237 instrument, nuclear magnetic resonance spectra were obtained on a Varian HFT-80 instrument, and mass spectra were determined on an AEI MS-30 (electron impact, EI) and Finnigan 4000 (chemical ionization, CI) instrument.

(7) B. J. Hunt and W. Ribgy, *Chem. Ind. (London)*, 1868 (1967).
(8) Most of the literature reports for the preparation of 1-vinylcyclohexene [e.g., P. A. Robins and J. Walker, *J. Chem. Soc.*, 642 (1952)] involve $KHSO_4$-catalyzed dehydration of 1-vinylcyclohexanol. It is critical that the $KHSO_4$ be not too acidic in order to prevent extensive polymerization and isomerization to 1- and 2-ethylcyclohexa-1,3-diene during dehydration. We prepared the dehydrating agent by adjusting the pH of an aqueous K_2SO_4 solution to 1.9 with H_2SO_4 and then evaporating the water.

Asymmetric Chemistry. Alcohol Effects upon the (+)-1,2,2-Trimethyl-1,3-bis(hydroxymethyl)-cyclopentane–Lithium Aluminum Hydride Reduction of Acetophenone

Thomas H. Johnson* and Kurtis C. Klein

Department of Chemistry, Kansas State University, Manhattan, Kansas 66506

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The synthesis of optically active compounds continues to command a good deal of attention. One widely studied aspect of this field has been the production of chiral carbinols from the reduction of achiral ketones with chiral-hydride reagents.[1-3] One method has employed lithium aluminum hydride and a chiral diol to effect asymmetric induction. A successful variation of this theme has employed 1 equiv of an achiral primary alcohol in addition to the chiral diol.[2,3] The success of this latter method was attributed to reaction of the achiral alcohol with the less sterically hindered hydride of the proposed diol–aluminum–dihydride intermediate.[2] The incipient monohydride would then be in a steric environment more conducive to asymmetric induction than would be the corresponding dihydride. Primary alcohols, usually ethanol or benzyl alcohol, had been used because of their anticipated stability to disproportionation in the tris(alkoxy)aluminum hydride stage.[4] The results of this paper clearly demonstrate that an appreciable enantiomeric excess, relative to ethanol, can be obtained by using other alcohols and, in fact, may be preferable to ethanol or benzyl alcohol.

In preparing a model system to study alcohol effects we felt it was important to prepare an optically active diol which was not only easy and inexpensive to prepare but devoid of other functional groups as well.[6] Such a diol was available in (+)-1,2,2-trimethyl-1,3-bis(hydroxymethyl)cyclopentane (1), which can be prepared in one step from readily available and inexpensive (+)-camphoric acid. Examination of a model of 1, after reaction with lithium aluminum hydride, suggested the presence of one hindered hydride (syn) and one very unhindered hydride (anti) as was desired.

Acetophenone was reduced by lithium aluminum hydride, 1, and an achiral alcohol in a molar ratio of 1:1:1:1. The results with various alcohols are given in Table I. As with other chiral diols,[2,3] the addition of an achiral alcohol to the reducing medium did increase the amount of enantiomeric excess although a decrease in reduction was also realized. Interestingly, ethanol and benzyl alcohol, two of the most used alcohols, showed the least improvement in enantiomeric excess. 2-Propanol proves to be a far better additive than either ethanol or benzyl alcohol. The difference between 2-propanol and ethanol on this reduction was tested in other solvents and 2-propanol was found to be the better additive in every instance (Table II). Reductions employing *tert*-butyl alcohol as the achiral alcohol also gave greater enantiomeric excesses than in ethanol and benzyl alcohol reactions but less than when 2-propanol was used (Table I).

The fact that the added achiral alcohols are having a demonstrable effect upon the reaction is apparent by comparison of the 7.7% enantiomeric excess value obtained when no achiral alcohol was used to those obtained for the various alcohols. When the reduction of acetophenone was carried out using lithium aluminum hydride and 1 in a ratio of 1:10:10 (ether–THF, 3:1), the enantiomeric excess in the resulting carbinol fell to 1.8%. These two sets of results suggest a difference in the two hydrides in the proposed dihydride intermediate. Unfortunately, this reaction is not quite as simple as it might appear. When the reduction of acetophenone with lithium aluminum hydride, 1, and 2-propanol in a ratio of 1:2:2:2 (ether–THF, 3:1) was run, the enantiomeric excess of the resulting carbinol fell to 8.3%. This experiment suggests that some disproportionation is occurring. Such an event would produce a variety of hydride species, only some of which would be chiral. Furthermore, some of these hydride species would be more effective reducing agents than others.[7] The results would seem to indicate that the achiral species are the more effective reducing agents.

The sum of this data suggests a couple of points which are germane to the problem of producing optically active alcohols via lithium aluminum hydride–chiral diol–achiral alcohol reducing systems. First, achiral alcohols such as 2-propanol and *tert*-butyl alcohol may well be better additives than the traditional ethyl and benzyl alcohols and their effect upon asymmetric induction should be tested in future systems. Second, the problem of (alkoxy)aluminum hydride disproportionations appears to be a real one and necessarily limits the amount of excess hydride which can be used in these reactions. As a consequence, reactions giving low conversions, e.g., the THF and dioxane reactions in Table II, cannot be increased by merely increasing, substantially, the amount of hydride reducing agent.

Table I. Reduction of Acetophenone in Ether–THF (3:1) by Lithium Aluminum Hydride, 1, and Achiral Alcohol[a]

alcohol	registry no.	yield, %[b]	ee, %[c]
none		96	7.7
methanol	67-56-1	82	10.1
ethanol	64-17-5	81	10.0
2-propanol	67-63-0	78	18.5
tert-butyl alcohol	75-65-0	76	13.1
benzyl alcohol	100-91-6	75	8.5

[a] The ratio of acetophenone, lithium aluminum hydride, 1, and achiral alcohol was 1:1:1:1. Where no achiral alcohol was used the ratio was 2:1:1. [b] Percent yield of methylphenylcarbinol. [c] Enantiomeric excess. Determined by dividing $[\alpha]_D$ for the isolated carbinol (*c* 5, EtOH) by 42.5 (the value for enantiomerically pure carbinol, ref 2) and multiplying by 100%. All reductions gave (+)-carbinol.

Table II. A Comparison of 2-Propanol and Ethanol in Various Solvents in the Reduction of Acetophenone[a]

solvent	alcohol	yield, %[b]	ee, %[c]
ether	ethanol	78	4.2
ether	2-propanol	71	5.3
ether–THF (3:1)[d]	ethanol	81	10.0
ether–THF (3:1)	2-propanol	78	18.5
THF	ethanol	43	7.2
THF	2-propanol	41	17.1
dioxane	ethanol	52	9.1
dioxane	2-propanol	42	12.5

[a] The ratio of acetophenone, lithium aluminum hydride, 1, and achiral alcohol was 1:1:1:1. [b] Percent yield of methylphenylcarbinol. [c] Enantiomeric excess. Determined by dividing $[\alpha]_D$ for the isolated carbinol (*c* 5, EtOH) by 42.5 (the value for enantiomerically pure carbinol, ref 2) and multiplying by 100%. All reductions gave (+)-carbinol. [d] This ratio of solvents represents an optimization for both yield and enantiomeric excess.

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Experimental Section

The ^1H NMR spectra were obtained on a Varian T-60 spectrometer using tetramethylsilane as an internal standard in deuteriochloroform. Infrared spectra were recorded on a Perkin-Elmer 137 spectrometer. Optical rotations were taken in ethanol using an ETL-NPL 143A automatic polarimeter. Elemental analysis was performed by Atlantic Microlab, Inc. Melting points were determined on a Fisher-Johns block and are uncorrected.

(+)-1,2,2-Trimethyl-1,3-bis(hydroxymethyl)cyclopentane (1). To a 1000-mL, three-necked, round-bottomed flask equipped with a mechanical stirrer, reflux condenser, and addition funnel were added 250 mL of anhydrous ether and 12.6 g (0.33 mol) of lithium aluminum hydride. To this stirred mixture was added, dropwise, 20.0 g (0.10 mol) of (+)-camphoric acid in 300 mL of anhydrous THF. After the addition was completed, the reaction was refluxed for 4 h. Then, the reaction was cooled to room temperature and quenched by the dropwise addition of 12 mL of water, followed by 12 mL of 15% aqueous sodium hydroxide, and finally by 35 mL of water. The precipitate was filtered and washed with copious amounts of THF. The filtrate was dried quickly over anhydrous sodium sulfate, filtered, and evaporated in vacuo to afford 14.2 g (83%) of 1, mp 128–131 °C. An analytical sample was prepared by sublimation (70 °C, 0.1 torr): mp 133–134 °C; $[\alpha]^{25}_D$ + 60.8 (*c* 2.5, EtOH); IR (KBr) 3300, 1050, 1080 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.78 (3 H, s), 1.00 (6 H, s), 1.25–2.10 (7 H, m), 3.20–3.75 (4 H, m). Anal. Calcd for $C_{10}H_{20}O_2$: C, 69.77; H, 11.63. Found: C, 69.70; H, 11.70.

General Procedures for Acetophenone Reductions. To a 250-mL, three-necked, round-bottomed flask equipped with a mechanical stirrer, reflux condenser, and addition funnel were added 1.00 g (0.025 mol) of lithium aluminum hydride and 100 mL of anhydrous ether. To this stirred solution was added, dropwise, 4.3 g (0.025 mol) of 1 in 40 mL of THF. The reaction was heated to reflux for 1 h after the addition of 1 had been completed. Then, 0.025 mol of achiral alcohol (Table I) in 20 mL of ether was added, dropwise, to the reaction and heated to reflux for another 1.5 h. The reaction was then cooled to room temperature and 3.0 g (0.025 mol) of acetophenone in 20 mL of ether was added, dropwise. After 2 h of additional reflux, the reaction was cooled to room temperature and quenched by the dropwise addition of 1 mL of water, followed by 1 mL of 15% aqueous sodium hydroxide, and finally by 3 mL of water. The precipitate was filtered and washed with 25 mL of ether. The filtrate was dried quickly over anhydrous sodium sulfate, filtered, and evaporated in vacuo. The resultant residue was then purified as previously described.[2]

Acknowledgment. The authors would like to thank Professor R. N. McDonald for helpful discussions.

Registry No.—1, 68510-42-9; (+)-camphoric acid, 124-83-4; acetophenone, 98-86-2; lithium aluminum hydride, 16853-85-3.

References and Notes

(1) For reviews see: J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions", Prentice-Hall, Englewood Cliffs, N.J., 1971; S.-I. Yamada and K. Koga in "Selective Organic Transformations", Vol. I, B. S. Thyagarajan, Ed., Wiley-Interscience, New York, 1970; D. Valentine, Jr., and J. W. Scott, *Synthesis*, 329 (1978).
(2) S. R. Landor, B. J. Miller, and A. R. Tatchell, *J. Chem. Soc. C*, 197 (1967).
(3) D. Seebach and H. Daum, *Chem. Ber.*, **107**, 1748 (1974); R. Haller and H. J. Schneider, *ibid.*, **106**, 1312 (1973).
(4) There have been a number of articles and comments on the stability of various (alkoxy)aluminum hydrides[5] but none of these have dealt with mixed alkoxides which are probably being dealt with here.
(5) H. Haubenstock and E. L. Eliel, *J. Am. Chem. Soc.*, **84**, 2363 (1962); D. J. Cram and F. D. Breene, *ibid.*, **75**, 6005 (1953); H. C. Brown and H. R. Deck, *ibid.*, **87**, 5620 (1965).
(6) Many of the chiral alcohols used in the literature contain amino and ether functions in addition to the hydroxy function(s). These have an apparent effect upon the reduction as well and their presence in this study would cloud the effects which this study is attempting to measure. For a dramatization of these secondary effects see ref 2 and references contained therein.
(7) H. C. Brown and R. F. McFarlin, *J. Am. Chem. Soc.*, **80**, 5372 (1958).

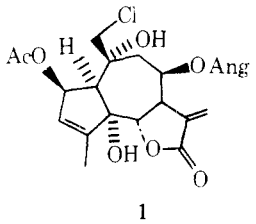
Communications

Three-Carbon Annelations. New Routes to the Nazarov Cyclization via Protected Cyanohydrins

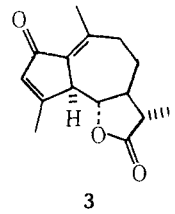
Summary: α'-Hydroxy vinyl ketones, prepared by the addition of anions of protected cyanohydrins to ketones, provide a useful entry to cyclopentenone annelation via the Nazarov cyclization.

Sir: We are currently investigating the synthesis of a number of sesquiterpene lactones which have been shown to possess cytotoxic, antitumor, and antifungal activity, e.g. eupachlorin acetate[1] (1), deacetylmatricarin[2] (2), and deacetoxymatricarin[3] (3). We envision a three-carbon annelation of a suitably functionalized cycloheptanone to obtain this end.

There are many interesting and elegant approaches to the formation of the cyclopentane ring; however, only a small fraction of these can be applied to schemes requiring a cyclopentane annelation.[4] The Nazarov cyclization,[5] despite potential utility, has found little use in this field. Ready availability of 3-keto-1,4-dienes or their equivalent would present a useful method for the annelative construction of the ring system we desire. We are pleased to report our initial findings hold promise as a general method for cyclopentenone annelation.



1



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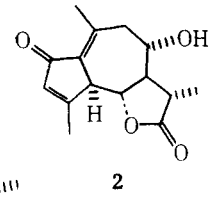
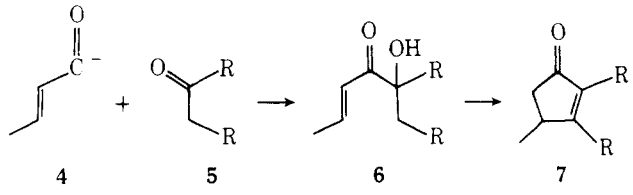


2

Our strategy to the cyclopentenones centers on the dehydration and subsequent Nazarov cyclization of α'-hydroxy enones such as 6. These are prepared by the addition of an acyl anion equivalent of crotonaldehyde 4 to the carbonyl compound 5, on which the annelation will take place.



4 5 6 7

We have found the use of the ethyl vinyl ether protected cyanohydrin[6] **8a** or the trimethylsilyl protected cyanohydrin[7] **8b** of crotonaldehyde to be effective acyl anion equivalents. Reaction of **8a** or **8b** with ketones proceeds as shown in Scheme I. Addition takes place exclusively at the α carbon[8] to give addition products of type **10** as is illustrated for cyclohexanone.

The Me_3SiCN adduct of crotonaldehyde is especially interesting in that intramolecular transfer of the trimethylsilyl group occurs with concomitant loss of cyanide, giving rise to addition products such as **12b** directly.[7a] The ethyl vinyl ether protected addition product, **10a**, requires acidic hydrolysis followed by treatment with base in order to unmask the requisite α-hydroxy enone **12c**.

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