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Stereoselective Synthesis of Furans by the Pd-Catalyzed Oshima–Utimoto Reaction

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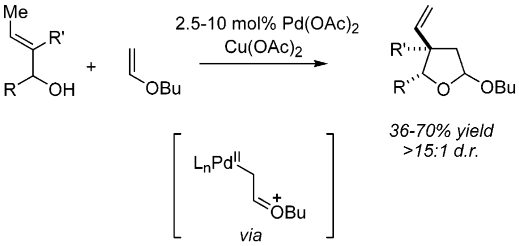
ABSTRACT

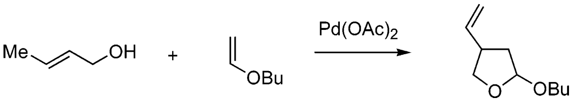


The Pd-catalyzed coupling of acyclic allylic alcohols with vinyl ethers was examined and found to proceed with 2.5–10 mol % of catalyst and to provide cyclic acetals with good stereoselection. The reaction is tolerant of a number of functional groups and can be used to generate quaternary centers in a stereoselective fashion.

Configurationally defined five-membered oxacycles are common structural elements in biologically active natural products. These motifs are particularly common in sesquiterpenes[1] and are found in a range of biologically active natural products in the guise of γ-lactones.[2] One might, therefore, expect that stereoselective catalytic methods for the construction of these frameworks would find significant utility in organic synthesis. Accordingly, we became interested in reports by the Oshima and Utimoto lab, which indicated that in the presence of 0.3−1 equiv of $Pd(OAc)_2$, vinyl ethers react directly with allyl alcohols to afford substituted five-membered cyclic acetals (Scheme 1).[3,4] Recognizing the strategic advantage that the Oshima−Utimoto reaction provides for the rapid assembly of both furans and lactones from simple precursors, we decided to investigate this reaction further. Whereas Larock[5] had uncovered stereoselection with cyclic substrates, stereoselection with acyclic substrates had not been evaluated. We, therefore, decided to study this issue and to examine issues regarding catalyst turnover.

Beginning with reaction conditions originally described by Oshima and Utimoto but using only 10 mol % of catalyst, we began to investigate the impact of various parameters on the reaction outcome. Whereas Oshima and Utimoto observed reaction at stoichiometric and 30 mol % of catalyst loading, it was found that the reaction proceeds equally well with only 10 mol % of catalyst. As noted in Table 1, the

Scheme 1



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[1] Fraga, B. *Nat. Prod. Rep.* **2004**, *21*, 669.

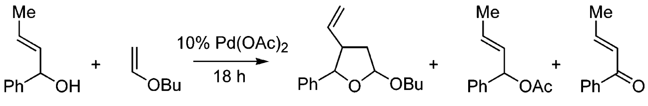
[2] For examples, see the following review: Koch, S. S. C.; Chamberlin, A. R. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier Science B. V.: Amsterdam, The Netherlands, 1995; Vol. 16, pp 687−725.

[3] (a) Fugami, K.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1987**, *28*, 809. (b) Fugami, K.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 2050. For a related palladium-catalyzed dimerization of allyl alcohol, see: (c) Hafner, W.; Prigge, H.; Smidt, J. *Liebigs Ann. Chem.* **1966**, 109. For application of a related process to the synthesis of mycalamide A, see: (d) Sohn, J. E.; Waizumi, N.; Zhong, H. M.; Rawal, V. H. *J. Am. Chem. Soc.* **2005**, ASAP.

[4] For palladium-catalyzed syntheses of cyclic ethers, see: Hosokawa, T.; Murahashi, S.-I. *Heterocycles* **1992**, *33*, 1079.

10.1021/ol051275s CCC: $30.25

Table 1. Survey of the Catalytic Oshima−Utimoto Reaction[a]



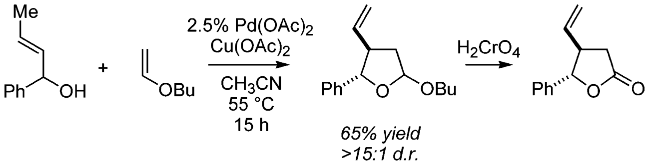
1 **2** **3** **4**

entry	oxidant	solvent	temp	%**1**	%**2**	%**3**	%**4**
1	$Cu(OAc)_2$	CH_3CN	25		68	9	
2	$Cu(OAc)_2$	CH_3CN	45	30	58	8	1
3	$Cu(OAc)_2$	CH_3CN	55		69	17	
4	$Cu(OAc)_2$	toluene	45	71	18		9
5	$Cu(OAc)_2$	THF	45	81	11		5
6	$Cu(OAc)_2$	$CHCl_3$	45		13	5	
7	$HOAc/Cu(OAc)_2$	CH_3CN	45	18	59	7	
8	$O_2/Cu(OAc)_2$	CH_3CN	45	13	37		42
9	O_2/pyridine	CH_3CN	45	42	26		28
10	O_2/pyridine	toluene	45	66	25		2
11	BQ	CH_3CN	45	50	18		7
12	BQ,HOAc	CH_3CN	45	9	57		
13	$K_2S_2O_8$	CH_3CN	45		13		

[a] Reaction conditions: 10 mol % of $Pd(OAc)_2$, 2.5 equiv of oxidant or 1 atm O_2, for 15 h, [**1**] = 1 M in indicated solvent. BQ = benzoquinone.

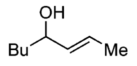
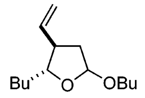
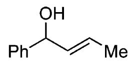
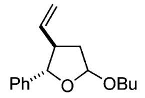
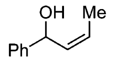
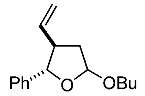
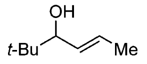
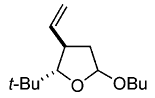
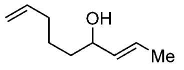
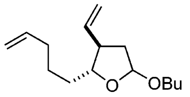
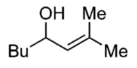
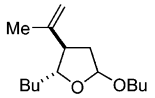
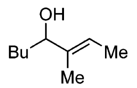
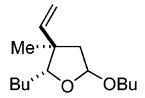
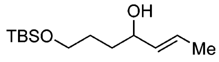
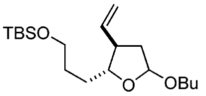
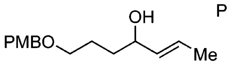
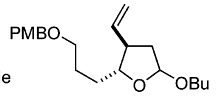
reaction is tolerant to mild heating, and comparable yields are obtained at room temperature and at 55 °C (entries 1−3, Table 1). A variety of other catalytic conditions were surveyed at 45 °C and the product yields determined by NMR versus an internal standard. As observed in Table 1, the product ratio and yield are highly dependent upon reaction conditions. Among O_2, $K_2S_2O_8$, $Cu(OAc)_2$, and benzoquinone, the latter two were most effective as stoichiometric oxidants, with benzoquinone being particularly effective in the presence of acetic acid.[6] Acetonitrile as solvent proved to be superior to toluene, THF, and chloroform; $Pd(OAc)_2$ proved to be superior to $PdCl_2$ and $Pd(TFA)_2$ (data not shown).

Scheme 2



With the effect of experimental conditions examined, we investigated the reaction at lower catalyst loading and examined the reaction stereoselectivity. As depicted in Scheme 2, it was found that when the reaction was carried out at 55 °C only 2.5 mol % of catalyst was required for effective conversion. In this case, a slight diminution in product yield was observed relative to reaction with 10 mol % of catalyst (compare to entry 3, Table 1). Further, while a 1:1 mixture of diastereomers was generated in the reaction, Jones oxidation revealed that the offending stereocenter is the anomeric carbon, and that the product was formed with a high level of 1,2 relative asymmetric induction.

Table 2. Scope of the Stereoselective Oshima−Utimoto Reaction[a]

entry	substrate	product	mol% Pd	% yield
1			10 2.5	61 65
2			10 2.5	69 65
3			10	70
4			10	36
5			10	50
6			10 2.5	75 50
7			10	50
8			10	58
9			10	36

[a] Reaction conditions: 10 mol % of $Pd(OAc)_2$, 2.5 equiv of $Cu(OAc)_2$, 55 °C for 15 h, 1 M in CH_3CN. Relative configuration between C-4 and C-5 is >15:1 in all cases. Ratio of epimers at anomeric carbon is ca. 1:1.

To ascertain the scope of the Oshima−Utimoto reaction, a series of substrates was examined (Table 2). All experiments were carried out at 55 °C and with 10 mol % catalyst loading since these conditions provided useful levels of conversion, even with sterically demanding substrates. As noted in the table, even an encumbered substrate, such as that in entry 6, can provide a reasonable yield with 2.5 mol % of catalyst. Similar to the example in Scheme 2, all of the reactions in Table 2 proceeded with >15:1 1,2-diastereoinduction, as determined by Jones oxidation of the acetal. From the data presented, it is apparent that this reaction is selective with both aliphatic and aromatic allyl alcohols as well as substrates with additional sites of unsaturation. The reaction is compatible with acid labile silyl protecting groups; however, the more coordinating *para*-methoxybenzyl ether

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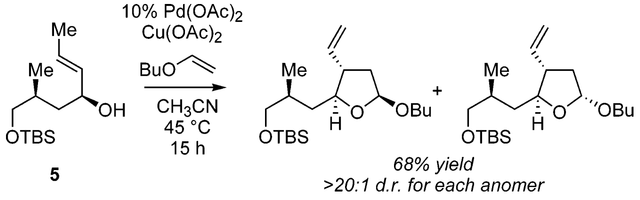
(5) (a) Larock, R. C.; Lee, N. H. *J. Am. Chem. Soc.* **1991**, *113*, 7815. (b) Larock, R. C.; Stinn, D. E. *Tetrahedron Lett.* **1989**, *30*, 2767. See also: (c) Kraus, G. A.; Thurston, J. *J. Am. Chem. Soc.* **1989**, *111*, 9203.

(6) Grennenberg, H.; Gogoll, A.; Bäckvall, J. E. *Organometallics* **1993**, *12*, 1790.

Scheme 3

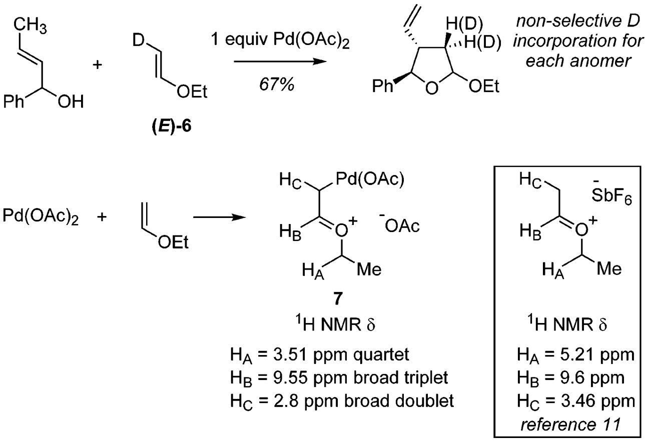


appears to inhibit the reaction. The olefin geometry does not appear to play a crucial role in this transformation as a *cis*- and *trans*-alkene both furnish the same stereoisomer of product in comparable yield and selectivity (compare entries 2 and 3). Notably, the reaction is also effective in forming a quaternary stereocenter with a high level of stereoinduction (entry 7).

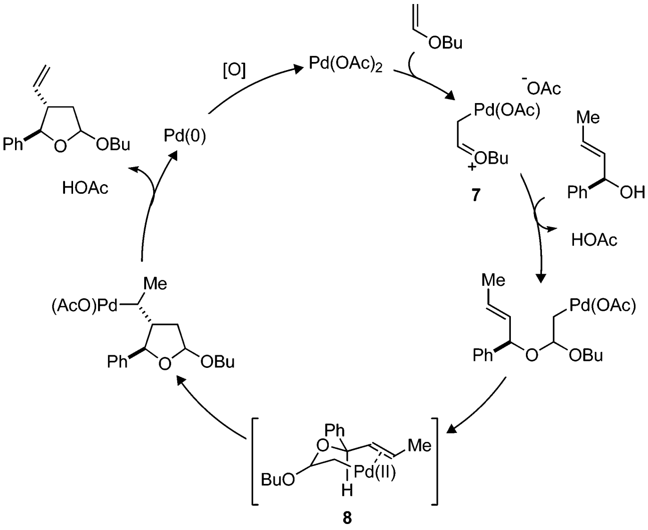
Considering that Pd catalysts can facilitate both allylic substitution reactions and alcohol oxidation reactions, the stereochemical integrity of the stereocenter in the reaction substrates will be of consequence to engaging the stereoselective Oshima−Utimoto reaction in asymmetric synthesis. Chiral allylic alcohol **5** provided a suitable substrate to probe for potential epimerization during the course of the Oshima reaction. Fortunately, upon subjection of **5** to the standard reaction conditions, the derived cyclic acetal could be isolated in good yield, and each anomer was furnished as a single diastereomer with the configuration as depicted in Scheme 3.

To learn about the mechanism of the Oshima−Utimoto reaction, we examined this process with deuterated vinyl ether (*E*)-**6** (Scheme 4).[7] Isolation of the reaction product and chromatographic separation of the acetal epimers revealed that the deuterium atom was scrambled at the methylene carbon of the furan ring. NMR analysis during the course of the reaction showed that vinyl ether (*E*)-**6** undergoes cis/trans isomerization more rapidly than the Oshima reaction occurs.[8] In a second experiment, 1 equiv of ethyl vinyl ether was combined with 1 equiv of Pd(OAc)$_2$ and was found to result in a structure consistent with oxonium ion **7**, as determined by ^{1}H NMR (1D, COSY) analysis (Scheme 4).[9,10] The spectral data for compound **7** are similar to those reported for the analogous oxonium ion derived from ethyl vinyl ether and fluoroantimonic acid in SO$_2$ solvent.[11] Notably, the formyl hydrogen was found to resonate at 9.6 ppm and appears as a triplet due to coupling with H$_C$ (J = 4.9 Hz).[12] Consistent with this assignment, the oxonium ion derived from deuterium-labeled substrate (*E*)-**6** exhibits a doublet for the formyl hydrogen resonance.

Scheme 4



Scheme 5



On the basis of the stereochemical outcome of the reaction and the observations mentioned above, it appears plausible that the reaction proceeds by addition of the allylic alcohol to oxonium ion **7**, as depicted in Scheme 5. Subsequent stereoselective carbopalladation of the tethered alkene through a transition structure that may resemble chairlike conformer **8** provides a rationale for the observed stereoinduction. Finally, β-H elimination would provide the reaction product and release a catalyst which requires reoxidation prior to re-formation of ion **7**. We posit that the lack of stereocontrol at the anomeric carbon results from a kinetic profile wherein nonselective addition of the alcohol to **7** is irreversible under

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[7] Keul, H.; Choi, H.-S.; Kuczkowski, R. L. *J. Org. Chem.* **1985**, *50*, 3365.

[8] For Pd-catalyzed isomerization of vinyl ethers, see: McKeon, J. E.; Fitton, P. *Tetrahedron* **1972**, *28*, 233.

[9] For IR characterization of a Pd−olefin complex derived from a vinyl ether and palladium acetate, see: Wakatsuki, Y.; Nozakura, S. I.; Murahashi, S. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 3426.

[10] An oxonium ion related to **7** has been postulated previously: (a) Henry, P. M. *J. Am. Chem. Soc.* **1972**, *94*, 7316. For a related iminium ion which appears to be involved in indole arylation, see: (b) Lane, B. S.; Brown, M. A.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, ASAP.

[11] Olah, G. A.; DeMember, J. R.; Mo, Y. K.; Svoboda, J. J.; Schilling, P.; Olah, J. A. *J. Am. Chem. Soc.* **1974**, *96*, 884.

[12] The ^{1}H NMR resonances for both H$_B$ and H$_C$ are broadened, indicating a fluxional process. The resonances for unreacted ethyl vinyl ether are unperturbed, suggesting the equilibrium transformation involving **6** includes a separate species. For a similar equilibrium process involving pyridine addition to a Pd(II) vinyl ether complex, see ref 9.

the reaction conditions and both epimers are processed with high 1,2-stereoinduction (control experiments indicate that the anomers do not interconvert under the reaction conditions, and that the product mixture reflects a kinetic ratio).

In conclusion, the Oshima−Utimoto reaction can be carried out in an efficient fashion using only 2.5−10 mol % of catalyst and allows for the stereoselective synthesis of five-membered oxacycles directly from simple starting materials. Applications of this transformation in the context of natural product synthesis are in progress, and future studies will address variants of this catalytic C−C bond forming process.

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Supporting Information Available: Characterization data and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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