Table IV. $^1$H NMR Data Relevant to Stereochemical Assignment (500 MHz, $CDCl_3$, δ)

| compd | H-2 | $J_{2,3}$, Hz | $H_{3,4}$ | H-6 | $CH_2$ |
|---|---|---|---|---|---|
| **16** | 6.31-6.33 | 1.0 | 6.10-6.19 | 4.05-4.17 | 3.44-3.57 |
| **20** | 5.09-5.11 | 1.56 | $H_3$, 6.04-6.07; $H_4$, 5.89-5.93 | 3.94-3.98 | 3.47-3.54 |
| **21** | 5.30 (whh = 6 Hz) | 1.83 | 5.99-6.61 | 3.75-3.80 | 3.34-3.46 |
| **22** | 4.71 (whh = 9 Hz) | 2.16 | $H_3$, 5.85-5.89; $H_4$, 5.69-5.73 | 3.82-3.87 | 3.36-3.50 |

to extend the scope of this reaction to substituted enol ethers and to other carbanions are in progress, including intramolecular examples. The extent of double-bond migration and the overall stereoselectivity will be determined.

The other method which was investigated was the Pd(0)-catalyzed alkylation of acetoxydihydropyrans. Dihydropyranyl acetates **15** and **16** were prepared by a modification of the method of Hurd and Edwards, using $Pb(OAc)_4$.[24] In a typical experiment **15** was treated with diethyl sodioformamidomalonate (**1**; 1 equiv) in the presence of $Pd(PPh_3)_4$ (0.1 equiv) and $PPh_3$ (1 equiv) in dry DMF under argon at 70 °C for 18 h to give 2-[formamidobis(ethoxycarbonyl)methyl]-5,6-dihydro-2*H*-pyran (**17**) in 83% yield after column chromatography.[25-27] Similarly, adducts **18–22** were prepared and the results are shown in Table II.[17] No products derived from carbanion attack at C-4 were observed. The stereoselectivity in the alkylation of *cis*-(methoxymethyl)dihydropyranyl acetate **16**[28] to give **20** occurred with net retention via the same double inversion observed by Trost and co-workers in both cyclic and acylic examples.[25,26] In contrast, the alkylation of **16** with phenylzinc chloride or vinylzinc chloride in the presence of 0.05 equiv of $Pd(PPh_3)_4$ in THF to give **21** or **22** occurred with inversion similar to that observed by Negishi and co-workers for cyclic allylic acetates.[29,30] The stereochemical assignments of products **20–22** were made on the basis of their $^{13}$C and $^1$H NMR spectra as shown in Tables III and IV. A very important criterion is the $^{13}$C NMR γ effect rule which assigns the less shielded C-6 to the cis isomer.[7]

These initial palladium-assisted alkylations of dihydropyranylacetates are completely regioselective and highly stereoselective, and the stereoselectivity thus far observed is identical with that observed for alkylations of carbocyclic allylic acetates. Experiments to extend the scope of this reaction to other substituted acetoxydihydropyrans and to other carbanions are in progress, including applications to the synthesis of *C*-glycoside-containing natural products.

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**Registry No.** **1**, 59227-56-4; **2**, 30412-43-2; **3**, 72071-39-7; **4**, 18424-77-6; **5**, 81790-57-0; **6**, 996-82-7; **7**, 18424-76-5; **8**, 81790-58-1; **9**, 81790-59-2; **10**, 81790-60-5; **11**, 81790-61-6; **12**, 81790-62-7; **13**, 54362-89-9; **14**, 81790-63-8; **15**, 52416-79-2; **16**, 81790-64-9; **17**, 81802-28-0; **18**, 81790-65-0; **19**, 81790-66-1; **20**, 81790-67-2; **21**, 81790-68-3; **22**, 81790-69-4; **23**, 81790-70-7; $Pd(CH_3CN)_2Cl_2$, 14592-56-4; $Pd(PPh_3)_4$, 14221-01-3; $C_6H_5ZnCl$, 28557-00-8; $CH_2$=$CHZnCl$, 78389-90-9; dihydrofuran, 1191-99-7.

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(27) Approximately 15% of 4-acetoxy-3,4-dihydro-2*H*-pyran formed in the allylic oxidation of dihydropyran could be conveniently removed by chromatography after the alkylation step. This suggests that allylic isomerization of **16** does not occur under the reaction conditions.
(28) Compound **16** was prepared as follows from 2-formyl-3,4-dihydro-2*H*-pyran:[31] (1) $NaBH_4$, $CH_3CH_2OH$, -5 °C[32]; (2) NaH, THF, $CH_3I$; (3) $Pb(OAc)_4$, PhH;[24] 40% overall yield. The $Pb(OAc)_4$ oxidation to give **16** was greater than 80% regioselective. In addition, this cis stereoselective allylic acetoxylation greatly enhanced the synthetic utility of this reaction. Additional examples which further define the stereoselectivity and mechanism of $Pb(OAc)_4$ oxidation of dihydropyrans will be the subject of a forthcoming paper (Dunkerton, L. V.; Serino, A. J., manuscript to be submitted for publication).
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## Reduction of α,β-Acetylenic Ketones to (*S*)-Propargyl Alcohols of High Enantiomeric Purity

*Summary:* (*S*)-Propargyl alcohols may be obtained in 86–96% enantiomeric purity by asymmetric reduction of α,β-acetylenic ketones with the 9-borabicyclo[3.3.1]nonane (9-BBN) adduct of nopol benzyl ether.

*Sir:* Optically-active propargyl alcohols are very useful precursors and intermediates in synthetic organic chemistry. The acetylene unit provides a convenient handle which may be transformed into a variety of functionalities. Thus propargyl alcohols have been used successfully in the synthesis of alkaloids,[1] pheromones,[2] prostaglandins,[3]

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0022-3263/82/1947-2814$01.25/0 

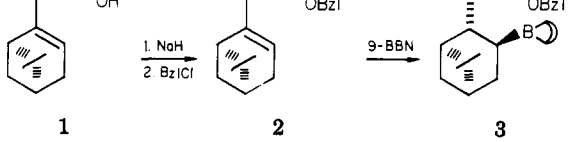
Table I. Reduction of α,β-Acetylenic Ketones with NB-Enantrane

| ketone RCOC≡CR′ | | | |
|---|---|---|---|
| R | R′ | % yield[a] | % ee[b] |
| $n$-$C_5H_{11}$ | H | 74 | 95 |
| $n$-$C_5H_{11}$ | $CH_3$ | 79 | 91 |
| $n$-$C_5H_{11}$ | $Si(CH_3)_3$ | 81[c] | 96 |
| $C_2H_5$ | $C_2H_5$ | 77 | 94 |
| cyclohexyl | $n$-$C_5H_{11}$ | 84 | 96 |
| $CH_3$ | $C_6H_5$ | 87 | 86 |
| $n$-$C_5H_{11}$ | $CO_2C_2H_5$ | 74 | 91 |

[a] Isolated yield. [b] Determined by analysis of the $Eu(hfc)_3$ shifted NMR spectrum. [c] During the oxidative workup the trimethylsilyl group was removed.

steroids,[4] and vitamins.[5] The most convenient method for the preparation of optically-active secondary propargyl alcohols is the asymmetric reduction of α,β-acetylenic ketones.[6] We have recently reported a highly effective and mild method for achieving these asymmetric reductions using *B*-3-pinanyl-9-BBN[6a] (Alpine-borane).[7] Starting with Alpine-borane derived from (+)-α-pinene one obtains the *R* enantiomer of the propargyl alcohol. The opposite enantiomer may be obtained by using Alpine-borane prepared from (−)-α-pinene. Both (+)- and (−)-α-pinene are commercially available. However, (−)-α-pinene is rather expensive and of lower optical purity[8] (approximately 82% ee). Since the limiting factor in obtaining high enantiomeric excesses with Alpine-borane is often the optical purity of the α-pinene, we have sought methods to improve the preparation of *S* alcohols.

We have examined the structurally related nopol[9] (1) as a low-cost alternative to (−)-α-pinene. Nopol was converted into the benzyl ether[10] (2) and hydroborated with 9-BBN to give the borane (3; NB-Enantrane).[11] Hydro-




1 2 3

boration of the nopol benzyl ether is slow in comparison to hydroboration of α-pinene but can be completed upon reflux in tetrahydrofuran (THF) overnight.

Reductions of α,β-acetylenic ketones[12] with NB-Enantrane are slow in comparison to Alpine-borane reductions. Nevertheless, complete reduction can be accomplished in 24–48 h at room temperature by using a twofold excess of organoborane and running the reaction without solvent.[13] Asymmetric inductions obtained in these reductions, using commercial nopol as a starting material, were about 85–89%. For example, 1-octyn-3-one was reduced to (*S*)-1-octyn-3-ol in 89% ee. Upon examination it was found the commercial nopol is approximately 94% optically pure.[14] We have found that it is possible to improve the optical purity of nopol of recrystallization of nopol as the (−)-α-methylbenzylamine salt of the half phthalate derivative.[15]

A series of α,β-acetylenic ketones were examined with the purified nopol borane (Table I). In general, both chemical and enantiomeric yields are high. In each case the (*S*)-propargyl alcohol is obtained. The reductions thus fit the steric model proposed for Alpine-borane reductions.[6a]

The following procedure is representative. An oven-dried, 50-mL, round-bottom 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.[16] Then 10.64 mL (5 mmol) of a 0.47 m THF solution of 9-BBN was added by 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. The THF was then evaporated by applying a water aspirator and stirring vigorously as a stream of nitrogen was passed over the solution. The flask was then filled with nitrogen and 0.275 g (2.5 mmol) of 4-heptyn-3-one was added. The slightly yellow mixture was stirred for 48 h at room temperature. Then, 0.43 mL (6 mmol) of freshly distilled propionaldehyde was added and the mixture stirred overnight.[17] The solution was diluted with 10 mL of dry THF and the organoborane oxidized[18] (1.7 mL of 3 M sodium hydroxide solution, 1.2 mL of 30% hydrogen peroxide, 2 h, 40–50 °C). After saturation with anhydrous potassium carbonate, the organic phase was separated, the water layer was extracted with ethyl ether, and the combined extracts were dried over anhydrous potassium carbonate. After evaporation of the solvents, the crude mixture was partly purified by a Kugelrohr distillation (pot temperature 150 °C, at 54 mm) and finally by column chromatography over silica gel (70–200 mesh), using hexane/diethyl ether (6:1). Thus, 0.215 g (76.8%) of 4-hep-

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(7) Alpine-borane is a trademark of Aldrich Chemical Co.

(8) Commercial (+)-α-pinene is generally 92% optically pure. It may be purified to nearly 100% optical purity (Brown, H. C.; Yoon, N. M. *Isr. J. Chem.* **1976/1977**, *15*, 12). Other methods for obtaining high optical purity α-pinene are currently under investigation (Brown, H. C.; personal communication.

(9) Nopol, 6,6-dimethylbicyclo[3.1.1]hept-2-ene-2-ethanol, is available from Aldrich Chemical Co.

(10) Nopol was treated with 1.25 equiv of sodium hydride in dimethoxyethane followed by benzyl chloride (1.5 equiv) and then refluxed overnight. Distillation gave an 80% yield, bp 112–114 °C (0.025 mmHg), $[\alpha]^{20}_D$ −27.8° (*c* 10, $CHCl_3$).

(11) NB-Enantrane as well as the corresponding borohydride (NB-Enantride, Midland, M. M.; Kazubski, A. *J. Org. Chem.* **1982**, *47*, in press) are trademarks of Aldrich Chemical Co.

(12) Prepared by oxidation of the propargyl alcohols with Jones reagent.

(13) Brown, H. C.; Pai, G. G. *J. Org. Chem.* **1982**, *47*, 1606. We thank Professor Brown for informing us of his results using neat Alpine-borane.

(14) The starting nopol gave a rotation of $[\alpha]^{20}_D$ −37.45 (neat, $d$ = 0.9602). A maximum rotation of −40.1° has been calculated for nopol prepared from β-pinene of known optical purity. Thompson, K. L., personal communication.

(15) 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 $[\alpha]^{20}_D$ −39.36° (neat). We are currently working on methods to improve the resolution.

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(17) The propionaldehyde liberates the remaining nopol benzyl ether and thus minimizes contamination by other alcohols. The reaction is usually complete within 1 h.

(18) In the reduction of ethyl 4-oxo-2-nonynoate an alternate workup was used. Diethyl ether was added followed by ethanolamine to precipitate the 9-BBN adduct.[6a]

(19) A. P. Sloan Foundation Fellow, 1978–1982.

tyn-3-ol [bp 110 °C (45 mm); $[\alpha]^{20}_D$ -4.85 (c 4, $CHCl_3$)] was obtained. Examination of the NMR spectrum in the presence of tris[3-((heptafluoropropyl)hydroxymethylene)-d-camphorato]europium(III) ($Eu(hfc)_3$) indicated an enantiomeric mixture of 97.2% S and 2.8% R (94.4% ee).

In conclusion, NB-Enantrane is an attractive substitute for Alpine-borane prepared from (-)-α-pinene. Owing to its easy preparation from cheap and commercially available nopol, it can be used for the prepartion of (S)-propargyl alcohols in large quantities and high yield. Nopol benzyl ether liberated in the reduction may be easily isolated during purification of the product and recycled.

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**Registry No.** (-)-1, 35836-73-8; (-)-1 phthalate, 81555-87-5; (-)-1 phthalate α-methylbenzylamine salt, 81601-67-4; (-)-2, 74851-17-5; 3, 81971-15-5; 1-octyn-3-one, 27593-19-7; 2-nonyn-4-one, 81971-16-6; 1-(trimethylsilyl)-1-octyn-3-one, 53210-14-3; 4-heptyn-3-one, 32398-68-8; 1-cyclohexyl-2-octyn-1-one, 81971-17-7; 4-phenyl-3-butyn-2-one, 1817-57-8; ethyl 4-oxo-2-nonynoate, 72036-38-5; (s)-1-octyn-3-ol, 32556-71-1; (s)-2-nonyn-4-ol, 81077-11-4; (s)-4-heptyn-3-ol, 81971-18-8; (s)-1-cyclohexyl-2-octyn-1-ol, 81971-19-9; (s)-1-phenyl-1-octyn-3-ol, 81555-86-4; (s)-ethyl 4-hydroxy-2-nonynoate, 81971-20-2.

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## Enzyme-Catalyzed Organic Synthesis: NAD(P)H Cofactor Regeneration Using Ethanol/Alcohol Dehydrogenase/Aldehyde Dehydrogenase and Methanol/Alcohol Dehydrogenase/Aldehyde Dehydrogenase/Formate Dehydrogenase[1]

*Summary:* An enzyme-catalyzed system potentially applicable to large-scale synthesis is described.

*Sir:* We have recently described a number of methods for regeneration of NAD(P)H from $NAD(P)^+$ for use in enzyme-catalyzed organic syntheses requiring nicotinamide cofactors.[2-8] In this paper we compare two additional useful schemes, and apply these schemes to syntheses producing 0.1–0.5-mol quantities of products (Figure 1). The first method is based on catalysis by two enzymes—alcohol dehydrogenase (ADH, EC 1.1.1.1) and aldehyde dehydrogenase (AldDH, EC 1.2.1.5)—and converts ethanol to acetate. This scheme has been demonstrated previously

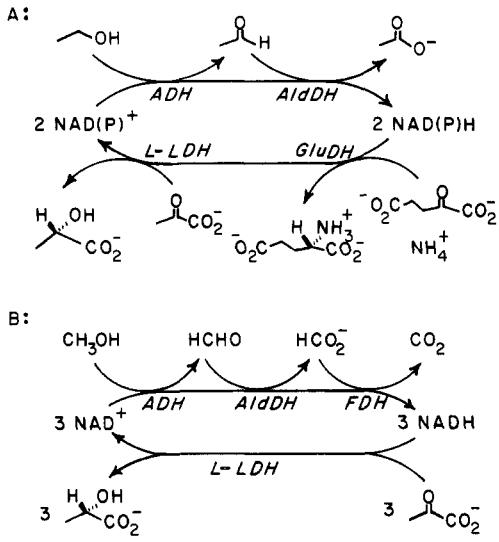


**Figure 1.** A: Regeneration of NAD(P)H using ethanol and alcohol dehydrogenase/aldehyde dehydrogenases. B: Regeneration of NADH using methanol and alcohol dehydrogenase/aldehyde dehydrogenase/formate dehydrogenase. Abbreviations: ADH, alcohol dehydrogenase from yeast (for NAD) or from *L. mesenteroides* (for NAD or NADP); AldDH, aldehyde dehydrogenase from yeast (for NAD or NADP); L-LDH, L-lactic dehydrogenase; GluDH, glutamic dehydrogenase; FDH, formate dehydrogenase.

in millimole-scale syntheses.[9,10] The second uses ADH, AldDH, and formate dehydrogenase (FDH, EC 1.2.1.2) and converts methanol to $CO_2$. The first generates 2 equiv of reduced nicotinamide cofactor/equiv of ethanol, and accepts either $NAD^+$ or $NADP^+$; the second generates 3 equiv of reduced nicotinamide cofactors/equiv of methanol but accepts only $NAD^+$. The relevant kinetic parameters for the enzymes in these schemes are summarized in Table I. The only feature of these parameters which requires specific comment concerns ADH: the enzyme from *Saccharomyces cerevisiae* has high specific activity with ethanol but is specific for $NAD^+$; that from *Leuconostoc mesenteroides* reduces both $NAD^+$ and $NADP^+$ but has lower specific activity.

In a representative procedure for NADH regeneration using ethanol as ultimate reducing agent (A, Figure 1), a 500-mL solution containing potassium pyruvate (15.1 g, 120 mmol), $NAD^+$ (50 μmol), ethanol (3.3 g, 70 mmol), and β-mercaptoethanol (39 mg, 0.5 mmol) was mixed with PAN-immobilized yeast ADH (90 units, 0.5 mL of gel),[11] AldDH (110 units, 10 mL of gel), and L-lactic dehydrogenase (L-LDH, 200 units, 0.5 mL of gel). The reaction mixture was stirred at 25 °C under argon, and the pH of the solution was controlled automatically at 8.0–8.2 by adding 2 N KOH through a peristaltic pump. More ethanol (3.3 g, 60 mmol) was added after 1 day. The reaction was complete in 2 days. The solution, after removal of the enzyme-containing gel, was concentrated to 20 mL and acidified with concentrated $H_2SO_4$ to pH 2.8, followed by addition of ethanol (200 mL). The precipitates were separated by filtration and discarded, and the filtrate was concentrated at room temperature to an oily residue. The residue was diluted with water (150 mL) and neu-

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