(q, 2 H), 3.91 (q, 2 H), 5.21 (broad, 1 H), and 5.33 ppm (broad, 1 H); IR (neat) (E)-3b 3090, 1700, 1612, 1215, and 1150 cm^{-1}; mass spectrum (3b) (70 eV) m/e 238 (55), 121 (base). Anal. Calcd for $C_{12}H_{17}NO$ (3a): C, 75.39; H, 8.90; N, 7.33. Found: C, 75.26; H, 8.86; N, 7.46. Calcd for $C_{14}H_{22}O_3$ (3b): C, 70.59; H, 9.24. Found: C, 70.44; H, 9.40.

General Procedure for the Grignard Additions. To 0.05 mol of anhydrous lithium perchlorate in 40 mL of anhydrous ethyl ether under nitrogen atmosphere was added 30 mL (0.075 mol) of a solution of 2.5 M RMgBr in ether. To the homogeneous mixture was added dropwise 0.05 mol of nitriles 3 in 30 mL of ether and refluxing (the final solution must be 0.5 mol/L for nitriles). The reaction was followed by VPC (Carbowax 20M 5%, 170 °C). When it was ended (16–24 h), 100 mL of water was added slowly to the cold greenish solution, then, 200 mL of 30% HCl was added and the mixture was stirred at room temperature for 24 h. The product was extracted with several portions of ether. The combined extracts were washed with dilute sodium bicarbonate and dried over anhydrous magnesium sulfate and the ether was evaporated to give essentially the diketones (1a–c). The product was purified by distillation when possible or by VPC (Carbowax 20M 5%, 170 °C). (See Table I.)

General Procedure for Acid Hydrolysis of Dienes 3. A solution of 0.05 mol of diene 3 in 50 mL of dioxane, 5 mL of dry acetic acid, or 5 mL of formic acid (98–100%) was refluxed and stirred until the disappearance of diene 3 (Carbowax 20M 5%, 170 °C). The solution was concentrated under reduced pressure and the residue was diluted in ether and washed with dilute sodium bicarbonate. After drying over magnesium sulfate, the solvent was removed giving the crude product which was purified by distillation. (See Table I.)

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Concerning the Reductive Alkylation of Epoxy Ketones

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Although the direct functionalization of α,β-unsaturated ketones at the α position may be achieved via generation of the thermodynamic enolate followed by addition of an electrophile, such a sequence inevitably forms the nonconjugated enone along with varying amounts of α', γ, and polyalkylated materials.[2] This transformation is not readily accomplished in cases where electron density at the γ position proves un-

desirable, due to the presence of eliminatable groups, or impossible, due to the lack of an appropriate acidic hydrogen. Procedures which minimize polyalkylation have appeared but these also require the availability of an acidic γ-hydrogen.[3] A conceptually inverse sequence which achieves the same functionalization has been described.[4] This latter sequence, which relies on the regiospecific attack of an organometallic on an epoxide α,β to a hydrazone, followed by hydrolytic cleavage of the hydrazone, suffers in that it is restricted to substrates which are not otherwise reactive toward alkyl anions or the vigorous hydrolysis conditions required.

Previous work[5,6] suggested that an intermediate in the Me$_2$CuLi reduction of epoxy ketones, themselves readily accessible from the corresponding enones,[7] is an alkoxy enolate. Alkylation of such an intermediate[8] followed by dehydration would be expected to lead directly to an α-functionalized enone, thus effecting the transformation 1 → 2. Such a reduction, alkylation sequence has been applied to epoxy ketones using Li/NH$_3$ as the reducing agent[9] and to α-bromo ketones using Me$_2$CuLi as the reducing agent.[10]

It was expected that if a cuprate reagent were in fact useable to form an alkoxy enolate that it would prove advantageous since cuprates (a) are known to be a milder, more selective reducing agent than metal in ammonia, thus in principle permitting the presence of unprotected ketones, esters, etc.,[11] (b) would directly form enolates in organic solvents rather than in ammonia, the former often being more amenable to further transformations,[12] and (c) are, on a small scale, more conveniently used in stoichiometric amounts than alkali metals. With these considerations in mind, we proceeded to examine the scope of such a procedure.

Results and Discussion

The dropwise addition of carvone oxide (3)[7] in ether to 2.1 equiv of Me$_2$CuLi in ether (−22 °C) followed by addition of MeI and sufficient HMPA to give a solvent composition ~15% HMPA in ether yielded, after acidic quench, 92% of alkylated hydroxy ketone 4 identical spectrally (NMR, IR) and by GC

8 R = H,H
9 R = (OCH$_2$CH$_2$O)

10 R = H,H
11 R = (OCH$_2$CH$_2$O)
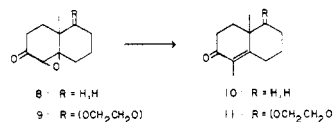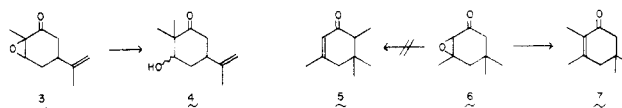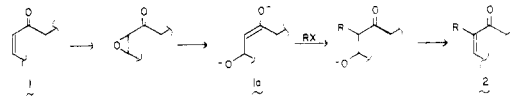
to the material obtainable from 3 by following the Li/NH$_3$, MeI sequence (80% reported).[9] Ommission of MeI gave, after dehydration,[13] only carvone. Similarly, isophorone oxide (6),[7] undergoing dehydration on workup, yielded 7 (88%).[14] None of the isomeric 5[15] which was independently prepared by alkylation (MeI),[16] reduction,[5a] and dehydration[13] of isophorone oxide was observed. Again, ommission of MeI returned only isophorone in nearly quantitative yield. Likewise, the epoxy octalones 8 and 9[6] were reductively alkylated and dehydrated to give 10 (85%)[3] and 11 (70%),[17] respectively; both compounds were identical (NMR, IR, GC) to authentic samples.[18] In neither case was any starting epoxide or unalkylated enone observed in the reaction product. Under our conditions, collapse to enone followed by conjugate addition does not appear

to be a competing process, contrary to the experience of Bull et al.[5a] who performed similar reductions but at higher temperatures.

We note several limitations to the procedure: (a) attempts to use such alkylating agents as BuI resulted in the formation of complex mixtures of products, presumably arising because alkylation with BuI is kinetically slower than proton transfer between alkoxy enolate and alkylated alkoxy ketone; (b) in several cases, reduction of epoxy ketones with Me_2CuLi, treatment with MeI, and finally acidic workup led at low temperatures (-22 °C or lower) to unalkylated hydroxy ketones $12 \rightarrow 13$ and $14 \rightarrow 15$, as shown by dehydration[13] to
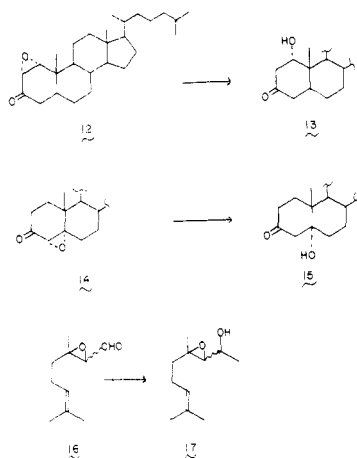
enones containing α-hydrogens (NMR), or at higher temperatures (>-22 °C) to complex mixtures of products (we believe this is again a result of proton transfer from alkylated alkoxy ketones to alkoxy enolates being kinetically faster than alkylation even with MeI when the alkoxy enolate salts are sufficiently hindered); (c) these alkoxy enolate salts are extremely unstable toward proton donors (it is imperative that all solvents and reagents be purified and dried immediately prior to use). Treatment of an epoxy aldehyde (**16**) with Me_2CuLi under these conditions gave an epoxy alcohol believed to be **17** (NMR, IR, MS) in accord with the work of Posner.[19]

That the species generated in these reductions ($1 \rightarrow 1a$) is a dilithium salt is shown by two experiments: reduction of carvone oxide (**3**) in ether with 2 equiv of Me_2CuLi generates a yellow precipitate which may be collected by filtration in a Schlenk tube; acid hydrolysis of the ether soluble material returns 1 equiv of carvone while hydrolysis of the yellow solid proceeds with the evolution of gas and the generation of 2 equiv of base (by titration). In a separate experiment, the yellow solid was collected and treated with 2 equiv of MeLi in ether to generate an ether soluble species which transfers Me– in a 1,4 sense to enones; the yellow precipitate thus appears to be 2 equiv of MeCu.

Finally, we note that these results contrast with the finding by C. Johnson[20] that Me_2CuLi directly α-methylates α,β-epoxy esters to form α-methyl β-hydroxy esters. This difference in reactivity possibly arises as a result of an ester enolate being thermodynamically less favorable than an otherwise equivalent ketone enolate, as is reflected by the difference in their pK_a's.[2a] We suggest that comparison of the reduction potentials of epoxy ketones and epoxy esters will provide an indirect measure of the energetics governing the partition in the mode of decomposition of cuprates by either electron transfer (to form in this case a β-alkoxy enolate) or alkyl group transfer (to form an α-methyl β-alkoxy ester).[21]

Experimental Section

Unless otherwise noted, nuclear magnetic resonance spectra were obtained on Varian T60 or A-60A spectrometers and are reported in parts per million (δ) downfield of internal Me_4Si, all integrations are ±10%, IR spectra were obtained on a Perkin-Elmer 137 or 727B, and mass spectra were obtained on a JEOL Model 07 spectrometer. GC conditions are described as needed. All solvents and materials were purified and dried immediately prior to use.[22] A typical reductive alkylation procedure is described below.

3-Hydroxy-5-isopropenyl-2,2-dimethylcyclohexanone (4). To a suspension of 404 mg of CuI in 10 mL of ether at -22 °C under argon was added 2 mL of 1.9 M MeLi in ether (just enough to redissolve the yellow MeCu precipitate as Me_2CuLi). To this was dropwise added 168 mg of **3** in 2 mL of ether. A yellow precipitate forms as the addition proceeds. After 5 min, 2 mL of HMPA and 1 mL of MeI were added; the homogeneous mixture was stirred at -22 °C for 30 min, and then allowed to warm to room temperature. The mixture was added to an aqueous NH_4Cl/ether (1:1) mixture, washed with 5% HCl aqueous, saturated $NaHCO_3$, and brine, dried, and evaporated to give 170 mg of oil: ν (film) 3450, 1707, 1654, 890; δ (CCl_4) 4.72 (m, 2), 3.6–3.4 (m, 1), 2.9–2.0 (m, 6), 1.81 (s, 3), 1.2 (br s, 6); GC (10 ft × 0.25 in., 5% SE-30 on Chromosorb G, 195 °C) 3.3 min (<1%, carvone), 3.9 min (<1%, **3**), 6.4 min (2%, 3-hydroxy-5-isopropenyl-2-methylcyclohexanone),[23] 8.3 min (95%, **4**); GCMS of **4**, m/e 182 (M^+, 36%), 164 (76%), 139 (100%), 123 (39%), 121 (51%), 97 (90%), 81 (94%).

Registry No.—**3**, 33204-74-9; **4**, 58008-71-2; **6**, 10276-21-8; **7**, 60417-86-9; **8**, 6432-29-7; **9**, 32137-01-2; **10**, 878-55-7; **11**, 33760-61-1; carvone, 99-49-0; 3-hydroxy-5-isopropenyl-2-methylcyclohexanone, 65378-69-0.

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