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Synthesis of polysubstituted tetrahydrofurans via Pd-catalyzed carboetherification reactions

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Abstract—Pd-catalyzed carboetherifications of 1-, 2-, or 3-substituted γ-hydroxy internal alkenes afford tetrahydrofuran products bearing three stereocenters in good yield with moderate to good stereoselectivity.
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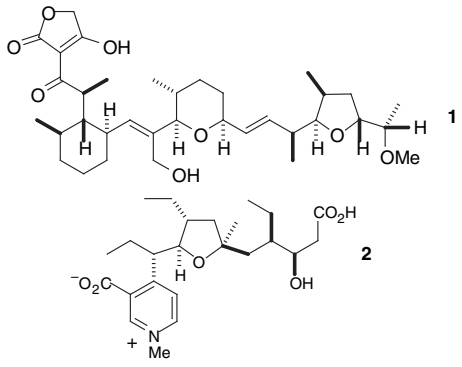
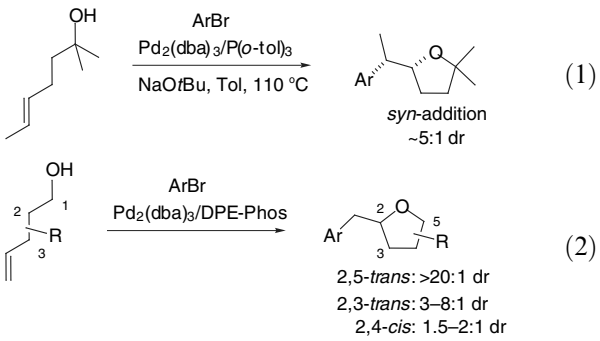
Multiply substituted tetrahydrofuran moieties are found in a broad array of biologically active molecules and natural products.[1] In many of these molecules, including the antifungal agents gambieric acids A–D,[2] the antiparasitic agent tetronasin (**1**),[3] and the cytotoxic agent simplakidine A (**2**),[4] stereocenters are displayed both around and also adjacent to the tetrahydrofuran ring. Thus, the development of methods that provide stereocontrolled access to polysubstituted tetrahydrofurans is of significant importance, and many strategies have been explored for the construction of such molecules.[5] However, few methods allow for the generation of the heterocyclic ring with simultaneous formation of a C–O bond, a C–C bond, and control of relative stereochemistry between two ring stereocenters and one exocyclic stereocenter.[6] Moreover, the applicability of these methods to the generation of 2-benzyl or 2-allyl tetrahydrofuran moieties of the type found in **1** and **2** has not been demonstrated.[6]



We have recently developed a new method for the stereoselective synthesis of substituted tetrahydrofurans via Pd-catalyzed carboetherification reactions of γ-hydroxyalkenes with aryl bromides.[7,8] These transformations lead to ring closure with generation of a C–O bond, a C–C bond, and up to two stereocenters in a single step. We have found that transformations of acyclic internal alkene substrates provide products resulting from *syn*-addition of the arene and the oxygen atom across the double bond with diastereoselectivities of ca. 5:1 (Eq. 1). In addition, reactions of terminal alkene substrates bearing substituents at the 1-, 2-, or 3-position afford disubstituted tetrahydrofurans with diastereoselectivities up to >20:1 (Eq. 2). Thus, these transformations have the potential to provide highly substituted tetrahydrofuran products from simple substrates in a stereocontrolled fashion.



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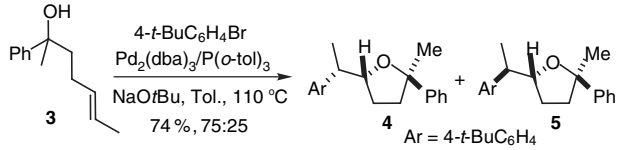
Although transformations of simple alcohols such as those shown in Eqs. 1 and 2 provided efficient access to tetrahydrofuran derivatives bearing two stereocenters, many key questions about the applicability of this methodology to more complex systems remained unanswered. It was not clear that substrates containing both an internal alkene and a substituent at C1, C2, or C3 would still afford products derived from *syn*-addition with synthetically useful levels of selectivity, or whether increased substitution would lead to a change in reaction mechanism to afford products resulting from *anti*-addition. In this letter we describe our preliminary studies on the stereoselective synthesis of tetrahydrofuran products bearing three stereocenters via Pd-catalyzed carboetherification reactions of γ-hydroxy alkenes with aryl bromides. These studies illustrate the potential utility of this methodology for the construction of complex heterocyclic molecules, and further support our stereochemical and mechanistic model for the carboetherification process.

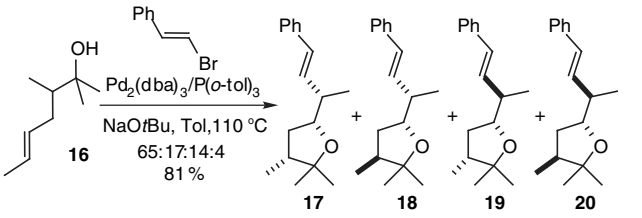
In a representative experiment, we examined the reaction of *E*-2-phenylhept-5-en-2-ol **3** (1.0 equiv) with 1-bromo-4-*tert*-butylbenzene (2.0 equiv) in the presence of NaO*t*-Bu (2.0 equiv) and catalytic amounts of $Pd_2(dba)_3$ (1 mol%) and P(*o*-tol)$_3$ (4 mol%).[9] These reaction conditions were derived from our earlier studies on Pd-catalyzed carboetherification reactions of internal alkenes.[7c] As shown in Eq. 3, this transformation provided a 75:25 mixture of tetrahydrofurans **4** and **5** in 74% yield.[10] Both diastereomers contained a *trans*-2,5-disubstituted tetrahydrofuran ring, and the major diastereomer derives from *syn*-addition across the alkene.[11]



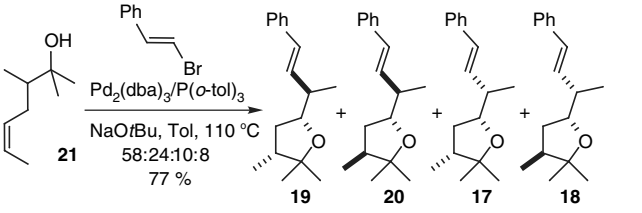
(3)

With this result in hand, we proceeded to examine the Pd-catalyzed reactions of several different unsaturated alcohols bearing stereocenters at C-1 or C-3 with various aryl bromides. The results of these experiments are shown in Table 1. As expected, the transformations proved to be both stereoselective and stereospecific. For example, the reaction of *E*-alkene **3** with 1-bromo-4-*tert*-butylbenzene afforded **4** as the major product (Eq. 3), whereas the analogous reaction of *Z*-alkene **6** provided **5** as the predominant isomer (entry 2). Similar stereospecificity was observed in reactions of 3-substituted substrates **7** and **8** (entries 3–8). However, in contrast to reactions of **3** and **6**, which provided only two isomeric products, transformations of **7** and **8** gave more complex mixtures of stereoisomers along with small amounts (ca. 1–3%) of unidentified isomeric products.[12] In all cases examined, the major products resulted from *syn*-addition across the double bond, and contained the expected 2,5-*trans*- or 2,3-*trans*-tetrahydrofuran stereochemistry. Similar yields and selectivities were obtained with a number of different aryl halides including derivatives that were heterocyclic (entry 1) or *o*-substituted (entries 3 and 6). Transformations of β-bromostyrene also afforded substituted tetrahydrofurans in good yields with useful levels of stereoselectivity (entries 4 and 7).

In our previous studies on carboetherification reactions of substrates bearing terminal alkenes and substituents at C2 we observed that *cis*-2,4-disubstituted tetrahydrofurans were formed in very good yield, but with low diastereoselectivity (ca. 2:1).[7a,b] This modest selectivity was also observed in reactions of 2-substituted alcohols **16** and **21**, which contain internal alkene moieties. As shown in Eq. 4, treatment of **16** with β-bromostyrene under our standard reaction conditions afforded a 65:17:14:4 mixture of diastereomers. As expected, the major product (**17**) resulted from *syn*-addition and contained a *cis*-2,4-disubstituted tetrahydrofuran ring. Similar results were obtained in the cyclization of *Z*-alkene substrate **21** (Eq. 5).



(4)

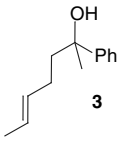
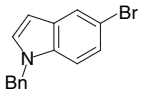
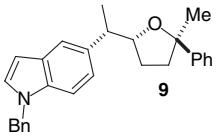
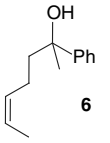
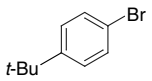
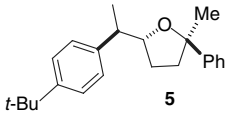
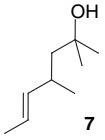
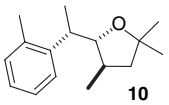
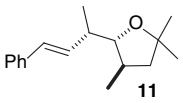
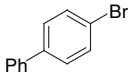
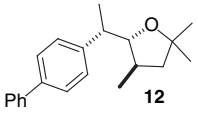
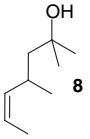
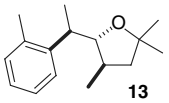
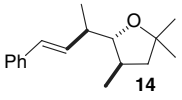
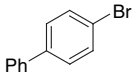
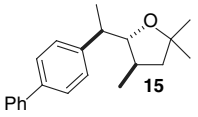


(5)

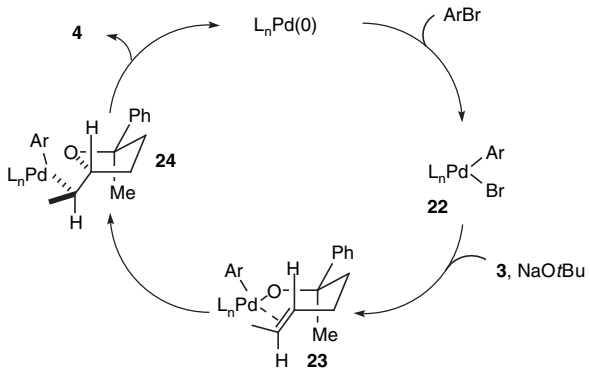
The stereochemical outcome of the reactions described in Eqs. 3–5 and Table 1 is consistent with our previously reported mechanistic hypothesis.[7] As shown in Scheme 1, oxidative addition of the aryl halide to Pd(0) would generate **22**, which could undergo transmetalation with the in situ generated sodium alkoxide to afford palladium(aryl)alkoxide complex **23**.[13] *syn*-Oxypalladation[7,14] would provide **24**, which could undergo carbon–carbon bond-forming reductive elimination to generate the observed product. The relative stereochemistry between C2 and C1′ would derive from the *syn*-oxypalladation step,[7a,c] whereas the stereochemistry around the tetrahydrofuran ring is likely controlled by a preference for pseudoequatorial orientation of bulky substituents in the transition state between **23** and **24**.[7a,b]

In conclusion, we have demonstrated that Pd-catalyzed carboetherification reactions of 1-, 2-, or 3-substituted γ-hydroxy internal alkenes provide access to tetrahydrofuran products bearing three stereocenters in good yields with moderate to good stereoselectivities. These studies suggest that the *syn*-addition manifold is the dominant mechanistic pathway in transformations of a variety of substrates with different substitution patterns. Further studies directed toward expanding the scope and dia-

Table 1. Synthesis of tetrahydrofurans via Pd-catalyzed carboetherification[a]

Entry	Alcohol	Aryl/vinyl halide	Major product	Selectivity[b] (%)	Isomer ratio (isolated)	Yield[c] (%)
1	 **3**		 **9**	75	75:25	60
2	 **6**		 **5**	80	80:20	68
3	 **7**		 **10**	81	81:12:7	70
4			 **11**	79	79:9:5:4[d]	60
5			 **12**	71	71:13:11:4	68
6	 **8**		 **13**	86	86:9:5	70
7			 **14**	79	79:7:7:6[d]	86
8			 **15**	79	79:21	68

[a] Conditions: 1.0 equiv alcohol, 2.0 equiv aryl or vinyl bromide, 2.0 equiv NaO*t*Bu, 1 mol % $Pd_2(dba)_3$, 4 mol % P(*o*-tol)$_3$, toluene (0.25 M), 110 °C.
[b] Percentage of major isomer present in isolated mixture.
[c] Average isolated yield of isomers obtained from two or more reactions.
[d] An additional unidentified isomeric product (1–3%) was also observed.



Scheme 1. Catalytic cycle.

stereoselectivity of these reactions along with applications toward the synthesis of biologically active natural products are currently underway.

Acknowledgments

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Supplementary data

Experimental procedures, characterization data for new compounds reported in Eqs. 3–5 and Table 1, and descriptions of stereochemical assignments. Supplementary data associated with this article can be found, in the online version, at online at doi:10.1016/j.tetlet.2006.02.066.

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8. For examples of Pd-catalyzed carboamination reactions that afford pyrrolidine products see: (a) Bertrand, M. B.; Wolfe, J. P. *Tetrahedron* **2005**, *61*, 6447–6459, and references cited therein; (b) Ney, J. E.; Wolfe, J. P. *Angew. Chem., Int. Ed.* **2004**, *43*, 3605–3608.
9. General procedure for palladium catalyzed reactions: A flame dried or oven dried Schlenk tube equipped with a magnetic stir bar was cooled under a stream of argon and charged with $Pd_2(dba)_3$ (4.6 mg, 0.005 mmol), P(*o*-tol)$_3$ (6.1 mg, 0.02 mmol), sodium *tert*-butoxide (96 mg, 1.0 mmol), and the aryl or vinyl bromide (1.0 mmol). The tube was purged with argon and toluene (2 mL), the alcohol substrate (0.5 mmol) and additional toluene (2 mL) were added. The reaction mixture was heated to 110 °C with stirring until the alcohol substrate was consumed as judged by 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, decanted, and concentrated in vacuo. The crude material was purified by flash chromatography on silica gel.
10. The ratios of isomers observed in crude reaction mixtures were similar to the isomeric ratios obtained upon purification.
11. The stereochemistry of the tetrahydrofuran products was determined through a combination of ^{1}H NMR NOE experiments and correlation of ^{1}H and ^{13}C NMR chemical shifts with those of previously reported compounds of known configuration. See the Supplementary data for complete details. See also Ref. 7.
12. For further discussion of the possible origin of other isomers, see Ref. 7c.
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