Enantioselective reduction of C=O and C=N bonds by TADDOL-containing aluminum hydride reagents based on $NaAlH_4$ and AlH_3

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Prochiral substrates (alkyl aryl ketones, cyclopropyl methyl ketone, 1-indanone, 1-tetralone, ethyl 2-oxo-4-phenylbutyrate, and *N*-(diphenylphosphinyl)acetophenoneimine) were subjected to asymmetric reduction with aluminum hydride reagents, which were prepared by modifications of $NaAlH_4$ or AlH_3 with chiral α,α,α´,α´-tetraaryl-1,3-dioxolane-4,5-dimethanols (TADDOL). The effects of the nature of the substituents in TADDOL, the structure of the prochiral substrate, and the reaction conditions on the stereochemistry of reduction were investigated. The highest enantioselectivity (70—90% *ee*) was achieved upon reduction of alkyl aryl ketones and *N*-(diphenylphosphinyl)acetophenoneimine with NaAl(TADDOLate)H_2 in THF or diglyme at a temperature from −70 to −20 °C. The mechanism of asymmetric induction in the reduction reactions of ketones with aluminum hydride reagents is discussed. The stereochemical results of reduction were explained by comparing three-dimensional models of the most probable transition states.

Key words: sodium aluminum hydride, aluminum hydride, chiral ligand, α,α,α´,α´-tetraaryl-1,3-dioxolane-4,5-dimethanol, ketones, imine, alcohols, α-phenylethylamine, reduction, asymmetric induction, mechanism.

Recently, the study of asymmetric reduction of ketones with aluminum hydride complexes, which were prepared by modifications of $MAlH_4$ and contained *O*,*O*-bidentate chiral ligands, *viz.*, 1,1´-bi-2-naphthol or TADDOL* (**1**), revealed that the enantioselectivity of reduction depends on the nature of the cation ($M^+ = Na^+$ or Li^+).[1] Thus, the optical yields of α-phenylethanol in the reactions of acetophenone with the NaAl(IPTOLate)H_2* or NaAl(CYTOLate)H_2* complexes prepared by modifications of $NaAlH_4$ were higher by a factor of 1.5—2 than those obtained by reduction of the same ketone with analogous complexes based on $LiAlH_4$. This fact was accounted for[1] by the difference in the nature of the ion pairs prevailing in solutions of the above-mentioned hydride reagents (this hypothesis is discussed in more detail below).

The aim of the present study was to prepare new TADDOL-containing hydride reagents **2** based on $NaAlH_4$ and tricoordinate chiral aluminum hydrides **3** and to compare their reactivities in asymmetric reduction of the C=O and C=N groups (Scheme 1).

* TADDOL is α,α,α´,α´-tetraaryl-1,3-dioxolane-4,5-dimethanol (**1**), IPTOL is 2,3-*O*-isopropylidene-1,1,4,4-tetraphenylbutanetetraol (**1a**), and CYTOL is 2,3-*O*-cyclohexylidene-1,1,4,4-tetraphenylbutanetetraol (**1d**) as their (2*R*,3*R*) or (2*S*,3*S*) enantiomers.

Results and Discussion

Reagents **2** and **3** (see Scheme 1) were prepared *in situ* in THF and other solvents. In addition, complex **2a** was isolated in the solid state and then used as the reducing agent. Carbonyl compounds **4** and **6** and *N*-(diphenylphosphinyl)acetophenoneimine (**8**) served as prochiral substrates in asymmetric reduction (Scheme 2). The results of the experiments are summarized in Tables 1—4.

As can be seen from Table 1 (entries *1—19*), the reactions of alkyl aryl ketones **4a—f** with reagents **2** ($M^+ = Na^+$) at temperatures from −20 to −70 °C proceeded with a high conversion of ketones (generally, 95—100%) and enantioselectivity of up to 90% *ee*, the results of asymmetric reduction being independent of the procedure used for the preparation of reagent **2** (*in situ* from $NaAlH_4$ and compound **1** or with the use of chiral hydride pre-isolated in the solid state; see entries *2*, *7*, and *10*).

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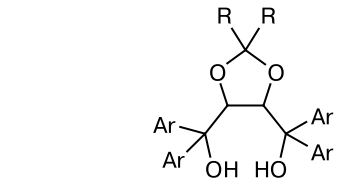
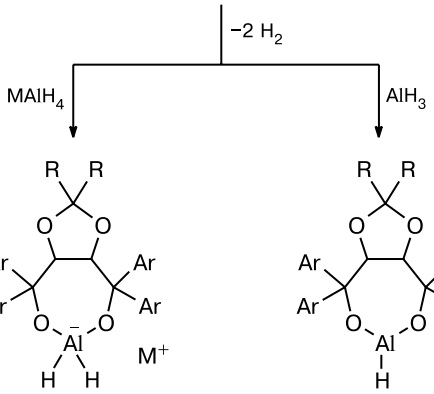
Scheme 1

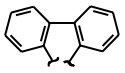


1a—g



2a—g: M = Na
2′a: M = Li

3a—f

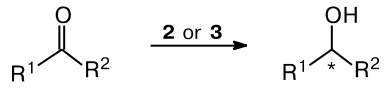
	R	R + R	Ar		R	R + R	Ar
a	Me	—	Ph	**e**	—		Ph
b	Et	—	Ph				
c	—	$(CH_2)_4$	Ph	**f**	Me	—	4-$MeOC_6H_4$
d	—	$(CH_2)_5$	Ph	**g**	Me	—	4-$Bu^tC_6H_4$

Compared to complexes **2** ($M^+ = Na^+$), tricoordinate aluminum hydrides **3** exhibit much lower reactivity and stereoselectivity in asymmetric reduction of alkyl aryl ketones. The reactions of reagents **3a—d** with ketones **4a—f** are characterized by moderate conversions of the ketones and moderate optical yields (see Table 1, entries *20—36*), whereas aluminum hydrides **3e** and **3f** reacted nonstereoselectively with low conversions of ketones **4** (entries *37* and *38*).

As can be seen from Table 2 (entries *1—15*), the enantioselectivities of the reactions of cyclopropyl methyl ketone (**4g**), ethyl 2-oxo-4-phenylbutyrate (**4h**), 1-indanone (**6a**), and 1-tetralone (**6b**) with reagents **2** ($M^+ = Na^+$) were much lower (15—40% *ee*) than those achieved in the reduction of alkyl aryl ketones (**4a—f**) (see Table 1). Unlike alkyl aryl ketones **4a—f**, cycloalkanones **6a,b** reacted with modified aluminum hydride **3** with higher enantioselectivities compared to their reactions with the $NaAlH_4$-based complexes (**2**) (see Table 2, *cf.* entries *4* and *16*, *5* and *17*, *10* and *18*).

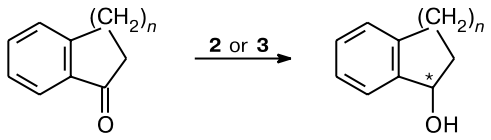
The asymmetric reduction of activated imine **8** with reagents **2** ($M^+ = Na^+$) (see Scheme 2, Table 3) is characterized by both high conversion and the *ee* values compa-

Scheme 2



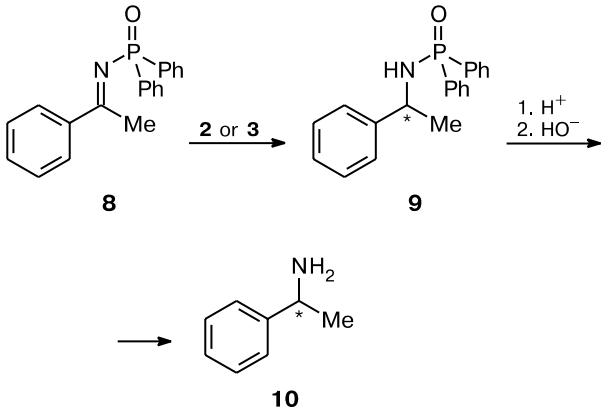
4a—h **5a—h**

	R^1	R^2		R^1	R^2
a	Ph	Me	**e**	2-Naphthyl	Me
b	Ph	Et	**f**	2-Fluorenyl	Me
c	Ph	Pr^i	**g**	Cyclopropyl	Me
d	1-Naphthyl	Me	**h**	CO_2Et	$(CH_2)_2Ph$



6a,b **7a,b**

n = 1 (**a**), 2 (**b**)



8 **9** **10**

rable with the results of reduction of alkyl aryl ketones (see Table 1). It should be noted that the nature of the R and Ar substituents in hydride complex **2** has no substantial effect on the conversion **8** → **9** and the optical yield of the product.

As in the case of reduction of alkyl aryl ketones,[1] the replacement of one of the hydride atoms in compound **2** with an additional achiral ligand, for example, with the ethoxy group, had no positive effect on reduction of imine **8** (see Table 3). Moreover, the replacement of H by EtO in reagent **2a** led to a twofold decrease in the optical yield in the reactions with imine **8** (see Table 3, *cf.* entries *2* and *3*, *4*). The similarity of reduction of alkyl aryl ketones and imine **8** is manifested also in the fact that reagents **3** appeared to be less reactive and stereoselective than reagents **2** (see Table 3, entries *15—20*).

The stereochemical result of reduction of imine **8** was established in two ways, *viz.*, by the determination of the enantiomeric composition of *N*-(diphenylphosphinyl)-

Table 1. Asymmetric reduction of alkyl aryl ketones **4a—f** with aluminum hydride reagents **2** ($M^+ = Na^+$) and **3** in THF giving rise to alcohols **5a—f**

Entry	Reagent	Configuration of **1**	SC	T_{red} /°C	Conversion (%)	*ee* (%)
1	**2a**	(*S*,*S*)	**4b**	−70	100	88 (*R*)
*2**	**2a**	(*S*,*S*)	**4b**	−70	98	90 (*R*)
3	**2a**	(*S*,*S*)	**4c**	−70	94	83 (*R*)
4	**2a**	(*S*,*S*)	**4c**	−20	100	76 (*R*)
5	**2a**	(*S*,*S*)	**4f**	−20	87	70 (*R*)
6	**2c**	(*R*,*R*)	**4b**	−20	99	78 (*S*)
*7**	**2d**	(*R*,*R*)	**4b**	−20	100	83 (*S*)
8	**2e**	(*R*,*R*)	**4a**	−70	100	85 (*S*)
9	**2e**	(*R*,*R*)	**4b**	−70	100	80 (*S*)
*10**	**2e**	(*R*,*R*)	**4b**	−20	100	75 (*S*)
11	**2e**	(*R*,*R*)	**4c**	−70	100	78 (*S*)
12	**2f**	(*R*,*R*)	**4a**	−20	100	73 (*S*)
13	**2f**	(*R*,*R*)	**4b**	−20	99	83 (*S*)
14	**2g**	(*R*,*R*)	**4a**	−70	100	83 (*S*)
15	**2g**	(*R*,*R*)	**4b**	−70	100	78 (*S*)
16	**2g**	(*R*,*R*)	**4c**	−70	100	85 (*S*)
17	**2h**	(*S*,*S*)	**4a**	−70	100	78 (*R*)
18	**2h**	(*S*,*S*)	**4b**	−70	100	84 (*R*)
19	**2h**	(*S*,*S*)	**4c**	−70	100	83 (*R*)
20	**3a**	(*R*,*R*)	**4a**	−20	83	42 (*S*)
21	**3a**	(*S*,*S*)	**4a**	−20	79	37 (*R*)
22	**3a**	(*R*,*R*)	**4b**	−20	76	54 (*S*)
23	**3a**	(*S*,*S*)	**4c**	−20	42	36 (*R*)
24	**3a**	(*R*,*R*)	**4d**	−20	62	47 (*S*)
25	**3a**	(*S*,*S*)	**4e**	−20	70	40 (*R*)
26	**3a**	(*S*,*S*)	**4f**	−20	70	34 (*R*)
27	**3b**	(*S*,*S*)	**4a**	−20	80	50 (*R*)
28	**3b**	(*R*,*R*)	**4b**	−20	100	44 (*S*)
29	**3c**	(*S*,*S*)	**4a**	−20	57	38 (*R*)
30	**3c**	(*R*,*R*)	**4b**	−20	91	30 (*S*)
31	**3d**	(*S*,*S*)	**4a**	−20	53	47 (*R*)
32	**3d**	(*R*,*R*)	**4b**	−20	100	52 (*S*)
33	**3d**	(*R*,*R*)	**4c**	−20	50	43 (*S*)
34	**3d**	(*R*,*R*)	**4d**	−20	77	31 (*S*)
35	**3d**	(*R*,*R*)	**4e**	−20	87	30 (*S*)
36	**3d**	(*R*,*R*)	**4f**	−20	70	40 (*S*)
37	**3e**	(*R*,*R*)	**4a**	−20	3	0
38	**3f**	(*R*,*R*)	**4a**	−20	16	7 (*S*)

Note. SC is the starting compound.
* Reduction was carried out with the use of the solid NaAl(IPTOLate)H_2·THF complex.

α-phenylethylamine (**9**) by HPLC and by enantiomeric analysis of *N*-acetyl-α-phenylethylamine (after hydrolysis of compound **9** and acetylation of amine **10**) by GLC. Both methods gave close *ee* values. In all reactions, the conversion **8** → **9** was detected by HPLC.

Since imine **8** and its analogs can be readily prepared from ketones **4** in two steps, their reduction with reagents **2** ($M^+ = Na^+$) opens up possibilities for the synthesis of other chiral amines from the corresponding aromatic ketones.

Table 2. Asymmetric reduction of compounds **4g,h** and **6a,b** with aluminum hydride reagents **2** ($M^+ = Na^+$) and **3** in THF giving rise to alcohols **5g,h** and **7a,b**, respectively

Entry	Reagent	Configuration of **1**	SC	T_{red} /°C	Conversion (%)	*ee* (%)
1	**2a**	(*S*,*S*)	**4g**	−20	80	25 (*R*)
2	**2a**	(*R*,*R*)	**4h**	−20	87	30 (*S*)
3	**2a**	(*S*,*S*)	**6a**	−70	25	20 (*R*)
4	**2a**	(*S*,*S*)	**6a**	−20	100	19 (*R*)
5	**2a**	(*S*,*S*)	**6b**	−20	32	16 (*R*)
6	**2c**	(*R*,*R*)	**4h**	−20	71	35 (*S*)
7	**2c**	(*S*,*S*)	**6a**	−20	100	21 (*R*)
8	**2c**	(*R*,*R*)	**6b**	−20	96	26 (*S*)
9	**2d**	(*R*,*R*)	**6a**	−70	7	39 (*S*)
10	**2d**	(*R*,*R*)	**6a**	−20	100	28 (*S*)
11	**2f**	(*R*,*R*)	**4h**	−20	90	32 (*S*)
12	**2f**	(*R*,*R*)	**6a**	−20	94	24 (*S*)
13	**2f**	(*R*,*R*)	**6b**	−20	97	15 (*S*)
14	**2g**	(*R*,*R*)	**6a**	−20	72	24 (*S*)
15	**2g**	(*R*,*R*)	**6b**	−20	97	26 (*S*)
16	**3a**	(*S*,*S*)	**6a**	−20	91	41 (*R*)
17	**3a**	(*S*,*S*)	**6b**	−20	17	40 (*R*)
18	**3d**	(*R*,*R*)	**6a**	−20	99	48 (*S*)
19	**3d**	(*R*,*R*)	**6b**	−20	49	31 (*S*)

Note. SC is the starting compound.

Table 3. Asymmetric reduction of *N*-(triphenylphosphinyl)acetophenoneimine (**8**) with aluminum hydride reagents **2** ($M^+ = Na^+$) and **3** in THF

Entry	Reagent	Configuration of **1**	T_{red} /°C	Conversion (%)	PA	*ee* (%)
1	**2a**	(*S*,*S*)	−70	98	**9**	77 (*R*)
2	**2a**	(*S*,*S*)	−20	97	**9 (10)**	79 (78) (*R*)
*3**	**2a**	(*R*,*R*)	−20	94	**9**	36 (*S*)
*4**	**2a**	(*S*,*S*)	−20	90	**9**	36 (*S*)
5	**2a**	(*R*,*R*)	+20	98	**9**	58 (*S*)
6	**2´a****	(*R*,*R*)	−20	99	**9**	30 (*S*)
7	**2´a****	(*S*,*S*)	−20	97	**9**	30 (*R*)
8	**2b**	(*R*,*R*)	−70	95	**10**	78 (*S*)
9	**2b**	(*R*,*R*)	−20	97	**10**	76 (*S*)
10	**2b**	(*R*,*R*)	+20	96	**10**	71 (*S*)
11	**2c**	(*R*,*R*)	−20	100	**9**	75 (*S*)
12	**2e**	(*R*,*R*)	−70	100	**9**	67 (*S*)
13	**2e**	(*R*,*R*)	−20	100	**9**	69 (*S*)
14	**2f**	(*R*,*R*)	−20	100	**9**	76 (*S*)
15	**3a**	(*S*,*S*)	−20	62	**9**	42 (*R*)
16	**3b**	(*R*,*R*)	−20	72	**9**	55 (*S*)
17	**3c**	(*S*,*S*)	−20	65	**9**	61 (*R*)
18	**3d**	(*R*,*R*)	−20	64	**9**	37 (*S*)
19	**3e**	(*R*,*R*)	−20	62	**9**	64 (*S*)
20	**3f**	(*R*,*R*)	−20	60	**9**	27 (*S*)

Note. PA is the product analyzed.
* Reduction was carried out with the use of complex **2a** ($M^+ = Na^+$) in which one of the hydride atoms is replaced by the ethoxy group.
** $M^+ = Li^+$.

Table 4. The effect of the solvent on the enantioselectivity of reduction of prochiral compounds **4b,e,h** and **8** with the reagents (**2**) ($M^+ = Na^+$)* to form compounds **5b,e,h** and **9**, respectively

Entry	Reagent	SC	Solvent	T_{red}**/°C	Conversion (%)	*ee* (%)
1	**2a**	**4b**	THF	−70	100	88 (*S*)
2	**2a**	**4b**	CH_2Cl_2	−70	86	43 (*S*)
3	**2a**	**4e**	THF	−20	96	71 (*R*)
4	**2a**	**4e**	Diglyme	−20	83	72 (*R*)
5	**2a**	**4h**	THF	−20	87	30 (*S*)
6	**2a**	**4h**	Toluene	−20	99	9 (*S*)
7	**2d**	**4b**	THF	−20	100	83 (*S*)
8	**2d**	**4b**	Toluene	−20	100	37 (*S*)
9	**2a**	**8**	THF	+20	98	58 (*S*)
10	**2a**	**8**	Et_2O—THF (5 : 1)	+20	99	29 (*S*)
11	**2a**	**8**	CH_2Cl_2	+20	100	16 (*S*)
12	**2a**	**8**	Et_3N—THF (1 : 5)	+20	100	24 (*S*)

Note. SC is the starting compound.
* The ligands, which were used for the preparation of reagents **2** by the *in situ* modification of $NaAlH_4$, have an (*R*,*R*) configuration, except for entries *3* and *4* in which the starting TADDOL has an (*S*,*S*) configuration.
** The time of reduction was 20 h at −70 °C and 2 h at −20 and +20 °C.

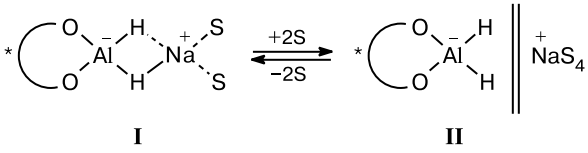
Hence, the degree of asymmetric induction in reduction at the C=O and C=N bonds by chiral aluminum hydride reagents depends substantially on their geometry (tri- or tetracoordinate aluminum) and the structure of the starting substrate. At the same time, the stereoselectivity of reduction is rather poorly sensitive to the nature of the R and Ar substituents in reagents **2** and **3**, except for hydrides **3e** and **3f** (see Table 1, entries *37* and *38*; Table 3, entry *20*).

As can be seen from Table 4, the enantioselectivity of hydrogenation of prochiral substrates with reagents **2** depends substantially on the nature of the solvent. The highest *ee* values were achieved in the reactions, which were carried out in THF or diglyme. The partial or complete replacement of these solvents by diethyl ether, dichloromethane, toluene, or hexane (in pure hexane, complexes **2** are insoluble) led to a decrease in the degree of asymmetric induction. This decrease was particularly substantial in the case of reduction in toluene.

Interestingly, an analogous increase in the stereoselectivity of reduction with increasing solvating ability of the solvent has been observed earlier[2] in the reactions of *N*-substituted α-amino ketones with $LiAl(OBu^t)_3H$.

The results of our study provide support for the previous assumption[1] that the equilibrium between contact (**I**) and solvent-separated (**II**) ion pairs plays an important role in solutions of TADDOL-containing aluminum hydride complexes, the solvent-separated ion pairs being responsible for high enantioselectivity of the process. Actually, high enantioselectivity was observed in the reduction reactions in THF and diglyme, *i.e.*, in solvents, which readily solvate cations[1] (Scheme 3).

Scheme 3



I **II**

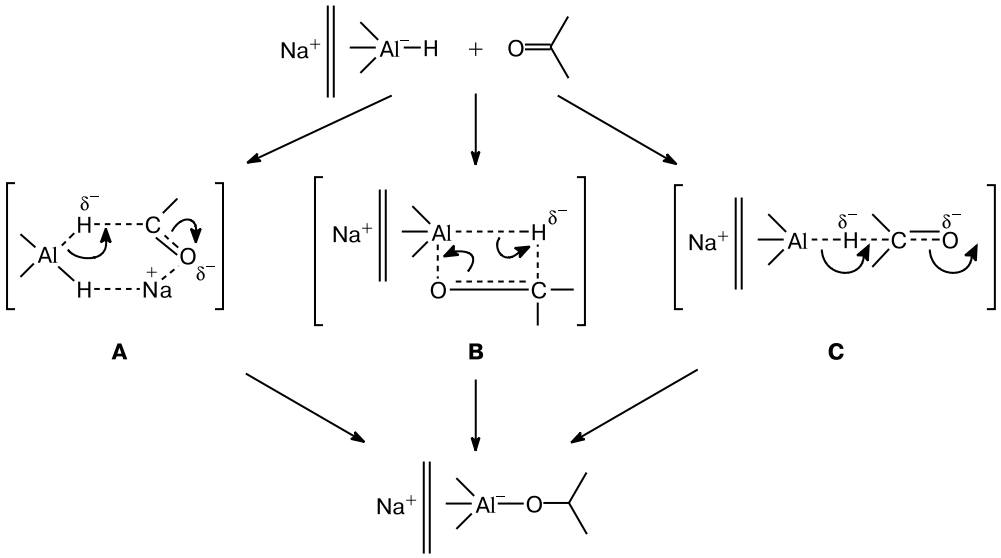
S is a solvent

This explanation is also supported by the experiment, in which an equimolar amount of 15-crown-5 (starting ketone **4a**, −20 °C) was added to a solution of complex **2a** in THF. The optical yield (76% *ee*; 100% conversion of **4a**) in the latter reaction was identical with that obtained without the addition of the crown ether. Besides, due to the lower strength of the hydride bond with the Na^+ cations compared to that with the Li^+ cations, contact ion pairs **I** containing $M^+ = Na^+$ dissociate to a greater extent (equilibrium **I** ⇌ **II** is shifted to the right), which ensures higher enantioselectivity of reduction. Actually, the enantioselectivity of the reactions of *N*-acylated imine **8** with complexes **2a** based on $NaAlH_4$ is twice as high as that of the reactions with the use of complex **2´a** based on $LiAlH_4$, all other factors being the same (see Table 3, *cf.* entries *2* and *6, 7*). This fact is in agreement with the results of the earlier study[1] in which the effect of the nature of the cation on the enantioselectivity of reduction of ketones was investigated.

Since reagents **2** ($M^+ = Na^+$) are of most interest for preparative purposes, we examined the aging stability of their solutions. After storage in THF at 20 °C for 3 days, reagents **2a,c,d** lost no more than 2—3% of active hydrogen, which was determined from the amount of H_2 liberated after their reactions with aqueous methanol. Comparative experiments on reduction of ketones **4** with the above-mentioned reagents both immediately after their preparation and after their storage at 20 °C for 3—5 days gave identical results. Moreover, reagents **2a,c,d** retained their enantioselectivity by no less than 90% even after storage of their solutions in THF for one month (20—25 °C) in spite of the loss of 20—30% of active hydrogen.

In addition to rather high aging stability (for reagents of this type), an advantage of reagents **2** ($M^+ = Na^+$) is the fact that the degree of asymmetric induction in reduction reactions with their participation depends only slightly, if at all, on the temperature. For example, an increase in the temperature of reduction of ketones **4a—f**

Scheme 4



with reagents **2** from −70 to −20 °C led to a decrease in *ee* for products **5a—f** by only 5—7% (see Table 1), whereas the enantioselectivities of reduction of ketone **6a** and imine **8** with reagent **2a** were 19—20 and 77—79% *ee*, respectively, both at −70 °C and −20 °C (see Table 2, entries *3* and *4*; Table 3, entries *1* and *2*). It should be emphasized that reduction of imine **8** with reagents **1a,b** gave rather high *ee* for the final product (58 and 71%, respectively) even in the experiments performed at room temperature (see Table 3, entries *5* and *10*). According to a typical procedure for reduction with reagents **2** ($M^+ = Na^+$), their initial concentrations in solutions were 0.05—0.1 mol L^{-1}. Depending on the solubility of reagents **2** and substrates, other concentrations of reagents **2** were also used (from 0.02 to 0.3 mol L^{-1}), which had no substantial effect on the final results and their reproducibility. In all experiments, the reproducibility was within the accuracy of GLC and HPLC analyses.

Earlier,[1] we have explained the stereochemistry of reduction of ketones with TADDOL-containing reagents based on $NaAlH_4$ (formation of (*S*)-*sec*-alkanols in the reactions of ketones with (*R*,*R*)-**2**) by invoking the cyclic transition state **A** (Scheme 4) postulated in the literature.[3] This transition state involves the Na^+ cation coordinated to the hydride and carbonyl groups. At the same time, we have noted that this explanation is contradictory to certain experimental facts.[1]

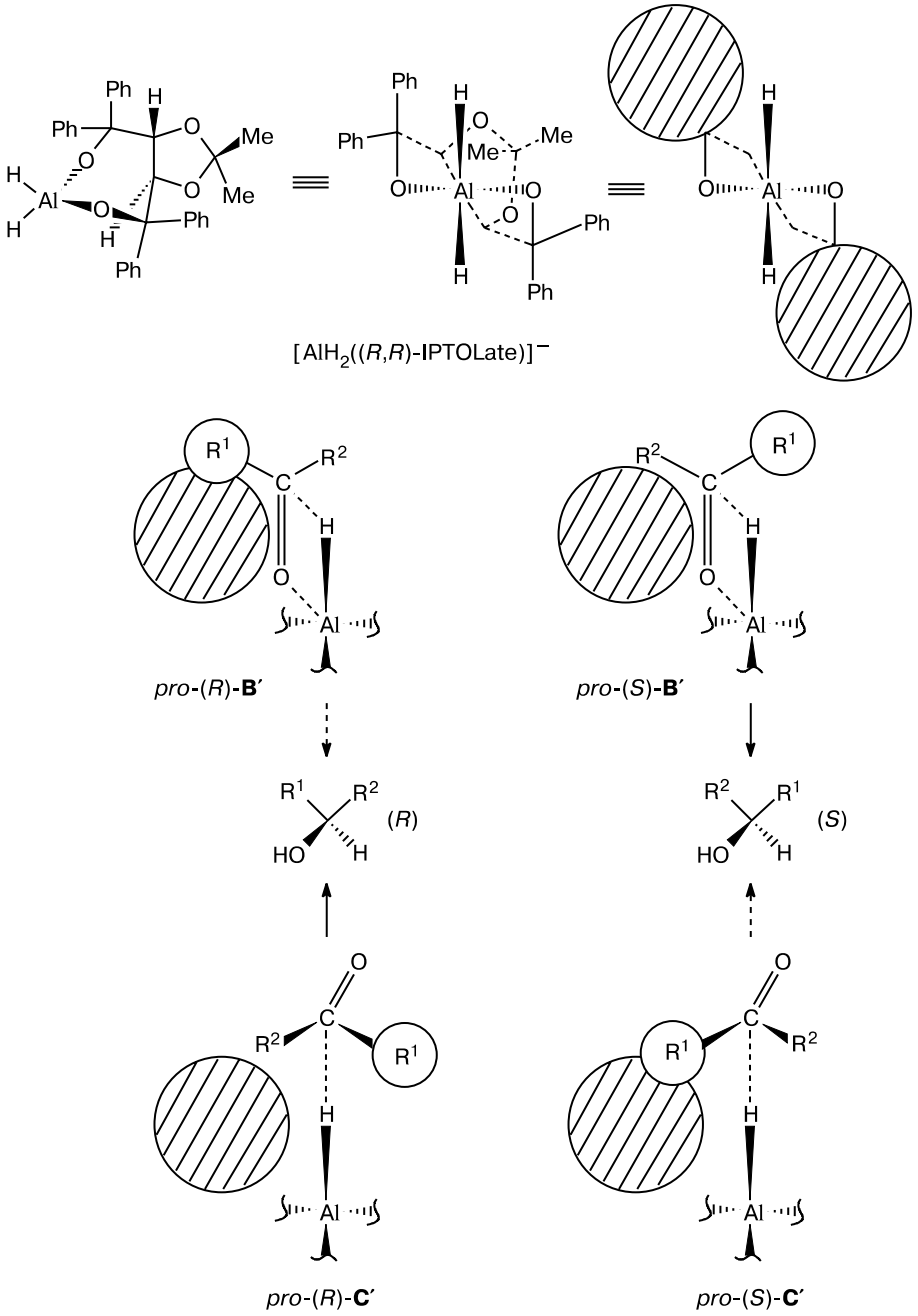
Analysis of the results of our further investigation on the reduction of ketones with chiral aluminum hydride reagents and the consideration of the structural models of the most probable transition states (TS) allowed us to propose the mechanism of asymmetric induction, which is consistent with the experimental data and accounts for the observed stereochemistry of the process.

For the hydride transfer from aluminum hydride to the ketone molecule, cyclic (**B**) and acyclic (**C**) transition states (see Scheme 4) have been considered.[4] It should be noted that the choice between these transition states could not be made based on the data on the kinetics of reduction of a series of cyclic ketones with the $LiAlH(OBu^t)_3$ and $LiAlD(OBu^t)_3$ reagents. Nevertheless, an analogous approach enabled us to explain the observed stereochemical characteristic features of the reactions under consideration. It should be noted that Scheme 4 reflects only the possible spatial configuration of TS, whereas finer aspects of the mechanism of reduction (hydride transfer or electron transfer to form the radical-ion pair[5]) remain beyond the scope of this scheme.

To examine the stereochemical models for the mechanism of reduction of ketones with reagents **2** and **3**, we chose the reactions of $NaAl(IPTOLate)H_2$ (**2a**) and Al(IPTOLate)H (**3a**) with acetophenone (**4a**) as examples. The three-dimensional structure of complex **2a** was postulated taking into account the results of X-ray diffraction analysis of $Ti(IPTOLate)_2$[6] and structural analogs of IPTOL.[7] The structure of complex **3a** was postulated taking into account the results of X-ray diffraction analysis of the trigonal-bipyramidal complex $AlH_3 \cdot 2THF$.[8]

According to Scheme 5, the sterically least and most hindered structures in the reduction reactions of ketones with reagent (*R*,*R*)-**2a**, which proceed through the four-center cyclic TS, are *pro*-(*S*)-**B´** and *pro*-(*R*)-**B´**, respectively, which agrees with the fact the (*S*)-enantiomer prevailed among the reaction products. By contrast, *pro*-(*S*)-**C´** is the sterically most hindered structure in the case of reduction of ketones through the acyclic TS **C´**, which indicates that the latter structure is less probable

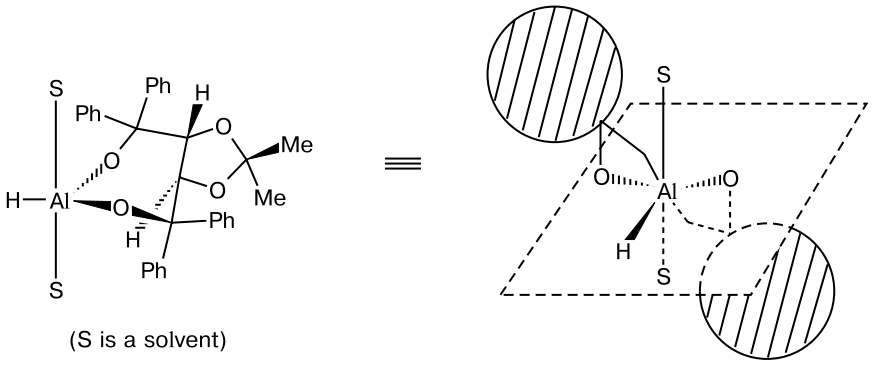
Scheme 5



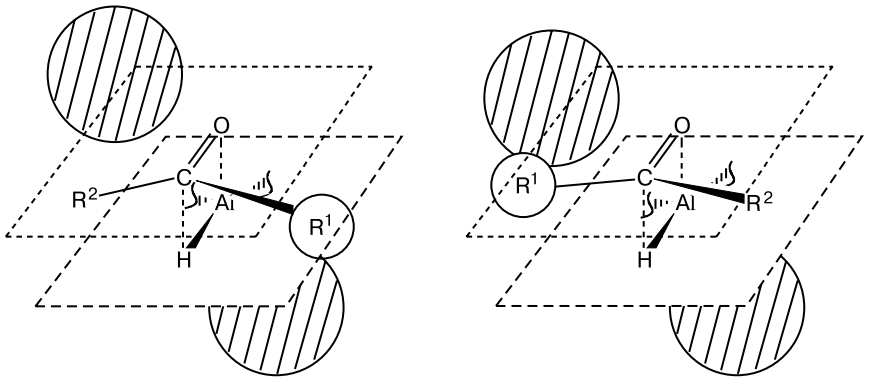
than *pro*-(*S*)-**B′** for the formation of the major (*S*)-enantiomer.

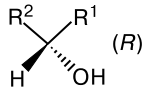
The consideration of the stereochemical models **B″** and **C″** as applied to the reduction of ketones with reagents **3** using the reaction of aluminum hydride **3a** with ketone **4a** as an example (Scheme 6) led us to the opposite conclusion. The reaction proceeding though the most favorable TS, *viz.*, through the sterically least hindered cyclic TS *pro*-(*R*)-**B″**, should lead to the predominant formation of (*R*)-alkanol, which is contradictory to the experimental data. In contrast to the cyclic mechanism, spatial modeling of acyclic TX **C″**, in which the plane of the ketone molecule is perpendicular to the plane of the hydride molecule, explains the fact that (*S*)-alkanol was obtained as the major product in the reaction of (*R*,*R*)-**3a** with ketone **4a**. According to the structure of *pro*-(*S*)-**C″**, the bulkier substituent R^1 is less sterically hindered due to which the formation of (*S*)-alkanol is more probable

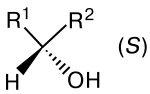
Scheme 6

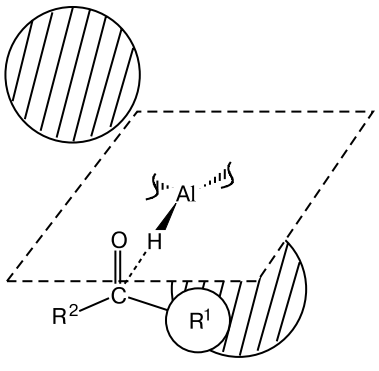


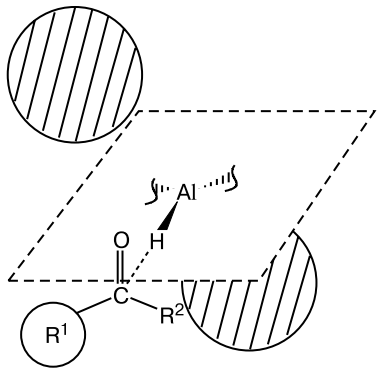
AlH((*R*,*R*)-IPTOLate)S_2











than the formation of (*R*)-alkanol (*cf.* the structure *pro*-(*R*)-**C″**).

The stereochemistry of reduction of α-oxo ester **4h** corresponds to the models presented in Schemes 5 and 6 assuming that the polar CO_2Et group possesses a more substantial discriminating effect in the case of the hydride attack of the oxo ester because of its better solvation in solution compared to the $(CH_2)_2Ph$ group.

To summarize, based on the consideration of the structural models shown in Schemes 5 and 6, the results of reduction of ketones with complexes **2** can be attributed to the formation of cyclic TS **B**, whereas the stereochemical result of reduction of ketones with reagents **3** can be accounted for by the formation of acyclic TS **C**. Apparently, the higher level of asymmetric induction achieved through TS **B** is associated with a more considerable steric discrimination in the structures *pro*-(*S*)-**B´** and *pro*-(*R*)-**B´** (see Scheme 5) compared to the alternative structures *pro*-(*S*)-**C″** and *pro*-(*R*)-**C″** (see Scheme 6).

Experimental

The NMR spectra were measured on a Bruker AC-200 instrument (200, 50.32, and 81.02 MHz for ^1H, ^{13}C, and ^{31}P, respectively). The following reagents were used: $NaAlH_4$ (Zeeland Chemicals), ketones **4a,b** and **6a,b**, and $LiAlH_4$ (Aldrich). The ligands (*S*,*S*)-**1a** [9] (m.p. 194—195 °C, $[\alpha]_D^{25}$ +65 (*c* 1, $CHCl_3$))[9], (*R*,*R*)-**1a** [9] (m.p. 195—196 °C, $[\alpha]_D^{20}$ −66 (*c* 1, $CHCl_3$)), (*S*,*S*)-**1b** [10] (m.p. 179 °C, $[\alpha]_D^{20}$ +80.5 (*c* 1, $CHCl_3$)), (*R*,*R*)-**1b** [10] (m.p. 178—179 °C, $[\alpha]_D^{20}$ −82 (*c* 1, $CHCl_3$)), (*S*,*S*)-**1c** [11] (m.p. 173—174 °C, $[\alpha]_D^{20}$ +38 (*c* 1, $CHCl_3$)), (*R*,*R*)-**1c** [11] (m.p. 173—175 °C, $[\alpha]_D^{20}$ −41 (*c* 1, $CHCl_3$)), (*S*,*S*)-**1d** [9] (m.p. 198—199 °C, $[\alpha]_D^{25}$ +70.6 (*c* 0.9, $CHCl_3$)), (*R*,*R*)-**1d** [9] (m.p. 199—200 °C, $[\alpha]_D^{25}$ −70.2 (*c* 1.8, $CHCl_3$)), (*R*,*R*)-**1e** [10] (m.p. 152—154 °C, $[\alpha]_D^{20}$ −55 (*c* 1, $CHCl_3$)), (*R*,*R*)-**1f** [9] (m.p. 106 °C, $[\alpha]_D^{20}$ −54.5 (*c* 1, $CHCl_3$)), (*S*,*S*)-**1g** [10] (m.p. 214—216 °C, $[\alpha]_D^{20}$ +59 (*c* 1, $CHCl_3$)) and imine **8** [12] (m.p. 135—137 °C; ^{31}P NMR ($CDCl_3$), δ: 17.31; ^1H NMR ($CDCl_3$), δ: 2.98 (s, 3 H, Me); 7.30—7.60 (m, 10 H, Ar); 7.90—8.15 (m, 5 H, Ar); ^{13}C NMR ($CDCl_3$), δ: 22.97, 23.14 (d, Me, two signals due to coupling with ^{31}P); 127.95—181.60 (15 signals, Ar, C=N))[12] were synthesized according to known procedures.

The compositions of the products of asymmetric hydrogenation of ketones **4a—c,e,f** were determined chromatographically according to a procedure described earlier.[1] The conversions of carbonyl compounds **4g,h** and **6b** into the corresponding alkanols and the enantiomeric compositions of reduction products **5g** (as acetate after esterification with Ac_2O), **5h**, and **7b** and amine **10** (after its transformation into the acetyl derivative by the reaction with Ac_2O) were determined by GLC on a Biokhrom-21 instrument equipped with a 30 m × 0.25 mm × 0.25 μm β-DEX™ quartz capillary column (Supelco); the pressure was 1 atm, methane was used as the nonadsorbable gas (NG). The column temperatures (°C) and retention times (min) were as follows: 50°C, NG, 1.5; **4g**, 3.6; (*S*)- and (*R*)-**5g**, 5.7 (enantiomers were not separated); acetate of (*S*)-**5g**, 15.3; acetate of (*R*)-**5g**, 18.7; 145°C, NG, 2.2; **4h**, 45.2; (*R*)-**5h**, 48.9; (*S*)-**5h**, 50.1; 130°C, NG 1.6, **6b** 24.6; (*S*)-**7b**, 29.1; (*R*)-**7b**, 30.1; 145°C, NG, 1.3; *N*-acetyl-(*S*)-**10**, 33.7; *N*-acetyl-(*R*)-**10**, 34.3. The conversions of ketone **4d**, 1-indanone (**6a**), and imine **8** and the enantiomeric compositions of the products of their reduction, *viz.*, **5d**, **7a**, and **9**, respectively, were determined by HPLC on a Laboratorny pristroje Praha chromatograph instrument; visualization was carried out with UV light, λ 254 nm, Chiralcel OD (Daicel), 4.6 × 250 mm, the rate of elution was 1 mL min^{-1}. The compositions of the mobile phases (hexane : propan-2-ol, v/v) and retention times (min) were as follows: 95:5, **4d**, 8.0; (*S*)-**5d**, 15.3; (*R*)-**5d**, 28; **6a**, 6.4; (*S*)-**7a**, 6.7; (*R*)-**7a**, 7.3; 90 : 10, (*R*)-**9**, 6.64; **8**, 8.0; (*S*)-**9**, 8.56. The assignment of the chromatographic peaks of the products to the (*R*)- or (*S*)-enantiomers was made with the use of (*R*)-(+)- and (*S*)-(−)-**5a** (Aldrich), (*R*)-(−)-**5h** (Fluka), (*R*)-(+)- and (*S*)-(−)-**10** (Zeeland Chemicals). The standards (*R*)- and (*S*)-**9** were prepared by acylation of the corresponding enantiomerically pure amines **10** with $Ph_2P(O)Cl$ (Aldrich). The assignment of the chromatographic peaks to the (*R*)- or (*S*)-enantiomers of **5b—f** and **7a,b** was made based on the order in which they were eluted from the column by analogy with alkanol **5a** (see above). To determine the configuration of the major enantiomer **5g**, which was derived from ketone **4g** in entry *1* (see Table 2), alcohol **5g** was isolated from the reaction mixture by distillation after which the minus sign of the angle of optical rotation was determined by polarimetry. This sign corresponds to an enantiomeric excess of (*R*)-**5g**.[13]

Reduction of ketones 4 and 6 and imine 8 with complexes 2 and 3 prepared *in situ* in THF was carried out with the use of the molar ratio $NaAlH_4$(or AlH_3) : TADDOL : substrate = 1.00 : 1.00 : 0.33 according to a procedure used for reduction of compounds **4a,b** with modified $NaAlH_4$.[1] A solution of AlH_3 in THF was prepared by the reaction of $NaAlH_4$ with an equimolar amount of HCl followed by separation of the precipitate of NaCl by decantation.

In the experiments on hydride reduction of imine **8**, unconsumed hydride was quenched by the dropwise addition of water to the reaction mixture cooled to 0 °C. After separation of aluminates, the reaction solution had an alkaline reaction. Under these condition, hydrolysis of unconsumed imine **8** and reduction product **9** was not observed. To prepare amine **10**, the reaction mixture was treated with a solution of HCl in MeOH and kept at ~20 °C for 3 h. The enantiomeric composition of amine **10** was determined by GLC.

Isolation of the solvate of sodium dihydrido(2,3-isopropylidenedioxy-1,1,4,4-tetraphenyl-1,4-butanediolato)aluminate with THF, NaAl(IPTOLate)H_2·THF. A solution of $NaAlH_4$ (5 mmol, 270 mg) in anhydrous THF (9 mL) was added to a stirred solution of IPTOL **1a** (5 mmol, 2.33 g) in THF (20 mL) at ~20 °C through a rubber septum with the use of a syringe. The process was accompanied by liberation of 223 mL of H_2 (standard conditions; the theoretical yield was 224 mL). The reaction mixture was stirred for 1 h and concentrated to ~5 mL *in vacuo* at ~20 °C. Then hexane (10 mL) was added, a copious precipitate being formed. The reaction mixture was concentrated to dryness as described above to obtain the powdered complex, which was dried *in vacuo* (1—2 Torr) at 40—45 °C for 1 h. The yield was 2.6 g (88%). According to the ^1H NMR spectroscopic data, the complex contained an equimolar amount of THF. Found (%): C, 71.52; H, 5.74. $C_{35}H_{34}AlNaO_5$. Calculated (%): C, 71.41; H, 5.82. The operations with the solid complex (weighing, *etc.*) should be carried out in air rather rapidly (5—10 min) to avoid

its decomposition. The complex was soluble in THF, diglyme, CH_2Cl_2, and Et_2O. This complex is stable under a dry atmosphere at 20 °C for at least one week.

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