Organic Chemistry

Asymmetric reduction of ketones with sodium aluminum hydride modified by various chiral diols

M. G. Vinogradov,[a] L. S. Gorshkova,[a] V. A. Pavlov,[a] O. V. Mikhalev,[a] G. V. Chel'tsova,[a] I. V. Razmanov,[a] V. A. Feraponton,[a] O. R. Malyshev,[a] and G. L. Heise[b]*

[a]*N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 47 Leninsky prosp., 117913 Moscow, Russian Federation. Fax: +7 (095) 135 5328. E-mail: ving@cacr.ioc.ac.ru*

[b]*Cambrex Corporation, One Meadowlands Plaza, East Rutherford, NJ 07073, USA. E-mail: gheise@boston.chirex.com*

New stereoselective reducing reagents were prepared *in situ* by modification of $NaAlH_4$ with various chiral diols. The efficiency of 1,4- and 1,3-diols as chiral auxiliaries in the reactions of alkyl aryl ketones with modified $NaAlH_4$ was considerably higher than that of 1,2-diols. The effect of the nature of the achiral ligand additionally introduced into the chiral hydride reagent on the enantioselectivity of ketone reduction was studied. It was proposed that the sodium cation does not necessarily participate at the stage governing the reaction stereochemistry.

Key words: sodium aluminum hydride, chiral diols, 1,1'-bis-2-naphthol, α,α,α',α'-tetraaryl-1,3-dioxolane-4,5-dimethanols, asymmetric reduction, enantiomers, ketones.

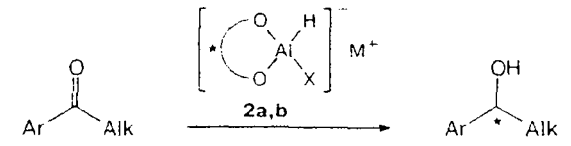
Lithium aluminum hydrides modified by chiral 1,1'-bis-2-naphthol (BINOL)[1] or α,α,α',α'-tetraaryl-1,3-dioxolane-4,5-dimethanols (TADDOL)[2] are known to reduce stereoselectively alkyl aryl ketones to optically active secondary alcohols. High enantioselectivity of the hydride reduction of ketones was observed only in the case where a monodentate achiral ligand, for example, EtOH or MeOH, was introduced into $LiAlH_4$ besides the chiral bidentate ligand. However, little data[3,4] are currently available on the reduction of carbonyl compounds and other substrates by $NaAlH_4$-derived chiral complexes; the reported optical yields are low.

This paper is the first communication devoted to the modification of $NaAlH_4$ with various chiral 1,2-, 1,3-, and 1,4-diols and to comparison of the efficiency of the resulting hydride complexes in the asymmetric reduction of prochiral substrates (taking the reduction of alkyl aryl ketones **1** as an example) (Scheme 1). For the synthesis of secondary alcohols **3** from ketones **1**, we prepared *in situ* reagents **2** containing either one or two hydride hydrogen atoms (X = H or OAlk or OAr).

Translated from *Izvestiya Akademii Nauk. Seriya Khimicheskaya*, No. 3, pp. 459—464, March, 2000.

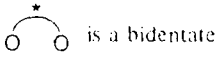
1066-5285/00/4903-0460 $25.00

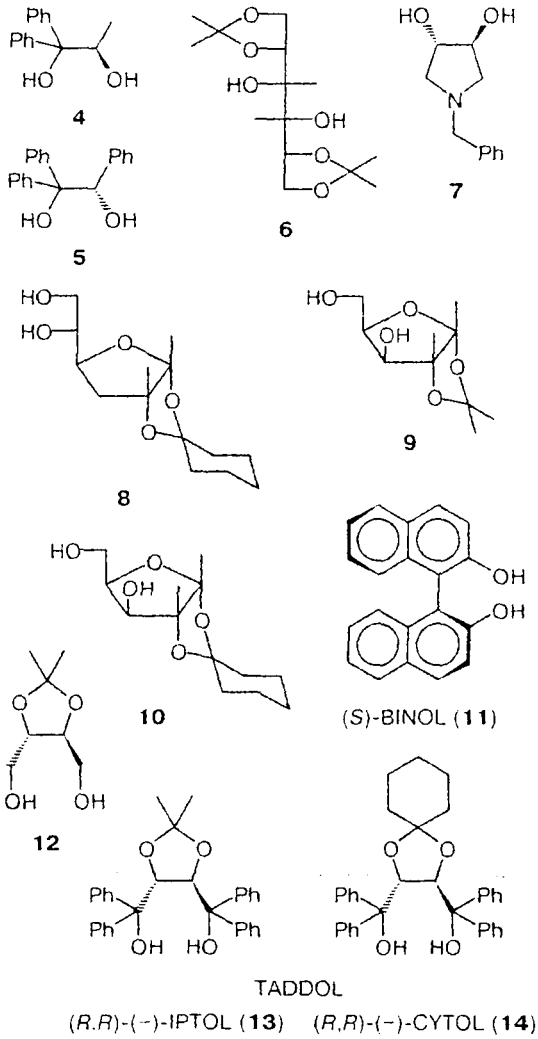
Scheme 1



$M^+ = Na^+$ (**a**), Li^+ (**b**); X = H, OAlk, OAr

	a	b	c	d	e	f
Ar	Ph	Ph	Ph	Ph	2-naphthyl	2-fluorenyl
Alk	Me	Et	Pr	Pr^i	Me	Me


is a bidentate ligand formed by chiral diol **4**—**14**.



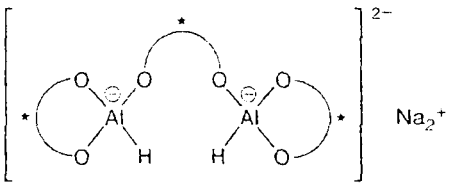
Results and Discussion

Sterically hindered 1,4-diols such as BINOL (**11**), IPTOL (**13**), and CYTOL (**14**) proved to be the most efficient ligands for the asymmetric reduction of ketones **1** with sodium aluminum hydride reagents **2a** (X = H) to arylalkylcarbinols **3** (70—90% *ee*) (Tables 1 and 2). 1,3-Diols **9** and **10** are somewhat less efficient chiral inductors than 1,4-diols; they exhibit only moderate enantioselectivity (30—50% *ee*), except for some experiments in which an additional achiral ligand (X) has been introduced in complex **2** (Table 3).

Unlike complexes **2a**, derived from 1,4- and 1,3-diols, sodium aluminum hydride reagents containing chiral ligands derived from 1,2-diols (**4**—**8**) exhibited a low degree of asymmetric induction in the reactions with alkyl aryl ketones (no more than 15% *ee* for secondary alcohol **3a** in the reaction with ketone **1a** in THF even at −70 °C).

Modification of $NaAlH_4$ by chiral 1,4-diols. As in the case of the BINOL-containing lithium aluminum hydride reagent,[1] asymmetric reduction of ketones by $NaAlH_4$ modified with the same ligand proceeded most efficiently when the reagent contained an additional achiral ligand (MeOH) (see Table 1). It should be noted that the reduction of ketone **1a** with sodium-containing complexes (**2a**, X = MeO) results in markedly (by 5—10%) higher *ee* values for alcohols **3a** than the reaction with lithium-containing reagent **2b** under the same conditions (*cf.* entries 1—6, Table 1).

The data of Table 1 (entries 7—9) demonstrate that BINOL can be used not only as a chiral inductor but simultaneously as an additional monodentate ligand if the initial Al : BINOL molar ratio is 1 : 1.5. In this case, the stereoselectivity of reduction of ketone **1a** might be due to the formation of binuclear complexes of type **A**.



A

Like the BINOL-containing monohydride reagent **2a** (X = OMe), the complex with the presumable structure **A** shows a higher enantioselectivity in the reaction with ketone **1a** than its lithium-containing analog (*cf.* entries 7—9, Table 1).

The greatest difference in enantioselectivity of reduction was observed for reactions involving dihydride complexes **2a** and **2b** (X = H). Thus the reaction of ketone **1a** with **2a** (X = H) occurred with a moderate optical yield (30—40% *ee*), whereas a similar reaction with Li^+-containing reagents **2b** (X = H) always afforded the racemic product to within the accuracy of GLC (*cf.* entries 10—14, Table 1).

By analogy with the BINOL-containing reagent[1] BINAL-H, the TADDOL-containing aluminum hydride complexes **2** can be designated by TADDAL-H_2 (X = H) or TADDAL-H (X = OR). As noted above, the

Table 1. Reduction of acetophenone (**1a**) with reagents **2a** and **2b** containing the BINOLate ligand

Entry	BINOL configuration	Aluminum hydride complex	Ligand X in complex **2**	Reaction conditions T/°C	Reaction conditions τ/h	Degree of conversion of ketone **1a** into secondary alcohol **3a** (%)	*ee* (%)
1	(*S*)	**2a**	MeO	−70	2	58	89 (*S*)
2	(*S*)	**2a**	MeO	−70	4	66	87 (*S*)
3	(*S*)	**2a**	MeO	−70	6	87	90 (*S*)
4	(*S*)	**2b**	MeO	−70	2	92	79 (*S*)
5	(*S*)	**2b**	MeO	−70	4	84	83 (*S*)
6	(*R*)	**2b**	MeO	−70	5	60	78 (*R*)[a]
7[b]	(*S*)	**2a**	0.5 	−70	2	72	73 (*S*)
8[b]	(*S*)	**2a**	0.5 	−70	3	80	65 (*S*)
9[b]	(*S*)	**2b**	0.5 	−70	2	93	34 (*S*)
10	(*S*)	**2a**	H	−20	2	94	31 (*S*)
11	(*S*)	**2a**	H	−70	2	91	38 (*S*)
12	(*R*)	**2b**	H	30	5	85	2 (*R*)[a]
13	(*S*)	**2b**	H	−20	2	100	0
14	(*S*)	**2b**	H	−70	2	100	0

Note. THF, the molar ratio Al : BINOL : XH : ketone = 1 : 1 : 1(0) : 0.33. The yields and *ee* are the average values over several parallel runs.

[a] Published data.[1]

[b] The molar ratio Al : BINOL = 1 : 1.5.

hydride reagents TADDAL-H_2 (**2a**, X = H), prepared by modification of $NaAlH_4$ with ligands **13** and **14** (see Table 2), exhibited high enantioselectivity in asymmetric reduction of alkyl aryl ketones **1a,b**. Meanwhile, similar reagents based on $LiAlH_4$ (**2b**, X = H) reduced the same ketones in markedly (1.5—2 times) lower optical yields (*cf.* entries 1 and 2, 19 and 20, Table 2).*

It should be emphasized that, unlike the case with the TADDOL-modified $LiAlH_4$,[2] replacement of the third hydride hydrogen atom in **2a** (X = H) by an achiral ligand such as alkanol or phenol did not result in a noticeable increase in the stereoselectivity of the reduction of ketones (*cf.* entries 3—12 and 15—18). Moreover, the reduction of ketone **1a** with a CYTOL-containing reagent **2a** (X = OCH_2CH_2OMe) in THF was absolutely nonstereoselective (entry 24). The possible explanation of this fact is presented below.

The presence of phenyl substituents in the chiral ligand plays an important role in the attainment of high enantioselectivity of the ketone reduction with TADDOLate-containing reagents **2a** (X = H). Without phenyl groups, as in 1,4-diol **12**, the corresponding dihydride reagent **2a** (X = H) does not show noticeable stereoselectivity in the reaction with ketone **1a**. Moderate enantioselectivity for this reagent was observed only at −70 °C in the presence of an additional achiral ligand (X = OEt) (entry 30).

Modification of $NaAlH_4$ with chiral 1,3-diols. Unlike the reaction considered above (with TADDOL-modified $NaAlH_4$), the reaction with $NaAlH_4$ modified by 1,3-diols **9** and **10** with replacement of the third hydride hydrogen atom in **2a** (X = H) by the ArO group led in some cases to a substantial increase in the optical yields of secondary alcohols **3**; the greatest effect was observed when a 4-*tert*-butylphenoxy group was introduced into $NaAlH_4$ in addition to chiral ligand **10** (see Table 3). However, the use of simple alcohols such as MeOH or $MeOCH_2CH_2OH$ for this purpose either deteriorated the process stereoselectivity (entry 2) or, as in the above-described example with CYTOL-derived reagent **2a** (X = OCH_2CH_2OMe), gave rise to a racemic product (entry 6).

The stereochemical outcome of the reduction with reagent **2a** derived from diol **10** (X = 4-$Bu^tC_6H_4O$) is appreciably affected by the structure of ketone **1**. The greater the size of the aryl fragment in the ketone, the higher the enantioselectivity of this reaction (*cf.* entries 7—12). The best result (89% *ee*) is attained in the reduction of ketone **1f**.

The mechanism of the reduction of ketones with aluminum hydride reagents 2a. Table 4 presents the data of the IR spectra of some reagents **2a** prepared *in situ* in THF. The IR spectrum of the dihydride complex derived from ligand **10** (X = H) exhibits an absorption band at 1660 cm^{-1} and the spectra of monohydride chiral complexes (X = MeO) have an absorption band at 1760—1770 cm^{-1}. When 1 equivalent of MeOH is added

* Recently it has been reported[2] that the reaction of equimolar amounts of acetophenone (**1a**) and $LiAlH_4$ modified with ligand **13** (the aluminum hydride complex **2b**, X = H) gives alcohol **3a** in an optical yield of no more than 40% *ee*, and the reaction of propiophenone (**1b**) with the same reagent results in an optical yield of 6% *ee*.

Table 2. Asymmetric reduction of ketones **1** with reagents **2** containing the TADDOLate ligand

Entry	TADDOL	BINOL configuration	Reagent	X	Ketone	Reaction conditions			Degree of **1**→**3** conversion (%)	Product	*ee* (%)
						Solvent	*T*/°C	τ/h			
1	**13**	(*R*,*R*)	**2a**	H	**1a**	Diglyme	0	20	95	**3a**	70 (*S*)
2	**13**	(*R*,*R*)	**2b**	H	**1a**	Diglyme	0	20	100	**3a**	48 (*S*)
3	**13**	(*R*,*R*)	**2a**	H	**1a**	THF	0	20	100	**3a**	68 (*S*)
4	**13**	(*R*,*R*)	**2a**	MeO	**1a**	THF	0	20	97	**3a**	65 (*S*)
5	**13**	(*R*,*R*)	**2a**	EtO	**1a**	THF	0	20	98	**3a**	60 (*S*)
6	**13**	(*R*,*R*)	**2a**	H	**1a**	THF	−20	20	100	**3a**	76 (*S*)
7	**13**	(*R*,*R*)	**2a**	H	**1b**	THF	−20	20	97	**3b**	82 (*S*)
8	**13**	(*R*,*R*)	**2a**	MeO	**1a**	THF	−20	20	78	**3a**	59 (*S*)
9	**13**	(*R*,*R*)	**2a**	Bu^{t}O	**1a**	THF	−20	20	48	**3a**	52 (*S*)
10	**13**	(*R*,*R*)	**2a**	RO*	**1a**	THF	−20	20	48	**3a**	61 (*S*)
11	**13**	(*R*,*R*)	**2a**	H	**1a**	Diglyme	−20	20	100	**3a**	77 (*S*)
12	**13**	(*R*,*R*)	**2a**	RO*	**1a**	Diglyme	−20	20	78	**3a**	76 (*S*)
13	**13**	(*R*,*R*)	**2a**	H	**1a**	THF	−70	24	95	**3a**	82 (*S*)
14	**13**	(*R*,*R*)	**2a**	H	**1b**	THF	−70	24	100	**3b**	87 (*S*)
15	**13**	(*S*,*S*)	**2a**	H	**1a**	Diglyme	0	5	91	**3a**	68 (*R*)
16	**13**	(*S*,*S*)	**2a**	Pr^{i}O	**1a**	Diglyme	0	5	82	**3a**	72 (*R*)
17	**13**	(*S*,*S*)	**2a**	PhO	**1a**	Diglyme	0	5	92	**3a**	65 (*R*)
18	**13**	(*S*,*S*)	**2a**	RO*	**1a**	Diglyme	0	5	94	**3a**	73 (*R*)
19	**14**	(*S*,*S*)	**2a**	H	**1a**	Diglyme	0	20	100	**3a**	72 (*R*)
20	**14**	(*S*,*S*)	**2b**	H	**1a**	Diglyme	0	20	100	**3a**	37 (*R*)
21	**14**	(*S*,*S*)	**2a**	H	**1a**	Diglyme	−20	20	100	**3a**	80 (*R*)
22	**14**	(*S*,*S*)	**2a**	H	**1a**	THF	−20	20	100	**3a**	78 (*R*)
23	**14**	(*S*,*S*)	**2a**	H	**1b**	THF	−20	20	84	**3b**	75 (*R*)
24	**14**	(*S*,*S*)	**2a**	RO*	**1a**	THF	−20	20	100	**3a**	0
25	**14**	(*S*,*S*)	**2a**	RO*	**1a**	Diglyme—THF 1 : 1	−20	20	94	**3a**	29 (*R*)
26	**14**	(*S*,*S*)	**2a**	RO*	**1a**	Diglyme	−20	20	76	**3a**	75 (*R*)
27	**14**	(*S*,*S*)	**2a**	H	**1a**	THF	−70	24	100	**3a**	85 (*R*)
28	**14**	(*S*,*S*)	**2a**	H	**1b**	THF	−70	24	100	**3b**	77 (*R*)
29	**12**	(*S*,*S*)	**2a**	OEt	**1a**	THF	−20	24	99	**3a**	8 (*R*)
30	**12**	(*S*,*S*)	**2a**	OEt	**1a**	THF	−70	24	64	**3a**	27 (*R*)

Note. The molar ratio Al : TADDOL : XH : **1** = 1 : 1 : 1(0) : 0.33. The yields and *ee* are the average values over several parallel runs.
* RO = $MeOCH_2CH_2O$.

Table 3. Asymmetric reduction of ketones **1** with reagent **2a** obtained from $NaAlH_4$ and 1,3-diol **9** or **10**

Entry	Chiral ligand	X	Ketone	Degree of conversion **1**→**3** (%)	Product (%)	*ee* (%)
1	**9**	H	**1a**	99	**3a**	20 (*S*)
2	**9**	MeO	**1a**	97	**3a**	14 (*S*)
3	**9**	PhO	**1a**	99	**3a**	32 (*S*)
4	**9**	4-Bu^{t}C$_6$H$_4$O	**1a**	99	**3a**	30 (*S*)
5	**10**	H	**1a**	99	**3a**	33 (*S*)
6	**10**	$MeOCH_2CH_2O$	**1a**	89	**3a**	0
7	**10**	4-Bu^{t}C$_6$H$_4$O	**1a**	99	**3a**	40 (*S*)
8	**10**	4-Bu^{t}C$_6$H$_4$O	**1b**	100	**3b**	39 (*S*)
9	**10**	4-Bu^{t}C$_6$H$_4$O	**1c**	70	**3c**	25 (*S*)
10	**10**	4-Bu^{t}C$_6$H$_4$O	**1d**	100	**3d**	47 (*S*)
11	**10**	4-Bu^{t}C$_6$H$_4$O	**1e**	60	**3e**	80 (*S*)
12	**10**	4-Bu^{t}C$_6$H$_4$O	**1f**	100	**3f**	89 (*S*)
13	**10**	2,6-(Bu^t)$_2$C$_6$H$_3$O	**1a**	62	**3a**	51 (*S*)

Note. The molar ratio $NaAlH_4$: 1,3-diol : XH : **1** = 1 : 1 : 1(0) : 0.33, THF, −20 °C, 24 h. The yields and *ee* are the average values over several parallel runs.

to the dihydride reagent prepared from diol **10**, the absorption band at 1660 cm^{-1} disappears and a band at 1760 cm^{-1} typical of a monohydride complex appears instead (Table 4).

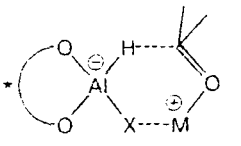
Table 4. Characteristics of the IR spectra of reagents **2a** prepared *in situ* from $NaAlH_4$ and chiral diols

Entry	Reagent **2a**		ν_{Al-H} /cm^{-1}	*D*	ε_{max}*
	Chiral ligand	X in complex **2a**			
1	**10**	H	1660	0.08	95
2	**10**	MeO	1760	0.03	20
3	**11**	MeO	1760	0.065	20
4	**13**	MeO	1770	0.085	70

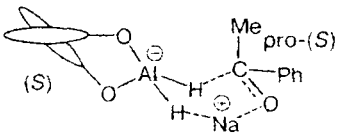
*The extinction coefficient ε_{max} (L mol^{-1} cm^{-1}) was calculated from the equation $\varepsilon_{max} = D/(c \cdot d)$, where $D = \log(I_0/I_{max})$ (I_0 and I_{max} are transmited light intensities for THF and for a solution of the hydride reagent, respectively), *c*/mol L^{-1} is the reagent concentration, and *d*/cm is the cell thickness.

The data obtained are in agreement with the results of an IR spectrometric study of lithium aluminum hydrides. Thus $LiAlH_2(OAr)_2$,[6] $LiAlH(OBu^t)_3$,[7] and LiAlH(BINOLate)(OMe)[1] exhibit IR spectra similar to those presented in Table 4 for $NaAlH_4$ derivatives. The IR spectra of reagents **2a** contain no absorption bands at about 1800—1900 cm^{-1}, characteristic of AlH_3 derivatives. The spectral data indicate that di- and monohydride reagents **2a** do not disproportionate in solution and do not dissociate to a noticeable degree to give substituted alanes; therefore, it is these compounds that appear to be responsible for the stereochemistry of the reduction of ketones.

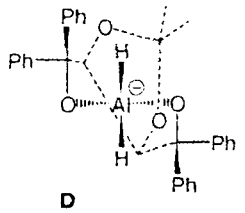
When considering the mechanism of reduction of carbonyl compounds with $LiAlH_4$ or with its derivatives (**2b**), researchers usually postulate the formation of a six-membered cyclic transition state of type **B** in which Li^+ is coordinated to the oxygen atom of the C=O group and thus activates it toward hydride reduction.[1—4] Proceeding from this hypothesis and using molecular models, we evaluated qualitatively the degree of steric hindrance in the possible configurations of the cyclic transition state **B** for the reactions of (*S*)-BINOL- (**11**) and (*R,R*)-IPTOL-containing (**13**) complexes **2a** (X = H) with ketone **1a**. This was done taking into account the X-ray diffraction data for structural analogs of diol **13**, IPTOL having 4-CF_3 substituents in the benzene rings[10] and $(IPTOLate)_2Ti$.[11]



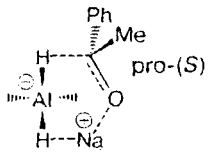
B



C



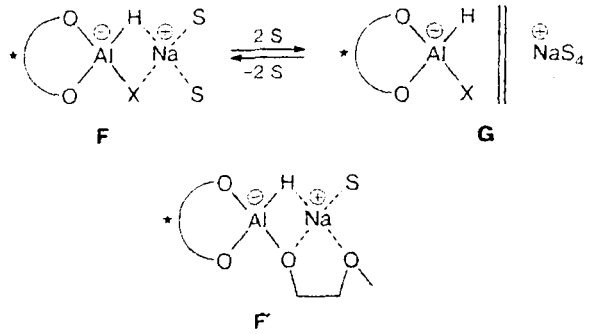
D



D′

Modeling of the possible configurations of transition state **B** for the reduction of **1a** by (*S*)-BINOL-containing complex **2a** showed that the least steric hindrance is ensured in the boat structure (**C**), in which the phenyl group occupies an equatorial position and the Na^+ ion and the more remote hydride hydrogen atom are located close to each other. Consideration of molecular models of the transition state for the reaction of ketone **1a** with the IPTOL derivative of $NaAlH_4$ (the Al atoms of structures **D** and **D′** should be superposed) demonstrated that a pseudoequatorial—pseudoaxial arrangement of the Ph and Me is sterically more favorable in this case, indicating a lower size discrimination between these groups compared to that in structure **C**.

Scheme 2



S is solvent.

Structures **C** and **D′**, preferred from the viewpoint of the least steric hindrance, account for the stereochemistry of the reduction of ketone **1a** with (*S*)-BINOL- and (*R,R*)-IPTOL-containing reagents **2a** (X = H), *i.e.*, for the fact that (*S*)-**3a** is formed in both cases. However, the idea that Li^+ or Na^+ participates in the transition state is inconsistent with the results of some of the above-cited experiments. In our opinion, satisfactory agreement with the experiment could be attained by assuming the existence of an equilibrium between various types of ion pairs in solutions of reagents **2**[5,9] (Scheme 2).

Presumably, hydrides **2a**, like nonmodified $LiAlH_4$ or $NaAlH_4$,[9] react with ketones **1** in THF or diglyme mainly as partially or completely dissociated ion pairs **G** (see Scheme 2).

This assumption is supported by the above-cited results of reduction of ketone **1a** with reagents **2a** containing a chiral bidentate ligand (**10**, **13**, **14**) and an additional achiral ligand, $-OCH_2CH_2OMe$ (see Tables 2 and 3). The presence of the 2-methoxyethoxy group in reagent **2a** should markedly increase the stability of the contact ion pairs designated in Scheme 2 by **F′**, which, unlike the solvent-separated ion pairs (**G**), apparently react with **1a** either less stereoselectively or give rise to the racemic product (**2a**). Apparently, the solvating capacity of THF is insufficient for the contact ion pair (**F′**) to be transformed into the solvent-separated one (**G**); this accounts for the low asymmetric induction or for the absence of enantioselectivity in the reduction of **1a** in THF by reagents **2a**, where X = OCH_2CH_2OMe (see Table 2, entries 10, 24; see Table 3, entry 6). Meanwhile, in diglyme, which solvates Na^+ cations much more efficiently due to chelation, the same reagents appear to react with ketone as solvent-separated ion pairs **G**, which presumably ensure the reaction enantioselectivity. It is notable that in a mixed THF—diglyme solvent, the optical yield was intermediate between those obtained for the reduction of **1a** in each solvent (see Table 2, entries 24—26).

The equilibrium between contact and dissociated ion pairs (see Scheme 2) also provides an explanation for

the higher enantioselectivity of the reduction of ketones with $NaAlH_4$-based reagents (**2a**) compared to similar $LiAlH_4$-based ones (**2b**) (see Tables 1 and 2). The Li^+ cation is a stronger acid than the Na^+ cation; therefore, the stability and, hence, the concentration of contact ion pairs **F**, which presumably react with the ketone nonstereoselectively, is expected to be higher for reagent **2b** (the bridging $Al^-—X—M^+$ bond is stronger if $M^+ = Li^+$).

As regards the common opinion concerning the activation of ketone by Li^+ or Na^+ ions incorporated into hydride reagent **2**, this activation does not seem to be necessary. Indeed, in accordance with the above-considered alternative mechanism of reduction of ketones **1** *via* transition state **B**, higher enantioselectivity would be expected in the case of reagents **2b** rather than **2a**, due not only to the formation of a stronger $Al^-—X—M^+$ bond but also to more effective activation of the carbonyl group by Li^+ ions. However, in reality, the opposite situation is observed. The assumption that the metal cation does not participate in the step determining the process stereochemistry in the enantioselective reduction of ketones by reagents **2** requires further experimental verification.

Experimental

The commercial reagents used were $NaAlH_4$ (Zeeland Chemicals); ligands **4**, **5**, and **11**—**13** (Aldrich); ketones **1a**—**f**. $LiAlH_4$ (Aldrich); anhydrous THF, diglyme (Fluka); ligands **6**,[12] **7**,[13] **8**,[14] **9**,[15] **10**,[16] and **14**[17] were synthesized as described in the literature.

The composition of the products of reduction of ketones **1a,b** was determined by capillary GLC on a Biokhrom-21 instrument using a 30 m × 0.25 mm × 0.25 μm β-DEX™ quartz capillary column (Supelco). The carrier gas (He) pressure upstream the column was 4 atm, the gas velocity through the column was 1 mL min^{-1}, the column temperature was 115 °C, and the temperatures in the detector and evaporation chamber were 150 °C. The retention time for a nonretainable gas (CH_4) in the column was 2 min. The retention times of the initial compounds and reaction products were as follows, min: **1a**, 9.4; (*R*)-**3a**, 12.8; (*S*)-**3a**, 13.4; **1b**, 14.1; (*R*)-**3b**, 19.8; and (*S*)-**3b**, 20.4. The products of asymmetric reduction of ketones **1c**—**f** were analyzed by HPLC on a Laboratorny pristroje Praha chromatographic instrument, UV detection, λ 254 nm, a 4.6×250 mm Chiralcel OD column (Daicel). Hexane containing 5 % (v/v) Pr^iOH was used as the mobile phase. The elution velocity was 1 mL min^{-1}, and the retention time for 1,3,5-tri-*tert*-butylbenzene (nonretainable compound) was 2.7 min. The retention times of the initial ketones and reaction products were as follows, min: **1s**, 3.7; (*S*)-**3s**, 4.3; (*R*)-**3s**, 5.0; **1d**, 3.5; (*S*)-**3d**, 4.3; (*R*)-**3d**, 5.1; **1e**, 12; (*S*)-**3e**, 16.0; (*R*)-**3e**, 16.2; **1f**, 6.6; (*S*)-**3f**, 15.0; and (*R*)-**3f**, 24.0.

Asymmetric reduction of ketones 1a—f by reagents 2a (general procedure). A solution of chiral diol (1.05 mmol) or a mixture of a chiral diol (1 mmol) and an achiral modifier (alcohol or phenol, 1 mmol) in THF (10 mL) was gradually added at −20 °C to a solution of $NaAlH_4$ (1 mmol) in THF (5 mL). The mixture was stirred for an additional 1 h. The thus prepared solution of reagent **2a** was cooled to the required temperature and ketone **1** (0.33 mmol) was injected therein through the rubber gasket using a microsyringe. The preparation of the hydride reagents and the reduction of ketones were carried out in anhydrous solvents under dry argon. The reaction mixture was quenched with a $MeOH—H_2O$ mixture (9 : 1), the solvent was removed *in vacuo*, and the residue was extracted with an ether—hexane mixture. A small portion of the extract was analyzed by GLC and (or) HPLC in order to determine the degree of ketone conversion and the enantiomeric composition of the resulting alcohol. The main bulk of the product was isolated by distillation or crystallization; the enantiomeric composition did not change during isolation.

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

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Received August 11, 1999;
in revised form October 7, 1999