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

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Asymmetric reduction of ketones with hydride complexes, which were prepared by *in situ* modification of $NaAlH_4$, 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.[1,2] 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.[3,4]

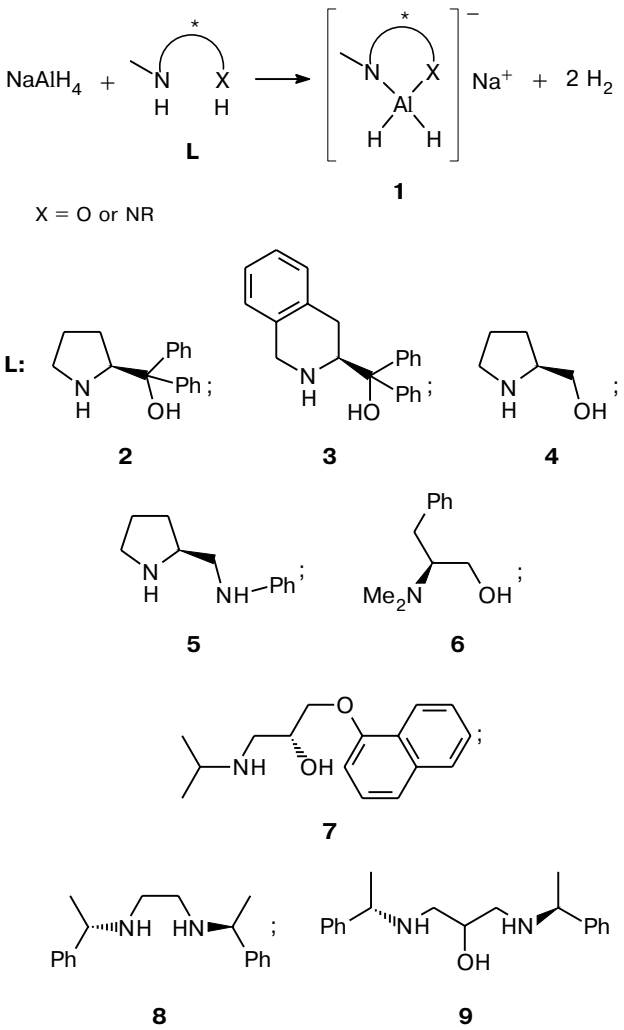
Recently, we have demonstrated[5] that asymmetric reduction of ketones by some hydride reagents, which were prepared by modification of $NaAlH_4$ with chiral diols, proceeds with higher enantioselectivity than reduction by analogous $LiAlH_4$ derivatives. This fact gave impetus to studies of the stereochemistry of reduction of ketones by hydride complexes based on $NaAlH_4$ 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 $NaAlH_4$ 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 $NaAlH_4$ and amino alcohol **2** in THF, has an absorption band at 1675 cm^{-1} (ε_{max} = 85) characteristic of vibrations of the Al—H bonds in sodium or lithium aluminum dihydride complexes.[5] At the same time, the IR spectrum does not have bands characteristic of Al—H bonds in monohydride complexes (1760—1770 cm^{-1}) or

Scheme 1



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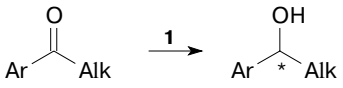
AlH_3 derivatives (1800—1900 cm^{-1}), which could be formed by disproportionation or dissociation of dihydride **1**.[5] These data indicate that it is the complex of general formula **1** that performs reduction of ketones **10** (Scheme 2), thus determining the stereochemistry of the reaction under study.

Scheme 2



10a—e **11a—e**

	a	b	c	d	e
Ar	Ph	Ph	1-naphthyl	2-naphthyl	2-fluorenyl
Alk	Me	Et	Me	Me	Me

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 $NaAlH_4$ 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_2OH and CH_2NHPh, 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 $NaAlH_4$ 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 $NaAlH_4$ 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-hydroxydiphenylmethyl-substituted pyrrolidine or piperidine ring are the most efficient chiral reagents for modification of $NaAlH_4$.

Experimental

Polarimetric measurements were carried out on a Jasco DIP-360 instrument (1-cm cell). The ^1H NMR spectra were recorded on a Bruker AC-200 instrument. Commercial $NaAlH_4$ and (*S*)-α-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.[6,7] The compositions of hydrogenation products of ketones **10a,b** and **10c—e** were determined by capillary GLC and HPLC, respectively, as described previously.[5]

Table 1. Reduction of ketones **10** with chiral complexes **1**, prepared *in situ* from $NaAlH_4$ and ligands **2—9** in THF

Run	Ligand	Ligand configuration	[Ligand]/[$NaAlH_4$]	Ketone	Reaction conditions		Conversion* **10**→**11** (%)	Product	*ee* (%)*
					T/°C	τ/h			
1	**2**	(*S*)	1 : 1	**10a**	−70	3	85	**11a**	92 (*R*)
2	**2**	(*S*)	1 : 1	**10a**	−20	3	92	**11a**	68 (*R*)
3	**2**	(*S*)	1 : 1	**10b**	−70	3	87	**11b**	67 (*R*)
4	**2**	(*S*)	1 : 1	**10c**	−70	3	0.6	**11c**	—**
5	**2**	(*S*)	1 : 1	**10d**	−70	3	26	**11d**	64 (*R*)
6	**2**	(*S*)	1 : 1	**10e**	−70	3	70	**11e**	93 (*R*)
7	**3**	(*S*)	1 : 1	**10a**	0***	24	72	**11a**	69 (*R*)
8	**3**	(*S*)	1 : 1	**10a**	20	24	82	**11a**	54 (*R*)
9	**4**	(*S*)	1 : 1	**10a**	−70	5	32	**11a**	47 (*R*)
10	**4**	(*S*)	1 : 1	**10a**	0	2	57	**11a**	10 (*R*)
11	**4**	(*S*)	1 : 1	**10a**	20	2	60	**11a**	0
12	**5**	(*S*)	1 : 1	**10a**	−70	3	15	**11a**	23 (*R*)
13	**6**	(*S*)	2 : 1	**10a**	−20	24	36	**11a**	19 (*R*)
14	**6**	(*S*)	2 : 1	**10a**	0	24	46	**11a**	19 (*R*)
15	**7**	(*S*)	1 : 1	**10a**	−20	24	8	**11a**	0
16	**8**	(*S*,*S*)	1 : 1	**10a**	−20	48	61	**11a**	5 (*R*)
17	**9**	(*S*,*S*)	1 : 1	**10a**	−20	48	60	**11a**	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 $NaAlH_4$ 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_2O, 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*)-α-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^iOH 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, $[\alpha]_D^{22}$ −36 (*c* 2, MeOH). Found (%): C, 61.42; H, 7.58; Cl, 19.22; N, 7.65. $C_{19}H_{28}Cl_2N_2O$. Calculated (%): C, 61.45; H, 7.60; Cl, 19.09; N, 7.54. ^{1}H NMR ($CDCl_3$—CCl_4, 1 : 1), δ: 1.50 (d, 6 H, 2 Me); 2.30—2.80 (m, 4 H, 2 CH_2N); 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.). ^{13}C NMR ($CDCl_3$—CCl_4, 1 : 1), δ: 24.2 (2 Me); 51.3, 57.8 (2 CH_2N); 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_3N (3 mL) in 95% EtOH (5 mL). Then a 1 : 1 ether—hexane mixture (15 mL) was added, the precipitate of $Et_3N \cdot HCl$ 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 $NaAlH_4$ without additional purification.

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