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Reduction of Ketones with $LiAlH_4$ Complexes of α,α,α',α'-Tetraaryl-1,3-dioxolane-4,5-dimethanols (TADDOLs)

A Combination of Enantioselective Reduction and Clathrate Formation with a Discussion of LAH Reagents Bearing C_2-Symmetrical Ligands*

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A complex prepared from one equivalent each of $LiAlH_4$, EtOH and a TADDOL (α,α,α',α'-tetraaryl-1,3-dioxolane-4,5-dimethanol) reduces aryl alkyl ketones to *sec.* alcohols with enantiomer ratios (er) up to 96 : 4. The chiral LAH derivative is used in two-fold excess in THF solution and at dry ice temperatures. The ability of TADDOLs to form clathrates diastereoselectively can be exploited to increase the er of the initially formed alcohols by a simple modification of the work-up procedure and hence, products of very high enantiopurity (er 99 : 1) can be isolated. When (*R*,*R*)-TADDOLs (from (*R*,*R*)-tartrate) are applied in the reaction, the 1-aryl-alkanols formed preferentially have (*S*) configuration, as for the products obtained with the corresponding (*P*)-BINOL and (*P*)-BIPHENOL derivatives. A common mechanistic model is discussed.

* Dedicated to Professor Vladimir Prelog on the occasion of his 90th birthday, with admiration of a great friend, teacher and colleague, and with thanks for his contributions to our science.

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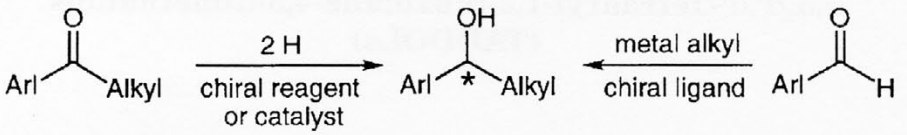
INTRODUCTION

There are two basic reactions by which secondary alcohols can be prepared enantioselectively, the – functionalizing – reduction of unsymmetrical ketones or the – C,C-bond-forming – nucleophilic addition to aldehydes (Scheme 1).

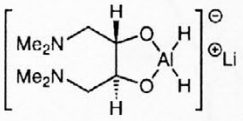


Scheme 1.

For both routes highly efficient catalytic methods now exist. Thus, the reduction of ketones[4] can be carried out with H_2 and a transition metal complex following Noyori's procedures,[5–8] with BH_3 and a oxazaborolidine[9] as in the work of Corey and Itsuno[10,11] or with $NaBH_4$ and a Co complex as shown by Mukaiyama.[12] In the most successful realization of enantioselective group transfer to aldehydes, organozinc or titanium reagents are employed in the presence of chiral amino alcohols (Noyori)[8,13] or Ti complexes of *N,N'*-1,2-cyclohexane-diyl-bistrifluoro-methanesulfonamide (CYDIS) (Ohno, Knochel)[14–16] or of α,α,α',α'-tetraaryl-1,3-dioxolane-4,5-dimethanol (TADDOL) (our group)[17,18]. There are numerous variants and applications of these procedures and it seems that we do not need any new methodologies for preparing secondary alcohols enantioselectively.

Having said this, it may look kind of atavistic to work on ketone reductions with chirally modified $LiAlH_4$ (LAH). This is one of the oldest approaches to enantioselective reductions using a reagent which is employed stoichiometrically[19–22] and it might be considered outdated not only by the methods mentioned above, but also by the procedures using chiral boranes which achieve record selectivities (Brown).[23–25]

However, as is evident from the title of the present paper, the motivation to study TADDOLate-modified LAH was two-fold: (i) Unlike any other previous applications of this method, the chiral ligand[26–30] is able to form clathrates[31–35] with the alcohol products[36] in case, so that the enantiopurity of the present originally formed alcohols can be augmented as part of the work-up procedure. (ii) We have included a mechanistic investigation which led to some general insights and conclusions about reactions involving C_2-symmetrical ligands.



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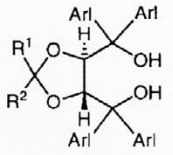
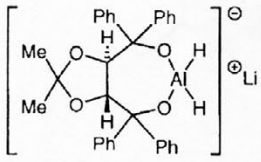
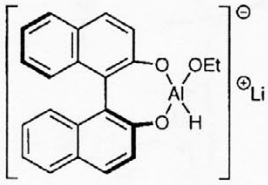


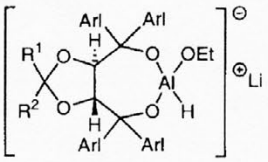
2
(specification of R^1, R^2, Arl see Table 1)



(*R,R*)-3



(*P*)-4



(*R,R*)-5
(specification of R^1, R^2, Arl see Table 1 and 3)

In our long-standing relationship with tartaric acid used as a chiral building block and in the preparation of chiral auxiliaries in both enantiomeric forms (EPC syntheses),[37] we have also made solvents[38–43] and ligands for LAH modifications,[44–47] *e.g.* **1**. At the time, this work was inspired by earlier attempts of the groups of Červinka[48] and Landor,[49] the enantioselectivities only being in the range of 50 to 75% ee. A new impulse to this research effort in our group was triggered by the synthesis of TADDOL **2** from tartaric acid in two or three steps.[26–29] This new class of diols turned out to be very useful for the synthesis of enantiomerically pure com-

TABLE I

Some TADDOLs synthesized in our group and used in the present study

	R^1	R^2	Arl
2a	Me	Me	Ph
ent-**2a**	Me	Me	Ph
2b	Me	Me	1-Naphthyl
2c	Me	Me	2-Naphthyl
2d	Me	Me	3,5-$(CF_3)_2$-Ph
2e	Ph	Ph	Ph
2f	*t*-Bu	H	Ph
2g	Ph	H	Ph
2h	1-Naphthyl	H	Ph

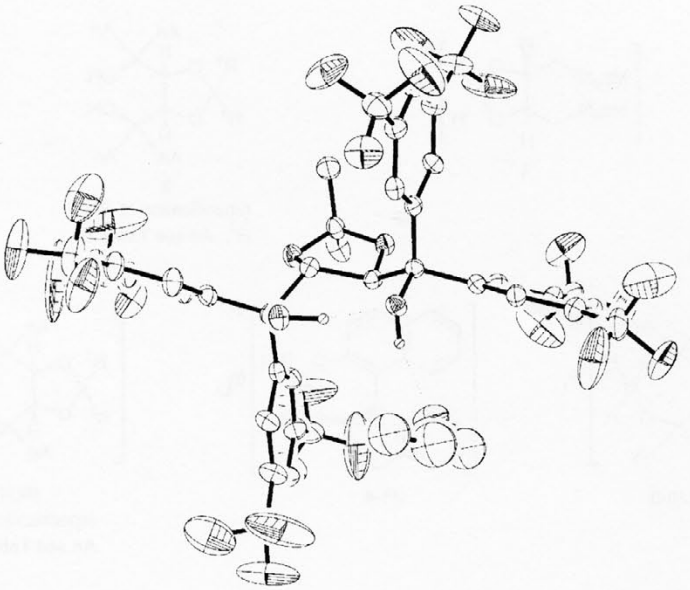


Figure 1. X-ray structure of the ether clathrate of ligand **2d**. The O- and F-atoms are shown as full thermal ellipsoids with shaded segments. All thermal ellipsoids are drawn to the 25% probabillity level. Two of the four CF_3-groups on the *quasi*-equatorial Ph-rings point towards the assumed substrate coordination site (*cf.* Figure 3).

pounds.[17,18,50–54] For a selection of different TADDOLs, see Table I and for a more complete list, see Table I in a recent full paper[51] and for an X-ray crystal structure of the TADDOL with 3,5-$(CF_3)_2$-substituted benzene rings,[55] see Figure 1.

During the investigation of the potential of these new ligands in the early eighties, we made attempts to enantioselectively reduce propiophenone by employing the chiral LAH derivative **3**.[56] These reactions were carried out under conditions which had been optimized by our group for reductions with **1**.[44] Using one equivalent of the chiral LAH-complex **3** and one equivalent of propiophenone, the reaction in ether at room temperature produced the corresponding *sec.* alcohol with only 6% ee. Variation of the ketones gave higher selectivities: 14% ee with 2-hexanone and up to 40% ee with acetophenone depending on the reaction time.[57] Considering these low selectivities, we did not carry out further experiments at that time.

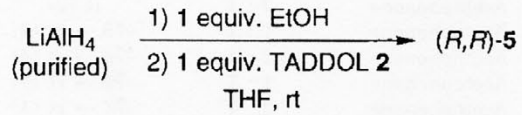
In the meantime, the pioneering work by Noyori *et al.* which described the enantioselective reduction of ketones by binaphthol-modified lithium aluminum hydride reagents was published.[58,59] They proved that high selectivities were only achievable with aluminum complexes bearing an additional alkoxide ligand, such that only a single hydride bound to aluminum

is present. It turned out that the best results were obtained with ethoxide as alkoxide ligand (see **4**) at very low temperatures (–100 °C) and using THF as solvent. Furthermore, a large excess of the reducing agent (up to four equivalents) was necessary. Noyori's success with the binaphthol ligand encouraged us to return to our efforts. We tested our TADDOL ligand **2a** under conditions similar to those reported for the BINOL ligand and the first experiment, the reduction of acetophenone, gave the corresponding *sec.* alcohol in 45% yield and with a selectivity of 94 : 6 (Table II, entry 1). This result prompted us to begin a systematic investigation using acetophenone as the standard substrate.

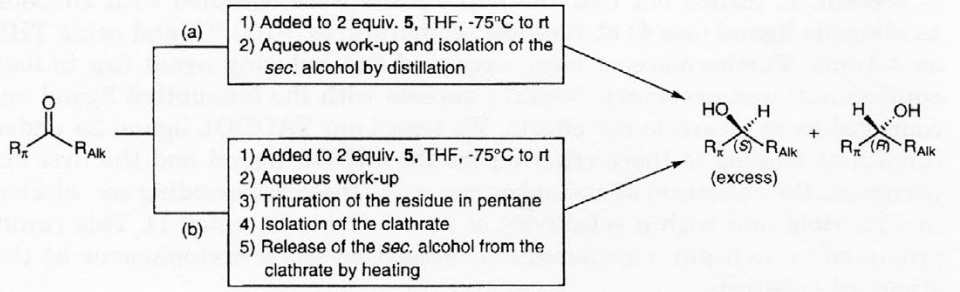
PREPARATIVE RESULTS

Mode of Complex Preparation. To avoid aging effects, we used only purified LAH (see experimental part) always handling it in a glove box. Aging effects are well known in LAH reductions[60,61] and were also observed in the BINAL-H reduction.[58,59] In our system, we found that the enantioselectivity dropped from 92 : 8 to 75 : 25 when LAH, which had been stored for over a fortnight, was employed in the reaction. Consequently, we never used LAH purified more than a week prior to use. The chiral reducing agent **5** was prepared by allowing LAH to react with one equivalent of ethanol and one equivalent of TADDOL **2** in THF (Scheme 2). The resulting complex **5** was not isolated and the ketone (0.5 equivalent) was added as a THF solution *via* syringe (Scheme 3a). As already mentioned by Noyori *et al.*, the preparation of the LAH-complex has to be repeated, *i.e.* the corresponding batch has to be discarded, if a considerable amount of precipitate separates. More recently, Marshall reported that heating of the LAH-complex solution improves the reproducibility of the reduction results.[62] In our case, the same influence of the precipitate was observed but heating of the solutions did not lead to any improvement.

Reaction Temperature. The very low reaction temperature of –100 °C (bath temperature), which has to be maintained over several hours in Noyori's system, represents one of the major disadvantages of this method and hence, we first looked at the effect of the reaction temperature with the TADDOLate **5**.



Scheme 2.



Scheme 3.

When acetophenone was added at –90 °C (internal temperature) and the reaction mixture was allowed to warm up to room temperature within 6.5 hours, the selectivity was 95 : 5 (Table II, entry 2). We therefore decided to go a step further and started the reaction at dry ice temperature (*ca.* –75 °C internal temperature measurement). After warming to room temperature within four hours and work-up, the *sec.* alcohol was isolated as a 95 : 5 mixture of (*S*)- and (*R*)-enantiomers (Table II, entry 3): the same selectivity as for entry 2 but in much higher yield (95%). Finally, to test whether low temperature is at all necessary for high selectivity, the reaction was run at room temperature and a selectivity of 82 : 18 (Table II, entry 4) was found.

TABLE II

Reductions of acetophenone and isobutyrophenone yielding the corresponding *sec.* alcohols at different temperatures and with different reducing agent / ketone ratios. The major product enantiomer has (*S*)-configuration in all cases.

Entry	Al-TADDOL-ate	Ketone	Al-TADDOL-ate / Ketone Ratio	Reaction Conditions *T*/°C (time/h)	*sec.* Alcohol	
					Yield %	Enantiomer Ratio (er)
1	**5a**	Acetophenone	2 : 1	–95 (5), –75 (10)	45	94 : 6
2	**5a**	Acetophenone	2 : 1	–90 → rt (6)	87	95 : 5
3	**5a**	Acetophenone	2 : 1	–74 → rt (4)	95	95 : 5
4	**5a**	Acetophenone	2 : 1	rt (2)	91	82 : 18
5	**5a**	Acetophenone	1 : 1	–76 → rt (4)	60	95 : 5
6	**5a**	Acetophenone	2 : 1	–76 → rt (4)	94	95 : 5
7	**5g**	Acetophenone	1 : 1	–79 → rt (4)	41	96 : 4
8	**5g**	Acetophenone	2 : 1	–78 → rt (4)	83	95 : 5
9	**5a**	Isobutyrophenone	4 : 1	–82 → rt (5)	91	96 : 4
10	**5a**	Isobutyrophenone	2 : 1	–79 → rt (4)	90	93 : 7

Ratio AlH-TADDOLate/Ketone. Besides the low temperature, another disadvantage of the reported system was the 4 : 1 molar ratio of reducing agent over ketone. Therefore, the influence of this ratio on the selectivity of our reagent was examined (Table II, entries 5–10). A 1 : 1 ratio gave the same selectivity but a considerably decreased yield (Table II, entry 5 and 7). A four-fold excess in the case of isobutyrophenone reduction gave no improvement in either yield or selectivity (Table II, entry 9).

Different RO Groups on Al. Variation of the alkoxy group from ethoxide to methoxide, isopropoxide, *t*- and *n*-butoxide decreased the selectivity but did not affect the yield.[58,63] All the experiments outlined above led to optimized reaction conditions for TADDOL **2** which are summarized in Scheme 3a.

It is our experience with TADDOL-ligands in other reactions that the substitution pattern on the ligands may have a great influence on enantioselectivities.[18,51,64] Therefore, eight TADDOLs with different substituents on the acetal center or with different aryl groups (see Table I) were tested in the reduction of acetophenone. It became clear that the ligands with very large aryl substituents (α-naphthyl, β-naphthyl and 3,5-$(CF_3)_2$-Ph) on the seven-membered chelate ring gave rise to poorer selectivities in comparison with the original TADDOL **2a** (entries 2–4, Table III). In the case of the CF_3-substituted ligand **2d**, practically no selectivity was observed. A similar but less drastic influence of the CF_3-substiuents was reported by Corey and Matsumura in an enantioselective Diels-Alder reaction.[55] We assume that the decrease in selectivity is due to both the steric hindrance and the electronic effect of the CF_3-groups (see the crystal structure of **2d** in Figure 1). Variation of the acetal substituents is of minor importance for the asymmetric induction. The pentaphenyl-TADDOLate **5g** gave the same enantiomeric excess as TADDOLate **5a** within the limits of our analysis. The same is true for the TADDOLates **5f** and **5h** bearing a *t*-butyl and a 1-naphthyl substitutent on the dioxolane ring. The only exception to this tendency is the hexaphenyl substituted TADDOLate **5e** which gave only a 75 : 25 selectivity in the model reaction.

Reduction of Different Ketones. As the intention was to develop a general method for the use of TADDOL ligands in the asymmetric reduction of ketones, over a dozen different substrates were reduced under our optimized conditions. First, the effects of varying alkyl groups were examined in the reduction of aryl alkyl ketones and this showed that the selectivity drops with increasing size of the alkyl group (Table III, entries 9–11). From methyl to ethyl and isopropyl, the changes are almost negligible but for *t*-butyl (Table III, entry 11), the tendency becomes obvious (enantiomer ratio 77 : 23). Next, the substitution pattern on the aromatic ring was varied. *Ortho*- and *para*-bromo-substitution had no effect on the reaction (≥ 95 : 5, entries 12 and 13 in Table III) but the more strongly electron-withdrawing *ortho*-fluorine caused a drop in selectivity (ratio 74 : 26). The electron donating *para*-

TABLE III

Enantiomer ratios and reaction conditions (see Scheme 3) for different TADDOL ligands and for the reduction of different ketones to the corresponding *sec.* alcohols

Entry	Al-TADDOLate (R^1, R^2, Arl as in 2)	Ketone	Reaction Conditions *T*/°C (time/h)	*sec.* Alcohol	
				Yield %	Enantiomer Ratio (er)
1	**5a**	Acetophenone	–74 → rt (4)	95	95 : 5
2	**5b**	Acetophenone	–62 → rt (4)	75	89 : 11
3	**5c**	Acetophenone	–74 → rt (4)	92	87 : 13
4	**5d**	Acetophenone	–78 → rt (4)	91	47 : 53
5	**5e**	Acetophenone	–78 → rt (4)	74	75 : 25
6	**5f**	Acetophenone	–82 → rt (6)	89	93 : 7
7	**5g**	Acetophenone	–78 → rt (4)	83	95 : 5
8	**5h**	Acetophenone	–80 → rt (5)	86	91 : 9
9	**5a**	Propiophenone	–82 → rt (4)	89	94 : 6
10	**5a**	Isobutyrophenone	–79 → rt (4)	90	93 : 7
11	**5a**	Pivalophenone	–72 → rt (5)	89	77 : 23
12	**5a**	2-Bromoacetophenone	–74 → rt (5)	76	95 : 5
13	**5a**	4-Bromoacetophenone	–80 → rt (5)	62	96 : 4
14	**5a**	2-Fluoroacetophenone	–94 → rt (6)	77	74 : 26
15	**5a**	4-Methoxyacetophenone	–71 → rt (5)	87	86 : 14
16	**5a**	2-Furyl methyl ketone	–76 → rt (6)	66	89 : 11
17	**5a**	1-Acetylcyclohexene	–63 → rt (5)	72	82 : 18
18	**5a**	1-Octyn-3-one	–78 → rt (4)	84	76 : 24
19	**5g**	1-Octyn-3-one	–78 → rt (4)	89	81 : 19
20	**5a**	Benzyl methyl ketone	–74 → rt (5)	82	21 : 79
21	**5a**	2-Octanone	–76 → rt (5)	83	61 : 39
22	**5a**	3-Nonanone	–76 → rt (4)	82	50 : 50

methoxy group also has an unfavorable influence (86 : 14). With the heteroaromatic furyl substituent (Table III, entry 16) or with acetylcyclohexene (Table III, entry 17), the enantioselectivities are moderate. With 1-octyn-3-one, the selectivity is 76 : 24 (Table III, entry 18) when employing the ligand **2a**. Surprisingly, this is the only substrate which gave a considerably better enantioselectivity with the pentaphenyl-substituted ligand **2g** (81 : 19, entry 19). However, our selectivities were exceeded by those reported by the Noyori group for this substrate type.[59] In the case of totally aliphatic ketones, rather poor selectivities were observed (Table III, entries 21, 22). For example, the reduction of 2-octanone leads to the corresponding alcohol with a disappointing enantiomer ratio of 61 : 39 and 3-nonanone gives a racemic product. With benzyl methyl ketone, a reversal of the selectivity was in fact found (er = 21 : 79, Table III, entry 20).

Enhancement of Enantiopurity by Clathrate Formation in the Crude Product Mixture. As it is well known in the literature[31–36] that TADDOLs enantioselectively form inclusion compounds with chiral alcohols, we at-

tempted to use this phenomenon to enhance the enantiopurity of our products by a special work-up procedure: after aqueous work-up, drying of the organic phase and evaporation of the solvents, pentane was added to the resulting oily residue. This led to an immediate precipitation of a white powder which was stirred with the supernatant liquid for 24 hours.[65] The solid was isolated by filtration and heated in a bulb-to-bulb distillation apparatus to yield the entrapped *sec.* alcohol (Scheme 3b). By applying this new work-up procedure for the reduction of acetophenone, 1-phenylethanol was isolated in 85% yield and with a ratio of (*S*)- and (*R*)-enantiomers of 97.5 : 2.5 (Table IV, entry 1). By repeating the trituration and isolation steps 3, 4 and 5 in Scheme 3b, the enantiomer ratio was increased to 98.5 : 1.5 and the overall yield remained at 73% (Table IV, entry 2). The same enrichment procedure led to excellent enantiomer ratios of more than 98.5 : 1.5 in the cases of 1-phenyl-1-propanol, 1-(2-fluorophenyl)-1-ethanol and 1-(1-cyclohexenyl)-1-ethanol. Unfortunately, only moderate yields were obtained in these latter cases (entries 3 to 5 in Table IV). A considerable enantiomer enrichment was also achieved for 2-furyl-1-ethanol and 3-benzyl-2-propanol (entries 6–7 in Table IV). This procedure failed for the reduction products of isobutyrophenone, pivalophenone, 2-octanone and 1-octyn-3-one. From these results, the conclusion that a branched substituent on the alcohol or a long aliphatic chain prevents the clathrate formation under these conditions can be drawn.

TABLE IV

Enantiomer ratios and reaction conditions (see Scheme 3b) for the reductions of different substrates with complex **5a** and with enantiomer enrichment by clathrate formation of the crude product

Entry	Ketone	Reaction Conditions *T*/°C (time/h)	*sec.* Alcohol	
			Yield %	Enantiomer Ratio (*S*)/(*R*)
1	Acetophenone	−78 → rt (4)	85	97.5 : 2.5
2	Acetophenone	−76 → rt (5)	73	98.5 : 1.5[a]
3	Propiophenone	−65 → rt (4)	43	98.5 : 1.5
4	2-Fluoroacetophenone	−78 → rt (4)	49	99 : 1
5	1-Acetylcyclohexene	−78 → rt (4)	38	98.5 : 1.5
6	2-Furyl methyl ketone	−78 → rt (4)	46	95.5 : 4.5
7	Benzyl methyl ketone	−78 → rt (4)	25	11.5 : 88.5

[a] Repeat of the trituration and isolation steps 3, 4 and 5 in Scheme 3b.

Thus, we have demonstrated that a simple modification of the work-up procedure can increase the enantiopurity of the alcohols formed in the LiAlTADDOLate hydride reductions due to the ability of TADDOLs to clathrate alcohols enantioselectively.

STRUCTURAL AND MECHANISTIC INVESTIGATIONS

Once a satisfying degree of optimisation for the reaction had been accomplished, we became curious about the mechanistical aspects of this enantioselective reduction. The first puzzling question was whether the reactive species is a mono- or a polynuclear complex which would not be unusual for lithium and aluminum derivatives.[66–68] Therefore, we checked whether the enantiopurity of the ligand was linearly correlated to the enantiomer ratio of the product.[69,70] It can be seen from Figure 2 that this is actually the case.

A linear correlation has also been observed for several metal-TADDOLate mediated reactions[50,71] with the Ti-TADDOLate catalyzed Diels-Alder reaction being an exception.[51] To gain information about the structure of the chiral LAH-complex (see formula **5a**) a deutero-THF solution of the reducing agent was examined by ^{1}H-NMR spectroscopy. In comparison to diisopropoxy-Ti-TADDOLate,[64] the methine protons of the TADDOL ligand in **5a** are shifted to higher field and split into two coupled doublets. The methyl groups at the acetal centre of **5a** give rise to two singlets, both at higher shift as compared to TADDOL **2a** itself. The non-equivalence of the methine and methyl protons indicates that the complex is no longer C_2-symmetric. A coupled quartet triplet system can be assigned to the ethanol ligand on the aluminum. The integral ratios suggest a TADDOL to ethanol ratio of 1 : 1 on the aluminum. Unfortunately, we were not able to assign signals to the resonance of the hydride. However, these results are sufficient for the confirmation of our suggested structure of the reducing complex as a seven-membered O–Al–O containing ring.

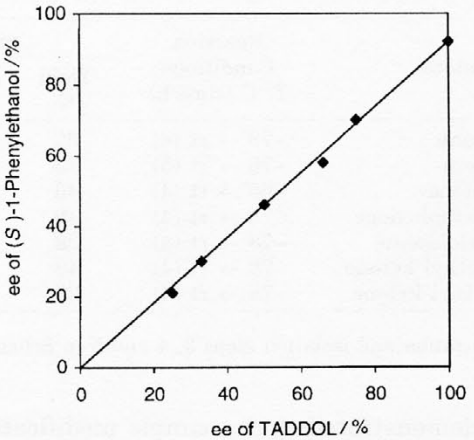


Figure 2. Linear relationship between enantiopurity of the ligand **2a** and the reduction product (*S*)-1-phenylethanol.

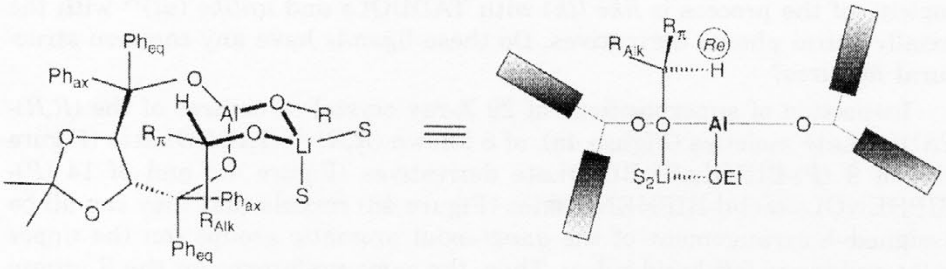


Figure 3. Schematic picture of the aluminum complex with the *sec.* alcohol after hydride transfer to the carbonyl C-atom. The unsaturated R_π-group is parallel to the *quasi*-axial Ph group of the ligand. The alkyl residue R_{Alk} is pointing towards the *quasi*-equatorial Ph group. S represents neutral solvent molecules. The shaded bars indicate the Ph groups of the ligand.

If we assume – as Noyori,[58,59] Yamamoto,[72] Meyers[73b] and their respective coworkers do – that the hydride is transferred in a bimetallic six-membered ring chair-like transition state, the product complex, which is initially formed, should be as pictured in Figure 3.

The hydride is added to the carbonyl carbon from the *Re* face with the unsaturated, usually larger R_π group in an equatorial position on the six-membered ring. In this arrangement, R_π is located parallel to a *quasi*-axial phenyl group and the saturated R_{Alk} points towards a *quasi*-equatorial phenyl ring on the other side of the TADDOL moiety.

The different selectivities obtained with different ketones are compatible with this model: the ideal substrate for our system is an aryl alkyl ketone with an unbranched alkyl substituent of moderate chain length. The arrangement in Figure 3 might be stabilized by a π-π-stacking effect of the ketone aryl substituent (R_π) with one of the *quasi*-axial phenyl groups (Ph_{ax}) of the TADDOL ligand (*cf.* the higher enantioselectivities of reductions of unsaturated ketones, such as 1-acetylcyclohexene, in comparison to dialkyl ketones which give almost racemic products). Highly branched alkyl groups such as *t*-butyl or long chain unbranched alkyl substituents are subject to steric interactions with the *quasi*-equatorial TADDOLate phenyl group (Ph_{eq}). The reaction of benzyl methyl ketone was found to proceed with a topicity opposite to that found in all the other cases (*Si* instead of *Re* hydride transfer). Consideration of Figure 3 shows that, for this latter substrate, π-π interaction between its aromatic ring and the *quasi*-axial phenyl group (Ph_{ax}) of the TADDOL in the Al complex might not be possible.

We notice that hydride transfer from the *Re* face is observed not only with (*R,R*)-TADDOLate modified LAH but also with the corresponding LAH derivatives of (*P*)-BINOL[58,59,72] and (*P*)-BIPHENOL.[73] Thus, the relative

topicity of the process is *like* (*lk*) with TADDOLs and *unlike* (*ul*)[74] with the axially chiral phenol derivatives. Do these ligands have any common structural features?

Inspection of superpositions of 29 X-ray crystal structures of the (*R*,*R*)-TADDOLate moieties (Figure 4a), of 8 known (*R*,*R*)-Ti-TADDOLates (Figure 4b), of 9 (*P*)-BINOLs/Ti-BINOLate derivatives (Figure 4c) and of 14 (*P*)-BIPHENOLs/metal-BIPHENOLates (Figure 4d) reveals that they can all be assigned λ arrangement of the *quasi*-axial aromatic groups (on the upper right and lower left hand sides). Thus, the same preference for the R_π group to occupy an equatorial position in a six-membered cyclic transition state appears to be the common feature of these reductions.

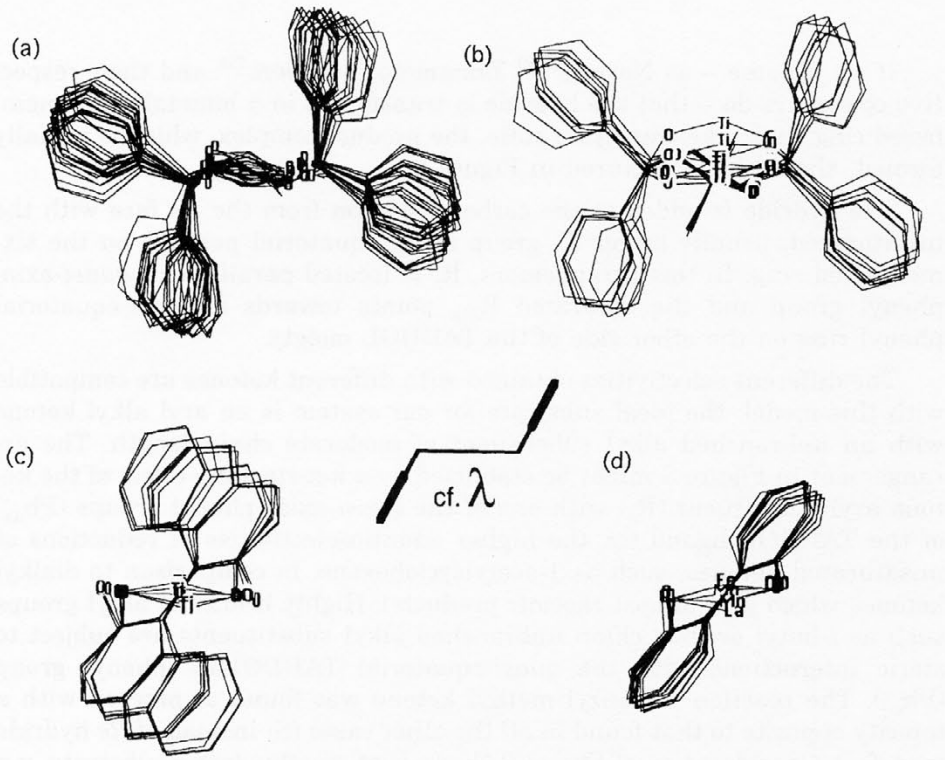


Figure 4. The superposition of a) 29 structures of TADDOLs and TADDOL analogues, b) the 8 known Ti-TADDOLates all in the (*R*,*R*)-configuration, c) 9 BINOLates and d) 14 BIPHENOL derivates in the (*P*)-configuration is shown. Some of these structures had to be inverted for this purpose. The arrangement of the *quasi*-axial aryl groups is designated λ.

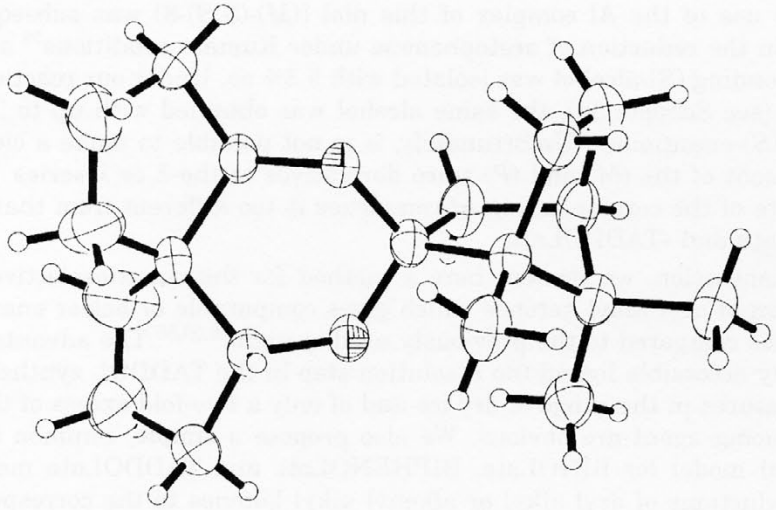
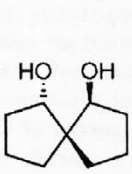
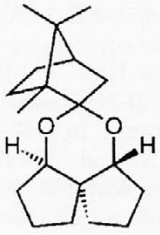


Figure 5. X-ray structure of (*P*)-(*R*,*R*)-**7**. The O-atoms are shown as full thermal ellipsoids with shaded segments, the C-atoms only as full thermal ellipsoids and the H-atoms as circles. All thermal ellipsoids are drawn to the 25% probabillity level.

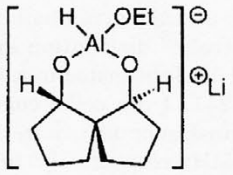
One ligand which does not seem to follow this rule is the spiro[4.4]nonane-1,6-diol (**6**).[75–77] As the data published on the assignment of the absolute configuration of **6** were confusing to us,[78] we decided to independently establish its sense of chirality.[79] We followed the synthetic route of Keay *et al.*[75] The two enantiomeric diols **6** were converted to their diastereoisomeric camphor acetals **7** which can be separated by flash chromatography. The resulting oily products were stored in a refridgerator (4 °C) overnight and we were happy to find that one of the diastereoisomers (R_f = 0.36, hexane) crystallized. By X-ray crystal structure analysis, this diastereoisomer turned out to be the (1*R*)-(+)-camphor acetal of the (*P*)-(*R*,*R*)-spiro [4.4]nonane-1,6-diol (*cf.* Figure 5). The other diastereoisomer, which did not crystallize, was cleaved to give the ligand (*M*)-(*S*,*S*)-**6** of 99% ee.



(*M*)-(*S*,*S*)-**6**



(*P*)-(*R*,*R*)-**7**



(*M*)-(*S*,*S*)-**8**

The use of the Al complex of this diol ((*M*)-(*S*,*S*)-**8**) was subsequently tested in the reduction of acetophenone under Kumars conditions[78] and the corresponding (*S*)-alcohol was isolated with 5.3% ee. Under our reaction conditions (see Scheme 3a), the same alcohol was obtained with up to 26% ee as the (*S*)-enantiomer. Unfortunately, it is not possible to make a clear-cut assignment of the (*M*) and (*P*) spiro derivatives to the δ or λ series, as the structure of the corresponding Al complexes is too different from that of Ti-BINOLate and -TADDOLate.

In conclusion, we present here a method for the enantioselective LAH reduction of aryl alkyl ketones which gives comparable or better enantioselectivities compared to the previously used system.[58,59,80] The advantages of a readily accessible ligand (no resolution step in the TADDOL synthesis), of temperatures in the range of dry ice and of only a two-fold excess of the chiral reducing agent are obvious. We also propose a simple, common stereochemical model for BINOLate, BIPHENOLate and TADDOLate mediated LAH reductions of aryl alkyl or alkenyl alkyl ketones to the corresponding secondary alcohols.

EXPERIMENTAL

Abbreviations used: GP (general procedure). HV (high vacuum, 0.01–0.001 Torr). RV (rotary evaporator). rt (room temperature).

TLC: Merck-TLC-F_{254} plates; visualization by UV_{254} light or by spraying with phosphomolybdic acid solution (phosphomolybdic acid 25 g, $Ce(SO_4)_2 \cdot 4H_2O$ 10 g, conc. H_2SO_4 60 mL, and H_2O 940 mL). Column chromatography at normal pressure (NC): Fluka silica gel 60 (mesh 70–230). Flash chromatography (FC): Fluka silica gel 60 (mesh 230–400) and a pressure of 0.2 bar. Capillary gas chromatography (CGC): Carlo Erba HRGC 5160 or Carlo Erba FRACTOVAP 4160 with integration by means of a Carlo Erba DP 700 CE data processing unit. The following chiral capillary columns were used: (a) FS-Hydrodex β-PM (50 m × 0.25 mm, Macherey & Nagel) or (b) FS-Lipodex E: 2,6-*O*-Pentyl-3-*O*-butyryl-γ-CD (50 m × 0.25 mm, Macherey & Nagel). The carrier gas was hydrogen (pressure: 100 kPa H_2) and the detection was accomplished by flame ionization. Melting points (uncorrected): in open capillary tubes with a Büchi-510 (Tottoli apparatus) using 50 °C range Anschütz-thermometer. Boiling points: the isolated products were distilled or the clathrates were heated up using a Büchi GKR-50 Kugelrohr apparatus (bulb-to-bulb distillation) and the given boiling points correspond to uncorrected air oven temperatures. Spaltrohr® distillation apparatus HMS 300-HV/C or Labodest 104/S (Fischer Labor- und Verfahrenstechnik GmbH, D-Meckenheim). Optical rotations, $[\alpha]_D$: Perkin-Elmer 241, 1 dm cells; concentration *c* in g/100 mL. IR spectra of $CHCl_3$ solutions: Perkin-Elmer 983, $\tilde{\nu}$ in cm^{-1}. ^1H- and ^{13}C-NMR spectra: Varian Gemini 200 (200 or 50 MHz respectively) or Bruker WM 300 (300 or 75 MHz respectively). TMS ($\delta = 0$) was used as a internal standard and all chemical shifts (δ) are given in ppm downfield of TMS in $CDCl_3$ solutions unless stated otherwise. The coupling constants (*J*) are given in Hz. Mass spectra (MS): VG-Tribrid spectrometer; *m*/*z* values

with relative intensity (%) in parentheses; M^+ is the molecular ion. Elemental analyses were performed by the Microanalytical Service Laboratory of the Laboratorium für Organische Chemie (ETH Zürich).

THF was initially distilled over KOH and then heated to reflux over Na/benzophenone (under argon) until the blue color of the benzophenone ketyl persisted; at this point the THF was distilled and handled by means of syringes and cannulas. All other solvents employed in the reactions were purchased from Fluka in *puriss p.a.* (*pro analysi*) quality. The solvents used for extraction or purification steps were bought in technical quality and distilled over P_2O_5. $LiAlH_4$ was obtained from Chemetall GmbH (D-Langelsheim) in *purum* quality. Dimethyl tartrate (Chemische Fabrik CH-Uetikon) was used as received without prior purification.

All other commercially available chemicals used were of *purum* quality or were purified and dried according to standard methods. (*R,R*)-Dimethyl-*O,O*-methylidene tartrate was prepared according to the literature.[29] The TADDOLs **2a**,[29] ent-**2a**,[29] **2b**,[29] **2c**,[29,30] **2f**,[28,29] **2g**,[28,36] and **2h**[64] were prepared following reported procedures. The glassware was dried for at least 24 h in an oven at 130 °C. The temperatures given in the Tables II–IV are measured as internal temperatures with a digital temperature detector (Pt 100).

*Preparation of the TADDOLs **2d** and **2e***

*(4R,5R)-2,2-Dimethyl-α,α,α',α'-tetrakis(bis(3,5-trifluoro-methyl)-phenyl)-1,3-dioxolane-4,5-dimethanol (**2d**)*

Following a known procedure[29] (*R,R*)-dimethyl-*O,O*-isopropylidene tartrate (5.5 g, 25 mmol) in THF (50 mL) was added to 3,5-bis(trifluoromethyl)-phenylmagnesium bromide (110 mmol; prepared from 3,5-bis(trifluoromethyl)-bromobenzene (32.2 g) and Mg (2.8 g)) in THF (90 mL). After work-up, the isolated brown syrup was purified by FC (8 × 30 cm SiO_2, pentane/ether 10 : 1, R_f = 0.45) leading to a light brown glass. Recrystallization from hexane, trituration overnight in pentane (30 mL) and drying of the resulting white powder under HV at 80 °C for 6 h afforded 6.1 g (24%) **2d**. M.p. 124–125 °C. $[\alpha]_D^{rt}$ = –23.3 (*c* = 1.0, $CHCl_3$). IR: $\tilde{\nu}$ = 3300, 1625, 1470, 1370, 1330, 1280, 1145, 1075, 1045, 1035, 980, 905, 880, 850, 630, 615. ^{1}H-NMR (300 MHz): δ = 8.06 (s, 4 arom H), 7.95 (s, 2 arom H), 7.85 (s, 2 arom H), 7.82 (s, 4 arom H), 4.66 (s, 2 OH), 4.27 (s, H-C(4) and H-C(5)), 1.11 (s, 2 CH_3). ^{13}C-NMR (75 MHz): δ = 145.77, 143.14, 132.99, 132.56, 132.46, 132.11, 132.03, 131.59, 131.14, 128.55, 128.24, 127.43, 124.92, 124.76, 122.92, 122.75, 121.3, 121.14, 111.03, 81.09, 26.58.

Anal. Calcd. for $C_{39}H_{22}O_4F_{24}$ (M_r = 1010.51): C 46.36, H 2.19%; found: C 45.94, H 2.03%.

*Preparation of **2e***

Benzophenone Dimethyl Acetal – According to a reported procedure,[81] benzophenone (100 g, 0.55 mol) and trimethyl orthoformate (170 mL, 1.55 mol) were dissolved in MeOH (225 mL) in a 1 L two-neck flask equipped with a condenser with drying tube and a gas inlet tube. With continual stirring, HCl gas was bubbled into this mixture for 20 min followed by 4 h of heating to reflux. The reaction flask was then stored overnight in a refridgerator (+4 °C) and the resulting crystals were isolated and dried under HV to give 117 g (93%) benzophenone dimethyl acetal. M.p. 107–108 °C

(lit.[82] m.p. 106–107 °C). ^{1}H-NMR (200 MHz): δ = 7.58–7.46 (m, 4 arom H), 7.38–7.18 (m, 6 arom H), 3.15 (s, OCH_3), 3.13 (s, OCH_3).

This procedure was repeated to obtain another 118 g (94%) of benzophenone dimethyl acetal.

(R,R)-Dimethyl-O,O-(diphenylmethylidene)tartrate – According to a literature procedure,[83] benzophenone dimethyl acetal (245 g, 1.07 mol), (*R,R*)-dimethyl tartrate (210.4 g, 1.18 mol), cyclohexane (1.15 L) and *p*-toluene sulfonic acid (10 g) were heated to reflux in a 2 L flask, fitted with a 100 cm *Spaltrohr* column (Labodest 104/S). The resulting MeOH was continuously distilled as an azeotropic mixture (cyclohexane/MeOH 54 °C) until the head temperature rose to 70 °C (reflux ratio 20 : 1). After cooling to rt, K_2CO_3 (1.5 g) was added to the resulting suspension and the remaining solvent was evaporated. The so isolated solid was recrystallized from MeOH (400 mL) to yield 306 g (84%) of (*R,R*)-dimethyl-*O,O*-(diphenylmethylidene)tartrate. M. p. 75.2–78.2 °C (lit.[84] m.p. 78–80 °C; lit.[85] m.p. 80–81 °C). $[\alpha]_D^{rt}$ = +53.7 (*c* = 1, $CHCl_3$) (lit.[84] $[\alpha]_D^{rt}$ = +51.5 (*c* = 1, $CHCl_3$); lit.[85] $[\alpha]_D^{rt}$ = +54.2 (*c* = 0.964, $CHCl_3$)).

The spectral data are identical to those in lit.[85]

*(4R,5R)-2,2-Diphenyl-α,α,α',α'-tetraphenyl-1,3-dioxolane-4,5-dimethanol (**2e**)* – Following our standard procedure,[29] (*R,R*)-dimethyl-*O,O*-(diphenylmethylidene)- tartrate (85.6 g, 250 mmol) in THF (720 mL) was added to phenylmagnesium bromide (1.1 mol, prepared from bromobenzene (172.8 g) and Mg (26.8 g)) in THF (800 mL). After work-up, hexane (1 L) to the isolated brown syrup was added and heated to reflux for 1.5 h with stirring. The yellow hexane solution was decanted from the insoluble material and EtOH (150 mL) was added whereby the slightly cloudy/turbid solution became clear. After a few minutes standing at rt, a precipitate formed. After 14 h (overnight), light yellow crystals (50 g) of the clathrate (**2e** ·EtOH) were isolated.

The remaining insoluble material (67.2 g) was treated again as described above (1 × 450 mL hexane/70 mL EtOH, 2 x 750 mL hexane/140 mL EtOH) to give another 41.8 g of the clathrate (**2e** ·EtOH). The remaining 17.8 g of insoluble material were purified by FC (4 x 30 cm SiO_2, toluene) yielding 12.7 g of **2e**. The so isolated light yellow powder (104.5 g in total) was heated at 90 °C/0.005 Torr for 12 h and triturated twice with pentane (500 mL) for *ca.* 2 d to remove the EtOH to yield **2e** (82.9 g, 56%) as a white powder. The residue of the mother liquor from the two triturations was purified by FC (4 x 15 cm SiO_2, toluene) to afford another 7.1 g of **2e**. Total yield of **2e**: 90.0 g (61%). R_f = 0.4 (toluene). M.p. 155.2–156.1 °C (lit.[85] m.p. 156–157 °C; lit.[86] m.p. 90–94 °C). $[\alpha]_D^{rt}$ = +177.1 (*c* = 1, $CHCl_3$), $[\alpha]_D^{rt}$ = +184.1 (*c* = 0.51, $CHCl_3$) (lit.[84] $[\alpha]_D^{rt}$ = +183.17 (*c* = 1, $CHCl_3$); lit.[85] $[\alpha]_D^{rt}$ = +187.7 (*c* = 0.505, $CHCl_3$)); lit.[86] $[\alpha]_D^{rt}$ = +160 (*c* = 1, $CHCl_3$).

Anal. Calcd. for $C_{41}H_{34}O_4$ (M_r = 590.72): C 83.36; H 5.80%; found: C 83.47, H 5.88%.

The spectral data are identical to those in lit.[85]

1-Octyn-3-one[87]

1-Octyn-3-ol (16.41 g, 130 mmol) was dissolved in acetone (35 mL) in a 500 mL three-necked flask fitted with an Ar balloon and a thermometer. A dark red solution of CrO_3 (13 g, 130 mmol) in water (40 mL) and concentrated sulfuric acid (11 mL) was added dropwise over 1.5 h. The reaction mixture was cooled with a water bath

keeping the temperature below 28 °C. A dark green precipitate was formed upon addition of the CrO_3 solution. The reaction mixture was stirred overnight at room temperature and diluted with water (200 mL). After extraction with ether (4 × 200 mL) the combined organic phases were washed twice with water (300 mL), dried over $MgSO_4$ and evaporated (RV). The resulting red oil was distilled initially through a 30 cm Vigreux column which afforded 10 g of product containing *ca.* 10% of starting material (b.p. 101–102 °C/79 Torr) and subsequently through a 30 cm *Spaltrohr* column (HSM 300-HV/C) at 99–100 °C/100 Torr (lit.[87] b.p. 74 °C/12 Torr) which yielded 1-octyn-3-one (4.7 g, 29%) as a pale yellow oil. ^{1}H-NMR (200 MHz): δ = 3.2 (s, H-C≡C), 2.58 (t, J = 8.0, CH_2-CO), 1.78–1.60 (m, CH_2-CH_3), 1.40–1.25 (m, 4 H), 0.90 (t, J = 8.0, CH_3-CH_2).

Purification of Commercially Available $LiAlH_4$[88]

Under an Ar atmosphere, $LiAlH_4$ (15.2 g) in Et_2O (120 mL) was stirred at rt overnight in a 250 mL flask. The insoluble grey residue was filtered off under Ar through a Ar-nutsch (sintered glass filter). Et_2O (20 mL) was added to the light grey filtrate, it was stirred for 3 h and again filtered through an Ar-nutsch. The resulting clear solution was carefully evaporated under reduced pressure (HV) leading to LAH (8.6 g, 57%) as a white powder. This powder was stored and handled in a glove box. *Caution: The residue in the Ar-nutsch is still very active and because of the remaining Et_2O, highly flammable. The destruction should accordingly be carried out with great care.*

*General Procedure for the Asymmetric Reduction of Ketones with the LAH-TADDOLate **5a** (GPA)*

In a 100 mL two-necked flask equipped with a 3-way tap and a rubber septum, THF (15 mL) was added to purified $LiAlH_4$ (380 mg, 10 mmol) *via* a syringe and stirred for 15 min at rt, by which time not all the $LiAlH_4$ was dissolved. This mixture was treated dropwise with EtOH (0.58 mL, 10 mmol) with rapid evolution of H_2 and after stirring for a period of 15 min, a solution of TADDOL **2a** (4.67 g, 10 mmol) in THF (15 mL) was added. Notably, the LAH-TADDOLate **5a** thus formed in THF was not completely soluble but the solution obtained contained only a very small amount of suspension. Note: If a large quantity of cloudy precipitate is visible, the preparation should be repeated from the beginning. This reduction reagent mixture was cooled to the internal temperatures indicated in the Tables II–IV (–78 °C: *i*-PrOH/CO_2; –100 °C: MeOH/liq. N_2), a solution of ketone (5 mmol) in THF (5 mL) was then added and allowed to warm to rt over the period specified in the Tables II–IV. After hydrolysis with MeOH (1 mL) and 2 N HCl (25 mL, acidic work-up) or a saturated Na_2SO_4 solution (70 mL, neutral work-up), the reaction mixture was extracted four times with 25 mL of ether. The combined organic layers were, in the case of acidic work-up first washed with a 2 N HCl solution (25 mL) then, in all cases, twice with H_2O (25 mL) and were subsequently dried over $MgSO_4$ and evaporated (RV). The resulting oily residue or foam was heated in a bulb-to-bulb distillation apparatus to remove the *sec.* alcohol. The complete removal of the *sec.* alcohol was confirmed by ^{1}H-NMR spectroscopy of the remaining solid. Normally, 4.5 g (97%) of the TADDOL **2a** was recovered.

General Procedure for the Reduction of Ketones Using Trituration after Work-up (GPB)

The asymmetric reduction was performed following GPA. But after work-up, the oily residue or foam was treated with pentane (30 mL) leading to a white precipitate which was stirred at rt for at least 14 h.[65] The resulting clathrate was filtered and heated in a bulb-to-bulb distillation apparatus to remove the *sec.* alcohol. The complete removal of the *sec.* alcohol was confirmed by ^{1}H-NMR spectroscopy of the remaining TADDOL.

(S)-(–)-1-Phenylethanol

Following GPA, acetophenone (0.58 mL, 5 mmol) in THF (5 mL) was added to the THF solution of **5a** at –74 °C over 10 min and allowed to warm to rt within 4 h. After acidic work-up, the isolated material was heated to 105–130 °C/18 Torr to yield (*S*)-(–)-1-phenylethanol (0.57 g, 95%) as a colorless oil: er = 95 : 5 determined by CGC: t_r = 31.82 (*R*); 32.56 (*S*) (column (a); *T* = 80 → 130 °C, rate = 1.0 °C/min). $[\alpha]_D^{rt}$ = –36.3 (neat), (lit.[61,89,90] $[\alpha]_D^{20}$ = +43.5 (neat), (*R*)-enantiomer).

The spectroscopic data are as expected.

(S)-(–)-1-Phenyl-1-propanol

Following GPA, propiophenone (0.66 mL, 5 mmol) in THF (5 mL) was added to the THF solution of **5a** (10 mmol) at –82 °C over 2 min and allowed to warm to rt within 4 h. After acidic work-up, the isolated material was heated to 128 °C/14 Torr to yield (*S*)-(–)-1-phenyl-1-propanol (0.61 g, 89%) as a colorless oil: er = 94 : 6 determined by CGC: t_r = 42.13 (*R*); 42.57 (*S*) (column (a); *T* = 80 → 150 °C, rate = 1.0 °C/min). $[\alpha]_D^{rt}$ = –24.9 (neat), $[\alpha]_D^{rt}$ = –40.5 (*c* = 5.15, $CHCl_3$), (lit.[89,91] $[\alpha]_D^{20}$ = –27.73 (neat), (*S*)-enantiomer; lit.[90] $[\alpha]_D^{20}$ = +45.5 (*c* = 5.15, $CHCl_3$), (*R*)-enantiomer).

The spectroscopic data are as expected.

(S)-(–)-2-Methyl-1-phenyl-1-propanol

Following GPA, isobutyrophenone (0.75 mL, 5 mmol) in THF (5 mL) was added to the THF solution of **5a** (10 mmol) at –79 °C over 2 min and allowed to warm to rt within 4 h. After acidic work-up, the isolated material was heated to 132 °C/14 Torr to yield (*S*)-(–)-2-methyl-1-phenyl-1-propanol (0.7 g, 90%) as a colorless oil: er = 93 : 7 determined by CGC: t_r = 107.78 (*R*); 108.42 (*S*) (column (a); *T* = 60 → 150 °C, rate = 0.5 °C/min). $[\alpha]_D^{rt}$ = –39.7 (*c* = 6.8, Et_2O), (lit.[61] $[\alpha]_D^{20}$ = +47.7 (*c* = 6.8, Et_2O), (*R*)-enantiomer).

The spectroscopic data are as expected.

(S)-(–)-2,2-Dimethyl-1-phenyl-1-propanol

Following GPA, pivalophenone (0.84 mL, 5 mmol) in THF (5 mL) was added to the THF solution of **5a** (10 mmol) at –72 °C over 2 min and allowed to warm to rt within 5 h. After acidic work-up, the isolated material was heated to 132 °C/14 Torr to yield (*S*)-(–)-2,2-dimethyl-1-phenyl-1-propanol (0.69 g, 89%) as a white fluffy solid: er = 77 : 23 determined by CGC: t_r = 54.9 (*S*); 55.78 (*R*) (column (a); *T* = 80 → 160 °C, rate = 1.0 °C/min). $[\alpha]_{578}^{rt}$ = –14.8 (*c* = 9.17, benzene), (lit.[91] $[\alpha]_{578}$ = +27.3 (*c* = 9, benzene), (*R*)-enantiomer).

The spectroscopic data are as expected.

(S)-(–)-1-(4-Bromophenyl)-1-ethanol

Following GPA, 4-bromoacetophenone (1.00 g, 5 mmol) in THF (5 mL) was added to the THF solution of **5a** (10 mmol) at –80 °C and allowed to warm to rt within 5 h. After neutral work-up, the isolated material was heated to 105 °C/14 Torr to yield (*S*)-(–)-1-(4-bromophenyl)-1-ethanol (0.63 g, 62%): er = 96 : 4 determined by CGC: t_r = 69.88 (*R*); 70.85 (*S*) (column (a); *T* = 80 → 160 °C, rate = 1.0 °C/min). $[\alpha]_D^{rt}$ = –29.1 (*c* = 1.64, MeOH), (lit.[92] $[\alpha]_D^{21}$ = +32.9 (*c* = 1.392, MeOH), (*R*)-enantiomer).

The spectroscopic data are as expected.

1-(2-Bromophenyl)-1-ethanol

Following GPA, 2-bromoacetophenone (0.67 mL, 5 mmol) in THF (5 mL) was added to the THF solution of **5a** (10 mmol) at –74 °C and allowed to warm to rt within 5 h. After acidic work-up, the isolated material was heated to 105 °C/14 Torr to yield 1-(2-bromophenyl)-1-ethanol (0.76 g, 76%): er = 95 : 5 determined by CGC: t_r = 65.45; 69.65 (column (a); *T* = 80 → 160 °C, rate = 1.0 °C/min). $[\alpha]_D^{rt}$ = –45.8 (*c* = 3.24, CH_2Cl_2).[93]

The spectroscopic data are as expected.

1-(2-Fluorophenyl)-1-ethanol

Following GPA, 2-fluoroacetophenone (0.61 mL, 5 mmol) in THF (5 mL) was added to the THF solution of **5a** (10 mmol) at –94 °C over 2 min and allowed to warm to rt within 6 h. After neutral work-up, the isolated material was heated to 105 °C/14 Torr to yield 1-(2-fluorophenyl)-1-ethanol (0.58 g, 77%): er = 74 : 26 determined by CGC: t_r = 33.26; 34.84 (column (a); *T* = 80 → 160 °C, rate = 1.0 °C/min). $[\alpha]_D^{rt}$ = –25.3 (*c* = 2.22, CH_2Cl_2).[93]

The spectroscopic data are as expected.

(S)-(–)-1-(4-Methoxyphenyl)-1-ethanol

Following GPA, 4-methoxyacetophenone (0.75 g, 5 mmol) in THF (5 mL) was added to the THF solution of **5a** (10 mmol) at –71 °C and allowed to warm to rt within 5 h. After neutral work-up, the isolated material was heated to 140–160 °C/14 Torr to yield (*S*)-(–)-1-(4-methoxyphenyl)-1-ethanol (0.66 g, 87%): er = 86 : 14 determined by CGC: t_r = 60.55 (*R*); 61.58 (*S*) (column (a); *T* = 80 → 160 °C, rate = 1.0 °C/min). $[\alpha]_D^{rt}$ = –56.6 (*c* = 2.58, $CHCl_3$), (lit.[94] $[\alpha]_D^{25}$ = –55.7 (*c* = 1.2, $CHCl_3$), (*S*)-enantiomer).

The spectroscopic data are as expected.

1-(2-Furyl)-1-ethanol

Following GPA, 2-furyl methyl ketone (0.55 g, 5 mmol) in THF (5 mL) was added to the THF solution of **5a** (10 mmol) at –76 °C over 2 min and allowed to warm to rt within 6 h. After neutral work-up, the isolated material was heated to 145 °C/14 Torr to yield 1-(2-furyl)-1-ethanol (0.31 g, 66%): er = 89 : 11 determined by CGC: t_r = 22.93; 23.38 (column (a); *T* = 65 → 120 °C, rate = 1.0 °C/min).[93]

The spectroscopic data are as expected.

(S)-(–)-1-(1-Cyclohexenyl)-1-ethanol

Following GPA, 1-acetyl-1-cyclohexene (0.64 mL, 5 mmol) in THF (5 mL) was added to the THF solution of **5a** (10 mmol) at –63 °C and allowed to warm to rt within 5 h. After acidic work-up, the isolated material was heated to 128 °C/14 Torr to yield (*S*)-(–)-1-(1-cyclohexenyl)-1-ethanol (0.46 g, 72%): er = 82 : 18 determined by CGC: t_r = 33.85 (*S*); 34.93 (*R*) (column (b); *T* = 60 → 120 °C, rate = 1.0 °C/min). $[\alpha]_D^{rt}$ = –6.3 (*c* = 0.64, $CHCl_3$), $[\alpha]_D^{rt}$ = –7.3 (*c* = 1.53, CH_2Cl_2), (lit.[95] $[\alpha]_D^{20}$ = –7.58 (*c* = 3.0, $CHCl_3$), (*S*)-enantiomer).

The spectroscopic data are as expected.

(S)-(–)-1-Octyn-3-ol

Following GPA, 1-octyn-3-one (0.73 mL, 5 mmol) in THF (5 mL) was added to the THF solution of **5a** (10 mmol) at –78 °C and allowed to warm to rt within 5 h. After acidic work-up, the isolated material was heated to 50–130 °C/15 Torr to yield (*S*)-(–)-1-octyn-3-ol (0.53 g, 84%): er = 76 : 24 determined by CGC: t_r = 22.90 (*S*); 23.42 (*R*) (column (a); *T* = 80 → 120 °C, rate = 1.0 °C/min). $[\alpha]_D^{rt}$ = –4.5 (neat), (lit.[4] $[\alpha]_D^{25}$ = +7.5 (neat), 86% ee, (*R*)-enantiomer).

The spectroscopic data are as expected.

(R)-(–)-1-phenyl-2-propanol

Following GPA, benzyl methyl ketone (0.67 mL, 5 mmol) in THF (5 mL) was added to the THF solution of **5a** (10 mmol) at –74 °C and allowed to warm to rt within 5 h. After acidic work-up, the isolated material was heated to 100–129 °C/15 Torr to yield (*R*)-(–)-1-phenyl-2-propanol (0.71 g, 82%): er = 79 : 21 determined by CGC: t_r = 31.51 (*R*); 32.34 (*S*) (column (b); *T* = 50 → 120 °C, rate = 1.0 °C/min, detection as trifluoroacetate).[51] $[\alpha]_D^{rt}$ = –22.84 (*c* = 5.25, benzene), (lit.[90,96] $[\alpha]_D^{20}$ = +41.8 (*c* = 5.26, benzene), (*S*)-enantiomer).

The spectroscopic data are as expected.

(S)-(+)-2-Octanol

Following GPA, 2-octanone (0.78 mL, 5 mmol) in THF (5 mL) was added to the THF solution of **5a** (10 mmol) at –76 °C over 5 min and allowed to warm to rt within 5 h. After acidic work-up, the isolated material was heated to 105–145 °C/17 Torr to yield (*S*)-(+)-2-octanol (0.55 g, 83%): $[\alpha]_{546}^{rt}$ = +2.43 (neat), 22% ee (lit.[97] $[\alpha]_{546}^{20}$ = +11.64 (neat), (*S*)-enantiomer).

The spectroscopic data are as expected.

3-Nonanol

Following GPA, 3-nonanone (0.78 mL, 5 mmol) in THF (5 mL) was added to the THF solution of **5a** (10 mmol) at –76 °C over 5 min and allowed to warm to rt within 4 h. After acidic work-up, the isolated material was heated to 105–135 °C/16 Torr to yield 3-nonanol (0.48 g, 86%): er = 50 : 50 determined by CGC: t_r = 68.33; 69.76 (column (a); *T* = 50 °C; detection as trifluoroacetate).[51,71]

The spectroscopic data are as expected.

Preparation of a Solution of the Chiral LAH-complex ***5a*** *in Deutero-THF for* ^{1}*H-NMR Spectroscopy*

In a 25 mL two-necked flask equipped with a 3-way tap and a rubber cap THF (5 mL) was added to purified $LiAlH_4$ (95 mg, 2.5 mmol) *via* a syringe and stirred at rt for 15 min. This solution was treated dropwise with EtOH (0.14 mL, 2.5 mmol) giving strong evolution of H_2 and after stirring for a period of 15 min, a solution of TADDOL **2a** (1.17 g, 2.5 mmol) in THF was added. After stirring for two hours at rt, the solvent was removed under HV forming a residue, which was dried under HV for 3 h. A small sample of this residue was dissolved in deutero-THF and analyzed. ^{1}H-NMR (200 MHz, d_8-THF): δ = 7.64–7.45 (m, 10 arom H), 7.23–7.01 (m, 10 arom H), 4.95 (d, J = 7.5, H-C(4) or H-C(5)), 4.73 (d, J = 7.5, H-C(4) or H-C(5)), 3.69 (q, CH_3-CH_2O), 1.10 (t, J = 7.5, CH_3-CH_2O), 0.58 (s, CH_3-C(2)), 0.53 (s, CH_3-C(2)).

*Preparation of (*M*)-(*S,S*)-Spiro[4.4]nonane-1,6-diol (****6****)*

The preparative route of Nieman *et al.*[75] was followed: ethyl 2-oxocyclopentanecarboxylate → 1-(3'-ethoxycarbonyl-propyl)-2-oxocyclopentanecarboxylic acid ethylester → 4-(2'-oxo-cyclopentyl)-butyric acid → spiro[4.4]nona-1,6-dione → spiro[4.4]nonane-1,6-diol → **7**. After separation of the diastereoisomers **7** by flash chromatography (R_f = 0.36 and 0.19, hexane), the first eluted diastereoisomer (R_f = 0.36, hexane) gave colorless crystals suitable for X-ray analysis by storing the pure substance overnight at 4 °C. By X-ray crystal structure analysis, this diastereoisomer turned out to be the (1*R*)-(+)-camphor acetal of the (*P*)-(*R,R*)-spiro[4.4]nonane-1,6-diol (*cf.* Figure 5). The other diastereoisomer (R_f = 0.19), which did not crystallize, was cleaved to give the diol (*M*)-(*S,S*)-**6**: er = 0.5 : 99.5 determined by CGC: t_r = 74.50; 76.47 (column (a); T = 55 → 150 °C, rate = 1.0 °C/min, detection as trifluoroacetate).[51] The spectroscopic data and the yields are as published.[75]

Crystal Structure Analyses of ***2d*** *and (P)-(R,R)-****7***

*(4R,5R)-2,2-Dimethyl-α,α,α',α'-tetrakis(bis(3,5-trifluoromethyl)-phenyl)-1,3-dioxolane-4,5-dimethanol (****2d****)*

$C_{39}H_{22}O_4F_{24} \cdot C_4H_{10}O$. M = 1010.6. Pale yellow crystals suitable for X-ray analysis were obtained by isothermic evaporation of a ether/pentane solution of **2d**. Determination of the cell parameters and collection of the reflection intensities were performed on an Enraf-Nonius-CAD4 four circle diffractometer (graphite monochromatized Mo-Kα radiation, λ = 0.71073 Å) at 298 K. Monoclinic, 0.4 × 0.4 × 0.5 mm, space group $P2_1$, a = 8.986(6), b = 20.521(4), c = 13.017(3) Å, β = 98.65(6)°, V = 2373(2) Å^3, Z = 2, D_c = 1.518 Mg m^{-3}, μ = 0.161 mm^{-1}, F(000) = 1092. Number of reflections measured 3237 (ω-scan, 2 < 2θ < 50°), 3010 unique reflections, of which 2541 with $I > 3\sigma(I)$ were used for determination (direct methods, SHELXS-86).[98] SHELXL-93[99] was used for structure refinement. The non-H-atoms of the TADDOL were refined anisotropically. The CF_3 groups showed a high degree of disorder, therefore the C-F distances were fixed to 1.3 Å. The neighbouring rest electron density peaks were refined isotropically. The occupation factors of all F-atoms were refined and converged to 80 and 85% for the main CF_3 positions and to 15 and 20% resp. for the minor CF_3 sites. The ether O-atom was refined anisotropically, whereas the four ether carbons were isotropically refined. The H-atoms bound to oxygen were located from differential *Fourier* syntheses and refined isotropically. All other H-atoms were added

to the structure with constant isotropic temperature factors on idealized postions and refined according to the riding model. Neither extinction nor absorption corrections were applied. The refinement converged at R = 0.056 (wR^2 = 0.149, number of variables 705).

*(P)-(R,R)-Spiro[4.4]nonane-1,6-diol-(1'R)-(+)-camphor Acetal (P)-(R,R)-***7**[75]

$C_{19}H_{30}O_2$. M = 290.45. Determination of the cell parameters and collection of the reflection intensities were performed on an Enraf-Nonius-CAD4 four circle diffractometer (graphite monochromatized Cu-Kα radiation, λ = 1.54184 Å) at 298 K. Monoclinic, 0.4 × 0.4 × 0.5 mm, space group $P2_1$, a = 11.080(2), b = 11.4199(7), c = 14.565(2) Å, β = 111.90(1)°, V = 1709.9(4) Å^3, Z = 4, D_c = 1.128 Mg m^{-3}, μ = 0.546 mm^{-1}, F(000) = 640. Number of reflections measured 3066 ($\omega/2\theta$-scan, $4 < 2\theta < 130°$), 3066 unique reflections, of which 2694 with $I < 2\sigma(I)$ were used for determination (direct methods, SHELXS-86).[98] SHELXL-93[99] was used for structure refinement. The non-H-atoms were refined anisotropically. All H-atoms were added to the structure with constant isotropic temperature factors on idealized postions and refined according to the riding model. Neither extinction nor absorption corrections were applied. The refinement converged at R = 0.071 (wR^2 = 0.214, number of variables 380).

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SAŽETAK

Redukcije ketona $LiAlH_4$ kompleksom α,α,α',α'-tetraaril-1,3-dioksolan-4,5-dimetiletanola (TADDOL)

Kombinacija enantioselektivne redukcije i nastajanja klatrata s raspravom o LAH-reagensima koji nose C_2-simetrične ligande

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Kompleks pripravljen iz jednakih množina $LiAlH_4$, EtOH i TADDOLa (α,α,α',α'-tetraaril-1,3-dioksolan-dimetanola) reducira arilalkilketone u *sec*-alkohole s enantiomernim omjerom (e.o.) do 96 : 4. Kiralni derivat LAH primijenjen je u dvostrukom suvišku u THF pri temperaturi suhog leda. Sposobnost TADDOLa da diastereoselektivno tvori klatrate može se iskoristiti za podizanje e.o. inicijalno nastalog alkohola jednostavnom modifikacijom postupka obradbe, te se tako mogu izolirati produkti vrlo visoke enantiomerne čistoće (e.o. 99 : 1) Kada je u redukciji primijenjen (*R,R*)-TADDOL (iz (*R,R*)-tartarata) nastali su 1-aril-alkanoli pretežito (*S*)-konfiguracije, kao što su i produkti dobiveni iz odgovarajućih (*P*)-BINOL i (*P*)-BIPHENOL derivata. Raspravlja se o zajedničkomu mehanističkom modelu.