Tetrahedron Letters, Vol. 34, No. 38, pp. 6041-6044, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

β-Hydroxysulfoximines in the Catalyzed Enantioselective Reduction of Ketones with Borane

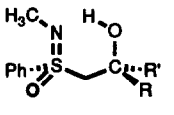
Carsten Bolm *[1] and Marcel Felder[1]

Department of Chemistry, University of Basel, St. Johanns-Ring 19, CH-4056 Basel (Switzerland)

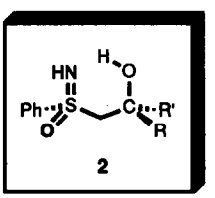
Key Words: Asymmetric Reduction, Sulfoximines, Enantioselective Catalysis

Abstract: Optically active β-hydroxysulfoximines catalyze the asymmetric borane reduction of ketones affording secondary alcohols in high yields with good enantioselectivities (up to 93% ee).

The enantioselective reduction of prochiral ketones is an important method for the synthesis of optically active secondary alcohols.[2] Particularly high enantiocontrol has been achieved in asymmetric borane reductions using *catalytic amounts* of chiral oxazaborolidines.[3] Several applications of this process for the synthesis of valuable chiral targets have been demonstrated.[4] The most interesting enantioselectivities have been achieved with systems which were derived from chiral vicinal amino alcohols. An early report by Johnson and Stark[5] describing the use of stoichiometric reducing reagents made by mixing β-hydroxysulfoximines of type **1** (1 equiv) with diborane (2 equiv), prompted us to investigate the possible use of chiral sulfoximine-metal complexes *as catalysts* in enantioselective reductions.[6]



1



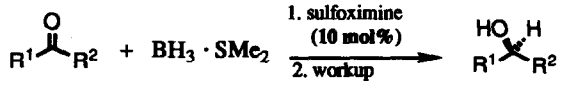
2

1/2a: R = R' = Ph
1/2b: R = R' = Me
2c: R = R' = *i*-Pr
2d: R---R' = Adamantyl
2e: R = Ph, R' = *i*-Pr

Although we found that catalytic amounts of β-hydroxysulfoximines **1**[7] were sufficient for an acceleration of the borane reduction of ketones, the enantioselectivies were disappointingly low.[8] However, mixtures of 0.1 equiv of β-hydroxysulfoximines **2** bearing an unsubstituted sulfoximine nitrogen, and 1.2 equiv of BH_3-dimethyl sulfide (DMS) complex in toluene effected rapid and complete reduction of a variety of prochiral ketones, giving the corresponding secondary alcohols as the only observed products in high yields (75-85%) with good enantiomeric excesses (up to 93% ee; Table). The reaction is fast at ambient temperature, but in order to achieve high enantioselectivities slow addition[9] of the ketone to the reducing mixture is essential. Thus, the reduction of acetophenone with BH_3·DMS in the presence of 10 mol% of (*S*)-**2a** gives (*R*)-1-phenylethanol with 76% ee when a toluene solution of the ketone is slowly added to a mixture

of borane and catalyst over a period of 3 h. In contrast, rapid mixing of all the reagents followed by quenching and workup after 10 min results in the formation of the alcohol with only 42% ee. The best results are obtained when the reaction is carried out at ambient temperature. Higher or lower temperatures (+70 or -10°C, respectively) result in decreased enantioselection. A catalytic amount less than 0.1 equiv of **2** gives the alcohol with lower enantiomeric excess (for **2b**: 0.05 equiv: 62% ee; 0.01 equiv: 38% ee), probably a consequence of competing noncatalyzed reductions by achiral borane complexes. After the reaction **2** is easly and efficiently recovered unchanged. The table summarizes the results obtained for a variety of ketones.[10] α-Haloacetophenones and protected α-hydroxy ketones gave the best results affording the corresponding reduced products in up to 84 and 93% ee, respectively. Highly reactive ketones[11] (entry 10) show much lower enantioselectivities presumably due to competition from the uncatalyzed reduction.[12]

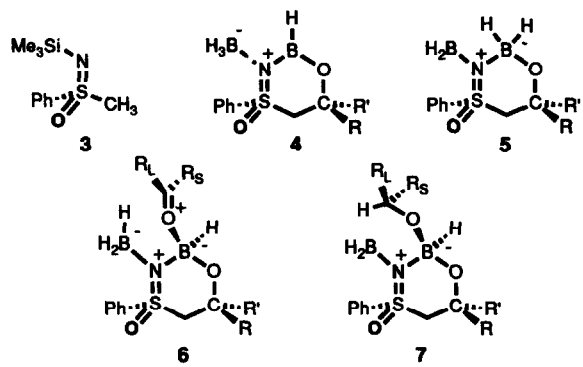
Table. Enantiomeric excesses resulting from catalyzed borane reductions of ketones using (*S*)-**2**



entry	ketone[a]	sulfoximine	% ee[b]	config[c]
1	$C_6H_5COCH_3$	**2a**	76	(*R*)
2	$C_6H_5COCH_2CH_3$	**2a**	73	(*R*)
3	$C_6H_5(CH_2)_2COCH_3$	**2a**	70	(*R*)
4	$C_6H_5COCH_2Cl$	**2a**	84	(*S*)
5	$C_6H_5COCH_2Br$	**2a**	81	(*S*)
6	$C_6H_5COCH_2O$-DMTr[d]	**2a**	93	(*S*)[e]
7	$C_6H_5COCH_2OSiPh_2t$-Bu	**2a**	92	(*S*)[e]
8	1-Indanone	**2a**	52	(*R*)
9	3-Acetylthiophene	**2a**	60	(*R*)[f,g]
10	$C_6H_5COCCl_3$	**2a**	8	(*R*)[g]
11	$C_6H_5COCH_3$	**2b**	70	(*R*)
12	$C_6H_5COCH_3$	**2c**	73	(*R*)
13	$C_6H_5COCH_3$	**2d**	74	(*R*)
14	$C_6H_5COCH_3$	**2e**	61	(*R*)

[a] All ketones were commercially available except entries 6, 7 (Ref. 3d for α-hydroxy ketone) and 10 (Wyvratt, J. M.; Hazen, G., G.; Weinstock, L. M. *J. Org. Chem.* **1987** , *52*, 944. Gallina, C.; Giordano, C. *Synthesis* **1989** , 466.). [b] Enantiomeric excesses were determined by HPLC or GC analysis with the exception of entries 6 and 7: ^{1}H NMR analysis of the bis-MTPA esters of the corresponding diols. [c] The absolute configurations were determined by comparison of optical rotations with literature values. [d] RO-DMTr = RO-CPh(*p*-$MeOC_6H_4)_2$ [e] Isolated as diols. [f] Absolute configuration was not determined in this case but was tentatively assigned based on mechanism. [g] Use of catecholborane under slightly modified reaction conditions gave alcohols of 67% ee (*R*) (entry 9) and 63% ee (*S*) (entry 10).

Optically active sulfoximines are readily available in both enantiomeric forms and several methods have been developed for the preparation of *N*-protected and *free* functionalized derivatives.[13] The *N*-unsubstituted β-hydroxysulfoximines **2** were synthesized in good yields by lithiation of optically active *N*-silyl-protected sulfoximine **3** followed by reaction of the resulting anion with a ketone and desilylation by methanolysis.[14] The results obtained in the borane reduction of acetophenone catalyzed by β-hydroxysulfoximines **2a-e** (Table; entries 1, 11-14) indicate that the substituents R and R' in the catalyst precursor have only a minor influence on the enantioselectivity. With the exception of **2e**,[15] all the compounds afford the corresponding alcohol with the same absolute stereochemistry and optical purities in the range of 70 - 76% ee. This is in contrast to the observations made with catalysts derived from *N*-alkylated β-hydroxysulfoximines **1** where the absolute configuration and the extent of enantioselectivity is highly dependent on the substituents at the β-carbon.[5,8]



Upon treatment of β-hydroxysulfoximine **2c** with an excess of BH_3·DMS at room temperature 2 equiv of hydrogen are evolved. Although the precise nature of the reducing species and its reaction mode are unknown, we tentatively suggest the formation of complexes of type **4**[16] and **5**. The substituents at the chiral sulfur atom dictate the conformation of the six-membered heterocycle in which the steric requirements of the phenyl group and the electronic properties of the sulfoximine oxygen direct the coordination of the ketone towards the less hindered β-face of the catalyst. A mechanism analogous to that proposed by Corey, for the catalytic asymmetric reduction by oxazaborolidines derived from β-amino alcohols via assembly **6**,[17] then explains the observed absolute stereochemistry of **7**[18] and the minor influence of substituents R and R' on the observed enantioselectivity.

Acknowledgement: We are grateful to the Schweizerischen Nationalfonds and the Ciba-Stiftung for financial support of this work. We also thank the Fonds der Basler Chemischen Industrie for a predoctoral fellowship for M.F., and J. Müller for preliminary investigations and stimulating discussions.

References and Notes:

1. New address: Fachbereich Chemie, Universität Marburg, Hans-Meerwein-Straße, D-35043 Marburg, Germany.
2. Reviews: a) Singh, V. K. *Synthesis* **1992**, 605. b) Nishizawa, M.; Noyori, R. In *Comprehensive Organic Synthesis;* Trost, B.; Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 8; pp 159. c) Brown, H. C.; Ramachandran, P. V. *Acc. Chem. Res.* **1992**, *25*, 16. d) Brown, H. C.; Park, W. S.; Cho, B. T.; Ramachandran, P. V. *J. Org. Chem.* **1987**, *52*, 5406. e) Midland, M. M. *Chem. Rev.* **1989**, *89*, 1553.
3. Reviews: a) Wallbaum, S.; Martens, J. *Tetrahedron: Asymmetry* **1992**, *3*, 1475. b) Corey, E. J. *Pure Appl. Chem.* **1990**, *62*, 1209. c) Lohray, B. B.; Bhushan, V. *Angew. Chem.* **1992**, *104*, 740; *Angew.*

Chem. Int. Ed. Engl. **1992**, *31*, 729. d) For a summary of very early work: Itsuno, S.; Nakano, M.; Miyazaki, K.; Masuda, H.; Ito, K.; Hirao, A.; Nakahama, S. *J. Chem. Soc., Perkin Trans 1* **1985**, 2039.

4. a) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C. -P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925. b) Corey, E. J.; Link, J. O. *Ibid.* **1992**, *114*, 1906. c) Corey, E. J.; Link, J. O. *Tetrahedron Lett.* **1992**, *33*, 3431. d) Corey, E. J.; Azimioara, M.; Sarshar, S. *Ibid.* **1992**, *33*, 3429 and references of earlier work by the Harvard group cited therein. e) Jones, T. K.; Mohan, J. J.; Xavier, L. C.; Blacklock, T. J.; Mathre, D. J.; Sohar, P. Turner Jones, E. T.; Reamer, R. A.; Roberts, F. E.; Grabowski, E. J. J. *J. Org. Chem.* **1991**, *56*, 763. f) DeNinno, M. P.; Perner, R. J.; Morton, H. E.; DiDomenico, S. *Ibid.* **1992**, *57*, 7115.
5. Johnson, C. R.; Stark, C. J. *Tetrahedron Lett.* **1979**, 4713.
6. For sulfoximine-metal complexes in asymmetric alkylations: a) Bolm, C.; Müller, J.; Schlingloff, G.; Zehnder, M.; Neuburger, M. *J. Chem. Soc., Chem. Commun.* **1993**, 182. b) Bolm, C.; Felder, M.; Müller, J. *Synlett* **1992**, 439.
7. *N*-Alkylated derivatives **1a,b** were prepared following the procedure given in: Johnson, C. R.; Lockard, J. P.; Kennedy, E. R. *J. Org. Chem.* **1980**, *45*, 264. General procedure for the synthesis of *N*-alkylated β-hydroxy sulfoximines: Johnson, C. R.; Stark, C. J. *J. Org. Chem.* **1982**, *47*, 1193.
8. For the reduction of acetophenone at room temperature using 0.1 equiv of (*S*)-**1a**: 10% ee (*S*); (*S*)-**1b**: 28% ee (*R*).
9. Following a recommendation given in: Wai, J. S. M.; Markó, I.; Svendsen, J. S.; Finn, M. G.; Jacobsen, E. N.; Sharpless, K. B. *J. Am. Chem. Soc.* **1989**, *111*, 1123.
10. **Typical Procedure.** To a well-stirred suspension of β-hydroxysulfoximine (*S*)-**2a** (0.068 g, 0.2 mmol) in toluene (4 ml) at room temperature was added BH_3·DMS (0.182 g, 2.4 mmol) under Ar. A solution of 2-chloroacetophenone (0.309 g, 2 mmol) in toluene (1 ml) was added slowly via a gas-tight syringe controlled by a syringe pump to the catalyst solution over a period of 3 h. The mixture was stirred for an additional 10 min and then hydrolyzed by the addition of 1 N aqueous HCl solution (3 ml). Water (ca. 10 ml) was added, and after separation of the layers the aqueous phase was extracted three times with ethyl acetate (20 ml). The combined organic extracts were washed with 2 N aqueous NaOH (20 ml) and brine (10 ml), dried over anhydrous Na_2SO_4, filtered, and then concentrated under reduced pressure. The residue was flash column chromatographed (silica gel, 7-10 g; eluent: petroleum ether - ethyl acetate, 7:1 v/v), affording 0.266 g (85% yield) of (*S*)-2-chloro-1-phenylethanol. The enantiomeric excess was determined to be 82% ee by HPLC analysis (Daicel Chiralcel OD); $[\alpha]^{25}_D$ +41° (*c* 3.11, cyclohexane). Hartgerink, J. W.; et al. [*Tetrahedron* **1971**, *27*, 4323] reported $[\alpha]^{25}_D$ -47.8° (*c* 2.8, cyclohexane) for the *R*-isomer. The use of freshly recrystallized ketone gave the alcohol with 84% ee.
11. Compare: a) Corey, E. J.; Link, J. O.; Sarshar, S.; Shao, Y. *Tetrahedron Lett.* **1992**, *33*, 7103. b) Corey, E. J.; Link, J. O.; Bakshi, R. K. *Ibid.* **1992**, *33*, 7107.
12. Preliminary studies indicate that in these cases the ee can be raised by the use of catecholborane as stoichiometric reductant.
13. Reviews: a) Johnson, C. R. *Aldrichim. Acta* **1985**, *18*, 3. b) Johnson, C. R. *Acc. Chem. Res.* **1973**, *6*, 341. c) Barbachyn, M. R.; Johnson, C. R. In *Asymmetric Synthesis*; *Vol. 4*, Morrison, J. D.; Scott, J., Eds.; Academic Press: New York, 1984; pp 227. d) Johnson, C. R. In *Comprehensive Organic Chemistry*; *Vol. 3*, Barton, D.; Ollis, W. D., Eds.; Pergamon Press: Oxford, 1979; pp 223. e) Oae, S.; Furukawa, N. *Sulfilimines and Related Derivatives*, ACS Monograph 179; American Chemical Society: Washington, 1983; pp 297.
14. The preparation of **3** and its lithiation were carried out using slight modifications to published procedures: a) Hwang, K. -J. *J. Org. Chem.* **1986**, *51*, 99. b) Hwang, K. -J.; Logusch, E. W.; Brannigan, L. H.; Thompson, M. R. *Ibid.* **1987**, *52*, 3435.
15. The relative configuration of (*SS*, 2*S*)-**2e** was determined by X-ray diffraction analysis.
16. A related boron-containing cyclic compound has been prepared by condensation of **2b** an phenylboronic acid (Bolm,C.; Müller, J. unpublished results). Its molecular structure was analyzed by X-ray diffraction and showed the ψ-axial and ψ-equatorial substituents at the sulfur atom in an overall almost planar arrangement.
17. Reduction from the *si* face of the ketone is also a consequence of the preferred complexation of the Lewis acid *anti* to the larger substituent R_L of the carbonyl compound: a) Reetz, M. T.; Hüllman, M.; Massa, W.; Berger, S.; Rademacher, P.; Heymann, P. *J. Am. Chem. Soc.* **1986**, *108*, 2405. b) Review: Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *Angew. Chem.* **1990**, *102*, 273; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 256.
18. The formation of the observed enantiomer could also be a result of the proposed hydride transfer via a chair transition state. Jones, D. K.; Liotta, D. C.; Shinkai, I.; Mathre, D. J. *J. Org. Chem.* **1993**, *58*, 799.

(Received in Germany 5 July 1993; accepted 26 July 1993)