Asymmetric Reduction of Ketoxime *O*-Alkyl Ethers with Chirally Modified $NaBH_4$–$ZrCl_4$

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Reducing agents prepared from sodium borohydride ($NaBH_4$), zirconium tetrachloride ($ZrCl_4$), and chiral amino alcohols have been successfully applied to the enantioselective reduction of oxime ethers. Optically active primary amines were obtained in high enantiomeric excess (≤95% e.e.) with good chemical yield. The extent of asymmetric synthesis was dependent on the solvent, the temperature, the structure of chiral amino alcohol, and the proportions [$NaBH_4$]:[$ZrCl_4$]:[chiral amino alcohol]:[oxime ether].

Much attention has been devoted to the asymmetric synthesis of optically active amines which are important starting materials for many biologically active compounds.[1] Meyers has developed a chiral alkaloid synthesis based on asymmetric alkylation of a carbanion adjacent to nitrogen.[2] Gawley has demonstrated the asymmetric alkylation of *N*-benzyloxazolidinones to give chiral amines in high optical purity.[3] Some diastereoselective alkylations of C=N double bonds in compounds such as imines[4] or hydrazone[5] have also been reported. Asymmetric hydroboration of olefins followed by amination is another approach to producing chiral amines with high optical purity.[6]

One of the easiest ways to obtain optically active amines is asymmetric reduction of C=N double bonds. Whereas asymmetric reduction of ketones has been intensively investigated,[7] only a few references appear in the literature on the corresponding reduction of compounds with C=N double bonds in ketoximes.[8] Lithium aluminium hydride ($LiAlH_4$)–monosaccharide complexes were used for the reduction of oximes to give chiral primary amines with optical yields up to 52% e.e.[9] Asymmetric hydrosilylation of acetophenone oxime gave the product in low selectivity.[10] In the case of the asymmetric reduction of Schiff bases RR'C=NR", R ≠ H, reduction led to secondary amines RR'HC–NHR".[11]

We have reported a new reducing agent prepared from zirconium tetrachloride ($ZrCl_4$) and sodium borohydride ($NaBH_4$).[12] This combined reducing agent has the ability to reduce not only C=O double bonds but also C=N double bonds. Ketoxime *O*-alkyl ethers are reduced readily to primary amines in good chemical yield under mild reaction conditions. We have reported preliminary results obtained from a novel method of asymmetric reduction of the C=N double bonds in oxime ethers using chirally modified $NaBH_4$–$ZrCl_4$.[13] We now report the details of the investigation which includes an examination of the effect of the substrate structure, the temperature, the solvent, the molar proportions of $NaBH_4$:$ZrCl_4$:amino alcohol, and the structure of chiral auxiliaries on the reduction enantioselectivity.

Table 1. Reduction with $NaBH_4$–$ZrCl_4$ in THF at room temperature.

Substrate	Product	Yield (%)
PhCHO	$PhCH_2OH$	95
PhCOMe	PhCH(Me)OH	96
$PhCO_2H$	$PhCH_2OH$	85
$PhCO_2Et$	$PhCH_2OH$	89
$PhCH_2COCl$	$PhCH_2CH_2OH$	90
$PhCONMe_2$	$PhCH_2NMe_2$	88
Cyclohexanone oxime	cyclohexylamine	85
Acetophenone *O*-methyloxime	$PhCH(Me)NH_2$	95
N-(1-Phenylethylidene)aniline	PhCH(Me)NHPh	92
$PhCH_2CN$	$PhCH_2CH_2NH_2$	92
$PhNO_2$	No reaction	
PhBr	No reaction	

Results and Discussion

The reducing properties of the combined reagent of $NaBH_4$–$ZrCl_4$ in tetrahydrofuran (THF) are shown in Table 1. This reagent can be used to advantage for the reduction of compounds including C=O double bonds, C=N double bonds,

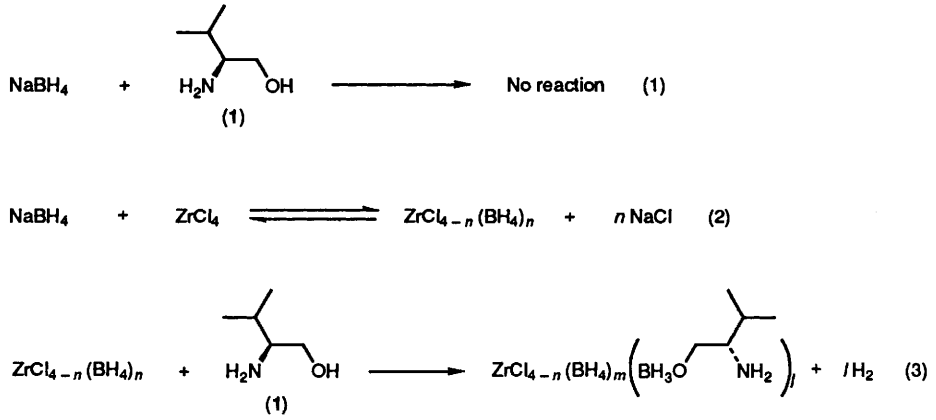


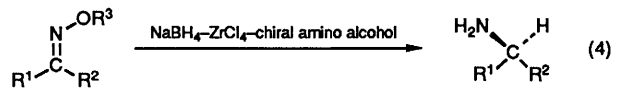
Table 2. Asymmetric reduction of ketoxime *O*-alkyl ethers with the reagent prepared from $NaBH_4$, Lewis acid, and chiral amino alcohol (**1**) in THF at room temperature.[a]

Run	R^1–C(=N–OR^3)–R^2 R^1	R^2	R^3	Chiral amine product Yield[b] (%)	E.e.[c] (%)	Config.
1	Ph	Me	Me	95	64[d]	*S*
2	Ph	Et	Me	93	66[e]	*S*
3	Ph	Pr	Me	90	61[f]	*S*
4	Ph	Me	Bz	91	69[d]	*S*
5	Ph	Et	Bz	88	72[e]	*S*
6	1-Naph	Me	Me	85	55[g]	*S*
7	2-Naph	Me	Me	90	61[h]	*S*
8	3,4-Dihdrohaphthalen-1(2*H*)-one oxime *O*-methyl ether			86	67[i]	*S*
9	Bu^t	Me	Me	78	42[j]	*S*
10	Acetophenone			95	12[k]	*R*
11[l]	Acetophenone			91	15[k]	*R*
12[l]	*N*-(1-Phenylethylidene)-aniline			87	17[m]	*R*

[a] $[NaBH_4]:[ZrCl_4]:[(1)]:[\text{oxime ether}]$ 40:40:15:12. [b] Isolated yield. [c] Determined by comparison of maximum rotation reported in the literature. [d] See ref. 17. [e] M. E. Warren and H. E. Smith, *J. Am. Chem. Soc.*, 1965, **87**, 1757. [f] Y. Yamamoto, H. Shimoda, J. Oda, and Y. Inoue, *Bull. Chem. Soc. Jpn.*, 1976, **49**, 3247. [g] H. Wolf, E. Bunnenberg, and C. Djerassi, *Chem. Ber.*, 1964, **97**, 533. [h] Optically pure sample is commercially available. [i] V. Ghishlandi and D. Vercesi, *Farmaco, Ed. Sci.*, 1971, **26**, 474. [j] H. E. Smith and H. E. Ensley, *Can. J. Chem.*, 1971, **49**, 2902. [k] U. Nagai, T. Shishido, R. Chiba, and H. Mitsuhashi, *Tetrahedron*, 1965, **21**, 1701. [l] $[NaBH_4]:[ZrCl_4]:[(1)]:[\text{substrate}]$ 60:15:15:12. [m] Ref. 11*c*.

and C≡N triple bonds. The usefulness of this reagent for the oxime reduction prompted us to investigate the application to the asymmetric reduction of oxime derivatives.

Suspension of $NaBH_4$ in dry THF is essentially inert to chiral amino alcohols as chiral auxiliary [equation (1)] and is unable to reduce ketoxime *O*-alkyl ethers. On the other hand, when $NaBH_4$ is combined with $ZrCl_4$ it reacts with chiral amino alcohols with evolution of hydrogen to form a chirally modified borohydride reagent. This reagent is considered to be a mixed borohydride on the basis of its preparation. The reducing species is presumably a mixture of zirconium aminoalkoxy borohydrides according to equations (2) and (3). This chiral reducing agent has the ability to reduce the C=N double bond of ketoxime *O*-alkyl ethers asymmetrically to give a primary amine [equation (4)]. As shown in Table 2, acetophenone



(4)

O-methyloxime was reduced with the chiral reducing agent prepared from $NaBH_4$, $ZrCl_4$, and (*S*)-valinol (**1**) to give (*S*)-1-phenylethylamine in 64% e.e. with 95% yield. All the reductions were carried out at room temperature in dry THF unless otherwise stated. In the series (oxime ether, R^2 = methyl, ethyl, propyl) there was little change in the selectivity of reduction: the selectivity ranged 61–66% e.e. (runs 1–3). The introduction of the bulkyl benzyl group in the ether substituent R^3 increases the asymmetric induction to some extent (runs 4, 5). With all experiments, this reagent consistently affords *S*-amine

Table 3. Effect of Lewis acid on the enantioselectivity in the reduction of acetophenone *O*-methyloxime in THF at room temperature.[a]

Run	Lewis acid	Chiral amino alcohol	1-Phenylethylamine Yield (%)	E.e. (%)	Config.
1	$ZrCl_4$	(1)	95	64	*S*
2	$ZrCl_4$	(4)	95	90	*S*
3	$SnCl_4$	(1)	53	17	*S*
4	$FeCl_3$	(1)	95	51	*S*
5	CuCl	(1)	0		
6	$ZnCl_2$	(1)	0		
7	$ZnBr_2$	(1)	0		
8	$AlCl_3$	(1)	0		
9	$ZnCl_2$ + $AlCl_3$	(1)	78	70	*S*
10	$ZnCl_2$ + $AlCl_3$	(4)	75	95	*S*

[a] $[NaBH_4]:[\text{Lewis acid}]:[\text{amino alcohol}]:[\text{oxime ether}]$ 40:40:15:12.

predominantly. The reduction of the *O*-methyloxime of a dialkyl ketone, 3,3-dimethylbutan-2-one, also yielded an amine enriched in the *S*-enantiomer but did not give a satisfactory optical yield (run 9). The reduction of acetophenone and *N*-(1-phenylethylidene)aniline with this reagent resulted in a lower enantioselectivity (runs 10–12).

Effect of Lewis Acid.—A combination of $NaBH_4$ and transition-metal halides has been frequently used in selective reductions.[14] In the asymmetric reduction of ketones with chirally modified borohydrides, addition of metal halides was reported to be useful in some cases.[15] Addition of several different kinds of Lewis acid was examined in this system (Table 3). Some Lewis acids such as $ZnCl_2$, $ZnBr_2$, or $AlCl_3$ were not effective in reducing the ketoxime *O*-alkyl ether. A mixture of $ZnCl_2$ and $AlCl_3$ (1:1) was effective in promoting the asymmetric reduction of ketoxime *O*-alkyl ethers to give the highest enantioselectivity (95% e.e.) observed (Table 3, run 10). However, removal of the mixed salts of zinc and aluminium encountered a difficulty which caused a lowering of the chemical yield. Separation of these salts from the recovered chiral auxiliary also presents difficulties. This resulted in low recovery yield of the chiral amino alcohol. Addition of $ZrCl_4$ gave high chemical and optical yields. Removal of the metal salts after reaction and isolation of the product were easy in the case of $ZrCl_4$.

Effect of Molar Proportions.—In the preparation of the chiral reducing agent the molar proportions $[NaBH_4]:[ZrCl_4]:[\text{chiral amino alcohol}]$ is an important factor in determining enantioselectivity in the reduction of oxime ethers. Under a variety of molar proportions the asymmetric reductions of acetophenone *O*-methyloxime were carried out. A summary of these experiments is given in Table 4. The chiral reducing agents prepared in the ratios shown in runs 1, 2, and 8 could not reduce the oxime ether. In these cases all the active hydride species for reduction of the oxime ether may be consumed by addition of compound (**1**). The molar proportions $[NaBH_4]:[ZrCl_4]:[(1)]$ = 3–4:1:1 gave relatively high enantioselectivities (runs 5 and 6). Large excess of the reducing agent decreased the enantioselectivity (runs 12 and 13). The use of a large amount of $ZrCl_4$ caused difficulty in the isolation of amine (run 13). An equimolar amount or a slight excess of chiral amino alcohol to $ZrCl_4$ was required for high stereoselectivity (runs 5, 6, and 14). Decrease of substrate (**1**) for a constant amount of reducing agent gave a considerable reduction in enantioselectivity (runs 16–19).

Table 4. Asymmetric reduction of acetophenone *O*-methyloxime with $NaBH_4$–$ZrCl_4$ in the presence of compound (1) at room temperature.

Run	$NaBH_4$ (mmol)	$ZrCl_4$ (mmol)	(1) (mmol)	Acetophenone *O*-methyloxime (mmol)	1-Phenylethylamine Yield (%)	E.e. (%)	Config.
1	15	15	15	12	0		
2	30	15	15	12	0		
3	40	20	15	12	85	73	*S*
4	40	40	15	12	95	64	*S*
5	45	15	15	12	78	88	*S*
6	60	15	15	12	96	81	*S*
7	75	15	15	12	93	18	*S*
8	30	7.5	15	12	0		
9	40	10	15	12	75	77	*S*
10	80	20	15	12	90	71	*S*
11	120	30	15	12	88	85	S
12	160	40	15	12	83	53	S
13	200	50	15	12	79	4.0	S
14	60	15	18	12	90	92	S
15	60	15	12	12	94	58	S
16	60	15	9	12	92	19	S
17	60	15	6	12	89	7.3	S
18	60	15	3	12	95	1.7	S
19	60	15	1.5	12	90	0.6	S

Table 5. The effect of the solvent on the asymmetric reduction of acetophenone *O*-methyloxime at room temperature.[a]

Solvent	1-Phenylethylamine Yield (%)	E.e. (%)	Config.
THF	95	81	*S*
Diethyl ether	48	82	*S*
Hexane	54	70	*S*
Benzene	88	41	*S*

[a] $[NaBH_4]$:$[ZrCl_4]$:[(1)]:[oxime ether] 60:15:15:12.

Table 6. The effect of reaction temperature on the reactivity and enantioselectivity in the reduction of acetophenone *O*-methyloxime in THF.[a]

Run	Temperature (°C)	1-Phenylethylamine Yield (%)	E.e. (%)	Config.
1	−78	0		
2	0	42	46	*S*
3	−78 to room temp.	89	48	*S*
4	0 to room temp.	93	29	*S*
5	room temp.	90	92	*S*
6	50	91	65	*S*

[a] $[NaBH_4]$:$[ZrCl_4]$:[(1)]:[oxime ether] 60:15:18:12.

Effect of Solvent.—From the study of the molar proportions in Table 4 the molar proportions $[NaBH_4]$:$[ZrCl_4]$:[(1)]:[oxime] = 60:15:15:12 were found to give reproducible values of high chemical and optical yield. These molar proportions were adopted for the study of the effect of the solvent (Table 5). THF, diethyl ether, hexane, and benzene are the solvents of choice. The chemical yields were affected by the choice of solvent. In benzene a lower optical yield was also observed. THF gave the highest chemical yield and satisfactory optical yield in this system.

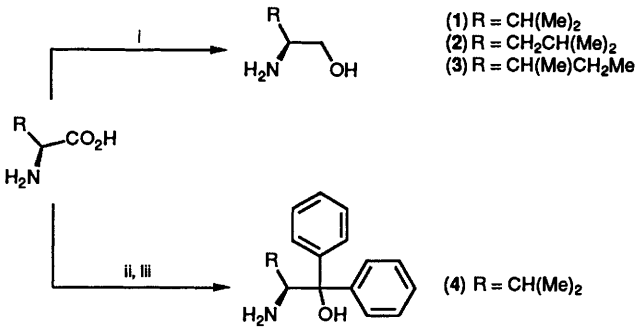
Table 7. Asymmetric reduction of acetophenone *O*-methyloxime with $NaBH_4$–$ZrCl_4$ in the presence of various chiral amino alcohols in THF.[a]

Run	Chiral amino alcohol	1-Phenylethylamine Yield (%)	E.e. (%)	Config.
1	(1)	96	81	*S*
2[b]	(4)	95	90	*S*
3	(4)	92	95	*S*
4[b]	(2)	95	43	*S*
5	(2)	90	54	*S*
6	(3)	89	42	*S*
7	(6)	95	35	*S*
8[c]	(6)	94	35	*S*

[a] $[NaBH_4]$:$[ZrCl_4]$:[(1)]:[oxime ether] 60:15:15:12. [b] $[NaBH_4]$:$[ZrCl_4]$:[(1)]:[oxime ether] 40:40:15:12. [c] Recycled polymer was used.

Effect of Temperature.—The temperature at which the oxime ether was added did have a significant effect as shown in Table 6. At −78 °C the chiral reducing agent could not reduce acetophenone *O*-methyloxime. Only moderate chemical and optical yields were obtained at 0 °C. At temperatures below room temperature the reduction of the oxime ether did not give satisfactory e.e.s. The highest e.e. with good chemical yield was obtained when the reduction was carried out at room temperature. The degree of asymmetric induction decreased again when the temperature was raised (50 °C).

Structural Variation within the Chiral Modifier.—The results obtained with the chiral amino alcohols (1), (2), (3), (4), and (6) as chiral modifiers in the reduction of acetophenone *O*-methyloxime are shown in Table 7. These chiral amino alcohols were readily prepared from (*S*)-amino acids (Scheme 1). Although the relatively bulky amino alcohol (4) having two phenyl groups gave the highest e.e. in this system, commercially available (*S*)-valinol (1) gave a sufficiently good e.e. Since the hydrochloride of amine (4) is insoluble in both diethyl ether and water it can be separated easily from the reaction mixture and can be isolated as the free amine in 80% recovered yield. It could be reused to give reproducible results.



Scheme 1. *Reagents:* i, $LiAlH_4$; ii, $SOCl_2$–MeOH; iii, PhMgBr.

It is always important to develop a polymer-supported reagent or catalyst which can be easily separated quantitatively from the reaction mixture by simple filtration.[16] Polymeric chiral amino alcohol (**6**) was prepared as shown in equation (5). Although the obtained optical yield was only 35% e.e., the polymeric amino alcohol was recovered almost quantitatively and was reused without loss of activity.

Experimental

M.p.s. were determined on a Yanagimoto hot-stage microscope and are uncorrected. ^1H (270 MHz) NMR spectra were recorded on a JEOL JNM-GX270 spectrometer with Me_4Si as internal standard. Analytical TLC was performed on Merck silica gel $60F_{254}$ pre-coated plates. Optical rotations were recorded with a JASCO DIP-140 polarimeter.

THF and diethyl ether were dried by distillation from sodium–benzophenone ketyl. All reactions were carried out in oven-dried (120 °C overnight) apparatus under a slight positive pressure of dry nitrogen. Benzene and hexane were distilled over CaH_2. $NaBH_4$ was dried *in vacuo* at 60 °C for 24 h prior to use. $ZnCl_2$ and $ZnBr_2$ were dried *in vacuo* at 60 °C for 5 h prior to use. $ZrCl_4$, $SnCl_4$, $FeCl_3$, CuCl, and $AlCl_3$, were used as supplied commercially.

General Procedure for the Asymmetric Reduction of Acetophenone O-*Methyloxime.*—To a mixture of $ZrCl_4$ (3.50 g, 15 mmol) in dry THF (50 ml) at room temperature under dry nitrogen was added $NaBH_4$ powder (2.27 g, 60 mmol). After the mixture had been stirred for 20 h, a solution of compound (**1**) (1.55 g, 15 mmol) in dry THF (10 ml) was added at room temperature and the mixture was stirred for a further 20 h. To 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 cooled to 0 °C and quenched by dropwise addition of water and 1M-HCl. After THF had been evaporated 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 1-phenylethylamine {1.40 g, 95% $[\alpha]_D^{22}$ −32.8° (neat)} which represents an 81% e.e. based on comparison with the maximum rotation {$[\alpha]_D$ −40.4° (neat)}.[17]

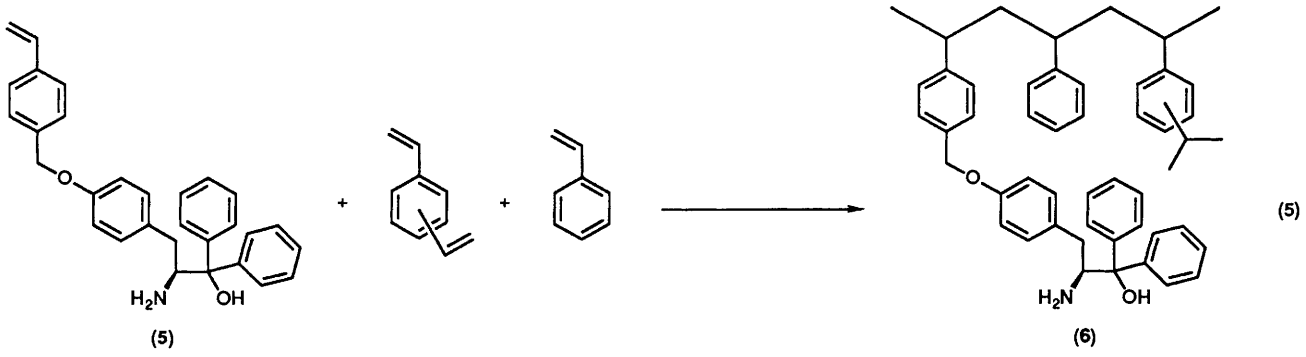
A number of other asymmetric reductions using different molar ratios of the reagents were performed under conditions similar to those described above.

Synthesis of Oxime Ethers.—Ketoximes were prepared by standard methods[18] and were purified by recrystallization. Oxime ethers used in this study were prepared according to the routes described previously.[8b]

Synthesis of Chiral Amino Alcohols.—Chiral amino alcohols (**1**)–(**3**) were prepared by $LiAlH_4$ reduction of the corresponding (*S*)-amino acids (*S*)-valine, (*S*)-leucine, and (*S*)-isoleucine, respectively.[19] Compound (**4**) was prepared from the reaction of (*S*)-valine methyl ester hydrochloride with phenyl Grignard reagent as described previously.[8b]

Preparation of Polymer-supported Chiral Amino Alcohol (**6**).—The polymer-supported reagent (**6**) was prepared by terpolymerization of the amino alcohol (**5**), styrene, and divinylbenzene according to the procedure described previously.[20]

Asymmetric Reduction of Acetophenone O-*Methyloxime using Polymer-supported Chiral Amino Alcohol* (**6**).—To a mixture of $ZrCl_4$ (3.50 g, 15 mmol) in dry THF (100 ml) at room temperature under dry nitrogen was added $NaBH_4$ powder (2.27 g, 60 mmol). After a mixture had been stirred for 20 h, dried polymer beads (**6**) (9.7 g; 1.55 mequiv. of chiral amino alcohol/g resin) and THF (70 ml) were added at room temperature and the mixture was stirred slowly for a further 20 h. To the resulting polymeric 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 cooled to 0 °C and quenched by dropwise addition of water and 1M-HCl. After the insoluble polymer beads had been filtered off, the aqueous layer was neutralized with NH_4OH and extracted with ethyl acetate and evaporated to give an oily residue. Bulb-to-bulb distillation afforded 1-phenylethylamine {1.38 g, 95%; $[\alpha]_D^{22}$ −14.28° (neat)} of 35% e.e. based on comparison with the maximum rotation.[17] Recovered polymer was neutralized with a mixture of NH_4OH and THF and washed successively with methanol, chloroform, THF, and methanol again. After the polymer (**6**) had been dried *in vacuo* at 40 °C for 20 h it could be used for the next reaction.



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