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Hydrogenolysis of α,β-Epoxyketone and Ester to Aldol in Pd(0)/HCOOH/Et$_3$N and H$_2$/Pd/C Reduction Media

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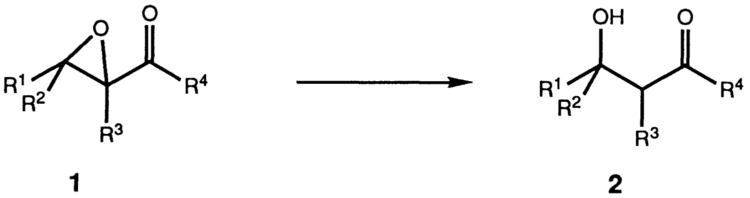
Hydrogenation of α,β-epoxycarbonyl compounds by using several catalysts and hydride sources was studied to obtain the corresponding β-hydroxy substrates.

β-Hydroxy carbonyl functionality which can be generally obtained by aldol reaction often appears as a partial structure in natural products.$^{1)}$ However, the aldol moiety is not always constructed by a conventional aldol reaction. Reductive cleavage of epoxyketone becomes an important choice in some cases. Many reagents are now available to achieve such reduction, but stoichiometric amounts of toxic reagents are often required.$^{2)}$ Recently, a new methodology has also been developed in our laboratory by use of a catalytic amount of selenide or telluride reagent as a mediator in an electrochemical system.$^{3)}$

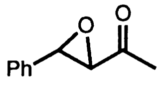
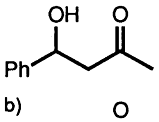
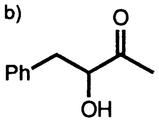
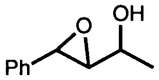
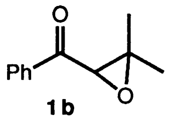
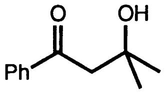
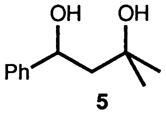
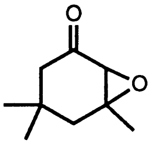
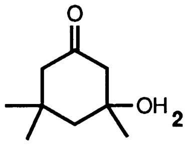
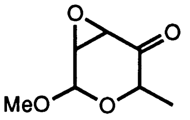
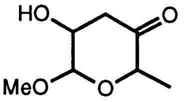
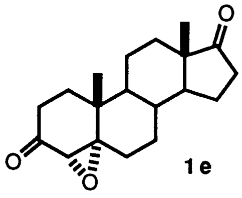
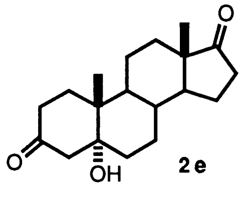
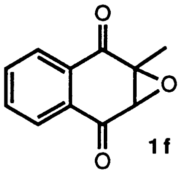
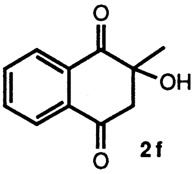
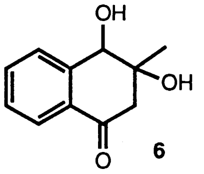
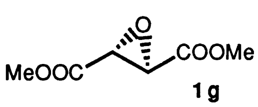
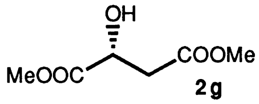
On the other hand, the palladium catalyzed rearrangement of α,β-epoxyketones to β-diketones has been reported.$^{4)}$ The combination of ammonium formate and Pd(0) is known to work as a mild reducing agent and has been widely used in the reduction of a number of functional groups.$^{5)}$ Such informations enabled us to examine a palladium catalyzed transformation of α,β-epoxycarbonyl compounds to aldols. Herein, we would like to report simple procedures to reduce epoxyketones and esters to the corresponding aldols by two different methods. One is a reduction with triethylammonium formate in the presence of palladium catalysts such as palladium acetate and dppe (method A) and the other is a hydrogenation in a Pd/C-THF system (method B).$^{6)}$



1 **2**

General procedures are as follows: [Method A] a mixture of substrate **1** (1 mmol), palladium acetate (0.05 mmol), dppe (0.1 mmol), triethylamine (2 mmol), and formic acid (2 mmol) in THF (3 ml) was refluxed under argon atmosphere. The usual workup and the purification by column chromatography gave the product **2**. [Method B] a mixture of substrate **1** (1 mmol) and 5%-Pd/C (100 mg) in THF (3 ml) was stirred under hydrogen atmosphere (1 atm) at room temperature. Filtration through a short celite pad followed by chromatography afforded **2**. The results are summarized in Table 1.

Table1. Palladium catalyzed reduction of α,β-epoxycarbonyl compounds

Entry	Substrate	Conditions	Products[a)]	Yield / %
1	 **1a**	$Pd(OAc)_2$, dppe HCOOH, Et_3N (A)	 **2a**	96
2	**1a**	$Pd(OAc)_2$, HCOOH, Et_3N [b)]	 **3**	81
3	**1a**	Pd/C, HCOOH, Et_3N [c)]	**3**	66
4	**1a**	Pd/C, H_2 (B)	**3**	81
5	**1a**	PtO_2, H_2 [d)]	 **4**	69
6	 **1b**	A	 **2b** 99  **5**	–
7		B	**2b** – **5**	89
8	 **1c**	A	 **2c**	41
9		B		55
10	 **1d** [e)]	A	 **2d** [e)]	–
11		B		76
12	 **1e**	A	 **2e**	–
13		B		76
14	 **1f**	A	 **2f** 54  **6**	–
15		B	**2f** – **6**	80
16	 **1g**	A	 **2g**	–
17		B		99

a) All products showed satisfactory spectra containing ^1H NMR and ^{13}C NMR and IR.

b) Carried out in the presence of $Pd(OAc)_2$ (5 mol%), HCOOH (2 equiv.), and Et_3N (2 equiv.) in refluxing THF. c) Carried out in the presence of Pd/C (100 mg for 1mmol of **1a**), HCOOH (2 equiv.), and Et_3N (2 equiv.) in refluxing THF. d) Carried out in the presence of PtO_2 (12 mg for 1mmol of **1a**) under H_2 atmosphere (1atm) in THF. e) Mixture of diastereomers.

Several hydrogenolysis conditions were examined for the present purpose. As shown in Entry 1, the reduction of **1a** with triethylammonium formate in the presence of palladium acetate and dppe proceeded smoothly to provide the corresponding aldol **2a** in 96% yield.$^{7)}$ However, lack of the phosphine ligand caused to cleave the benzylic position selectively to give the acyloin **3** (Entry 2). The same results were obtained by use of palladium on charcoal (Entries 3 and 4).$^{8)}$ On the other hand, hydrogenation over platinum oxide gave the epoxy alcohol **4** as a diastereomeric mixture (Entry 5). Reduction of **1b** under the condition A gave **2b** quantitatively (Entry 6). Hydrogenolysis of **1b** (Entry 7), however, produced 1,3-diol **5**, because the aromatic ketone is susceptible toward the condition B. The aliphatic compound **1c** can be also reduced, but the product **2c** is not stable enough to tolerate the condition A (Entry 8). Isophorone was obtained in 48% yield along with 41% of the aldol **2c**. Since Pd(0) species are sensitive to steric bulkiness,$^{4,5)}$ the sterically congested epoxyketone **1e** was recovered under the condition A (Entry 12). In contrast, simple hydrogenolysis of **1e** gave **2e** in 76% yield (Entry 13). Selective cleavage of the epoxide **1f** at the secondary position occurred under the condition A to give **2f** (Entry 14), however, further reduction to **6** proceeded under the condition B (Entry 15).

Reduction of the epoxyester **1g** was also attempted (Entries 16 and 17). The condition B gave rise to an unnatural form of dimethyl malate (**2g**, $[\alpha]_D$ +10.7 (c 3.3, EtOH); lit.$^{9)}$ +9.5 (c 2.5, EtOH)) in a quantitative yield. Thus obtained **2g** which can be also prepared in several ways from tartrate$^{9)}$ is a versatile building block for natural product syntheses.$^{10)}$

In conclusion, the hydrogenolysis over palladium on charcoal was found to be effective for the reductive cleavage of the α,β-epoxycarbonyl compounds, where benzyl group could not be compatible. On the other hand, the reduction with formate by homogeneous palladium catalyst is useful but sensitive to the steric congestion of the substrate. These simple procedures can be conducted under mild conditions, so that such complementary manners open acceptable ways to aldol derivatives.

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3) T. Inokuchi, M. Kusumoto, and S. Torii, J. Org. Chem., in press.

4) M. Suzuki, A. Watanabe, and R. Noyori, J. Am. Chem. Soc., 102, 2095 (1980).

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6) Hydrogenation on Pd/C in methanol has been carried out in macrolide synthesis; E. J. Corey, K. C. Nicolaou, and L. S. Melvin Jr., J. Am. Chem. Soc., 97, 654 (1975). However, to our knowledge, the scope and the limitation of the hydrogenolysis were not investigated.

7) The following reaction path is plausible. Nucleophilic opening of the epoxide ring with Pd(0) gives **7**. Reaction of **7** with formate produces **8**, which undergoes decarboxylation followed by reductive elimination to afford the expected compound **2**.

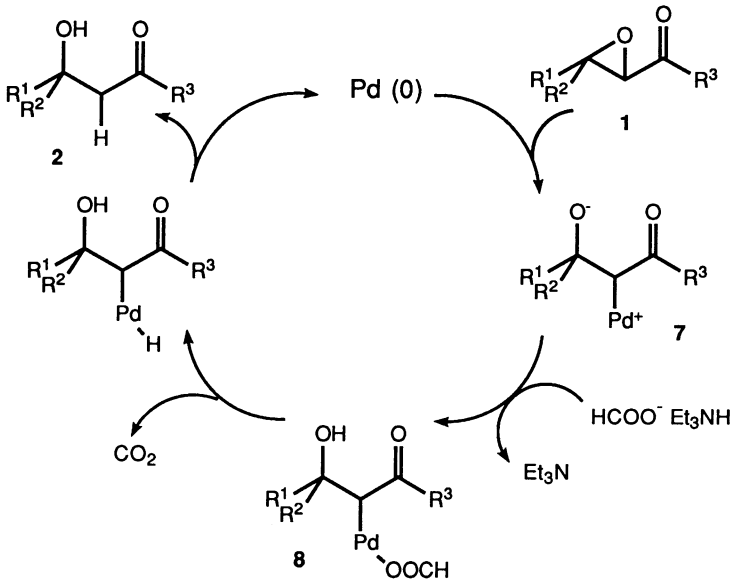

Fig. 1. Plausible reaction path.

8) The reductive deprotection of benzyl group under this condition is known: see Ref. 5.

9) H. Wynberg and E. G. J. Staring, J. Am. Chem. Soc., 104, 166 (1982); S. Henrot, M. Larcheveque, and Y. Petit, Synth. Commun., 16, 183 (1986); E. J. Corey, A. Marfat, and D. J. Hoover, Tetrahedron Lett., 22, 1587 (1981); E. Hungerbuler, D. Seebach, and D. Wasmuth, Helv. Chim. Acta, 64, 1467 (1981); M. Alpegiani and S. Hanessian, J. Org. Chem., 52, 278 (1987).

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