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Asymmetric Reduction of Prochiral Arylketones With Chiral 2,2′-Dihydroxy-1,1′-binaphthyl — Borane Complexes***

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Reduction of eight aryl ketones with borane complexes containing (—)(*S*)-2,2′-dihydroxy-1,1′-binapthyl as a chiral auxiliary yielded (with one exception) (*R*)-alcohols with enantiomeric purities up to 54% (as determined with chiral NMR-shift reagents and/or by enantioselective chromatography on triacetylcellulose). In two cases addition of aromatic amines caused a significant increase of e.e. together with a reversal of the absolute chirality (from *R* to *S*). Models for a possible transition state are discussed.

(Keywords: Enantiomeric purity; Absolute chirality; Recycling chromatography on triacetylcellulose; Transition state)

Asymmetrische Reduktion prochiraler Arylketone mit chiralen 2,2′-Dihydroxy-1,1′-binaphthyl-Borankomplexen

Reduktion von acht Arylketonen mit chiralen Borankomplexen aus (—)(*S*)-2,2′-Dihydroxy-1,1′-binapthyl und $BH_3 \cdot THF$ oder $BH_3 \cdot (CH_3)_2S$ lieferte (mit einer Ausnahme) optisch aktive (*R*)-Alkohole mit optischen Ausbeuten bis zu 54%. In zwei Fällen führte Zusatz aromatischer Amine zu einer signifikanten Erhöhung von e.e. unter gleichzeitiger Konfigurationsumkehr (*R* zu *S*). Modelle für einen möglichen Übergangszustand werden diskutiert.

Introduction

Asymmetric reductions are valuable synthetic tools and have therefore been widely studied during the last years [1], not only with regard to the syntheses of natural products [2] but also to mechanistic aspects.

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*** Dedicated to Prof. Dr. Dr. mult. h. c. *V. Gutmann* on the occasion of the 65th anniversary of his birthday.

Chiral hydrides used for reducing prochiral ketones to optically active alcohols are usually prepared *in situ*, mainly by treating a chiral auxiliary with "BH_3" or $LiAlH_4$ [3].

The possible recovery of the chiral auxiliary with little or no loss of optical activity is an additional attractive feature of these methods—especially on a preparative scale.

In several cases excellent enantiomeric purities (e.e.) were achieved by employing torsional isomeric biaryls or chiral aminoalcohols as auxiliary [4]. However, even small variations of the reaction conditions and/or of the structures of the reactants may give rise to sometimes dramatic changes in the asymmetric induction. It is apparent from previous results that high optical yields are obtained whenever the reduction is effected by only one (defined) species in a highly ordered transition state.

In many cases appropriate models allow correct predictions as to the absolute chiralities of the alcohols produced [5]. The geometry of the transition state(s) may be described by a sixmembered ring consisting of boron, ketone and Li-alcoholate or amine (for a "chiral $LiAlH_4$" or a "chiral borane", resp., [3 b, 5]).

Results and Discussion

Since we required several optically active aromatic alcohols we have studied asymmetric reductions of appropriate arylketones with reagents from "BH_3" and 2,2′-dihydroxy-1,1′-binaphthyl as chiral auxiliary; the latter is easily accessible in optically active form and can smoothly be recovered after the reduction—therefore it has been used frequently as a chiral auxiliary in several asymmetric syntheses.

$BH_3 \cdot THF$ or $BH_3 \cdot (CH_3)_2S$ were used as borane sources. Racemic 2,2′-dihydroxy-1,1′-binapthyl was prepared by oxidative coupling of 2-naphthol with $FeCl_3$ [6] and resolved according to Ref. [7] ($[\alpha]_D = -34.5°$ in *THF*).

Previous results had revealed that an arene-ring adjacent to C=O increases the optical yields in asymmetric reductions of ketones considerably; therefore we chose acetophenone and its homologues including the more crowded isobuyrophenone as first examples. Benzyl-methyl-ketone was also included since in this case phenyl is separated from CO by one carbon (for cyclic ketones *vide infra*).

The results of the reductions of these ketones with (—)(*S*)-2,2′-dihydroxy-1,1′-binaphthyl/$BH_3 \cdot THF$ (1 : 1) in *THF* at 20 °C for 20 hours are compiled in Table 1. Whereas the chemical yields were almost quantitative, the optical yields (e.e., determined both by optical rotation and by the NMR-shift method and checked by asymmetric chroma-

Table 1. *Reduction of arylketones with (—)(S)-2,2'-dihydroxy-1,1'-binaphthyl/BH_3 (1:1) in THF (at 40 °C, 20 hours)*[a]

R^1—CO—R^2		$[\alpha]^{20}$	R^1—CHOH—R^2 e.e. [%][b]		
R^1	R^2	[°]	opt. rot.	NMR	config.
phenyl	methyl	+10.7	24	25	(+)*R*
phenyl	ethyl	+8.3	18	21	(+)*R*
phenyl	*n*-propyl	+11.0	24	26	(+)*R*
phenyl	*i*-propyl	—1.6	3	4	(—)*S*
benzyl	methyl	—3.8	10	10	(—)*R*
1-napthyl	methyl	+3.8	5	4	(+)*R*
1-Indanone		—11.5	30	41	(—)*R*
1-Tetralone		—16.3	50	54	(—)*R*

[a] BH_3 was used as $BH_3 \cdot THF$ or as $BH_3 \cdot (CH_3)_2S$. With the former equilibration takes place within 2–3 h (stirring at room temperature), while the latter requires a longer reaction time. In both cases the optical yields are almost the same, but the conversion decreases from ca. 100% to 60–70% with $BH_3 \cdot (CH_3)_2S$ instead of $BH_3 \cdot THF$ as a borane source.

[b] For the determination of e.e. see the experimental part.

tography on triacetylcellulose, see Exp. Part) vary from 3—54% depending strongly on the ketone. All *sec.* alcohols produced (except 1-phenyl-2-methyl-propanol-1) had (*R*)-chirality; the latter (with two residues of about equal "size") was, however, obtained with very low enantiomeric excess (ca. 3%).

This fact (*R*-chirality!) is remarkable with respect to previous results (cf. Ref. [3 b]).

A slight temperature dependence was observed in the asymmetric reduction of acetophenone with the justmentioned reagent affording the following optical yields at various temperatures; e.e. [%] (°C): 14 (0), 22 (20), 25 (40) and 23 (reflux; 56); i.e. with a maximum of e.e. at around 40 °C.

Since an aromatic ring may give rise to a high degree of order within a transition state, all changes of electronic or steric effects at the arene ought to have some influence on the asymmetric induction. This should also be the case by varying the torsional angle between the arene plane and the C=O group. Thus cyclic ketones with a rigid (ground state) conformation or at least with restricted mobility might produce such effects: 1-Indanone with a largely planar structure, 1-tetralone with the C=O-group twisted from the benzene plane by appr. 15° and 1-acetyl-naphthaline with a

Table 2. *Asymmetric reduction of arylketones of different conformational mobilities*

Run No.	Chiral reagent prepared from 1 equiv. of (—)*S*-2,2′-dihydroxy-1,1′-binaphthyl and	Ketone[a]	Time of[b] reaction [h]			Conversion [%]	Optical rotation [°]	e.e. (%)		Config.
			A	B	C			opt. rot.	NMR or chrom.	
1	1 $BH_3 \cdot (CH_3)_2S$[c]	1	12	—	20	68	+11.0	24	26	(+)*R*
2		2	16	—	26	50	+3.8	5	4	(+)*R*
3		3	17	—	6	71	—15.2	39	41	(—)*R*
4		4	6	—	66	80	—16.3	50	54	(—)*R*
5	2 $BH_3 \cdot (CH_3)_2S$	1	5	—	20	95	+4.7	10	9	(+)*R*
6		2	5	—	21	86	+5.6	6	6	(+)*R*
7		3	16	—	5	100	—7.9	20	25	(—)*R*
8		4	5	—	18	100	—7.7	24	22	(—)*R*
9	1 $BH_3 \cdot (CH_3)_2S$	1	4	22	25	37	—2.9	6	6	(—)*S*
10	1 $C_6H_5NH_2$	2	4	26	40	43	—3.9	5	4	(—)*S*
11		3	2	63	25	23	—0.8	2	<3	(—)*R*
12		4	3	24	24	35	—1.5	4	<3	(—)*R*
13	2 $BH_3 \cdot (CH_3)_2S$	1	2	14	20	100	—19.8	44	48	(—)*S*
14	1 $C_6H_5NH_2$	2	4	26	40	100	—39.0	52	51	(—)*S*
15		3	3	17	5	100	—2.8	7	11	(—)*R*
16		4	3	16	32	100	+1.1	3	<3	(+)*S*
17	2 $BH_3 \cdot (CH_3)_2S$	1	3	3	25	90	+17.3	38	41	(+)*R*
18	2 CH_3OH	2	2	16	20	100	+24.7	33	31	(+)*R*
19		3	4	5	14	100	—17.5	45	47	(—)*R*
20		4	2	3	15	100	—13.8	42	45	(—)*R*

[a] 1 = acetophenone, 2 = 1-acetylnaphthalin, 3 = 1-indanone, 4 = 1-tetralone.
[b] See experimental part (general procedure).
[c] In equivalents.

Table 3. *Reduction of acetophenone with chiral borane complexes under addition of aromatic amines (at 20 °C)*

Run No.	Reagent from 1 equiv. of (—)(*S*)-2,2′-dihydroxy-1,1′-binaphthyl and $BH_3 \cdot THF$		Amine[a]	Reaction time[b] [h]			Conversion e.e [%]	1-Phenylethanol [%] based on		Config.
	borane (equiv.)	amine (equiv.)		A	B	C		opt. rot.	NMR	
21	1	—	—	3	—	20	100	25	22	(+)(*R*)
22	1	1	I	2	2	20	60	9	8	(—)(*S*)
23	1	1	II	2	3	17	58	19	22	(—)(*S*)
24	1	1	III	1	2	20	73	25	26	(—)(*S*)
25	2	—	—	2	—	20	100	6	5	(+)(*R*)
26	2	1	I	2	2	18	100	47	47	(—)(*S*)
27	2	1	II	2	2	17	100	18	19	(—)(*S*)
28	2	1	III	3	2	20	100	41	44	(—)(*S*)
29	2	2	I	2	1	17	100	32	35	(—)(*S*)
30	2	2	II	2	4	14	77	25	24	(—)(*S*)
31	2	2	III	4	2	20	76	42	44	(—)(*S*)

[a] I: aniline, II: N-methylaniline, III: 1-aminonaphthaline.
[b] See experimental part (general procedure).

highly mobile acetyl group seemed to be appropriate models and their reductions were compared with that of acetophenone. The e.e. values of the optically active alcohols obtained by reducing these ketones with "chiral boranes" [all containing one mole of (—)(*S*)-2,2′-dihydroxy-1,1′-binaphthyl with varying amounts of borane] are compiled—together with their absolute chiralities—in Table 2.

In the case of indanone a prolonged reaction time resulted in a decreasing yield of alcohol because of the formation of some hydrocarbon.

On addition of aniline as a complexing agent, in several cases a remarkable reversal of the enantioselectivity takes place (see Table 2: runs 9, 10, 13, 14 and 16). This effect was studied in some detail employing also N-methylaniline and 1-aminonaphthaline as additives; as can be seen from Table 3 the primary arylamines afford higher enantiomeric purities.

Transition State and Absolute Chiralities

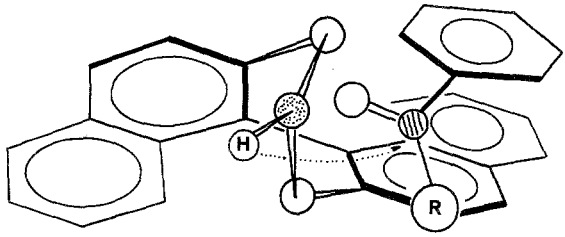
The results described so far allow the assumption that the geometry of the transition state involved should be entirely different from those proposed for similar reactions. For a relevant model two facts have to be taken into account:

(1) In the reduction with a borane/2,2′-dihydroxy-1,1′-binaphthyl complex (for 2,2′-dihydroxy-6,6′-dimethyl-biphenyl cf. Ref. [3 b]) the alcohols have an absolute chirality "opposite" to this of the biaryl (*R* vs. *S*; see Tables 1 and 2).

(2) A change in the chirality of the alcohol takes place if *R* in the prochiral ketone becomes sufficiently bulky—but only if using the binaphthylreagent (and not with the biphenyl complex, cf. Ref. [3 b]).

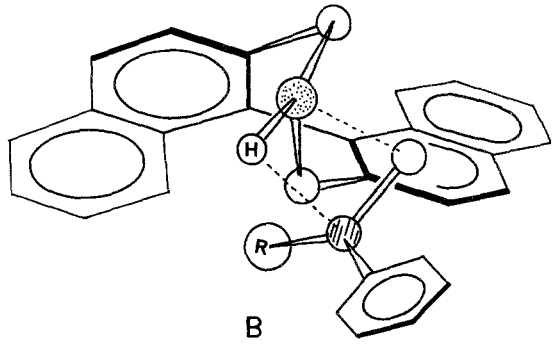
These observations may be interpreted by (at least) two different transition states depending on steric and electronic requirements both of reagent and substrate. One of them (A) is based on a positive π—π-interaction between the chiral moiety and the aryl residue of the ketone as shown in Fig. 1. As can be deduced from *Dreiding* models, for an interaction of the lonepair electrons of C = O with boron a torsional angle of 10–15° should be especially favourable. Such an arrangement facilitates bonding between boron and the carbonyl-oxygen together with a preferred attack of the hydride on the *Re*-side of the prochiral center.

This transition state A might be involved if (1) no severe steric interactions occur between a bulky alkyl group (of the ketone) and the arene (of the auxiliary), and (2) if a "parallel" arrangement is not prevented by bulky substituents. The former (1) is valid in the case of butyrophenone (cf. Table 1) and the latter (2) occurs with 2,2′-dihydroxy-6,6′-dimethylbiphenyl.



A

Fig. 1. Transition state A (in schematic representation)



B

Fig. 2. Transition state B (in schematic representation)

In these cases—if (1) and/or (2) are operative—a transition state (B) as depicted in Fig. 2 with a maximum distance between phenol-oxygen and the arylgroups of the ketone (caused by π—π-repulsion) might be conceivable.

Reductions with complexes from two equivalents of borane proceed with moderate optical but nearly quantitative chemical yields (Table 2). This fact could be interpreted by a higher hydride activity together with a lower enantioselectivity due to a less defined geometry of the reagent; hydride repulsion might thereby increase the torsional (biaryl) angle from appr. 45° to 90°. Nevertheless, also in these cases a model as outlined in Fig. 1 may explain the enantioselectivity of the reduction.

Addition of methanol results in a remarkable increase both of conversion and asymmetric induction (see Table 2: runs 17–20) since the alcohol probably consumes the more active but less selective hydride(s).

As can be seen from Tables 2 and 3, complexation with arylamines causes a pronounced effect only for noncyclic ketones (together with a

surprising change of alcohol-configuration; vide supra). This effect may be due to an effective competition of the amine with acetophenone in the formation of a charge transfer complex (similar to the representation in Fig. 1) and favouring thereby a reduction via a transition state similar to that depicted in Fig. 2. These results could, however, also be explained by a transition state as suggested in Ref. [3 b].

Conclusion

Asymmetric reductions of aryl-alkyl-ketones with chiral biaryl-borane-complexes proceed with high chemical and modest to good optical yields, which strongly depend as well on the ratio of auxiliary to borane as on "additives" such as methanol or arylamines; the latter give also rise to a reversal in enantioselectivity.

These results can be interpreted by (at least) two different transition states (A and B, Figs. 1 and 2), for the preference of which steric interactions and/or electronic effects are responsible.

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Experimental

All reactions were conducted under Ar on a vacuum line. Optical rotations were measured on a Perkin-Elmer-241 polarimeter in a thermostatted 1 dm-cell (at 20 ± 0.1 °C). The ^{1}H-NMR-spectra were recorded on a Bruker WP-80 spectrometer in $CDCl_3$.

The ketones (cf. Tables 1 and 2) were purified by distillation at reduced pressure. $BH_3 \cdot THF$ was employed as an 1-molar solution, stored under Ar at —18 °C. $BH_3 \cdot (CH_3)_2S$ was a commercial product (neat liquid, 10molar). *THF* (analytical grade) was dried over $LiAlH_4$ and distilled immediately before use. All glassware was dried in an oven (overnight).

General Procedure for the Asymmetric Reductions (see Table 2, runs 1–20)

To a solution of 180 mg (0.625 mmol) of (—)(*S*)-2,2′-dihydroxy-1,1′-binaphthyl in 2 ml of *THF* (prepared under Ar) 0.625 mmol (63 μl—runs 1–4 and 9–12) and 1.25 mmol, resp. (125 μl—runs 5–8 and 13–20) of $BH_3(CH_3)_2S$ in 2 ml of *THF* were added with a syringe through a septum. After stirring the mixture at 20 °C for the time stated (under "A" in Table 2) aniline (runs 9–16) or methanol (runs 17–20), each reagent diluted with 2 ml of *THF*, was added and the stirring continued (cf. time "B"). Then a solution of 0.5 mmol of the ketone in *THF* (2 ml) was added dropwise with stirring and the reaction followed by TLC. After the time

given in column "C" water (1 ml) was added and the mixture diluted with ether (10 ml); the solution was washed with water (once), 1 *N*-KOH (twice)—the products from 9–16 had to be extracted also with 2*N*-HCl in order to remove aniline—and finally with water, dried over sodium sulfate and evaporated *in vacuo*.

In all cases the extent of the reduction could be estimated by 80 MHz ^{1}H-NMR-spectroscopy of the crude mixtures (by integrating significant signals).

The alcohols were then isolated by preparative TLC (on silicagel in ligroin/ethylacetate, 7 : 3). The isolated yields are 60–80%.

Enantiomeric Purities

All e.e. values (cf. tables) were determined by optical rotation based on the highest reported values (cf. [8]). In addition one of the following methods was applied for control:

1) ^{1}H-NMR-using Eu(*hfc*)$_3$ as chiral shift reagent and determining the e.e. values by integration of the diastereomeric protons next to the chiral centers.

2) Enantioselective chromatography on microcrystalline triacetylcellulose (column: 15 × 360 mm, particle size 15–25 μm) using an equipment for "continuous flow—recycling-chromatography" as described in detail in Ref. [9]. The e.e.-values were determined by graphic integration of the peaks detected at 254 nm.

	k_1	k_2	α	Number of cycles for complete separations [9]
1-Indanol	0.16	0.19	1.19	14
1-(1-Naphthyl)ethanol	0.73	0.82	1.12	9

References and Notes

[1] For recent reviews see *Morrison JD* (ed) (1983) Asymmetric synthesis, vol 2. Academic Press, New York. a) *Midland MM*, Reduction with chiral boron reagents. p 45. b) *Grandbois ER, Howard SI, Morrison JD*, Reductions with chiral modifications of lithium aluminium hydride. p 71

[2] *Noyori R, Tomino I, Yamada M, Nishizawa M* (1984) J Amer Chem Soc 106: 6717

[3] See for instance: a) *Asami M, Mukaiyama T* (1979) Heterocycles 12: 499. b) *Suda H, Kanoh S, Umeda N, Nakajo T, Motoi M* (1983) Tetrahedron Lett 24: 1513

[4] a) *Itsuno S, Nakano M, Miyazaki K, Masuda H, Ito K, Hirao A, Nakahama S* (1985) J Chem Soc Perk Trans I: 2093. b) *Noyori R, Tomino I, Tanimoto Y* (1979) J Amer Chem Soc 101: 3129

[5] *Noyori R, Tomino I, Tanimoto Y, Nishizawa M* (1984) J Amer Chem Soc 106: 6709

[6] *Pummerer R, Prell E, Rieche A* (1926) Ber Dtsch Chem Ges 59: 2159

[7] *Kyba EP, Gokel GW, Jong F de, Koga K, Sousa LR, Siegel MG, Kaplan L, Sogah GDY, Cram DJ* (1977) J Org Chem 42: 4173

[8] For highest reported values of optical rotations see: (*R*)-1-phenylethanol, $[\alpha]_D + 45.5°$ (*Me*OH): *Huisgen R, Rüchart C* (1957) Liebigs Ann Chem 601: 21; (*S*)-1-phenylpropanol, $[\alpha]_D$—47.03° (acetone): *Kwart K, Hoster DP* (1967) J Org Chem 32: 1867; (*S*)-1-phenylbutanol, $[\alpha]_D$—45.2° (benzene): see Ref. [4b]; (*S*)-1-phenyl-2-methylpropanol, $[\alpha]_D$—49° (ether): *MacLeod R, Welch FJ, Mosher HS* (1960) J Amer Chem Soc 82: 876; (*S*)-1-phenyl-2-propanol, $[\alpha]_D + 37.8°$ ($CHCl_3$): *Nordlander JE, Kelly WJ* (1969) J Amer Chem Soc 91: 996; (*S*)-1-naphthylethanol, $[\alpha]_D$— 78.9° (ethanol): *Balfe MP, Downer EAW, Evans AA, Kenyon J, Poplett R, Searle CE, Tarnoky AL* (1946) J Chem Soc 797; (*S*)-indanol, $[\alpha]_D + 38.9°$ ($CHCl_3$): *Hückel W, Mössner F* (1960) Liebigs Ann Chem 637: 57; (*S*)-1-tetralol, $[\alpha]_D + 32.7°$ ($CHCl_3$): *Davies AG, White AM* (1952) J Chem Soc 3300

[9] *Schlögl K, Widhalm M* (1984) Monatsh Chem 115: 1113

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