Asymmetric Reduction of Ketoxime *O*-Alkyl Ethers with Sodium Borohydride–Lewis Acid

Shinichi Itsuno,* Yoshiki Sakurai, Koji Shimizu, and Koichi Ito
School of Materials Science, Toyohashi University of Technology, Tempaku-cho, Toyohashi, Aichi 440, Japan

Novel hydride agents formed by combining Lewis acids with sodium borohydride ($NaBH_4$) reduce quantitatively ketoxime *O*-alkyl ethers to the corresponding optically active primary amines with high enantioselectivities (up to 95% e.e.) in the presence of chiral amino alcohols.

The asymmetric reduction of ketoximes is a potentially important method for the preparation of enantiomerically pure amines. Although many asymmetric reductions of ketones with chirally modified hydride complexes give high optical yields,[1] useful asymmetric conversions of ketoximes and imine derivatives to amines have been sparse.[2] Rhodium(I)-catalysed asymmetric hydrogenation of imines has been reported[3] to give chiral secondary amines; the highest optical yield obtained was 91% e.e.

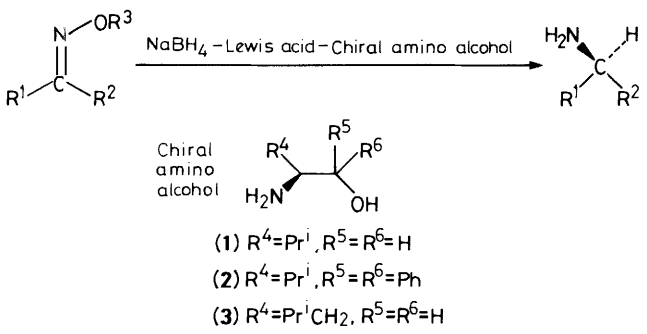
Recently we reported that $NaBH_4$–$ZrCl_4$ reduces ketoxime *O*-alkyl ethers under mild conditions.[4] In connection with our studies on enantioselective synthesis using chirally modified borohydrides[5] we now report the asymmetric reduction of ketoxime *O*-alkyl ethers.

A suspension of $NaBH_4$ in THF is essentially inert to chiral amino alcohols and is unable to reduce ketoxime *O*-alkyl ethers. On the other hand, when combined with a Lewis acid such as $ZrCl_4$ $NaBH_4$ reacts with chiral amino alcohols with evolution of hydrogen to form a chiral borohydride reagent. This chirally modified borohydride has the ability to reduce the C=N double bond of ketoxime *O*-alkyl ethers asymmetrically to give primary amines (see Table). This reagent is considered to be a mixed

Table. Asymmetric reduction of ketoxime *O*-alkyl ethers with the reagent prepared from $NaBH_4$ and a Lewis acid in the presence of a chiral amino alcohol

			$R'-\overset{\overset{N-OR^3}{\|}}{C}-R^2$			Chiral amine product		
Run	Lewis acid	Chiral amino alcohol	R^1	R^2	R^3	Yield[a] (%)	e.e.[b] (%)	Config.
1	$ZrCl_4$	(1)	Ph	Me	Me	95	64[c]	*S*
2	$ZrCl_4$	(1)	Ph	Et	Me	93	66[d]	*S*
3	$ZrCl_4$	(1)	Ph	Pr	Me	90	61[e]	*S*
4	$ZrCl_4$	(1)	Ph	Me	$PhCH_2$	91	69[c]	*S*
5	$ZrCl_4$	(1)	Ph	Et	$PhCH_2$	88	72[d]	*S*
6	$ZrCl_4$	(1)	1-Naph	Me	Me	85	55[f]	*S*
7	$ZrCl_4$	(1)	2-Naph	Me	Me	90	61[g]	*S*
8	$ZrCl_4$	(1)	3,4-dihydro-naphthalen-1(2*H*)-one oxime *O*-methyl ether			86	67[h]	*S*
9	$ZrCl_4$	(1)	Bu[t]	Me	Me	78	42[i]	*S*
10	$ZrCl_4$	(2)	Ph	Me	Me	95	90[c]	*S*
11	$ZrCl_4$	(3)	Ph	Me	Me	95	43[c]	*S*
12	$SnCl_4$	(1)	Ph	Me	Me	53	17[c]	*S*
13	$FeCl_3$	(1)	Ph	Me	Me	95	51[c]	*S*
14	$ZnCl_2$	(1)	Ph	Me	Me	0	—	—
15	$ZnBr_2$	(1)	Ph	Me	Me	0	—	—
16	$AlCl_3$	(1)	Ph	Me	Me	0	—	—
17	$ZnCl_2 + AlCl_3$	(1)	Ph	Me	Me	78	70[c]	*S*
18	$ZnCl_2 + AlCl_3$	(2)	Ph	Me	Me	75	95[c]	*S*
19	$ZrCl_4$	(1)	Acetophenone			95	12[j]	*R*

[a] Isolated yield. [b] Determined by comparison of maximum rotation reported in the literature. [c] See ref. 7. [d] M. E. Warren and H. E. Smith, *J. Am. Chem. Soc.*, 1965, **87**, 1757. [e] Y. Yamamoto, H. Shimoda, J. Oda, and Y. Inoue, *Bull. Chem. Soc. Jpn.*, 1976, **49**, 3247. [f] H. Wolf, E. Bunnenberg, and C. Djerassi, *Chem. Ber.*, 1964, **97**, 533. [g] Optically pure sample is commercially available. [h] V. Ghishlandi and D. Vercesi, *Farmaco, Ed. Sci.*, 1971, **26**, 474. [i] H. E. Smith and H. E. Ensley, *Can. J. Chem.*, 1971, **49**, 2902. [j] U. Nagai, T. Shishido, R. Chiba, and H. Mitsuhashi, *Tetrahedron*, 1965, **21**, 1701.



borohydride on the basis of its preparation but the mechanism of reaction is not yet fully understood.

As shown in the Table the introduction of the bulky benzyl group in the ether substituent R^3, increases the asymmetric induction to some extent (run 4,5). Higher enantioselectivity was obtained when the diphenyl derivative (**2**) of the chiral amino alcohol (**1**) was used (run 10). With all examples, this reagent consistently affords the *S*-amine predominantly. The reduction of the *O*-methyloxime of a dialkyl ketone, 3,3-dimethylbutan-2-one, also yielded amine enriched in the *S*-enantiomer but did not give a satisfactory optical yield (run 9). The reduction of acetophenone with this reagent resulted in a lowering of the stereoselectivity (run 19). $SnCl_4$ and $FeCl_3$ are also effective Lewis acids for the reduction of ketoxime *O*-alkyl ether. Addition of $ZnCl_2$, $ZnBr_2$, or $AlCl_3$ to $NaBH_4$ was not effective, but a mixture of $ZnCl_2$ and $AlCl_3$ (1 : 1) was effective in the asymmetric reduction of a ketoxime *O*-alkyl ether to give the highest enantioselectivity (95% e.e.) observed (run 18). The chiral amino alcohols are easily prepared from L-amino acids[6] or are commercially available.

The following procedure for the reduction of acetophenone *O*-methyloxime with $NaBH_4$–$ZrCl_4$–(**2**) is illustrative. To $ZrCl_4$ (9.32 g, 40 mmol) in dry THF (50 ml) at room temperature under an atmosphere of dry nitrogen was added $NaBH_4$ powder (1.51 g, 40 mmol). After the mixture had been stirred for 20 h, a solution of (**2**) (3.83 g, 15 mmol) in dry THF (10 ml) was added at room temperature and stirring continued for a further 20 h. Into the resulting chiral reducing agent was added acetophenone *O*-methyloxime (1.79 g, 12 mmol) and the mixture was stirred for 2 days at room temperature; it was then quenched by dropwise addition of water and 1M HCl at 0 °C. After the insoluble salt (**2**)·HCl, had been filtered off, the aqueous layer was neutralized with NH_4OH and extracted with ethyl acetate; the organic layer was then dried ($MgSO_4$) and evaporated to give an oily residue. Bulb-to-bulb distillation afforded the 1-phenylethylamine {1.38 g, 95%, $[\alpha]_D^{22}$ −36.4 (neat)} which represents a 90% e.e. based on comparison with the maximum rotation.[7]

References

1 See: 'Asymmetric Synthesis,' ed. J. D. Morrison, Academic Press, London, 1983, vol. 2, chapters 2—4.

2 (*a*) S. Itsuno, K. Tanaka, and K. Ito, *Chem. Lett.*, 1986, 1133; (*b*) S. Itsuno, M. Nakano, K. Ito, A. Hurao, M. Owa, N. Kanda, and S. Nakahama, *J. Chem. Soc., Perkin Trans. 1*, 1985, 2614; (*c*) S. R. Landor, Y. M. Chan, O. O. Sonola, and A. R. Tatchell, *ibid.*, 1984, 493; (*d*) R. O. Hutchins, A. A. Magid, Y. P. Stercho, and A. Wambsgaus, *J. Org. Chem.*, 1987, **52**, 704; (*e*) M. F. Grundon, W. A. Kahn, D. R. Boyd, and W. R. Jacson, *J. Chem. Soc. C*, 1971, 2557; (*f*) M. Yamada, M. Takeda, and T. Iwakuma, *J. Chem. Soc., Perkin Trans. 1*, 1983, 265; (*g*) R. Annunziata, M. Cinquini, and F. Cozzi, *Chem. Lett.*, 1982, 339; (*h*) B. Krzyzanowska and W. J. Stec, *Synthesis*, 1982, 270.

3 G.-J. Kang, W. R. Cullen, M. D. Fryzuk, B. R. James, and J. P. Kutney, *J. Chem. Soc., Chem. Commun.*, 1988, 1466.

4 S. Itsuno, Y. Sakurai, and K. Ito, *Synthesis*, 1988, 995.

5 S. Itsuno, *J. Synth. Org. Chem. Jpn.*, 1987, **45**, 101.

6 S. Itsuno, M. Nakano, K. Miyazaki, H. Masuda, K. Ito, A. Hirao, and S. Nakahama, *J. Chem. Soc., Perkin Trans. 1*, 1985, 2039.

7 W. Theilaker and H. G. Winkler, *Chem. Ber.*, 1954, **87**, 691.

Received 17*th April* 1989; *Paper* 9/01594I