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Brønsted Acid Catalyzed Asymmetric Reduction of Ketones and Acyl Silanes Using Chiral *anti*-Pentane-2,4-diol

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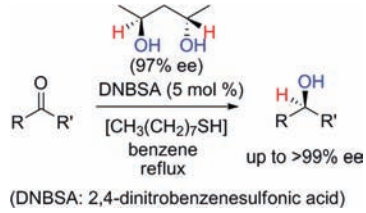
ABSTRACT



Ketones and acyl silanes were reduced to the corresponding alcohols by a simple procedure employing *anti*-1,3-diol and a catalytic amount (5 mol %) of 2,4-dinitrobenzenesulfonic acid in benzene at reflux. Asymmetric induction reached up to >99% ee when a chiral pentane-2,4-diol of 97% ee was used.

Ketone reduction to the corresponding secondary alcohol is undoubtedly an important and fundamental reaction in organic synthesis. A number of methods for the reduction of ketones and reducing agents have been developed,[1] and asymmetric reduction has also been studied extensively over the past few decades.[2] Meerwein−Ponndorf−Verley (MPV) reduction, which has long been known from the independent discoveries of Meerwein, Ponndorf, and Verley, has distinctive usefulness in organic synthesis.[3] Various modifications and improvements of the MPV reduction have been studied by using metal alkoxides (usually aluminum alkoxides) as reducing agents.[4] A metal ion activates the carbonyl group to be reduced and also promotes hydrogen transfer from the C−H bond of the alcohol. We report here a metal-free asymmetric reduction of ketones that uses a chiral *anti*-1,3-diol under the catalysis of a Brønsted acid. In this reduction, the 1,3-diol works as a reducing agent and does not give an acetal. Remarkably, a higher reactivity of acyl silanes than aliphatic ketones is noted.

In the course of our study on stereoselective reduction of 24-oxocholesterol derivatives,[5] we tried to prepare a chiral acetal **3** derived from 24-oxocholesteryl benzoate **1** and (2*S*,4*S*)-pentane-2,4-diol **2** in order to test the diastereoselective reduction of acetal **3** with aluminum hydride reagents, as reported by Yamamoto.[6] Acetalization employing diol **2** and pyridinium *p*-toluenesulfonate (PPTS) in benzene at reflux with continuous azeotropic removal of water gave

(1) (a) *Handbook of Reagents for Organic Synthesis, Oxidizing and Reducing Agents*; Burke, S. D., Danheiser, R. L., Ed.; Wiley: New York, 1999. (b) *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Ed.; Pergamon Press: New York, 1991; Vol. 8.

(2) (a) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Ed.; Springer: New York, 1999. (b) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994. (c) Noyori, R.; Ohkuma, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 40–73.

(3) Review: Wilds, A. L. *Org. React.* **1944**, *2*, 178–223.

(4) (a) Evans, D. A.; Nelson, S. G.; Gagne, M. R.; Muci, A. R. *J. Am. Chem. Soc.* **1993**, *115*, 9800–9801. (b) Fujita, M.; Takarada, Y.; Sugimura, T.; Tai, A. *Chem. Commun.* **1997**, 1631–1632. (c) Ooi, T.; Miura, T.; Maruoka, K. *Angew. Chem., Int. Ed.* **1998**, *37*, 2347–2349. (d) Ooi, T.; Itagaki, Y.; Miura, T.; Maruoka, K. *Tetrahedron Lett.* **1999**, *40*, 2137–2138. (e) Campbell, E. J.; Zhou, H.; Nguyen, S. T. *Org. Lett.* **2001**, *3*, 23912393. (f) Campbell, E. J.; Zhou, H.; Nguyen SonBinh, T. *Angew. Chem., Int. Ed.* **2002**, *41*, 1020–1022.

(5) Matsuo, J.; Kozai, T.; Nishikawa, O.; Hattori, Y.; Ishibashi, H. *J. Org. Chem.* **2008**, *73*, 6902–6904.

(6) (a) Mori, A.; Fujiwara, J.; Maruoka, K.; Yamamoto, H. *Tetrahedron Lett.* **1983**, *24*, 4581–4584. (b) Mori, A.; Fujiwara, J.; Maruoka, K.; Yamamoto, H. *J. Organomet. Chem.* **1985**, *285*, 83–94.

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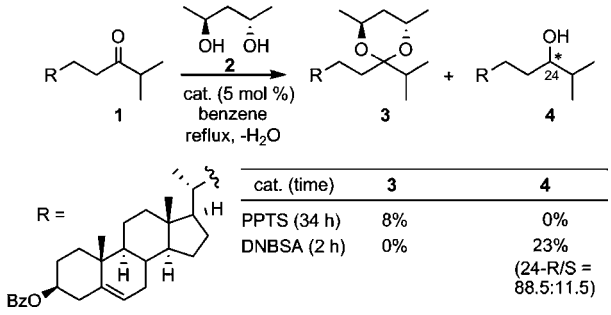
acetal **3** in only 8% yield, probably due to steric hindrance[7] around the carbonyl group of **1** (Scheme 1). In the screening

Scheme 1. Brønsted Acid Controlled Selectivity between Acetalization and Reduction of Ketone **1** with Diol **2** (97% ee)



cat. (time)	3	4
PPTS (34 h)	8%	0%
DNBSA (2 h)	0%	23% (24-R/S = 88.5:11.5)

of other catalysts for the acetalization,[8] it was unexpectedly found that the use of 2,4-dinitrobenzenesulfonic acid (DNBSA) did not give the desired acetal **3** but gave alcohol **4** directly in 23% yield (24-*R*/*S* = 88.5:11.5, Scheme 1). Thus, diol **2** reduced ketone **1** by the catalysis of DNBSA. Brønsted acid-catalyzed reduction of ketones with alcohols[1b,9] has not been reported to date, and the observed high stereoselectivity, which is better than that of Corey−Bakshi−Shibata (CBS) reduction[10] (24-*R*/*S* = 76:24[5]), prompted us to investigate this reduction in more detail.

First, various 1,3-diols including **2** were employed in the DNBSA-catalyzed reduction of ketone **5** to the corresponding alcohol **6** in order to investigate what structural factors in diols were needed for reduction of the ketone (Table 1). The use of 1,3-propanediol and **2** gave **6** in 9% and 27% yields, respectively, whereas *meso*-*syn*-1,3-diol **7** gave the corresponding acetal **8** in 55% yield along with a trace amount of **6** (entries 1−3). Since the use of *anti*-1,2-diol and *anti*-1,4-diol did not give the reduction product **6**,[11] the *anti*-1,3-diol structure was essential for smooth reduction of the ketone. The employment of (±)-*anti*-diol **9**, which did not have any hydrogens at its 3-position, did not give **6** but afforded *β*-alkoxy ketone **10** in 32% yield (entry 4). When a sterically demanding (±)-diol **11** was used, the yield of reduction product **6** increased to 46% yield (entry 5). Next, an additive to improve efficiency in reduction of ketone **5** with diol **2** was explored. After extensive trials, it was found that addition of 1.1 equiv of octanethiol improved the yield of alcohol **6** to 62% yield.[12] In this case, *β*-octylthio ketone **12** and *β*-octylthio alcohol **13** were also isolated in 52% and

(7) Dauben, W. G.; Gerdes, J. M.; Look, G. C. *J. Org. Chem.* **1986**, *51*, 4964–4970.

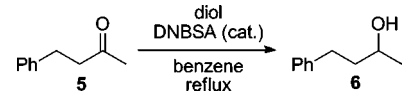
(8) Acetalization using TsOH gave **3** in 12% yield along with 4% yield of **4**.

(9) For the combined use of aluminum alkoxides and Brønsted acids, see : (a) Kow, R.; Nygren, R.; Rathke, M. W. *J. Org. Chem.* **1977**, *42*, 826–827. (b) Akamanchi, K. G.; Varalakshmy, N. R. *Tetrahedron Lett.* **1995**, *36*, 3571–3572.

(10) (a) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986–2012. (b) Itsuno, S. *Org. React.* **1998**, *52*, 395–576.

(11) (2*R*,3*R*)-Butane-2,3-diol and (2*S*,5*S*)-hexane-2,5-diol were employed for *anti*-1,2-diol and *anti*-1,4-diol, respectively.

Table 1. Effect of Diols and an Additive in DNBSA-Catalyzed Reduction of Ketone **5** to Alcohol **6**[a]



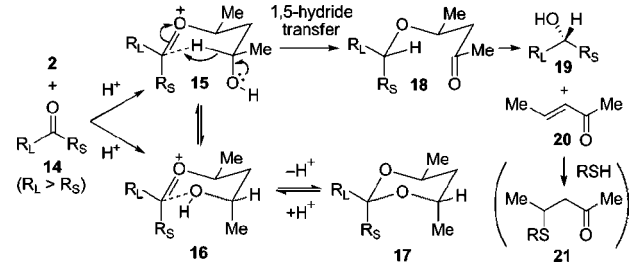
entry	diol	6 (%)[b]	other product (%)[b]
1	OH OH	9	nd[c]
2	OH OH 7	trace	Ph O O 8 (55%)
3	OH OH 2[d]	27[e]	nd[c]
4	OH OH (±)-9	0	Ph O O 10 (32%)
5	i-Pr i-Pr OH OH (±)-11	46	nd[c]
6[f]	OH OH 2[d]	62[g] 57[h]	$C_8H_{17}S$ O 12 (52%) + $C_8H_{17}S$ OH 13 (15%)

[a] General conditions: diol (1.1 equiv), DNBSA (5 mol %), **5** (0.3 mmol), benzene (10 mL), reflux, 2 h, a Dean−Stark apparatus. [b] Isolated yield. [c] Not determined. [d] 97% ee. [e] 49% ee (*R*). [f] Octanethiol (1.1 equiv) was used as an additive. [g] 48% ee (*R*). [h] A Dean−Stark apparatus was not used.

15% yields, respectively (entry 6, vide infra). Under non-dehydrative conditions (without continuous removal of water by a Dean−Stark apparatus), 57% yield of alcohol **6** was obtained. Thus, continuous removal of water was not necessarily required for the present reduction.

A plausible mechanism for Brønsted acid catalyzed reduction of ketones with *anti*-(2*S*,4*S*)-pentane-2,4-diol **2** is shown in Scheme 2. Acetalization of ketone **14** with diol **2**

Scheme 2. Plausible Mechanism for DNBSA-Catalyzed Reduction of Ketone **14** to Alcohol **19** by Using *anti*-1,3-Diol **2**



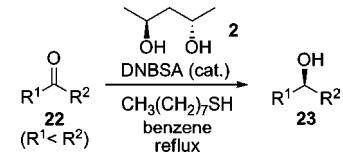
in the presence of Brønsted acid gives acetal **17** via oxocarbenium ion **16**. DNBSA, a strong Brønsted acid, also catalyzes stereoselective ring cleavage of **17** to regenerate oxocarbenium ion **16**.[6,13] Oxocarbenium ion **15** bearing two

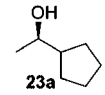
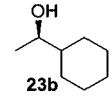
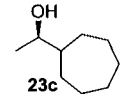
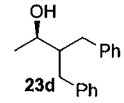
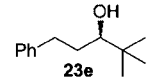
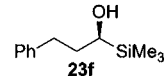
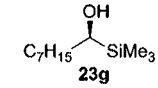
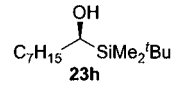
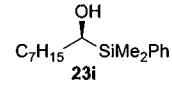
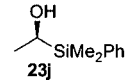
methyl groups in equatorial positions is formed by C−C bond rotation in **16** as well as directly by reaction with ketone **14** and diol **2**. Then 1,5-hydride transfer proceeds via the six-membered transition state shown in oxocarbenium ion **15** to afford β-alkoxy ketone **18**.[14,15] Brønsted acid-catalyzed elimination of the β-alkoxy ketone **18** gives alcohol **19** and enone **20**. The involvement of β-alkoxy ketone **18** and enone **20** was suggested by isolation of the β-alkoxy ketone **10** and the β-alkylthio ketone **12**, respectively, as mentioned above (Table 1, entries 4 and 6).[16] The effect of octanethiol, which improved the efficiency of the reduction of ketone **14** to alcohol **19**, can be explained by decreasing competitive reduction of enone **20** with diol **2** by its transformation to β-alkylthio ketone **21**, whose steric circumstance around the carbonyl group is more crowded than that of **20**. In the case of diol **11** (Table 2, entry 5), the competitive reduction of in situ-formed enone is diminished to some extent because of its steric hindrance.

The scope and limitations and also asymmetric induction of the present DNBSA-catalyzed reduction of ketones **22** with diol **2** were investigated (Table 2). Aliphatic methyl ketones having secondary alkyl groups **22a**−**d** gave the corresponding alcohols **23a**−**d** in moderate yield and with high asymmetric induction (82−93% ee, entries 1−4). *tert*-Butyl ketone **22e** gave alcohol **23e** in >99% ee in spite of a low chemical yield (21%, entry 5). Interestingly, reduction of acyl trimethylsilanes[17] **22f**,**g** proceeded smoothly in the absence of octanethiol[18] to give alcohols **23f**,**g** in 81−84% yields and in 98% ee (entries 6 and 7).[19] Reduction of acyl *tert*-butyldimethylsilane **23h** and acyl dimethylphenylsilane **23i**,**j** also proceeded efficiently to afford the corresponding alcohols in high yields and in high ees (entries 8−10). The observed higher efficiency of the reduction of acyl silanes compared with ketones, in the absence of octanethiol, is caused by the higher reactivity of acyl silanes. The latter can be ascribed to its raised HOMO level, caused by the interaction between C−Si bond (σ_{C-Si}) orbital and nonbonding orbital of carbonyl oxygen (n_O).[20] As shown in Scheme 2, highly asymmetric selectivity induced by chiral diol **2** is explained by location of the larger substituent of ketone (R_L) in the equatorial position of the intermediate **15**.

In summary, we have developed a Brønsted acid-catalyzed asymmetric reduction of ketones and acyl silanes that uses

Table 2. DNBSA-Catalyzed Asymmetric Reduction of Various Ketones **22a**−**e** and Acyl Silanes **22f**−**j** with Chiral Diol **2**[a]



entry	alcohol **23**	time	yield (%)[b]	ee (%)[c]
1	 **23a**	1.5 h	57[d]	93
2	 **23b**	1.5 h	52[d]	87
3	 **23c**	2.0 h	50	82
4	 **23d**	4.0 h	42	82
5	 **23e**	3.0 h	21	>99
6[e]	 **23f**	0.5 h	83	98
7[e]	 **23g**	0.5 h	81	98
8[e]	 **23h**	1.0 h	74	99
9[e]	 **23i**	0.5 h	78	92
10[e]	 **23j**	5 min	85	95

[a] General conditions: ketone **22** (0.4 mmol), **2** (97% ee, 1.1 equiv), DNBSA (5 mol %), octanethiol (1.1 equiv), benzene (10 mL), reflux, a Dean−Stark apparatus. [b] Isolated yield unless otherwise mentioned. [c] Determined by chiral HPLC (see the Supporting Information). [d] Determined by ^{1}H NMR analysis using an internal standard. [e] Octanethiol was not used.

(12) Various thiols were tested, and more nucleophilic thiols gave better results: PhSH (40%), *p*-MeOC$_6$H$_4$SH (50%). The effect of octanethiol was not observed when diol **11** was used instead of **2** because conjugate addition of thiol to in situ formed enone was difficult.

(13) Acetals were not obtained from *anti*-1,3-diol when DNBSA was used as a Brønsted acid catalyst.

(14) For Lewis acid-promoted 1,5-hydride transfer of oxocarbenium ion, see: (a) Shaw, P. E. *J. Org. Chem.* **1966**, *31*, 2116–2119. (b) Martin, O. R.; Rao, S. P.; El-Shenawy, H. A.; Kurz, K. G.; Cutler, A. B. *J. Org. Chem.* **1988**, *53*, 3287–3292.

(15) Aluminum reagent-catalyzed reductive cleavage of chiral acetal **17** to β-alkoxy ketone **18** was reported by Yamamoto and Ishihara. See: (a) Ishihara, K.; Hanaki, N.; Yamamoto, H. *J. Am. Chem. Soc.* **1991**, *113*, 7074–7075. (b) Ishihara, K.; Hanaki, N.; Yamamoto, H. *Synlett* **1993**, 127–129. (c) Ishihara, K.; Hanaki, N.; Yamamoto, H. *J. Am. Chem. Soc.* **1993**, *115*, 10695–10704.

(16) Enone was isolated when (4*S**,6*S**)-2,8-dimethylnonane-4,6-diol was employed instead of **2**.

(17) Review : (a) Ricci, A.; Degl'Innocenti, A. *Synthesis* **1989**, 647–660. (b) Bonini, B. F.; Comes-Franchini, M.; Fochi, M.; Mazzanti, G.; Ricci, A. *J. Organomet. Chem.* **1998**, *567*, 181–189. (c) Cirillo, P. F.; Panek, J. S. *Org. Prep. Proc. Int.* **1992**, *24*, 553–582.

(18) In the presence of octanethiol, alkenylsulfide was obtained. See: Bonini, B. F.; Comes-Franchini, M.; Fochi, M.; Mazzanti, G.; Peri, F.; Ricci, A. *J. Chem. Soc., Perkin Trans. 1* **1996**, *280*, 3–2809.

(19) For asymmetric reduction of acyl silanes, see: (a) Buynak, J. D.; Strickland, J. B.; Hurd, T.; Phan, A. *J. Chem. Soc., Chem. Commun.* **1989**, 89–90. (b) Soderquist, J. A.; Anderson, C. L.; Miranda, E. I.; Rivera, I.; Kabalka, G. W. *Tetrahedron Lett.* **1990**, *31*, 4677–4680. (c) Takeda, K.; Ohnishi, Y.; Koizumi, T. *Org. Lett.* **1999**, *1*, 237–239. (d) Arai, N.; Suzuki, K.; Sugizaki, S.; Sorimachi, H.; Ohkuma, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 1770–1773.

(20) (a) Bock, H.; Alt, H.; Seidl, H. *J. Am. Chem. Soc.* **1969**, *91*, 355–361. (b) Yoshida, J.; Itoh, M.; Matsunaga, S.; Isoe, S. *J. Org. Chem.* **1992**, *57*, 4877–4882.

chiral *anti*-pentane-2,4-diol **2** as a reducing agent. DNBSA was found to be an effective Brønsted acid, and addition of octanethiol improved the efficiency of the reduction of ketones, whereas reduction of acyl silanes proceeded smoothly in the absence of octanethiol. The metal-free procedure for the present asymmetric reduction of ketones and acyl silanes is convenient for preparing optically active secondary alcohols.

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Supporting Information Available: Detailed experimental procedures and full spectroscopic characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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