The direct and chemospecific prenylation of simpler terpenes to more complex terpenes should prove to be a useful approach to such compounds. The fact that trisubstituted double bonds can be created with complete stereochemical control enhances the utility of this scheme for such a purpose.

**Acknowledgment.** We wish to thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the National Science Foundation for their generous support of our programs. L.W. expresses his gratitude to the Deutsches Forschungs Gemeinschaft for a fellowship for part of his stay in these laboratories.

## References and Notes

(1) (a) For an early elegant solution to the squalene problem, see J. W. Cornforth, R. H. Cornforth, and K. K. Mathew, *J. Chem. Soc.*, 2539 (1959). (b) For a review see B. M. Trost, *Acc. Chem. Res.*, **3**, 120 (1970); also B. M. Trost in "Insect Juvenile Hormones", J. J. Menn and M. Beroza, Ed., Academic Press, New York, N.Y., 1972, pp 217–236.

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(3) B. M. Trost and P. E. Strege, *J. Am. Chem. Soc.*, **97**, 2534 (1975); B. M. Trost and L. Weber, *ibid.*, **97**, 1611 (1975), and earlier references therein.

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(6) H. C. Volger, *Recl. Trav. Chim. Pay-Bas*, **87**, 225 (1968).

(7) L. D. Pettit and D. S. Barnes, *Fortschr. Chem. Forsch.*, **28**, 85 (1972); F. R. Hartley, *Chem. Rev.*, **69**, 799 (1969); R. G. Denning, F. R. Hartley, and L. M. Venanzi, *J. Chem. Soc. A*, 324 (1967); R. G. Denning and L. M. Venanzi, *ibid.*, 336 (1967); F. R. Hartley and L. M. Venanzi, *ibid.*, 330 (1967).

(8) A higher chemospecificity was observed with methyl farnesoate compared to geranylacetone: B. M. Trost, T. J. Dietsche, and T. J. Fullerton, *J. Org. Chem.*, **39**, 737 (1974). Conformation of the molecules in solution and/or neighboring-group participation provide possible rationalizations.

(9) This compound crystallized only at low temperature and was a yellow oil at room temperature. Nevertheless a satisfactory elementary analysis was obtained on the oil and NMR gave no indication of the presence of any isomers.

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(11) For alternative approaches see J. Meinwald, A. M. Chalmers, T. E. Pliske, and T. Eisner, *Chem. Commun.*, 86 (1969); D. H. Miles, P. Loe, W. S. Johnson, A. F. Kluge, and J. Meinwald, *Tetrahedron Lett.*, 3019 (1972).

(12) We thank Professor C. J. Sih for this sample.

(13) For a discussion of the NMR spectra of various isomers, see J. W. K. Burrell, R. F. Garwood, L. M. Jackman, E. Oskay, and B. C. L. Weedon, *J. Chem. Soc. C*, 2144 (1966).

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*Received July 22, 1975*

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## Reductions with Copper Hydride. New Preparative and Mechanistic Aspects

*Summary:* Simple copper hydride reagents are described which reduce conjugated carbonyl compounds to the saturated derivatives; a special effect of added *sec*-butyl alcohol allows reduction of acrylates and labeling experiments establish the sources of the added hydrogens.

*Sir:* Since the first suggestions of unique reduction reactions promoted by complex copper hydrides,[1] related reagents have been shown to be of general utility for conversion of organic halides and sulfonate esters to hydrocarbons,[2–4] and for conversion of $\alpha,\beta$-unsaturated ketones into saturated ketones.[4,5] The reagents suggested to be most effective are obtained by generation of CuH at −50°, solubilization with a second ligand, and filtration at low temperature.[4,5] No general procedures for reduction of $\alpha,\beta$-unsaturated esters have been reported.

Using the general technique of earlier workers,[1,2] we have developed simple preparations of effective copper-based reagents which provide efficient 1,4 reduction of both conjugated ketones *and* esters, including two examples of acetylenic esters. The reductions show features associated with electron-transfer processes, including a dramatic increase in efficiency in difficult cases with 2-butanol in the medium. In contrast to reduction of halides to hydrocarbons,[2] these reactions involve transfer of a hydrogen atom from the copper hydride to carbon, specifically the $\beta$ carbon of the unsaturated carbonyl system.

The complex hydrido–metallic species are prepared according to eq 1 and 2. The species involving the lithium cation (eq 1, here referred to as Li complex) and the parallel species with the sodium cation (eq 2, Na complex) are obtained as brown-black suspensions in tetrahydrofuran by simply mixing the reagents at 0° under argon and stirring for 30 min. A series of unsaturated ketones and esters were studied in reaction with both the Li complex and the Na complex; the more efficient conversions are displayed in Table I. Cyclic enones are best reduced with the Li complex, as the Na complex gives lower yields (60–70%). With chalcone and the ester examples, the Na complex gives better results, especially in the presence of excess 2-butanol. In the examples of entries 6, 7, 9, and 10, high molecular weight products were the main products with the Li complex and with the Na complex in the absence of added alcohol.

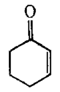
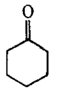
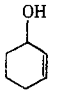
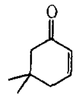
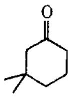
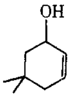
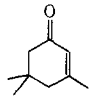
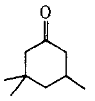
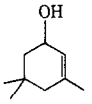
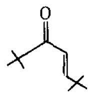
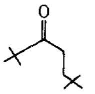
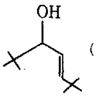
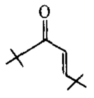
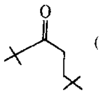
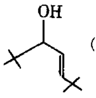
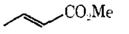
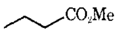
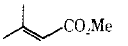
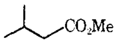
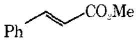
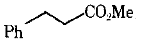
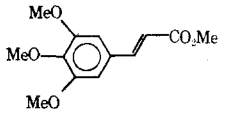
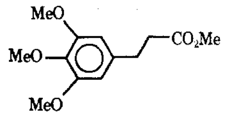
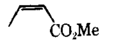
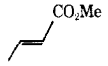
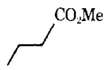
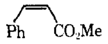
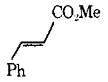
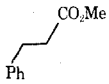
$$2\mathrm{LiAlH(OCH_3)_3} + \mathrm{CuBr} \xrightarrow[\mathrm{THF}]{0^\circ} \text{“Li complex”} \qquad (1)$$

$$\mathrm{NaAlH_2(OCH_2CH_2OCH_3)_2} + \mathrm{CuBr} \xrightarrow[\mathrm{THF}]{0^\circ} \text{“Na complex”} \qquad (2)$$

The procedure is exemplified by the reduction of methyl 3,4,5-trimethoxycinnamate. Vitride[6] (70% in benzene, 2.24 ml, 16.0 mmol of hydride) was added dropwise to a suspension of cuprous bromide[7] (1.44 g, 8.0 mmol) in 15 ml of THF at 0°. After 30 min, the mixture was cooled to −78° and 2-butanol (1.6 ml, 18.0 mmol) was added, followed by a solution of methyl 3,4,5-trimethoxycinnamate (252 mg, 1.0 mmol) in 4 ml of THF. The mixture was stirred at −20° for 2 hr, quenched with 4 ml of water, and poured into saturated aqueous ammonium chloride. After dilution with ether, the organic layer was washed successively with water and aqueous ammonium chloride solution and concentrated to afford a residue of essentially pure methyl (3,4,5-trimethoxyphenyl)propionate. Short-path distillation [90° (0.01 Torr)] gave a pure sample,[8] 242 mg, 93% yield.

The reductions of 2,2,6,6-tetramethylhept-4-en-3-one and methyl cinnamate were studied in some detail. Both Li complex and Na complex give high yields and selective 1,4 reduction with the ketone. Neither reagent gives high yields of methyl 3-phenylpropionate when allowed to react with methyl cinnamate in THF. In this case, a major product (isolated in 20–28% yield) is dimethyl *meso*-3,4-diphenyladipate (**1**).[9] The formation of **1**, an example of hydrodimerization characteristic of electrolytic reduction,[10] and the tendency to form higher molecular weight products

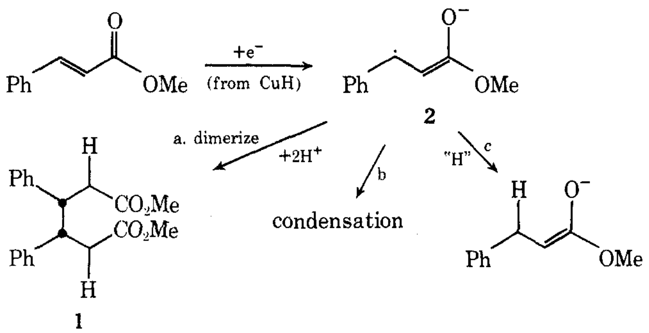
**Table I**
**Reductions with Copper Hydride[a]**

| Entry | Substrate | CuH complex[b] | Products (% yield) | |
|---|---|---|---|---|
| 1 |  | Li |  (84) |  (3) |
| 2 |  | Li |  (92) |  (6) |
| 3 |  | Li |  (98)[c] |  (2) |
| 4 |  | Li |  (87) |  (12) |
| 5 |  | Na |  (98)[c] |  (1) |
| 6 | $PhCOCH{=}CHPh$ | Na[d] | $PhCOCH_2CH_2Ph$ (65)[e] | $PHCH(OH)CH{=}CHPh$ (0) |
| 7 |  | Na[d] |  (84) | |
| 8 |  | Na |  (92) | |
| 9 |  | Na[d] |  (82)[c] | |
| 10 |  | Na[d] |  (92)[c] | |
| 11 | $CH_3C{\equiv}CCO_2Me$ | Na[f] |  (29)<br> (25)<br> (18) | |
| 12 | $PhC{\equiv}CCO_2Me$ | Na[f] |  (56)<br> (21)<br> (6) | |

[a] All reactions were run for 1 hr at −20° according to the general procedure detailed in the text without added 2-butanol unless otherwise noted. The yields were determined by quantitative GPC analysis, after isolation of the crude organic product mixture, using internal standards and pure samples of each of the products for calibration. All reactions were complete unless otherwise noted. [b] Li refers to the Li Complex of eq 1. Na refers to the Na Complex of eq 2. [c] The yield is based on pure material isolated by distillation. [d] The medium contained 15 mol equiv of 2-butanol. [e] The yield is based on starting material not recovered (85% conversion). [f] This reaction was quenched after 15 min at −20°.

may be rationalized by means of an initial electron-transfer step to give an intermediate radical anion, **2**. This transient intermediate could account for oligomeric products through preferential coupling (path a) or condensation with the starting ester (path b), instead of the hydrogen transfer (path c) that leads to the desired monomeric reduction product. Consistent with this scheme and previous studies of electron-transfer reactions of enones,[11] addition of 2-butanol (~15 mol equiv) to the reaction mixture tends to favor the simple reduction product.

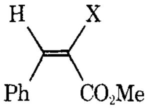
The source of "H" in step c is clearly the hydride originating from the aluminum hydride species in eq 1. For ex-



ample, when the Li complex was prepared from $LiAlD(OCH_3)_3$[12] and allowed to react with methyl cinnamate, methyl 3-deuterio-3-phenylpropionate was obtained in 20% yield.[13] With same reagent, 2,2,6,6-tetramethylheptenone gave 2,2,6,6-tetramethyl-5-deuterio-3-heptanone in 87% yield.[14] With the Li complex under the usual conditions, but with $D_2O$ being added instead of water during isolation, methyl cinnamate led to 3-phenylpropionate with deuterium only in the $\alpha$ position.[15] These results suggest that the hydrogen added in the $\beta$ position arises from the copper hydride, while the hydrogen added in the $\alpha$ position results from protons in the medium or added during isolation.

That the 2-butanol acts as a proton donor (and not a hydrogen atom donor, from C-2) was shown by the formation of unlabeled methyl phenylpropionate (82% yield) from reduction of methyl cinnamate in the presence of 2-deuterio-2-butanol.[16] On the other hand, 2-butanol-*O-d* leads to methyl phenylpropionate with 24% deuterium at the $\alpha$ position (~50% labeling of one proton) and <1% deuterium in the $\beta$ position. The effectiveness of 2-butanol appears to result from selective proton transfer—slow toward the copper hydride but rapid enough toward an intermediate (e.g., **2**) to inhibit oligomerization reactions.[17]

Two acetylenic esters undergo successful reduction. The reaction with methyl phenylpropiolate is highly selective for single stage reduction, giving predominately the cis-unsaturated ester upon proteolytic isolation. Consistent with an $\alpha$-carboxyvinyl metal intermediate (e.g., **4**), the yield and geometry of the products depend on temperature and duration of reaction before quenching.[18] Longer reaction times give lower yields and more trans isomer. Quenching with $D_2O$ provides a mixture of *cis*- and *trans*-cinnamates with >98% $\alpha$ deuterium (i.e., **5**) from methyl phenylpropiolate and the Na complex.[19,20]



**4**, X = Cu
**5**, X = D

## References and Notes

(1) G. M. Whitesides, J. S. Fillipo, Jr., E. R. Stredronsky, and C. P. Casey, *J. Am. Chem. Soc.*, **91**, 6542 (1969).
(2) S. Masamune, P. A. Possy, and G. S. Bates, *J. Am. Chem. Soc.*, **95**, 6452 (1973).
(3) T. Yoshida and E-i. Negishi, *Chem. Commun.*, 762 (1974).
(4) S. Masamune, G. S. Bates, and P. E. Georghion, *J. Am. Chem. Soc.*, **96**, 3686 (1974).
(5) R. K. Boeckman, Jr., and R. Michalak, *J. Am. Chem. Soc.*, **96**, 1623 (1974). This paper includes one example of reduction of an acrylate in 40% yield. No general method of reduction of conjugated esters is claimed, however.
(6) Eastman Chemical's sodium bis(2-methoxyethoxy)aluminum hydride in benzene.
(7) Cuprous bromide and iodide were purified according to the procedure of G. B. Kauffman and L. A. Teter, *Inorg. Synth.*, **7**, 9 (1963).
(8) The purity and identity of this compound were established by spectral ($^1$H NMR, ir, mass) and chromatographic (GPC) means.
(9) Compound **1** was identified by interpretation of $^1$H NMR and mass spectra and by comparison of melting point with the literature value: found mp 174–175°; literature mp 174–175° [D. Y. Curtin and S. Dayagi, *Can. J. Chem.*, **42**, 867 (1964)].
(10) Cf., K. W. Bowers, R. W. Giese, J. Grimshaw, H. O. House, N. H. Kolodny, K. Kronberger, J. P. Kaplan, and J. F. Simcone, *J. Am. Chem. Soc.*, **92**, 2800 (1970).
(11) H. O. House and M. J. Umen, *J. Org. Chem.*, **38**, 3893 (1973), and references therein.
(12) This compound was prepared from lithium aluminum deuteride and methyl alcohol in tetrahydrofuran. A filtered, titrated solution of lithium aluminum deuteride was employed.
(13) The deuterium was ascertained to be specifically at the $\beta$ position by $^1$H NMR analysis, using rare earth shift reagents to separate and simplify the multiplets due to the $\alpha$- and $\beta$-hydrogen atoms. Integration of the NMR signals and abundances of peaks in the molecular ion region of the mass spectrum suggested replacement of one hydrogen by deuterium to the extent of ~85%.
(14) The position of the deuterium in the 2,2,6,6-tetramethyl-5-deuterio-3-heptanone was obvious from the $^1$H NMR spectrum ($CDCl_3$). The multiplet which appears as a triplet ($J$ = 7.8 Hz) of area 2 at $\delta$ 1.50 in 2,2,6,6-tetramethylheptan-3-one now appears as triplet of triplets at $\delta$ 1.50, of area 1.1 ($J_{H_\alpha-H_\beta}$ = 7.8 Hz, $J_{H_\beta-D_\beta}$ = 1.0 Hz). The area of the signals (doublet of triplets) due to the $\alpha$ hydrogens is 2.0 (no deuterium incorporation). The relative abundances of ions in the parent ion region of the mass spectrum also indicated the presence of one deuterium in ~90% of the molecules.
(15) The extent of incorporation was low (45% of one hydrogen in the $\beta$ position), perhaps owing to exchange with aqueous solutions during isolation. The experiment was designed to show the absence of proton (deuteron) delivery to the $\beta$ position.
(16) The labeled alcohol was prepared by reduction of acetone with lithium aluminum deuteride and contained >96% deuterium at C-2 by NMR analysis.
(17) On the other hand, methyl alcohol is too reactive toward the copper hydride species and drastically decreases the reducing ability, while *tert*-butyl alcohol has no significant effect on the reactions.
(18) Maximum yield is obtained after 15 min at −20° (cis, 55%; trans, 21%) but drops if the reaction is quenched after 30 min at 0° (cis, 14%; trans, 13%).
(19) The extent of deuterium incorporation was determined by NMR spectral analysis, using integration of the signal appearing at $\delta$ 5.90 (d, $\alpha$ H, $J$ = 13 Hz, cis isomer), and $\delta$ 6.38 (d, $\alpha$ H, $J$ = 16 Hz, trans isomer). Cf., K. Brocklehurst, H. S. Price, and K. Williamson, *Chem. Commun.*, 884 (1968).
(20) We are pleased to acknowledge financial support for this work from the National Institutes of Health (AI-08687).
(21) Recipient of a Camille and Henry Dreyfus Teacher-Scholar Grant (1973–1978).
(22) NIH Postdoctoral Trainee, 1972–1973.

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*Received August 6, 1975*

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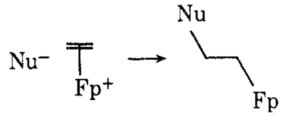
## Metal Assisted C—C Bond Formation. Use of a Methyl Vinyl Ketone Complex in Michael Condensations

*Summary:* Methyl vinyl ketone complexed by $C_5H_5Fe(CO)_2{}^+$ is shown to be a powerful acceptor of nucleophiles in Michael-type reactions.

*Sir:* The addition of kinetically generated enolates to vinyl ketones is generally complicated by polymerization of the acceptor component under the aprotic conditions required to minimize proton transfer and consequent equilibration of the donor enolate.[1]

It has recently been shown[2] that the polymerization problem may be resolved through the use of $\alpha$-silylated vinyl ketones, and a number of such reagents have been successfully employed with regiospecifically generated lithium enolates in ring annelation reactions.[2,3]

Since we had previously reported[4] that enolates of $\beta$-dicarbonyls could be condensed with isolated olefins activated by coordination with $\eta^5$-$C_5H_5Fe(CO)_2{}^+$ (eq 1), we were



(1)

$Fp \equiv \eta^5\text{-}C_5H_5Fe(CO)_2$

led to consider extension of these reactions to Michael condensations. Moreover, the powerful activating influence exerted upon an olefin by metal complexation left open the possibility that such reactions might also be effected with regiospecifically generated enol derivatives.

The present paper describes the use of a novel methyl vinyl ketone acceptor component (**2**) in both electroneutral and cationic Michael-type condensations.