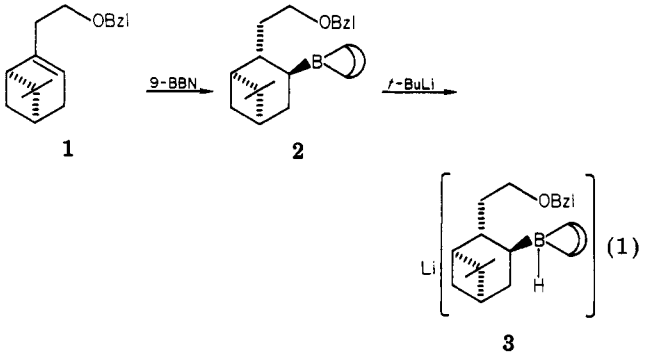
NB-Enantride, a New Chiral Trialkylborohydride for the Asymmetric Reduction of Ketones

Summary: NB-Enantride, prepared by hydroboration of nopol benzyl ether with 9-borabicyclo[3.3.1]nonane (9-BBN) followed by treatment with *tert*-butyllithium, is a new asymmetric reducing agent which is especially effective for aliphatic ketones such as 2-butanone.

Sir: One of the easiest methods for the preparation of optically active alcohols is the asymmetric reduction of prochiral ketones. Among other methods[1] this transformation may be achieved by the use of metal hydrides in which chiral organic moieties are ligated to the metal. The use of chirally modified metal hydrides for the reduction of prochiral ketones continues to be actively studied, and high asymmetric reductions have been reported in individual cases.[2] Most of the effective reagents are derived from modifications of lithium aluminum hydride. Only limited success has been achieved for borohydride derived reagents.[3] For example, lithium *B*-(isopinocampheyl)-9-borabicyclo[3.3.1]nonane hydride (Alpine-hydride) reduced ketones to *R* alcohols of modest (3–37% ee) enantiomeric purity.[4] This lack of enantioselectivity is very surprising in view of the very high stereoselectivities obtained with trialkylborohydrides such as L-Selectride.

We have observed that the 9-BBN derivative of nopol benzyl ether[5] (1), NB-Enantrane (2), can be successfully used in the asymmetric reduction of α,β-acetylenic ketones.[6] The *S* propargyl alcohols are obtained in 86–96% ee. Since the organoborane is readily available, we undertook an investigation of the corresponding hydride, 3 (NB-Enantride), for asymmetric reductions. We felt that



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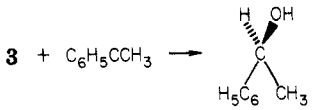
incorporation of an oxygen into the chiral ligand would provide a fixed coordination site for the lithium and hence to a more rigid and thus more sterically demanding transition state.[7]

Table I. Asymmetric Reductions of Ketones with NB-Enantride

ketone	% ee[a]	ketone	% ee[a]
acetophenone	70 (*S*)	3,3-dimethyl-2-butanone	2 (*S*)
α,α,α-trifluoroacetophenone	50 (*R*)[b]	4-methyl-2-pentanone	30 (*S*)
butyrophenone	54 (*S*)	3-methyl-2-butanone	68 (*S*)
β-ionone	20 (*S*)	2-butanone	76 (*S*)
4-heptyn-3-one	30 (*R*)	2-octanone	79 (*S*)
4-phenyl-3-butyn-2-one	10 (*S*)		

[a] Determined by NMR analysis using $Eu(dcm)_3$. The absolute configuration was determined by comparison of the sign of rotation to literature values. [b] The enantiomeric excess was determined by HPLC using a Pirkle column: Pirkle, W. H.; Finn, J. M. *J. Org. Chem.* **1981**, *46*, 2935.

The reduction of acetophenone at −78 °C with NB-Enantride prepared from commercial nopol gave (*S*)-1-phenylethanol in 57% ee[8] (eq 2). Much better results



(2)

(70% ee[9]) were obtained by using purified nopol[10] and performing the reaction at −100 °C. The results were very encouraging since the corresponding reduction with Alpine-hydride provides only a 17% ee.[4] While there are several reagents which will achieve this level of asymmetric induction, the ease of preparation of the NB-Enantride makes it an attractive reagent.

One of the major drawbacks of all chiral metal hydride reducing agents is that they are effective only for aromatic ketones. Thus the highly effective chiral binaphthyl/lithium aluminum hydride reagent reduces 2-octanone in only 24% ee.[2a] These results are to be expected in light of the proposed mechanism for asymmetric reductions which requires a dovetailing of large and small groups on the reducing agent and carbonyl.[11] Since a methyl and a straight-chain alkyl group have virtually the same steric size, the two faces of the carbonyl cannot be distinguished. We thus investigated the reduction of 3,3-dimethyl-2-butanone which has a large steric difference in the two groups flanking the carbonyl. Surprisingly only a 2% ee was obtained. Fortunately, the reductions of 2-butanone and 2-octanone were also investigated, and asymmetric inductions of 76 and 79% ee were obtained. Examination

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(4) Krishnamurthy, S.; Vogel, F.; Brown, H. C. *J. Org. Chem.* **1977**, *42*, 2534.

(5) Nopol (6,6-dimethylbicyclo[3.1.1]hept-2-ene-2-ethanol) is commercially available from Aldrich Chemical Co. It is converted to the benzyl ether by treatment with 1.25 equiv of sodium hydride in dimethoxyethane followed by benzyl chloride (1.5 equiv) and then refluxed overnight. Distillation gives an 80% yield: bp 112–114 °C (0.025 mm); $[\alpha]^{20}_D$ −27.8° (*c* 10, $CHCl_3$).

(6) Midland, M. M.; Kazubski, A., *J. Org. Chem.*, in press.

(7) This hypothesis proved to be fortuitous since the compound derived from myrtenol benzyl ether, with one less carbon in the side chain, was ineffective in reduction of acetophenone (15% ee).

(8) A variety of other nopol ethers (methyl, MEM, THP, TBDMS) as well as an amine derivative (pyrrolidine) were also tried. These usually gave poorer results.

(9) By NMR using a chiral shift reagent. The material gave a rotations of $[\alpha]^{25}_D$ −32.6° (neat) and $[\alpha]^{25}D$ −37.15 (*c* 2.6 cyclopentane). Literature values are $[\alpha]^{21}_D$ 43.5° (neat) (MacLeod, R.; Welch, F. J.; Mosher, H. S. *J. Am. Chem. Soc.* **1960**, *82*, 876) and $[\alpha]_D$ 43.1° (*c* 7, cyclopentane) (Yamaguchi, S.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 1870). These values correspond to optical purities of 75% and 86%, respectively.

(10) Commercial nopol gives a rotation of $[\alpha]^{20}_D$ −37.45° (neat, d = 0.9602). This was purified by the following procedure. Nopol phthalate was prepared by refluxing nopol and phthalic anhydride in toluene for 3 h [74% yield; mp 80–81 °C; $[\alpha]^{20}_D$ −27.15° (*c* 10, $CHCl_3$)]. The (−)-α-methylbenzylamine salt was prepared in acetone and recrystallized from acetonitrile/methanol (10:1) [mp 138–139 °C; $[\alpha]^{20}_D$ −21.32° (*c* 3, $CHCl_3$)]. The regenerated nopol gave a rotation of $[\alpha]^{20}_D$ −39.96° (neat). We are currently working on methods to improve the resolution.

(11) Reference 1a, Chapter 5.

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of other ketones revealed a trend of decreasing asymmetric induction with increasing size of the alkyl group. These results as well as results for other ketones are presented in Table I.

The reduction products were generally isolated in 70–80% yield. In most cases the *S* alcohol was obtained. Thus the reduction occurs as depicted in eq 2 with the sterically larger group occupying the phenyl position. In the case of α,α,α-trifluoroacetophenone and 4-heptyn-3-one the *R* enantiomer is produced since the priorities of the sterically small and large groups are reversed. (However, with 4-phenyl-3-butyn-2-one the reduction does occur in the opposite steric sense.) The hydride thus gives the opposite configuration of that obtained with the corresponding borane. Thus the NB-Enantride gives (*S*)-phenylethanol while the Alpine-borane prepared from (−)-α-pinene would give the *R* enantiomer.[12]

The following procedure is typical. An oven-dried, 50-mL, round-bottomed flask equipped with a septum-capped side arm, magnetic stirring bar, reflux condenser, and stopcock adaptor connected to a mercury bubbler was assembled while hot and flushed with a stream of nitrogen. Then 10.64 mL (5 mmol) of a 0.47 M THF solution of 9-BBN was added by a syringe followed by a solution of 1.408 g (5.5 mmol) of nopol benzyl ether in 5 mL of THF. The solution was refluxed overnight and cooled to a room temperature, and 5 mL of dry diethyl ether and 5 mL of dry pentane were added. The mixture was cooled to −78 °C (dry ice–acetone bath), and 3.95 mL (5 mmol) of a 1.27 M pentane solution of *tert*-butyllithium was introduced dropwise. The resulting slightly yellow solution was stirred for 0.5 h at −78 °C, and then it was added dropwise by using a double-ended needle.[13] to a solution of 0.577 g (4.5 mmol) of 2-octanone in 40 mL of a THF/Et_2O/pentane (4:1:1) mixture in a 100 mL reaction flask cooled to −100 °C [petroleum ether (30–60 °C)/isopropyl alcohol/acetone (4:1:1)/liquid N_2 bath].[14] After the addition, the reaction mixture was stirred at −100 °C for 3 h. The excess of hydride was then destroyed by an addition of 1-mL of ethanol, and the solution was brought to the room temperature. The organoborane was oxidized (1.7 mL of 3 M sodium hydroxide, 1.2 mL of 30% hydrogen peroxide, 1 h at 40–50 °C) and the mixture saturated with anhydrous potassium carbonate. The organic phase was separated, the aqueous phase was extracted with ether, and the combined extracts were dried over anhydrous potassium carbonate. After evaporation of the solvents, the crude mixture was partially purified by Kugelrohr distillation (pot temperature 140 °C, 2.5 mm) and finally by column chromatography[15] over silica gel (70–200 mesh) with hexane/ether (5:1). Thus 0.446 g (76% yield) of 2-octanol [bp 80 °C (27 mm, Kugelrohr distillation); $[\alpha]^{25}_D$ +7.33° (neat, d = 0.838) [lit.[16] $[\alpha]^{25}_D$ +9.57° (neat)]] was obtained. Examination of the NMR specturm in the presence of tris(dicampholylmethanato)europium(III) [Eu(dcm)$_3$][17] indicated an enantiomeric mixture of 89.5% *S* and 10.5% *R* (79% ee).[18]

In conclusion, NB-Enantride is a new and very attractive reducing agent for the asymmetric reductions of ketones. Its high efficiency in the case of straight-chain aliphatic ketone reductions is noteworthy. The cause of this remarkable selectivity remains to be explored.

Editor's Note: This paper was originally scheduled to appear in the April 9, 1982 issue along with the communication by Brown and Pai (ref 12). Due to an error in our office, this did not occur. We apologize for the delay in publication.

Acknowledgment. We thank the National Institutes of Health (Grant No. GM-24517) for support of this work. We thank Professor R. Noyori for data on the absolute configuration of β-ionol and Professors J. D. Morrison and H. S. Mosher for calling our attention to the structure of nopol. NB-Enantrane, NB-Enantride, Alpine-borane, Alpine-hydride, and L-Selectride are trademarks of Aldrich Chemical Company.

Registry No. 1, 74851-17-5; 3, 81572-37-4; (*S*)-1-phenylethanol, 1445-91-6; (*R*)-α-(trifluoromethyl)benzyl alcohol, 10531-50-7; (*S*)-1-phenyl-1-butanol, 22135-49-5; (*S*)-β-ionol, 81600-95-5; (*R*)-4-heptyn-3-ol, 81555-85-3; (*S*)-4-phenyl-3-butyn-2-ol, 81555-86-4; (*S*)-3,3-dimethyl-2-butanol, 1517-67-5; (*S*)-4-methyl-2-pentanol, 14898-80-7; (*S*)-3-methyl-2-butanol, 1517-66-4; (*S*)-2-butanol, 4221-99-2; (*S*)-2-octanol, 6169-06-8; acetophenone, 98-86-2; α,α,α-trifluoroacetophenone, 434-45-7; butyrophenone, 495-40-9; β-ionone, 14901-07-6; 4-heptyn-3-one, 32398-68-8; 4-phenyl-3-butyn-2-one, 1817-57-8; 3,3-dimethyl-2-butanone, 75-97-8; 7-methyl-2-pentanone, 108-10-1; 3-methyl-2-butanone, 563-80-4; 2-butanone, 78-93-3; 2-octanone, 111-13-7; nopol, 35836-73-8; nopol phthalate, 81555-87-5; nopol phthalate (−)-α-methylbenzylamine, 81601-67-4; 9-BBN, 280-64-8.

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(15) In the case of low-boiling alcohols, distillation under atmospheric pressure was used. The alcohol was then purified by preparative gas chromatography.
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(17) McCreary, M. D.; Lewis, D. W.; Wernick, D. L.; Whitesides, G. M. *J. Am. Chem. Soc.* **1974**, *96*, 1038.
(18) When unpurified nopol was used, material of 66% ee was obtained.
(19) Alfred P. Sloan Foundation Fellow, 1978–1982.

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Reaction of 2-Methoxyethyl Hemiacetals with Allylsilanes in the Presence of Titanium Tetrachloride: Regioselective C–O Bond Cleavage of the Unsymmetrical Acetals

Summary: Reaction of 2-methoxyethyl hemiacetals with allylsilanes in the presence of titanium tetrachloride gave the corresponding homoallyl ethers in good yields by the regioselective C–O bond cleavage of the hemiacetals. A new carbon-homologative cyclization was described as an application of this selective reaction. Furthermore, the information obtained from this study made clear the exact mode of the cleavage of (2-methoxyethoxy)methyl (MEM) ether; titanium tetrachloride should facilitate the elimination of the methoxyethoxy group from the MEM ether by an effective bidentate chelation.

Sir: It has been elaborated considerably that symmetrical acetals react with allylsilanes in the presence of Lewis acids to give homoallyl ethers.[1] We report here the regiose-

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