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Palladium-Catalyzed Synthesis of Tetrahydrofurans from γ-Hydroxy Terminal Alkenes: Scope, Limitations, and Stereoselectivity

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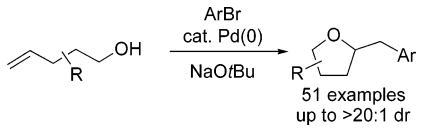

A new, stereoselective synthesis of substituted tetrahydrofurans via Pd-catalyzed reactions of aryl and vinyl bromides with γ-hydroxy terminal alkenes is described. This transformation affords *trans*-2,5- and *trans*-2,3-disubstituted tetrahydrofurans with up to >20:1 dr. This methodology also provides access to bicyclic and spirocyclic tetrahydrofuran derivatives in good yield with 10−20:1 dr. The scope and limitations of these transformations are discussed in detail, as are the effect of substrate sterics and electronics on yield and stereoselectivity. A proposed mechanism of these transformations is presented along with a model that rationalizes the stereochemical outcome of the reactions.

Introduction

A wide variety of interesting biologically active molecules contain substituted tetrahydrofuran subunits.[1] For example, the annonaceous acetogenins are a large family of natural products with a diverse range of biological activities including antitumor, antihelmic, antimalarial, antimicrobial, and antiprotozoal.[2] Substituted tetrahydrofurans are also found in polyether antibiotics,[3] lignans,[4] and C-glycosides.[5]

Due to the medicinal importance of compounds bearing tetrahydrofuran units, there has been considerable interest in the development of efficient, stereoselective methods for the preparation of the tetrahydrofuran ring.[1−6] However, few methods have been described that allow for formation of a tetrahydrofuran ring from an acyclic precursor with concomitant formation of both a new stereogenic center and a new carbon−carbon bond at the C1′-position.[7] These methods are effective for the preparation of tetrahydrofurans bearing ester functionality at C1′ but often exhibit only modest stereocontrol (ca. 1−3:1) for the preparation of 2,3- and 2,5-disubstituted products and do not allow for the installation of aryl, vinyl, or alkyl chains at C1′.[7]

We recently reported a new method for the stereoselective synthesis of tetrahydrofurans from aryl or vinyl bromides and γ-hydroxyalkenes.[8−13] These reactions lead

(1) Hou, X.-L.; Yang, Z.; Wong, H. N. C. *Prog. Heterocycl. Chem.* **2002**, *14*, 139−179.

(2) (a) Alali, F. Q.; Liu, X.-X.; McLaughlin, J. L. *J. Nat. Prod.* **1999**, *62*, 504−540. (b) Figadere, B. *Acc. Chem. Res.* **1995**, *28*, 359−365. (c) Zafra-Polo, M. C.; Figadere, B.; Gallardo, T.; Tormo, J. R.; Cortes, D. *Phytochemistry* **1998**, *48*, 1087−1117.

(3) (a) Faul, M. M.; Huff, B. E. *Chem. Rev.* **2000**, *100*, 2407−2474. (b) *Polyether Antibiotics: Naturally Occurring Acid Ionophores*; Westley, J. W., Ed.; Marcel Dekker: New York, 1982; Vols. 1 and 2.

(4) Ward, R. S. *Nat. Prod. Rep.* **1999**, *16*, 75−96.

(5) (a) Nicotra, F. *Top. Curr. Chem.* **1997**, *187*, 55−83. (b) Postema, M. H. D. *Tetrahedron* **1992**, *48*, 8545−8599.

(6) (a) Elliott, M. C. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2301−2323. (b) Harmange, J. C.; Figadere, B. *Tetrahedron: Asymmetry* **1993**, *4*, 1711−1754.

(7) (a) Semmelhack, M. F.; Bodurow, C. *J. Am. Chem. Soc.* **1984**, *106*, 1496−1498. (b) Semmelhack, M. F.; Kim, C.; Zhang, N.; Bodurow, C.; Sanner, M.; Dobler, W.; Meier, M. *Pure Appl. Chem.* **1990**, *62*, 2035−2040. (c) Semmelhack, M. F.; Epa, W. R. *Tetrahedron Lett.* **1993**, *34*, 7205−7208. (d) Semmelhack, M. F.; Shanmugam, P. *Tetrahedron Lett.* **2000**, *41*, 3567−3571. (e) Hayes, P. Y.; Kitching, W. *J. Am. Chem. Soc.* **2002**, *124*, 9718−9719. (f) Gracza, T.; Jäger, V. *Synlett* **1992**, 191−193. (g) Gracza, T.; Hasenöhrl, T.; Stahl, U.; Jäger, V. *Synthesis* **1991**, 1108−1118. (h) Mikami, K.; Shimizu, M. *Tetrahedron* **1996**, *52*, 7287−7296.

(8) A portion of this work has been previously communicated. See: Wolfe, J. P.; Rossi, M. A. *J. Am. Chem. Soc.* **2004**, *126*, 1620−1621.

(9) For related transformations of γ-aminoalkenes that afford nitrogen heterocycles, see: (a) Ney, J. E.; Wolfe, J. P. *Angew. Chem., Int. Ed.* **2004**, *43*, 3605−3608. (b) Lira, R.; Wolfe, J. P. *J. Am. Chem. Soc.* **2004**, *126*, 13906−13907.

(10) For related transformations of γ-alkylidene malonates that afford carbocycles see: (a) Balme, G.; Bouyssi, D.; Lomberget, T.; Monteiro, N. *Synthesis* **2003**, 2115−2134. (b) Balme, G.; Bouyssi, D.; Faure, R.; Gore, J.; Van Hemelryck, B. *Tetrahedron* **1992**, *48*, 3891−3902.

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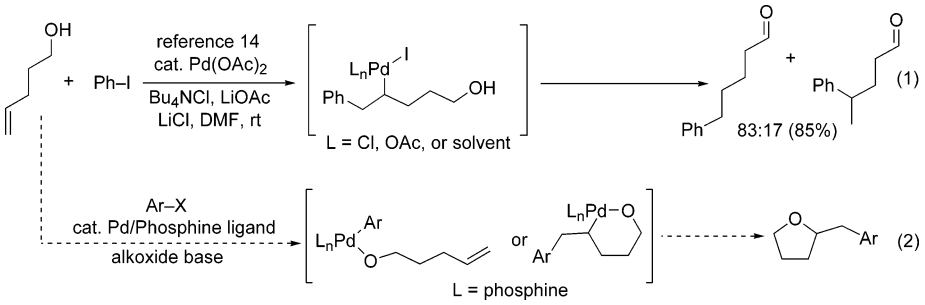
SCHEME 1



to the formation of both a C−O and a C−C bond along with up to two new stereocenters in a single step. Transformations of γ-hydroxyalkenes bearing substituents at the 1- or 3-position proceed with good to excellent levels of diastereoselectivity (up to >20:1 dr). However, reactions of substrates that are substituted at the 2-position afford products with low dr (ca. 2:1). In this paper, we describe the development, scope, and limitations of the synthesis of substituted tetrahydrofurans from 4-penten-1-ol derivatives. We also describe unexpected electronic effects that influence the chemical yield of these transformations and present further studies on the effect of substituent size on the diastereoselectivity of these transformations. Finally, we propose a refined model to explain the stereochemical outcome of these transformations.

Results

Development and Optimization of Reaction Conditions. Larock has previously demonstrated that the Pd-catalyzed reaction of 4-penten-1-ol with aryl halides in the presence of a weak base ($NaHCO_3$) affords 5-arylpentanal products (eq 1, Scheme 1), which are believed to derive from Heck-type olefination of the aryl halide followed by reversible β−hydride elimination.[14] We felt that the synthesis of 2-benzyltetrahydrofurans from a similar combination of substrates (eq 2, Scheme 1) could be achieved through two key modifications of the Larock conditions: (1) use of a stronger base, which would lead to deprotonation of the alcohol substrate and provide access to intermediate palladium alkoxides,[15] and (2) use of a palladium/phosphine catalyst that would promote tetrahydrofuran formation via alkene insertion followed by reductive elimination. We reasoned that the reactivity of the intermediate palladium alkoxide complex could be controlled by varying the steric and electronic properties of the phosphine ligands.

In our preliminary experiments, we examined the reaction of 4-penten-1-ol with 2-bromonaphthalene (eq 3) using a catalyst comprised of $Pd_2(dba)_3$ and P(*o*-tol)$_3$ and found that the desired tetrahydrofuran product was formed in 20% isolated yield when NaO-*t*-Bu was employed as base.[16] The main side product observed in this transformation was naphthalene, which derives from Pd-catalyzed reduction of the aryl bromide. Previous studies have shown that aryl halides undergo Pd-catalyzed reduction in the presence of an alcohol and a base by a mechanism involving β-hydride elimination from a Pd(Ar)(OR) intermediate.[17] Chelating bis(phosphine) ligands are known to decrease the rate of β-hydride elimination reactions,[18] and we were pleased to find that use of dpe-phos[19] as ligand increased the yield of the desired product to 45%.

This yield was further improved to 76% by adding 2 equiv of both the aryl bromide and NaO-*t*-Bu to the reaction mixture. Further experiments demonstrated that use of the dppb ligand provided results comparable to those obtained with dpe-phos. However, most other ligands and bases that were examined provided unsatisfactory results (Table 1). A brief survey of reaction media showed that use of toluene as solvent provided similar results to those obtained in THF. However, reactions conducted in polar solvents such as DMF and acetonitrile gave little or no desired products.

Synthesis of 2-Monosubstituted and 2,2-Symmetrically Disubstituted Tetrahydrofurans. Transformations of 4-penten-1-ol (**1**) and the analogous symmetrically substituted tertiary alcohol derivatives **3** and **4** proceed in moderate to good yield with a variety of electron-neutral aryl bromides (Table 2).[20] This method is amenable to the synthesis of spirocyclic ring systems (entries 11−12), and ortho-substitution on the aryl bromide is tolerated (entries 9 and 12). High regioselec-

(11) For related transformations of γ-hydroxy allenes, see: (a) Kang, S.-K.; Baik, T.-G.; Kulak, A. N. *Synlett* **1999**, 324−326. (b) Walkup, R. D.; Guan, L.; Mosher, M. D.; Kim, S. W.; Kim, Y. S. *Synlett* **1993**, 88−90.

(12) For related transformations of γ-hydroxy alkynes, see: Luo, F. T.; Schreuder, I.; Wang, R. T. *J. Org. Chem.* **1992**, *57*, 2213−2215.

(13) For related heteroannulations of internal alkynes with *o*-haloanilines, *o*-halophenols, and related compounds, see: Larock, R. C.; Yum, E. K.; Doty, M. J.; Sham, K. K. C. *J. Org. Chem.* **1995**, *60*, 3270−3271.

(14) Small amounts of 5-aryl-4-penten-1-ol products were also observed. See: Larock, R. C.; Leung, W.-Y.; Stoltz-Dunn, S. *Tetrahedron Lett.* **1989**, *30*, 6629−6632.

(15) Bryndza, H. E.; Tam, W. *Chem. Rev.* **1988**, *88*, 1163−1188.

(16) 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.

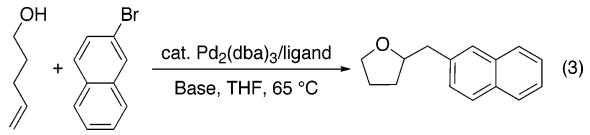
(17) (a) Widenhoefer, R. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 6504−6411 and references therein. (b) Mann, G.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 13109−13110.

(18) (a) Jensen, D. R.; Schultz, M. J.; Mueller, J. A.; Sigman, M. S. *Angew. Chem., Int. Ed.* **2003**, *42*, 3810−3813. (b) Steinhoff, B. A.; Stahl, S. S. *Org. Lett.* **2002**, *4*, 4179−4181 and references therein.

(19) Ligand abbreviations: dppe = 1,2-bis(diphenylphosphino)-ethane; BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl; dppf = 1,1′-bis(diphenylphosphino)ferrocene; dppb = 1,1′-bis(diphenylphosphino)butane; xantphos = 9,9-dimethyl-4,5-bis(diphenylphosphino)-xanthene; dpe-phos = bis(2-diphenylphosphinophenyl)ether. All ligands are readily available from commercial sources.

(20) Most reactions proceeded to completion in ca. 2 h as judged by GC analysis of crude reaction mixtures.

TABLE 1. Optimization Studies[a]



entry	ligand	base	GC yield (%)	isolated yield (%)
1	P(*o*-tol)$_3$	$KHCO_3$	0[g,h]	
2	P(*o*-tol)$_3$	NaOAc	0[g,h]	
3	P(*o*-tol)$_3$	$NaHCO_3$	0[g,h]	
4	P(*o*-tol)$_3$	K_2CO_3	0[g,h]	
5	P(*o*-tol)$_3$	Et_3N	0[g,h]	
6	P(*o*-tol)$_3$	Na_2CO_3	0[g,h]	
7	P(*o*-tol)$_3$	LiO-*t*-Bu	5	
8	P(*o*-tol)$_3$	KO-*t*-Bu	11	
9	P(*o*-tol)$_3$	NaO-*t*-Bu	17	20
10	PPh_3	NaO-*t*-Bu	0[h]	
11	P(2-furyl)$_3$	NaO-*t*-Bu	0[g,h]	
12	*t*-Bu$_2$P(*o*-biphenyl)	NaO-*t*-Bu	0	
13	Cy$_2$P(*o*-biphenyl)	NaO-*t*-Bu	<3	
14[b]	Pd[P(*t*Bu)$_3$]$_2$	NaO-*t*-Bu	0[h]	
15[c]	Pd[P(Cy)$_3$]$_2$	NaO-*t*-Bu	0[h]	
16	dppe	NaO-*t*-Bu	<1	
17	(±)-BINAP	NaO-*t*-Bu	0[g,h]	
18	dppf	NaO-*t*-Bu	8	
19	dppb	NaO-*t*-Bu	52	
20	xantphos	NaO-*t*-Bu	40	
21	dpe-phos	NaO-*t*-Bu	55	45
22[d]	dpe-phos	NaO-*t*-Bu	79	
23[e]	dpe-phos	NaO-*t*-Bu	80	
24[f]	dpe-phos	NaO-*t*-Bu	93	76

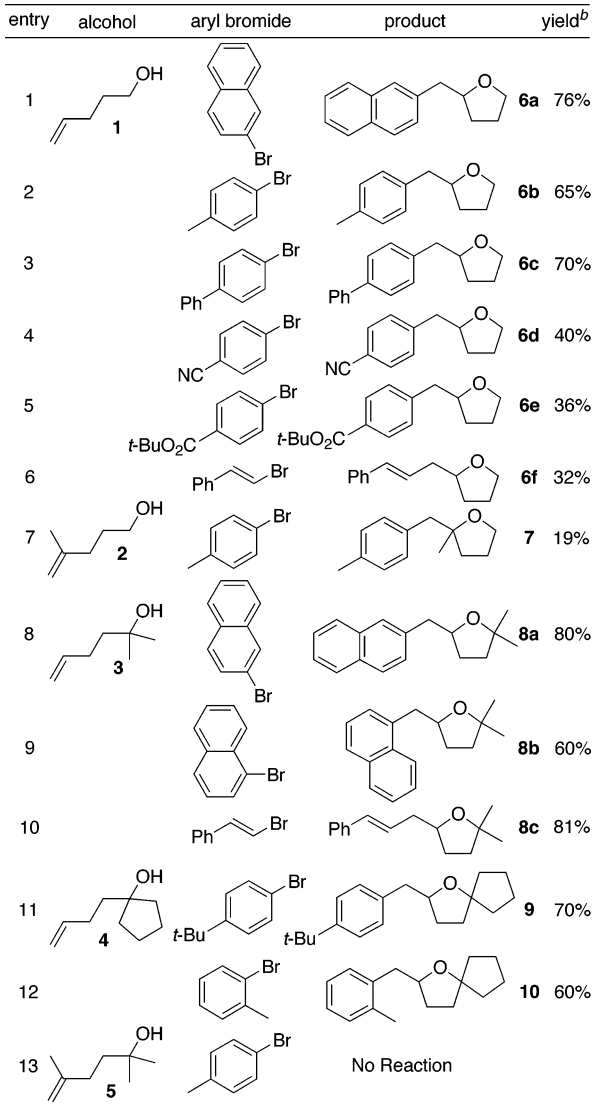
[a] Conditions: 1.0 equiv of alcohol, 1.1 equiv of ArBr, 1.2 equiv of NaO-*t*-Bu, 1 mol % of $Pd_2(dba)_3$, 4 mol % of ligand (monodentate ligands) or 2 mol % of ligand (bidentate ligands), solvent (0.25 M), 65 °C. [b] Pd[P(*t*-Bu)$_3$]$_2$ used in place of $Pd_2(dba)_3$/ligand. [c] Pd[P(Cy)$_3$]$_2$ used in place of $Pd_2(dba)_3$/ligand. [d] 2.0 equiv of base used. [e] 2.0 equiv of ArBr used. [f] 2.0 equiv of ArBr and 2.0 equiv of base used. [g] Less than 10% of the starting material was consumed. [h] Naphthalene was the sole product detected by GC analysis of the crude reaction mixture.

tivity (>20:1) for 2-benzyltetrahydrofuran formation was observed in all reactions examined in these studies.[21]

The main side products in these reactions are arenes derived from reduction of the aryl halide[22] and/or ethers derived from *O*-arylation/vinylation of the alcohol substrate.[23,24] These side reactions are more problematic with primary alcohol substrates. For example, a significantly lower yield was obtained in the reaction of β-bromostyrene with 4-penten-1-ol (32%, entry 6) than in the analogous reaction with **3** (81%, entry 10) due to competing *O*-vinylation of the primary alcohol. The *O*-arylation reactions are most problematic with electron-deficient aryl bromides such as 4-bromobenzonitrile (entry 4) and *tert*-butyl-4-bromobenzoate (entry 5).

In contrast, reactions of electron−neutral aryl halides proceed efficiently with both primary and tertiary alcohols. For example, the reaction of 2-bromonaphthalene with 4-penten-1-ol proceeded in 76% isolated yield (entry 1) and treatment of 2-bromonaphthalene with 2-methyl-4-hexen-2-ol (**3**) afforded an 80% isolated yield of the tetrahydrofuran product **8a** (entry 8).

TABLE 2[a]



[a] Conditions: 1.0 equiv of alcohol, 2.0 equiv of ArBr, 2.0 equiv of NaO-*t*-Bu, 1 mol % of $Pd_2(dba)_3$, 2 mol % of dpe-phos, THF (0.13−0.25 M), 65 °C. [b] Yields represent average isolated yields for two or more experiments.

The steric properties of the alcohol substrate also have a large effect on the overall reactivity in these transformations. Substrates **2** and **5**, which are substituted with a methyl group at the internal olefinic carbon, are less reactive than the unsubstituted analogues **1** and **3**. As shown in Table 2, the reaction of **1** with 4-bromotoluene proceeded in 65% yield at 65 °C, whereas the reaction of primary alcohol **2** with 4-bromotoluene afforded a modest 19% yield of tetrahydrofuran **7**. The tertiary alcohol **5** failed to react with 4-bromotoluene even when heated to 140 °C in xylenes.

Stereoselective Synthesis of 2,5-Disubstituted and 2,5,5-Trisubstituted Tetrahydrofurans. As shown in Table 3, the reactions of aryl bromides with several different 4-penten-1-ol derivatives bearing C-1 substit-

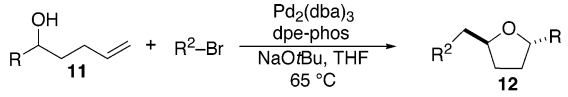
(21) No evidence for the formation of regioisomeric products in reactions of terminal alkene substrates was obtained in analysis of crude reaction mixtures by ^1H NMR and GC.

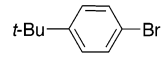
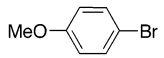
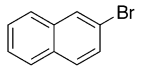
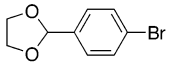
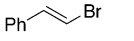
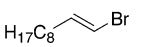
(22) It is likely that oxidation of the alcohol accompanies reduction of the aryl bromide. However, the aldehyde side products that would be generated in this process were not detected and are likely unstable under the reaction conditions. See ref 17.

(23) Only trace amounts of side products derived from Heck arylation of the olefin were detected.

(24) Side products were characterized by ^1H and ^{13}C NMR spectroscopy and MS. See the Supporting Information.

TABLE 3[a]



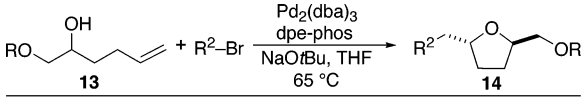
Entry	Substrate	R	R^2	Product	Yield[b]	dr
1	**11a**	Me		**12a**	43%[c]	>20:1
2	**11b**	Et		**12b**	37%[c]	>20:1
3	**11c**	*t*-Bu			No Reaction	---
4	**11d**	CO_2Et			0%[d]	---
5	**11e**	Ph		**12c**	62%	>20:1
6	**11e**	Ph		**12d**	60%	>20:1
7	**11e**	Ph		**12e**	61%	>20:1
8	**11e**	Ph		**12f**	37%	>20:1
9	**11e**	Ph		**12g**	29%	>20:1

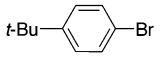
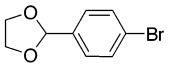
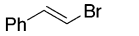
[a] Conditions: 1.0 equiv of alcohol, 2.0 equiv of ArBr, 2.0 equiv of NaO-*t*-Bu, 1 mol % of $Pd_2(dba)_3$, 2 mol % of dpe-phos, THF (0.13−0.25 M), 65 °C. [b] Yields represent average isolated yields for two or more experiments. [c] A reductive workup was employed to facilitate removal of a ketone side product. See the Supporting Information for complete details. [d] Heck arylation was observed.

uents were examined. In all transformations, a single tetrahydrofuran product was formed with >20:1 diastereoselectivity favoring the *trans*-stereoisomer.[25,26] The size of the R group did not have an impact on the stereoselectivity of the transformations. However, the steric bulk of the R group had a pronounced effect on chemical yield. For substrates with alkyl substituents (R = Me, Et, *t*-Bu) the yield of tetrahydrofuran products decreased and larger amounts of ketone side products were formed as the size of the alkyl group increased. For example, the reaction of 1-bromo-4-*tert*-butylbenzene with 5-hexen-2-ol (**11a**, entry 1) afforded a 43% yield of the desired product (**12a**), whereas the analogous reaction of 6-hepten-3-ol (**11b**) proceeded in 37% yield (entry 2) and the transformation of 2,2-dimethyl-6-hepten-3-ol (**11c**) did not provide a tetrahydrofuran product. Reactions of 1-phenyl-4-penten-1-ol with aryl bromides (**11e**, Table 3, entries 5−9 and Table 5, entry 3) typically afforded yields of 60−69%, although lower yields (29−37%) were obtained when vinyl bromides were employed as the coupling partners due to competing *O*-vinylation of the alcohol (entries 8 and 9). The nature of the aryl/vinyl bromide did not have a noticeable effect on the stereoselectivity of these transformations. An alcohol substrate bearing a strongly electron withdrawing ester substituent at the 1-position (**11d**) afforded only products of Heck arylation of the alkene moiety; no tetrahydrofuran products were observed (entry 4).[24]

Curiously, reactions of 1-alkoxymethyl substituted substrates provided significantly higher yields than were

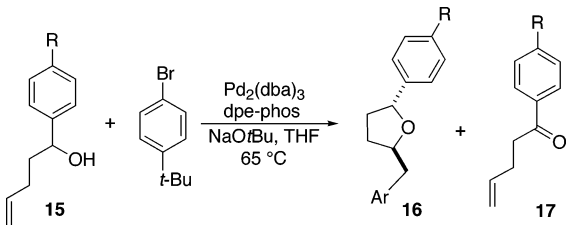
TABLE 4[a]



Entry	Substrate	R	R^2	Product	Yield[b]	dr
1	**13a**	Me		**14a**	72%	>20:1
2	**13b**	TBS		**14b**	68%	>20:1
3	**13c**	BHT		**14c**	81%	>20:1
4	**13b**	TBS		**14d**	52%	>20:1
5	**13b**	TBS		**14e**	38%	>20:1

[a] Conditions: 1.0 equiv of alcohol, 2.0 equiv of ArBr, 2.0 equiv of NaO-*t*-Bu, 1 mol % of $Pd_2(dba)_3$, 2 mol % of dpe-phos, THF (0.13−0.25 M), 65 °C. [b] Yields represent average isolated yields for two or more experiments.

TABLE 5[a]



entry	substrate	R	product	yield[b] (%)	dr	**16/17**[c]
1	**15a**	CN	**16a**	76	>20:1	>20:1
2	**15b**	CF_3	**16b**	64	>20:1	>20:1
3	**11e**	H	**16c**	69	>20:1	>20:1
4	**15c**	OMe	**16d**	58	>20:1	5:1
5	**15d**	$N(Me)_2$	**16e**	35	>20:1	3:1

[a] Conditions: 1.0 equiv of alcohol, 2.0 equiv of ArBr, 2.0 equiv of NaO-*t*-Bu, 1 mol % of $Pd_2(dba)_3$, 2 mol % of dpe-phos, THF (0.13−0.25 M), 65 °C. [b] Yields represent average isolated yields for two or more experiments. [c] The formation of *tert*-butylbenzene in amounts comparable to the amount of **17** observed in these reactions was detected by GC analysis.

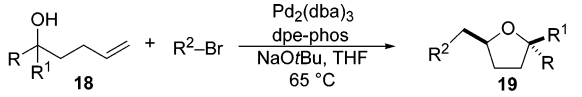
obtained in transformations of substrates bearing a 1-methyl or 1-ethyl group. To further probe this effect, substrates bearing different alcohol protecting groups were treated with 1-bromo-4-*tert*-butylbenzene under the optimized reaction conditions (Table 4). These reactions afforded the desired tetrahydrofurans with high diastereoselectivities and isolated yields of 68−81%. No clear correlation between protecting group size and chemical yield was observed, suggesting that the high yields obtained with these substrates is not due to a chelation effect. As observed in reactions of primary alcohol substrates, a low yield was obtained with a vinyl bromide coupling partner (entry 5) due to competing *O*-vinylation of the substrate.

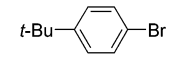
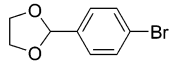
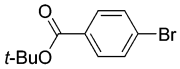
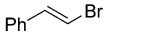
In the absence of chelation, the relatively high yields obtained in reactions of 1-alkoxymethyl-substituted alcohols could potentially derive from the electron-withdrawing nature of the alkoxy substituent. To further explore the effects of electronics on these transformations, a series of 1-aryl-4-penten-1-ols bearing various substituents in the para position of the aryl group were prepared and treated with 1-bromo-4-*tert*-butylbenzene in the presence of NaO-*t*-Bu and the $Pd_2(dba)_3$/dpe-phos catalyst. As shown in Table 5, as the electron-donating ability

(25) Stereochemistry of tetrahydrofuran products was established by nOe experiments or by comparison of NMR spectra to related compounds of known configuration. See the Supporting Information for complete details.

(26) Diastereomeric ratios were determined by ^1H NMR and/or GC analysis of crude reaction mixtures.

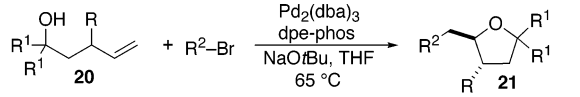
TABLE 6[a]

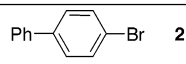
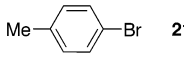
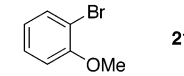
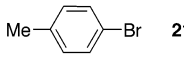
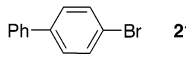


Entry	Substrate	R	R^1	R^2	Product	Yield[b]	dr
1	**18a**	Et	Me		**19a**	59%	3:1
2	**18b**	Ph	Me		**19b**	77%	>20:1
3	**18b**	Ph	Me		**19c**	84%	>20:1
4	**18b**	Ph	Me		**19d**	70%	4:1
5	**18b**	Ph	Me		**19e**	58%	>20:1

[a] Conditions: 1.0 equiv of alcohol, 2.0 equiv of ArBr, 2.0 equiv of NaO-*t*-Bu, 1 mol % of $Pd_2(dba)_3$, 2 mol % of dpe-phos, THF (0.13−0.25 M), 65 °C. [b] Yields represent average isolated yields for two or more experiments.

TABLE 7[a]



Entry	Substrate	R	R^1	R^2	Product	Yield[b]	dr
1	**20a**	Me	H		**21a**	78%	3:1
2	**20b**	Et	H		**21b**	66%	6:1
3	**20b**	Et	H		**21c**	57%	8:1
4	**20c**	Ph	H		**21d**	51%	18:1
5	**20d**	*t*-Bu	H		**21e**	55%	>20:1
6	**20e**	Me	Me		**21f**	78%	8:1

[a] Conditions: 1.0 equiv of alcohol, 2.0 equiv of ArBr, 2.0 equiv of NaO-*t*-Bu, 1 mol % of $Pd_2(dba)_3$, 2 mol % of dpe-phos, THF (0.13−0.25 M), 65 °C. [b] Yields represent average isolated yields for two or more experiments.

of the *p*-substituent increased, the yield of the desired product **16** decreased and the amount of oxidized side product **17** increased.[24] These results suggest that inductive effects have a larger impact on yield than chelation effects in reactions of 1-alkoxymethyl substituted substrates.

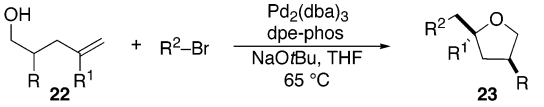
The stereoselectivity of transformations involving tertiary alcohol substrates bearing two different groups at the 1-position was also briefly examined. As shown in Table 6, high diastereoselectivities are obtained in reactions involving electron-rich or -neutral aryl/vinyl halides provided that the two substituents (R and R^1) are sufficiently different in size. For example, the Pd-catalyzed reaction of 3-methyl-6-hetpen-3-ol (**18a**, R = Et, R^1 = Me) with 1-bromo-4-*tert*-butylbenzene provided a 59% yield of the tetrahydrofuran product **19a** as a 3:1 mixture of diastereomers (entry 1). In contrast, the analogous transformation of 1-phenyl-5-hexen-2-ol (**18b**, R = Ph, R^1 = Me) afforded the desired product in 77% yield with >20:1 diastereoselectivity (entry 2). The use of *β*-bromostyrene as a coupling partner with **18b** provided a slightly lower chemical yield (58%) of the tetrahydrofuran product (entry 5), although diastereoselectivity was high (>20:1). In contrast, the reaction of **18b** with the electron-deficient *tert*-butyl-4-bromobenzoate proceeded in excellent yield (70%) but modest (4:1) diastereoselectivity (entry 4). Resubjection of each isolated diastereomer of **19d** to the reaction conditions demonstrated that the diastereomers do not interconvert, and the stereoselectivity is kinetically controlled.

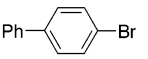
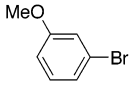
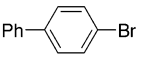
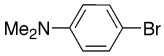
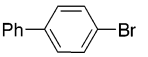
Stereoselective Synthesis of 2,3-Disubstituted Tetrahydrofurans. As shown in Table 7, transformations of 4-penten-1-ol derivatives bearing a substituent at the 3-position afford *trans*-2,3-disubstituted tetrahydrofuran products with good to excellent levels of diastereocontrol. In contrast to reactions of substrates bearing substituents at the 1-position, the stereoselectivity in these reactions was dependent on both the size of the 3-substituent and the size of the substituents at the 1-position. For example, the reaction of 3-methyl-4-penten-1-ol (**20a**) with 4-bromobiphenyl provided the desired product **21a** in 78% yield with modest (3:1) diastereoselectivity (entry 1). In contrast, the reaction of the analogous tertiary alcohol substrate **20e** proceeded in similar (78%) yield but with 8:1 diastereoselectivity (entry 6). The stereoselectivity of these transformations improved as the size of the 3-subsituent was increased from methyl (3:1) to *tert*-butyl (>20:1). Additionally, the size of the aryl bromide also had a small influence on the diastereoselectivity in these transformations. The reaction of 3-ethyl-4-penten-1-ol (**20b**) with a para-substituted aryl bromide afforded **21b** 66% yield with 6:1 dr (entry 2), whereas treatment of this substrate with an ortho-substituted aryl bromide afforded a 57% yield of the tetrahydrofuran product **21c** as an 8:1 mixture of diastereomers (entry 3).

Synthesis of 2,4-Disubstituted Tetrahydrofurans. In contrast to reactions that afford 2,5- and 2,3-disubstituted tetrahydrofurans, transformations that produce 2,4-disubstituted tetrahydrofurans proceeded with generally low (1−2:1) diastereoselectivity (Table 8). For example, treatment of 2-methyl-4-penten-1-ol (**22a**) with 4-bromobiphenyl under standard reaction conditions afforded a 1.5:1 mixture of diastereomeric 2,4-disubstituted tetrahydrofuran products in 70% yield (entry 1); a slight preference for the *cis*-diastereomer was observed. Increasing the size of the 2-substituent from methyl to *tert*-butyl did not lead to significant improvements in selectivity. Despite the low diastereoselectivities of these transformations, the tetrahydrofuran products were obtained in good to excellent yields. It is noteworthy that the reaction of substrate **22e** (R = Me, R^1 = Me) with 4-bromobiphenyl afforded an 88% yield of the desired product (entry 7). This result sharply contrasts to the analogous reaction of **2** (Table 2, entry 7, R = H, R^1 = Me) which proceed in low yield. The high yield obtained in the reaction of **22e** may derive from a Thorpe-Ingold conformational effect induced by the C-3 substituent,[27] which could potentially increase the rate of the desired cyclization reaction relative to the rate of competing alcohol oxidation/aryl bromide reduction side reactions.

(27) (a) Allinger, N. L.; Zalkow, V. *J. Org. Chem.* **1960**, *25*, 701−704. (b) Jager, J.; Graafland, T.; Schenk, H.; Kirby, A. J.; Engberts, J. B. F. N. *J. Am. Chem. Soc.* **1984**, *106*, 139−143.

TABLE 8[a]

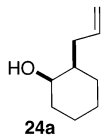
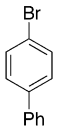
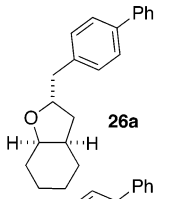
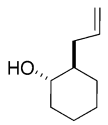
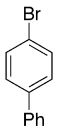
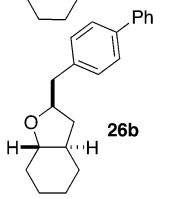
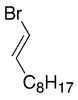
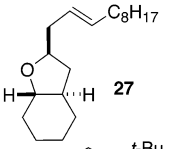
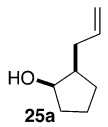
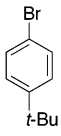
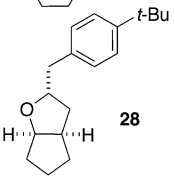
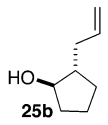
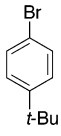


Entry	Substrate	R	R^1	R^2	Product	Yield[b]	dr
1	**22a**	Me	H		**23a**	70%	1.5:1
2	**22b**	Et	H		**23b**	88%	1.5:1
3	**22c**	Ph	H		**23c**	84%	2:1
4	**22d**	*t*-Bu	H		**23d**	88%	1.5:1
5	**22d**	*t*-Bu	H		**23e**	77%	2:1
6	**22d**	*t*-Bu	H		**23f**	66%	2:1
7	**22e**	Me	Me		**23g**	88%	1:1

[a] Conditions: 1.0 equiv of alcohol, 2.0 equiv of ArBr, 2.0 equiv of NaO-*t*-Bu, 1 mol % of $Pd_2(dba)_3$, 2 mol % of dpe-phos, THF (0.13−0.25 M), 65 °C. [b] Yields represent average isolated yields for two or more experiments.

Synthesis of Fused Bicyclic Oxygen Heterocycles. The utility of this transformation for the synthesis of fused bicyclic oxygen heterocycles from 2-allyl-1-cycloalkanols was also briefly explored (Table 9). The stereochemistry of the starting material has a pronounced effect on both the chemical yield and diastereoselectivity of these reactions. For example, the Pd-catalyzed reaction of *cis*-2-allylcyclohexanol (**24a**) with 4-bromobiphenyl afforded bicyclic product **26a** in 60% yield as a 10:1 mixture of diastereomers. In contrast, the analogous reaction of *trans*-2-allylcyclohexanol (**24b**) provided a 70% yield of **26b** with >20:1 diastereoselectivity (entry 2). Transformation of *cis*-2-allylcyclopentanol (**25a**) to *cis*-fused product **28** proceeded in modest yield with excellent (>20:1) dr (entry 4). However, the preparation of the analogous *trans*-fused product from *trans*-2-allylcyclopentanol (**25b**) was not achieved; the sole product detected was 2-allylcyclopentanone (entry 5).

TABLE 9[a]

Entry	Alcohol	R^2–Br	Product	Yield[b]	dr
1	 **24a**		 **26a**	60%	10:1
2	 **24b**		 **26b**	70%	>20:1
3			 **27**	40%	>20:1
4	 **25a**		 **28**	53%	>20:1
5[a,b]	 **25b**			0%[c]	—

[a] Conditions: 1.0 equiv of alcohol, 2.0 equiv of ArBr, 2.0 equiv of NaO-*t*-Bu, 1 mol % of $Pd_2(dba)_3$, 2 mol % of dpe-phos, THF (0.13−0.25 M), 65 °C. [b] Yields represent average isolated yields for two or more experiments. [c] Oxidation of the alcohol substrate to 2-allylcyclopentanone was observed.

Discussion

Synthetic Scope and Limitations. The palladium-catalyzed reaction of γ-hydroxy terminal alkenes with aryl bromides allows for the synthesis of a variety of substituted tetrahydrofuran products under relatively mild reaction conditions. This transformation is effective for the preparation of 2,5-, 2,4-, and 2,3-disubstituted tetrahydrofurans as well as spirocyclic and fused bicyclic heterocycles. A number of common functional groups are well tolerated, including nitriles, acetals, *tert*-butyl esters, silyl ethers, and *N,N*-dimethylanilines. In all reactions examined, high regioselectivites for 2-benzyltetrahydrofuran derivatives are observed.

The highest yields in these reactions are obtained with electron-neutral or electron-rich aryl bromides, and in many cases tertiary alcohols afford higher yields of products than primary and secondary alcohols. The main side products formed in these reactions are ethers that result from *O*-arylation or *O*-vinylation of the alcohol and arenes and aldehdyes or ketones, which derive from oxidation of the alcohol substrate with concomitant reduction of the aryl bromide. These side reactions are more problematic with primary and secondary alcohol substrates, and larger amounts of *O*-arylated products are observed when electron-deficient aryl bromides are employed as coupling partners.

The yields of products in these transformations are dependent on the steric properties of both the alcohol and the aryl bromide coupling partner. In general, reactions of alcohol substrates bearing large substituents at the 1- or 3-positions provide lower yields than the corresponding reactions of less hindered substrates; competing oxidation/reduction processes are more problematic with substrates that are sterically encumbered. Bulky, ortho-substituted aryl bromides are also less efficiently transformed than meta- or para-substituted derivatives. The nature of the aryl or vinyl bromide has little impact on the diastereoselectivity of these transformations when electron-rich or -neutral aryl halides are employed. In contrast, use of an electron-deficient aryl bromide led to a significant decrease in diastereoselectivity in the preparation of a 2,5,5-trisubstituted tetrahydrofuran product (Table 6, entry 4).

The electronic properties of the alcohol affect the chemical yield of these transformations but do not appear to have a significant impact on stereocontrol. Higher

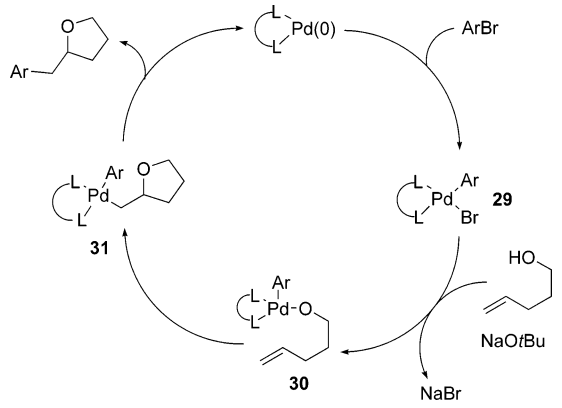


FIGURE 1. Proposed catalytic cycle.

yields of tetrahydrofuran products are obtained in reactions of substrates bearing weak electron-withdrawing groups (e.g., p-C_6H_4CN) at the 1-position than in corresponding reactions of substrates bearing weak electron-donating groups (e.g., p-C_6H_4OMe) at the 1-position. The more electron-rich substrates provide increased amounts of oxidation/reduction side products. However, strong C-1 electron-withdrawing groups (e.g., CO_2Et) inhibit the reaction and result in the formation of Heck-olefination products.

Mechanism and Stereochemistry. A plausible catalytic cycle for the conversion of γ-hydroxyalkenes and aryl bromides to 2-benzyltetrahydrofuran derivatives is shown above (Figure 1).[8] Oxidative addition of the aryl bromide to a LnPd(0) complex would provide **29**, which could be transformed into palladium(aryl)(alkoxide) intermediate **30** upon reaction with the alcohol substrate and NaOt-Bu.[17] Intermediate **30** could undergo intramolecular insertion of the alkene into the Pd−O bond[28] to afford **31**, which would undergo C−C bond-forming reductive elimination[29] to provide the 2-benzyltetrahydrofuran with concomitant regeneration of the Pd(0) catalyst. This proposed mechanism is supported by the fact that reactions of internal alkene substrates afford products derived from syn-addition of the oxygen and the aryl group across the carbon−carbon double bond.[8,30−32] This mechanistic proposal is also consistent with the observation of oxidation/reduction side products, which could derive from β-hydride elimination from **30**, and with the formation of *O*-arylated side products, which would derive from C−O bond-forming reductive elimination of **30**.[17]

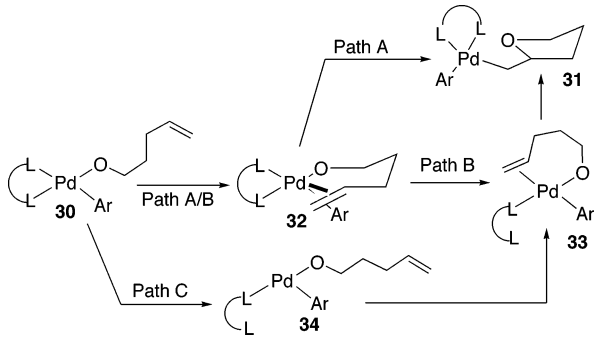


FIGURE 2. Proposed insertion mechanism.

The decreased yields observed with increasing steric hindrance around the alkene or the alcohol are likely due to a decrease in the rate of alkene insertion as the size of substituents near the reacting sites increases, which leads to increased amounts of side products from competing β-hydride elimination. The electronic effects observed in reactions of 1-substituted 4-penten-1-ols (Table 5) are likely due, in part, to changes in the rate of β-hydride elimination, which should be facilitated by electron-donating groups at C1 and inhibited by electron withdrawing groups.[33] It is also possible that weak electron-withdrawing groups at C-1 may increase the rate of the desired transformation by increasing the acidity of the OH proton, which would facilitate deprotonation of the alcohol substrate, or by decreasing the strength of the Pd−O bond, which may facilitate the alkene insertion.[34] The fact that the Pd-catalyzed reaction of **11d** with 1-bromo-4-*tert*-butylbenzene provides only Heck-type products (Table 3, entry 4) suggests that if the alkoxide is not sufficiently nucleophilic, the Heck arylation is faster than formation of the requisite Pd−alkoxide intermediate.

The precise mechanistic details of the alkene insertion into the Pd−O bond have not yet been elucidated. However, the most likely pathways involve either direct insertion of the alkene via five-coordinate intermediate **32** (Figure 2, path A) to afford **31**[35] or insertion through four coordinate intermediate **33** that is formed by an associative ligand substitution process (Figure 2, path B) that also proceeds through five-coordinate complex **32**.[36] Dissociative ligand substitution processes (Figure 3, path C) are extremely rare in reactions of d-8,16-electron palladium(II) complexes;[37,38] the two known examples both involve complexes bearing large and

(28) (a) Bryndza, H. E. *Organometallics* **1985**, *4*, 406−408. (b) Bryndza, H. E.; Calabrese, J. C.; Wreford, S. S. *Organometallics* **1984**, *3*, 1603−1604. (c) Hayashi, T.; Yamasaki, K.; Mimura, M.; Uozumi, Y. *J. Am. Chem. Soc.* **2004**, *126*, 3036−3037.

(29) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 4981−4991.

(30) Tetrafluoroethylene undergoes selective insertion into the Pt−O bond of (dppe)Pt(Me)(OMe). See ref 28a,b.

(31) Related transformations of γ-aminoalkenes to pyrrolidines have been shown to proceed through an analogous mechanism. Experimental evidence in the pyrrolidine-forming reactions supports the idea that alkene insertion occurs into the Pd-heteroatom bond rather than the Pd-carbon bond. See ref 9a.

(32) Although we currently favor this mechanism, an alternative mechanism involving alkene insertion into the Pd−C bond followed by C−O bond-forming reductive elimination cannot be unambiguously ruled out in all instances. This mechanistic pathway would also likely proceed via a cyclic, chelated intermediate such as **32**, or **35**. High 1,4 asymmetric induction would be unlikely if insertion into the Pd−C bond occurred from an acyclic, unchelated intermediate. For further details, see ref 8.

(33) There is a significant buildup of positive charge on the C1 carbon in the transition state leading to β-elimination. Thus, substrates bearing electron-donating C1 substituents are more prone to β-elimination than substrates with electron-withdrawing substituents. See: Mueller, J. A.; Sigman, M. S. *J. Am. Chem. Soc.* **2003**, *125*, 7005−7013.

(34) For a discussion on the effect of Pt−O bond strength on rates of CO insertion, see: Dockter, D. W.; Fanwick, P. E.; Kubiak, C. P. *J. Am. Chem. Soc.* **1996**, *118*, 4846−4852.

(35) The insertion of tetrafluoroethylene into the Pt−O bond of (dppe)Pt(Me)(OMe) has been shown to occur through a five-coordinate intermediate. See ref 28a.

(36) For a discussion of mechanistic issues in related alkene insertions into Pd−C bonds, see: (a) Ashimori, A.; Bachand, B.; Calter, M. A.; Govek, S. P.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6488−6499. (b) Oestreich, M.; Sempere-Culler, F.; Machotta, A. B. *Angew. Chem., Int. Ed.* **2005**, *44*, 149−152. (c) Samsel, E. G.; Norton, J. R. *J. Am. Chem. Soc.* **1984**, *106*, 5505−5512.

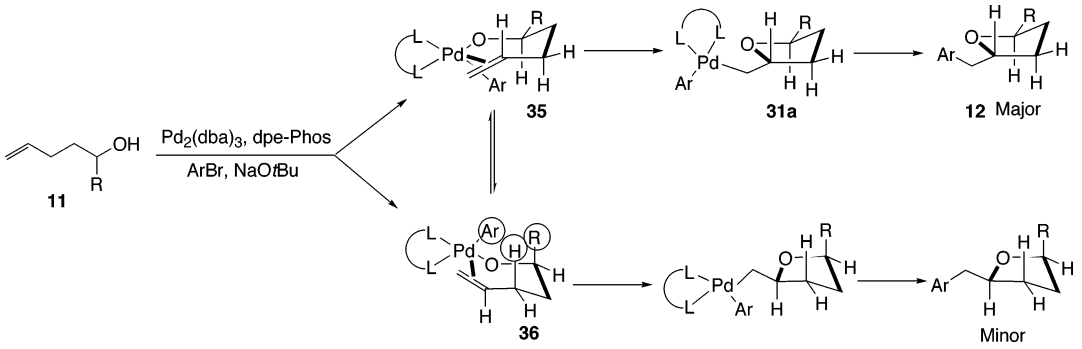


FIGURE 3. Stereochemistry of 2,5-disubstituted tetrahydrofuran products.

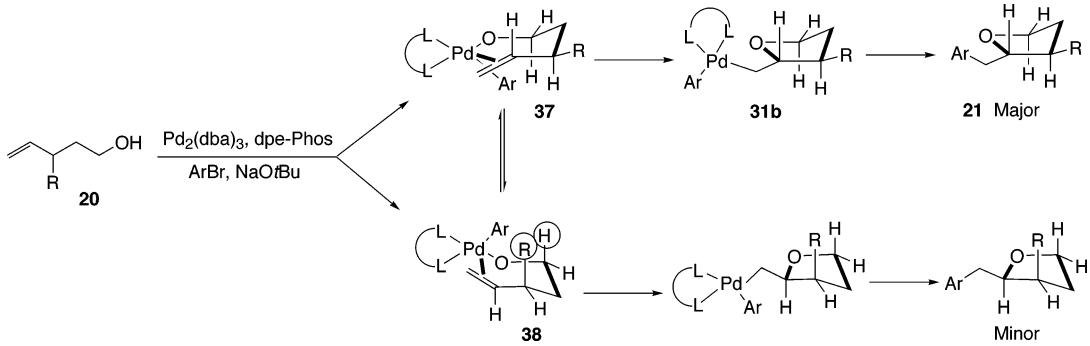


FIGURE 4. Stereochemistry of 2,3-disubstituted tetrahydrofuran products.

exceptionally labile monodentate ligands. Thus, **34** is unlikely to be an intermediate along the pathway from **30** to **31**.

The palladium-catalyzed conversion of 1-substituted γ−hydroxy alkenes to *trans*-2,5-disubstituted tetrahydrofurans (Tables 3−5) proceeds with generally excellent levels of diastereoselectivity (dr ≥ 20:1), and the size of the 1-substituent does not appear to have a significant impact on the stereoselectivity of these transformations. In contrast, although 3-substituted γ-hydroxyalkenes are efficiently transformed to *trans*-2,3-disubstituted tetrahydrofurans (Table 7), the diastereomeric ratio of the products is highly dependent on the size of the 3-substituent and is also affected by the presence of disubstitution at the 1-position of the substrate. To explain the stereochemical outcome of these transformations, we suggest that the stereochemistry determining step of the reaction is the insertion of the alkene into the Pd−O bond of intermediate **30** (Figure 2).[32] As shown above (Figure 3), we propose that the conversion of a 1-substituted γ-hydroxyalkene (**11**) to a *trans*-2,5-disubstituted tetrahydrofuran (**12**) proceeds via conformer **35** in which the R substituent is oriented in a pseudoequatorial position to minimize nonbonding interactions with the C-3 hydrogen substituent *and the aryl group or phosphine ligand bound to the Pd complex*.[39] The combination of these two interactions would disfavor reaction through conformer **36** in which the R group is oriented in a pseudoaxial position regardless of whether the insertion proceeds directly through five-coordinate intermediate **32** to **31** (Figure 2, path A) or through the associative substitution mechanism (**30** → **32** → **33**→ **31**) shown in Figure 2, path B. The alkene insertion via conformer **35** would afford intermediate **31a**, which would provide the observed *trans*-2,5-disubstituted product **12** upon C−C bond-forming reductive elimination.

We propose that the conversion of a 3-substituted γ-hydroxyalkene (**20**) to a *trans*-2,3-disubstituted tetrahydrofuran (**21**) likely proceeds through a similar mechanism via conformer **37** in which the R group is placed in a pseudoequatorial orientation (Figure 4). However, in contrast to the cyclization of a 1-substituted substrate, the only unfavorable interaction that is present in conformer **38** is the developing 1,3-diaxial interaction between the C-3 substituent and the axial C-1 hydrogen. The C-3 carbon is extended out of the coordination plane of the square planar metal complex, which leads to little or no interaction between the C-3 substituent and the metal-bound aryl group (or phosphine ligand). Thus, an axial orientation of the C-3 substituent leads to a smaller difference in energy between conformers **37** and **38** (Figure 4) than exists between conformers **35** and **36** (Figure 3), and observed diastereoselectivities are more dependent on the size of the R group in reactions of 3-substituted alcohol substrates than in transformations

(37) (a) Tobe, M. L. In *Comprehensive Coordination Chemistry*; Wilkinson, G., Gilard, R. D., McCleverty, J. A., Eds.; Pergamon: Oxford, 1987; Vol. 1, pp 281−329. (b) Cross, R. J. *Adv. Inorg. Chem.* **1989**, *34*, 219−291.

(38) The very rare examples of dissociative ligand substitution at d-8,16-electron Pd(II) complexes involve the extremely bulky, monodentate, and unusually labile ligands tris(2,4,6-trifluoromethylphenyl)-phosphine and P(*o*-tolyl)$_3$. See: (a) Bartolome, C.; Espinet, P.; Martin-Alvarez, J. M.; Villafane, F. *Eur. J. Inorg. Chem.* **2004**, 2326−2337. (b) Louie, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **1995**, *117*, 11598−11599.

(39) The insertion of alkenes into Pd−C bonds in intramolecular Heck reactions occurs through a conformation in which the alkene π-bond and the Pd−C bond are eclipsed. The analogous insertion into the Pd−O bond via an eclipsed conformation is depicted in Figures 3 and 4. See: Link, J. T. *Org. React*. **2002**, *60*, 157−534.

of alcohols bearing a 1-substituent. Further evidence for the importance of the developing 1,3-diaxial interaction is provided by the observation that stereoselectivity is higher (dr = 8:1) in the transformation of a 3-substituted alcohol bearing a *gem*-dimethyl group at C-1 (Table 7, **20e**) than the analogous reaction of the corresponding primary alcohol substrate (Table 7, **20a**, dr = 3:1).

In contrast to the reactions of 1- and 3-substituted γ-hydroxyalkenes, transformations of substrates bearing substituents at the 2-position proceed with low levels (1−2:1) of diastereoselectivity. The reasons for this low stereoselectivity are not entirely clear, but it is possible that the energy difference between the pseudoequatorial and the pseudoaxial orientation of the substituent is relatively low. The only potential 1,3-diaxial interaction would occur between the 2-substituent and the substituent at the internal position of the alkene, which would be much smaller than a typical 1,3-diaxial interaction due to the 120° bond angle between the groups on the sp^2-hybridized carbon.

The origins of the decreased diastereoselectivity observed in the reaction of **18b** with the electron-deficient aryl bromide *tert*-butyl-4-bromobenzoate are not clear. It is possible that reactions of electron-deficient arenes proceed through a different mechanism than that outlined in Figure 1.[40]

Conclusion

In conclusion, the palladium-catalyzed reaction of aryl bromides with γ-hydroxyalkenes is a new and useful method for the stereoselective construction of a wide variety of substituted tetrahydrofuran derivatives from readily available precursors. This transformation allows for the installation of a tetrahydrofuran moiety on a broad range of arenes and has a number of potential applications toward the synthesis of interesting biologically active compounds. Further studies on transformations of substrates bearing internal alkenes and applications of this methodology to the synthesis of complex molecules are currently underway.

(40) Diastereoselectivities in related Pd(II)-catalyzed carbonylations of 1-substituted 4-penten-1-ols that proceed via a Wacker-type mechanism are typically in the range of 1−3:1. See ref 7a−d.

Experimental Section

General Procedure for the Palladium Catalyzed Synthesis of Tetrahydrofurans. An oven or flame-dried Schlenk tube was cooled under a stream of argon or nitrogen and charged with $Pd_2(dba)_3$ (1 mol % complex, 2 mol % Pd), dpephos (2 mol %), NaO-*t*-Bu (2.0 equiv), and the aryl bromide (2.0 equiv). The tube was purged with argon or nitrogen, and the alcohol substrate (1.0 equiv), and THF (4 mL/mmol aryl bromide) were added. The reaction mixture was heated to 65 °C with stirring until the alcohol substrate was consumed as judged by capillary GC analysis. The reaction mixture was cooled to rt, and saturated aqueous NH_4Cl (2 mL) and ethyl acetate (10 mL) were added. The layers were separated, and the aqueous layer was extracted with ethyl acetate (2 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was then purified by flash chromatography on silica gel.

2-Naphthalen-2-ylmethyltetrahydrofuran (6a). Reaction of 43 mg (0.5 mmol) of 4-penten-1-ol with 2-bromonaphthalene (208 mg, 1.0 mmol) following the general procedure afforded 80 mg (76%) of the title compound as a pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83−7.79(m, 3 H), 7.70 (s, 1 H), 7.52−7.40 (m, 3 H), 4.22−4.17 (m, 1 H), 3.96−3.92 (m, 1 H), 3.80−3.76 (m, 1 H), 3.13−3.09 (dd, *J* = 6.0, 13.5 Hz, 1 H), 2.96−2.92 (dd, *J* = 6.5, 13.5 Hz, 1H), 1.99−1.83 (m, 3 H), 1.67−1.62 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.8, 133.8, 132.4, 128.1, 128.09, 127.9, 127.8, 127.76, 126.1, 125.5, 80.2, 68.3, 42.3, 31.3, 25.9; IR (film) 1062 cm^{-1}. Anal. Calcd for $C_{15}H_{16}O$: C, 84.87; H, 7.60. Found: C, 84.70; H, 7.51.

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Supporting Information Available: Characterization data for all new compounds in Tables 2−9. This material is available free of charge via the Internet at http://pubs.acs.org.

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