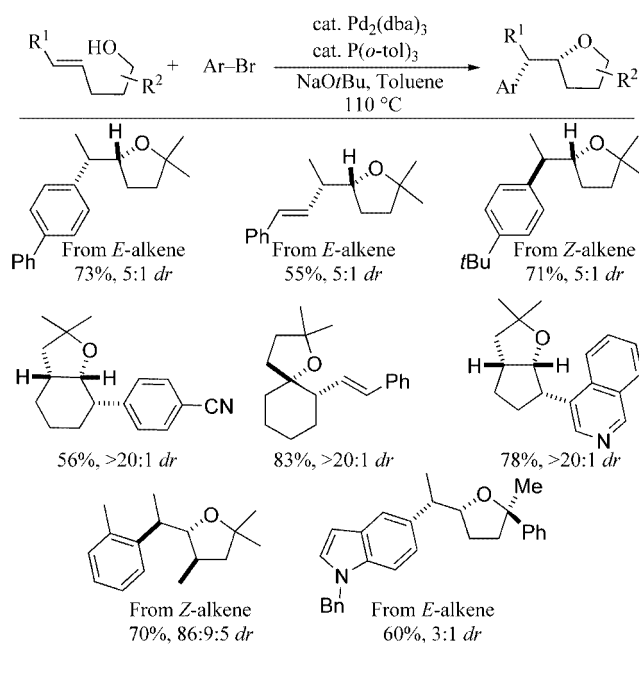
The mechanism of the Pd^0^-catalyzed carboetherification most likely involves initial oxidative addition of the aryl bromide to the Pd^0^/phosphane complex to afford **37**, which is then converted into the (aryl)(alkoxide)palladium complex **38** through reaction with the alcohol substrate in the presence of NaO*t*Bu (Scheme 7). The alkoxide complex **38** then undergoes a *syn*-oxypalladation process, which is an uncommon transformation in both catalytic and stoichiometric reactions of palladium alkoxides.[29]
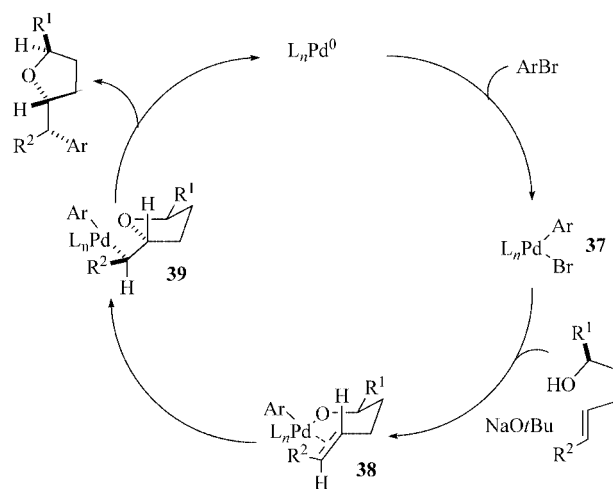

Scheme 7. Catalytic cycle.

The resulting complex **39** undergoes C–C bond-forming reductive elimination to provide the observed product with regeneration of the Pd^0^ catalyst.[29] The observed product stereochemistry derives from *syn*-oxypalladation through

an organized cyclic transition state in which the substrate substituents assume pseudoequatorial orientations to avoid 1,3-diaxial interactions. The intermediacy of the (aryl)(alkoxide)palladium complex **38** is supported by the observation of side products that derive from β-hydride elimination or C–O bond forming reductive elimination of this species. Other plausible mechanisms, such as Heck-type carbopalladation or *anti*-alkoxypalladation, can be ruled out on the basis of stereoselectivity, regioselectivity, and product stereochemistry.[29]

The mechanism outlined above (Scheme 7) accounts for the observed product stereochemistry and explains the high regioselectivity for five-membered ring formation. However, this mechanism predicts that high *syn*-addition diastereoselectivity should be observed, which contrasts with our results that indicate acyclic internal alkenes cyclize with ca. 3–5:1 *dr*.

Deuterium labeling studies have shown that this diminished stereoselectivity results from reversible β-hydride elimination side reactions that occur after the oxypalladation step.[29] As shown below (Scheme 8), the Pd-catalyzed carboetherification of **40** afforded a 4:1 mixture of **41** and **42**;[30] the minor diastereomer (**42**) was deuterated at C2 rather than the expected benzylic carbon. The minor diastereomer **42** is generated through β-hydride elimination of **43** to afford **44**, which undergoes reinsertion of the alkene into the Pd–H bond with the opposite regiochemistry to provide **45**. Rotation about the C–C bond, followed by β-deuteride elimination generates **46**, which can undergo reinsertion of the alkene into the Pd–D bond, followed by reductive elimination to yield **42**. High diastereoselectivity for *syn*-addition is observed with internal cyclic alkenes, as an analogous mechanism for isomerization after oxypalladation is not accessible.[29]
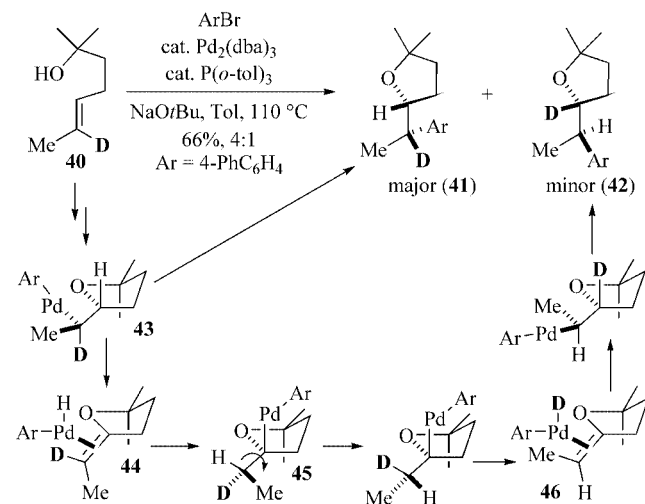
Scheme 8.

In recent studies Yeh has extended the scope of Pd-catalyzed alkene carboetherification reactions to include 1,3-diene substrates.[32] For example, treatment of **47** with a mixture of Pd(PPh₃)₄ and dpe-phos in the presence of NaO*t*Bu and 4-bromoanisole afforded **48** in a 65% yield

[Equation (11)]. The mechanism of these transformations is believed to be similar to that described in Scheme 7. These reactions are also effective with cyclic dienes (e.g. **49**), although the formation of 1,4-addition products (e.g. **50**) is observed [Equation (12)]. This presumably occurs via rearrangement of an intermediate allylpalladium complex generated through *syn*-oxypalladation.
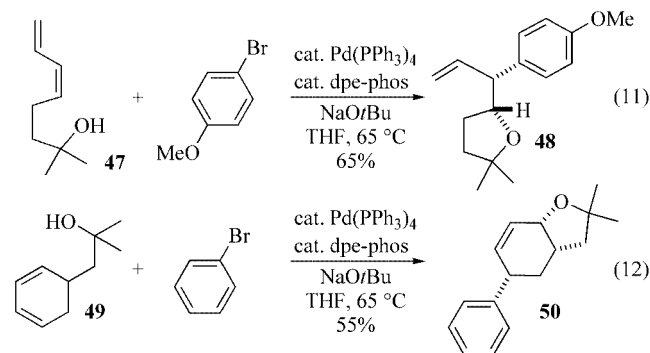
Carboamination of γ-(Arylamino)alkenes with Aryl/Alkenyl Bromides

Having successfully developed a new Pd-catalyzed carboetherification reaction of γ-hydroxyalkenes with aryl bromides, we sought to broaden the scope of this chemistry to allow for the construction of nitrogen heterocycles. However, it seemed likely that the synthesis of pyrrolidines from γ-aminoalkenes could be more problematic, as Pd(Ar)(NR₂) complexes are known to undergo relatively fast C–N bond-forming reductive elimination,[33] which could lead to competing N-arylation of the substrate. Moreover, a search of the literature revealed that previous efforts to effect the Pd-catalyzed carboamination of γ-(benzylamino)alkenes with aryl iodides were unsuccessful.[34]

In our initial experiments we focused on the use of γ-aminoalkenes bearing N-aryl substituents due to the ease of synthesis and handling of these substrates. As expected, competing N-arylation of the starting material was problematic when the Pd₂(dba)₃/dpe-phos catalyst was employed. However, the ligands dppe and dppb, which are known to slow the rate of C–N bond forming reductive elimination,[33] provided satisfactory results. For example, treatment of N-phenyl-4-pentenylamine (**51**) with 2-bromonaphthalene in the presence of NaO*t*Bu and catalytic amounts of Pd₂(dba)₃ and dppb afforded pyrrolidine **52** in a 94% yield [Equation (13)].[35,36]
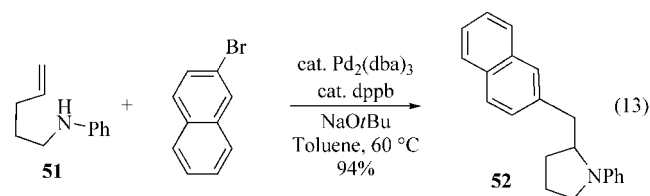
The Pd-catalyzed carboamination reactions of γ-(arylamino)alkenes are effective for substrates bearing electron-rich, -neutral, or -poor N-aryl substituents; higher yields

and better regioselectivities[36] are obtained with electron-poor substrates (Table 3). A number of different aryl bromides are coupled in good yields, although competing *N*-arylation is observed in some transformations of electron-deficient aryl bromides. Excellent stereoselectivities are obtained in reactions that afford *cis*-2,5-disubstituted or *trans*-2,3-disubstituted products. The mechanism of these reactions is analogous to that shown in Scheme 7. However, the preference for the formation of *cis*-2,5-disubstituted products likely derives from pseudoaxial orientation of the group adjacent to nitrogen to minimize A$^{(1,3)}$-strain in the transition state for *syn*-aminopalladation.

Table 3. Carboamination of γ-(arylamino)alkenes with aryl bromides.
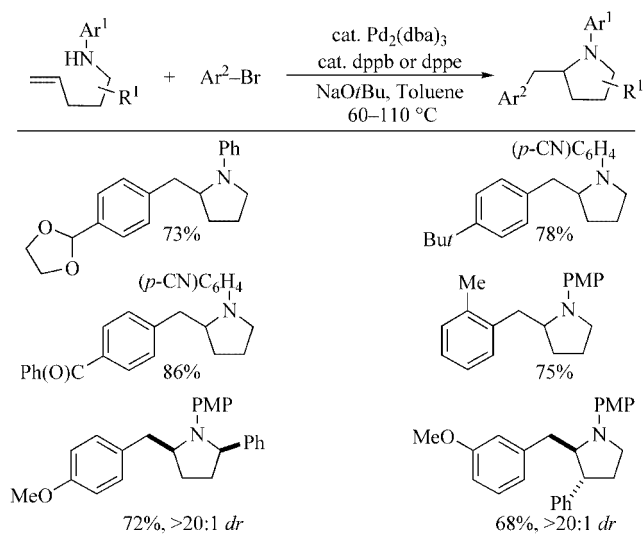
The palladium-catalyzed carboamination reactions of γ-(arylamino)alkenes with alkenyl bromides proved to be more challenging due to competing *N*-vinylation of the starting material. However, this problem was solved through the use of P(2-furyl)$_3$ as the ligand for palladium (Table 4).[37] This change in catalyst structure presumably slows C–N bond-forming reductive elimination and thus facilitates the desired transformation. The reactions proceed with diastereoselectivities that are similar to those observed with aryl bromide substrates.

In some cases the *N*-arylamine starting materials employed in the reactions described above were prepared through Pd-catalyzed *N*-arylation reactions of primary amines,[33] which represents an overall two-step/two-pot synthesis of *N*-aryl-2-benzylpyrrolidines from γ-aminoalkenes. We reasoned that a more efficient means of effecting this transformation would be to conduct both the *N*-arylation and the carboamination reaction in one flask in a tandem process. However, achieving this transformation was not straightforward, as different phosphane ligands were required for each step. In order to overcome this obstacle, we developed a procedure for in situ modification of catalyst structure through phosphane ligand exchange.[37,38] In a representative experiment, 2-allylaniline was treated

Table 4. Carboamination of γ-(arylamino)alkenes with alkenyl bromides.
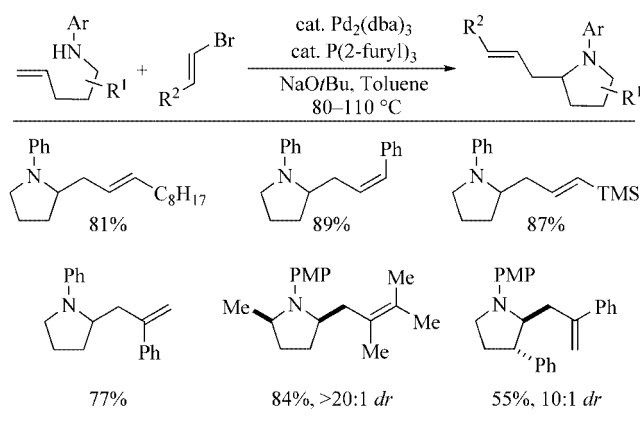
with 1 equiv. of *tert*-butyl (4-bromo)benzoate, 2.1 equiv. of NaO*t*Bu, and catalytic amounts of Pd$_2$(dba)$_3$ and 2-(di-*tert*-butylphosphanyl)biphenyl. The reaction was monitored by GC analysis of aliquots, and when the aryl bromide was consumed a catalytic amount of dpe-phos was added. The mixture was stirred for 10 min, and then 1 equiv. of 4-bromochlorobenzene was added. This protocol afforded indoline **53** in an 85% yield (Table 5), and proved to be amenable to the construction of several different derivatives (e.g. **54–55**). The conversion of primary aliphatic amines to pyrrolidines **56–57** was accomplished using a slightly modified procedure in which dppe was employed as the second ligand.

Table 5. Pd-catalyzed tandem *N*-arylation/carboamination.
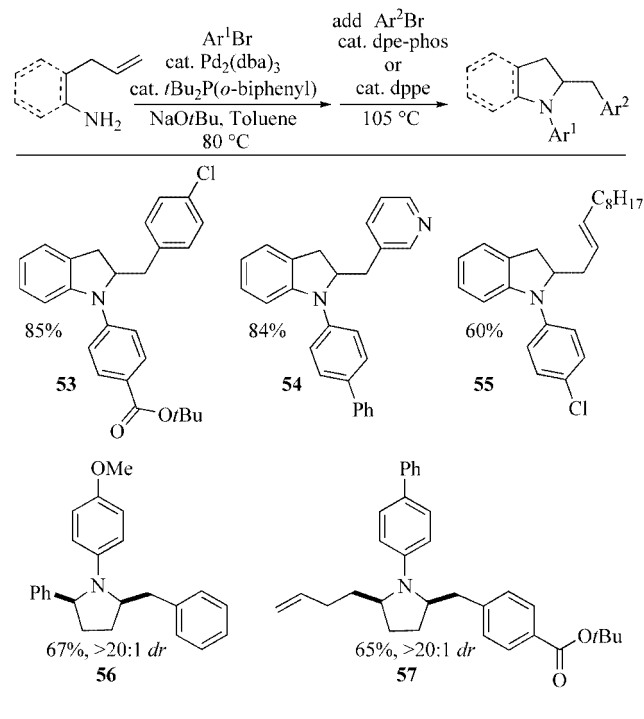
The carboamination reactions of terminal alkene substrates generally proceed uneventfully to afford the expected pyrrolidine product. However, our initial efforts to effect the carboamination of γ-(arylamino)cycloalkene **58** led to a surprising result (Scheme 9).[39] The expected product **64** was formed in only a modest yield, along with three other side products (**63**, **65**, **66**). All four products likely derive from (aryl)(amido)palladium complex **59**, which is generated in a manner similar to alkoxide complex **38** described above (Scheme 7). The diarylamine **63** is produced by C–N bond forming reductive elimination of **59**, whereas the other three products are generated after *syn*-aminopalladation of **59** to yield **60**. Carbon–carbon bond forming reductive elimination of **60** gives the expected product **64**. However, competing β-hydride elimination can also occur from **60** to provide the alkene complex **61**. Displacement of the alkene from **61** affords the oxidative cyclization product **65**, and reinsertion of the alkene into the Pd–H of **61** bond with reversed regiochemistry, followed by C–C bond forming reductive elimination from **62** provides **66**.[35]
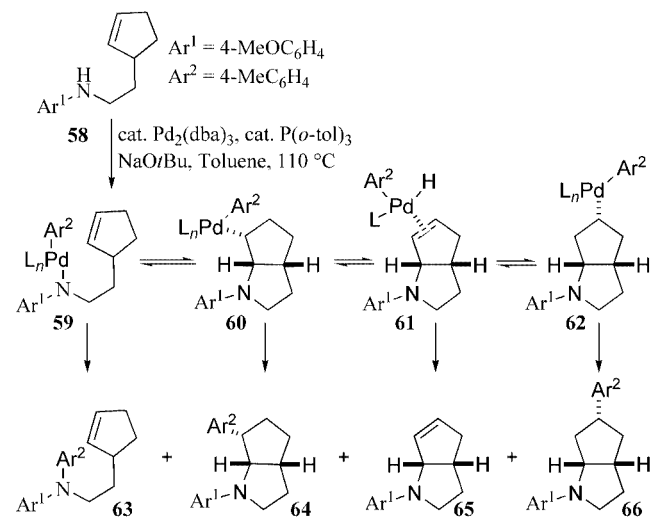

Scheme 9.
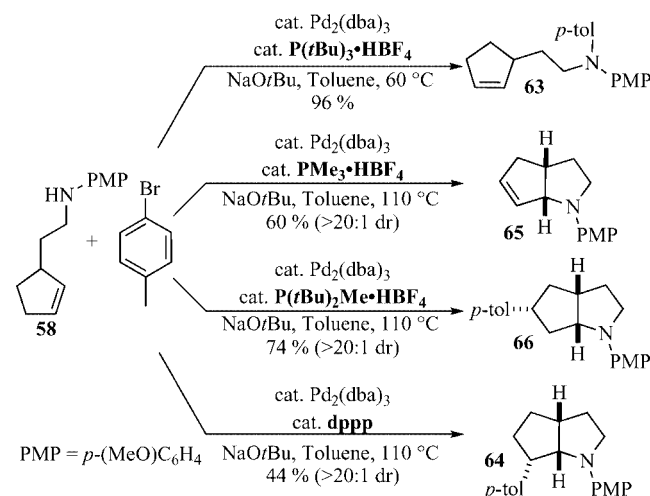
Scheme 10.

Subsequent studies led to the development of reaction conditions that could selectively provide any of these four products with the use of an appropriate phosphane ligand,[39] as the relative rates of the various transformations can be controlled by changing the steric and electronic properties of the catalyst (Scheme 10). For example, the Pd-catalyzed reaction of **58** with 4-bromotoluene can be tuned to selectively provide **63** [96%, P(*t*Bu)₃], **65** (60%, PMe₃), **66** [74%, P(*t*Bu)₂Me], or **64** (44%, dppp). A number of products analogous to **64** and **66** were prepared by using different aryl bromides and/or substrates bearing different groups on nitrogen (Figure 1).
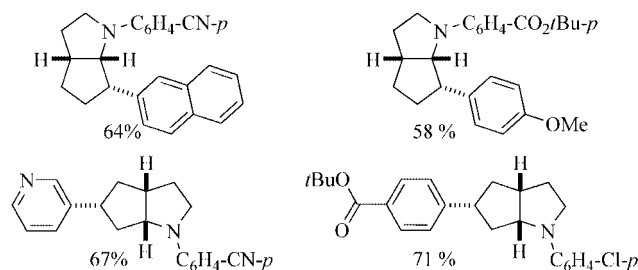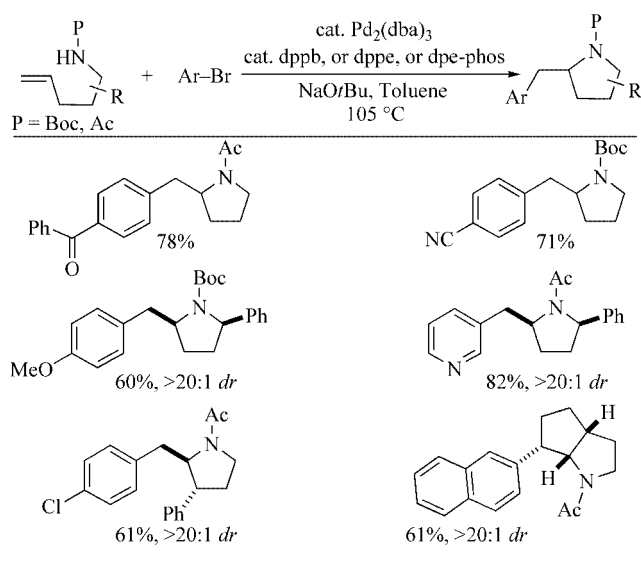

Figure 1. Analogs of **64** and **66**.

Carboamination of *N*-Protected γ-Aminoalkenes with Aryl/Alkenyl Bromides

The palladium-catalyzed carboamination reactions of γ-(arylamino)alkenes described above are very effective for the construction of substituted *N*-arylpyrrolidines. However, further elaboration of these products is complicated by the difficulties associated with deprotection of *N-p*-methoxyphenyl groups, and the lack of suitable methods for cleavage of other *N*-aryl moieties. Moreover, reactions of electron-rich (*p*-methoxyphenyl-substituted) substrates suffered from formation of significant amounts (ca. 10%) of 3-arylpyrrolidine side products,[35] and from competing *N*-arylation with electron-poor aryl bromide coupling partners.
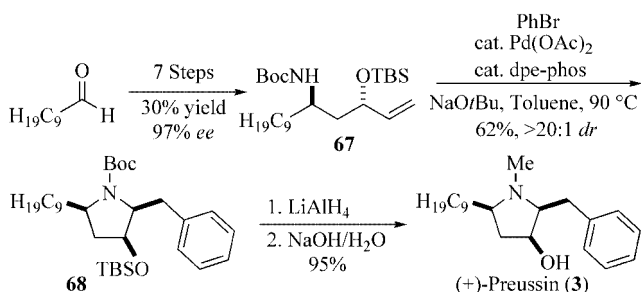
In order to address these problems, we developed conditions to effect the Pd-catalyzed carboamination of *N*-protected γ-aminoalkene substrates. After some experimentation, we found that starting materials bearing *N*-Boc or *N*-acyl protecting groups were efficiently transformed to substituted pyrrolidines in good yields, with diastereoselectivities similar to those obtained with γ-(arylamino)alkene substrates (Table 6).[40] In addition, the formation of regioisomeric side products was not observed, and the transformations are effective with electron-poor aryl bromides and alkenyl bromides. Cleavage of these protecting groups can be accomplished under standard conditions.[41]

In order to further illustrate the scope and utility of this method, we elected to pursue a total synthesis of the alkaloid natural product (+)-preussin (**3**).[42] This compound was first isolated in 1988 from the fermentation extracts of *Preussia sp.* and *Aspergillis ochraceus*,[7a] and was initially reported to possess modest antifungal activity.[7a,43] How-

Table 6. Synthesis of *N*-protected pyrrolidines.

conversion of the carbamate to a methyl group, and TBAF for the desilylation. These conditions tolerate functional groups such as ketones that are not compatible with Li-AlH₄.
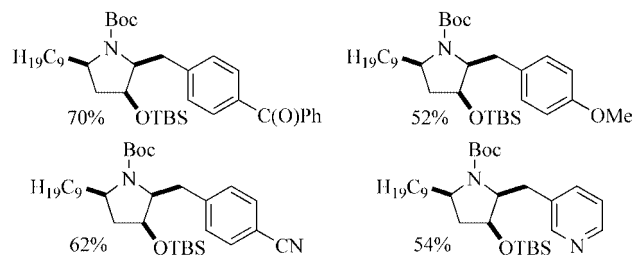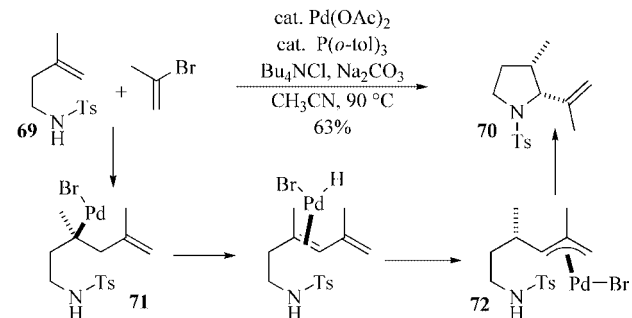

Figure 2. Preussin analogs.

ever, more recent assays have shown that preussin induces apoptosis in several human tumor cell lines,[7b] inhibits cyclin-E kinase (IC$_{50}$ = 500 nm),[7b] and exhibits antiviral activity.[7c] Although preussin has been a popular target for total synthesis efforts,[44] nearly all of the prior syntheses of this molecule install the phenyl moiety early in the synthetic sequence, and are thus not well suited for the rapid generation of preussin analogs bearing different aromatic moieties.

Our approach to (+)-preussin is outlined below in Scheme 11. The key intermediate **67** is prepared in seven steps (30% overall yield, 97% *ee*) from decanal, and is converted to pyrrolidine **68** in a 62% yield and >20:1 *dr* via a Pd-catalyzed carboamination reaction using bromobenzene as the electrophile. This intermediate is then transformed to the natural product through reduction with LiAlH₄, followed by workup with aqueous NaOH.

Pd⁰-Catalyzed 1,1-Carboamination Reactions of Alkenes That Afford Pyrrolidine Products

As described above, the palladium-catalyzed carboamination reactions of γ-aminoalkenes with aryl and alkenyl bromides effect 1,2-addition of the amino group and the aryl/alkenyl group across the double bond to afford 2-benzyl or 2-allylpyrrolidines. In contrast, the synthesis of 2-vinylpyrrolidines has been accomplished by Larock and Weinreb through Pd⁰-catalyzed 1,1-carboamination reactions of β-(tosylamino)alkenes with alkenyl bromides.[45] For example, treatment of **69** with 2-bromopropene in the presence of a palladium catalyst provides **70** in a 63% yield (Scheme 12). These reactions proceed via oxidative addition of the alkenyl bromide to Pd⁰, followed by carbopalladation to generate **71**. This intermediate undergoes β-hydride elimination/reinsertion to give allylpalladium complex **72**, which cyclizes to provide the pyrrolidine product. Both *E*- and *Z*-alkenyl bromides afford the same product; the alkene stereochemistry is lost through isomerization of intermediates analogous to **72**. Very high diastereoselectivity is reported for the formation of *cis*-2,3-disubstituted pyrrolidine **70**. However, the preparation of 2,4- or 2,5-disubstituted products has not been described.

Scheme 11.

Scheme 12.

The strategy described above effects the installation of the aryl moiety one step from the end of the sequence, and is amenable to the preparation of a variety of preussin analogs (Figure 2). We have also developed mild conditions for the final reduction/deprotection sequence that employ a mixture of formic acid and aqueous formaldehyde for the

Intramolecular Carboetherification/Carboamination of γ-Hydroxy- or γ-Aminoalkenes

The construction of molecules that contain two rings joined by a C–C bond with a stereocenter at both points of

attachment remains a challenging and significant problem in organic synthesis, as this subunit is displayed in a number of important compounds.[46] We have developed a new approach to these structures using intramolecular carboetherification and carboamination reactions of alkenes bearing tethered aryl bromides.[47] As shown below [Equation (14)], treatment of the *E*-alkene **73** with catalytic amounts of Pd$_2$(dba)$_3$ and PCy$_3$·HBF$_4$ in the presence of NaO*t*Bu affords **74** in a 71% yield with >20:1 *dr*. The reactions of aniline-containing substrates are stereospecific, and the products result from *syn* addition of the aryl group and the nitrogen atom across the double bond.
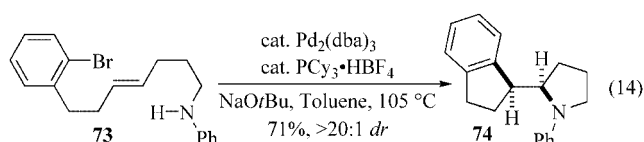
The analogous reactions of substrates bearing tethered alcohols are also stereospecific. However, either product diastereomer can be selectively obtained from a single alkene starting material with the use of an appropriate catalyst (Scheme 13). For example, the Pd$_2$(dba)$_3$/P[(*p*-MeO)-C$_6$H$_4$]$_3$ catalyzed reaction of the *Z*-alkene **75** provides the *syn*-addition product **77** in a 54% yield with 8:1 *dr*, but use of a catalyst derived from Pd$_2$(dba)$_3$ and (±)-BINAP affords *anti*-addition product **79** in a 60% yield with 18:1 *dr*.
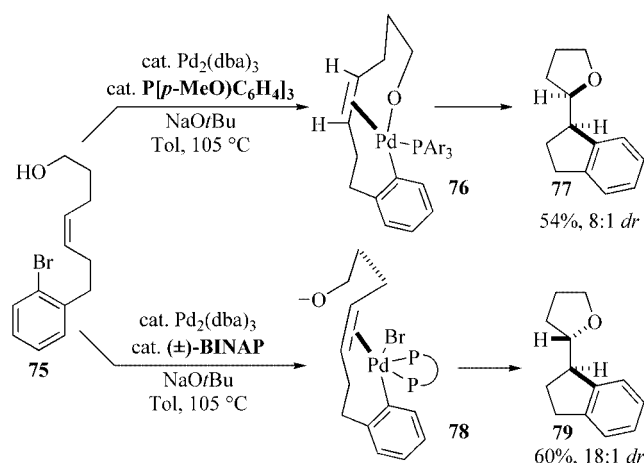

Scheme 13.

The change in the stereochemical outcome of these reactions results from a catalyst-dependent change in reaction mechanism.[47] As shown in Scheme 13, the *syn*-addition product likely derives from *syn*-oxypalladation of macrocyclic palladium(aryl)(alkoxide) complex **76**, whereas the *anti*-addition product likely results from *anti*-alkoxypalladation via the alkene complex **78**. This change in mechanism may be due to a relatively slow rate of palladium alkoxide

formation with BINAP as ligand, as intermediate **78** is coordinatively saturated, and the exchange of alkoxide for bromide most likely occurs through an associative mechanism.

Pd^0 and Pd^{II}-Catalyzed Carboamination of *N*-Allylureas

Substituted cyclic ureas are found in a number of interesting biologically active molecules, including HIV protease inhibitors and non-natural peptide analogs.[48] These compounds are typically prepared from acylation of 1,2-diamines with phosgene or phosgene equivalents.[49] However, the synthesis of 1,2-diamines often requires multistep sequences. In recent work, cyclic ureas have been prepared from *N*-allylureas by Pd^0-catalyzed reactions with aryl bromides [Equation (15)],[50] and by Pd^{II}-catalyzed carbonylative cyclizations [Equation (16)].[19b–19d] The *N*-allylurea starting materials can be prepared in one step from readily available allylic amines, and the reactions are effective with a variety of different *N*-allylureas and aryl halides.
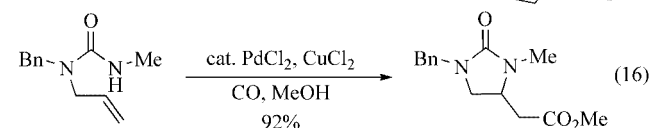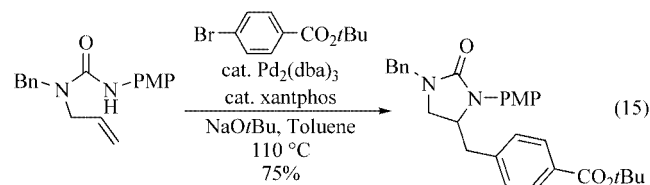
Summary and Outlook

Palladium-catalyzed carboamination and carboetherification reactions are efficient, convergent, and useful methods for assembling substituted tetrahydrofurans and pyrrolidines. Many transformations proceed in high yield and diastereoselectivity, and the starting materials are readily available. Although much progress has been made in this area, many challenges remain to be addressed in the future. New catalysts will likely permit cyclizations of more highly substituted alkenes, and new chiral catalysts may lead to asymmetric versions of these reactions. The development of mild reaction conditions that tolerate a broad range of functional groups would significantly expand the scope of these methods, and the use of these reactions in new tandem transformations should permit the rapid generation of complex structures in a straightforward manner.

Acknowledgments

[1] a) F. Q. Alali, X.-X. Liu, J. L. McLaughlin, *J. Nat. Prod.* **1999**, *62*, 504–540; b) M. C. Zafra-Polo, B. Figadere, T. Gallardo, J. R. Tormo, D. Cortes, *Phytochemistry* **1998**, *48*, 1087–1117.

[2] M. M. Faul, B. E. Huff, *Chem. Rev.* **2000**, *100*, 2407–2474.

[3] M. Saleem, H. J. Kim, M. S. Ali, Y. S. Lee, *Nat. Prod. Rep.* **2005**, *22*, 696–716.

[4] E. J. Kang, E. Lee, *Chem. Rev.* **2005**, *105*, 4348–4378.

[5] a) D. O'Hagen, *Nat. Prod. Rep.* **2000**, *17*, 435–446; b) A. Mitchinson, A. Nadin, *J. Chem. Soc., Perkin Trans. 1* **2000**, 2862–2892; c) G. Massiot, C. Delaude, *Alkaloids* **1986**, *27*, 269–322.

[6] R. G. Powell, D. Weisleder, C. R. Smith Jr., W. K. Rohwedder, *Tetrahedron Lett.* **1970**, *11*, 815–818.

[7] a) R. E. Schwartz, J. Liesch, O. Hensens, L. Zitano, S. Honeycutt, G. Garrity, R. A. Fromtling, J. Onishi, R. Monaghan, *J. Antibiot.* **1988**, *41*, 1774–1779; b) T. V. Achenbach, P. E. Slater, H. Brummerhop, T. Bach, R. Müller, *Antimicrob. Agents Chemother.* **2000**, *44*, 2794–2801; c) T. G. Kinzy, J. W. Harger, A. Carr-Schmid, J. Kwon, M. Shastry, M. Justice, J. D. Dinman, *Virology* **2002**, *300*, 60–70.

[8] a) B. A. Sobin, F. W. Tanner Jr., *J. Am. Chem. Soc.* **1954**, *76*, 4053; b) O. Schwardt, U. Veith, C. Gaspard, V. Jäger, *Synthesis* **1999**, 1473–1490.

[9] M. Shibano, S. Kitagawa, G. Kusano, *Chem. Pharm. Bull.* **1997**, *45*, 505–508.

[10] a) T. L. B. Boivin, *Tetrahedron* **1987**, *43*, 3309–3362; b) J.-C. Harmange, B. Figadere, *Tetrahedron: Asymmetry* **1993**, *4*, 1711–1754; c) M. Pichon, B. Figadere, *Tetrahedron: Asymmetry* **1996**, *7*, 927–964; d) J. P. Wolfe, M. B. Hay *Tetrahedron* **2006**, in press.

[11] For a recent Microreview that describes the synthesis of tetrahydropyrans, see: P. A. Clarke, S. Santos, *Eur. J. Org. Chem.* **2006**, 2045–2053.

[12] For notable exceptions, see: a) K. Mikami, M. Shimizu, *Tetrahedron* **1996**, *52*, 7287–7296; b) E. S. Sherman, S. R. Chemler, T. B. Tan, O. Gerlits, *Org. Lett.* **2004**, *6*, 1573–1575.

[13] M. F. Semmelhack, C. Bodurow, *J. Am. Chem. Soc.* **1984**, *106*, 1496–1498.

[14] For additional studies in this area, see: a) M. F. Semmelhack, N. Zhang, *J. Org. Chem.* **1989**, *54*, 4483–4485; b) M. McCormick, R. Monahan III, J. Soria, D. Goldsmith, D. Liotta, *J. Org. Chem.* **1989**, *54*, 4485–4487; c) M. F. Semmelhack, C. Kim, N. Zhang, C. Bodurow, M. Sanner, W. Dobler, M. Meier, *Pure Appl. Chem.* **1990**, *62*, 2035–2040; d) Y. Tamaru, T. Kobayashi, S. Kawamura, H. Ochiai, M. Hojo, Z. Yoshida, *Tetrahedron Lett.* **1985**, *26*, 3207–3210.

[15] M. F. Semmelhack, W. R. Epa, A. W.-H. Cheung, Y. Gu, C. Kim, N. Zhang, W. Lew, *J. Am. Chem. Soc.* **1994**, *116*, 7455–7456.

[16] a) G. C. Paddon-Jones, N. L. Hungerford, P. Hayes, W. Kitching, *Org. Lett.* **1999**, *1*, 1905–1907; b) M. F. Semmelhack, P. Shanmugam, *Tetrahedron Lett.* **2000**, *41*, 3567–3571; c) P. Y. Hayes, W. Kitching, *J. Am. Chem. Soc.* **2002**, *124*, 9718–9719.

[17] G. C. Paddon-Jones, C. S. P. McErlean, P. Hayes, C. J. Moore, W. A. Konig, W. Kitching, *J. Org. Chem.* **2001**, *66*, 7487–7495.

[18] M. Babjak, P. Kapitan, T. Gracza, *Tetrahedron* **2005**, *61*, 2471–2479.

[19] a) L. S. Hegedus, G. F. Allen, D. J. Olsen, *J. Am. Chem. Soc.* **1980**, *102*, 3583–3587; b) Y. Tamaru, T. Kobayashi, S. Kawamura, H. Ochiai, Z. Yoshida, *Tetrahedron Lett.* **1985**, *26*, 4479–4482; c) Y. Tamaru, M. Hojo, H. Higashimura, Z. Yoshida, *J. Am. Chem. Soc.* **1988**, *110*, 3994–4002; d) Y. Tamaru, M. Hojo, Z. Yoshida, *J. Org. Chem.* **1988**, *53*, 5731–5741; e) H. Harayama, H. Okuno, Y. Takahashi, M. Kimura, K. Fugami, S. Tanaka, Y. Tamaru, *Tetrahedron Lett.* **1996**, *37*, 7287–7290; f) Y. Tamaru, M. Kimura, *Synlett* **1997**, 749–757; g) H. Harayama, A. Abe, T. Sakado, M. Kimura, K. Fugami, S. Tanaka, Y. Tamaru, *J. Org. Chem.* **1997**, *62*, 2113–2122.

[20] For related reactions of aminoallenes, see: D. Lathbury, P. Vernon, T. Gallagher, *Tetrahedron Lett.* **1986**, *27*, 6009–6012.

[21] W.-H. Ham, Y. H. Jung, K. Lee, C.-Y. Oh, K.-Y. Lee, *Tetrahedron Lett.* **1997**, *38*, 3247–3248.

[22] C.-Y. Oh, K.-S. Kim, W.-H. Ham, *Tetrahedron Lett.* **1998**, *39*, 2133–2136.

[23] M. F. Semmelhack, W. R. Epa, *Tetrahedron Lett.* **1993**, *34*, 7205–7208.

[24] a) C. C. Scarborough, S. S. Stahl, *Org. Lett.* **2006**, *8*, 3251–3254; b) For an example of oxidative amination of two equivalents of norbornene with TsNH$_2$ that affords a tricyclic pyrrolidine, see: J. L. Brice, J. E. Harang, V. I. Timokhin, N. R. Anastasi, S. S. Stahl, *J. Am. Chem. Soc.* **2005**, *127*, 2868–2869.

[25] K.-T. Yip, M. Yang, K.-L. Law, N.-Y. Zhu, D. Yang, *J. Am. Chem. Soc.* **2006**, *128*, 3130–3131.

[26] For related transformations of γ-hydroxy allenes or alkynes see: a) G. Balme, D. Bouyssi, T. Lomberget, N. Monteiro, *Synthesis* **2003**, 2115–2134; b) S.-K. Kang, T.-G. Baik, A. N. Kulak, *Synlett* **1999**, 324–326; c) R. D. Walkup, L. Guan, M. D. Mosher, S. W. Kim, Y. S. Kim, *Synlett* **1993**, 88–90; d) F. T. Luo, I. Schreuder, R. T. Wang, *J. Org. Chem.* **1992**, *57*, 2213–2215.

[27] a) J. P. Wolfe, M. A. Rossi, *J. Am. Chem. Soc.* **2004**, *126*, 1620–1621; b) M. B. Hay, A. R. Hardin, J. P. Wolfe, *J. Org. Chem.* **2005**, *70*, 3099–3107.

[28] Prior to our studies, Trost noted that a Pd$_2$(dba)$_3$/P(*o*-tol)$_3$-catalyzed Heck arylation of an enyne bearing a γ-hydroxy group produced a small amount of a tetrahydrofuran derivative as a minor side product. In our hands, these conditions provided only a trace amount of 2-(2-naphthylmethyl)tetrahydrofuran (**36**) in the reaction of 4-penten-1-ol with 2-bromonaphthalene. See: B. M. Trost, W. Pfrengle, H. Urabe, J. Dumas, *J. Am. Chem. Soc.* **1992**, *114*, 1923–1924.

[29] M. B. Hay, J. P. Wolfe, *J. Am. Chem. Soc.* **2005**, *127*, 16468–16476.

[30] These reactions also afford small amounts of 2-methyl-3-aryl tetrahydrofuran side products, which are believed to derive from β-hydride elimination of the C3 hydrogen atom in intermediate **45**. For further details, see ref.[29].

[31] M. B. Hay, J. P. Wolfe, *Tetrahedron Lett.* **2006**, *47*, 2793–2796.

[32] M.-C. P. Yeh, W.-C. Tsao, L.-H. Tu, *Organometallics* **2005**, *24*, 5909–5915.

[33] a) A. R. Muci, S. L. Buchwald, *Top. Curr. Chem.* **2002**, *291*, 131–209; b) J. F. Hartwig, in: *Modern Arene Chemistry* (Ed.: D. Astruc), Wiley-VCH, Weinheim, **2002**, pp. 107–168.

[34] G. Fournet, G. Balme, J. Gore, *Tetrahedron* **1990**, *46*, 7763–7774.

[35] J. E. Ney, J. P. Wolfe, *Angew. Chem.* **2004**, *116*, 3689–3692; *Angew. Chem. Int. Ed.* **2004**, *43*, 3605–3608.

[36] Small amounts (ca. 1–10%) of 3-aryl-2-methylpyrrolidine regioisomers were generated in these transformations, and are formed through the mechanism described in footnote 30.

[37] J. E. Ney, M. B. Hay, Q. Yang, J. P. Wolfe, *Adv. Synth. Catal.* **2005**, *347*, 1614–1620.

[38] a) R. Lira, J. P. Wolfe, *J. Am. Chem. Soc.* **2004**, *126*, 13906–13907; b) Q. Yang, J. E. Ney, J. P. Wolfe, *Org. Lett.* **2005**, *7*, 2575–2578.

[39] J. E. Ney, J. P. Wolfe, *J. Am. Chem. Soc.* **2005**, *127*, 8644–8651.

[40] M. B. Bertrand, J. P. Wolfe, *Tetrahedron* **2005**, *61*, 6447–6459.

[41] T. W. Greene, P. G. M. Wuts, *Protective Groups in Organic Synthesis*, 3rd ed., Wiley, New York, **1999**.

[42] M. B. Bertrand, J. P. Wolfe, *Org. Lett.* **2006**, *8*, 2353–2356.

[43] a) J. H. Johnson, D. W. Phillipson, A. D. Kahle, *J. Antibiot.* **1989**, *42*, 1184–1185; b) K. Kasahara, M. Yoshida, J. Eishima, K. Takesako, T. Beppu, S. Horinouchi, *J. Antibiot.* **1997**, *50*, 267–269.

[44] For a recent review, see: B. Basler, S. Brandes, A. Spiegel, T. Bach, *Top. Curr. Chem.* **2005**, *243*, 1–42.

[45] a) G. D. Harris Jr., R. J. Herr, S. M. Weinreb, *J. Org. Chem.* **1992**, *57*, 2528–2530; b) G. D. Harris Jr., R. J. Herr, S. M. Weinreb, *J. Org. Chem.* **1993**, *58*, 5452–5464; c) R. C. Larock, H. Yang, S. M. Weinreb, R. J. Herr, *J. Org. Chem.* **1994**, *59*, 4172–4178.

[46] a) M. Ukiya, T. Akihisa, K. Yasukawa, Y. Kasahara, Y. Ki-mura, K. Koike, T. Nikaido, M. Takido, *J. Agric. Food Chem.* **2001**, *49*, 3187–3197; b) A. Spinella, E. Mollo, E. Trivellone, G. Cimino, *Tetrahedron* **1997**, *53*, 16891–16896; c) H. R. Arthur, P. D. S. Ko, H. T. Cheung, *Phytochemistry* **1974**, *13*, 2551–2557.

[47] J. S. Nakhla, J. W. Kampf, J. P. Wolfe, *J. Am. Chem. Soc.* **2006**, *128*, 2893–2901.

[48] a) J. Dumas, *Curr. Opin. Drug. Disc. Dev.* **2002**, *5*, 718–727; b) J.-M. Kim, T. E. Wilson, T. C. Norman, P. G. Schultz, *Tetrahedron Lett.* **1996**, *37*, 5309–5312; c) W. M. Kazmierski, E. Fur-fine, Y. Gray-Nunez, A. Spaltenstein, L. Wright, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5685–5687.

[49] G. Sartori, R. Maggi, in: *Science of Synthesis* (*Houben-Weyl Methods of Molecular Transformations*), vol. 18 (Eds.: S. V. Ley, J. G. Knight), Thieme, Stuttgart, **2005**, pp. 665–758.

[50] J. A. Fritz, J. S. Nakhla, J. P. Wolfe, *Org. Lett.* **2006**, *8*, 2531–2534.