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Selective reduction of aldehydes via BINOL–Zr complex

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Abstract—An easily assembled catalyst from (±)-BINOL (1,1′-bi-naphthol) and $Zr(O^iPr)_4 \cdot {}^iPrOH$ selectively reduces aldehydes at room temperature. Ketones remain intact under these conditions. A catalytic amount of BINOL–Zr complex in the presence of 2-propanol also effectively reduces a variety of chiral and achiral aldehydes. © 2001 Published by Elsevier Science Ltd.

In syntheses of complex natural products and their analogues, reductions and oxidations are usually unavoidable[1] and generally most important in designing synthetic strategies. To reduce one of the carbonyls in a multifunctional compound the other carbonyls must be temporarily protected. To eliminate protection and deprotection steps when one carbonyl is desired to be reduced in the presence of other carbonyl groups, synthetic chemists often take advantage of reactivity differences caused by electronic and steric effects. Tuning up the reducing power of the reagents is an alternative approach. However, except for hydroxyl group directed selective reductions of carbonyls,[2] few conditions reduce selectively one carbonyl group in the presence of another.[3] To the best of our knowledge, there are no hydride reagents that reduce effectively only aldehydes and leave ketones intact at room temperature.[4] Such a reagent would be very useful especially in the syntheses of polyoxygenated natural products. In this context, we wish to report a selective reduction of aldehydes using (±)-BINOL (1,1′-bi-napthol) and $Zr(O^iPr)_4 \cdot {}^iPrOH$.

We have been seeking reduction conditions that reduce only aldehydes in the presence of ketones using a catalytic amount of reagents. For this purpose, the reduction requires weaker reducing power than sodium borohydride and reducing power comparable to $NaCNBH_3$. The Meerwein–Pondorf–Verley (MVP) reduction might be a method in which the reduction power can be tuned by changing the center metals and ligands. The homogeneous MVP reduction using aluminum isopropoxide in 2-propanol can reduce aldehydes;[5] however, these conditions give rise to significant amounts of ketone reduction products. Group IVA transitionmetallocene complexes such as Cp_2ZrH_2, Cp_2HfH_2, $Cp_2Zr(O^iPr)_2$, and $Cp_2Hf(O^iPr)_2$ were successfully applied to the MVP-type reduction in 2-propanol at high temperature (130°C), and reduced 3-ketobutanal to 1-hydroxy-3-butanone after 8 h in 90–94% yields.[6] We first examined more reactive catalysts using readily accessible group IVB alkoxides.[7] $Ti(O^iPr)_4$, $Ti(O^tBu)_4$, and $Zr(O^tBu)_4$ are widely used for the center metal of a variety of ligands, and these catalysts are very useful for many catalytic asymmetric reactions.[8] Because $Zr(O^iPr)_4$ is polymer-like and possesses poor solubility in conventional organic solvents, few successful applications of $Zr(O^iPr)_4$ in catalytic asymmetric reactions have been recorded.[9] We observed that the complex generated from relatively air and moisture less sensitive $Zr(O^iPr)_4 \cdot {}^iPrOH$ and (±)-BINOL in the presence of 4 Å MS[10] in toluene effectively reduced aldehydes. By using the electrospray mass spectral technique developed by Marshall and co-workers,[11] we were able to obtain useful information on the molecular formulas of BINOL–Zr complexes.[12] Interestingly, the structures of the complexes are influenced significantly by the solvent. In toluene solution a 1:1 mixture of BINOL and $Zr(O^iPr)_4 \cdot {}^iPrOH$ formed a complex which contains six Zr atoms. The catalyst generated in polar solvents such as nitriles was smaller containing four Zr atoms.

The catalyst generated in toluene at 60°C for 30–60 minutes showed the most reproducible results for chiral and achiral aldehydes using a stoichiometric amount of catalyst. Many substrates tested afforded the corresponding alcohols in 1 h at room temperature without addition of 2-propanol (Table 1). However, the sterically congested aldehyde, Garner aldehyde[13] (entry 14), requires a longer reaction time, and the reduction of an

Keywords: selective reduction; BINOL; zirconium complex.

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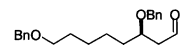
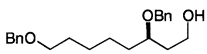
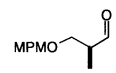
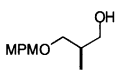
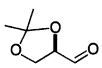
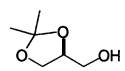
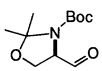
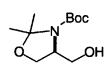
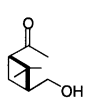
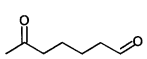
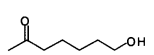
Table 1. Selective reduction of aldehydes via (±)-BINOL and $Zr(O^iPr)_4$·^{i}PrOH[a]

Entry	Aldhydes and Keto-Aldehydes	Conditions (Reaction Time)	Product	Yield (%)
1	Benzaldehyde	100 mol% (1 h)	Benzyl alcohol	100
2	Benzaldehyde	15 mol% (5 h)	Benzyl alcohol	100
3	Hydrocinnamaldehyde	15 mol% (10 h)	3-Phenyl-1-propanol	95
4	Octanal	100 mol% (1 h)	1-Octanol	100
5	Octanal	15 mol% (18 h)	1-Octanol	100
				
6	Benzyloxy-acetaldehyde	100 mol% (1 h)	Benzyloxy-ethanol	95
7	Benzyloxy-acetaldehyde	15 mol% (9 h)	Benzyloxy-ethanol	95
				
8	(*R*)-3,8-dibenzyloxyoctanal	100 mol% (1 h)	(*R*)-3,8-dibenzyloxyoctanol	93
9	(*R*)-3,8-dibenzyloxyoctanal	15 mol% (15 h)	(*R*)-3,8-dibenzyloxyoctanol	90
				
10	(*S*)-3-(4'-methoxyphenyl)-methoxy-2-methylpropanal	100 mol% (1 h)	(*S*)-3-(4'-methoxyphenyl)-methoxy-2-methylpropanol	95
11	(*S*)-3-(4'-methoxyphenyl)-methoxy-2-methylpropanal	15 mol% (18 h)	(*S*)-3-(4'-methoxyphenyl)-methoxy-2-methylpropanol	85
				
12	(*R*)-3,4-*O*-Isopropylidene-3,4-dihydroxybutanal	100 mol% (1 h)	(*R*)-3,4-*O*-Isopropylidene-3,4-dihydroxybutanol	95
13	(*R*)-3,4-*O*-Isopropylidene-3,4-dihydroxybutanal	15 mol% (8 h)	(*R*)-3,4-*O*-Isopropylidene-3,4-dihydroxybutanol	90
				
14	(*S*)-1,1-dimethylethyl-2,2-dimethyl-4-formyloxazolidine-3-caboxylate (Garner aldehyde)	100 mol% (4 h)	(*R*)-4-hydroxymethyl-2,2-dimethyloxazolidine-3-carboxylic acid tert-butyl ester	100
15	Garner aldehyde	30 mol% (12 h)	(*R*)-4-hydroxymethyl-2,2-dimethyloxazolidine-3-carboxylic acid tert-butyl ester	70
16	6-Oxo-hexanoic acid methyl ester	100 mol% (10 h)	6-Hydroxy-hexanoic acid methyl ester	100
17	2-Octynal	100 mol% (0.5 h)	2-Octynol	100
18	2-Octynal	10 mol% (3 h)	2-Octynol	100
19	*trans*-Cinnamaldehyde	100 mol% (1 h)	Cinnamyl alcohol	50
				
20	(1*S*, 3*S*)-*cis*-dimethyl-3-acetyl-2,2-dimethylcyclobutane-acetaldehyde (*cis*-Pinanoic aldehyde)	100 mol% (1 h)	(1*S*, 3*S*)-*cis*-dimethyl-3-acetyl-2,2-dimethylcyclobutanemethanol (*cis*-Pinanonic alcohol)	98
				
21	*cis*-Pinanoic aldehyde	10 mol% (10 h)	*cis*-Pinanonic alcohol	85
22	6-Oxo-heptanal	100 mol% (1 h)	6-Oxo-heptanol[b]	95
22	6-Oxo-heptanal	10 mol% (10 h)	6-Oxo-heptanol[b]	95

[a]All reactions were carried out in a 1 mmol scale at room temperature.
[b]The compound was characterized as its hemiketal by ^{1}H NMR.

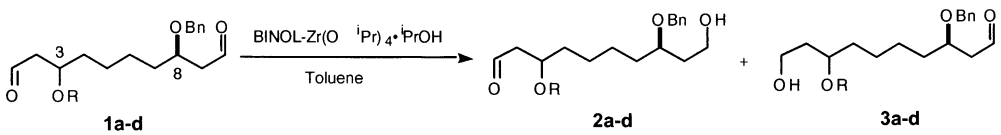
α,β-unsaturated aldehyde proceeded in only unsatisfactory yield (entry 19). As expected 10–15 mol% of the BINOL–Zr complex reduced the aldehydes selectively at room temperature within 5–18 h in the presence of 10 equivalents of 2-propanol to afford the corresponding alcohols in 80–100% yields (Table 1). The reduction of 2-octynal was faster than that of octanal under both stoichiometric and catalytic conditions (entries 17 and 18). Alkanones, acetophenone, and benzophenone were not reduced with stoichiometric amounts of BINOL–Zr complex even after 4 h.[14] Indeed, the reduction of keto-aldhydes under either stoichiometric or catalytic conditions afforded keto-alcohols in good yields (entries 20–22). Less hindered aldehydes such as octyl aldehyde could be reduced by an equivalent of catalyst even at −40°C in 36 h. Therefore, the catalyst generated from BINOL and $Zr(O^iPr)_4{\cdot}^i$PrOH is far more reactive than conventional aluminum alkoxides for the MVP reductions.

An intriguing possibility was that the regioselective reduction of dialdehydes could be achieved via the BINOL–Zr catalyst. Considering data provided by the electrospray mass spectra of the catalyst (calculated mass = 2651.364), the rather large catalyst might recognize the bulkiness of the β-functionalities of dialdehydes. To test the feasibility of this approach, we first synthesized (3*S*,8*R*)-, (3*R*,8*R*)-dialdehydes[15] having different protecting groups at C3 and C8 hydroxyl groups (TBS or TIPS at C3 and Bn at C8). Treatment of **1a** (3*R*, R = TBS) with an equimolar amount of (*S*)- or (*R*)-BINOL–Zr complex at 0°C for 1 h furnished the mono-aldehyde in 50% yield without significant amounts of the diol (less than 5%) with selectivities of **2b**:**3b** = 4.9:1 and 4.8:1, respectively.[16] Reduction of the dialdehyde possessing a bulkier protecting group at C3, **1b** (3*R*, R = TIPS), gave better regioselectivity (**2b**:**2c** = 14:1 (for (*S*)-BINOL), **2b**:**2c** = 13:1 (for (*R*)-BINOL)) than in the case of **1a**. The regioselective reduction of **1d** was achieved using either (*S*)- or (*R*)-BINOL–Zr to afford the mono-aldehyde **2d** exclusively. The experiments summarized in Table 2 imply that regardless of the chirality of BINOL–Zr complex, chiral dialdehydes of type **1a**–**1d** could be reduced selectively at the less hindered site. The regioselective reductions of chiral dialdehydes reported here using the BINOL–Zr complex have not previously been reported by using boron, aluminum, tin associated reducing reagents, and the aluminum alkoxide mediated MPV-type reductions.[17]

In summary, the catalyst generated from BINOL[18] and $Zr(O^iPr)_4{\cdot}^i$PrOH is very effective for specific reduction of aldehydes. This catalyst recognizes β-chiral centers of the dialdehydes. The scope and limitations of the recognition of chiral carbonyl compounds using BINOL–metal complexes are currently under investigation.

Representative procedure for (1S,3S)-cis-3-acetyl-2,2-dimethylcyclobutaneacetaldehyde (cis-pinonic aldehyde). Stoichiometric reduction: A suspension of $Zr(O^iPr)_4{\cdot}^i$PrOH (339 mg, 0.886 mmol) and (±)-BINOL (252 mg, 0.8 mmol) in toluene (3 mL) was stirred at 60°C for 1 h. To the reaction mixture was added *cis*-pinonic aldehyde (131 mg, 0.886 mmol) as a toluene solution (1 mL). After 1 h at rt, the reaction mixture was quenched with saturated $NaHCO_3$ (3 mL) and extracted with ether. The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The crude mixture was purified by silica gel chromatography (hexanes:EtOAc = 2:1) to afford *cis*-pinonic alcohol (120 mg, 90%). *Catalytic reduction*: A suspension of $Zr(O^iPr)_4{\cdot}^i$PrOH (339 mg, 0.886 mmol), (±)-BINOL (252 mg, 0.886 mmol), and 4 Å MS (400 mg) in toluene (3 mL) was stirred at 60°C for 1 h. To the reaction mixture was added *cis*-pinonic aldehyde (810 mg, 5.91 mmol) in toluene (3 mL), followed by freshly distilled 2-propanol (4.5 mL, 59.1

Table 2. Regioselective reduction of dialdehydes via (*S*)- or (*R*)-BINOL and $Zr(O^iPr)_4{\cdot}^i$PrOH



1a-d **2a-d** **3a-d**

Entry	Substrate	R	Condition[a]	Selectivity (**2**:**3**)[b]	Yield (%)[f]
1	**1a** (3*R*)	TBS	(*S*)-BINOL	**2a**:**3a** = 4.9:1	50[c]
2	**1a** (3*R*)	TBS	(*R*)-BINOL	**2a**:**3a** = 4.8:1	50[c]
3	**1b** (3*R*)	TIPS	(*S*)-BINOL	**2b**:**3b** = 14:1	78[d]
4	**1b** (3*R*)	TIPS	(*R*)-BINOL	**2b**:**3b** = 13:1	76[d]
5	**1c** (3*S*)	TBS	(*S*)-BINOL	**2c**:**3c** = 5.5:1	60[d]
6	**1c** (3*S*)	TBS	(*R*)-BINOL	**2c**:**3c** = 6.0:1	65[d]
7	**1d** (3*S*)	TIPS	(*S*)-BINOL	**2d**:**3d** = 100:0	70[e]
8	**1d** (3*S*)	TIPS	(*R*)-BINOL	**2d**:**3d** = 100:0	80[e]

[a] All reactions were carried out at 0°C.
[b] Selectivities of the products were established by ^{1}H NMR.
[c] 40% of **1a** was recovered after the reaction.
[d] 10–15% of **1c** was recovered.
[e] 5–10% of **1d** was recovered.
[f] The diol was isolated in less than 5%.

mmol). After 10 h at rt, the reaction mixture was quenched with saturated $NaHCO_3$ (5 mL) and extracted with ether. The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification using the same condition as for the stoichiometric reduction afforded *cis*-pinonic alcohol (754 mg, 85%).

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References

1. *Total Synthesis of Natural Products*; The Chemical Society of Japan: Japan, 2000; Vol. 45.
2. (a) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560; (b) Evans, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1990**, *112*, 6447.
3. (a) Maruoka, K.; Araki, Y.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 2650; (b) Cha, J. S.; Kim, E. J.; Kwon, O. O.; Kim, J. M. *Synlett* **1995**, 331.
4. Tris[(3-ethyl-3-pentyl)oxy]alumiun hydride and $LiAlH(^tBuO)_3$ have been utilized for the selective reduction of aldehydes. The selective reduction of aldehydes using those reagents requires careful control of the amount of reagents and temperature (−78 to 0°C), see: (a) Krishnamurthy, S. *J. Org. Chem.* **1981**, *46*, 4628; (b) Hecker, S. J.; Heathcock, C. H. *J. Am. Chem. Soc.* **1986**, *108*, 4586. For other conditions for attempting the selective reduction of aldehyde, see: (c) Yamamoto, Y.; Toi, H.; Sonoda, A.; Murahashi, S. *J. Am. Chem. Soc.* **1975**, *98*, 1965; (d) Maki, Y.; Kikuchi, K.; Sugiyama, H.; Seto, S. *Tetrahedron Lett.* **1977**, 263; (e) Kim, S.; Kang, J.; Yang, S. *Tetrahedron Lett.* **1984**, *25*, 2985 and references cited therein.
5. For reports on this subject using modified alumina, see: (a) Ponser, G. H.; Runquist, A. W. *Tetrahedron Lett.* **1975**, 3601; (b) Ponser, G. H.; Runquist, A. W.; Chapdelaine, M. J. *J. Org. Chem.* **1977**, *42*, 1202.
6. Nakano, T.; Umano, S.; Kino, Y.; Ishii, Y.; Ogawa, M. *J. Org. Chem.* **1988**, *53*, 3752.
7. The MVP reduction of reactive aldehydes (e.g. 4-nitrobenzaldehyde, 4-chlorobenzaldehyde, and 4-cyanobenzaldehyde) using $Zr(O^iPr)_4$ in 2-propanol was reported, see: Weidmann, B.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 31.
8. Ishitani, H.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc.* **1997**, *119*, 7153 and references cited therein.
9. Bedeschi, P.; Casolari, S.; Costa, A. L.; Tagliavini, E.; Umani-Ronchi, A. *Tetrahedron Lett.* **1995**, *36*, 7897.
10. It was realized that an addition of 4 Å MS is not necessary for stoichiometric reductions.
11. Senko, M. W.; Hendrickson, C. L.; Emmett, M. R.; Shi, S. D. H.; Marshall, A. *J. Am. Soc. Mass Spectrom.* **1997**, *8*, 970.
12. These results will be reported elsewhere.
13. Garner, P.; Park, J.-M. *J. Org. Chem.* **1987**, *52*, 2361.
14. Less than 30% reduction of acetophenone was observed after 48 h at room temperature.
15. Kurosu, M.; Lorca, M., manuscript in preparation.
16. The yield of mono-aldehyde could be improved up to 80% using 3 equivalents of BINOL–Zr complex at 0°C in 30 minutes.
17. Larock, R. C. *Comprehensive Organic Transformations*, 2nd ed.; VCH: New York, 1999.
18. (*S*)- and (*R*)-BINOL are now available from Kankyo Kagaku Center Co., Ltd. at approximately US $ 0.75 per gram.