Reduction of Aldehydes and Ketones by Transfer Hydrogenation with 1,4-Butanediol
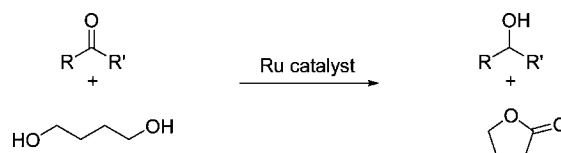
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**ABSTRACT**

1,4-Butanediol has been used as the hydrogen donor in transfer hydrogenation reactions. The equilibrium is driven by the formation of γ-butyrolactone, and the diol is therefore not required in excess.

Transfer hydrogenation reactions are widely used for the reduction of ketones and aldehydes.[1] Isopropanol is often used as a convenient hydrogen donor but is required in excess in order to drive the reduction process. Thus, for the reduction of a ketone with a similar oxidation potential to acetone, the addition of 50 equiv of isopropanol will be required to give a 1:50 ratio of ketone **1** to alcohol **2** (Scheme 1).

Scheme 1. Equilibrium in Transfer Hydrogenation Reactions
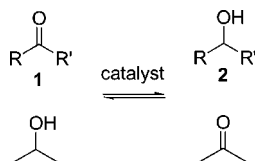
However, for ketones with oxidation potentials that are different from acetone, the equilibrium position is shifted in favor of the more stable ketone. For example, the addition

of 50 equiv of isopropanol to acetophenone will reach an equilibrium position at approximately 96% conversion.[2]

We therefore wished to identify an alcohol which could donate hydrogen essentially irreversibly and thereby overcome the equilibrium problem inherent with using isopropanol. Alternative (nonalcoholic) hydride donors such as triethylamine/formic acid[3] and Hantzsch esters[4] have been used in the reduction of carbonyl compounds.

We have previously reported that levulinic acid ($CH_3COCH_2CH_2CO_2H$) is a good hydrogen acceptor since the alcohol that is formed readily lactonizes, driving the equilibrium for oxidation of alcohols.[5] We chose to investigate the use of diols as reducing agents, since they would be expected to undergo lactol formation and further oxidation to the lactone, as shown in Scheme 2. Although diols have previously been oxidized to lactones using ruthenium catalyzed transfer hydrogenation[6] and dehydrogenation,[7] we

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(1) (a) Zassinovich, G.; Mestroni, G.; Gladiali, S. *Chem. Rev.* **1992**, *92*, 1051. (b) Palmer, M. J.; Wills, M. *Tetrahedron: Asymmetry* **1999**, *10*, 2045. (c) Gladiali, S.; Alberico, E. *Chem. Soc. Rev.* **2006**, *35*, 226.

(2) Adkins, H.; Elofson, R. M.; Rossow, A. G.; Robinson, C. C. *J. Am. Chem. Soc.* **1949**, *71*, 3622.
(3) Fujii, A.; Hashiguchi, S.; Uematsu, N.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 2521.
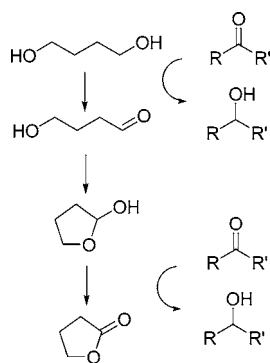(4) Yang, J. W.; List, B. *Org. Lett.* **2006**, *8*, 5653.
(5) Wise, N. J.; Williams, J. M. J. *Tetrahedron Lett.* **2007**, *48*, 3639.
(6) (a) Murahashi, S. I.; Naota, T.; Ito, K.; Maeda, Y.; Taki, H. *J. Org. Chem.* **1987**, *52*, 4319. (b) Lin, Y. R.; Zhu, X. C.; Zhou, Y. F. *J. Organomet. Chem.* **1992**, *429*, 269. (c) Suzuki, T.; Morita, K.; Tsuchida, M.; Hiroi, K. *Org. Lett.* **2002**, *4*, 2361.

Scheme 2. 1,4-Butanediol as a Hydrogen Donor

are unaware of the use of diols as the stoichiometric reducing agent for a range of carbonyl compounds.

We have recently been using $Ru(PPh_3)_3(CO)H_2$ in the presence of bidentate phosphine ligands to catalyze transfer hydrogenation reactions.[8] We therefore chose to use this catalyst to assess the viability of diols as reducing agents.

Scheme 3. Reduction of Propiophenone by Transfer Hydrogenation[a]
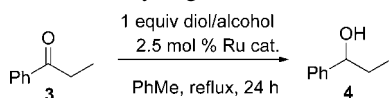
[a] Ru cat. = $Ru(PPh_3)_3(CO)H_2$.

In preliminary experiments, we examined the reduction of propiophenone **3** to 1-phenylpropanol **4** using $Ru(PPh_3)_3$-$(CO)H_2$ with a variety of diols in comparison with alcohols (Scheme 3, Table 1).

**Table 1.** Diols and Alcohols Used in the Reduction of Propiophenone

entry	diol/alcohol	conversion (%)[a]
1	*n*-butanol	6
2	*tert*-butanol	0
3	1,3-propanediol	9
4	1,4-butanediol	96
5	1,5-pentanediol	50
6	1,6-hexanediol	26

[a] Determined from the ^{1}H NMR spectrum.

As expected, the use of *n*-butanol (entry 1) led to a low conversion in the reduction of propiophenone **3**. The equilibrium is disfavored by the relatively low stability of butanal

with respect to propiophenone **3**. With no α-hydrogens, *tert*-butanol is totally unsuccessful as a reducing agent. However, the diols were all more successful than the use of a primary alcohol, with 1,4-butanediol providing a promising conversion under these conditions. The presence of unreacted diol and lactone was observed in the ^{1}H NMR spectrum, although there was no evidence of the presumed intermediate lactol.

We then applied the use of 1,4-butanediol as a reducing agent to the conversion of a range of carbonyl compounds (Scheme 4, Table 2). The use of (o-$Ph_2PC_6H_4$)$_2$O (DPEphos)

Scheme 4. Reduction of Other Carbonyl Compounds with 1,4-Butanediol
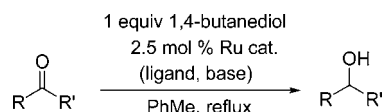
and potassium *tert*-butoxide as additives provided a slightly more reactive catalyst.

Table 2. Alcohols Formed by Reduction of the Carbonyl Compound with 1,4-Butanediol

entry	alcohol formed	conversion (%)[a]
1		91[b]
2		87
3		98 (79)[b]
4		90 (84)[b]
5		92 (88)[b]
6		100 (91)
7		100
8		100 (61)[c]
9		100 (81)
10		100 (82)[b]
11		100 (92)

[a] Reactions were carried out using $Ru(PPh_3)_3(CO)H_2$ (2.5 mol %), DPEphos (2.5 mol %), *t*-BuOK (5 mol %) with 1,4-butanediol (1 equiv) on a 1 mmol scale in 1 mL of toluene at reflux for 24 h. Isolated yields are given in parentheses. [b] 48 h. [c] We assume that the lower isolated yield is due to the volatility of cyclohexanol.

(7) (a) Ichikawa, N.; Sato, S.; Takahashi, R.; Sodesawa, T.; Inui, K. *J. Mol. Catal. A: Chem.* **2004**, *212*, 197. (b) Zhao, J.; Hartwig, J. F. *Organometallics* **2005**, *24*, 2441.

(8) Slatford, P. A.; Whittlesey, M. K.; Williams, J. M. J. *Tetrahedron Lett.* **2006**, *47*, 6787.

All of the ketones were successfully reduced using 1,4-butanediol, even tetralone (entry 1) and *p*-methoxyacetophenone (entry 2) which are particularly stable, although longer reaction times were required to achieve reduction. Other aryl alkyl ketones (entries 3−5), dialkyl ketones (entries 6−8), and aldehydes (entries 9−11) were also successfully reduced.

Although isolation of the alcohols by column chromatography was convenient, we have also demonstrated that the alcohol can be purified by treatment with aqueous sodium hydroxide. 1,4-Butanediol is water soluble, and treatment of γ-butyrolactone with 2 M NaOH led to hydrolysis, leaving only the alcohol behind in the organic solvent. Using this method, benzyl alcohol and cyclohexanol were recovered unchanged from a 1:1:1 mixture of alcohol, γ-butyrolactone and 1,4-butanediol.

We were interested in combining the use of 1,4-butanediol as a reducing agent with the use of methyl levulinate as an oxidant, and this process led to the formation of the lactones **5** and **6** as shown in Scheme 5.

Scheme 5. Combined Use of 1,4-Butanediol with Methyl Levulinate Leading to Two Lactones[a]
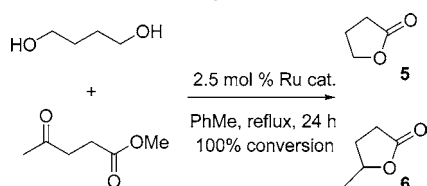

[a] Ru cat. = Ru(PPh₃)₃(CO)H₂, DPEphos, *t*-BuOK (1:1:2).

Having established that 1,4-butanediol could be successfully used as the stoichiometric reducing agent in transfer hydrogenation reactions, we wished to evaluate the use of this reagent in asymmetric transfer hydrogenation. The Noyori catalyst derived from [Ru(*p*-cymene)Cl₂]₂ and (*S,S*)-TsDPEN is known to be highly selective for the reduction of ketones using isopropanol in excess as the reducing agent.[9] We found that, although 1,4-butanediol could be used in this

(9) Hashiguchi, S.; Fujii, A.; Takahara, J.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc*. **1995**, *117*, 7562.

Scheme 6. Transfer Hydrogenation with Noyori Catalyst[a]
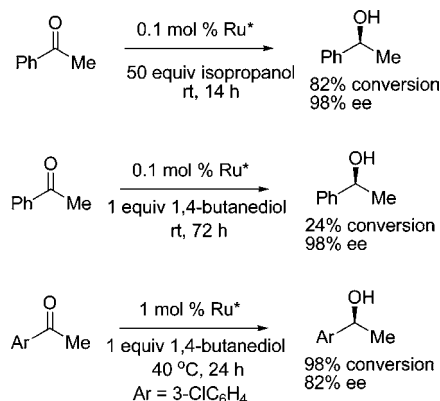
[a] Ru* = [Ru(*p*-cymene)Cl₂]₂/(*S,S*)-TsDPEN/KOH (1:4:8).

process, the reaction rate was significantly lower than with isopropanol (Scheme 6). With 50 equiv of isopropanol, we achieved an 82% conversion in 14 h, whereas with one equivalent of isopropanol, only 24% conversion was achieved, even after 72 h. Increasing the catalyst loading and temperature led to almost complete reduction of 3-chloroacetophenone but with a reduced enantioselectivity, presumably due to the higher temperature employed.

We assume that the slower rate observed with 1,4-butanediol is a consequence of the initial oxidation of a primary alcohol to the aldehyde, which is less favorable than oxidation of a secondary alcohol to a ketone.

In summary, we have demonstrated that 1,4-butanediol can be used for the reduction of carbonyl compounds by transfer hydrogenation. An excess of this reagent is not required due to the formation of γ-butyrolactone. We are currently exploring the scope of this process with alternative catalysts.

Supporting Information Available: Experimental procedures and compound characterization are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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