Direct Synthesis of Cyclic Ketals of Acetophenones by Palladium-Catalyzed Arylation of Hydroxyalkyl Vinyl Ethers

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Received August 5, 1997[⊗]

Reaction of 2-hydroxyethyl vinyl ether, 4-hydroxybutyl vinyl ether, or di(ethylene glycol) vinyl ether with aryl triflates, aryl bromides, or iodobenzene in presence of a catalytical amount of palladium acetate and the bidentate ligand DPPP provides a direct entry to cyclic ketals of acetophenones. It is postulated that the reaction proceeds via an initial α-arylation of the vinyl ethers to give labile aryl vinyl ether intermediates, which undergo subsequent ketalization in presence of protons in the reaction media. The method merits attention due to the simplicity of the experimental procedure and the possibility of selective ketal formation in the presence of an additional carbonyl group.

Introduction

We recently reported an unexpected binding mode of an HIV protease inhibitor with a cyclic sulfamide as a core structure.[1] A discrete water molecule has been identified in the space interfacing two aromatic groups (P1 and P2) of the inhibitor,[2] and molecular modelling suggested to us that the oxygen atoms of certain ketals (e.g. 1,3-dioxolanes), attached to one of the aromatic rings, should provide a suitable mimic of the bridging water molecule. We desired a synthetic method that in one step would allow substitution of an halide or triflate on an aromatic ring for a cyclic ketal and that did not rely on ketalization catalyzed by strong acid.

We herein report a direct synthesis of protected acetophenones[3] accomplished by palladium-catalyzed arylation[4] of hydroxyalkyl vinyl ethers[5] and subsequent ring-closing.[6]

Results

The arylation studies were performed starting from three, commercially available, hydroxyalkyl vinyl ethers **1a**−**c** (Table 1). The aryl triflates **2a**,**d**−**g**, aryl bromides **2b**,**h**, and iodobenzene **2c** were reacted with the vinyl ethers to furnish the ketals **3a**−**h** (Table 1). The reactions with the triflates were performed by using 2 equiv of the vinyl ethers, a catalytic amount of palladium acetate (0.03 equiv), 1,3-bis(diphenylphosphino)propane (DPPP) as ligand (0.06 equiv), and a stoichiometric amount of triethylamine (1.5 equiv) as the base in DMF at 80 °C (Table 1).[7] Reactions with the aryl triflates **2a** and **2d** provided a good isolated yield of the corresponding cyclic ketals (entries 1 and 8) while a considerably lower yield was encountered when the electron deficient **2e** was subjected to the same reaction conditions.[8] However, treatment with dry acetic acid at 80 °C prior to workup (entry 9) or increasing the temperature to 130 °C after complete consumption of **2e** (entry 10) resulted in good yields of **3e**. Reactions of phenyl triflate with the 4-hydroxybutyl vinyl ether **1b** (entry 2) and di(ethylene glycol) vinyl ether **1c** (entry 3) proceeded smoothly, but we were unable to isolate the nine-membered cyclic ketal from the arylation of 6-hydroxyhexyl vinyl ether, since decomposition occurred during attempted purification on silica. Utilizing $Pd(0)(DPPP)_2$[9] as catalyst gave a comparable yield to reactions with the palladium acetate/DPPP combination (entry 4). Employing bromobenzene or iodobenzene as arylating agents required addition of thallium(I) acetate to control the regioselectivity in the Heck reaction (entries 5 and 6).[5b] This additive had a reversed effect on the ketalization rate and was also found to suppress the reaction rate starting from phenyl triflate.[10] Boosting of the reaction temperature after 24 h or adding dry acetic acid promoted the ring-closing reactions also in the thallium-assisted reactions (entries 7 and 13). Entries 11−13 demonstrate three examples where a carbonyl group is attached to the aromatic substrate. A substitution of the leaving group for the

[⊗] Abstract published in *Advance ACS Abstracts,* October 1, 1997.

(1) (a) Hultén, J.; Bonham, N. M.; Nillroth, U.; Hansson, T.; Zuccarello, G.; Bouzide, A.; Åqvist, J.; Classon, B.; Danielson, U. H.; Karlén, A.; Kvarnström, I.; Samuelsson, B.; Hallberg, A. *J. Med. Chem.* **1997**, *40*, 885−897. (b) Bäckbro, K.; Löwgren, S.; Österlund, K.; Atepo, J.; Unge, T.; Hultén, J.; Bonham, N. M.; Schaal, W.; Karlén, A.; Hallberg, A. *J. Med. Chem.* **1997**, *40*, 898−902.

(2) Bäckbro, K.; Hultén, J.; Löwgren, S.; Bonham, N. M.; Schaal, W.; Karlén, A.; Hallberg, A.; Unge, T. Manuscript in preparation.

(3) (a) Meskens, F. A. J. *Synthesis* **1981**, 501−522. (b) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; Wiley-Interscience: New York 1991; pp 175−198. (c) Kunz, H.; Waldmann, H. *Comprehensive Organic Synthesis*; Trost, B. M., Flemming, I., Eds.; Pergamon Press: Oxford 1991; vol. 6, pp 675−684.

(4) For reviews on the Heck reaction see: (a) Heck, R. F. *Org React.* **1982**, *27*, 345−363. (b) Heck, R. F. *Palladium Reagents in Organic Synthesis*; Academic Press: London 1985; pp 276−290. (c) Heck, R. F. *Comprehensive Organic Synthesis*; Trost, B. M., Flemming, I., Eds.; Pergamon Press: Oxford 1991; vol. 4, pp 833-863. (d) de Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2379−2411. (e) Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2−7. (f) Tsuji, J. *Palladium Reagents and Catalysts: Innovations in Organic Chemistry*; John Wiley & Sons: Chichester, 1995; pp 125−168. (g) Jeffery, T. *Advances in Metal-Organic Chemistry*; Liebeskind, L. S. Ed.; JAI Press Inc: Greenwich, CT, 1996; vol. 5, pp 153−260. For Heck arylation of heteroatom-substituted double bonds see: (h) Daves, G. D., Jr.; Hallberg, A. *Chem. Rev.* **1989**, *89*, 1433−1445.

(5) For internal arylation of acyclic vinyl ethers see: (a) Cabri, W.; Candiani, I.; Bedeschi, A.; Santi, R. *J. Org. Chem.* **1990**, *55*, 3654−3655. (b) Cabri, W.; Candiani, I.; Bedeschi, A.; Penco, S.; Santi, R. *J. Org. Chem.* **1992**, *57*, 1481−1486. For an earlier report of preferential formation of internal arylation products see: (c) Hallberg, A.; Westfelt, L.; Holm, B. *J. Org. Chem.* **1981**, *46*, 5414−5415.

(6) For a somewhat related transformation of organic halides or organic triflates to cyclic hemiacetals see: (a) Mandai, T.; Hasegawa, S.; Fujimoto, T.; Kawada, M.; Nokami, J.; Tsuji, J. *Synlett* **1990**, 85−86. (b) Arcadi, A.; Bernocchi, E.; Cacchi, S.; Marinelli, F. *Tetrahedron* **1991**, *47*, 1525−1540.

(7) No terminal *β*-products were detected (GC-MS) in DPPP-controlled arylations of hydroxyalkyl vinyl ethers.

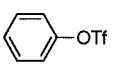
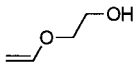
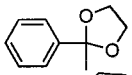
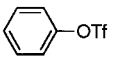
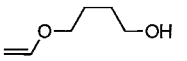
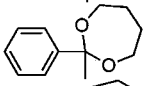
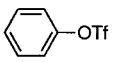
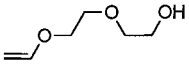
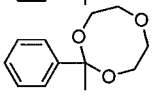
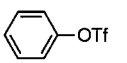
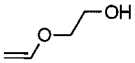
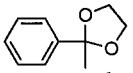
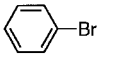
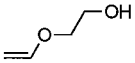
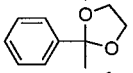
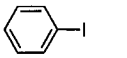
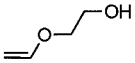
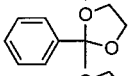
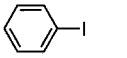
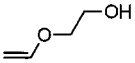
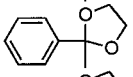
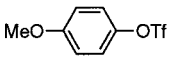
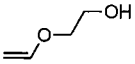
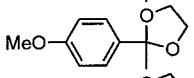
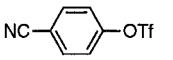
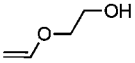
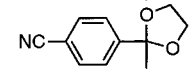
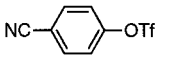
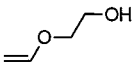
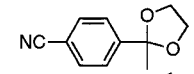
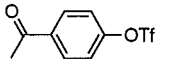
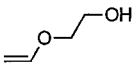
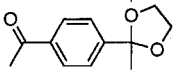
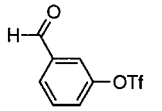
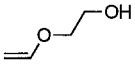
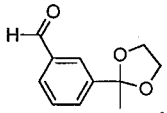
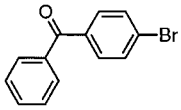
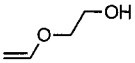
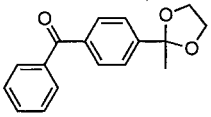
(8) In this case, only a small amount of product **3e** was formed (18% isolated yield after 120 h at 80 °C).

(9) Mason, M. R.; Verkade, J. G. *Organometallics* **1992**, *11*, 2212−2220.

(10) The addition of 1.2 equiv of TlOAc to a reaction performed according to entry 1 (Table 1) resulted in a slower formation of **3a** (82% isolated yield after 44 h at 80 °C).

S0022-3263(97)01454-0 CCC: $14.00

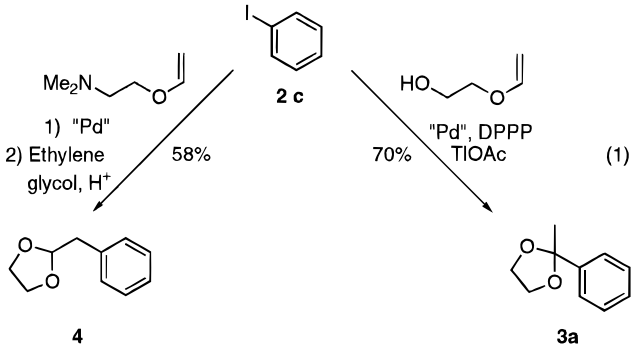
Table 1. Palladium-Catalyzed Selective Synthesis of Cyclic Ketals from Aryl Triflates or Aryl Halides[a]

entry	aryl halide or aryl triflate		vinyl ether		reaction conditions	product		isolated yield[b]
1		**2a**		**1a**	24h, 80°C		**3a**	83%
2		**2a**		**1b**	24h, 80°C		**3b**	84%
3		**2a**		**1c**	24h, 80°C		**3c**	33%
4		**2a**		**1a**	Pd(DPPP)$_2$, 24h, 80°C		**3a**	83%[c]
5		**2b**		**1a**	TlOAc, 144h, 80°C		**3a**	81%
6		**2c**		**1a**	TlOAc, 144h, 80°C		**3a**	70%
7		**2c**		**1a**	1) TlOAc, 24h, 80°C 2) 4h, 130°C		**3a**	62%[d]
8		**2d**		**1a**	16h, 80°C		**3d**	91%
9		**2e**		**1a**	1) 16h, 80°C 2) HOAc, 6h		**3e**	78%[e]
10		**2e**		**1a**	1) 16h, 80°C 2) 5h, 130°C		**3e**	65%[d]
11		**2f**		**1a**	1) 24h, 80°C 2) HOAc, 2h		**3f**	86%[e]
12		**2g**		**1a**	1) 24h, 80°C 2) HOAc, 2h		**3g**	76%[e]
13		**2h**		**1a**	1) TlOAc, 16h, 80°C 2) HOAc, 4h		**3h**	75%[e]

[a] The aryl halide or aryl triflate (5.0 mmol, 1.0 equiv), hydroxyalkyl vinyl ether (10.0 mmol, 2.0 equiv), $Pd(OAc)_2$ (0.15 mmol, 0.03 equiv), DPPP (0.30 mmol, 0.06 equiv), Et_3N (7.5 mmol, 1.5 equiv) and, if present, TlOAc (6.0 mmol, 1.2 equiv, entries 5-7 and 13) were heated at 80 °C under nitrogen in 15 mL of DMF. [b] Based on the aryl halide or aryl triflate. >95% Purify by GC-MS. [c] $Pd(0)DPPP_2$ was utilized as palladium catalyst instead of $Pd(OAc)_2$/DPPP. [d] The reaction temperature was increased to 130 °C after complete consumption of the aryl halide or aryl triflate (GC-MS). [e] 5 mL of dry HOAc was added after complete consumption of the aryl bromide or aryl triflate (GC-MS).

ketal function was achieved in all three cases, and no products derived from transketalization were observed. The synthesis of **3g** was especially noteworthy since the protected methyl ketone was introduced in the presence of an aldehyde functionality. Thus it is possible to reverse the chemoselectivity and to assemble a molecule with a blocked ketone without affecting the reactive aldehyde carbonyl group.[11]

Finally, we wished to extend our investigation to include a synthetic process to obtain the complementary acetal **4**. Chelation-controlled terminal (β) phenylation[12] and subsequent acetalization of 2-(dimethylamino)ethyl vinyl ether was examined and observed to afford the expected single product **4** in a reasonable isolated yield (eq 1). This methodology offers a new route to protected arylacetaldehydes.



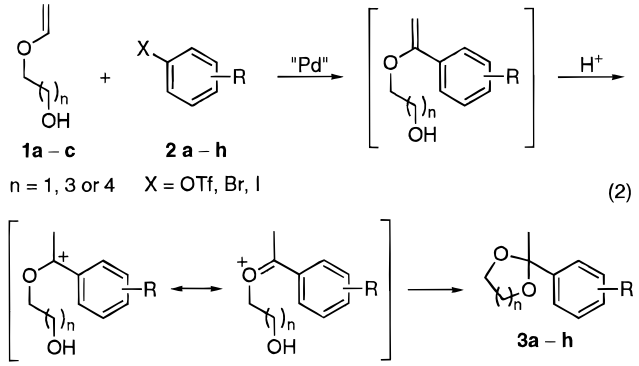
Discussion

For a successful preparative reaction, a highly selective internal (α) arylation of the hydroxyalkyl vinyl ether is

(11) We are aware of only one additional methodology for selective ketalization of ketones in the presence of aldehydes (reversed chemoselectivity). (a) Kim, S.; Kim, Y. G.; Kim, D. *Tetrahedron Lett.* **1992**, *33*, 2565−2566. For a recent example of a selective acetalization of an aromatic aldehyde in the presence of a ketone see: Tateiwa, J.; Horiuchi, H.; Uemura, S. *J. Org. Chem.* **1995**, *60*, 4039−4043.

(12) (a) Andersson, C.-M.; Larsson, J.; Hallberg, A. *J. Org. Chem.* **1990**, *55*, 5757−5761. (b) Larhed, M.; Andersson, C.-M.; Hallberg, A. *Acta. Chem. Scand.* **1993**, *47*, 212−217. (c) Larhed, M.; Andersson, C.-M.; Hallberg, A. *Tetrahedron* **1994**, *50*, 285−304. For an example of chelating vinyl ethers containing phosphorous derivatives see: (d) Badone, D.; Guzzi, U. *Tetrahedron Lett.* **1993**, *34*, 3603−3606.

a prerequisite. Cabri has rationalized the regiochemical outcome dictated by bidentate ligands, e.g. DPPP, in terms of generation of a cationic organopalladium π-complex[13] followed by a comparatively rapid,[14] electronically controlled insertion.[5a,b] In reactions with haloarenes the required cationic species can be created through addition of halide abstractors such as thallium[15] or silver salts.[16] We assume that the ketals are formed according to the reaction sequence outlined in the eq 2.

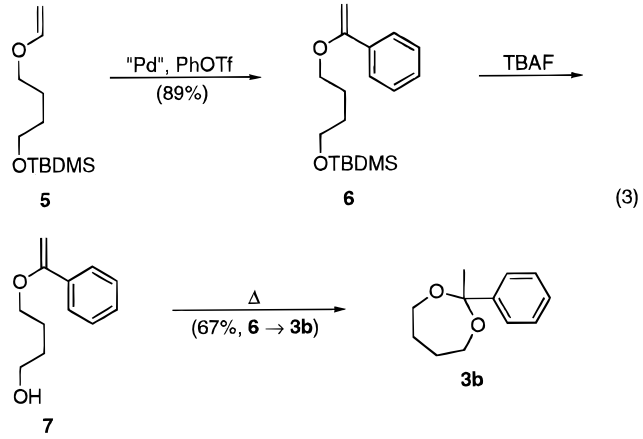


(2)

We have previously shown that the amino function in 2-(dimethylamino)ethyl vinyl ether has a strong β-directing effect in the palladium-catalyzed arylation of this olefin.[12a–c] However, in the presence of the bidentate DPPP, α-arylation occurred exclusively, which probably is a consequence of the lack of a coordination site to accommodate the olefin amino group.[12c] It appears that a similar situation governs the selectivity for α-arylation in the present reaction. Interestingly, arylation experiments performed with the 2-hydroxyethyl vinyl ether (**1a**) or ethylene glycol butyl vinyl ether,[17] with monodentate triphenylphosphine as supporting ligand, resulted in a mixture of α- and β-arylation in both cases. This result is not consistent with chelation control by palladium–oxygen coordination.[18]

The ketal formation, we anticipate, occurs by acid-catalyzed ring-closure after internal arylation of the vinylic ether.[19] Terminal protonation[20] ($HNEt_3^+$ or HOAc) of the double bond generates an oxocarbonium ion and the ketalization arises through internal nucleophilic attack of the hydroxy group (eq 2). Thus, the slow cyclization experienced with electron-deficient substrates (entries 9–13) or after addition of weakly basic thallium(I) acetate (entries 5–7 and 13) is explained by insufficient protonation. In agreement with this proposition, an increased concentration of the oxygen-stabilized carbocation (by acid addition) or an enhanced rate of the internal nucleophilic attack (by raising the temperature) affords efficient ketalization. It is noteworthy that, the ring-closing reaction is not observed with the non-α-arylated hydroxyalkyl vinyl ethers (**1a**–**1c**) under our reaction conditions.

Additional insight into this mechanistic speculation was provided by the reaction of the α-arylated vinyl ether **7** (prepared by arylation of the corresponding 4-(*tert*-butyldimethylsiloxy)butyl vinyl ether followed by desilylation). This intermediate underwent ketalization upon distillation (eq 3) or after treatment with acid (HOAc or NH_4Br), rendering support for involvement of an acid-catalyzed rather than Pd(II)-promoted cyclization.[21] Furthermore, the appearance of significant amounts of the α-arylated, but not ketalized, products in GC-MS samples obtained during the reactions (entries 5–7 and 9–13) corroborate a reaction pathway involving an acid-promoted ring-closure.



(3)

Conclusion

We have demonstrated that palladium-catalyzed arylation of commercially available hydroxyalkyl vinyl ethers constitutes a facile direct method for preparation of ketals of acetophenones. Although only a limited number of examples are provided here, we believe that the ease of operation and, in particular, the suitability of the present method for the preparation of selectively blocked dicarbonyl compounds will prove to be useful in synthetic work.

(13) The triflate anion is fully dissociated from Pd(II) in DMF. See: (a) Jutand, A.; Mosleh, A. *Organometallics* **1995**, *14*, 1810–1817. (b) Brown, J. M.; Hii, K. K. M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 657–659.

(14) (a) Siegbahn, P. E. M. *J. Organomet. Chem.* **1994**, *478*, 83–93. (b) Brown, J. M.; Pérez-Torrente, J. J.; Alcock, N. W.; Clase, H. J. *Organometallics* **1995**, *14*, 207–213. (c) Kawataka, F.; Shimizu, I.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 654–660. (d) Crisp, G. T.; Gebauer, M. G. *Tetrahedron* **1996**, *52*, 12465–12474.

(15) Leading references for use of thallium(I) additives. (a) Grigg, R.; Loganathan, V.; Santhakumar, V.; Sridharan, V.; Teasdale, A. *Tetrahedron Lett.* **1991**, *32*, 687–690. (b) Carfagna, C.; Musco, A.; Sallese, G.; Santi, R.; Fiorani, T. *J. Org. Chem.* **1991**, *56*, 261–263. (c) Sonesson, C.; Larhed, M.; Nyqvist, C.; Hallberg, A. *J. Org. Chem.* **1996**, *61*, 4756–4763. (d) Ripa, L.; Hallberg, A. *J. Org. Chem.* **1996**, *61*, 7147–7155. See also ref 5b.

(16) For beneficial effects of silver additives see: (a) Karabelas, K.; Westerlund, C.; Hallberg, A. *J. Org. Chem.* **1985**, *50*, 3896–3900. (b) Karabelas, K.; Hallberg, A. *J. Org. Chem.* **1986**, *51*, 5286–5290. (c) Abelman, M. M.; Oh, T.; Overman, L. E. *J. Org. Chem.* **1987**, *52*, 4130–4133. (d) Larock, R. C.; Gong, W. H. *J. Org. Chem.* **1989**, *54*, 2047–2050. (e) Sato, Y.; Sodeoka, M.; Shibasaki, M. *Chem. Lett.* **1990**, 1953–1954. For a recent application of silver additives in Heck reactions see: (f) Ripa, L.; Hallberg, A. *J. Org. Chem.* **1997**, *62*, 595–602.

(17) $CH_3(CH_2)_3OCH_2CH_2OCH{=}CH_2$.

(18) For examples of Pd(II)-oxygen coordination in Heck reactions see: (a) Bernocchi, E.; Cacchi, S.; Ciattini, P. G.; Morera, E.; Ortar, G. *Tetrahedron. Lett.* **1992**, *33*, 3073–3076. (b) Jeffery, T. *Tetrahedron Lett.* **1993**, *34*, 1133–1136. (c) Kang, S.-K.; Jung, K.-Y.; Park, C.-H.; Namkoong, E.-Y.; Kim, T.-H. *Tetrahedron Lett.* **1995**, *36*, 6287–6290. (d) Kang, S.-K.; Lee, H.-W.; Jang, S.-B.; Kim, T.-H.; Pyun, S.-J. *J. Org. Chem.* **1996**, *61*, 2604–2605. See also ref 6b.

(19) For acid-catalyzed cyclization of hydroxyalkyl vinyl ethers see: (a) McClelland, R. A.; Watada, B.; Lew, C. S. Q. *J. Chem. Soc., Perkin Trans. 2* **1993**, 1723-1727. (b) Deslongchamps, P.; Dory, Y. L.; Li, S. *Helv. Chim. Acta* **1996**, *79*, 41–50.

(20) (a) Jones, D. M.; Wood, N. F. *J. Chem. Soc.* **1964**, 5400–5403. (b) Salomaa, P.; Kankaanperä, A.; Lajunen, M. *Acta Chem. Scand.* **1966**, *20*, 1790–1801. (c) Kresge, A. J.; Chen, H. J. *J. Am. Chem. Soc.* **1972**, *94*, 2818–2822. (d) Burt, R. A.; Chiang, Y.; Kresge, A. J.; Szilagyi, S. *Can. J. Chem.* **1984**, *62*, 74–76.

(21) (a) Heumann, A. *Stereochemistry of Organometallic and Inorganic Compounds*; Bernal, I., Ed.; Elsevier: Amsterdam, 1994; vol. 5, pp 557–623. For a recent example of Pd(II)-catalyzed acetalization of olefins see: (b) Hosokawa, T.; Yamanaka, T.; Itotani, M.; Murahashi, S.-I. *J. Org. Chem.* **1995**, *60*, 6159–67.

Experimental Section

Procedures. All reactions were carried out under nitrogen in heavy-walled Pyrex tubes sealed with a screw-cap fitted with a Teflon gasket silicon septum. ^{1}H and ^{13}C NMR spectra were measured in $CDCl_3$ solution at 270 MHz and 67.8 MHz, respectively. Mass spectra were recorded at an ionzing voltage of 70 eV (EI). The mass detector was interfaced with a gas chromatograph equipped with a HP-1 (25 m × 0.20 mm) capillary column. Importantly, to be able to monitor the cyclization of the intermediate α-arylated vinyl ethers (and avoid ketalization on the column) the GC-column and the injector must be in good condition. IR spectra were recorded on a FTIR spectrometer. Column chromatography was performed on silica gel, using Kieselgel S (0.032−0.063 mm, Riedel-de Haen), or on aluminum oxide, using Aluminiumoxid 90 (0.063−0.200 mm, Merck). Elemental analyses were performed by Micro Kemi AB, Uppsala, Sweden, or Analytische Laboratorien, Prof. Dr. H. Malissa und G. Reuter GmbH, Lindlar, Germany.

Materials. Vinyl ethers **1a**−**c** and ethylene glycol butyl vinyl ether were obtained from Aldrich. The organic halides, palladium(II) acetate, 1,3-bis(diphenylphosphino)propane (DPPP), thallium(I) acetate, ammonium bromide, imidazole, *tert*-butyldimethylsilyl chloride (TBDMSCl), *p*-toluenesulfonic acid monohydrate, and tetrabutylammonium fluoride in THF (1 M) were purchased from commercial suppliers and were used directly as received. Acetic acid was dried over phosphorus pentoxide and triethylamine was distilled from potassium hydroxide prior to use. DMF, ethylene glycol, and *tert*-butyl methyl ether were stored over 4 Å molecular sieves. The aryl triflates (trifluoromethanesulfonates) were synthesized from the corresponding phenols using an excess of triflic anhydride and 2,4,6-trimethylpyridine, essentially following a literature procedure[22] and are known compounds (**2a**,[5b] **2d**,[23] **2e**,[5b] **2f**,[23] and **2g**[24]). Structure and purity of isolated compounds were determined by NMR, GC-MS, and FTIR. Products **3a**,[25] **3c**,[26] **3d**,[25b] **3e**,[27] and **4**[28] are known compounds.

Synthesis of Cyclic Ketals (3a−h, Table 1). General Procedure. In a screw-capped Pyrex tube $Pd(OAc)_2$ (0.034 g, 0.15 mmol) and DPPP (0.124 g, 0.30 mmol) were suspended in 10 mL of dry DMF under nitrogen. To the mixture were added aryl halide or aryl triflate **2a**−**h** (5.0 mmol), Et_3N (0.76 g, 7.5 mmol), hydroxyalkyl vinyl ether **1a**−**c** (10 mmol) and, if present, TlOAc, (1.58 g, 6.0 mmol, entries 5−7 and 13) together with 5 mL of DMF. The tube was purged with nitrogen for 2 min, sealed, and stirred in an oil bath at 80 °C for 16−144 h (see Table 1 for details). Small aliquots were periodically removed, partitioned between diethyl ether and 0.1 M NaOH, and the organic phase was analyzed by GC-MS. After complete consumption of the aryl halide or aryl triflate, the reaction was either (1) interrupted, or in the case of incomplete ketal formation, (2) dry HOAc was added (5 mL, 80 °C, entries 9 and 11−13), or alternatively, (3) the reaction temperature was increased to 130 °C (entries 7 and 10). See Table 1 for details. After cooling, the reaction mixture was carefully poured into an aqueous solution of K_2CO_3 (10%, 50 mL (100 mL in entries 9 and 11−13)) and was extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with saturated NaCl solution (50 mL), dried over K_2CO_3, and concentrated. The resulting crude products were purified by bulb-to-bulb distillation in a Kugelrohr apparatus and/or by flash column chromatography to afford pure ketals **3a**−**h** (Table 1, >95% pure by GC-MS).

2-Methyl-2-phenyl-1,3-dioxepan (3b, Table 1). Yellow oil, 0.805 g (84%, >95% pure by GC-MS). Bulb-to-bulb distillation (0.4 mmHg, oven temperature ∼80 °C). MS *m*/*z* (relative intensity, 70 eV) 177 (87), 147 (48), 105 (100); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.51 (d, J = 7 Hz, 2H), 7.37−7.25 (m, 3H), 3.84−3.76 (m, 2H), 3.65−3.56 (m, 2H), 1.79−1.54 (m, 4H), 1.50 (s, 3H). Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.87; H, 8.48.

2-(4-Acetylphenyl)-2-methyl-1,3-dioxolane (3f, Table 1). White crystals, 0.884 g (86%, >95% pure by GC-MS). Purified by bulb-to-bulb distillation (0.4 mmHg, oven temperature ∼120 °C) and column chromatography (SiO_2, pentane/diethyl ether 2/1). MS *m*/*z* (relative intensity, 70 eV) 191 (100), 147 (38), 119 (8), 87 (18);^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.92 (d, J = 8.5 Hz, 2H), 7.56 (d, J = 8.5 Hz, 2H), 4.08−4.02 (m, 2H), 3.78−3.72 (m, 2H), 2.58 (s, 3H), 1.63 (s, 3H); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 197.7, 148.5, 136.6, 128.3, 125.5, 108.4, 64.5, 27.3, 26.6; IR (neat) 1697 cm^{-1}. Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84. Found: C, 70.0; H, 7.0.

2-(3-Formylphenyl)-2-methyl-1,3-dioxolane (3g, Table 1). Yellow crystals, 0.726 g (76%, >95% pure by GC-MS). Purified by bulb-to-bulb distillation (0.4 mmHg, oven temperature ∼130 °C) and column chromatography (SiO_2, pentane/diethyl ether 2/1). MS *m*/*z* (relative intensity, 70 eV) 177 (100), 133 (48), 105 (10), 87 (23); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 10.03 (s, 1H), 8.00 (s, 1H), 7.86−7.72 (m, 2H), 7.51 (t, J = 7.8 Hz, 1H), 4.11−4.00 (m, 2H), 3.83−3.73 (m, 2H), 1.67 (s, 3H), ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 192.2, 144.7, 136.4, 131.3, 129.0, 128.9, 126.8, 108.2, 64.5, 27.4; IR (neat) 1700 cm^{-1}. Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29. Found: C, 68.4; H, 6.2.

2-(4-Benzoylphenyl)-2-methyl-1,3-dioxolane (3h, Table 1). Thick yellow oil, 1.00 g (75%, >95% pure by GC-MS). The excess of **1a** was removed by bulb-to-bulb distillation (8 mmHg, oven temperature ∼90 °C). Purified by column chromatography (SiO_2, isohexane/diethyl ether 3/1). MS *m*/*z* (relative intensity, 70 eV) 253 (100), 209 (22), 152 (5), 105 (12); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.85−7.72 (m, 4H), 7.65−7.53 (m, 3H), 7.48 (app t, J = 7 Hz, 2H), 4.11−4.01 (m, 2H), 3.83−3.74 (m, 2H), 1.69 (s, 3H), ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 196.4, 148.0, 137.7, 137.2, 132.5, 130.2, 130.1, 128.4, 125.4, 108.6, 64.7, 27.6; IR (neat) 1664 cm^{-1}. Anal. Calcd for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01. Found: C, 76.4; H, 6.1.

Preparation of Pd(0)(DPPP)$_2$.[9] In the workup of **3a** (Table 1, entry 1), yellow crystals precipitated in the diethyl ether/K_2CO_3 (10%) interface. The crystals were isolated by filtration, washed with diethyl ether, and dried *in vacuo* providing a 55% yield (77 mg) based on $Pd(OAc)_2$. The product was identified by X-ray crystallography.[9]

Synthesis of Phenylacetaldehyde Ethylene Acetal (4, Eq 1).[28] (*E*)/(*Z*)-[2-[2-(Dimethylamino)ethoxy]ethenyl]benzene was prepared from iodobenzene (0.51 g, 2.5 mmol) and 2-(dimethylamino)ethyl vinyl ether (0.35 g, 3.0 mmol) as previously described.[12a] After the reaction mixture was cooled, diethyl ether (50 mL) was added, and the organic mixture was washed with 0.1 M NaOH (2 × 25 mL). The combined aqueous layers were further extracted with diethyl ether (2 × 25 mL). All three organic layers were combined, washed with saturated NaCl solution (50 mL), dried with K_2CO_3, and concentrated. The crude (*E*)/(*Z*)-[2-[2-(dimethylamino)ethoxy]ethenyl]benzene was mixed with *p*-toluenesulfonic acid monohydrate (1.90 g, 10 mmol) and ethylene glycol (10 mL) in *tert*-butyl methyl ether (10 mL). The reaction mixture was stirred at 40 °C until GC-MS indicated complete consumption of the vinyl ether (18 h). The solution was poured into an aqueous solution of K_2CO_3 (10%, 50 mL) and was extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with saturated NaCl solution (50 mL), dried over K_2CO_3, and concentrated. The resulting crude product was purified by column chromatography on aluminum oxide (pentane/diethyl ether 19/1) to afford pure **4** (eq 1, >95% pure by GC-MS).

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(24) Echavarren, A. M.; Stille, J. K. *J. Am. Chem. Soc.* **1988**, *110*, 1557−1565.
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(26) (a) Einhorn, J.; Bacquet, C.; Lelandais, D. *J. Heterocycl. Chem.* **1980**, *17*, 1345−47. (b) Oshima, T.; Nagai, T. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 3979-3980.
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4-(*tert*-Butyldimethylsilyloxy)butyl Vinyl Ether (5, Eq 3). **5** was prepared according to the method described by Corey.[29] 4-Hydroxybutyl vinyl ether **1b** (5.81 g, 50 mmol) and imidazole (10.21 g, 150 mmol) were mixed in DMF (50 mL) under nitrogen. The reaction mixture was cooled to 0 °C, *tert*-butyldimethylchlorosilane (11.31 g, 75 mmol) was added, and the reaction mixture was allowed to reach room temperature overnight. The reaction mixture was then poured into diethyl ether (250 mL) and was washed with water (2 × 150 mL) and saturated NaCl solution (150 mL). The organic phase was thereafter dried (K_2CO_3) and concentrated to a yellow oil. Purification by column chromatography (SiO_2, pentane) and bulb-to-bulb distillation (10 mmHg, oven temperature ∼115 °C) gave pure **5** (9.39 g, 81%) as a clear oil (>95% pure by GC-MS). MS *m*/*z* (relative intensity, 70 eV) 215 (1), 173 (24), 131 (67), 101 (100);^{1}H NMR ($CDCl_3$, 270 MHz) δ 6.47 (dd, J = 14.4 Hz, J = 6.8 Hz, 1H), 4.17 (dd, J = 14.4 Hz, J = 2.0 Hz, 1H), 3.97 (dd, J = 6.9 Hz, J = 2.0 Hz, 1H), 3.70 (t, J = 6.3 Hz, 2H), 3.64 (t, J = 6.3 Hz, 2H), 1.76−1.57 (m, 4H), 0.89 (s, 9H), 0.05 (s, 6H). Anal. Calcd for $C_{12}H_{26}O_2Si$: C, 62.55 ; H, 11.37. Found: C, 62.7; H, 11.6.

α-[4-(*tert*-Butyldimethylsilyloxy)butoxy]styrene (6, Eq 3). In a screw-capped Pyrex tube $Pd(OAc)_2$ (0.034 g, 0.15 mmol) and DPPP (0.124 g, 0.30 mmol) were suspended in 10 mL of dry DMF under nitrogen. To the mixture were added phenyl triflate (1.13 g, 5.0 mmol), Et_3N (0.76 g, 7.5 mmol), and **5** (1.73 g, 7.5 mmol) was added together with 5 mL of DMF. The tube was purged with nitrogen for 2 min, sealed, and stirred in an oil bath at 80 °C for 6 h. After cooling, the reaction mixture was poured into an aqueous solution of K_2CO_3 (10%, 50 mL) and was extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with saturated NaCl solution (50 mL), dried over K_2CO_3, and concentrated. The resulting crude products were purified by bulb-to-bulb distillation (0.5 mmHg, oven temperature ∼130 °C) to afford **6** (1.36 g, 89%) as a pale yellow oil (>95% pure by GC-MS). MS *m*/*z* (relative intensity, 70 eV) 249 (34), 177 (19), 147 (53), 103 (100); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.67−7.58 (m, 2H), 7.37−7.29 (m, 3H), 4.63 (d, J = 2.6 Hz, 1H), 4.19 (d, J = 2.6 Hz, 1H), 3.87 (t, J = 6.3 Hz, 2H), 3.69 (t, J = 6.3 Hz, 2H), 1.92−1.80 (m, 2H), 1.77−1.66 (m, 2H), 0.90 (s, 9H), 0.06 (s, 6H). Anal. Calcd for $C_{18}H_{30}O_2Si$: C, 70.53; H, 9.86. Found: C, 70.8; H, 10.0.

Ring-Closing of α-(4-Hydroxybutoxy)styrene (7) upon Heating (Eq 3). Deprotection of 6 (0.50 g, 1.63 mmol) was performed with tetrabutylammonium fluoride in THF (4.1 mL, 1M) at rt. After complete consumption of 6 (30 min), the reaction mixture was diluted with diethyl ether (50 mL) and was washed with an aqueous solution of K_2CO_3 (10%, 2 × 25 mL). Additional extraction of the combined aqueous phases was performed with diethyl ether (2 × 50 mL). The organic phases were combined and thereafter washed with saturated NaCl solution (50 mL), dried (Na_2SO_4), and concentrated to a yellow oil. Attempted purification of 7 by bulb-to-bulb distillation (0.5 mmHg, oven temperature ∼170 °C) gave pure 3b (0.21 g, 67%) as a clear oil (>95% pure by GC-MS). All attempts to isolate 7 by column chromatography resulted in significant ketalization and/or hydrolysis.

General Procedure for Acid-Mediated Ring-Closing of α-(4-Hydroxy-butoxy)styrene (7). The deprotected **7** was prepared from **6** as described under "Ring-Closing of α-(4-Hydroxybutoxy)styrene upon Heating" and was subjected to an analogous ether/water workup. The isolated crude **7** was thereupon heated in the presence or absence of $Pd(OAc)_2$, with added acids (HOAc or NH_4Br) or without added acids. In a screw-capped Pyrex tube were suspended $Pd(OAc)_2$, if present (0.00175 g, 0.0078 mmol), and DPPP (0.00645 g, 0.0156 mmol) in 1.0 mL of dry DMF under nitrogen. To the mixture were added Et_3N (0.039 g, 0.39 mmol) and crude **7** (0.050 g, ∼0.26 mmol) together with the acids, if present (anhydrous HOAc (0.3 mL), or NH_4Br (0.061 g, 0.62 mmol)). The tube was purged with nitrogen for 20 s, sealed, and stirred in an oil bath at 80 °C for 16 h. After cooling, the reaction mixture was poured into an aqueous solution of K_2CO_3 (10%, 10 mL) and was extracted with diethyl ether (2 × 10 mL). The combined organic layers were washed with saturated NaCl solution (10 mL), dried over K_2CO_3, and concentrated. The resulting crude products were analyzed by GC-MS and ^{1}H NMR. In summary, the reactions conducted in absence of added acid produced no cyclized product while all reactions with added HOAc or NH_4Br afforded ring-closure. The reactions performed with HOAc resulted in complete ketalization, but the use of NH_4Br provided mixtures of ketal **3b** and vinyl ether **7** (**3b**/**7** ≈ 2). The addition of $Pd(OAc)_2$ did not promote cyclization.

Acknowledgment. We thank the Swedish Natural Science Research Council for financial support and Dr. Staffan Sundell for performing the X-ray structure analysis of $Pd(0)DPPP_2$.

JO971454Q

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