Asymmetric reduction of acetophenone and propiophenone by NaAl(IPTOLate)H_2 combined with enantiomeric enrichment of the reaction product as an inclusion complex with IPTOL

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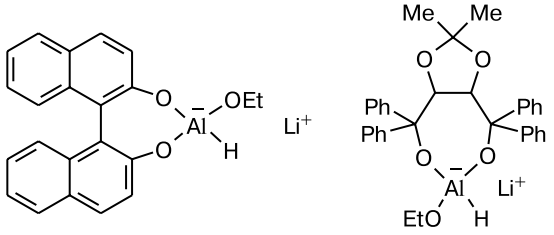
An improved procedure was developed for asymmetric reduction of acetophenone and propiophenone by the chiral reagent NaAl(IPTOLate)H_2. This procedure is based on isolation of the chiral alcohol that formed as a crystalline host—guest complex with the IPTOL ligand. The enantiomeric enrichment of the product was as high as 97% *ee*. The ability of IPTOL and its analogs to form host—guest complexes with a number of ether-type solvents, 1-phenylethanol, and 1-phenylpropan-1-ol as well as thermal stabilities of IPTOL-containing complexes with these alcohols were studied.

Key words: asymmetric reduction of alkyl phenyl ketones, enantiomeric enrichment of alcohols, chiral host—guest complex, sodium aluminum hydride, α,α,α´,α´-tetraaryl-1,3-dioxolane-4,5-dimethanol.

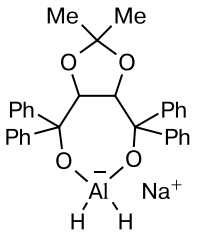
In recent years, a number of efficient catalytic processes have been developed for asymmetric reduction of prochiral C=C, C=O, and C=N bonds.[1—8] At the same time, it is often convenient to perform organic syntheses with the use of reagents containing a stoichiometric amount of a chiral inducing agent,[9—11] particularly, if the latter can be immobilized on the surface of a solid carrier or recovered after completion of the reaction and thus used repeatedly.[11—13]

Chiral aluminum hydride reagents find wide application in asymmetric reduction of the carbonyl group. In these reactions, BINOL- and TADDOL-containing* reagents **1**,[14—16] **2**,[16—18] and **3** [19,20] and their close structural analogs [14—20] exhibit the highest enantioselectivity.

However, reduction of ketones by reagents **1** and **2** did not give reproducible results due to low stability of compounds **1** and **2**.[14,17] In addition, high enantioselectivity of reduction of ketones by reagent **2** was achieved only with the use of freshly purified $LiAlH_4$ (with the storage time of no longer than a week).[17]



1 **2**



3a

(NaAl[IPTOLate]H_2)

* BINOL is 1,1´-bi-2-naphthol; TADDOL is α,α,α´,α´-tetraaryl-1,3-dioxolane-4,5-dimethanol; IPTOL is 2,3-*O*-isopropylidene-1,1,4,4-tetraphenylthreitol as their (*R*) and (*S*) or (*R*,*R*) and (*S*,*S*) enantiomers.

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Unlike monohydride reagents **1** and **2**, dihydride reagent **3a** and its analogs prepared with the use of $NaAlH_4$ give stable solutions in THF, DME, or diglyme and retain their enantioselectivity even upon storage of solutions at room temperature for one month. Reduction of ketones by reagent **3a** and its analogs **3b**—**h** based on other TADDOL ligands (**4b**—**h**) gave reproducible results.[19,20] From the aforesaid, it can be concluded that among presently known chiral aluminum hydrides, compounds **3** are reducing reagents of choice for asymmetric reduction of ketones.

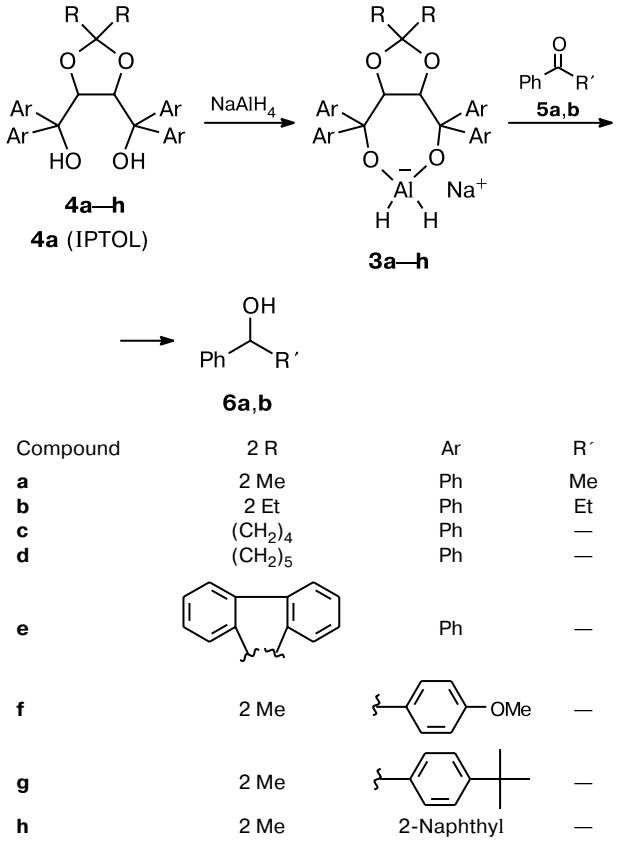
It is known that the TADDOL ligands not only can act as chiral inducing agents in the asymmetric synthesis[18] but also can be used for the resolution of racemic compounds into enantiomers through the formation of crystalline molecular host—guest complexes (HGC).[21—23] For example, cocrystallization with TADDOL can allow one to resolve various alcohols, including 1-arylalkan-1-ols, into enantiomers.[24—26] The fact that the latter are produced upon asymmetric reduction of the corresponding ketones by TADDOL-containing aluminum hydride reagents, makes it possible to increase the optical yields of alcohols owing to their isolation as inclusion complexes with TADDOL. A combination of asymmetric reduction of ketone and enantiomeric enrichment (AREE) of the alcohol that formed in one tandem process was carried out for the first time[17] with the use of hydride complex **2** in the step of reduction of ketone. However, this approach has not gained further acceptance[18] apparently because of insufficient stability of solutions of **2**.[17]

The aim of the present study was to perform AREE using reagents **3** and develop a convenient preparative procedure for the synthesis of chiral alcohols from alkyl phenyl ketones **5** based on this process (Scheme 1). To accomplish this aim, the TADDOL ligands should satisfy particular requirements. In addition to their ability to stereoselectively form host—guest complexes with one of the enantiomers of alcohols **6**, the TADDOL ligands should not form stable host—guest complexes with the solvent used for performing AREE. Since reduction by reagents **3** is carried out in ether-type solvents,[19,20] we studied the ability of TADDOL to give host—guest complexes with a number of ethers.

As can be seen from Table 1, the TADDOL ligands most readily formed host—guest complexes with diglyme. By contrast, no host—guest complexes with Et_2O were isolated. Tetrahydrofuran and DME are intermediate between the two above-mentioned solvents.

According to the data from X-ray diffraction analysis of the molecular complex of diol **4c** with diglyme (DGM) (Fig. 1), the ligand and diglyme molecules are linked to each other by the O(3)H...O(5) (H...O, 2.03 Å; O—H...O, 153.9°) and O(8)H...O(7) (H...O, 1.89 Å; O—H...O, 168.0°) hydrogen bonds. The diol molecules involved in

Scheme 1



the complex are similar in geometry. The spiro-fused five-membered rings adopt an envelope conformation. The C(5) and O(2) atoms deviate from the plane through the remaining atoms of the ring by 0.60 Å (**A**), 0.62 Å (**B**) and —0.49 Å (**A**), —0.50 Å (**B**), respectively. The substituents at C(6) and C(7) have an equatorial orientation (torsion angles: O(1)—C(6)—C(7)—C(9), 144.2(5)° (**A**) and 143.6(4)° (**B**); C(1)—O(1)—C(6)—C(8), —128.2(5)° (**A**) and —127.0(5)° (**B**)). In the complex, the diglyme mol-

Table 1. Ability of compounds **4a**—**h** to form crystalline host—guest complexes with ether-type solvents

Solvent	n^a							
	4a	**4b**	**4c**	**4d**	**4e**	**4f**	**4g**	**4h**
THF	0	0	1	1	1	0	0	—[b]
DME	0	0	0.5	1	0	0	—[c]	—[c]
Diglyme	0.5	0	0.5	0.5	0.5	0	1.5	1

[a] n is the number of moles of the solvent per mole of TADDOL in the crystalline product; for Et_2O, $n = 0$.
[b] Crystallization did not occur.
[c] Crystallization was not carried out.

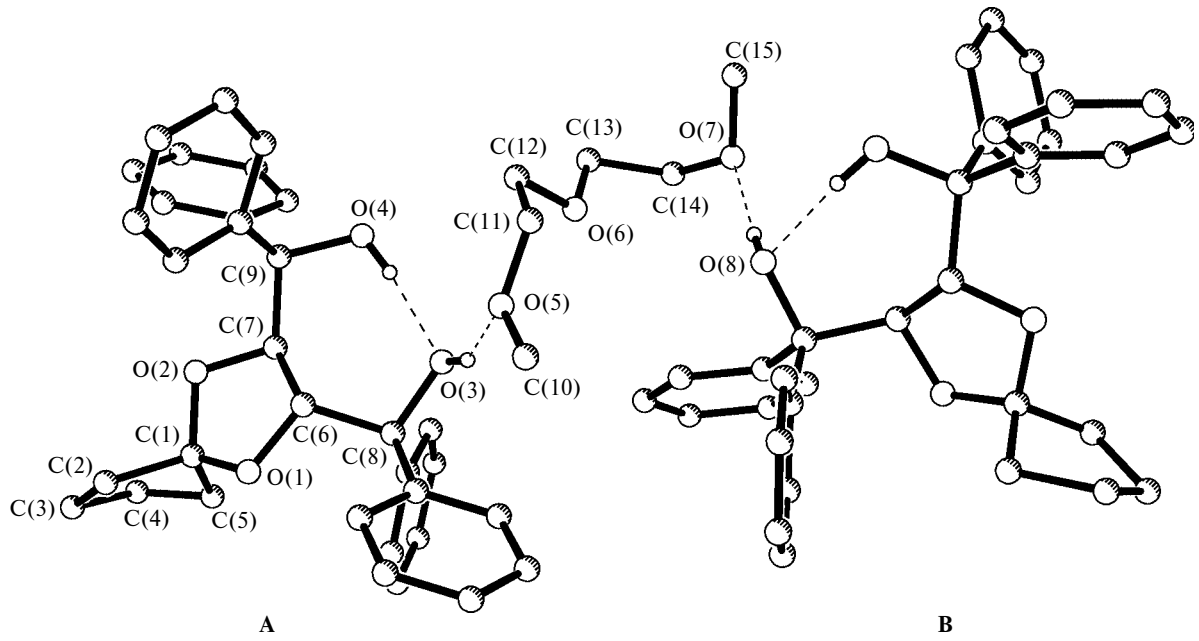


Fig. 1. Association of the diglyme molecule with two molecules of diol **4c** (**A** and **B**) in the crystalline complex 2 · (**4c**) · DGM.

ecule assumes a g-gtt-gt conformation. The torsion angles are given below.

Torsion angle	φ/deg
C(15)—O(7)—C(14)—C(13)	−61.3(7)
O(7)—C(14)—C(13)—O(6)	−57.1(7)
C(14)—C(13)—O(6)—C(12)	148.9(6)
C(13)—O(6)—C(12)—C(11)	−159.6(5)
O(6)—C(12)—C(11)—O(5)	−73.5(6)
C(12)—C(11)—O(5)—C(10)	170.9(5)

The crystals of the complex of (*R*,*R*)-**4a** with diglyme are characterized by a high degree of order (Fig. 2). In the crystals, the diol and ether molecules form linear helical chains, and the unit cell corresponding to one turn of the helix contains six diol molecules and three ether molecules.

To examine the possibility of performing AREE, we chose the model asymmetric reduction of acetophenone (**5a**) by reagent **3a** in THF, because it proceeds with an enantioselectivity up to 90% *ee*,[19] and diol **4a** forms a

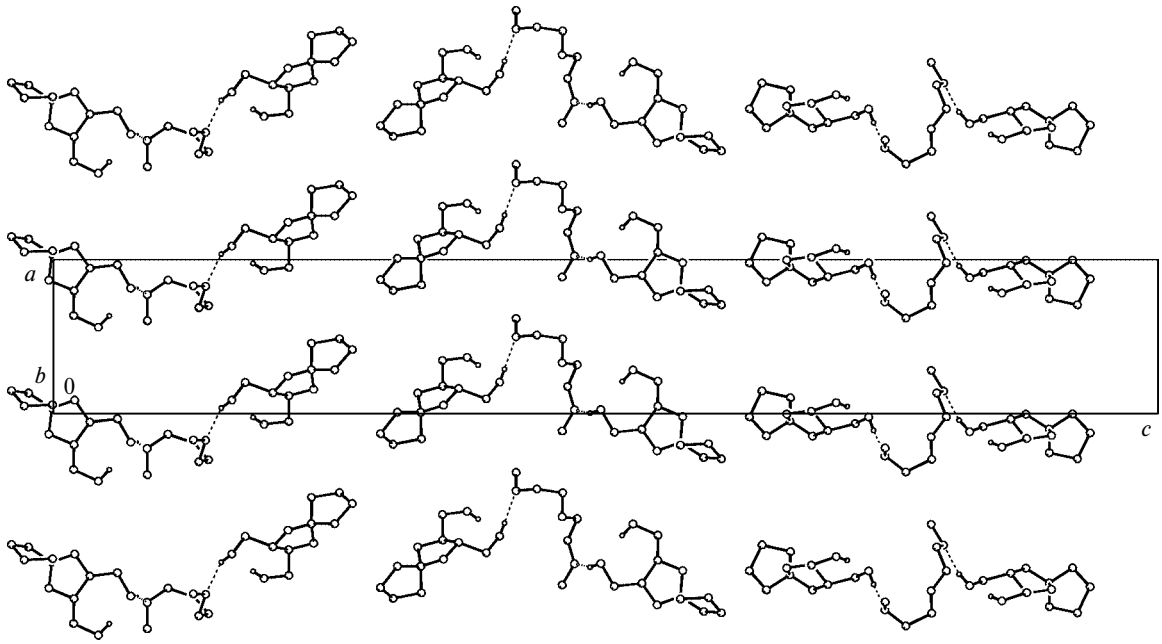


Fig. 2. Crystal structure of the complex 2 · (**4c**) · DGM projected along the axis *c*.

Table 2. Ability of compounds **4a—h** to form crystalline host—guest complexes with alcohols **6a**,**b**

Alcohol	n^a				
	4a	**4b**	**4e**	**4f**	**4g**
6a	0.5 [b]	0.5	0	0	0
6b	0.5	0.5	—	1	0

[a] See the note in Table 1.
[b] The composition of the complex corresponds to the data published in the literature.[25]

complex with alcohol **6a** (Table 2) and does not give a host—guest complex with THF (see Table 1).

With the aim of modeling the second step of AREE (enantiomeric enrichment of product **6**), we carried out experiments on resolution of racemic alcohols **6a** and **6b** into enantiomers by inclusion crystallization with (*S*,*S*)-IPTOL in a suspension of the latter in hexane, because this procedure[25] allows one to minimize losses of the ligand and product in the course of crystallization. The results of our study (Table 3) demonstrated that the yield of the host—guest complex containing (*R*)-**6a** (90—95% *ee*) depended substantially on the concentration of *rac*-**6a** in hexane (runs 1—4) (IPTOL is virtually insoluble in hexane), the maximum yield of the host—guest complex (95%) being achieved when the concentration of *rac*-**6a** was higher than 0.06 mol L^{-1}. After twofold crystallization of the host—guest complex in a suspension of (*S*,*S*)-IPTOL in hexane, *rac*-**6a** involved in the host—guest complex was virtually completely resolved; the yield of the latter was 90% (run 5). It is remarkable that the efficient resolution of alcohol **6b** in a suspension of IPTOL in hexane was achieved at its substantially higher concentration in solution (run 6).

Since data on the properties of the host—guest complexes of diols **4** with 1-arylalkan-1-ols are lacking in the literature, we estimated their thermal stabilities. As can be seen from Table 4, the complex **6b**·2 IPTOL was more readily subjected to thermal decomposition, *viz.*, it was completely decomposed at 100 °C after 0.5 h. It should be emphasized that thermal decomposition of the host—guest complex was not accompanied by racemization of alcohols **6a** and **6b** as well as of diol **4a** involved in the complex.

Table 3. Dependence of the degree of enantiomeric enrichment of *rac*-**6a**,**b** on the conditions of inclusion crystallization in a suspension of (*S*,*S*)-IPTOL in hexane

Run	Alcohol	C^a /mol L^{-1}	Yield of HGC (%)	*ee* (*R*) (%)[b]
1	**6a**	0.0125	<20	93
2	**6a**	0.025	40	95
3	**6a**	0.0625	95	90
4	**6a**	0.125	95	92
5	**6a**	0.17	90 [c]	98 [c]
6	**6b**	0.5	78	88

[a] The concentration of *rac*-**6** in the initial mixture.
[b] The degree of enantiomeric enrichment of **6a** involved in the host—guest complex.
[c] The result was obtained after twofold inclusion crystallization.

Table 4. Thermal stabilities of the complexes (*R*)-**6a**·2[(*S*,*S*)-IPTOL] (I) and (*S*)-**6b**·2[(*R*,*R*)-IPTOL] (II)

HGC[a]	*T*/°C	τ/h	Loss of **6a** (mol.%)	*ee* (%) (GLC)[b]
I	25	7	0	90
	70	7	0	88
	100	5 min	3	91
	100	0.5	33	89
	100	1	80	90
	100	5	100	88
II	25	7	0	85
	100	0.5	100	86

[a] The host—guest complexes were heated at 1—2 Torr. The degree of thermal dissociation of the host—guest complexes was determined by ^{1}H NMR spectroscopy.
[b] The optical purity of **6a** involved in the host-guest complex.

Based on the above-mentioned results, we developed a preparative AREE process with the use of NaAl(IPTOLate)H_2 (**3a**) as the reducing reagent, which made it possible to prepare chiral alcohols **6a**,**b** from ketones **5a**,**b** with higher enantioselectivity (up to 97% *ee*) compared to that achieved under standard conditions of reduction.[19,20] It should also be noted that the optical purity of the final product is virtually independent of the enantioselectivity of reduction of ketone **5** by reagent **3a** (the first step of the AREE process) if it is in the range of 75—90% *ee*. As a result, reduction need not be carried out with deep cooling (from −70 to −100 °C) because cooling to −20 °C is often sufficient to achieve the above-mentioned values of *ee*.[19,20] The procedure developed in the present study opens up possibilities for improving the enantioselectivity of reduction of carbonyl compounds, which react with TADDOL-containing aluminum hydride complexes with lower enantioselectivity compared to alkyl aryl ketones.[20]

Experimental

The NMR spectra were recorded on a Bruker AC-200 spectrometer. The ligands were synthesized and the reaction products were analyzed as described earlier.[19,20]

The X-ray diffraction data were collected on an automated Siemens P3/PC diffractometer (λMoKα, graphite monochromator, θ/2θ scanning technique, $2\theta_{max} = 50°$).

Study of the ability of ether-type solvents to form host—guest complexes with TADDOL (4). A solution of TADDOL in a cho-

sen solvent was concentrated almost to dryness at atmospheric pressure and room temperature for several hours. The solid precipitate was filtered off, washed with cold light petroleum, and dried without heating at 1—2 Torr.

In the case of the use of diglyme as the solvent, crystallization was induced by adding hexane. The composition of the crystalline product was analyzed by NMR spectroscopy. The results of the study are given in Table 1.

Study of the ability of alcohols 6a,b to form host—guest complexes with various TADDOL. Alcohol **6** and TADDOL in a molar ratio of 4 : 1 were dissolved in a 1 : 1 ether—hexane mixture and crystallization was performed by slow evaporation of the solvent. The crystalline product was dried at ~20 °C and then at 70 °C and 1—2 Torr for 3 h. The results of the study are given in Table 2.

Resolution of *rac*-6a,b by the formation of the host—guest complex in a suspension of IPTOL in hexane. Alcohol **6** (0.125 mmol) was added to a suspension of IPTOL (0.25 mmol) in hexane (the amount of the solvent varied from 0.5 to 10 mL) and the suspension was stirred at ~20 °C for 72 h. The crystalline product was analyzed by ^{1}H NMR spectroscopy. The yield of the host—guest complex (IPTOL : **6** = 2 : 1) was calculated from the integral intensities of the signals corresponding to IPTOL and alcohol **6**. The degree of enantiomeric enrichment of **6** involved in the host—guest complex was determined by GLC. The results of the study are given in Table 3.

When modeling the second step of AREE, heptane was used along with hexane, and the identical results were obtained. Under the conditions of the real AREE process, heptane (having the higher boiling point) is the solvent of choice in the step of formation of the inclusion complex. Upon partial concentration of the ether—heptane mixture (see the procedure described below), the remaining solution was to a larger degree enriched with the hydrocarbon solvent, which is favorable for an increase in the yield of the crystalline complex **6** · 2 IPTOL.

Synthesis of alcohol (*R*)-6a from ketone 5a under conditions of the AREE process. A solution of $NaAlH_4$ (1.08 g, 20 mmol) in freshly distilled THF (40 mL) was added dropwise with stirring to a solution of (*S*,*S*)-IPTOL (9.32 g, 20 mmol) in THF (70 mL) for 1 h. Then the reaction mixture was stirred for 1 h. Acetophenone (1.17 mL, 10 mmol) was added with stirring to the resulting solution cooled to −20 °C through a rubber septum using a syringe. The reaction mixture was kept at a temperature from −18 to −20 °C for 2 days and then allowed to slowly warm to ~20 °C. An excess of the hydride was quenched by adding 90% methanol. The solvent was distilled off *in vacuo* and the residue was extracted with ether (3×40 mL). The extract was successively washed with 1 *M* HCl and water and then dried with Na_2SO_4. The solution was concentrated to 20—25 mL, a threefold excess (by volume) of heptane was added, and the resulting suspension was stirred for 5 h. The solvent was distilled off to ~1/2 of the initial volume. The suspension was stirred for 5 h and kept at ~20 °C for one day. The crystalline host—guest complex was filtered off, washed with a small amount of cold heptane, and dried at 1—2 Torr and ~20 °C for 1 h and then at 70 °C for 3 h. To isolate alcohol **6a** from the host—guest complex, the latter was heated in an apparatus for vacuum distillation at 100—150 °C and 1—2 Torr, the alcohol that eliminated being collected in a trap cooled with dry ice. Compound (*R*)-**6a** was obtained in a yield of 0.74 g (62%) with an optical purity of 97% *ee*, and (*S*,*S*)-IPTOL was recovered in a yield of 7.9 g (85% of the amount used in the reaction). The latter can be again used in the same process.

Under similar conditions, alcohol **6b** was prepared from ketone **5b** in 53% yield with an optical purity of 96% *ee*.

X-ray diffraction study of the host—guest complex 2 (4c) · DGM. The crystals of the complex belong to the trigonal system. At 20 °C, $a = 9.357(2)$ Å, $c = 58.21(2)$ Å, $V = 4414(2)$ Å, $d_{calc} = 1.263$ g cm^{-3}, space group $P3_1$, $Z = 3$.

The structure was solved by direct methods using the SHELXTL PLUS program package. The positions of the hydrogen atoms were calculated geometrically (except for the H atoms of the hydroxy groups, which were revealed from a difference electron density synthesis) and refined using the riding model with fixed $U_{iso} = nU_{eq}$ of the nonhydrogen atoms to which the corresponding hydrogen atoms are bound (n = 1.5 for the methyl groups and 1.2 for the remaining hydrogen atoms). The refinement based on F^2 by the full-matrix least-squares method with anisotropic thermal parameters for nonhydrogen atoms using 5162 reflections converged to $wR_2 = 0.154$ ($R_1 = 0.058$ using 3405 reflections with $F > 4\sigma(F)$, $S = 1.02$).

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