Available online at www.sciencedirect.com

SCIENCE DIRECT®

Tetrahedron Letters

Tetrahedron Letters 47 (2006) 463–465

Highly enantioselective reduction of ketones by chiral diol-modified lithium aluminum hydride reagents

Yunlai Ren,[a,b] Xinzhe Tian,[c] Kunpeng Sun,[a] Jian Xu,[a,b] Xianlun Xu[a,*] and Shijie Lu[a]

[a]*State Key Laboratory for Oxo Synthesis and Selective Oxidation, Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences, 342 Tianshui Road, Lanzhou 730000, China*
[b]*Graduate School of Chinese Academy of Sciences, Beijing 100039, China*
[c]*School of Chemistry and Chemical Engineering, Shandong University, Jinan 250100, China*

Received 1 November 2005; accepted 11 November 2005
Available online 29 November 2005

Abstract—Some readily available chiral diols from indene and D-mannitol were investigated as chiral modifiers in lithium aluminum hydride reduction of ketones, and it was discovered that further modification of these reducing reagents by a simple a-amino alcohol resulted in a remarkable increase in optical yield. Among the investigated chiral modifiers, chiral diol **1** gave the highest enantioselectivities.

Asymmetric reduction of prochiral ketones offers an especially attractive entry to enantiomerically pure secondary alcohols.[1] In this field, some reagents have been elaborated by the modification of $LiAlH_4$ with alkaloid,[2] sugars,[3] and amino alcohols.[4] In spite of the numerous chiral auxiliaries available for asymmetric lithium aluminum hydride reduction of ketones, only binaphthol (BINOL)[5] and spiro[4,4]nonane-1,6-diol[6] are satisfactorily employable. However, costliness of these chiral auxiliaries always restricts their applications in industries. Therefore, the search for new, effective and inexpensive chiral auxiliaries is still an important pursuit.

Our interest has been focused on synthesis and applications of some chiral products from readily available natural substances, which mainly include carbohydrate derivatives.[7] In this letter, we report asymmetric reduction of ketones by using complexes of $LiAlH_4$ with some chiral diols from commercially available indene and D-mannitol, and it was discovered that further modification of these reducing reagents by a simple a-amino alcohol resulted in a remarkable increase in optical yield. Among the investigated chiral modifiers, chiral diol **1** gave the highest enantioselectivities.

Chiral diols **1**–**5** (Fig. 1) were readily obtained in one or three steps by standard procedures described in previous literatures from commercially available indene[8] or D-mannitol.[9] The chiral diol **1** has an interesting configuration and its key feature is that it possesses two phenyl rings, which restrict its conformational flexibility. The four stereogenic carbon centers in the backbone dictate the orientation of the phenyl rings, and the structure is similar to that of the axially dissymmetric BINOL according to their molecular models.[8]

We first tested the effectiveness of the chiral diol **1** as chiral modifier in asymmetric lithium aluminum hydride reduction of acetophenone (Table 1, entries 1–4). Without further modification of this reagent by a simple a-amino alcohol, only 14% ee was obtained. The disappointing low level of asymmetric induction prompted us to examine further modification of the reagent by a simple a-amino alcohol. Fortunately, when a simple alcohol (*N*,*N*-dimethylethanolamine) was used, the result of the reaction was excellent, and afforded optically active secondary alcohols with 93% ee. As bulkiness of alkyl group attached to the amino group increased, both the yield and enantioselectivity remarkably decreased, which probably resulted from coordination of the amino group to aluminum atom in the possible transition states

---

Keywords: Asymmetric reduction; Ketone; Diol; Lithium tetrahydridoaluminate.

* Corresponding author. Tel.: +86 09314968217; fax: +86 09318277088; e-mail: xlxu@ns.lzb.ac.cn

0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.11.062

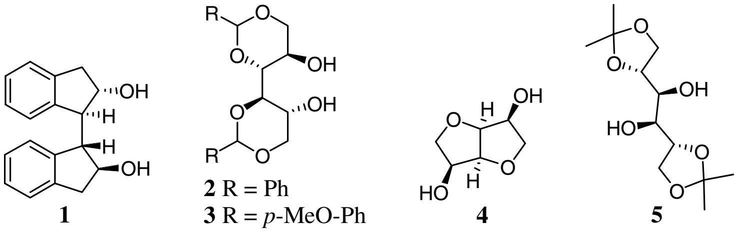

Figure 1. Chiral diols used in asymmetric lithium aluminum hydride reduction of ketones.

Table 1. Asymmetric reduction of ketones by using complexes of $LiAlH_4$ with chiral diol and a-amino alcohol[a]

Entry	Diol	Ketone	a-Amino alcohol	Yield (%)	ee (%)	Confign[b]
1	**1**	$PhCOCH_3$		100	14	*S*
2	**1**	$PhCOCH_3$	$(Me)_2NC_2H_4OH$	89	93	*S*
3	**1**	$PhCOCH_3$	$(Et)_2NC_2H_4OH$	83	84	*S*
4	**1**	$PhCOCH_3$	$(i\text{-}Bu)_2NC_2H_4OH$	42	75	*S*
5	**1**	$PhCO\text{-}n\text{-}C_4H_9$	$(Me)_2NC_2H_4OH$	86	96	*S*
6	**1**	$PhCOCH(CH_3)_2$	$(Me)_2NC_2H_4OH$	94	88	*S*
7	**1**	$PhCOC(CH_3)_3$	$(Me)_2NC_2H_4OH$	93	83	*S*
8	**1**	2-Naphth-COPh	$(Me)_2NC_2H_4OH$	91	98	*S*
9	**1**	$p\text{-}Cl\text{-}PhCOCH_3$	$(Me)_2NC_2H_4OH$	81	76	*S*
10	**1**	$p\text{-}MeO\text{-}PhCOCH_3$	$(Me)_2NC_2H_4OH$	81	94	*S*
11	**1**	$n\text{-}C_4H_9COCH_3$	$(Me)_2NC_2H_4OH$	85	18	*R*
12	**1**	$n\text{-}C_8H_{17}COCH_3$	$(Me)_2NC_2H_4OH$	92	60	*R*
13	**2**	2-Naphth-COPh	$(Me)_2NC_2H_4OH$	78	23	*S*
14	**3**	2-Naphth-COPh	$(Me)_2NC_2H_4OH$	67	35	*S*
15	**4**	2-Naphth-COPh	$(Me)_2NC_2H_4OH$	88	12	*S*
16	**5**	2-Naphth-COPh	$(Me)_2NC_2H_4OH$	92	67	*R*

[a] Reaction conditions are shown in Ref. 11.

[b] The absolute configuration was determined by optical rotation (Refs. 9 and 10).

6 or **7** (Fig. 2). The coordination of the amino group to aluminum center probably accelerates the dissociation of the hydrogen from aluminum, and simultaneously accelerates the transfer of the hydrogen from aluminum to carbonyl carbon. So increasing bulkiness of amino group would hold back the coordination of amino group to aluminum, and then results in a decrease of the yield.

A series of other ketones were then used to test the asymmetric inductive capability of the chiral auxiliary **1** (Table 1, entries 5–12). With alkyl phenyl ketones, the optical yield enhanced gradually in going from acetophenone to the ketone bearing a long primary alkyl group, and then decreased slightly as the bulkiness of alkyl group increased. On the other hand, the substituent attached to phenyl group has a remarkable effect on the enantioselectivity. 4-Chloroacetophenone 33 only gave 76% ee, while 4-methoxyacetophenone gave 94% ee. Asymmetric reduction of some dialkyl ketones was also investigated, but disappointing results were obtained.

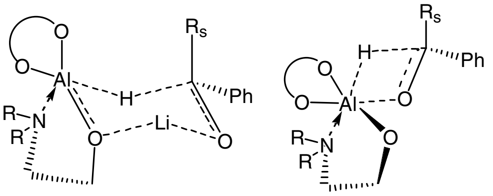

Figure 2. Two of the possible transition state models for the reduction of alkyl phenyl ketones by chiral diol 1-modified lithium aluminum hydride reagent.

Above behaviors are slightly inconsistent with the literature reports,[5] where chiral binaphthol was used as chiral modifier in the reduction of alkyl phenyl ketones, and it was found that bulkiness of alkyl group had a remarkable effect on the enantioselectivity of the reaction. However, in this letter, this kind of steric effects are unobvious. It probably results from more flexible configuration of the chiral diol **1** compared with BINOL, the flexible configuration would be expected to produce more complicated transition states. Moreover, it is puzzling that asymmetric reduction of 2-naphthyl phenyl ketone gave secondary alcohol with high enantioselectivity, which is almost the same as the results of asymmetric reduction of alkyl phenyl ketones. So far, according to the results in Table 1, we cannot affirm the mechanism of this reaction because this reaction is influenced by steric effects and various electronic factors. In addition, in the possible transition states for this reaction, the carbonyl function may coordinate to Li or Al atom (Fig. 2). A further investigation of the mechanism is underway.

Among the above results, 2-naphthyl phenyl ketone gave the highest enantioselectivity (entry 8), so this substrate was then used to test asymmetric inductive capability of the chiral modifiers **2**–**5** (entries 13–16). With chiral diol **2**, a optical yield of 23% was obtained, while the optical yield is up to 12%, as described in the previous paper,[9] in asymmetric reduction of some alkyl phenyl ketones or dialkyl ketones. Chiral diols **3**–**5** were also used as auxiliaries in asymmetric reduction of 2-naphthyl phenyl ketone, but disappointing results were obtained.

In conclusion, in this letter, some readily available chiral diols from indene and D-mannitol were investigated as chiral modifiers in lithium aluminum hydride reduction of ketones, and it was discovered that the addition of a simple a-amino alcohol resulted in a remarkable increase in optical yield. Among the investigated chiral modifiers, chiral diol **1** gave the highest enantioselectivities. In spite of the excellent enantioselectivities, it is useful to search for readily available and inexpensive reagents in enantioselective reduction.

Acknowledgements

The authors wish to thank National Nature Science Foundation of China (No. 29933050) for financial support.

References and notes

1. (a) Valentine, D. J.; Scott, J. W. *Synthesis* **1978**, 329–356; (b) Singh, V. K. *Synthesis* **1992**, 605–617; (c) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986–2012.
2. (a) Cervinka, O. *Collect. Czech. Chem. Commun.* **1965**, *30*, 1684–1691; (b) Cervinka, O.; Belovsky, O. *Collect. Czech. Chem. Commun.* **1967**, *32*, 3897–3901.
3. (a) Landor, S. R.; Miller, B. J.; Tatchell, A. R. *J. Chem. Soc. C* **1966**, 1822–1825; (b) Landor, S. R.; Miller, B. J.; Tatchell, A. R. *J. Chem. Soc. C* **1967**, 197–201.
4. (a) Yamaguchi, S.; Mosher, H. S.; Pohland, A. *J. Am. Chem. Soc.* **1972**, *94*, 9254–9255; (b) Yamaguchi, S.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 1870–1877; (c) Jacquet, I.; Vigneron, J. P. *Tetrahedron Lett.* **1974**, *15*, 2065–2068; (d) Vigneron, J. P.; Jacquet, I. *Tetrahedron* **1976**, *32*, 939–944; (e) Terashima, S.; Tanno, N.; Koga, K. *Chem. Lett.* **1980**, 981–984.
5. (a) Noyori, R.; Tomino, I.; Tanimoto, Y.; Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6709–6716; (b) Noyori, R.; Tomino, I.; Yamada, M.; Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6717–6725.
6. Srivastava, N.; Mital, A.; Kumar, A. *J. Chem. Soc., Chem. Commun.* **1992**, 493–494.
7. (a) Zhou, H. Y.; Hou, J. G.; Chen, J.; Lu, S. J.; Fu, H. X.; Wang, H. Q. *J. Organomet. Chem.* **1997**, *543*, 227–228; (b) Zhou, H. Y.; Lu, S. J.; Hou, J. G. *Chem. Lett.* **1996**, 339–342; (c) Yuan, J. C.; Lu, S. J. *Tetrahedron Lett.* **2001**, *42*, 4069–4073; (d) Wang, A. L.; Lu, S. J.; Fu, H. X.; Wang, H. Q.; Huang, X. Y. *Carbohydr. Res.* **1996**, *281*, 301–305; (e) Lu, S. J.; Li, X. D.; Wang, A. L. *Catal. Today* **2000**, *63*, 531–536.
8. Yang, X. W.; Shen, J. H.; Da, C. S.; Wang, H. S.; Su, W.; Liu, D. X.; Wang, R.; Choi, M. C. K.; Chan, A. S. C. *Tetrahedron Lett.* **2001**, *42*, 6573–6575.
9. Baggett, N.; Stribblehill, P. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1123–1126.
10. (a) Schmid, C. R.; Bryant, J. D.; Dowlatzedah, M.; Phillips, J. L.; Prather, D. E.; Schantz, R. D.; Sear, N. L.; Vianco, C. S. *J. Org. Chem.* **1991**, *56*, 4056–4058; (b) Debost, J. L.; Gelas, J.; Horton, D. *J. Org. Chem.* **1983**, *48*, 1381–1382; (c) Yamaguchi, S.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 1870–1877.
11. In a typical experimental procedure, a-amino alcohol (0.6 mmol) and chiral diol (0.6 mmol) were added to a stirred solution of $LiAlH_4$ (0.6 mmol) in diethyl ether (4 mL) at room temperature. After 2 h, this solution was cooled to −78 °C, a diethyl ether solution (0.5 mL) of 0.2 mmol of ketone was dropwise added. After the reaction mixture was stirred for 10 h, the excess hydride was decomposed by the dropwise addition of water at −78 °C. Diethyl ether was removed under reduced pressure, then the residue was dissolved in 6 N HCl and extracted with diethyl ether. The organic layer was successively washed with saturated $NaHCO_3$, water, and dried over Na_2SO_4. The yield and ee were determined by GC with a chiraldex capillary column or HPLC with a Daicel chiracel OD-H column.