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Stereoselective Synthesis of Tetrahydrofurans via the Palladium-Catalyzed Reaction of Aryl Bromides with γ-Hydroxy Alkenes: Evidence for an Unusual Intramolecular Olefin Insertion into a Pd(Ar)(OR) Intermediate

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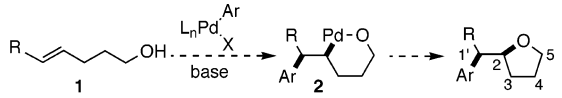
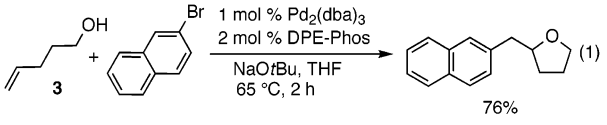
The tetrahydrofuran moiety is a commonly occurring structural feature of a large number of biologically active natural products, many of which contain substituents at the 1′-, 2-, and 5-positions of the ring.[1,2] Thus, there has been a long-standing interest in the stereoselective synthesis of substituted tetrahydrofurans, and a number of different methods have been devised for their preparation.[2] However, only three methods allow for ring closure with concomitant formation of both a new stereogenic center and a new C−C bond at the C1′-position.[3] These methods tend to exhibit only modest (ca. 1−3:1) stereoselectivity for the preparation of 2,3- and 2,5-disubstituted tetrahydrofurans and are limited to a narrow range of substrates. Herein we describe a new, stereoselective method for the synthesis of substituted tetrahydrofurans from γ-hydroxy alkenes that forms both a C−C and a C−O bond and up to two new stereocenters; extremely high diastereoselectivities (≥18:1) are observed for the formation of 2,5- and 2,3-disubstituted tetrahydrofurans. We also report our initial studies on the mechanism of this transformation, which suggest the reaction proceeds via an unusual intramolecular insertion of an olefin into a Pd(Ar)(OR) intermediate.

During the course of our studies on late transition metal-mediated sp^3 carbon−heteroatom bond-forming reactions we became interested in the possibility of capturing the organopalladium intermediate generated in a Heck reaction with a heteroatom nucleophile.[4−7] For example, reaction of a γ-hydroxy alkene (**1**) with an ArPdX species in the presence of a base could afford organopalladium intermediate **2**, which could undergo reductive elimination to provide a substituted tetrahydrofuran with the generation of two stereocenters and two bonds (Scheme 1).

Scheme 1

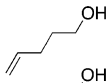
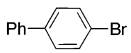
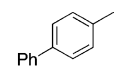
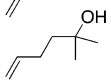
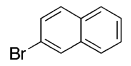
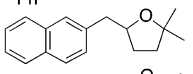
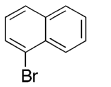
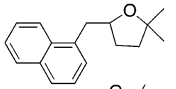
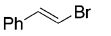
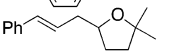
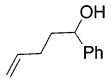
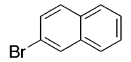
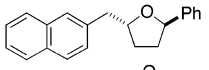
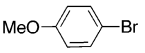
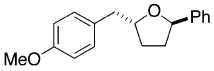
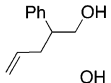
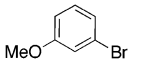
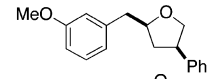
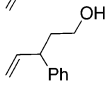
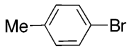
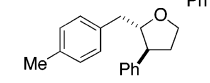
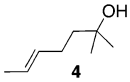
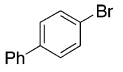
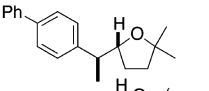
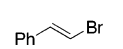
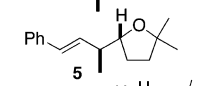
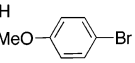
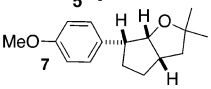


Larock has previously demonstrated that Pd-catalyzed reactions of aryl halides with 4-penten-1-ol typically afford aldehyde and/or alcohol products resulting from Heck-insertion/β-hydride elimination processes.[8,9] However, we felt that the formation of tetrahydrofurans could be achieved with a judicious choice of palladium catalyst. Our initial experiments focused on the reaction of 4-penten-1-ol (**3**) with 2-bromonaphthalene (eq 1). We found that small



amounts (ca. 20%) of the desired tetrahydrofuran were formed in the presence of catalytic $Pd_2(dba)_3$/P(*o*-tol)$_3$ with NaO*t*Bu as base.[10]

Table 1. Tetrahydrofuran Synthesis[a]

entry	alcohol	aryl bromide	product	yield (%)[b]
1				70
2				80
3				60
4				81[c]
5				60 (>20:1 dr)
6				62 (>20:1 dr)
7				84 (2:1 d r)
8				51 (18:1 d r)
9	 4			73[d] (5:1 d r)
10			 5	55[c,d] (5:1 d r)
11	 6		 7	69[e] (>20:1 dr)

[a] Conditions: 1.0 equiv alcohol, 2.0 equiv ArBr, 2.0 equiv NaO*t*Bu, 1 mol % $Pd_2(dba)_3$, 2 mol % DPE-Phos, THF (0.25 M), 65 °C, 2 h. [b] Yields represent average isolated yields for two or more experiments. [c] This material contained ca. 5% of a regioisomeric product. [d] The reaction was conducted with 4 mol % P(*o*-tol)$_3$ as ligand in toluene solvent at 110 °C. [e] The reaction was conducted with 2.5 mol % $Pd_2(dba)_3$/10 mol % P(*o*-tol)$_3$ in toluene at 110 °C for 48 h.

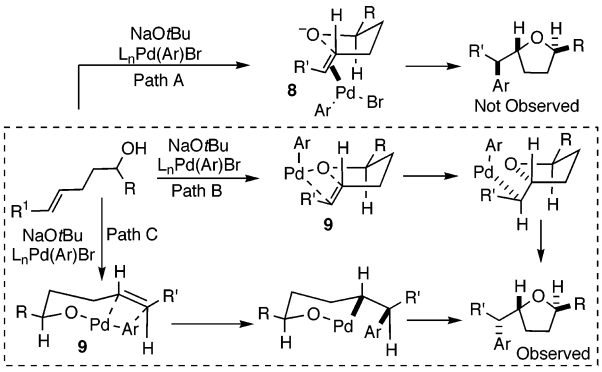
Use of DPE-Phos[11] as ligand increased the yield of this transformation, and when an excess of the aryl bromide and base (2.0 equiv each) were employed, the desired product was obtained in 76% isolated yield.[12]

As shown in Table 1, a variety of primary, secondary, and tertiary γ-hydroxy alkenes react with electron-rich and -neutral aryl bromides to provide tetrayhdrofuran products in good yield; vinyl bromides may also be employed as coupling partners (Table 1, entries 4 and 10).[13] The main side products observed in these reactions are dehalogenated arenes along with aldehydes/ketones resulting from oxidation of the alcohol substrates. Only trace amounts of arylated "Heck-type" products were formed.

Substituted γ-hydroxy alkenes undergo cyclization with good to excellent levels of diastereoselectivity. *trans*-2,5-Disubstituted

10.1021/ja0394838 CCC: $27.50

Scheme 2. Possible Mechanistic Pathways



and *trans*-2,3-disubstituted products are obtained from the corresponding 1- and 3-substituted alcohols, respectively, in ≥18:1 dr (Table 1, entries 5, 6, 8).[14,15] Reaction of a 2-substituted alcohol substrate proceeded with modest (2:1) stereoselectivity, affording the corresponding *cis*-2,4-disubstituted product (entry 7).[14,15] Tetrahydrofurans with *anti*-1′,2-stereochemistry (entries 9−10) were obtained in reactions of *trans*-disubstituted olefin **4**.[14,15] Reaction of cyclic olefin **6** afforded bicyclic product **7** with >20:1 diastereoselectivity (entry 11).

The stereochemical outcome of these reactions can be used to analyze possible mechanisms of this transformation. The high regoioselectivity of these reactions coupled with the high diastereoselectivity observed in the formation of *trans*-2,5-disubstituted products suggests that the initial step of this process *is not intermolecular carbopalladation*; it is unlikely that high 1,4-asymmetric induction would be achieved without chelation/direction by the substrate. Furthermore, previously described Heck arylations of **3** afford mixtures (ca. 5:1) of regioisomeric products,[8] whereas our reactions typically afford ≥95:5 regioselectivity.

Three other mechanisms could potentially account for the formation of tetrahydrofuran products under these conditions (Scheme 2). The elegant studies of Semmelhack have shown that Pd(II)-catalyzed carbonylations of γ-hydroxy alkenes proceed via Wacker-type *trans*-hydroxypalladation of a Pd(II)−olefin complex.[3a−c,4−6] The related reaction of a Pd(Ar)(X)−olefin complex bearing a tethered alkoxide (**8**) could potentially afford 2-benzyl-substituted tetrahydrofurans (Path A). However, this pathway would provide *syn*-1′,2-disubstituted products from *trans*-olefin substrate **4** rather than the *anti*-1′,2-disubstituted products that are observed. Thus, this mechanism can be ruled out on the basis of product stereochemistry.[16]

The remaining two mechanistic pathways would both provide products with the observed *anti*-1′,2-stereochemistry. Reaction of alcohol **4** with NaO*t*Bu and a Pd(Ar)Br complex would lead to the formation of a Pd(Ar)(OR) intermediate (**9**),[17,18] which could undergo insertion of the olefin into the Pd−O bond[19] (Scheme 2, Path B) followed by C−C bond-forming reductive elimination.[20] Alternatively, **9** could undergo insertion of the olefin into the Pd−C bond followed by sp^3 C−O bond-forming reductive elimination (Path C).[21] In both mechanisms the high 2,5- and 2,3-diastereoselectivites would arise from the substrate reacting through an organized, cyclic transition state in which the substitutents are oriented in pseudoequatorial positions. We are unable to differentiate between these two possible mechanisms with our current data. The intramolecular insertion of an olefin into a Pd(Ar)(OR) complex is unprecedented in catalytic reactions, as is sp^3 C−O bond-forming reductive elimination in nonallylic systems. Related transformations are precedented in stoichiometric reactions of Pt- or Ni-complexes, but are rare.[19,21]

In conclusion, we have developed a new, stereoselective, palladium-catalyzed synthesis of substituted tetrahydrofurans from γ-hydroxy alkenes. In contrast to related Pd(II)-catalyzed alkoxycarbonylation reactions,[3a−c,4−6] these new reactions *do not proceed through a Wacker-type mechanism*. Further studies on the scope, limitations, applications, and mechanism of these reactions are currently underway.

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Supporting Information Available: Characterization data for all new compounds in Table 1 and eq 1, information describing stereochemical assignments, and complete details of optimization studies (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Trost has noted the formation of a tetrahydrofuran side product in the Heck arylation of an enyne bearing a secondary OH group and suggested a mechanism of intermolecular carbopalladation to account for its formation. See: Trost, B. M.; Pfrengle, W.; Urabe, H.; Dumas, J. *J. Am. Chem. Soc.* **1992**, *114*, 1923−1924.
(10) Use of weaker bases (e.g., K_2CO_3, Et_3N) did not afford the desired products.
(11) DPE-Phos = bis(2-diphenylphosphinophenyl)ether.
(12) See Supporting Information for details of optimization studies.
(13) Reactions of electron-deficient aryl bromides afforded low yields of desired products; competing O-arylation of the substrate was observed. Reactions of aryl iodides were slow and gave large amounts of arene and ketone side products; only small amounts of the desired tetrahydrofurans were formed.
(14) Stereochemistry of tetrahydrofuran products was established by nOe experiments or by comparison of NMR spectra to related compounds of known configuration. See Supporting Information for complete details.
(15) Diastereomeric ratios were determined by ^{1}H NMR and/or GC analysis of crude reaction mixtures.
(16) The stereoselective conversion of **6** to **7** provides further evidence against this mechanism. We thank a reviewer for this suggestion.
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(18) The ketone side products observed in these reactions likely arise from β-hydride elimination reactions of Pd-alkoxide intermediates. See footnote 17.
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