

ENANTIOSELECTIVE REDUCTION OF KETONES WITH β -HYDROXYSULFOXIMINE-BORANE COMPLEXES

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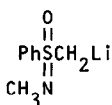
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Abstract: Optically pure β -hydroxysulfoximines were treated in toluene solution at -78°C with 2 equiv. of gaseous diborane. The resulting borane complexes were used to reduce prochiral ketones at -78°C ; alcohols with optical purities ranging from 3 to 82% were obtained.

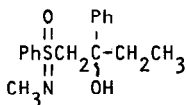
The asymmetric synthesis of alcohols by reduction of prochiral ketones with optically active reducing agents has received considerable attention.¹ Although various boron hydride derivatives have proven to be exceptionally useful in the asymmetric hydroboration of alkenes^{1,2a} and the asymmetric reduction of prochiral carbonyl compounds^{2b}, relatively little attention has been devoted to the use of optically-active amine-borane complexes. Borane complexes of (*S*)-1-phenyl-2-propanamine³, (*R*)- and (*S*)-1-phenylethanamine⁴, and methyl esters of (*S*)-amino acids⁵ have been explored as asymmetric reducing agents; all have proven to be rather ineffective in producing alcohols of high optical purity. Amine-boranes, in general, are sluggish reducing agents for carbonyl compounds in the absence of proton or Lewis acid catalysis.⁶

As part of a continuing program on the exploration of sulfoximine chemistry⁷, we have examined the borane complexes of β -hydroxysulfoximines. It is the unusually high reactivity and relatively high asymmetric inductions observed in carbonyl reductions with these complexes that we describe here.

Reaction of (*S*)-*N*-methylphenylsulfonylmethylmethylithium (**1**)⁸ with 1-phenyl-1-propanone gave diastereomers **2a** and **2b** which were separated by chromatography on silica gel. Diastereomer **2a** eluted prior to **2b**; diastereomer **2a** yields (+)-2-phenyl-2-butanol when treated with Raney nickel. Addition of **1** to *l*-menthone at -78°C gave, as the major product, β -hydroxysulfoximine **3**.⁹

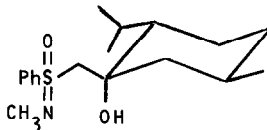


1



2a (mp $88-89^\circ\text{C}$)

2b (mp 105°C)



3 (mp 116°C)

The β -hydroxysulfoximines were dissolved in toluene, the solutions were cooled to -78°C and 2 molar equivalents of diborane gas¹⁰ were bubbled into the solution followed by the addition of one equivalent of ketone. During the subsequent to the addition of the ketones, gas evolved from the reaction mixtures. The reactions were stirred at -78°C for two hours, the toluene was then removed at low pressure and the mixture was quenched by addition to 6N sulfuric acid. The alcohol products (Table I) were extracted into diethyl ether or hexane. The β -hydroxysulfoximines were recovered by neutralization of the aqueous layer. We emphasize that the borane was introduced as a gas into the toluene solutions; the presence of tetrahydrofuran or other borane-complexing ligands has a deleterious effect in these reactions.

We suggest that the active reducing agents at -78°C are complexes of type 4 and not type 5. When a toluene solution of β -hydroxysulfoximine at -78°C is treated with diborane and quenched with acid 3 molar equivalents of hydrogen gas (excess over control using only toluene) was produced. When the borane- β -hydroxysulfoximine complex was allowed to warm to 25°C , a sluggish reducing reagent was formed which released only 2 molar equivalents of hydrogen gas (excess over control). We tentatively suggest that complexes of type 5 are formed at the elevated temperature. The control experiments shown using acetophenone (Table I) indicate that both simple sulfoximines and alcohols at low temperatures in toluene are capable of promoting borane reductions of carbonyl compounds. The borane complex of d-ephedrine, generated at -78°C in toluene, reduced acetophenone to yield 1-phenylethanol of low optical purity.

In enantioselective reductions of prochiral ketones the highest optical yields are generally obtained with alkyl aryl ketones^{1,11}, e.g., Table I. Apparently it is important that the groups flanking the carbonyl be differentiated both sterically and electronically.

The results which we have described suggest that the chemistry of borane derivatives in non-participating solvents is an area worthy of additional investigation.

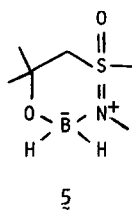
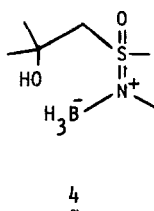
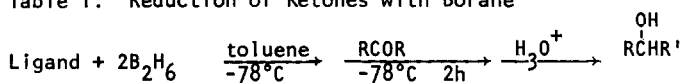


Table I. Reduction of Ketones with Borane



R	R'	Ligand	Alcohol		
			yield (%)	optical purity (%)	Absolute Configuration
Ph	CH ₃	<u>2a</u>	80	60 ^d	S
		<u>2b</u>	92	57	R
		<u>3</u>	66	82	S
		none	11	0	-
		A ^a	84	5	S
		B ^b	73	0	
		C ^c	72	3	S
Ph	C ₂ H ₅	<u>2a</u>	66	33 ^e	S
		<u>2b</u>	74	74	R
		<u>3</u>	48	29	S
Ph	<u>n</u> -C ₃ H ₇	<u>2a</u>	66	31 ^f	S
		<u>2b</u>	81	70	R
		<u>3</u>	52	30	S
Ph	<u>i</u> -C ₃ H ₇	<u>2a</u>	67	3 ^g	S
		<u>2b</u>	53	8 ^h	R
		<u>3</u>	81	11	R
CH ₃	<u>n</u> -C ₆ H ₁₃	<u>2b</u>	79	8	R
CH ₃	<u>i</u> -C ₃ H ₇	<u>2b</u>	46	9 ⁱ	R
CH ₃	<u>i</u> -C ₄ H ₉	<u>2b</u>	48	3 ^j	R
CH ₃	<u>t</u> -C ₄ H ₉	<u>2b</u>	60	22 ^k	R

^aA=(S)-N,S-Dimethyl-S-phenylsulfoximine; ^bB=t-Butyl alcohol; ^cC=d-Ephedrine; ^dBased on $[\alpha]_D$ in cyclopentane concentration dependence studies by C. J. Reich, Ph.D. Dissertation, Stanford University, 1976; ^eBased on $[\alpha]_D^{20}$ 47.1 (CHCl₃), I. Jacquet and J. P. Vigneron, *Tetrahedron Lett.*, 2065 (1974); ^fBased on $[\alpha]_D^{22}$ 45.9° (benzene), *idem.*; ^gBased on $[\alpha]_D^{20}$

47.7 (ether), *idem.*; ^hBased on $[\alpha]_D^{17}$ 9.79 (ethanol), R. H. Pickard and J. Kenyon, J. Chem. Soc., 2058 (1907); ⁱBased on $[\alpha]_D$ 5.34 (ethanol), Handbook of Chemistry and Physics, 57th Ed. (1976); ^jBased on $[\alpha]_D^{30}$ 20.3 (neat) R. H. Pickard, and J. Kenyon, J. Chem. Soc., 99, 45(1911); ^kBased on $[\alpha]_D^{20}$ 3.31 (benzene), H. S. Mosher and S. Yamaguchi. J. Org. Chem., 38, 1870 (1973).

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References and Notes

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9. The addition of organometallic reagents to menthone favors the carbonyl face trans to the isopropyl group [M. Perry and Y. Maroni-Barnaud, Bull. Soc. Chim. Fr., 3574 (1969); J. Philippe, M. Capman, and W. Chodkiewicz, ibid., 2248(1971)].
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11. For an exception see S. Krishnamurthy, F. Vogel, and H. C. Brown, J. Org. Chem., 42, 2534(1977).

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