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ASYMMETRIC REDUCTION OF AROMATIC KETONES WITH BORANE–AMINE COMPLEXES MODIFIED WITH OPTICALLY PURE 2,2'-DIHYDROXY-6,6'-DIMETHYLBIPHENYL

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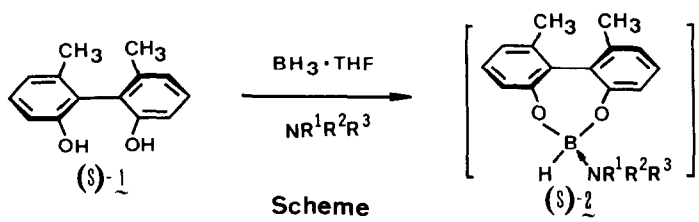
Summary : Highly enantioselective reduction of prochiral aromatic ketones was achieved with a chiral reagent (2) prepared from BH_3·THF, optically pure 2,2'-dihydroxy-6,6'-dimethylbiphenyl (1), and an achiral amine.

Asymmetric reductions of prochiral ketones with chirally modified aluminum hydrides have been extensively studied and some of them have realized extremely high enantioselectivity [1]. On the other hand, a little attention has been paid to the use of borane for such reduction, and it seems that no satisfactory results have been reported but few cases [2].

Cram et al.[3] and Noyori et al.[1a] have reported that chiral reagents containing an axially dissymmetric 1,1'-binaphthyl moiety possess high ability of enantioface discrimination. We have been investigating on systhesis and application of optically active biphenyl derivatives having C_2 axis as likely as 1,1'-binaphthyl and reported previously asymmetric reduction of alkyl phenyl ketones with a reagent from $LiAlH_4$ and 2,2'-diamino-6,6'-dimethylbiphenyl [4]. As a continuation of the investigation, we wish to describe herein the same reduction as above with a chiral borane–amine complex (2) prepared in situ from BH_3·THF, 1, and an achiral amine (Scheme).



Scheme

The chiral ligand 1 was synthesized from m-cresol as starting material through several steps in about 43% overall yield by the method described in the literature [5]. Resolution of 1 was carried out by the method used for the case of 2,2'-dihydroxy-1,1'-binaphthyl by Cram [6]. Racemic hydrogen phosphate derived from 1 was easily resolved with chinconidine and quinine. Then each of the enantiomers was subjected to a reductive cleavage to give 38% of (R)-1, mp 159–160°C, $[\alpha]_D^{25}$ +90.0°(c 1.03, EtOH) and 37% of (S)-1, mp 159–160°C, $[\alpha]_D^{25}$ -88.9°(c 1.03, EtOH) [7] [Yield was based on (RS)-1].

Table Asymmetric reduction of alkyl phenyl ketones (RCOPh) with chiral reagent 2 [a]

Exp.	Substrate R	Chiral reagent Config. of 2	Chiral reagent Additive amine	Reaction conditions Temp. °C	Reaction conditions Time h	Alcohol produced C.Y. [b] %	Alcohol produced O.Y. [c] % (config.)
1	CH_3	(R)	$C_6H_5NH_2$	0	2	63	42 (R)
2 [d]		(R)	$C_6H_5NH_2$	0	48	39	75 (R)
3 [e]		(R)	$C_6H_5NH_2$	0	2	50	41 (R)
4 [e]		(R)	$C_6H_5NH_2$	0	2	50	33 (S)
5		(S)	$C_6H_5NH_2$	50	2	98	42 (S)
6		(S)	$C_6H_5NH_2$	30	2	95	43 (S)
7		(S)	$C_6H_5NH_2$	-30	2	38	10 (S)
8		(S)	$C_6H_5NH_2$	-78	24	69	0 -
9		(R)	none	0	2	63	4 (R)
10 [d]		(R)	none	0	24	96	22 (R)
11		(R)	$C_6H_5NHCH_3$	0	2	58	57 (R)
12 [d]		(R)	$C_6H_5NHCH_3$	0	72	85	75 (R)
13		(R)	$C_6H_5N(CH_3)_2$	0	16	42	18 (R)
14		(S)	β-$C_{10}H_7NH_2$	0	2	54	55 (S)
15		(R)	o-$C_6H_2(CH_3)NH_2$	0	2	59	45 (R)
16		(S)	C_5H_5N	0	2	61	0 -
17		(S)	o-$C_6H_4(NO_2)NH_2$	0	2	71	5 (S)
18		(S)	m-$C_6H_4(NO_2)NH_2$	0	2	84	65 (S)
19 [d]		(R)	m-$C_6H_4(NO_2)NH_2$	0	48	98	84 (R)
20		(R)	p-$C_6H_4(NO_2)NH_2$	0	2	81	59 (R)
21		(R)	p-$C_6H_4(OCH_3)NH_2$	0	2	55	47 (R)
22		(S)	2,4-$C_6H_3(NO_2)_2NH_2$	0	2	65	0 -
23		(R)	$C_6H_5CH_2NH_2$	0	2	85	3 (R)
24		(S)	n-$C_4H_9NH_2$	0	2	74	36 (S)
25		(S)	t-$C_4H_9NH_2$	0	2	67	17 (S)
26		(S)	$C_6H_{11}NH_2$	0	2	64	28 (S)
27		(S)	piperidine	0	2	97	17 (S)
28	C_2H_5	(R)	$C_6H_5NH_2$	0	24	45	48 (R)
29	C_3H_7	(R)	$C_6H_5NH_2$	0	24	42	51 (R)
30	t-C_4H_9	(S)	$C_6H_5NH_2$	0	24	39	19 (S)

a) The reaction was carried out using 2 equiv. of the reducing reagent. Equimolar amount of $BF_3 \cdot Et_2O$ was added except otherwise mentioned. b) Chemical yield was determined by GLC. c) Optical yield was evaluated on the basis of the the following specific rotations: (R)-1-phenylethanol, $[\alpha]^{23}_D$ +45.5° (MeOH) reported by R. Huisgen and C. Ruchardt, Liebigs Ann. Chem., **601**, 31 (1956); (S)-1-phenylpropanol, $[\alpha]^{21}_D$ -47.03° (acetone) reported by K. Kwart and D.P. Hoster, J. Org. Chem., **32**, 1896 (1967); (S)-1-phenylbutanol, $[\alpha]^{22}_D$ -45.2° (c 4.81, benzene) reported in ref. 1a; (R)-1-phenyl-2,2-dimethylpropanol, $[\alpha]^{28}_D$ +36.2° (ether) reported by M. Macleod, F.G. Welch and H.S. Mosher, J. Am. Chem. Soc., **82**, 876 (1966). d) $BF_3 \cdot Et_2O$ was not added. e) The solvent was replaced with ether (Exp. 3) or toluene (Exp. 4) on a vacuum line.

A typical experimental procedure is exemplified by the reduction of acetophenone. To a 1.85 M THF solution of BH_3 (5.91 mmol) placed under nitrogen atmosphere was added (R)-1 in THF (0.635 M, 5.46 mmol) with stirring at 0°C[8]. Stirring was continued for 1 h at ambient temperature, then aniline in THF (1.39 M, 5.59 mmol) was added at 0°C [9] and the resulting white suspension was stirred for additional 1 h at this temperature to give a chiral reagent. To this were added 0.820 M THF solution of acetophenone (2.46 mmol) and $BF_3 \cdot Et_2O$ (2.46 mmol). The mixture was stirred for 2 h at 0°C to give a clear solution and then the reaction was quenched by adding a few drops of 6 N HCl. The usual workup gave an oil. It was then purified by evaporative distillation, followed by preparative GLC to afford (R)-enriched 1-phenylethanol in 62.6% yield. $[\alpha]_D^{25}$ +23.1°(c 2.55, MeOH). It means the optical yield (O.Y.) of 50.8%. And more than 90% of (R)-1 was recovered from the alkaline extract without any noticeable racemization.

The results are summerized in the table. Exploratory reductions of acetophenone with a reagent 2 (R^1,R^2,R^3:H,H,Ph) gave the following facts. Tetrahydrofuran was preffered as solvent and the O.Y. was maximun at 0°C. A rise in temperature up to 50°C decreased the yield only in an extent of 10%, but a lowering decreased it surprisingly. At -78°C, the reduction took place with no selection. Such temperature-dependence of the selection seems to be an unusual case that has been reported only rarely[10]. And the addition of $BF_3 \cdot Et_2O$ equimolar to the ketone accelerated the rate of reduction as reported by Jones [11], but it affected unfavorably on the selection.

Effect of additive amine on the enantioselection was examined by using various kinds of amine. All amines except pyridine and benzylamine enhanced the O.Y. to some extent. Relatively high yields were obtained when primary and secondary N-arylamines were used. Here also an increase in O.Y. of about 20% was observed in the absence of $BF_3 \cdot Et_2O$, where the highest selectivity (O.Y., 84%) was obtained by using m-nitroaniline. Aliphatic amines having higher basicity improved chemical yield in general. However, they were not as effective as N-arylamine in the extent of selection. The results suggest that both the amino hydrogen and the aromatic ring of amine play an important role in the enantioselective reduction.

The configuration of the preferentially formed enantiomer always agreed with that of 1 independent of the amine and substrate used. It is obvious that relative bulk of the substituents in the ketone cannot account for the result. The configurational bias in the produced alcohol can be interpreted in terms of a conformation in transition state. The probable structure in the reaction of acetophenone and (S)-2 containing aniline is schematically illustrated in the figure. The six-membered chair conformation having axial-alkyl and equatorial-phenyl groups is favored over the diastereomeric one, since in the latter case severe steric and electronic repulsions[1a] between phenyl group and phenoxy oxygen at 1,3-diaxial positions are conceivable from the examination by the CPK molecular model. The model also suggests the existence of $\pi-\pi$ interaction between one phenyl π-system in the biphenyl and that of N-aryl at vicinal positions[12]. The interaction can be enhanced by an introduction of electron withdrawing group into the N-aryl nuclei. Accordingly the transient conformation becomes to be held more tightly and thus a better enantioselection

should be achieved. This expectation was realized by using m-nitroaniline as an additive. But o-nitroaniline and 2,4-dinitroaniline, which may be advantageous for the π-π interaction, showed almost no selection. This is attributable to their inabilities in coordination because of extremely weak basicities (pKa; -0.23 and -4.3, respectively).

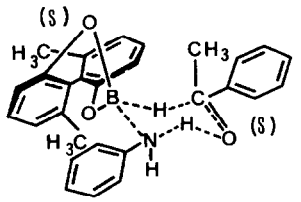


Figure Schematical structure of a preferred transition state in the reaction of acetophenone and (S)-2.

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8. Upon addition of equimolar amount of BH_3·THF to 1, 1.85 equiv. of hydrogen liberated slowly.
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