

# Asymmetric reduction of ketones with sodium aluminum hydride modified with chiral amino alcohols

M. G. Vinogradov,<sup>a\*</sup> O. V. Mikhalev,<sup>a</sup> V. A. Pavlov,<sup>a</sup> V. A. Ferapontov,<sup>a</sup> O. R. Malyshev,<sup>a</sup> and G. L. Heise<sup>b</sup>

<sup>a</sup>N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 47 Leninsky prosp., 119991 Moscow, Russian Federation.

Fax: +7 (095) 135 5328. E-mail: ving@cacr.ioc.ac.ru

<sup>b</sup>Cambrex Corporation, One Meadowlands Plaza, East Rutherford, NJ 07073, USA

Asymmetric reduction of ketones with hydride complexes, which were prepared by *in situ* modification of NaAlH<sub>4</sub> with various chiral amino alcohols or diamines, was studied. The highest enantioselectivity (up to 93% *ee*) was achieved using 2-(hydroxydiphenylmethyl)pyrrolidine as a chiral inducing agent.

**Key words:** ketones, sodium aluminum hydride, chiral alcohols, amino alcohols, diamines, asymmetric reduction.

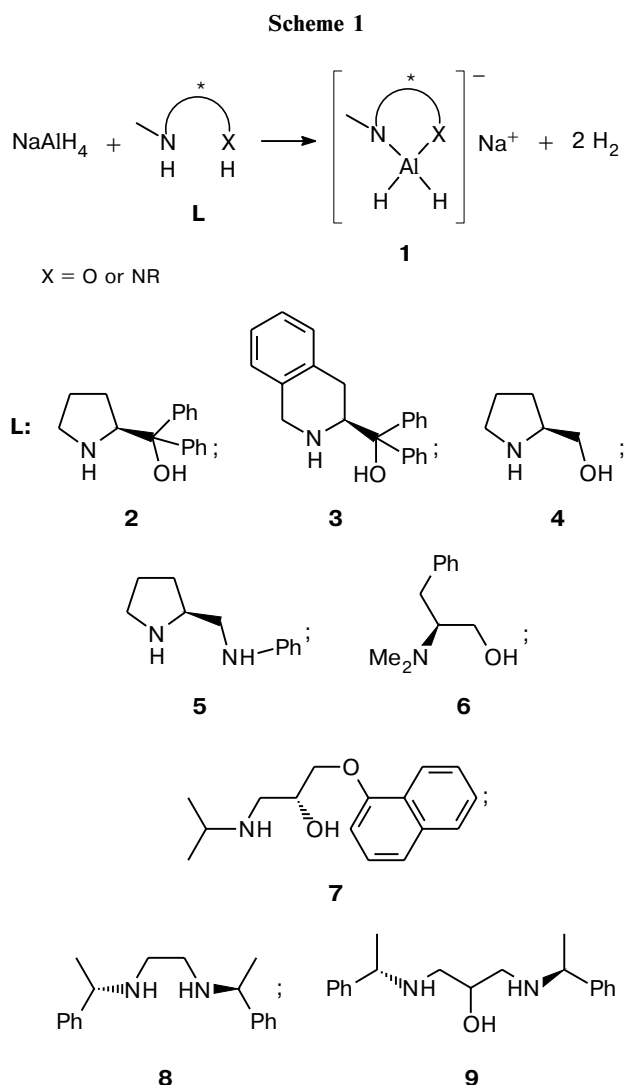
Catalytic methods for asymmetric hydrogenation have been developed intensively in recent years.<sup>1,2</sup> Simultaneously, reduction with chiral aluminum-hydride reagents, which proceeds under mild conditions and does not require special chemical apparatus for operations with hydrogen under pressure, have attracted attention of researchers.<sup>3,4</sup>

Recently, we have demonstrated<sup>5</sup> that asymmetric reduction of ketones by some hydride reagents, which were prepared by modification of NaAlH<sub>4</sub> with chiral diols, proceeds with higher enantioselectivity than reduction by analogous LiAlH<sub>4</sub> derivatives. This fact gave impetus to studies of the stereochemistry of reduction of ketones by hydride complexes based on NaAlH<sub>4</sub> which contain chiral 1,2-*N,O*- or 1,2-*N,N*-bidentate ligands. These complexes have not been used previously as chiral reducing agents. The results of this investigation are discussed in the present work.

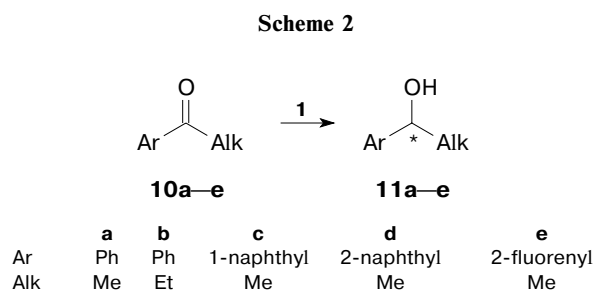
## Results and Discussion

We prepared chiral dihydride reagents with the assumed structures **1** by the *in situ* reactions of NaAlH<sub>4</sub> with equimolar amounts of bidentate amino alcohols **2–4** or **7** or diamines **5** or **8**. In all cases, two moles of hydrogen were eliminated (Scheme 1). For comparison, tridentate ligand **9** and amino alcohol **6** containing the tertiary amino group were tested as chiral inducing agents.

The IR spectrum of dihydride **1**, which was prepared from NaAlH<sub>4</sub> and amino alcohol **2** in THF, has an absorption band at 1675 cm<sup>-1</sup> ( $\epsilon_{\max} = 85$ ) characteristic of vibrations of the Al–H bonds in sodium or lithium aluminum dihydride complexes.<sup>5</sup> At the same time, the IR spectrum does not have bands characteristic of Al–H bonds in monohydride complexes (1760–1770 cm<sup>-1</sup>) or



AlH<sub>3</sub> derivatives (1800–1900 cm<sup>-1</sup>), which could be formed by disproportionation or dissociation of dihydride **1**.<sup>5</sup> These data indicate that it is the complex of general formula **1** that performs reduction of ketones **10** (Scheme 2), thus determining the stereochemistry of the reaction under study.



The highest enantioselectivity of reduction (up to 93% *ee*) was achieved using amino alcohol **2** as an inducing agent (Table 1, runs 1–6). It should be noted that the reactivity of 1-acetonaphthone in the reaction with the above-mentioned reagent appeared to be more than an order of magnitude lower than that with 2-acetonaphthone (*cf.* the degrees of conversion of ketones **10c** and **10d** in runs 4 and 5, respectively). The reaction involving NaAlH<sub>4</sub> modified with ligand **3**, which is structurally similar to ligand **2**, proceeded with moderate enantioselectivity (55–70% *ee*) (see Table 1, runs 7 and 8). The enantioselectivity of the reaction using ligands **4** or **5**, which are structural analogs of ligand **2** but contain less bulky substituents at position 2 of the pyrrolidine ring (CH<sub>2</sub>OH and CH<sub>2</sub>NHPh, respectively),

is far lower (see Table 1, runs 9–12). In the case of reagent **1** containing ligand **4**, the pronounced dependence of the enantioselectivity of reduction on the temperature was observed (see Table 1, runs 9–11; *cf.* Ref. 5).

Aluminum-hydride reagents prepared by modification of NaAlH<sub>4</sub> with ligands **6–9** proved to be inefficient or poorly efficient in the reaction under study (see Table 1, runs 12–17).

Apparently, the stereochemistry of hydrogenation of aromatic ketones with reagents **1** is determined by the configuration of the chiral ligand. Thus in the case of NaAlH<sub>4</sub> modified with ligands possessing the (*S*) configuration, the corresponding (*R*) enantiomers of **11** were obtained as the major products of asymmetric reduction.

Therefore, of all amino alcohols and diamines under study, amino alcohols **2** and **3** containing the 2-hydroxy-diphenylmethyl-substituted pyrrolidine or piperidine ring are the most efficient chiral reagents for modification of NaAlH<sub>4</sub>.

## Experimental

Polarimetric measurements were carried out on a Jasco DIP-360 instrument (1-cm cell). The <sup>1</sup>H NMR spectra were recorded on a Bruker AC-200 instrument. Commercial NaAlH<sub>4</sub> and (*S*)- $\alpha$ -phenylethylamine (Zeeland Chemicals, USA) were used. Ligands **2** and **4–7** and THF were purchased from Fluka. Ligands **3** and **8** were synthesized according to known procedures.<sup>6,7</sup> The compositions of hydrogenation products of ketones **10a,b** and **10c–e** were determined by capillary GLC and HPLC, respectively, as described previously.<sup>5</sup>

**Table 1.** Reduction of ketones **10** with chiral complexes **1**, prepared *in situ* from NaAlH<sub>4</sub> and ligands **2–9** in THF

Run	Ligand	Ligand configuration	[Ligand] [NaAlH <sub>4</sub> ]	Ketone	Reaction conditions		Conversion* 10→11 (%)	Product	<i>ee</i> (%)*
					<i>T</i> /°C	$\tau$ /h			
1	<b>2</b>	( <i>S</i> )	1 : 1	<b>10a</b>	–70	3	85	<b>11a</b>	92 ( <i>R</i> )
2	<b>2</b>	( <i>S</i> )	1 : 1	<b>10a</b>	–20	3	92	<b>11a</b>	68 ( <i>R</i> )
3	<b>2</b>	( <i>S</i> )	1 : 1	<b>10b</b>	–70	3	87	<b>11b</b>	67 ( <i>R</i> )
4	<b>2</b>	( <i>S</i> )	1 : 1	<b>10c</b>	–70	3	0.6	<b>11c</b>	—**
5	<b>2</b>	( <i>S</i> )	1 : 1	<b>10d</b>	–70	3	26	<b>11d</b>	64 ( <i>R</i> )
6	<b>2</b>	( <i>S</i> )	1 : 1	<b>10e</b>	–70	3	70	<b>11e</b>	93 ( <i>R</i> )
7	<b>3</b>	( <i>S</i> )	1 : 1	<b>10a</b>	0***	24	72	<b>11a</b>	69 ( <i>R</i> )
8	<b>3</b>	( <i>S</i> )	1 : 1	<b>10a</b>	20	24	82	<b>11a</b>	54 ( <i>R</i> )
9	<b>4</b>	( <i>S</i> )	1 : 1	<b>10a</b>	–70	5	32	<b>11a</b>	47 ( <i>R</i> )
10	<b>4</b>	( <i>S</i> )	1 : 1	<b>10a</b>	0	2	57	<b>11a</b>	10 ( <i>R</i> )
11	<b>4</b>	( <i>S</i> )	1 : 1	<b>10a</b>	20	2	60	<b>11a</b>	0
12	<b>5</b>	( <i>S</i> )	1 : 1	<b>10a</b>	–70	3	15	<b>11a</b>	23 ( <i>R</i> )
13	<b>6</b>	( <i>S</i> )	2 : 1	<b>10a</b>	–20	24	36	<b>11a</b>	19 ( <i>R</i> )
14	<b>6</b>	( <i>S</i> )	2 : 1	<b>10a</b>	0	24	46	<b>11a</b>	19 ( <i>R</i> )
15	<b>7</b>	( <i>S</i> )	1 : 1	<b>10a</b>	–20	24	8	<b>11a</b>	0
16	<b>8</b>	( <i>S,S</i> )	1 : 1	<b>10a</b>	–20	48	61	<b>11a</b>	5 ( <i>R</i> )
17	<b>9</b>	( <i>S,S</i> )	1 : 1	<b>10a</b>	–20	48	60	<b>11a</b>	0

\* The results averaged over several runs are given.

\*\* We failed to determine the *ee* value for **11c** due to the low conversion of ketone **10c**.

\*\*\* At temperatures below 0 °C, the results were not reproducible.

**Asymmetric hydrogenation of ketones 10 (general procedure).** A 0.5 M solution of the chiral ligand in THF was added with stirring to a 0.3 M solution of NaAlH<sub>4</sub> in THF cooled to -20 °C. The reaction mixture was stirred at this temperature, then warmed to -20 °C during 1 h, and kept at this temperature for 3 h. The resulting solution of reagent **1** was cooled to the required temperature (see Table 1) and added dropwise with stirring to a 1 M solution of ketone in THF (the molar ratio **1/10** = 3). After completion of the reaction, the mixture was treated with aqueous MeOH (MeOH—H<sub>2</sub>O, 9 : 1 v/v) and then with a 1 N HCl solution until the mixture became weakly acidic and extracted with ether. The solvent was evaporated and the residue was analyzed by GLC or HPLC.

**(S,S)-N,N'-Bis(1-phenylethyl)-1,3-diaminopropan-2-ol (9).** A solution of (*S*)- $\alpha$ -phenylethylamine (2.57 mL, 20 mmol) and freshly distilled epichlorohydrin (0.39 mL, 5 mmol) in MeOH (20 mL) was refluxed for 30 min. Then the reaction mixture was concentrated *in vacuo*. The residue was dissolved in Pr<sup>i</sup>OH and treated with HCl. The precipitate that formed was filtered off and pure diamino alcohol **9** was obtained as dihydrochloride in a yield of 1.22 g (66%). T.decomp. 255 °C, [ $\alpha$ ]<sub>D</sub><sup>22</sup> -36 (*c* 2, MeOH). Found (%): C, 61.42; H, 7.58; Cl, 19.22; N, 7.65. C<sub>19</sub>H<sub>28</sub>Cl<sub>2</sub>N<sub>2</sub>O. Calculated (%): C, 61.45; H, 7.60; Cl, 19.09; N, 7.54. <sup>1</sup>H NMR (CDCl<sub>3</sub>—CCl<sub>4</sub>, 1 : 1),  $\delta$ : 1.50 (d, 6 H, 2 Me); 2.30—2.80 (m, 4 H, 2 CH<sub>2</sub>N); 3.20 (br.s, 3 H, 2 NH and OH); 3.70—4.00 (m, 3 H, 2 CHN and CHO); 7.10—7.60 (m, 10 H, arom.). <sup>13</sup>C NMR (CDCl<sub>3</sub>—CCl<sub>4</sub>, 1 : 1),  $\delta$ : 24.2 (2 Me); 51.3, 57.8 (2 CH<sub>2</sub>N); 58.1, 58.7 (2 CHN); 68.6 (CHO); 126.5, 127.0, 128.5, 144.7 (arom.).

Diamino alcohol dihydrochloride **9** was treated with Et<sub>3</sub>N (3 mL) in 95% EtOH (5 mL). Then a 1 : 1 ether—hexane mixture (15 mL) was added, the precipitate of Et<sub>3</sub>N · HCl that formed was filtered off, and the filtrate was concentrated to

dryness *in vacuo*. Pure ligand **9** was obtained as an oil in a yield of 0.95 g (96%). The ligand was used for modification of NaAlH<sub>4</sub> without additional purification.

This work was financially supported by the Cambrex Corporation (USA).

## References

1. T. Naota, H. Takaya, and S.-I. Murahashi, *Chem. Rev.*, 1998, **98**, 2599.
2. R. Noyori and S. Hashiguchi, *Acc. Chem. Res.*, 1997, **30**, 97.
3. A. K. Beck, R. Dahinden, and F. N. M. Kühnle, *Reductions in Organic Synthesis. Recent Advances and Practical Applications; ACS Sympos. Ser.*, 1996, **641**, 53.
4. H. Haubenstock, in *Asymmetric Reductions with Chiral Complex Aluminum Hydrides and Tricoordinate Aluminum Reagents; Topics in Stereochemistry*, Eds. N. L. Alinger, E. L. Eliel, and S. H. Wilen, Intersci. Publ., 1983, **14**, 231.
5. M. G. Vinogradov, L. S. Gorshkova, V. A. Pavlov, O. V. Mikhalev, G. V. Chel'tsova, I. V. Razmanov, V. A. Ferapontov, O. R. Malyshev, and G. L. Heise, *Izv. Akad. Nauk, Ser. Khim.*, 2000, 459 [*Russ. Chem. Bull., Int. Ed.*, 2000, **49**, 459].
6. K. Hayashi, Y. Ozaki, K. Nunami, and N. Yoneda, *Chem. Pharm. Bull.*, 1983, **31**, 312.
7. G. Märkl and G. Yu Jin, *Tetrahedron Lett.*, 1980, **21**, 3467.

Received August 18, 2000;  
in revised form November 4, 2000