Catalytic Method for the Reduction of Lactones to Lactols

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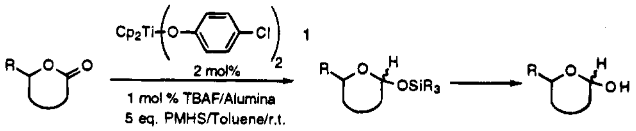
The development of selective catalysts for use in organic synthesis is of great current interest.[1,2] Additional challenges to the chemist include the development of processes which employ easily manipulated reagents, and which can be carried out at ambient temperature without the need for rigorously anhydrous and/or anaerobic conditions. For a long time diisobutylaluminum hydride (DIBALH) has been the reagent of choice for the reduction of lactones to lactols.[3] While its utility has been demonstrated innumerable times, it is not without drawbacks. First, reactions which employ DIBALH for this transformation must be carried out at low temperature, usually −78 °C. In addition, a stoichiometric quantity of an air- and moisture-sensitive reagent must be used. In this paper we describe an efficient catalytic process for the conversion of lactones to lactols. It should be noted that the overall transformation proceeds at room temperature and pressure and uses inexpensive, air-stable materials.

In the past few years we have reported several titanium-based catalyst systems for the reduction of esters to primary alcohols.[4] While we have had success in developing catalysts for this transformation, the development of a related protocol with which to effect the partial reduction of esters to the corresponding aldehydes has proved elusive.[5] A subset of this transformation is the reduction of lactones to lactols. Recently we discovered that the species generated by the addition of 2 equiv of *n*-BuLi[6] to Cp_2TiCl_2 in the presence of a silane is capable of catalyzing the conversion of lactones to their silyl lactols.[4d] This discovery prompted us to investigate whether we could develop this initial finding into a useful catalyst system.

Moreau and co-workers recently reported that titanocene bis(phenoxides) are capable of polymerizing primary silanes at 50 °C or below.[7] We reasoned that the active catalyst in this process was related to the Cp_2Ti-H species which we believe is the active catalyst in our ester reduction protocol. It was in this context that we studied whether the combination of $Cp_2Ti(p\text{-}ClC_6H_4O)_2$ (**1**)[8] with polymethylhydrosiloxane (PMHS)[9] could be employed for the partial reduction of lactones. As shown in Scheme 1, ~2 mol % of **1** in the presence of a subcatalytic amount of TBAF and 5 equiv of PMHS is an active catalyst system for lactone hydrosilylation.[10] It is of considerable interest that the entire process is carried out at room temperature. A simple workup (aqueous NaOH or TBAF/H_2O) yields the free lactols, usually in excellent yield. In order to explore the scope of this new method, the reduction of a series of substrates was investigated (Table 1). The procedure has been shown to be extremely efficient for a great variety of five- and six-membered ring lactones, affording the corresponding lactols in high yields. In general, 2 mol % of the catalyst was used; however, the proportion of the titanium catalyst can be reduced to 0.5 mol % without any decrease in yield (entry 2). The system tolerates aromatic halides (entries 7, 8) as well as α-substituted lactones (entries 10−12). When optically pure lactones were reduced, no sign of epimerization of the chiral center α to the carbonyl was observed (entries 10, 12).

Scheme 1



Although an exhaustive study has not yet been undertaken, we have found some limitations. For example, hydrosilylation of the sterically hindered substrate α,α-diphenyl-γ-butyrolactone led to a 1:1 mixture of lactol/diol, whereas the reduction of a larger ring lactone, ϵ-caprolactone, gave the corresponding diol as the sole product.

While we have not examined the mechanism in detail, the outcome of the reaction can be rationalized as shown in Scheme 2. As previously, we assume that titanocene(III) hydride **2** or its equivalent is the active catalyst.[4a,11,12] Initial insertion of the lactone into the titanium−hydrogen bond affords the titanium

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(1) Hydrosilylation: (a) Brunner, H.; Nishiyama, H.; Itoh, K. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993; Chapter 6. (b) Nishiyama, H.; Yamaguchi, S.; Park, S. B.; Itoh, K. *Tetrahedron: Asymmetry* **1993**, *4*, 143 and references therein.

(2) Hydrogenation: (a) Takaya, H.; Ohta, T.; Noyori, R. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993; Chapter 1. (b) Noyori, R. *Asymmetric Catalysis In Organic Synthesis*; John Wiley & Sons, Inc.: New York, 1994; Chapter 2.

(3) (a) Winterfeldt, E. *Synthesis* **1975**, 617. (b) Bloch, R.; Gilbert, L. *J. Org. Chem.* **1987**, *52*, 4603. (c) Suginome, H.; Yamada, S. *J. Org. Chem.* **1985**, *50*, 2489.

(4) (a) Berk, S. C.; Kreutzer, K. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1991**, *113*, 5093. (b) Berk, S. C.; Buchwald, S. L. *J. Org. Chem.* **1992**, *57*, 3751. (c) Barr, K. J.; Berk, S. C.; Buchwald, S. L. *J. Org. Chem.* **1994**, *59*, 4323. (d) Berk, S. C, Ph.D. Thesis, Massachusetts Institute of Technology, 1994.

(5) (a) Larock, R. C. *Comprehensive Organic Transformations: A guide to Functional Group Preparations*; VCH Publishers: New York, 1989; pp 621−622 and references therein. For other examples of reduction from the carboxylic acid oxidation state to the aldehyde oxidation state, see: (b) Corriu, R. J. P.; Lanneau, G. F.; Perrot, M. *Tetrahedron Lett.* **1987**, *28*, 3941; (c) **1988**, *29*, 1271. (d) Yoon, N. M.; Ahn, J. H.; An, D. K.; Shon, Y. S. *J. Org. Chem.* **1993**, *58*, 1941. (e) Fukuyama, T.; Lin, S.-C.; Li, L. *J. Am. Chem. Soc.* **1990**, *112*, 7050.

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(7) Bourg, S.; Corriu, R. J. P.; Enders, M.; Moreau, J. J. E. *Organometallics* **1995**, *14*, 564.

(8) Titanocene bis(phenoxides) can be easily prepared from Cp_2TiCl_2 and the corresponding phenols in one step. They are crystalline, air-stable complexes; see: Andra, K. *J. Organomet. Chem.* **1968**, *11*, 567.

(9) For the use of polymethylhydrosiloxane as a reducing agent, see: (a) Lipowitz, J.; Bowman, S. A. *J. Org. Chem.* **1973**, *38*, 162. (b) Coumbe, T.; Lawrence, N. J.; Muhammad, F. *Tetrahedron Lett.* **1994**, *35*, 625. Jaxa-Chamiec, A.; Shah, V. P.; Kruse, L. I. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1705.

(10) (a) Typical experimental procedure: In a dry Schlenk flask under argon were added $Cp_2Ti(p\text{-}ClC_6H_4O)_2$ (21 mg, 0.05 mmol), TBAF on alumina (15%) (40 mg, 0.025 mmol), and 3 mL of dry toluene. To the orange slurry was added PMHS (0.75 mL, 12.5 mmol) *via* syringe, resulting in a small amount of bubbling. The reaction mixture was stirred at room temperature for 5−10 min, resulting in a change in color from orange to dark blue. The reaction mixture was cooled with a cold water bath, and δ-decanolactone (0.45 mL, 2.5 mmol) was added dropwise *via* syringe. The reaction mixture was stirred at room temperature and monitored by TLC. After consumption of the starting material was complete (0.5−5 h), the catalyst was deactivated by exposure to air and the reaction mixture was diluted with THF (10 mL) and treated with 1 M NaOH (15 mL). [**CAUTION:** vigorous bubbling!]. The two-phase mixture was stirred for 1 h or until the organic layer became clear. The organic layer was diluted with ether, extracted twice with 1 M NaOH, washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. Flash column chromatography (SiO_2, hexane/EtOAc) afforded 407 mg of the corresponding lactol (94%). (b) An alternative workup for base-sensitive compounds proceeds as follows: The toluene was removed *in vacuo* and the residue dissolved in THF (15 mL). Water (0.3 mL) and 1 M TBAF/THF (0.3 mL) were added [**CAUTION:** vigorous bubbling!], and the reaction mixture was refluxed for 2 h. The resultant precipitate was removed by filtration and the filtrate dried ($MgSO_4$), evaporated *in vacuo*, and purified by flash column chromatography. (c) In some cases, activation of the precatalyst (color change to blue) required warming to 50−70 °C for several minutes. (d) In certain examples, prior filtration of the starting lactone through neutral alumina was necessary in order for the reaction to go to completion.

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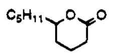
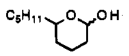
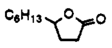
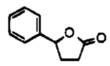
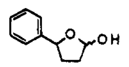
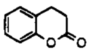
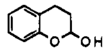
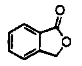
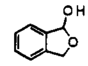
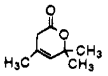
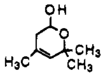
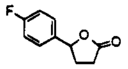
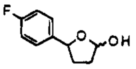
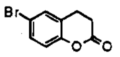
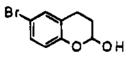
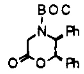
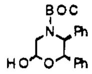
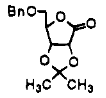
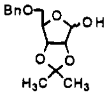
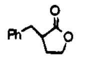
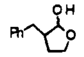
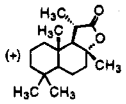
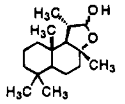
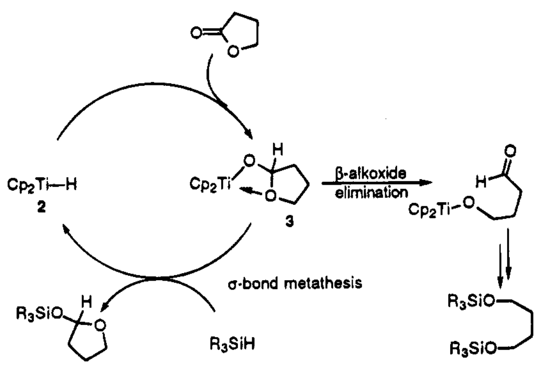
Table 1

Entry	Lactone	Lactol	mol % cat.	workup[a]	Yield (%)[b]
1			2	A	94[c]
2			0.5	A	97[d]
3			2	A	96
4			2	B	87[e]
5			2	B	75[f]
6			2	A	89
7			2	A	96
8			5	B	69[g]
9			5	A	92[h]
10			2	A	91
11			2	A	93
12			3	A	94[i]

[a] Workup A: THF/1 M NaOH, 1 h room temperature. Workup B: H_2O/1 M TBAF in THF, reflux 2 h. [b] Yields refer to isolated products of >95% pure material. Unless otherwise noted, no diol detected in the crude ^{1}H NMR. All compounds were characterized by IR, ^{1}H NMR, and ^{13}C NMR. [c] Lactol/diol ratio = 70/1 (GC). [d] Lactol/diol ratio >40/1. The same reaction was run using 1 mol % catalyst on a 100 mmol scale (93% yield). [e] Lactol/diol ratio = 30/1. [f] Lactol/diol ratio = 5.5/1. [g] 5 mol % catalyst was required for the reaction to go to completion. [h] THF was used as a solvent. [i] Oxidation back to the lactone with PCC/CH_2Cl_2 at room temperature gave a single diastereomer (GC and ^{1}H NMR).

Scheme 2



alkoxide **3**, in which the ring oxygen atom is coordinated to titanium. Alkoxide **3** may then participate in a σ-bond metathesis[13] process with a silane to regenerate the titanium hydride with concomitant generation of the silylated lactol. At this stage, the role of the fluoride is unclear. Control experiments indicate that it is not simply enhancing the silane reactivity *via* a pentacovalent silicon species.[14] Since similar results have been observed when the precatalyst is activated with a small amount of $PhSiH_3$ in the absence of TBAF, we believe that the fluoride ion only participates in the catalyst activation process.

In summary, we have developed an efficient catalytic process for the conversion of five- and six-membered ring lactones to lactols. The reaction proceeds at room temperature and uses air-stable, inexpensive PMHS as a hydride source. These features make this new procedure an attractive alternative to DIBALH. Studies to clarify the reaction mechanism and to further determine the scope of this and related transformations are in progress.

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Supporting Information Available: Detailed experimental procedures for the reduction of lactones as well as spectroscopic and analytical characterization of the products listed in Table 1 (7 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(11) It is possible that several titanium species are present in the reaction mixture. Titanium(III) hydrides, silyltitanium(IV) hydrides, bimetallic silyltitanium hydrides, and bimetallic titanium hydrides have been reported in the literature and may be able to reduce carbonyl groups.[12]

(12) (a) Harrod, J. F.; Mu, Y.; Samuel, E. *Can. J. Chem.* **1992**, 2980. (b) Harrod, J. F.; Ziegler, T.; Tschink, V. *Organometallics* **1990**, *9*, 897. (c) Samuel, E.; Mu, Y.; Harrod, J. F.; Dromzee, Y.; Jeannin, Y. *J. Am. Chem. Soc.* **1990**, *112*, 3435. (d) Aitken, C. T.; Harrod, J. F.; Samuel, E. *J. Am. Chem. Soc.* **1986**, *108*, 4059.

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