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Asymmetric reduction and Meerwein-Ponndorf-Verley reaction of prochiral aromatic ketones in the presence of optically pure 1-aryl-2,2-dimethylpropane-1,3-diols

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Abstract. In THF solution, NaBH₄ in the presence of (*S*)-(-)-1-(2-chlorophenyl)-2,2-dimethylpropane-1,3-diol together with 2-chlorobenzoic acid reduced propiophenone to 1-phenylpropan-1-ol in up to 40% enantiomeric excess (*ee*). Only 21% *ee* was obtained without an added acid. (*R*)-(-)-butane-1,3-diol and (*R*)-(+)-1,1'-binaphthalene-2,2'-diol did not form clear solutions with NaBH₄ in THF and only gave a low *ee*. Of the organic acid additives investigated, (*S*)-(-)-4-(2-chlorophenyl)-5,5-dimethyl-2-hydroxy-1,3,2-dioxaphosphorinane 2-oxide gave the highest *ee* (46%). However, with AlCl₃/NaBH₄/(*S*)-(-)-1-(2-chlorophenyl)-2,2-dimethylpropane-1,3-diol in THF the best result was obtained (*ee* 55%).

Asymmetric Meerwein-Ponndorf-Verley (MPV) reductions of acetophenone by isopropanol in the presence of these chiral diols as auxiliary have also been carried out. For the case of aluminium triisopropoxide, (*R*)-(-)-1-phenyl-2,2-dimethylpropane-1,3-diol and acetophenone(1/1/1), an *ee* of up to 20% for 1-phenylethanol was obtained whereas with (*R*)-(+)-1,1'-binaphthalene-2,2'-diol an *ee* of 32% was obtained. Lanthanide triisopropoxides, Ln(OⁱPr)₃, have also been used. Of the various lanthanides (Ln = La, Y, Er, Tb, and Eu) the Er triisopropoxide with chiral (*R*)-(-)-1-phenyl-2,2-dimethylpropane-1,3-diol gave the best result; 46% *ee* for 1-phenylethanol. Lanthanide chloride diisopropoxides, LnCl(OⁱPr)₂, were also used as catalysts; although these have high catalytic activities they unfortunately give little chiral recognition.

Introduction ^a

There have been numerous studies of asymmetric reductions of prochiral carbonyl compounds mediated by NaBH₄ or LiAlH₄ modified with optically pure alcohols¹⁻⁷. Examples of auxiliaries used for asymmetric reduction, both with and without a C₂ symmetry axis, are 1,2 : 5,6-di-*O*-isopropylidene-D-glucofuranose (DIPGF), 1,2 : 5,6-di-*O*-cyclohexylidene-D-glucofuranose (DCHGF) and (*S*)-(-)-1,1'-binaphthalene-2,2'-diol⁸⁻¹¹. However, interest still remains high in finding cheaper but effective chiral modifiers of hydride reducing agents¹²⁻¹⁶. Another approach to reduction is asymmetric Meerwein-Ponndorf-Verley reductions of prochiral ketones¹⁷. It has been shown that catalysis of these reactions is possible using, for example, lanthanide alkoxides provided with chiral ligands. For example, Van Bekkum et al. reported that a 32% enantiomeric excess of 1-phenylethanol was obtained on reduction of acetophenone by using the catalyst

dene-D-glucofuranose (DIPGF), 1,2 : 5,6-di-*O*-cyclohexylidene-D-glucofuranose (DCHGF) and (*S*)-(-)-1,1'-binaphthalene-2,2'-diol⁸⁻¹¹. However, interest still remains high in finding cheaper but effective chiral modifiers of hydride reducing agents¹²⁻¹⁶. Another approach to reduction is asymmetric Meerwein-Ponndorf-Verley reductions of prochiral ketones¹⁷. It has been shown that catalysis of these reactions is possible using, for example, lanthanide alkoxides provided with chiral ligands. For example, Van Bekkum et al. reported that a 32% enantiomeric excess of 1-phenylethanol was obtained on reduction of acetophenone by using the catalyst

^a Nomenclature and abbreviations

2-acetonaphthone = 1-(naphthalen-2-yl)ethanone
acetophenone = 1-phenylethanone
2-acetylthiophene = 1-(thien-2-yl)ethanone
DIPGF = 1,2 : 5,6-di-*O*-isopropylidene-D-glucofuranose
DCHGF = 1,2 : 5,6-di-*O*-cyclohexylidene-D-glucofuranose
ee = enantiomeric excess
GC = gas chromatography
HPLC = high-performance liquid chromatography
isobutyric acid = 2-methylpropanoic acid
LA = Lewis acid
ⁱPr = isopropyl
isopropanol = propan-2-ol
MPV reaction = Meerwein-Ponndorf-Verley reaction
2-(1-naphthyl)ethanol = naphthalene-2-ethanol
1-phenylethanol = *a*-methylbenzenemethanol
phenylglyoxal = *a*-oxobenzeneacetaldehyde
1-phenylpropan-1-ol = *a*-ethylbenzenemethanol
propiophenone = 1-phenylpropan-1-one
THF = tetrahydrofuran
2-(2-thienyl)ethanol = thiophene-2-ethanol
trimethyl orthoformate = trimethoxymethane

Scheme 1.

Table I Asymmetric reduction of prochiral aromatic ketones with sodium borohydride in THF in the presence of (S)-(-)-2 and 6^a.

Entry	Ketone	Product	Yield ^b (%)	[α] _D ²⁰ ₅₈₉	Optical yield (%)	Abs. conf.
1	PhCOCH ₃	PhCHOHCH ₃	98	-16.8°	32	S
2	PhCOCH ₂ CH ₃	PhCHOHCH ₂ CH ₃	100	-16.9°	40	S
3	PhCO(CH ₂) ₂ CH ₃	PhCHOH(CH ₂) ₂ CH ₃	100	-18.7°	43	S
4	PhCOCH(CH ₃) ₂	PhCHOHCH(CH ₃) ₂	100	-21.5°	45	S
5	2-acetylthiophene	2-(2-thienyl)ethanol	97	-8.1°	34	S
6	2-acetonaphthone	2-(1-naphthyl)ethanol	100	-15.6°	37	S

^a Reaction conditions: solvent THF (100 ml), chiral diol (S)-(-)-2 (10 mmol), NaBH₄ (10 mmol), acid 6 (10 mmol), ketone (2.5-3 mmol); r.t., 3 days.^b Isolated yield of products. ^c The enantiomeric excess (ee%) of 1-phenyl-propanol-1 (entry 2) was determined by HPLC, the other values are optical yields based on known rotations²⁵.

La(OⁱPr)₃, provided with the chiral ligand 1,2 : 5,6-di-*O*-isopropylidene-D-mannitol with isopropanol as reductant¹⁸. Krohn and Knauer have recently reported zirconium-catalyzed Meerwein-Ponndorf-Verley reactions^{18b}. Using a chiral samarium(III) catalyst and isopropanol, Evans' group reported¹⁹ that the *S* enantiomer of 1-(2-chlorophenyl)ethanol was obtained in 97% ee by MPV reduction of the corresponding ketone.

The present work was rigidly coupled to one class of compounds, namely the readily available and optically pure 1-aryl-2,2-dimethylpropane-1,3-diols **1-3**²⁰⁻²³ (Scheme 1). Our goal was to see how effective these compounds can be as chiral auxiliaries in asymmetric reductions. Although only modest enantiomeric excesses have been obtained, we think that our experiences in deriving proper combinations of reagents and reaction conditions are of interest.

Results and discussion

A. Asymmetric reduction of prochiral aromatic ketones by chirally modified NaBH₄

NaBH₄ with (S)-(-)-2 and 2-chlorobenzoic acid **6** in THF (Table I) gave a 40% ee (enantiomeric excess) of 1-phenylpropan-1-ol for the reduction of propiophenone (entry 2). This result is similar to that obtained with combinations such as NaBH₄/carboxylic-acid/DIPGF⁸ or DCHGF¹¹, namely ee values around 40% for the asymmetric reduction of prochiral aromatic ketones.

For clean reactions and reasonable ee values, the reaction solution in THF must remain homogenous for two days until the reduction of ketone is complete. Different orders of addition of reactants in the preparation of chirally modified NaBH₄ have a large effect on whether a completely homogeneous solution system is formed and also on the enantiomeric excesses. For instance, after reaction of diol (S)-(-)-2 with

NaBH₄ in THF, acid **6** was then added to the reaction solution. In this case, a gelatinous precipitate in the reaction mixture was immediately observed; the ketone was added to this gel. A lower ee (15% for 1-phenylpropan-1-ol) was obtained. A higher ee (40%) was obtained by an addition process in which acid **6** was added first to NaBH₄ and then diol (S)-(-)-2 was added (see entry 2 in Table I); the solution remained homogenous.

Aromatic ketones with different alkyl chains are all reduced with similar ee values. The yields of chiral benzyl alcohols after work-up are nearly quantitative (Table I). No ketones were detected by ¹H-NMR analysis of the products.

The overall chemical transformations involved are likely those given in general terms in Scheme 2^{10,24}. Asymmetric reduction of propiophenone in the presence of (S)-(-)-2 and **6** may proceed through the transition-state model suggested in Scheme 3 in which the correctness of Scheme 2 is presumed. This (speculative) model leads to the observed *S* facial selectivity.

It has been reported that many carboxylic acids may be used as reagents to modify NaBH₄. Our experiments show that different carboxylic acids have different effects on the asymmetric reduction of propiophenone. Some results are shown in Table II. Acids have to be added to obtain reasonable ee values. Only 21% ee was obtained without acid (entry 1 in Table II).

The difference between benzoic acid (**8**) and 2-chlorobenzoic acid (**6**) is surprising. The difference likely arises from the fact that the reaction solution with **6** stayed clear during the reaction. Phosphoric acid (-)-7 gave the best ee (46%, see entry 3 in Table II), but this acid is much more expensive than **6**. Again, the solution remains homogeneous. Note (entry 4) the poorer results with (+)-7, which points to matched and mismatched pairs. In the case of benzoic acid (**8**) and isobutyric acid (**9**), a gelatinous precipitate formed before adding propiophenone. The direct result of this phenomenon was lower ee (6% and 9%, see entry 5 and 6 in Table II).

diol* = chiral diol

Ar = Ph, naphthyl, thienyl

R = CH₃, CH₂CH₃, CH₂CH₂CH₃, CH(CH₃)₂, CHO

Table II Effect of different organic acids on asymmetric reduction of propiophenone^a

Entry	NaBH ₄ /acid/2 ^b	Yield (%)	ee (%) ^c	Abs. conf.
1	No acid	100	21	<i>S</i>
2	NaBH ₄ /6/2	100	40	<i>S</i>
3	NaBH ₄ (-)/7/2	100	46	<i>S</i>
4	NaBH ₄ /(+)/7/2	100	25	<i>S</i>
5	NaBH ₄ /8/2	100	6	<i>S</i>
6	NaBH ₄ /9/2	100	9	<i>S</i>

^a Reaction conditions: THF (100 ml); chiral diol (*S*)-(-)-2 (10 mmol), NaBH₄ (10 mmol) acid (10 mmol), propiophenone (2.5-3 mmol); r.t., 3 days. ^b For structural formulae, see Scheme 1. ^c Enantiomeric excess (*ee*, %) was determined by HPLC.

Table III Effect of different chiral diols on the asymmetric reduction of propiophenone with NaBH₄/6^a.

Entry	Diol	Yield (%)	ee (%) ^b	Abs. conf.
1	2	100	40	<i>S</i>
2	1	100	38	<i>S</i>
3	3	100	20	<i>S</i>
4	5	100	8	<i>S</i>
5	4	100	5	<i>S</i>

^a Reaction conditions: THF (100 ml), chiral alcohol (5 mmol), NaBH₄ (10 mmol) acid 6 (10 mmol), propiophenone (2.5-3 mmol); r.t., 3 days.

^b Enantiomeric excess (*ee*, %) was determined by HPLC.

Table IV Effect of different Lewis acids (LA) on the asymmetric reduction of propiophenone in the presence of (*S*)-(-)-2^a.

Entry	NaBH ₄ /LA ^b (%)	Yield (%)	ee (%) ^c	Abs. conf.
1	NaBH ₄ /10/2	100	49	<i>R</i>
2	NaBH ₄ /11/2	100	55	<i>S</i>
3	NaBH ₄ /12/2	100	28	<i>S</i>
4	NaBH ₄ /13/2	20	13	<i>S</i>
5	NaBH ₄ /14/2	17	0	-

^a Reaction conditions: THF (100 ml), chiral diol (*S*)-(-)-2 (10 mmol), NaBH₄ (10 mmol) Lewis acid (10 mmol), propiophenone (2.5-3 mmol); r.t., 3 days. ^b LA (Lewis acid): zinc dichloride (**10**), aluminium trichloride (**11**), caesium trichloride (**12**), titanium tetrachloride (**13**), tin tetrachloride (**14**). ^c Enantiomeric excess (*ee*, %) was determined by HPLC.

Table V Effect of different solvents on the asymmetric reduction of prochiral aromatic ketone^a.

Entry	Reagent ^b	Ketone	Solvent	Alcohol yield (%) ^d	ee ^c %	Abs. conf.
1	I	PhCOCH ₂ CH ₃	THF	100	21	<i>S</i>
2	I	PhCOCH ₂ CH ₃	C ₆ H ₆	100	15	<i>S</i>
3	II	PhCOCH ₂ CH ₃	THF	100	40	<i>S</i>
4	II	PhCOCH ₂ CH ₃	C ₆ H ₆	87	26	<i>S</i>
5	II	PhCOCHO	THF	88	6	<i>R</i>
6	II	PhCOCHO	C ₆ H ₆	75	10	<i>R</i>

^a Reaction condition: THF (100 ml), chiral 1,3-diol (10 mmol), NaBH₄ (10 mmol) acid (10 mmol), ketone (2.5-3 mmol), r.t., 3 days for THF, 5 days for benzene. ^b I = NaBH₄/(*S*)-(-)-2, P = NaBH₄/6(*S*)-(-)-2. ^c Enantiomeric excess (*ee*, %) was determined by HPLC. ^d Isolated yields of products.

Table VI Results of asymmetric reduction of propiophenone by chirally modified LiAlH₄^a.

Entry	LiAlH ₄ /6/EtOH	THF (ml)	Yield (%)	ee ^b (%)	Abs. conf.
1	^c LiAlH ₄ /(<i>R</i>)-1/EtOH	15	100	27	<i>S</i>
2	^c LiAlH ₄ /(<i>R</i>)-1/EtOH	50	100	20	<i>S</i>
3	^c LiAlH ₄ /(<i>S</i>)-2/EtOH	50	100	9	<i>S</i>
4	^d LiAlH ₄ /(<i>S</i>)-2/EtOH	75	100	3	<i>S</i>
5	^d LiAlH ₄ /(<i>S</i>)-2/EtOH	100	100	4	<i>S</i>
6	^d LiAlH ₄ /(<i>R</i>)-1/EtOH	100	100	6	<i>S</i>

^a Reaction conditions: chiral diol (5 mmol), LiAlH₄ (5 mmol), ethanol (5 mmol), propiophenone (1.7 mmol); -100°C for 2 h and then -78°C for 8 h in THF. ^b Enantiomeric excess (*ee*, %) was determined by HPLC. ^c LiAlH₄ in THF (1M solution). ^d LiAlH₄ powder.

Scheme 3.

Morrison et al.¹⁰ have observed that an acid modifier should be chosen on the basis of whether a completely homogeneous reaction system is formed or not.

Not only the carboxylic acid but also the alcohol influences the formation of a completely homogeneous solution. Diol (*R*)-(-)-1 gives similar results in the asymmetric reduction of propiophenone (Table III) whereas diol (*S*)-(-)-3 did not give a good result (entry 3). Neither (*R*)-(-)-5 (see entry 4) nor (*R*)-(+)-4 (entry 5) formed homogeneous solutions and very low *ee* values were obtained. (*S*)-(-)-2 and (*R*)-(-)-1 are clearly most efficient as chiral modifying materials. These can be easily recovered in excellent yield (usually 95-97%) and used repeatedly.

Five metal chlorides were investigated as additives instead of organic acids (Table IV). The metal chlorides form homogeneous solutions with NaBH₄ and chiral diols except for SnCl₄, which gave also a very low chemical yield (17%) and racemic product (entry 5). The reaction rate was very slow for TiCl₄ and only a 20% yield was obtained after 3 days at room temperature (entry 4). The opposite configuration of the product, (*R*)-1-phenylpropan-1-ol, was obtained on the addition of ZnCl₂. This agrees with literature precedent^{10a}. When (*R*)-(-)-2 (instead of the usual *S* enantiomer) was used as modifier, (*R*)-1-phenylpropan-1-ol was obtained. This result agrees with literature observations⁹. The additive AlCl₃ gave the highest *ee* (55%). When a solution of AlCl₃ in THF was added to the mixture of NaBH₄ and chiral diol in THF, a lower *ee* (around 25%) was obtained. When solid AlCl₃ was used, the result was better (55% *ee*). Perhaps the reason for the lower *ee* in the former case is that the THF-AlCl₃ complex is less reactive than AlCl₃ itself.

Scheme 4.

There is some effect of the solvent (THF or benzene) on reactions and yields both with and without added organic acid (Table V). It is clear that the reaction period is shorter in THF than in benzene and the *ee* values are slightly higher. $\text{NaBH}_4/6/(S)-(-)-\mathbf{2}$ did not form a homogeneous solution in benzene, which led to a lower *ee* (21%, see entries 3 and 4 in Table V). The reaction carried out in THF led to a higher *ee* (40%). In the case of phenylglyoxal, lower yields of 1-phenyl-ethane-1,2-diol and *ee* were obtained (entries 5 and 6 in Table V); competing polymer formation lowered the yield. Lithium aluminium hydride was also investigated as a reducing agent. Chirally modified LiAlH_4 was prepared by two methods: mixing LiAlH_4 powder with chiral diol in THF for one hour and with absolute ethanol (1 eq.) for another hour at ambient temperature, or mixing LiAlH_4 solution in THF (1 M) with chiral diol in THF for one hour and with absolute ethanol (1 eq.) for another hour at 0°C . The results of asymmetric reduction of propiophenone are given in Table VI. A homogeneous solution of LiAlH_4 in THF leads to higher enantiomeric excesses and is better than a suspension of powdered LiAlH_4 in THF. In contrast with the NaBH_4 system, chiral diol $(S)-(-)-\mathbf{2}$ is not as good a modifier. The volume of solvent (THF) has some effect on the *ee* of asymmetric reduction of propiophenone (see entries 1 and 2).

B. Asymmetric Meerwein-Ponndorf-Verley (MPV) reduction of prochiral ketones using chiral nonracemic 1-phenyl-2,2-dimethylpropane-1,3-diols as ligands

MPV reductions, wherein aluminum isopropoxide, $\text{Al}(\text{O}^i\text{Pr})_3$, is used stoichiometrically, have advantages relative to NaBH_4 or LiAlH_4 . The reduction of aldehydes or ketones proceeds readily under mild conditions and excellent yields can be

obtained (80-100%). In general, a stoichiometric amount or a larger excess of reagent is desirable for reduction for aromatic ketones and aldehydes.

An investigation of asymmetric MPV reductions of prochiral ketones was carried out by using $\text{Al}(\text{O}^i\text{Pr})_3$ and 1-aryl-2,2-dimethylpropane-1,3-diols as ligands in the presence of isopropanol/THF at a given temperature (see Scheme 4). The results are given in Table VII.

A catalytic amount of $\text{Al}(\text{O}^i\text{Pr})_3$ (10 mol%) led to no reduction at room temperature even over a period of 3 days (see entry 3)²⁶. Stoichiometric amounts or half-stoichiometric amounts of $\text{Al}(\text{O}^i\text{Pr})_3$ are normally used in the reduction of acetophenone. Six chiral diols were used as chiral ligands in asymmetric MPV reduction of acetophenone. Of these, $(R)-(+)-\mathbf{1}$ gave the highest *ee* (33%, see entry 13). $(R)-(-)-\mathbf{1}$ and $\mathbf{15}$ gave the same enantiomeric excess (21%, see entries 8 and 14 in Table VI). $(S)-(-)-\mathbf{2}$ did not give a result entirely analogous to $(R)-(-)-\mathbf{1}$; only 11% *ee* was obtained (see entry 2 in Table VII).

Excess chiral diol relative to $\text{Al}(\text{O}^i\text{Pr})_3$ induced reversal of configuration of 1-phenyl-ethanol to $(R)-(+)$ with low *ee* (3%, see entry 6); we do not understand why this occurs. Less chiral diol led to low *ee*; 8% or 0% was obtained (see entries 5 and 9). The experiment was carried out several times and each time similar results were obtained. A higher reaction temperature led to a lower *ee*. When the reaction was carried out at room temperature for 3 days (entry 2) a yield of 92% was obtained; the same yield could be obtained even with half the amount of $\text{Al}(\text{O}^i\text{Pr})_3$ at 60°C for 1 day (see entry 7). The *ee* dropped even lower, however. It is helpful for increased reaction rate that molecular sieves are used to absorb moisture in the reaction mixture (see entry 10 in Table VII). In the above reactions no side-reactions were observed as deter-

Table VII Results of an asymmetric MPV reduction of acetophenone by $\text{Al}(\text{O}^i\text{Pr})_3$ with chiral nonracemic diols as ligands.

Entry	Diol ^a	React. time (days)	Temp. ($^\circ\text{C}$)	$\text{Al}(\text{O}^i\text{Pr})_3$ / diol/ketone	Yield ^b (%)	<i>ee</i> ^c (%)	Alcohol Abs. conf.
1	1	3	r.t.	1/1/1	75	20	<i>S</i>
2	2	3	r.t.	1/1/1	92	11	<i>S</i>
3	2	3	r.t.	0.1/0.1/1	0	0	-
4	1	1	r.t.	1/1/1	28	20	<i>S</i>
5	1	3	r.t.	0.5/0.25/1	62	8	<i>S</i>
6	1	3	r.t.	0.5/1/1	86	3	<i>R</i>
7	1	1	60	0.5/0.5/1	91	5	<i>S</i>
8	1	3	r.t.	0.5/0.5/1	62	21	<i>S</i>
9	2	3	r.t.	0.5/0.05/1	48	0	-
10	2	3	r.t.	0.5/0.5/1	86	6	<i>S</i>
11	2	3	r.t.	0.5/0.5/1	78	7	<i>S</i>
12	3	2	r.t.	0.5/0.5/1	39	2	<i>S</i>
13	4	3	r.t.	0.5/0.5/1	69	33	<i>S</i>
14	15	3	r.t.	0.5/0.5/1	26	21	<i>S</i>
15	16	4	r.t.	0.5/0.5/1	21	0	-

^a Diols are: $(R)-(-)-1$ -phenyl-2,2-dimethyl-propanediol-1,3 (**1**); $(S)-(-)-1$ -(2-chlorophenyl)-2,2-dimethyl-propanediol-1,3 (**2**); $(S)-(-)-1$ -(2-methoxyphenyl)-2,2-dimethyl-propanediol-1,3 (**3**); $(R)-(+)$ 1,1'-binaphthalene-2,2'-diol (**4**); 1,2:5,6-di-isopropylidene-D-mannitol (**15**); $(-)$ -diisopropyl tartrate (**16**). ^b Yields were determined by NMR based on ketone. ^c Enantiomeric excess (*ee*) was determined by rotation and GC. ^d Added molecular sieves 4 Å.

Scheme 5.

Scheme 6.

M = La, Ce, Er, Y, Eu, Yb, Tb

Scheme 7.

mined by NMR and GC. Chiral diol was recovered almost in quantitative yield (> 95%). Rotation measurements on the chiral diols showed there had been no racemization and also no structural change during the reduction processes.

The mechanism of MPV reduction has been discussed by Ashby²⁷ (see Scheme 5). A (speculative) model for asymmetric MPV reduction of acetophenone by $\text{Al}(\text{O}^i\text{Pr})_3$ and chiral diol **1** is given in Scheme 6. In this case, the carbonyl group is oriented equatorially with the bulky phenyl group of acetophenone pointing away from the phenyl attached to the six-ring. Hydride from axially bound isopropoxide attacks preferentially the *re* face of the carbonyl. If the carbonyl is complexed axially and the isopropoxide equatorially, then, on basis of the same steric consideration, attack of hydride would occur from the *si* face of the carbonyl. The relatively low inductions may result from the fact that on the basis of differences in electronegativities, there is no basis for distinction between the two oxygen atoms.

Lanthanide triisopropoxides were synthesized by refluxing isopropanol adducts ($\text{LnCl}_3 \cdot 3\text{HO}^i\text{Pr}$), ($\text{Ln} = \text{La}, \text{Yb}, \text{Er}, \text{Y}, \text{Tb}, \text{Eu}$), and sodium isopropoxide in isopropanol and toluene²⁸. These adducts can also be obtained by successive action of methyl orthoformate and isopropanol²⁹. Scheme 7 shows the procedure for preparation of these lanthanide triiso-

Table VIII Results of catalytic MPV reactions with $\text{Ln}(\text{O}^i\text{Pr})_3$ in the asymmetric reduction of acetophenone with (*R*)-(-)-1-phenyl-2,2-dimethyl-propanediol **1** as ligand.

Entry	$\text{Ln}(\text{O}^i\text{Pr})_3$	Catalyst ratio (mol %)	Temp./time	Yield(%) ^a	<i>ee</i> (%) ^b	Alcohol abs. conf.
1	$\text{La}(\text{O}^i\text{Pr})_3$	10	r.t./3d	86	17	<i>S</i>
2	$\text{La}(\text{O}^i\text{Pr})_3$	10	60°C/2h	92	5	<i>S</i>
3 ^c	$\text{La}(\text{O}^i\text{Pr})_3$	10	r.t./3d	98	-	-
4	$\text{La}(\text{O}^i\text{Pr})_3$	40	r.t./3d	90	18	<i>S</i>
5	$\text{La}(\text{O}^i\text{Pr})_3$	5	r.t./3d	63	16	<i>S</i>
6	$\text{La}(\text{O}^i\text{Pr})_3$	2	r.t./3d	43	17	<i>S</i>
7	$\text{Y}(\text{O}^i\text{Pr})_3$	10	r.t./3d	85	12	<i>S</i>
8	$\text{Er}(\text{O}^i\text{Pr})_3$	10	r.t./3d	62	46	<i>S</i>
9	$\text{Eu}(\text{O}^i\text{Pr})_3$	10	r.t.	83	3	<i>S</i>
10	$\text{Yb}(\text{O}^i\text{Pr})_3$	10	r.t.	23	0	-
11	$\text{Tb}(\text{O}^i\text{Pr})_3$	10	r.t.	44	0	-

^a Yields were determined by NMR. ^b Enantiomeric excess (*ee*) was determined by rotation and GC. ^c Without ligand.

Table IX Reduction of ketones catalyzed by $\text{LnCl}(\text{O}^i\text{Pr})_2$ ($\text{Ln} = \text{La}, \text{Y}$).

Entry	Ln	Ketone	Ratio catalyst (mol%)	Temp./time	Alcohol Yield(%) ^a
1 ^b	La	acetophenone	20	r.t./3d	72
2	La	acetophenone	20	r.t./3d	98
3	La	acetophenone	10	60°C/2h	99
4	La	$\text{PhCOCH}(\text{CH}_3)_2$	10	60°C/2h	99
5	La	cyclohexanone	10	60°C/2h	98
6	La	acetophenone	10	60°C/2h	96
7	La ^c	acetophenone	10	60°C/2h	13
8	Y	acetophenone	20	r.t./3d	99

^a Yields were determined by NMR based on ketone. ^b (*R*)-(-)-1-Phenyl-2,2-dimethyl-propanediol-1,3 (**1**) was used as ligand in the reduction; *ee* 13%.

^c $\text{LaCl}_2\text{O}^i\text{Pr}$ was used as catalyst in the reaction.

propoxides. The triisopropoxides of La, Yb, Er, Y, Tb, and Eu are readily prepared by this one pot method; yields are in the range of 75–85%. The alkoxides are sparingly soluble in hexane and remain associated with NaCl in this solvent. Addition of pentane induces precipitation of most of the sodium chloride. Purification can be accomplished by recrystallization from isopropanol. Lanthanide alkoxides can be analysed by acidimetric, complexometric, and argentometric titrations as well as analysis of infrared spectra^{30a}. An acidimetric analysis was performed in this work^{30b}.

Asymmetric MPV reductions of acetophenone were carried out in the presence of $\text{Ln}(\text{O}^i\text{Pr})_3$ with (*R*)-(-)-1-phenyl-2,2-dimethylpropane-1,3-diol (**1**) as chiral ligand. The reduction results are given in Table VIII.

Asymmetric MPV reductions of acetophenone were chiefly carried out at room temperature because higher temperature led to a lower *ee*. For instance, when an asymmetric MPV reduction with $\text{La}(\text{O}^i\text{Pr})_3$ was carried out at 60°C, only 5% *ee* was obtained; however, around 16–18% *ee* could be obtained at room temperature (see entries 1–5 in Table VIII). Different ratios of catalyst $\text{La}(\text{O}^i\text{Pr})_3$ and acetophenone appeared only to give different chemical yields (see entries 3 and 4 in Table VIII). Six metal triisopropoxides were examined as catalysts in asymmetric reduction of acetophenone under similar conditions. Of these metals, erbium triisopropoxide, $\text{Er}(\text{O}^i\text{Pr})_3$ gave the best *ee* (46%) (see entry 8 in Table VIII). $\text{Yb}(\text{O}^i\text{Pr})_3$ and $\text{Tb}(\text{O}^i\text{Pr})_3$ gave low chemical yields and no *ee* (see entries 10 and 11 in Table VIII). It is generally considered that addition of chiral ligands causes a decrease of reactivity for MPV reductions because of replacement of the isopropoxide by these bulky ligands³¹. In the experiments above we observed such effects and lower chemical yields were obtained with a ligand (see entry 1 and 3 in Table VIII). However, no side-reactions such as production of carboxylic esters were observed in the MPV reduction procedure.

Rathke et al. reported³¹ in 1977 the effects of various protic acids on the aluminium *tert*-butoxide induced oxidation of cyclohexanol by benzaldehyde. They found that the rate of oxidation is markedly enhanced by an acid-to-aluminium ratio of 0.5 for HCl , FSO_3H , $\text{CH}_3\text{CH}_2\text{CO}_2\text{H}$, and $\text{CF}_3\text{CO}_2\text{H}$, with $\text{CF}_3\text{CO}_2\text{H}$ giving the greatest rate enhancement. This is the earliest report of use of $\text{AlCl}(\text{O}^i\text{Pr})_2$ as catalyst in MPV and Oppenauer reactions.

When adducts of $\text{LnCl}_3(\text{O}^i\text{Pr})_n$ were refluxed with two equivalents of sodium isopropoxide in isopropanol and toluene, lanthanide chloride diisopropoxide $\text{LnCl}(\text{O}^i\text{Pr})_2$ could be formed in analogy to the *Rathke* et al. report³¹ (see Scheme 8). Some preliminary reaction results using these lanthanide chloride diisopropoxides as catalysts are given in Table IX. Good chemical yields could be obtained, but only low *ee* values were obtained in asymmetric reduction of acetophenone with chiral (*R*)-(-)-1-phenyl-2,2-dimethylpropane-1,1-diol **1** as ligand.

Table IX shows that lanthanide chloride diisopropoxides have high catalytic activity under the given reaction times and temperatures. In the presence of a chiral diol the reductions proceed slower (compare entries 1 and 2 in Table IX). The activities of $\text{LnCl}(\text{O}^i\text{Pr})_2$ with or without complexed NaCl remain about the same. $\text{LaCl}_2\text{O}^i\text{Pr}$ as catalyst has lower catalytic activity (see entry 7 in Table IX).

In general¹⁷, metal alkoxide bonds have a highly polar character. Highly electronegative alkoxide groups react readily with several proton-donating organic molecules such as

water, alcohols, carboxylic acids, hydroxy acids, *b*-diketones, and alkanolamines. In these cases, the alkoxide is replaced by another organic ligand. In addition, metal alkoxides may act as weak Lewis acids. This combination of ligand exchangeability and Lewis-acidic character gives metal alkoxides their catalytic capacity. Aluminium(III) has a high charge density and a good Lewis-acidic character, but relatively poor ligand exchangeabilities. Therefore, usually stoichiometric amounts are required, and the produced alcohol has to be liberated by aqueous acidification. *Rathke* et al.³¹ have demonstrated that the rates are increased significantly by addition of acids. The effect is to provide Al^{III} with more electronegative ligands leading to an increase of the rate of exchange of groups on Al^{III} . The higher catalytic activity of $\text{LaCl}(\text{O}^i\text{Pr})_2$ also can be anticipated from this explanation.

We may conclude that chiral nonracemic 1-aryl-2,2-methylpropane-1,3-diols can be used as chiral modifiers of NaBH_4 or LiAlH_4 in the asymmetric reduction of prochiral ketones and as chiral auxiliaries in Meerwein-Ponndorf-Verley reactions. Reasonable enantiomeric excesses and yields can be obtained in these reactions.

Experimental

Materials and measurements

Optically pure 1-aryl-2,2-dimethylpropane-1,3-diols and (*S*)-(-)-1-4-(2-chlorophenyl)-5,5-dimethyl-2-hydroxy-1,3,2-dioxaphosphorinane 2-oxide (**7**) were prepared according to literature methods²³. Aluminium triisopropoxide was bought from Acros (formerly Janssen). Other metal isopropoxides were synthesized according to literature methods¹⁸. The alkoxide concentration was determined by acidimetric titration^{31b}. The other chemicals used in this work were commercially available from Acros. Chemicals used in this work were not purified further. All reactions were carried out under nitrogen atmosphere.

HPLC analyses were performed on Waters liquid-chromatographic system and a Lambda-Max Model 480 LC spectrophotometer as well as a Hewlett-Packard model HP3396A recording integrator/plotter. A chiral stationary phase column (250 × 4.0 mm) OD from Dical Chemical Industries, LTD., 20°C, was used for *ee* determinations. Hexane and isopropanol (97.5/2.5, v/v) were used as flowing phase, flow speed: 1 ml/min, detected at 254 nm. GC analyses were performed on a Hewlett-Packard 5890A gas chromatograph equipped with a 50-m WCOT fused-silica capillary GC column coated with CP cyclodextrin-B-2,3,6-M-19 (Chrompack No. 7501) and a Hewlett-Packard 3396 series II integrator. Analysis was carried out using an oven temperature of 120°C and an injection and detection temperature of 200°C.

General procedure for reduction of prochiral ketones by NaBH_4 with chiral 1-aryl-2,2-dimethylpropane-1,3-diols and acids as auxiliaries

To a stirred suspension of NaBH_4 (0.38 g, 10 mmol) in THF (20 ml) was added a solution of the acid (10 mmol) in THF (20 ml). The solution was stirred 30 min during which time H_2 evolved. Then chiral diol (10 mmol) was added all at once, followed by another 10 ml of THF as a rinse. After stirring 3–4 hours, the ketone (2.5–3 mmol) was added to the reaction solution all at once. The mixture was stirred for 3–4 days. Then work-up was carried out.

The reaction mixture was hydrolysed by water (30 ml) with considerable gas evolution. The solution was extracted with ether (30 ml) and the aqueous layer was separated and was extracted once more with ether (80 ml). The ether layers were combined, washed once with brine (40 ml) and dried over anhydrous Na_2SO_4 . Evaporation was carried out under reduced pressure after filtration. An oily material containing product alcohol and starting chiral diol was obtained. The mixture was subjected to bulb-to-bulb distillation under reduced pressure. Normally the alcohol was obtained as first fraction and then the chiral diol was recovered (95–97%). The optical rotations of the chiral diols were unchanged after recovery. Carboxylic acid was not recovered in this procedure. The enantiomeric excesses of products were measured by rotation and NMR. No ketone was detected by NMR; *ee* values were measured further by HPLC.

In the case of (*R*)-(-)-butane-1,3-diol (**5**, see entry 4 in Table III), the diol **5** was extracted with aqueous 5% NaOH and ether in the work-up procedure, and the ether solution contained only alcohol from reduction of ketone. Solvents were evaporated under reduced pressure to obtain the

M = La, Y

Scheme 8.

alcohol. The measurement of the *ee* value of the alcohols was carried out by the above mentioned methods.

In the case of acid **7** (see entries 3 and 4 in Table II), **7** was recovered by the following method. The aqueous solution after extraction by ether was concentrated under reduced pressure into a smaller volume and then neutralized to pH 7 with HCl (10%). The phosphoric acid separated as a fine crystalline precipitate (recovery yield 98%); there was no change in the phosphoric acid as measured by NMR and rotation.

(*R*)-(+)-**4** (see entry 5 in Table III) was recovered by the following procedure. Ether was added twice to the reaction mixture and extracted twice with aqueous 10% NaOH. The product 1-phenylpropan-1-ol remained after evaporation of ether solution and was purified further by evaporation under reduced pressure. The aqueous solution containing (*R*)-(+)-**4** was neutralized by aqueous 20% HCl. (*R*)-(+)-**4** was filtered off as a solid in 99% yield.

General procedure for reduction of prochiral ketones by LiAlH₄ with 1-aryl-2,2-dimethyl-propane-1,3-diols and ethanol

To a mixture of 5 ml of LiAlH₄ solution (1 M in THF) and THF (4 ml) was added slowly a solution of the chiral diol (0.9 g, 5 mmol) in dry THF (5 ml) at 0°C under nitrogen atmosphere. The mixture was stirred for 1 h at the same temperature. Absolute ethanol in dry THF (2 ml) was added slowly and the mixture was stirred another hour. After cooling the reaction solution to -100°C, the prochiral ketone (1.7 mmol) in dry THF (2 ml) was added into the solution. The mixture was stirred for 2 h at -100°C and then at -78°C for 8 h.

The reaction was quenched by the addition of HCl (5%, 10 ml) and water (25 ml) and work-up was carried out. The mixture was extracted three times with ether (50 ml each time) and organic extracted solution was washed by saturated sodium-carbonate solution (50 ml). Then, the organic phase was dried over MgSO₄. After filtration and evaporation of solvents, the residue was separated by bulb-to-bulb distillation under reduced pressure; an oily product distilled over first. The chiral diol was recovered as a fraction with higher boiling point.

General procedure of asymmetric MPV reductions of acetophenone with Al(OⁱPr)₃

A mixture of Al(OⁱPr)₃ (10 mmol), THF (20 ml), and HOⁱPr (20 ml) was stirred until a clear solution was obtained. After a chiral diol (10 mmol) had been added and the mixture had been stirred for another 2 h, acetophenone (10 mmol) and 4 Å sieves (0.3 g) were added and the mixture stirred for a given time at a given temperature. Acetone was removed by distillation for 10 min once every 12 h under reduced pressure followed by addition 2-5 ml of isopropanol. The reaction was quenched by addition of aqueous HCl (5%, 20 ml). The mixture was extracted two times with ether (50 ml each time). The combined ether layers were washed with saturated aqueous Na₂CO₃ solution (20 ml) and then with water (30 ml). The organic layer was dried over MgSO₄. The products were isolated by a bulb-to-bulb distillation after filtration, in which chiral diols also were recovered (yield > 95%). Rotation measurements on the chiral diols showed there was no racemization and also no structural change during the reduction processes.

Preparation of La(OⁱPr)₃ and asymmetric MPV reductions of acetophenone

A mixture of LaCl₃·7H₂O (1.86 g, 5 mmol) and trimethyl orthoformate (5 ml) was stirred under nitrogen at 40-45°C for 1 h. Isopropanol (10 ml) was added and the solution was concentrated to 5 ml under reduced pressure (20 mmHg). This procedure was repeated four times to remove all methanol. The mixture was evaporated to dryness, after which a white adduct of isopropanol and LaCl₃ was obtained. Isopropanol (5 ml) and toluene (5 ml) were added. The mixture was heated to reflux and a clear solution was obtained. A NaOⁱPr solution (15 mmol) was obtained by refluxing a mixture of HOⁱPr (5 ml), toluene (5 ml) and Na (0.345 g, 15 mmol). The stock solution was added into the above adduct solution at once during reflux, and then the mixture was refluxed for another 15 h. After cooling to room temperature, the mixture was either directly used in next step of the reaction or further treated to remove NaCl by centrifugation.

In an asymmetric MPV reduction procedure, (*R*)-(-)-1-phenyl-2,2-dimethyl-propane-1,3-diol (**1**, 4 mmol) was added to the above solution, and then the mixture was stirred another 2 h at room temperature. Acetophenone (20 mmol) and 4 Å sieves (0.3 g) were added all at once and the mixture was stirred for the given time at the given temperature. Acetone was removed by distillation for 10 min once every 12 h under reduced pressure and 2-5 ml of isopropanol were then added each time. The reaction was quenched by addition of aqueous HCl (5%, 15 ml). The mixture was extracted two times with ether (30 ml each time). The

combined ether layers were washed by saturated aqueous Na₂CO₃ solution (15 ml) and then by water (20 ml). The organic layer was dried over MgSO₄. The products were isolated by a bulb-to-bulb distillation after filtration, in which the chiral diols also were recovered. Separation and rotation measurement on chiral diols showed there was no racemization during these reduction processes.

Methods for preparation for other metal triisopropoxides were the same as the above procedure.

General procedure for the catalysed reduction of ketones with LnCl(OⁱPr)₂

Diisopropoxide lanthanide chloride LnCl(OⁱPr)₂ synthesized by above procedure for lanthanide isopropoxides. So, the mixture of one equivalent of lanthanide and two equivalent of sodium isopropoxide was refluxed for 15 h. After cooling to room temperature, ketones were added and reaction mixtures were stirred for a given time at a given temperature. Work-up was carried out according to the above procedure.

In an asymmetric reduction procedure, a chiral diol was added to the lanthanide diisopropoxide chloride solution at room temperature and then the mixture was stirred another 2 h. Then a carbonyl compound was added; the work-up procedure was the same as previously described.

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 $[\alpha]_{589}^{20} 47.03$ (c ?, acetone)
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