

The Chemistry of Carbanions. XII. The Role of Copper in the Conjugate Addition of Organometallic Reagents

Herbert O. House, William L. Respess, and George M. Whitesides

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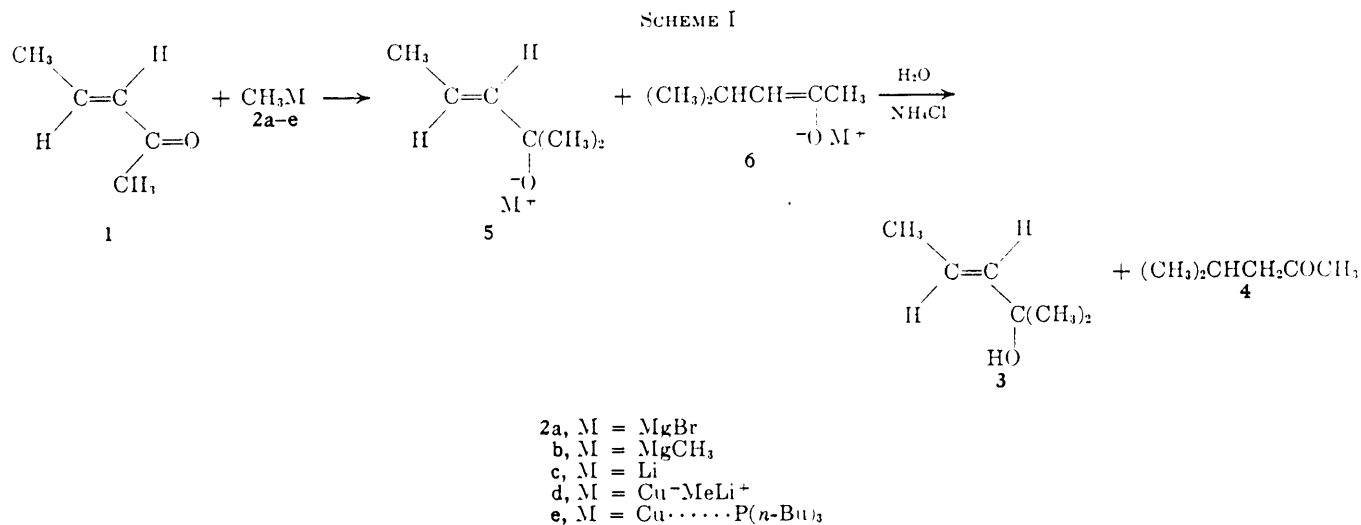
Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

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The reaction of *trans*-3-penten-2-one (1) with methyl lithium and with methylmagnesium has been studied to learn the effect of added copper salts on the reaction rate and the proportions of reaction products 3 and 4. These studies have led to the development of two organocopper reagents which have the stoichiometry $\text{Li}^+\text{Me}_2\text{Cu}^-$ and $\text{MeCuP}(n\text{-Bu})_3$ and which very selectively add a methyl group to the β carbon of an α,β -unsaturated ketone. Although the conjugate addition of a 0.2 M solution of the methylcopper-tri-*n*-butylphosphine complex to the unsaturated ketone 1 is complete in less than 0.05 sec, the same reagent does not add to the carbonyl function of saturated ketones or esters even after reaction periods of 30 min or more. Investigation of the stereochemistry of enolate anions produced by conjugate addition of these organocopper reagents provides direct experimental evidence that these reactions do not involve a cyclic six-centered transition state. Other reactions and properties of these organocopper reagents are also described.

In continuing our earlier studies² of the reaction of organometallic reagents with ketones, we wished to learn how the reaction of an α,β -unsaturated ketone (*e.g.*, 1) with an organomagnesium compound could be diverted from its normal course (1,2 addition to form 3) to favor conjugate addition (or 1,4 addition to form 4) by the presence of a small amount (1–5 mole %) of a copper compound.^{3–5} For this reason, we

The relative reaction rates were obtained by use of the previously described^{2b} flowing stream reactor which provided a total reaction time of 0.06–0.07 sec before quenching. The yields and product compositions were determined with suitably calibrated gas chromatographic equipment. Table I summarizes the results of these studies. Since the reaction rate data suffer from certain previously discussed^{2b} systematic errors,



have studied the relative reaction rates and the product distributions obtained from reaction of *trans*-3-penten-2-one (1) with various methyl organometallic reagents 2 (Scheme I).

(1) This research has been supported by research grants from (a) the Petroleum Research Fund (grant no. 594-A); (b) the Directorate of Chemical Sciences, Air Force Office of Scientific Research (Grant No. AF-AFOSR-573-64); (c) the National Science Foundation (Grant No. GP-2018).

(2) (a) H. O. House, D. D. Traficante, and R. A. Evans, *J. Org. Chem.*, **28**, 348 (1963); (b) H. O. House and D. D. Traficante, *ibid.*, **28**, 355 (1963); (c) H. O. House and H. W. Thompson, *ibid.*, **28**, 360 (1963); (d) H. O. House and W. L. Respass, *ibid.*, **30**, 301 (1965).

(3) (a) This effect of copper salts was first noted by M. S. Kharasch and P. O. Tawney, *J. Am. Chem. Soc.*, **63**, 2308 (1941). For related studies of the catalytic effects of metal salts, see (b) M. S. Kharasch, S. C. Kleiger, J. A. Martin, and F. R. Mayo, *ibid.*, **63**, 2305 (1941); (c) M. S. Kharasch and F. L. Lambert, *ibid.*, **63**, 2315 (1941); (d) M. S. Kharasch and E. K. Fields, *ibid.*, **63**, 2316 (1941). (e) For a general review of copper-catalyzed reactions, see R. G. R. Bacon and H. A. O. Hill, *Quart. Rev. (London)*, **19**, 95 (1965).

(4) For studies of copper-catalyzed conjugate additions to unsaturated esters, see (a) J. Munch-Petersen, *J. Org. Chem.*, **22**, 170 (1957); (b) J. Munch-Petersen, *Acta Chem. Scand.*, **12**, 2007 (1958); (c) J. Munch-Petersen and V. K. Andersen, *ibid.*, **15**, 271, 293 (1961); (d) J. Munch-Petersen, C. Bretting, P. M. Jorgensen, S. Refn, V. K. Andersen, and A. Jart, *ibid.*, **15**, 277 (1961); (e) V. K. Andersen and J. Munch-Petersen, *ibid.*, **16**, 947 (1962);

we have made no effort to derive kinetic orders from these measurements. Except in the cases noted, solutions containing the ketone 1 plus any additives were mixed with the organometallic reagent in the flowing stream reactor. From reactions run in a flask (reaction times of 10–45 min) where the additive

(f) S. Jacobsen, V. Bitsch, and J. Munch-Petersen, *ibid.*, **17**, 825 (1963); (g) T. Kindt-Larsen, V. Bitsch, I. G. K. Andersen, A. Jart, and J. Munch-Petersen, *ibid.*, **17**, 1426 (1963); (h) V. Bitsch, S. Jacobsen, I. G. K. Andersen, and J. Munch-Petersen, *ibid.*, **17**, 1433 (1963); (i) B. H. Nielsen and J. Munch-Petersen, *J. Organometal. Chem.*, **2**, 493 (1964).

(5) For other studies of conjugate additions of organomagnesium compounds see (a) E. R. Alexander and G. R. Coraor, *J. Am. Chem. Soc.*, **73**, 2721 (1951); (b) E. T. McBee, Y. S. Kim, and H. P. Braendlin, *ibid.*, **84**, 3154 (1962); (c) A. J. Birch and M. Smith, *Proc. Chem. Soc.*, 356 (1962); (d) Y. Inouye and H. M. Walborsky, *J. Org. Chem.*, **27**, 2706 (1962); (e) R. Filler and Y. S. Rao, *ibid.*, **27**, 3348 (1962); (f) R. F. Church, R. E. Ireland, and D. R. Shridhar, *ibid.*, **27**, 707 (1962); (g) R. C. Fuson, T. San, and J. Diekmann, *ibid.*, **27**, 1221 (1962); (h) R. E. Lutz and C. L. Dickerson, *ibid.*, **27**, 2040 (1962); (i) H. Mori, *Chem. Pharm. Bull. (Tokyo)*, **12**, 1224 (1964); *Chem. Abstr.*, **62**, 1710 (1965); (j) M. Torigoe and J. Fishman, *Tetrahedron Letters*, No. 19, 1251 (1963); (k) I. N. Rozhkov and S. M. Makin, *Zh. Obshch. Khim.*, **34**, 59 (1964); *Chem. Abstr.*, **60**, 10576 (1964); (l) W. J. Wechter, *J. Org. Chem.*, **29**, 163 (1964); (m) J. Klein, *Tetrahedron*, **20**, 465 (1964); (n) R. E. Lyle and F. J. Troscianiec, *J. Org. Chem.*, **24**, 333 (1959).

TABLE I

REACTION OF EXCESS METHYL ORGANOMETALLIC DERIVATIVES WITH *trans*-3-PENTEN-2-ONE (1) IN A FLOWING-STREAM REACTOR (REACTION TIME 0.06-0.07 SEC) AT 25-30°

Organometallic reagent	Additive ^a (mole %)	Solvent	% reaction	% conjugate addn in the product
MeMgBr	...	Et ₂ O	29	14
MeMgBr	<i>n</i> -Bu ₃ PCuI (1.2)	Et ₂ O	>99	99
MeMgBr	<i>n</i> -Bu ₃ PCuI (1.2) + isoprene (286)	Et ₂ O	>99	98
MeMgBr	<i>n</i> -Bu ₃ PCuI (1.2) + <i>n</i> -Bu ₃ P (6.9)	Et ₂ O	>99	96
Me ₂ Mg	...	Et ₂ O	97	19
Me ₂ Mg	<i>n</i> -Bu ₃ PCuI (2.4)	Et ₂ O	>99	82
MeLi	...	Et ₂ O	>99	<1
MeLi	<i>n</i> -Bu ₃ PCuI (1.2)	Et ₂ O	>99	9
MeCuP(<i>n</i> -Bu) ₃ ^b	LiI ^b	Et ₂ O	>99	>99
MeMgBr	...	Et ₂ O-THF (ca. 1:1)	37	13
MeMgBr	<i>n</i> -Bu ₃ PCuI (0.9)	Et ₂ O-THF (ca. 1:1)	91	68
MeMgBr	CuBr ₂ (0.91)	Et ₂ O-THF (ca. 1:1)	72	64
MeMgBr	Cu(OAc) ₂ (0.89)	Et ₂ O-THF (ca. 1:1)	67	64
MeMgBr	...	Et ₂ O-DME (ca. 1:1)	98	3
MeMgBr	<i>n</i> -Bu ₃ PCuI (0.92)	Et ₂ O-DME (ca. 1:1)	98	20

^a The amount of additive used is expressed as a percentage of the number of moles of organometallic reagent added. The concentrations of reagents was adjusted such that each mole of ketone was mixed with approximately 4 moles of methylmagnesium bromide, 4 moles of methyllithium, or 2 moles of dimethylmagnesium. ^b In this case the organocopper reagent was prepared by adding 1 mole of *n*-Bu₃PCuI to 1 mole of methyllithium.

was mixed with the organometallic reagent before the ketone solution was added, the product distributions (Table II) were comparable with those obtained in the flowing-stream reactor.

TABLE II

REACTION OF EXCESS METHYL ORGANOMETALLIC DERIVATIVES WITH *trans*-3-PENTEN-2-ONE (1) IN ETHER SOLUTION FOR 10-45 MIN

Organometallic reagent	Additive ^a (mole %)	% conjugate addn
MeMgBr	<i>n</i> -Bu ₃ PCuI (1.0) ^b	99
MeMgBr	Cu(OAc) ₂ (1.0) ^c	80
MeMgBr	<i>n</i> -Bu ₃ PAGI (1.0) ^c	19
MeMgBr	CuI (50) ^c	96
Me ₂ Mg	CuI (99) ^c	94
MeLi	CuI (103) ^c	>99
MeLi	CuI (50)	>99
MeLi	<i>n</i> -Bu ₃ PCuI (109)	>99
MeLi	CuI (50) + pyridine ^d	>99

^a Unless otherwise noted, the additive was added to an ethereal solution of the organometallic reagent and then the ketone 1 was added. ^b In this case, a solution of the ketone and the copper derivative was added to the organometallic reagent. ^c In this case, the organometallic reagent was heterogeneous. See the Experimental Section for details. ^d In this case, pyridine was the principal solvent, the solvent volumes being 35 ml of pyridine and 5.3 ml of ether.

Before considering the experiments with preformed organocopper reagents several general phenomena should be noted.

1. The proportions of 1,2 and 1,4 addition are approximately the same irrespective of whether methylmagnesium bromide or dimethylmagnesium is the organomagnesium reagent employed. Differences of similar magnitude have been reported elsewhere.^{2a,4f} Just as was true for saturated ketones,^{2b} the reaction with dimethylmagnesium is substantially faster than the reaction with methylmagnesium bromide.

2. As has been noted frequently (e.g., ref. 5h), methyllithium is more reactive than methylmagnesium bromide and strongly favors 1,2 addition rather than 1,4 addition. Since the reactions of the ketone 1 with methyllithium and with dimethylmagnesium

were both too rapid for measurement in our apparatus, we have no experimental measure of which reagent is the more reactive.

3. The presence of even 1 mole % of a copper salt in the reaction medium very markedly accelerates the over-all rate of reaction as well as enhancing the proportion of the conjugate addition product. If the reaction is to be run in ether solution, there is a distinct advantage to the addition of the copper catalyst as the ether-soluble copper(I) iodide-tri-*n*-butylphosphine complex.^{6,7} However, when a mixture of tetrahydrofuran and ether is used as the reaction solvent, the catalytic effect of any of the soluble copper(I) or copper(II) derivatives is approximately equal. It should further be noted that the addition of a catalytic amount of the silver iodide-tri-*n*-butylphosphine complex to methylmagnesium bromide did not catalyze conjugate addition. However, this latter reaction mixture was heterogeneous and we have no reason to believe that any soluble methylsilver species was present.

4. As had been noted previously,^{2a} the proportion of conjugate addition is not significantly diminished by the presence of a substantial amount of isoprene in the reaction mixture. We therefore continue to believe that the conjugate addition process does not involve the addition of a free alkyl radical to the conjugated system contrary to the suggestion of Rozhkov and Makin.^{5k}

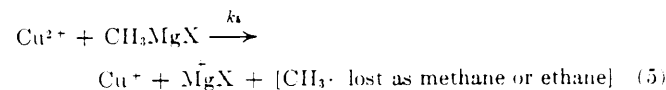
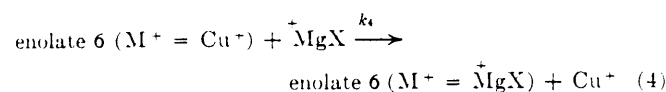
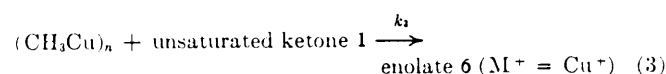
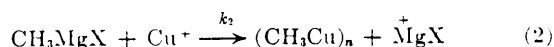
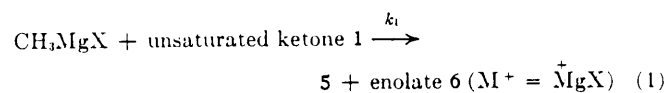
5. The effect of solvent on the reaction rate and proportion of conjugate addition is of interest. The presence of tetrahydrofuran (THF) in the reaction solution increases the rate of 1,2 addition slightly and appears to repress the rate of the copper-catalyzed

(6) The advantage noted⁶ for using a tetrahydrofuran solution of copper(II) acetate, rather than copper(I) chloride, is apparently simply a result of the very low solubility of copper(I) chloride.

(7) (a) G. B. Kaufman and L. A. Teter, *Inorg. Syn.*, **7**, 9 (1963). (b) Ebullioscopic measurements in nonpolar media indicate this material to be a tetramer: F. G. Mann, D. Purdie, and A. F. Wells, *J. Chem. Soc.*, 1503 (1936). (c) A complete X-ray structure of the triethylarsine complex and a partial analysis of the structure of the tri-*n*-butylphosphine complex [A. F. Wells, *Z. Krist.*, **94**, 447 (1936)] indicate both complexes to be tetramers in the crystalline state with copper atoms at the corners of a tetrahedron.

conjugate addition. This trend is more striking with 1,2-dimethoxyethane (DME) which accelerates substantially the rate of 1,2 addition. This increased rate of 1,2 addition is in general agreement with the enhanced reactivity of alkylmagnesium derivatives when 1,2-dimethoxyethane is present.⁸

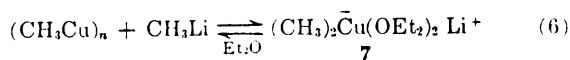
These observations can be reconciled with the general scheme illustrated in the following equations (1-5) in which the copper(I) reactant is represented as a methylcopper species for simplicity. The final eq 5 is applicable only if the catalytic amount of copper



salt is added as a copper(II) species. To explain the experimental observations, one must assume that each of the rate constants $k_2 - k_5$ is much larger than k_1 . The rapidity of these reactions may be appreciated by considering that in less than 0.07 sec, the cycle of reactions 2-4 is repeated many times so that the methylcopper intermediate can successfully compete with the methylmagnesium reagent whose concentration is 100 times greater. In other words, all of the reactions 2-4 need to be approximately 10^3 times faster than reaction 1 which itself has a half-life of approximately 0.1 sec.

The foregoing considerations suggested the desirability of studying the reactions of the methylcopper species which is postulated to be the reactive intermediate. Methylcopper may be obtained as a yellow, insoluble and apparently polymeric, solid by reaction of copper(I) iodide [or other copper(I) salts] with methyllithium or methylmagnesium derivatives in ether solution at temperatures below 0°. The same product may be obtained less efficiently by the reaction of methyllithium or a methylmagnesium derivative with a copper(II) salt; in this case the first equivalent of organometallic reagent is oxidized by the copper(II) species resulting in the formation of a copper(I) salt which then yields methylcopper.⁹ If the insoluble methylcopper is treated with a second molar equivalent of methyllithium, a pale yellow to colorless

etheral solution is obtained.^{2a} We consider this solution to contain a complex dimethylcopper(I) anion such as 7. This structure is analogous to other re-



ported polyalkylmetal anions.¹⁰ The state of aggregation and degree of solvation of this dimethylcopper species is not presently known and the monomeric dietherate 7 is written for simplicity. Although we have been unable to find a solvent for methylcopper which will permit measurement of the nmr spectrum, the nmr data for the dimethylcopper anion and several related compounds are summarized in Table III.¹¹ The nmr methyl signal for the dimethylcopper anion remains sharp (half-bandwidth 1.8 cps) even at relatively low temperatures. From this observation and the shift in both the methyl signal and the ¹³CH coupling constant as excess methyllithium is added, we conclude that the equilibrium represented in eq 6 lies far to the right; the sharpness of the signals also argues against the presence of substantial concentrations of paramagnetic copper(II) species in these solutions. The subsequently described low order of reactivity of the lithium dimethylcopper species with carbonyl functions also indicates that the equilibrium position of reaction 6 lies far to the right.

TABLE III
NMR DATA FOR VARIOUS DERIVATIVES OF METHYLCOPPER IN ETHER SOLUTION

Reactants, concn in moles l.	Temp. °C	Chemical shift, cps above (CH ₃) ₄ Si (bandwidth at half-height, cps)	J _{CH} , cps
MeLi (1.42)	Ca. 30	110.5	96.5
MeLi (1.52) + CuI (0.76)	Ca. 30	66	108.5
MeLi (0.20) + CuI (0.10)	33	62 (0.6)	...
	-43	61 (0.8)	...
	-62.5	69.5 (1.2)	...
MeLi (1.63) + CuI (0.54)	Ca. 30	78.5	105
MeLi (0.20) + CuI (0.067)	33	77.5 (0.6)	...
	-26	78.5 (3.8)	...
	-43	78 (8.6)	...
	-62.5	72 (5.8) + 112 (br)	...
MeLi (0.20) + CuI (0.05)	-75	71 (ca. 4) + 114 (ca. 9) ^a	...
MeLi (1.09) + nBu ₃ PCuI (1.09)	Ca. 30	36.5	113
MeLi (0.53) + nBu ₃ PCuI (0.53)	31	50 (0.7)	...
	-26	51.5 (1.2)	...
	-57	47.5 (2.4)	...

^a The areas under these two peaks are approximately equal suggesting that equilibration between a species having the stoichiometry Me₂Cu-Li⁺ and methyllithium has been retarded at -60 to -70°.

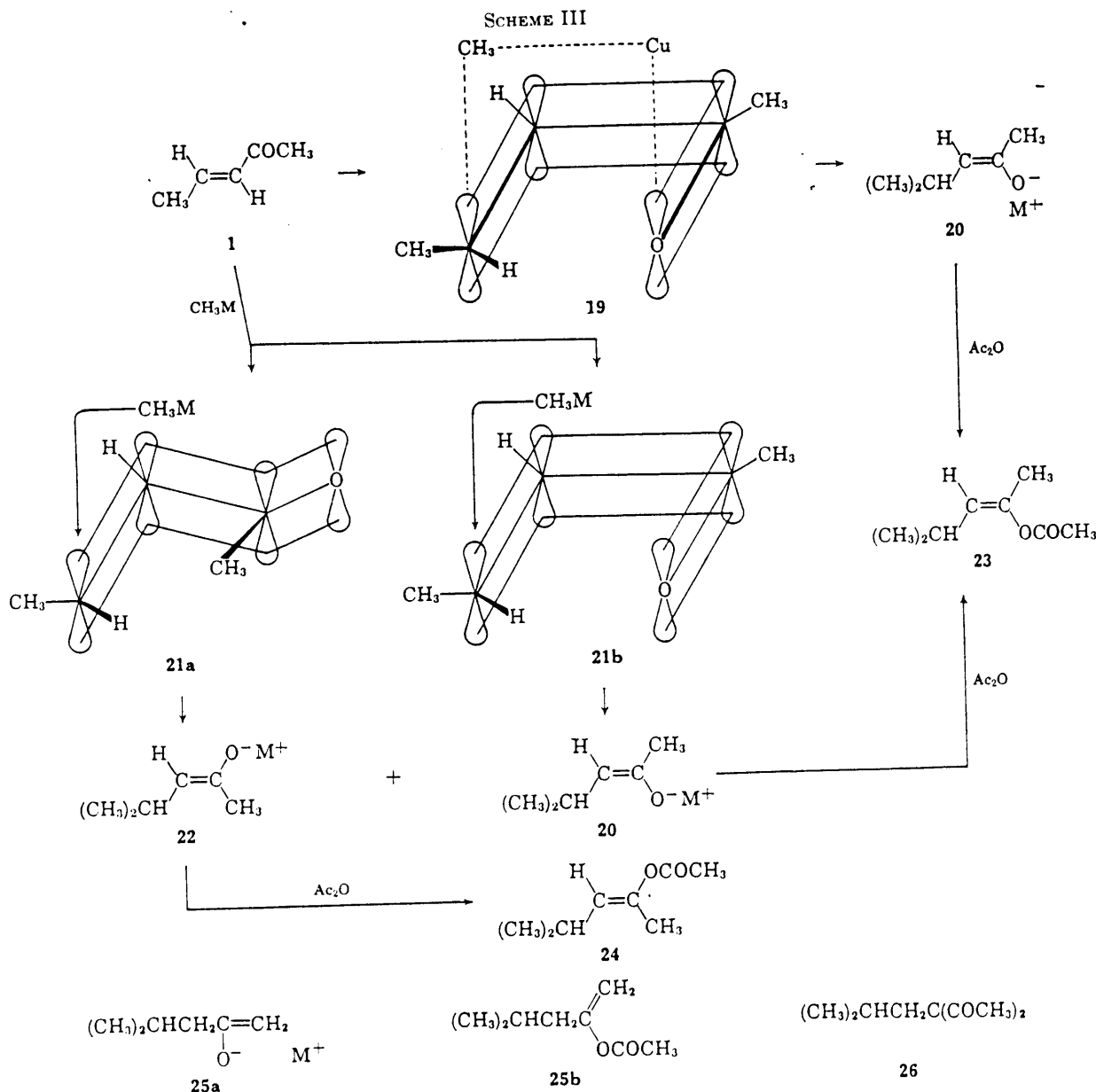
A second method for obtaining an ether-soluble derivative of methylcopper consists of adding 1 equiv of tri-n-butylphosphine. This preparation is more conven-

(8) (a) L. I. Zakharkin, O. Y. Okhlobystin, and K. A. Bilevitch, *Tetrahedron*, **21**, 881 (1965). (b) L. I. Zakharkin, O. Y. Okhlobystin, and B. N. Strunin, *J. Organometal. Chem.*, **4**, 349 (1965). (c) In an apparently related observation, the addition of hexamethylphosphoramide to an etheral solution of benzylmagnesium bromide was found to enhance the degree of dissociation of the carbon-magnesium bond: H. F. Ebel and R. Schneider, *Angew. Chem., Internat. Ed. Engl.*, **4**, 878 (1965).

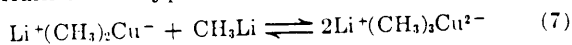
(9) (a) H. Gilman, R. G. Jones, and L. A. Woods, *J. Org. Chem.*, **17**, 1630 (1952). (b) For related studies of ethyl and phenyl derivatives of copper(I), see H. Gilman and J. M. Straley, *Rec. Trav. Chim.*, **55**, 821 (1936). For recent studies of the decomposition of methylcopper, see (c) C. E. H. Bawn and F. J. Whitby, *J. Chem. Soc.*, 3926 (1960); (d) G. Costa, A. Camus, and N. Marsch, *J. Inorg. Nucl. Chem.*, **27**, 281 (1965); (e) G. Costa and G. DeAlti, *Gazz. Chim. Ital.*, **87**, 1273 (1957); *Chem. Abstr.*, **52**, 19452 (1958).

(10) (a) C. Beermann and K. Clauss, *Angew. Chem.*, **71**, 627 (1959); (b) D. J. Pasto and R. Snyder, *J. Org. Chem.*, **30**, 1634 (1965); (c) G. Wittig, F. J. Meyer, and G. Lange, *Ann.*, **571**, 167 (1951).

(11) These spectra were determined by Mr. Roger A. Latham in our laboratories.



have no firm evidence requiring the existence of an equilibrium of the type illustrated in eq 7 although our



nmr data (Table III) would be consistent with such a process.

The foregoing results demonstrate that methylcopper and its derivatives 7 and 8 have the ability to react very rapidly with conjugated carbon-carbon double bonds while at the same time being either inert or relatively unreactive toward carbon-oxygen double bonds. Treatment of naphthalene with the phosphine complex 8 and treatment of norbornene^{13,14} with either the phosphine complex 8 or the lithium dimethylcopper 7 yielded no products corresponding to the addition of a methyl group to either naphthalene or norbornene. Although this matter is currently being investigated more thoroughly, it would appear that the copper

reagents add readily only to certain carbon-carbon multiple bonds which are part of conjugated systems. It should be noted in passing that the preformed copper reagents 7 and 8 offer considerable synthetic utility in that it would be practical to add these copper derivatives to the carbon-carbon double bond of a conjugated ketone selectively while *unprotected ketone, ester, or carboxylic acid functions were present in the same molecule.*

We next turned our attention to the question of how the methyl group is transferred from a methylcopper derivative to the β position of an α,β -unsaturated ketone. The arguments for and against a cyclic transition state (as in 19) for this process have been reviewed elsewhere.^{2,5a,5m} Our recent studies of the stereochemical integrity of lithium enolates in the absence of proton-donating molecules¹⁵ suggested a procedure which would provide a direct measure of the stereochemistry of conjugate addition. As illustrated in Scheme III, the cyclic transition state 19 in which the metal atom is partially bonded both to the leaving

(13) Certain lithium reagents have been reported to add to the strained carbon-carbon double bond of norbornene [J. E. Mulvaney and Z. G. Gardlund, *J. Org. Chem.*, **30**, 917 (1965)] and to naphthalene [J. A. Dixon, D. H. Fishman, and R. S. Dudinyak, *Tetrahedron Letters*, No. 12, 613 (1964)].

(14) An isolable complex of norbornene and copper(I) chloride has been reported by D. R. Arnold, D. J. Trecker, and E. B. Whipple, *J. Am. Chem. Soc.*, **87**, 2596 (1965).

(15) (a) H. O. House and B. M. Trost, *J. Org. Chem.*, **30**, 1341, 2502 (1965); (b) H. O. House and V. Kramar, *ibid.*, **28**, 3362 (1963).

alkyl group and to the carbonyl oxygen atom requires the exclusive formation of the *cis*-enolate anion **20**, whereas any addition process such as **21** which does not require partial bonding of the metal atom to the carbonyl oxygen should lead to a mixture of the *trans*-(**22**) and *cis*-(**20**) enolate anions. Since these enolates **20** and **22** are produced in the presence of excess organometallic reagent, each anion should retain its stereochemistry and could be acetylated to form the corresponding enol acetate **23** or **24**.¹⁵ The equilibrium mixture of the corresponding potassium enolate anions in 1,2-dimethoxyethane (DME) is known^{15b} to contain 18% of the *cis*-enolate **20**, 7% of the *trans*-enolate **22**, and 75% of the terminal enolate **25a**; consequently, any equilibration of these enolate anions would favor the *cis*-enolate **20** and, also, could be detected by formation of the enol acetate corresponding to the terminal enolate **25a**.

The results of this and several related experiments are summarized in Table IV. From these data, one

TABLE IV

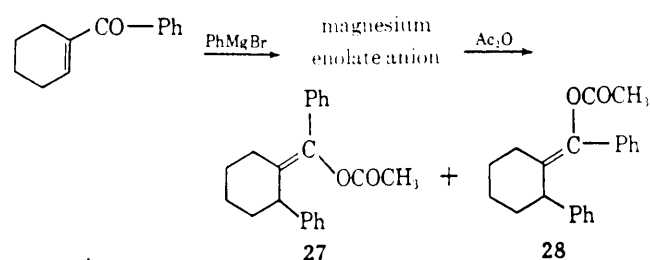
PREPARATION AND ACETYLATION OF THE ENOLATE ANIONS **20** AND **22** DERIVED FROM 4-METHYL-2-PENTANONE (**4**)

Reactants	Solvent	Yield of acetylated enolates, %	Product composition, %— <i>cis</i> -Enol acetate 23	<i>trans</i> -Enol acetate 24	diketone 26
Unsaturated ketone 1 + Li ⁺ Me ₂ Cu ⁻	Et ₂ O	68	26	59	15
Unsaturated ketone 1 + MeMgBr + 1 mole % (<i>n</i> -Bu) ₂ PCuI	Et ₂ O	72	36	3	61
Unsaturated ketone 1 + MeMgBr	Et ₂ O	12	Ca. 63	Ca. 1	Ca. 36
Enol acetates ^a + MeLi	DME	75	82	18	<1
Enol acetates ^b + MeLi	Et ₂ O	72	72	22	6
Enol acetates ^a + MeMgBr	Et ₂ O	71	49	3	48

^a A mixture of enol acetates containing 81% of the *cis* isomer **23** and 19% of the *trans* isomer **24** was added to 2 equiv of the organometallic reagent (cf. ref 15). ^b A mixture of enol acetates containing 75% of the *cis* isomer **23** and 25% of the *trans* isomer **24** was added to 2 equiv of the organometallic reagent.

can conclude a minimum of 69% of the mixture of enolate anions **20** and **22** produced from reaction of the unsaturated ketone **1** with lithium dimethylcopper (**7**) is the *trans* isomer **22**. This constitutes direct experimental proof that at least 69% of this conjugated addition did not proceed via the cyclic transition state **19** and we see no reason to suppose that any significant fraction of this reaction proceeded by such a pathway. Attempts to perform analogous experiments with methylmagnesium bromide, either with or without the addition of a catalytic amount of a copper(I) species were complicated in the acetylation step by the formation of substantial amounts of C-acetylated product, the diketone **26**.¹⁶ Orienting experiments in which known mixtures of the enolate anions **20** and **22** were generated from the enol acetates¹⁵ **23** and **24** demonstrated that C-

acylation was favored slightly by the use of ether rather than 1,2-dimethoxyethane as a solvent and, especially, by the presence of magnesium rather than lithium as the counter ion of the enolate anion. Although this phenomenon is of interest in connection with our concurrent studies of enolate anion reactions and will be discussed elsewhere, the formation of predominantly the C-alkylated product with the methylmagnesium derivatives in the present study proved to be particularly unfortunate. Perusal of that data in Table IV reveals that more *trans*-enolate **22** than *cis*-enolate **23** is converted to the C-acetylated product. Consequently, although it would appear that the *trans*-enolate anion **22** is formed in substantial amounts in all cases, we can provide unambiguous proof for this contention only in the reaction of the unsaturated ketone **1** with lithium dimethylcopper. However, it should be noted that a recent publication¹⁷ describes trapping the enolate anions from benzoylcyclohexene and phenylmagnesium bromide by acetylation to form a 1:1 mixture of the enol acetates **27** and **28**. This observation like our own clearly is not compatible with a cyclic transition state analogous to **19** (which would have led exclusively to the enol acetate **27** in this case).

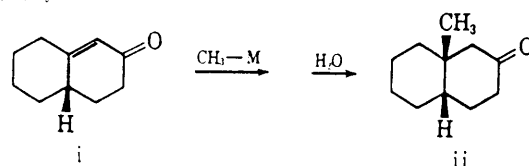


We had hoped also to learn from the aforementioned enolate trapping experiments whether the conjugate addition of methylcopper derivatives and methylmagnesium derivatives have different stereochemical requirements. We had obtained the same stereoisomer (introduction of an axial phenyl group) in previous reactions of $\Delta^8,9$ -octal-1-one with either a phenylmagnesium or a phenylcopper derivative.^{18,19} Similar results have been obtained with methyl derivatives.^{18,19} All of the above studies suffer from the disadvantage that the systems studied gave significant amounts of only one of the two possible stereoisomer adducts and, consequently, may not have been sensitive to small steric differences. The first demonstration that the steric requirements are different for the conjugate addition of phenylmagnesium and phenylcopper derivatives was provided in a study of asymmetric induc-

(17) S. K. Malhotra and F. Johnson, *J. Am. Chem. Soc.*, **87**, 5493 (1965).

(18) (a) W. J. Wechter, *J. Org. Chem.*, **29**, 163 (1964); (b) H. Mori, *Chem. Pharm. Bull. (Tokyo)*, **12**, 1224 (1964); *Chem. Abstr.*, **62**, 1710 (1965).

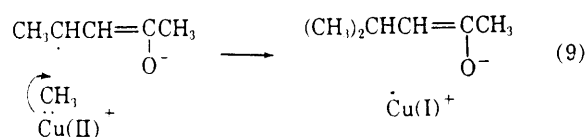
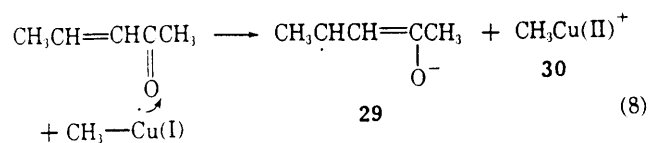
(19) (a) Addition of methylmagnesium derivatives to $\Delta^8,9$ -octal-2-one systems (e.g., **i**) typically gives the *cis*-fused 2-decalone product (e.g., **ii**). (b) A. J. Birch and M. Smith, *Proc. Chem. Soc.*, 356 (1962); (c) R. F. Church, R. E. Ireland, and D. R. Shridhar, *J. Org. Chem.*, **27**, 707 (1962); (d) M. Torigoe and J. Fishman, *Tetrahedron Letters*, No. 19, 1251 (1963). However, these observations need not be incompatible with the foregoing examples since the bridgehead methyl group is necessarily axial with respect to one of the two cyclohexane rings.



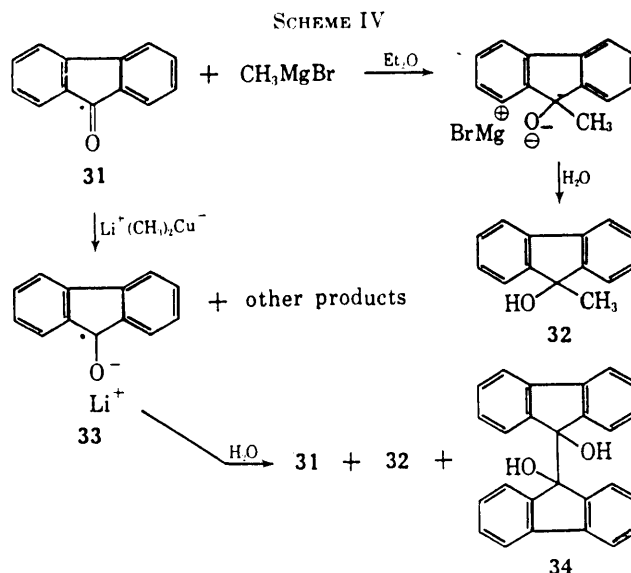
(16) The spectral properties of this product, described in the experimental section, are not in accord with the recent claim that this product exists as a nonchelated *trans*-enol.

tion by Inouye and Walborsky.²⁰ A second example of this phenomenon appears probable in the recent work of Marshall and Anderson.²¹ In an effort to find a system where we could study this phenomenon, we prepared the unsaturated ketone 12; earlier studies^{2d} of the addition of methylmagnesium derivatives to 4-*t*-butylcyclohexanone suggested that we might expect little preference for attack of methylmagnesium derivatives either *cis* or *trans* to the *t*-butyl group. In practice, reaction of the ketone 12 with methylcopper (either in catalytic or stoichiometric amount) yielded a single stereoisomeric ketone 16 accompanied by small amounts of the alcohol 17. The configuration of the ketone 16 was determined by degradation to the known²² alcohol 18. Unfortunately, our plan was thwarted at this point because the reaction of the unsaturated ketone 16 with methylmagnesium bromide gave only the alcohol 17; no conjugate addition product 16 could be detected. Consequently, we are unable to elaborate on the difference between conjugate addition of alkylcopper and alkylmagnesium derivatives until a more satisfactory system for study is found.

Although the aforementioned data exclude a cyclic 1,4-addition process as the predominant pathway for the conjugate addition of organocopper compounds, the possibility remains that formation of a coordination complex between the conjugated olefin and the organocopper reagent is an important first step in the reaction path. The presence of either excess tri-*n*-butylphosphine (Table I) or pyridine (Table II) in the reaction mixtures had no observed effect although these additives might be expected to compete with the unsaturated ketone for coordination positions on copper. Also, we could discern no evidence for the formation of a copper(I)-ketone complex from examining the infrared, nmr, and ultraviolet spectra of ether solutions containing the ketone 1 and the copper(I) iodide-tri-*n*-butylphosphine complex. As an hypothesis to guide further work, we are prompted to suggest that the reaction of methylcopper with the unsaturated ketone involves either a partial or complete electron transfer to form either a charge-transfer complex or the ion radical 29. Subsequent transfer of a methyl radical from a transient methylcopper(II) species 30 or collapse of the charge-transfer complex would complete the addition sequence.

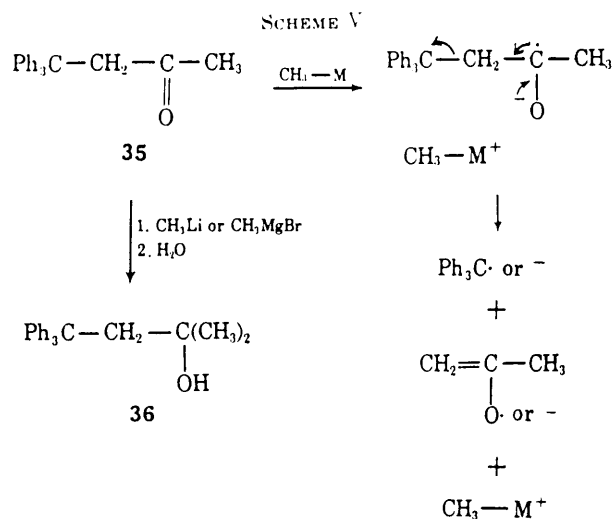


Some evidence favoring this idea was found in the reaction of lithium dimethylcopper (7) with fluorenone (31) (Scheme IV) in ether solution. Although the addition of fluorenone to an ethereal solution of methylmagnesium bromide resulted in rapid addition to form the alcohol 32, this reaction with lithium dimethyl-



copper (7) yielded a deep green solution as soon as the reagents were mixed. The color of the solution was rapidly discharged on addition of air or water and the electron spin resonance (esr) spectrum²³ of the solution was consistent with the presence of an anion radical such as 33; the same radical species appeared to result from reaction of an ethereal solution of fluorenone with lithium metal.²⁴ Hydrolysis of the green solution obtained from fluorenone and lithium dimethylcopper(I) afforded a mixture of fluorenone (31) and the alcohols 32 and 34.^{24b} The fact that a radical anion was observed does not, of course, prove that it was an intermediate in the addition reaction.

In an ancillary experiment, we examined the reactions of the triphenyl ketone 35 (Scheme V), with methyl-



(23) We are indebted to Professor Kerry Bowers and Mr. Peter Lehman for these measurements.

(24) (a) For a review of earlier work and a discussion of the transfer of electrons from carbanions to unsaturated systems, see G. A. Russell, E. G. Janzen, and E. T. Strom, *J. Am. Chem. Soc.*, **86**, 1807 (1964). For studies of the fluorenone anion radical, see (b) W. E. Bachmann, *ibid.*, **55**, 1179 (1933); (c) H. E. Bent and A. J. Harrison, *ibid.*, **66**, 969 (1944); (d) D. J. Marantz and E. Warhurst, *Trans. Faraday Soc.*, **51**, 1375 (1955); (e) B. J. McClelland, *ibid.*, **57**, 1458 (1961); (f) A. Mathias and E. Warhurst, *ibid.*, **58**, 948 (1962); (g) H. V. Carter, B. J. McClelland, and E. Warhurst, *ibid.*, **56**, 455 (1960); (h) V. M. Kazakova and Y. K. Syrkin, *Zh. Strukt. Khim.*, **3**, 536 (1962); (i) P. B. Ayscough and R. Wilson, *J. Chem. Soc.*, 5412 (1963); (j) N. Hirota and S. I. Weissman, *J. Am. Chem. Soc.*, **86**, 2537, 2538 (1964); (l) R. Dehl and G. K. Fraenkel, *J. Chem. Phys.*, **39**, 1793 (1963); (m) I. D. Morozova and M. E. Dyatkina, *Dokl. Akad. Nauk SSSR*, **146**, 830 (1962).

(20) Y. Inouye and H. M. Walborsky, *J. Org. Chem.*, **27**, 2706 (1962).

(21) J. A. Marshall and N. H. Anderson, *ibid.*, **31**, 667 (1966).

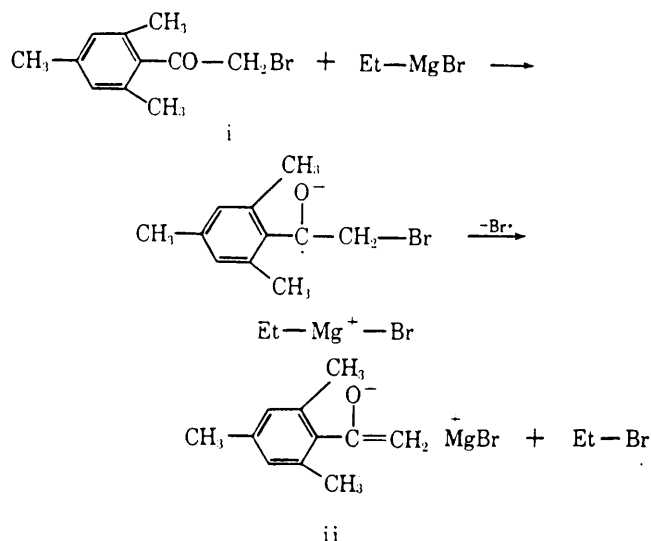
(22) F. D. Greene and A. Fang, to be published.

lithium and with methylmagnesium bromide. It was our thought that, if the intermediate ketyl were formed, it might fragment as indicated at a rate comparable with the addition of a methyl group.²⁵ However, in all cases examined, the expected addition product was formed in greater than 90% yield and no evidence was obtained for the presence of a triphenylmethyl carbanion or free radical.

Experimental Section²⁶

Preparation of Starting Materials—Ethereal solutions (approximately 1 *M*) of methylmagnesium bromide, dimethylmagnesium (from dimethylmercury), and methyl lithium (from methyl bromide) were prepared and standardized (with phenyldimethylsilyl chloride) as previously described.^{2,27} Authentic samples of the tertiary allylic alcohol 3 and the saturated ketone 4 were described previously.²⁸ The preparative route, oxidation of *trans*-3-penten-2-ol, used previously²⁸ for the unsaturated ketone 1 gave a crude product which was difficult to separate from small amounts of the starting alcohol. Consequently, this ketone 1 was subsequently prepared by a Wittig reaction. In a typical run, a solution of 91.50 g (0.228 mole) of acetyl-methylenetriphenylphosphorane [mp 205–207° (lit.²⁸ mp 209–210°)] in 300 ml of methylene chloride was treated with a solution of 25 g (0.57 mole) of acetaldehyde in 50 ml of methylene chloride. After the solution had been refluxed for 6 hr and then allowed to stand for 6 hr, the solvent was distilled from

(25) The reaction of α -bromo derivatives of hindered ketones (e.g., i) with Grignard reagents to form enolate anions (e.g., ii) may be pictured as a comparable process.



For examples, see (a) C. H. Fisher, H. R. Snyder, and R. C. Fuson, *J. Am. Chem. Soc.*, **54**, 3665 (1932); (b) E. P. Kohler and M. Tishler, *ibid.*, **54**, 1594 (1932); (c) S. Binns, J. S. G. Cox, E. R. H. Jones, and B. G. Ketcheson, *J. Chem. Soc.*, 1161 (1964); (d) E. R. H. Jones and D. A. Wilson, *ibid.*, 2933 (1965).

(26) All melting points are corrected and all boiling points are uncorrected. Unless otherwise stated magnesium sulfate was employed as a drying agent. The infrared spectra were determined with a Perkin-Elmer, Model 237, infrared recording spectrophotometer fitted with a grating. The ultraviolet spectra were determined with a Cary recording spectrophotometer, Model 14. The nmr spectra were determined at 60 Mc with a Varian, Model A-60, nmr spectrometer; all chemical shifts are expressed in parts per million relative to internal tetramethylsilane. The mass spectra were obtained with a CEC, Model 21-130, mass spectrometer. The microanalyses were performed by Dr. S. M. Nagy and his associates and by the Scandinavian Micro-analytical Laboratory. All reactions involving organometallic reagents were run under a nitrogen atmosphere unless otherwise noted.

(27) (a) H. O. House and W. L. Respess, *J. Organometal. Chem.*, **4**, 95 (1965). (b) Throughout this study, the magnesium employed was a single lot of Eastman Kodak's Grignard grade magnesium metal. Although we have no indication that trace impurities in the magnesium are influencing our results, all of the data reported for magnesium compounds in this paper utilized the same lot of magnesium so that any effect of trace impurities should be constant.

(28) F. Ramirez and S. Dershowitz, *J. Org. Chem.*, **22**, 41 (1957).

the mixture through an 80-cm Vigreux column, and the residue was diluted with 200 ml of pentane. After the crystalline triphenylphosphine oxide had been collected, the organic filtrate was concentrated and fractionally distilled to separate 19.24 g (75.5%) of the ketone 1, a colorless liquid, bp 113–119°, n_D^{20} 1.4352 (lit.²⁹ bp 121–122.5°, n_D^{20} 1.4342). The infrared absorption and gas chromatogram³⁰ of this sample corresponded to the same data for the previously described²⁸ sample of the *trans* ketone 1. Reaction of 5.11 g (51 mmoles) of the saturated ketone 4 with 75 mmoles of methylmagnesium bromide in 75 ml of ether for 30 min, followed by hydrolysis with aqueous ammonium chloride and the usual isolation procedure, yielded 3.47 g (59%) of the saturated alcohol 9, bp 129–131°, n_D^{20} 1.4130 (lit.³¹ bp 130–132°, n_D^{20} 1.4140). The sample has infrared absorption³² at 3610 and 3480 cm^{-1} (unassociated and associated OH) with nmr³² peaks at δ 2.43 (1 H broad singlet shifted by the addition of pyridine, OH), 1.34 (2 H doublet

with $J = 5.5$ cps, CH_2), 1.15 [6 H singlet, $(\text{CH}_3)_2\text{CO}$], and 0.94 [6 H doublet with $J = 6$ cps, $(\text{CH}_3)_2\text{C}$] as well as a broad multiplet in the region δ 1.3–2.0 (1 H, $>\text{CH}$). The mass spectrum exhibits no molecular ion peak, but has relatively abundant fragment peaks at m/e 101 ($\text{M} - \text{CH}_3$), 59 [$(\text{CH}_3)_2\text{C}=\text{OH}$], 57, 43, 41, and 31. Subsequently described mixtures of the ketones 1 and 4 and the alcohols 3 and 9 were analyzed by gas chromatography.³⁰ The gas chromatography equipment was calibrated with known mixtures prepared from authentic samples and weighed samples of cumene were added as internal standards to permit yield calculations. The retention times³⁰ of these components follow: saturated ketone 4, 20.6 min; saturated alcohol 9, 26.8 min; unsaturated alcohol 3, 29.1 min.; cumene, 34.4 min; and unsaturated ketone 1, 45.7 min. The tri-*n*-butylphosphine complex of copper(I) iodide [white needles from isopropyl alcohol, mp 74–74.5° (lit.³³ mp 75°)] was prepared as previously described.³⁴ The solvents, tetrahydrofuran (THF) and 1,2-dimethoxyethane (DME), used for certain of the organometallic reactions were purified by distillation from lithium aluminum hydride just prior to use.

The various organocopper(I) reagents employed were prepared by adding the ethereal organolithium or organomagnesium solutions to a slurry of copper(I) iodide in anhydrous ether. Although these additions were initially performed at -78° after which the solutions were warmed to 0° , in subsequent experiments the initial mixing and the subsequent reactions were effected at 0° . When 1 equiv of either methyl lithium or a methylmagnesium derivative was added to copper(I) iodide, a yellow precipitate of methylcopper separated. Addition of excess methylmagnesium compound had no apparent effect on this insoluble methylcopper but the addition of an additional equivalent of methyl lithium dissolved the precipitate to give a colorless to pale tan solution. This change appears to be reversible since methylcopper was often observed to reprecipitate from solutions of lithium dimethylcopper which were treated with the unsaturated ketone 1. The addition of 1 equiv of methyl lithium to an ether solution of the copper(I) iodide-tri-*n*-butylphosphine complex at 0° resulted in the formation of a colorless solution. When an ethereal solution of 1.0 equiv of methylmagnesium bromide was added to an ethereal solution of 1.0 equiv of tri-*n*-butylphosphine-copper(I) iodide complex, a yellow precipitate of methylcopper separated and was not redissolved by the addition of excess methylmagnesium bromide. This is apparently a result of the facts that formation of magnesium salts of the dimethylcopper(I) anion is not favorable and that the first equivalent of tri-*n*-butylphosphine is complexed with magnesium halide. It was possible to obtain an ethereal solution of the methylcopper-tri-*n*-butylphosphine complex from the Grignard reagent by adding 1.0 equiv of methylmagnesium bromide to an ether solution containing both 1.0 equiv of tri-*n*-butylphosphine and 1.0 equiv of the tri-*n*-butylphosphine-copper(I) iodide complex. The nmr data for ether solu-

(29) A. L. Wilds and C. Djerassi, *J. Am. Chem. Soc.*, **68**, 1715 (1951).

(30) A 4-m gas chromatography column containing two different packings was employed for this analysis. The first half of the column was packed with a suspension of 4-methyl-4-nitropimelonitrile on Chromosorb P and the second half of the column was packed with Carbowax, No. 1540, suspended on Chromosorb P.

(31) W. J. Hickinbottom, D. Peters, and D. G. M. Wood, *J. Chem. Soc.*, 1360 (1955).

(32) Determined as a solution in carbon tetrachloride.

TABLE V
 RATES OF REACTION OF *trans*-3-PENTEN-2-ONE (1) AND 4-METHYL-2-PENTANONE (4) WITH ORGANOMETALLIC REAGENTS

Ketone (mmoles)	Organometallic reagent (mmoles)	Additive ^a (mmoles)	Solvent (ml)	Reac- time, sec	% ^b reac- tion	Yields, % ^c				% conjugate addn in the product
						1	3	4	9	
1 (2.48)	MeMgBr (8.80)	...	Et ₂ O (37.6)	0.062	29	67	24	4	..	14
1 (2.48)	MeMgBr (11.30)	...	Et ₂ O (22.6)-THF (20)	0.067	37	59	31	4	..	13
1 (2.47)	MeMgBr (11.10)	...	Et ₂ O (22.2)-DME (20)	0.068	98	2	90	3	..	3
1 (2.48)	Me ₂ Mg (4.40)	...	Et ₂ O (37.6)	0.062	97	2	76	18	..	19
1 (2.50)	MeLi (8.80)	...	Et ₂ O (37.6)	0.062	>99	..	98	<1	..	<1
1 (2.60)	MeLi (8.80)	<i>n</i> -Bu ₃ PCuI (0.102)	Et ₂ O (37.6)	0.062	>99	..	89	8	..	9
1 (2.50)	Me ₂ Mg (4.40)	<i>n</i> -Bu ₃ PCuI (0.103)	Et ₂ O (37.6)	0.062	>99	..	17	79	..	82
1 (2.52)	MeMgBr (8.80)	<i>n</i> -Bu ₃ PCuI (0.103)	Et ₂ O (37.6)	0.062	>99	..	1	95	..	99
1 (2.52)	MeMgBr (8.80)	<i>n</i> -Bu ₃ PCuI (0.104) + isoprene (25.2)	Et ₂ O (37.6)	0.062	>99	..	2	95	..	98
1 (2.55) ^d	MeMgBr (8.80)	<i>n</i> -Bu ₃ PCuI (0.107) + <i>n</i> -Bu ₃ P (0.604)	Et ₂ O (37.6)	0.062	>99	..	4	87	..	96
1 (2.50)	MeMgBr (11.30)	<i>n</i> -Bu ₃ PCuI (0.102)	Et ₂ O (22.6)-THF (20)	0.067	91	8	28	58	..	68
1 (2.48)	MeMgBr (11.30)	CuBr ₂ (0.103) ^e	Et ₂ O (22.6)-THF (20)	0.067	72	27	26	45	..	64
1 (2.48)	MeMgBr (11.30)	Cu(OAc) ₂ (0.100) ^e	Et ₂ O (22.6)-THF (20)	0.067	67	31	23	41	..	64
1 (2.54)	MeMgBr (11.30)	<i>n</i> -Bu ₃ PCuI (0.102)	Et ₂ O (22.2)-DME (20)	0.068	98	2	77	20	..	20
1 (2.50)	<i>n</i> -Bu ₃ PCuMe ^f (8.30)	...	Et ₂ O (36.6)	0.065	>99	93	..	99
4 (2.52)	MeMgBr (8.80)	...	Et ₂ O (37.6)	0.062	5	91	5	...
4 (2.51)	MeMgBr (8.80)	<i>n</i> -Bu ₃ PCuI (0.104)	Et ₂ O (37.6)	0.062	5	89	5	...

^a The specified additives were in the reservoir with the ketone solution prior to reaction. ^b The per cent reaction was calculated as follows: per cent recovery of starting material (100)/total per cent yield or recovery of materials from the reaction mixture. ^c These per cent yields, or recovery, calculated from the gas chromatographic data, are based on the amount of starting ketone employed. ^d The data for this run are based on a single experiment. ^e These copper(II) salts, although insoluble in ether, were soluble in the tetrahydrofuran solution of the ketone in the reactant reservoir. ^f This reagent was preformed in ether solution at 0° from 8.30 mmoles of methyl lithium and 8.63 mmoles of *n*-Bu₃PCuI. No decomposition of the reagent in the reactor prior to mixing was apparent.

tions of lithium dimethylcopper(I) and the tri-*n*-butylphosphine complex of methylcopper (I) are summarized in Table III.

Procedure for Kinetic Studies.—The flowing-stream apparatus was assembled and calibrated as previously described.^{2b} In one reservoir of the apparatus was placed 25 ml of an ethereal solution containing 12.5 mmoles of methylmagnesium bromide, 12.5 mmoles of methyl lithium, or 6.25 mmoles of dimethylmagnesium. A solution of approximately 2.5 mmoles of *trans*-3-penten-2-one (1) or 4-methyl-2-pentanone (4), a weighed amount of cumene (approximately 20 mg as an internal standard), and measured amounts of any other additives in 20 ml of solvent (ether, THF, or DME) was placed in the second reservoir.³³ These solutions were forced through the mixing chamber and reaction tube under a positive nitrogen pressure equivalent to 50 cm of mercury until the ketone reservoir just emptied (the organometallic was always in excess). The reaction solutions were quenched in a cold (0°), vigorously stirred mixture of 20 ml of methanol and 15 ml of water, a quenching mixture which gave a homogeneous mixture at the end of the reaction. The resulting reaction mixture was saturated by the addition of ammonium chloride which caused separation of the organic and aqueous phases. The ether layer was separated and washed with saturated, aqueous ammonium chloride and the combined aqueous phases were extracted with petroleum ether. The combined organic solutions were dried over calcium sulfate and then analyzed by gas chromatography.³⁰ The results of these reactions are summarized in Table V; except where noted all of the yield data are average values obtained from two or more runs. In no case did the average values reported differ from individual values by more than 1%. To determine reaction times and mixing ratios, the apparatus was calibrated with ether *vs.* ether, ether *vs.* ethereal 0.5 *M* methylmagnesium bromide, ether *vs.* ethereal 0.5 *M* methylcopper-tri-*n*-butylphosphine complex, ether *vs.* tetrahydrofuran, ether *vs.* 1,2-dimethoxyethane, and with the preformed reaction mixture from the ketone 1 and methylmagnesium bromide. The molar quantities and reaction times listed in Table V have been corrected from these calibration data.

(33) The temperatures of the initial solutions ranged from 25 to 28°. As noted previously (ref 2b), the fact that these kinetic runs are necessarily adiabatic in character results in a significant increase (i.e., 5–10°) in the temperature of the reaction solutions as they are mixed and pass down the reaction tube. At the concentration levels where we are working, this is an inherent error in our measurements and has led us to conclude that more elaborate control of the temperatures of our initial solutions is a superfluous precaution.

Procedure for Other Product Studies.—A solution of the organometallic reagent and any added copper derivative in 25 ml of ether was prepared and the solution was maintained at 0° while an ethereal solution of the ketone 1 or 4 and a weighed amount of cumene (as an internal standard) was added, rapidly and with stirring. The reaction mixture was stirred for the specified time (Table VI) and then added to aqueous ammonium chloride. The ether extract of the resulting reaction mixture was dried and analyzed by gas chromatography.³⁰ In certain of our early experiments, in which the organometallic reagent was hydrolyzed by the addition of aqueous ammonium chloride to the reaction mixture, an additional product, the saturated alcohol 9, was also produced. A collected³⁰ sample of this product was identified by the previously described authentic sample by comparison of gas chromatographic retention times and infrared spectra. The following experiment was performed to demonstrate that the saturated alcohol is not formed in the original reaction mixture but rather during the hydrolysis procedure in which aqueous ammonium chloride is added to the reaction solution. A solution of 421 mg (5.01 mmoles) of the ketone 1 and 398 mg of cumene in 40 ml of ether was added, dropwise and with stirring, to 40 ml of an ethereal solution containing 20 mmoles of methylmagnesium bromide. The reaction mixture was stirred at room temperature for 75 min and then a 25-ml aliquot of the solution was added to aqueous ammonium chloride. Analysis³⁰ of the ethereal layer obtained by this procedure indicated the presence of the saturated ketone 4 (17% yield) and the unsaturated alcohol 3 (74% yield) corresponding to 19% of conjugate addition product. Aqueous ammonium chloride was added to the remaining 55 ml of reaction solution. Analysis³⁰ of the resulting ethereal layer indicated the presence of the saturated ketone 4 (14% yield), the saturated alcohol 9 (4% yield), and the unsaturated alcohol 3 (73% yield) corresponding to 20% conjugate addition products 4 and 9.

The reactions studied are summarized in Table VI. Except where noted, the results are average values obtained from two or more experiments. In no case did the average values reported in the table differ from individual values by more than 3%. Unless otherwise noted, the reaction mixtures were hydrolyzed by adding them to aqueous ammonium chloride solution. In cases where the reverse procedure (addition of aqueous ammonium chloride to the reaction mixture) was used, the percentage of the product derived from conjugate addition is derived from the sum of the yields of saturated ketone 4 and saturated alcohol 9.

In an additional experiment, 643 mg (5.0 mmoles) of naphthalene was added to a solution of lithium dimethylcopper(I)

TABLE VI
 REACTION OF *trans*-3-PENTEN-2-ONE (1) AND 4-METHYL-2-PENTANONE (4) WITH ORGANOMETALLIC REAGENTS

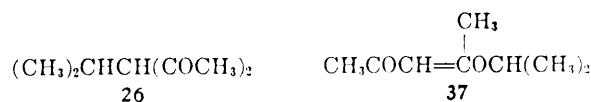
Ketone (mmoles)	Organometallic reagent (mmoles)	Additive ^a (mmoles)	Ether, ml	Reaction time, min	Yields, % ^b			-% conjugate addn in the product
					3	4	9	
1 (3.13) ^{c,d}	MeMgBr (12.5)	<i>n</i> -Bu ₃ PCuI ^e (0.125)	50	10	1	72	18	99
1 (3.24) ^{c,d}	MeMgBr (12.5)	Cu(OAc) ₂ ^f (0.12)	50	45	20	56	24	80
1 (3.10) ^c	MeMgBr (12.5)	<i>n</i> -Bu ₃ PAGI ^g (0.125)	50	10	69	16	...	19
1 (3.13)	MeMgBr (12.7)	CuI ^h (6.29)	50	25	4	87	...	96
1 (3.10)	Me ₃ Mg (6.34)	CuI ⁱ (6.29)	50	25	6	85	...	94
1 (3.16)	MeLi (12.2)	CuI ⁱ (12.6)	50	45	...	96	...	>99
1 (3.16)	MeLi (12.5)	CuI ^j (6.30)	50	25	...	94	...	>99
1 (1.24)	MeLi (5.00)	<i>n</i> -Bu ₃ PCuI ^k (5.48)	20	45	...	93	...	>99
1 (2.50) ^c	MeLi (10.0)	CuI (5.0) + pyridine	40.3 ^l	Ca. 1	...	89	...	>99
4 (3.12)	MeLi (12.2)	CuI (12.6) ⁱ	50	45	...	90	2	...
4 (2.47)	MeLi (10.0)	<i>n</i> -Bu ₃ PCuI ^k (10.1)	40	45	...	89	<1	...
4 (1.28) ^c	MeLi (5.02)	CuI (2.50) ^j	20	2	...	69	20	...
4 (2.48)	MeLi (10.0)	CuI (4.99) ^j	40	60	...	35 ^m	31 ^m	...
4 (2.50) ^c	MeLi (10.0)	CuI (3.31) ^j	40	2	...	1	99	...
4 (2.46) ^c	MeLi (10.0)	...	40	15	...	1 ⁿ	99	...

^a The specified additive was mixed with the organometallic solution in the reaction flask and then the ethereal solution of the ketone was added. ^b These per cent yields, calculated from the gas chromatographic data, are based on the amount of starting ketone employed. ^c These data are derived from a single experiment. ^d In this experiment, hydrolysis was accomplished by adding aqueous ammonium chloride to the reaction mixture. ^e In this case, an ether solution of the copper(I) complex and the ketone was added to the organometallic reagent. ^f The Grignard reagent solution turned black (presumably colloidal metallic copper) as soon as the copper(II) acetate was added. This organometallic reagent was then deliberately allowed to stand for 3 hr to see how much catalytic activity would be lost. ^g In this case the ether solution containing both the ketone and the silver iodide-tri-*n*-butylphosphine complex was added to the Grignard reagent. The addition resulted in the generation of a bright red solution which rapidly blackened (probably from the deposition of metallic silver). ^h No reaction was observed when the ethereal Grignard reagent was added to copper(I) iodide at -78°. However, a suspension of yellow solid (presumably methylcopper) formed but did not dissolve as the mixture was warmed to 0°. ⁱ A suspension of yellow solid (presumably methylcopper) formed when the organometallic reagent was added to copper(I) iodide at -78° and did not dissolve as the solution warmed to 0°. ^j The addition of ethereal methyllithium to copper(I) iodide at -78° resulted in the initial formation of a yellow precipitate which redissolved as the remainder of the methyllithium was added. ^k The addition of ethereal methyllithium to the tri-*n*-butylphosphine-copper(I) iodide complex at 0° resulted in the formation of a colorless solution. ^l In this reaction a solution of copper(I) iodide in pyridine was treated with ethereal methyllithium at 0°. After this mixture had been stirred at 0° for 5 min, a solution of the ketone in pyridine was added. The volumes of solvents used were 35 ml of pyridine and 5.3 ml of ether. ^m These data are typical of a number of experiments in which the ketone 4 was allowed to react with excess lithium dimethylcopper for relatively long periods of time (5-60 min). The amount of starting ketone 4 recovered decreased more rapidly than the yield of alcohol 9 increased. Since examination of high-temperature gas chromatograms of the crude reaction product failed to reveal an additional peak, the nature of the additional product(s) being formed in this reaction is not known. ⁿ This small amount of recovered ketone presumably resulted from a small amount of enolate anion formed in a side reaction.

[from 1.906 g (10 mmoles) of copper(I) iodide and 20 mmoles of methyllithium] in 50 ml of ether. The mixture was stirred for 15 min in an ice bath and then for 30 min at room temperature. After the organometallic reagent had been hydrolyzed by the addition of aqueous ammonium chloride, the organic layer was separated and analyzed by gas chromatography.^{30,34} Only naphthalene was detected in this solution and 1-methylnaphthalene and 2-methylnaphthalene (which would have been resolved) were not detected. The naphthalene recovered from this reaction was identified with an authentic sample by a mixture melting point determination and by comparison of infrared spectra. Analogous reactions were run with a mixture of norbornene and either an ethereal solution of lithium dimethylcopper(I) or an ethereal suspension of methylcopper. In both cases, only norbornene was detected^{30,34} in the recovered solution of the organic products and collected³⁰ samples of the products were identified with an authentic sample of norbornene by comparison of retention times and infrared spectra.

Acetylation of the Enolate Anions Derived from Ketone 4.—Authentic samples of the previously described^{15b} enol acetates 23, 24, and 25b were prepared by the reaction of the ketone 4 with isopropenyl acetate^{15b} or with acetic anhydride and perchloric acid in carbon tetrachloride.^{15a} For subsequent gas chromatographic³⁴ analyses, anisole was employed as an internal standard. The retention times follow: saturated ketone 4, 8.7 min; *cis*-enol acetate 23, 19.0 min; terminal enol acetate 25b, 22.4 min; *trans*-enol acetate 24, 24.6 min.; and anisole 30.6 min. The equilibrium mixture of these enol acetates (neat at 100°) was previously found^{15b} to contain 73% *cis* isomer 23, 22% *trans* isomer 24, and 5% terminal unsaturated isomer 25b. To obtain an authentic sample of the C-acetylation product, the diketone 26, a mixture of 10.0 g (0.100 mole)

of acetylacetone, 22.86 g. (0.13 mole) of isopropyl iodide, 13.0 g (0.094 mole) of anhydrous potassium carbonate, and 25 ml of acetone was refluxed for 20 hr. The resulting mixture was concentrated, diluted with ether, filtered, and distilled to separate the unchanged reactants from a 1.189-g (8.4%) fraction of colorless liquid, bp 68-72° (12 mm), *n*_D²⁰ 1.4430, which contained the monoalkylated products.^{35,36} This product contained³⁴ ca. 70% of the β diketone 26 (first eluted) and ca. 30% of the O-alkylated product 37 (eluted second). A collected³⁴ sample of the diketone 16 was identified with a subse-



quently described sample by comparison of infrared spectra and gas chromatographic retention times. A collected³⁴ sample of the second product, one of the stereoisomers of the enol ether 37, has infrared absorption³² at 1680 (conjugated C=O) and 1580 cm⁻¹ (conjugated C=C) with an ultraviolet maximum³² at 261 mμ (ε 16,200) and nmr absorption³² at δ 5.34 (1 H par-

(35) The pure β diketone 26 is reported to boil at 183-185° [J. T. Adams and C. R. Hauser, *J. Am. Chem. Soc.*, **67**, 284 (1945)] or 82-86° (20 mm) [E. H. Man, F. C. Frostick, Jr., and C. R. Hauser, *ibid.*, **74**, 3228 (1952)] and to give a negative ferric chloride test [F. G. Younz, F. C. Frostick, Jr., J. J. Sanderson, and C. R. Hauser, *ibid.*, **72**, 3635 (1950)].

(36) The preparation of the diketone 26 by the alkylation of the sodium derivative of acetylacetone has been recently reported by S. T. Yoffe, E. M. Popov, K. V. Vatsuro, E. K. Tulikova, and M. I. Kabachnik, *Tetrahedron*, **18**, 923 (1962). The physical constants reported for this preparation were bp 82-83° (20 mm), *n*_D²⁰ 1.4420, in close agreement with our values. In a subsequent publication, Y. N. Molin, S. T. Yoffe, E. E. Zaez, E. K. Salov'eva, E. E. Kugucheva, V. V. Voevodskii, and M. I. Kabachnik [*Izv. Akad. Nauk SSSR, Ser. Khim.*, 1556 (1965); *Chem. Abstr.*, **64**, 1916 (1966)] have also concluded that their product is a mixture.

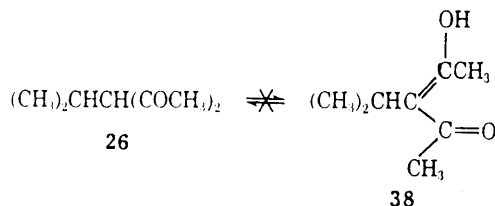
(37) Determined as a solution in 95% ethanol.

(34) A gas chromatography column packed with silicone fluid, no. 710 suspended on Chromosorb P was employed for this analysis.

tially resolved multiplet, half-bandwidth 2 cps vinyl CH), 4.38 (1 H, seven-line signal with $J = 6$ cps, OCH), 2.17 and 2.02 [two 3 H singlets (the long-range coupling of one of these signals with the vinyl CH signal was not resolved), CH_3CO and $\text{CH}_3\text{C}=\text{C}$], and 1.28 [6 H doublet with $J = 6$ cps, $(\text{CH}_3)_2\text{C}$]. The mass spectrum of the sample has a molecular ion peak at m/e 142 with abundant fragment peaks at m/e 100, 85, 43, and 41.

Anal. Calcd. for $\text{C}_8\text{H}_{14}\text{O}_2$: C, 67.57; H, 9.93. Found: C, 67.29; H, 9.84.

The infrared, ultraviolet [$(\lambda_{\text{max}} 262 \text{ m}\mu (\epsilon 6500))$],³⁷ and nmr absorption of the original monoalkylated product mixture corresponded very well to a mixture of **26** and **37**; furthermore, the spectra of this mixture corresponded very closely to the published curves³⁶ for the supposedly partially enolized sample of the diketone **26**. Thus, we conclude that the published³⁶ report that the diketone **26** is in equilibrium with a *trans*-enol form (*i.e.* **38**) is erroneous.



A cold (0°) solution of lithium dimethylcopper(I) [from 1.196 g (6.28 mmoles) of copper(I) iodide, 12.6 mmoles of methyl-lithium, and 24.6 ml of ether] was treated with a solution of 273 mg (3.25 mmoles) of the unsaturated ketone **1** in 25 ml of ether. After the solution had been stirred for 15 min, it was added, with stirring, to 6.12 g (60 mmoles) of acetic anhydride. The resulting mixture was stirred for 30 min, mixed with 30 ml of pentane, and 30 ml of cold (0°), saturated, aqueous sodium bicarbonate, and then stirred for an additional 1 hr. Solid sodium bicarbonate was added until the carbon dioxide evolution ceased; then the organic layer was separated and the aqueous phase was extracted with pentane. The combined organic solutions were dried, concentrated, mixed with 214 mg of anisole (as internal standard), and analyzed.³⁴ The calculated yields were 18% of the *cis*-enol acetate **23**, 40% of the *trans*-enol acetate **24**, and 10% of the diketone **26**. A collected³⁴ sample of the diketone **26** has infrared absorption³² at 1690 cm^{-1} with shoulders at *ca.* 1715 and 1725 cm^{-1} ($\text{C}=\text{O}$ stretch of a 1,3-diketone) with broad ultraviolet absorption³⁷ at $280\text{--}290 \text{ m}\mu$ ($\epsilon 189$) indicating the absence of any significant amount of enol in this sample. The nmr spectrum³⁸ has peaks at δ 3.15 [1 H doublet, line separation 10 cps with further splitting apparent but not resolved, $\text{CH}(\text{CO})_2$], 1.75 (6 H singlet, CH_3CO), and 0.50 [6 H doublet with $J = 6.5$ cps, $(\text{CH}_3)_2\text{C}$] as well as a broad multiplet in the region δ 1.8–2.4 (1 H, $>\text{CH}$). The mass spectrum has a weak molecular ion peak at m/e 142 with abundant fragment peaks at m/e 100, 85, and 43. Collected³⁴ samples of the enol acetates **23** and **24** were identified with authentic samples by comparison of retention times, infrared spectra, and mass spectra.

To a cold (0°) solution of 12.5 mmoles of methylmagnesium bromide in 25 ml of ether was added, dropwise and with stirring over a 30-min period, a solution of 252 mg (3.0 mmoles) of the unsaturated ketone **1** and 48 mg (0.12 mmoles) of tri-*n*-butylphosphine-copper(I) iodide complex in 25 ml of ether. The cold reaction mixture was stirred for an additional 10 min and then added to 10.0 g (98 mmoles) of acetic anhydride and subjected to the previously described isolation and analysis.³⁴ The calculated yields were 26% of the *cis*-enol acetate **23**, 2% of the *trans*-enol acetate **24**, and 44% of the diketone **26**. Collected³⁴ samples of the *cis*-enol acetate **23** and the diketone **26** were identified with previously described samples by comparison of infrared spectra, mass spectra, and retention times.

A solution of 522 mg (6.21 mmoles) of the unsaturated ketone **1** in 50 ml of ether was added to a cold (0°) solution of 25.0 mmoles of methylmagnesium bromide in 50 ml of ether. The resulting solution was stirred for 20 min, added to 20.0 g (196 mmoles) of acetic anhydride, and then subjected to the previously described isolation and analysis.³⁴ The calculated yields of products

derived from conjugate addition were 7.4% of the *cis*-enol acetate **23**, 0.05% of the *trans*-enol acetate **24**, and 4.1% of the diketone **26**. Collected³⁴ samples of the *cis*-enol acetate **23** and the diketone **26** were identified with authentic samples by comparison of retention times and infrared and mass spectra.

The following experiments were performed using previously described procedures¹⁵ to examine the effect of cation and solvent on the position of acetylation of the enolate anions **20** and **22**. The addition of 269 mg (1.9 mmoles) of a mixture of enol acetates (81% of the *cis* isomer **23** and 19% of the *trans* isomer **24**) to a solution of 3.8 mmoles of methyl-lithium in 5 ml of 1,2-dimethoxyethane almost completely discharged the red color of the triphenylmethyl anion indicator. The resulting solution was added to 5.06 g (50 mmoles) of acetic anhydride and then the previously described reaction and isolation procedures were followed. The pentane solution of the organic products contained³⁴ 82% of the *cis*-enol acetate **23** and 18% of the *trans*-enol acetate **24**; the calculated yields were 61% of **23** and 14% of **24**. In agreement with earlier studies,¹⁵ none of the C-acetylated product, the diketone **26**, was detected. An analogous experiment utilized 331 mg (2.33 mmoles) of a mixture of enol acetates (75% of the *cis* isomer **23** and 25% of the *trans* isomer **24**) and 4.8 mmoles of methyl-lithium in 8 ml of ether.³⁹ After the resulting solution had been stirred for 15 min (during which time a precipitate started to form) and then quenched in 6.00 g (59 mmoles) of acetic anhydride, the pentane solution of the organic products contained³⁴ 72% of the *cis*-enol acetate **23**, 22% of the *trans*-enol acetate **24**, and 6% of the diketone **26**; the calculated yields were 51% of **23**, 16% of **24**, and 5% of **26**. Similarly, the solution obtained from 7.2 mmoles of methylmagnesium bromide and 463 mg (3.26 mmoles) of an enol acetate mixture (81% of the *cis* isomer **23** and 19% of the *trans* isomer **24**) in 8 ml of ether³⁹ was stirred for 15 min and then quenched in 5.30 g (52 mmoles) of acetic anhydride. The pentane solution of the organic products contained³⁴ 49% of the *cis*-enol acetate **23**, 3% of the *trans*-enol acetate **24**, and 48% of the diketone **26**; the calculated yields were 35% of **23**, 2% of **24**, and 34% of **26**. Collected³⁴ samples of the *cis*-enol acetate **23** and the diketone **26** were identified with previously described samples by comparison of retention times, infrared spectra, and mass spectra.

4-*t*-Butylcyclohexylideneacetic Acid (11) and Derivatives.—A 16.6-g (0.34 mole) sample of a dispersion of 52% sodium hydride in mineral oil was washed repeatedly with pentane and the remaining sodium hydride was suspended in 400 ml of 1,2-dimethoxyethane. To this suspension was added, dropwise and with stirring over a 2-hr period, a solution of 79.00 g (0.353 mole) of ethyl diethylphosphonoacetate in 100 ml of 1,2-dimethoxyethane. The resulting solution was stirred for an additional hour and then a solution of 50.00 g (0.325 mole) of 4-*t*-butylcyclohexanone in 200 ml of 1,2-dimethoxyethane was added dropwise and with stirring over a 90-min period. When the addition was complete, the resulting suspension (sodium diethylphosphate precipitated during the addition) was stirred for 15 min and then diluted with water and extracted with ether. After the ethereal extract had been dried and concentrated, fractional distillation separated unchanged *t*-butylcyclohexanone followed by the conjugated ethyl ester **10** as a colorless liquid, bp $77\text{--}84^\circ$ (0.1 mm), n_D^{20} 1.4773. The product exhibited a single peak on gas chromatography³⁴ and has infrared absorption³² at 1720 (conjugated ester $\text{C}=\text{O}$) and 1650 cm^{-1} (conjugated $\text{C}=\text{C}$) with an ultraviolet maximum³⁷ at $222 \text{ m}\mu$ ($\epsilon 14,900$). The nmr spectrum³² has peaks at δ 5.52 (1 H broad singlet, vinyl CH), 4.07 [2 H quadruplet with $J = 7$ cps (ethoxyl CH_2) superimposed on a broad multiplet attributable to one aliphatic CH], and 0.88 (9 H singlet, $(\text{CH}_3)_3\text{C}$] as well as a triplet (at δ 1.25 with $J = 7$ cps, ethoxyl CH_3) superimposed on complex absorption in the region δ 1.1–2.4 (aliphatic CH). The mass spectrum has a molecular ion peak at m/e 224 with abundant fragment peaks at m/e 140, 112, 94, 95, 57, 55, 43, and 41.

Anal. Calcd for $\text{C}_{14}\text{H}_{22}\text{O}_2$: C, 74.95; H, 10.78. Found: C, 74.67; H, 10.65.

(38) Determined as a pure liquid with tetramethylsilane present as an external standard.

(39) We were unable to use triphenylmethane as an indicator for this reaction because the addition of triphenylmethane to an ether solution of methyl-lithium or methylmagnesium bromide does not result in the formation of a red color of the triphenylmethyl anion within a 30-min period. This observation indicates that, in ether solution (unlike in 1,2-dimethoxyethane), either the formation of triphenylmethyl-lithium is very slow or the triphenylmethyl-lithium is not dissociated.

A solution of 20.0 (0.50 mole) of sodium hydroxide and 50.76 g (0.23 mole) of the conjugated ethyl ester 10 in 75 ml of water and 225 ml of ethanol was stirred at room temperature for 4 days and then diluted with 300 ml of ether. The organic layer was separated and washed with saturated, aqueous sodium bicarbonate. The combined aqueous solutions were neutralized (to pH 4) with aqueous hydrochloric acid and extracted repeatedly with ether. This latter ethereal extract was dried and concentrated to leave 38.12 g of the crude solid acid 11, mp 77–81°. Recrystallization from pentane afforded 35.18 g (79.1%) of the pure acid 11 as white needles, mp 92–93°. The sample has broad infrared absorption³² in the 3- μ region (associated OH) with peaks at 1690 (conjugated carboxyl C=O) and 1645 cm^{-1} (conjugated C=C) and an ultraviolet maximum⁴⁰ at 223 $m\mu$ (ϵ 16,000). The nmr spectrum³² has peaks at δ 12.52 (1 H broad singlet, COOH), 5.53 (1 H broad singlet, vinyl CH), and 0.88 [9 H singlet (CH_3)₃C] as well as broad multiplets in the regions δ 1.0–2.5 (8 H, aliphatic CH) and δ 3.8–4.2 (1 H). This latter peak, which also is evident in the previously described ethyl ester 10 and the subsequently described crude methyl ester 14 is apparently attributable to the equatorial C-2 hydrogen atom which is *cis* to (and consequently eclipsed with) the ester or acid function.⁴¹

Anal. Calcd. for $\text{C}_{12}\text{H}_{20}\text{O}_2$: C, 73.43; H, 10.27. Found: C, 73.34; H, 10.22.

Following the procedure outlined above, 10.52 g (50 mmoles) of methyl diethylphosphonoacetate was treated successively with 1.316 g (55 mmoles) of sodium hydride and 7.713 g (50 mmoles) of 4-*t*-butylcyclohexanone in 1,2-dimethoxyethane.⁴² Distillation of the organic product afforded 6.10 g (58%) of the crude methyl ester 14 as a colorless liquid, bp 139–142° (8 mm). The product has infrared absorption³² at 1720 (conjugated ester C=O) and 1650 cm^{-1} (conjugated C=C) with ultraviolet absorption³⁷ at 219 $m\mu$ (ϵ 18,300). The nmr spectrum³² has peaks at δ 5.46 (1 H broad singlet, vinyl CH), 3.55 (3 H singlet, OCH_3), and 0.82 [9 H singlet, (CH_3)₃C] with a broad multiplet in the region δ 1.0–2.5 (8 H, aliphatic CH) and a broad doublet (separation 13 cps) centered at δ 3.85 (1 H, equatorial C_2H *cis* to carbomethoxyl function).⁴¹ The mass spectrum has a molecular ion peak at m/e 210 with abundant fragment peaks at m/e 126, 95, 57, 41, and 29. A 2.10-g. (10 mmoles) sample of the crude ester 14 was saponified by reaction with 1.12 g (20 mmoles) of potassium hydroxide in 50 ml of refluxing methanol for 19.5 hr.⁴² The reaction mixture was concentrated, diluted with water, extracted with ether, acidified with aqueous hydrochloric acid, and again extracted with ether. After the acidic, ethereal extract had been washed with aqueous sodium chloride and dried, concentration left 1.82 g (93%) of the crude liquid product with ultraviolet absorption³⁷ at 216 $m\mu$ (ϵ 3150).⁴³ The failure of the acidic product to crystallize and its low ultraviolet extinction coefficient suggested that the vigorous conditions used in this saponification had partially isomerized the conjugated ester 14 (or acid 11) to the unconjugated double-bond isomer. This suspicion was confirmed by esterifying 0.70 g (3 mmoles) of the crude liquid acid with excess ethereal diazomethane. The crude neutral product contained³⁴ four components with the following retention times and relative peak areas: 69% of the nonconjugated ester 15 (13.2 min); 19% of the conjugated ester 14 (16.2 min); 3% of unknown component A (20.2 min); and 12% of unknown component B (22.8 min). A collected³⁴ sample of the conjugated ester 14 was identified with the previously described sample by comparison of infrared and mass spectra. A collected sample³⁴ of the nonconjugated methyl ester 15 has infrared absorption³² at 1745 (ester C=O) and 1670 cm^{-1} (weak, C=C) with only end absorption in the ultraviolet³⁷ [210 $m\mu$ (ϵ 536)]. The nmr spectrum³² has singlets at δ 3.69 (3 H, OCH_3) and 0.88 [9 H, (CH_3)₃C] with broad peaks centered at δ 5.63 (1 H, vinyl CH) and 2.93 (2 H, CH_2CO) and a complex multiplet in the region δ 1.0–2.5 (7 H, aliphatic CH). The mass spectrum has a

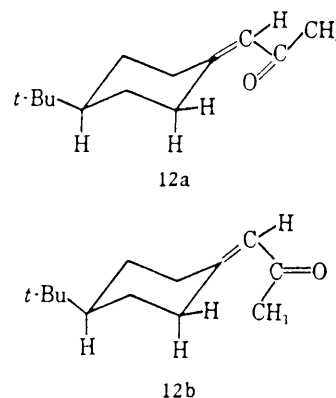
molecular ion peak at m/e 210 with abundant fragment peaks at m/e 122, 93, 80, 79, 57, and 41.

Anal. Calcd. for $\text{C}_{13}\text{H}_{22}\text{O}_2$: C, 74.24; H, 10.54. Found: C, 74.19; H, 10.65.

Preparation of the Unsaturated Alcohol 17.—To a solution of 38.0 mmoles of methyllithium in 20 ml of ether was added, dropwise and with stirring over a 30-min period, a solution of 2.00 g (9.0 mmoles) of the unsaturated ester 10 in 30 ml of ether. After the reaction mixture had been stirred overnight, it was poured into aqueous ammonium chloride solution (adjusted to pH 7–8 with ammonia) and the organic layer was separated and combined with the ether extract of the aqueous phase. The organic solution was dried and concentrated to leave 1.49 g (79.3%) of the crude alcohol 17 as white solid, mp 55–60°. Sublimation afforded the pure alcohol 17 as white needles, mp 61–62°. The sample has infrared absorption³² at 3590 and 3450 cm^{-1} (unassociated and associated OH) with nmr peaks³² at δ 5.47 (1 H broad singlet, vinyl CH), 1.34 [6 H singlet, (CH_3)₃CO], and 0.90 [9 H singlet, (CH_3)₃C] as well as broad multiplets in the regions δ 3.2–3.6 (1 H, OH, shifted by the addition of pyridine) and δ 1.0–2.5 (9 H, aliphatic CH). The mass spectrum exhibits no molecular ion peak but has abundant fragment peaks at m/e 93, 58, 57, 43, and 41.

Anal. Calcd. for $\text{C}_{14}\text{H}_{26}\text{O}$: C, 79.93; H, 12.46. Found: C, 79.71; H, 12.33.

Preparation of the Unsaturated Ketone 12.—To a cold (0°) solution of 25.05 g (0.13 mole) of the unsaturated acid 11 in 100 ml of ether was added, dropwise and with vigorous stirring over a 1.5-hr period, a solution of 0.27 mole of methyllithium in 140 ml of ether. The resulting solution was stirred for an additional 11 hr and then added to cold, aqueous ammonium chloride. The organic layer was separated, combined with the ether extract of the aqueous phase, dried, and concentrated to leave 24.19 g of the crude ketone 12 as a pale yellow liquid. The gas chromatogram³⁴ of this product suggested that it was composed of the ketone 12 (eluted second as 13) contaminated with 2–3% of the alcohol 17 (eluted first). Since attempts to purify this product by fractional distillation or by gas chromatography resulted in partial isomerization of the product to the subsequently described unconjugated isomer 13, a pentane solution of the ketone 12 was cooled to Dry Ice temperature to separate the ketone as fine white needles which remelted below room temperature (approximate mp -1 to $+4^\circ$). This low-temperature recrystallization process was repeated several times and then the sample was dried under reduced pressure to give 7.95 g of the conjugated ketone 12 as a colorless liquid, n_D^{20} 1.4895. The product has infrared absorption³² at 1690 (conjugated C=O) and 1620 cm^{-1} (conjugated C=C); these two peaks are of approximately equal intensity suggesting that the molecule exists primarily in the *cisoid* conformation⁴⁴ 12a presumably to avoid the equatorial hydrogen–methyl interaction which would



be present in the transoid conformation 12b. The sample has ultraviolet maxima³⁷ at 242 $m\mu$ (ϵ 14,600) and 313 $m\mu$ (ϵ 108) and nmr peaks³⁷ at δ 5.90 (1 H broad singlet, vinyl CH), 2.97 (3 H singlet, CH_3CO), and 0.86 [9 H singlet, (CH_3)₃C] as well as a broad doublet (separation 12 cps) centered at δ 3.86 (1 H, equatorial C_2H *cis* to carbonyl function)⁴¹ and a broad multiplet in the region δ 1.0–2.5 (aliphatic CH). The mass spectrum has a molecular ion peak at m/e 194 with abundant fragment peaks at m/e 95, 80, 57, 43, and 41.

(40) Determined as a solution in *n*-heptane.

(41) C. F. H. Hawth, D. Stauffacher, P. Niklaus, and A. Melera, *Helv. Chim. Acta*, **48**, 1087 (1965).

(42) This experiment was performed by Dr. W. G. Kenyon in our laboratories.

(43) I. Tomoskozi and G. Janzso [*Chem. Ind. (London)*, 2085 (1962)] report the acid 11 as a liquid, bp 135–140° (2 mm). It may well be that the liquid product reported by these authors, like our liquid acid reported here, is a mixture of unconjugated and conjugated isomers.

(44) R. L. Erksine and E. S. Waigant, *J. Chem. Soc.*, 3425 (1960).

Anal. Calcd for $C_{15}H_{20}O$: C, 80.35; H, 11.41. Found: C, 80.45; H, 11.31.

Although the above sample of the purified conjugated ketone **12** gives a single peak on gas chromatography,³⁴ a collected sample of this peak had infrared absorption³² at 1720 cm^{-1} (nonconjugated $C=O$). The nmr spectrum³² of this collected sample has peaks at δ 2.99 (2 H broad singlet, CH_2CO), 2.09 (3 H singlet, $COCH_3$), and 0.88 [9 H singlet, $(CH_3)_3C$] as well as broad peak centered at δ 5.67 (1 H, vinyl CH) and a complex multiplet in the region δ 1.1–2.5 (aliphatic CH). The mass spectrum of the sample has a molecular ion peak at m/e 194 with abundant fragment peaks at m/e 95, 80, 57, 43, and 41. Consequently, we conclude that the ketone **12** isomerized to the unconjugated isomer **13** on our gas chromatography column. An attempt to distill a crude sample of the ketone **12** afforded a distillate whose infrared absorption indicated it to be a mixture of isomeric ketones **12** and **13**. The gas chromatogram³⁴ of the crystalline alcohol **17** exhibited two partially resolved peaks; a collected³⁴ sample of these peaks has spectra indicating that it is a mixture of two or more dienes which have been formed by dehydration of the alcohol **17** on the gas chromatograph. The infrared spectrum³² of this collected sample has no absorption in the $3\text{-}\mu$ region attributable to a hydroxyl function; the mass spectrum has a molecular ion peak at m/e 192 with abundant fragment peaks at m/e 135, 121, 93, 79, 69, 57, 55, and 41.

Addition of Organometallic Reagents to the Ketone 12.—To a cold (0°) solution of lithium dimethylcopper(I) [from 7.621 g (40 mmoles) of copper(I) iodide and 80 mmoles of methyl lithium] in 160 ml of ether was added, dropwise and with stirring, a solution of 3.883 g (20 mmoles) of the unsaturated ketone **12** in 160 ml of ether. The reaction mixture was stirred for 30 min and then added to aqueous ammonium chloride. After the organic layer had been separated and combined with the ethereal extract of the aqueous phase, the combined ethereal solutions were dried and concentrated. The residual yellow oil (4.18 g) contained³⁴ 96% of the conjugate addition product **16** (eluted second) and 4% of the alcohol **17** (eluted first as a mixture of dienes). Distillation of this material afforded 3.574 g of fractions boiling in the range $45\text{--}58^\circ$ (0.1 mm); however, each of the fractions was contaminated³⁴ with a small amount of the alcohol. A collected³⁴ sample of the peak derived from the alcohol **17** had infrared absorption and a gas chromatographic retention time corresponding to the dienes obtained from gas chromatography of the pure alcohol **17**. A collected³⁴ sample of the ketone **16**, a colorless liquid, has infrared absorption³² at 1715 cm^{-1} ($C=O$). The nmr spectrum³² has singlets at δ 2.28 (2 H, CH_2CO), 2.03 (3 H, $COCH_3$), 0.95 (3 H, CH_3C), and 0.84 [9 H, $(CH_3)_3C$] superimposed on a broad multiplet in the region δ 0.9–2.5 (aliphatic CH); the sharpness of these singlets suggests that the ketone is predominantly a single stereoisomer. This conclusion is substantiated by the subsequently described peracid oxidation of the ketone **16**. The mass spectrum of the ketone exhibits no molecular ion peak and has abundant fragment peaks at m/e 152, 96, 95, 94, 81, 57, 43, and 41.

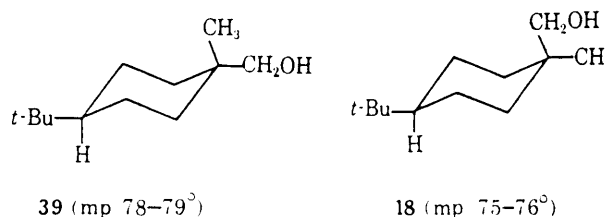
Anal. Calcd. for $C_{15}H_{20}O$: C, 79.93; H, 12.46. Found: C, 79.98; H, 12.37.

A solution of 80 mg (0.20 mmole) of the tri-*n*-butylphosphine-copper(I) iodide complex and 997 mg (4.94 mmoles) of the unsaturated ketone **12** in 40 ml of ether was added, dropwise and with stirring over a 30-min period, to 40 ml of a cold (0°), ethereal solution containing 20 mmoles of methylmagnesium bromide. After the mixture had been stirred for an additional 10 min, it was subjected to the previously described isolation procedure to separate 1.02 g of organic product as a yellow oil. This product contained³⁴ ca. 74% of the ketone **16** and ca. 26% of the alcohol **17**.

A solution of 1.04 g (5.2 mmoles) of the ketone **12** in 40 ml of ether was added, dropwise and with stirring, to a cold (0°) solution of 20 mmoles of methylmagnesium bromide in 40 ml of ether. After the reaction mixture had been stirred at room temperature for 30 min, it was subjected to the previously described isolation procedure to separate 1.04 (93%) of the alcohol **17** as a white solid, mp $60\text{--}62^\circ$, which was identified with the previously described product by comparison of infrared spectra. None of the conjugate addition product **16** could be detected in either the infrared spectrum or the gas chromatogram³⁴ of the crude product.

Per Acid Oxidation of the Ketone 16.—A solution of peroxytrifluoroacetic acid [from 5.0 ml (55 mmoles) of trifluoroacetic

anhydride and 1.0 ml (37 mmoles) of aqueous 88% hydrogen peroxide] in 10 ml of methylene chloride was added, dropwise and with stirring over a 15-min period, to a cold (0°) mixture of 2.52 g (12 mmoles) of the ketone **16** (distilled material which contained ca. 4% of the alcohol **17**), 13.0 g of disodium hydrogen phosphate, and 15 ml of methylene chloride.⁴⁵ The resulting mixture was refluxed, with stirring, for 1 hr and then filtered, and the residue was washed with methylene chloride. The combined methylene chloride solutions were washed with aqueous sodium bicarbonate, dried, and concentrated to leave 2.22 g of colorless liquid. This crude product had infrared peaks³² at 1740 (acetate $C=O$) and 1780 cm^{-1} (trifluoroacetate $C=O$) and exhibited two peaks on gas chromatography which we believe to be the acetate and trifluoroacetate of alcohol **18**. A solution of the crude oxidation product (2.22 g, ca. 9.8 mmoles) and 1.20 g (30 mmoles) of sodium hydroxide in 20 ml of methanol and 20 ml of water was stirred under a nitrogen atmosphere for 36 hr and then diluted with ether. The organic layer was separated, combined with the ethereal extract of the aqueous layer, dried, and concentrated to leave 1.54 g (71% based on the ketone **16**) of the crude alcohol **18** as a white solid, mp $70\text{--}72^\circ$. Before purification, this crude product was compared with authentic samples³² of the stereoisomeric alcohols **18** and **39**.



The stereoisomers **18** and **39** were only partially resolved on our gas chromatograph,⁴⁶ the alcohol **18** being eluted more rapidly. On thin layer chromatography,⁴⁷ the axial hydroxymethyl isomer **18** was eluted more rapidly than the alcohol **39**. The infrared spectra³² of the two isomers exhibit significant differences in the fingerprint region. By all of these criteria (gas chromatography, thin layer chromatography, and infrared), our crude alcohol contained the alcohol **18** and none of the isomeric alcohol **39** was detected. Sublimation of our crude product (at 0.05 mm) afforded the pure alcohol **18** as white plates, mp $75.5\text{--}76^\circ$, identified with the authentic sample³² by a mixture melting point determination and by comparison of infrared, nmr, and mass spectra.

Anal. Calcd for $C_{12}H_{18}O$: C, 78.19; H, 13.13. Found: C, 77.93; H, 12.99.

Reaction of 1,1,1-Triphenylbutan-3-one (35) with Organometallic Reagents.—A solution of 15.01 g (53 mmoles) of chloromercuriacetone (mp $101\text{--}103^\circ$, lit.⁴⁸ mp $103\text{--}104^\circ$) and 13.99 g (53 mmoles) of triphenylmethyl chloride in 150 ml of benzene was refluxed for 24 hr and then cooled, washed successively with aqueous sodium hydroxide and with water, dried over calcium chloride, and concentrated. The solid residue was recrystallized from methyl ethyl ketone to separate 4.081 g of ketone **35** as white prisms, mp $141\text{--}142^\circ$ (lit.⁴⁸ mp $140\text{--}141^\circ$). The sample has infrared absorption⁴⁹ at 1725 cm^{-1} ($C=O$) with a series of weak (ϵ 500–820) ultraviolet maxima³⁷ in the region $250\text{--}275\text{ m}\mu$. The nmr spectrum³⁰ has singlets at δ 7.47 (15 H, aryl CH), 3.98 (2 H, CH_2CO), and 1.92 (3 H, CH_3CO).

The ketone **35** (4.0 g or 13 mmoles) was added to a solution of 66 mmoles of methylmagnesium bromide in 40 ml of ether and the resulting solution was stirred overnight and then mixed with aqueous ammonium chloride. The organic layer was separated, combined with the ether extract of the aqueous phase, dried, and concentrated to leave 3.617 g of white solid.

(45) The procedure of W. D. Emmons and G. B. Lucz, *J. Am. Chem. Soc.*, **77**, 2287 (1955).

(46) A gas chromatography column packed with the polymeric ester of ethylene glycol and adipic acid suspended on Chromosorb P was employed for the analysis.

(47) The analysis was performed on plates coated with silicic acid and eluted with a benzene (2 volumes)–ether (3 volumes) mixture.

(48) (a) A. N. Nesmeyanov, I. F. Lutsenko, and Z. M. Tumanova, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 601 (1949); (b) for a description of the infrared and nmr spectra of this substance, see ref 15a, p 2503, footnote 12.

(49) Determined as a solution in chloroform.

(50) Determined as a solution in deuteriochloroform.

This crude product contained⁵¹ the alcohol (eluted most slowly) and two minor components, one of which corresponded in R_f value to the starting ketone **35** and the other to a material believed to be an olefin. A 500-mg sample of the product was chromatographed on 25 g of Woelm alumina (activity grade II) to separate 481 mg of the alcohol **36**, mp 123–124°, eluted with hexane-ethyl acetate mixtures. Recrystallization from aqueous methanol afforded the alcohol as white prisms, mp 123.5–124°, with infrared absorption⁴⁹ at 3580 cm^{-1} (O-H) and a series of weak (ϵ 470–790) ultraviolet maxima⁵⁷ in the region 250–280 $\text{m}\mu$ as well as intense end absorption. The sample has nmr singlets⁵⁰ at δ 0.99 (6 H, $(\text{CH}_3)_2\text{CO}$) and 3.06 (2 H, CH_2) as well as a complex multiplet in the region δ 7.0–7.7 (15 H, aryl CH).

Anal. Calcd for $\text{C}_{23}\text{H}_{24}\text{O}$: C, 87.30; H, 7.65. Found: C, 87.32; H, 7.60.

An ethereal solution of the ketone **35** was then allowed to react with an excess of each of the reagents methylmagnesium bromide, dimethylmagnesium, and methylolithium. In each case, analysis⁵¹ of the crude product (obtained in 90–94% yield) indicated the presence of the alcohol **36** and no by-product was detected. Recrystallization of each crude product gave a sample of the pure alcohol (yields 68–75%) which was identified with the previously described sample by comparison of infrared spectra.

Reaction of Fluorenone (**31**) with Methylcopper Derivatives.—

An authentic sample of 9-fluorenol, prepared by reduction of fluorenone with sodium borohydride in methanol, separated from benzene as white needles, mp 154–155° (lit.⁵² mp 156–156.5°). Reaction of fluorenone (1.005 g or 5.6 mmoles) with 12.4 mmoles of methylmagnesium bromide in 15 ml of ether for 30 min followed by the usual isolation procedure yielded 603 mg (55%) of 9-methyl-9-fluorenol (**32**) as white plates from benzene, mp 173–175° (lit.⁵³ mp 174–175°). Other than the yellow color of the starting ketone **31**, no color was evident at any point during the reaction. Similarly the addition of fluorenone to an ethereal solution of excess methylolithium resulted in the loss of the yellow color of the starting material to give a colorless solution. The alcohol **32** has infrared absorption⁴⁹ at 3575 and 3390 cm^{-1} (unassociated and associated OH) with nmr absorption⁵⁰ at δ 1.63 (3 H, singlet, CH_3) and 2.03 (1 H singlet shifted by the addition of pyridine, OH) as well as a multiplet in the region δ 7.0–7.8 (8 H, aryl CH).

To a cold (0°) solution of lithium dimethylcopper [from 7.61 g (40 mmoles) of copper(I) iodide and 80 mmoles of methylolithium] in 100 ml of ether was added a solution of 3.60 g (20 mmoles) of fluorenone in 100 ml of ether. The addition resulted in the immediate formation of a dark green solution. Comparable ethereal solutions from other runs had a broad, low-intensity absorption ($\epsilon > 10$ –20) in the region of 540–560 $\text{m}\mu$ with more intense peaks ($\epsilon > 100$ –200) in the visible region at 441 and 417

$\text{m}\mu$.⁵⁴ The reaction mixture was poured into aqueous ammonium chloride (adjusted to pH 7–8 with ammonia) and the ether solution of the organic products was separated, dried, and concentrated to leave 3.78 g of yellow solid. A 1.00-g aliquot of the crude product was dissolved in benzene and diluted with hexane to precipitate 913 mg of white solid, mp 126–133°. The infrared⁴⁹ and nmr⁵⁵ absorption of the crude product suggested that it is a mixture of comparable amounts of the methylfluorenol **32** and the diol **34**. An analogous mixture, mp 129–135°, was obtained from a solution of fluorenone and lithium dimethylcopper which was stirred for only 2 min before hydrolysis. Fractional recrystallization of a portion of the above white solid from ethanol separated the methyl alcohol **32**, mp 174–175°, which was identified with an authentic sample by a mixture melting point determination and comparison of infrared spectra. Fractional crystallization of the white solid reaction product from a benzene-hexane mixture separated the diol **34** as white needles, mp 186–187° dec (lit.^{24b} mp 188–190° dec). This product has infrared absorption⁴⁹ at 3600 and ca. 3400 cm^{-1} (unassociated and associated OH) with nmr⁵³ multiplets centered at δ 3.12 (2 H, OH) and in the region δ 6.9–7.6 (16 H, aryl CH). The gas chromatogram⁵⁶ of the white solid product (**32** + **34**) exhibited three peaks corresponding in retention time to the peaks obtained from fluorenone, 9-fluorenol, and 9-methyl-9-fluorenol. Thus, it seems probable that the diol **34** is decomposing on the column or in the inlet system to form fluorenone and 9-fluorenol.^{24b} The chromatogram⁵⁶ of the mother liquor remaining after separation of the mixture of alcohols **32** and **34** exhibited one major peak corresponding to fluorenone.

In an additional experiment, a solution of 181 mg (1.0 mmole) of fluorenone in 25 ml of ether was added to a solution of the methylcopper-tri-*n*-butylphosphine complex [from 5.0 mmoles of methylolithium and 2.001 g (5.1 mmoles) of copper(I) iodide-tri-*n*-butylphosphine complex] in 25 ml of ether. The solution became dark green in color as the solutions were mixed and had a visible spectrum comparable to that described above. The identity of the species formed from either lithium dimethylcopper or the methylcopper-tri-*n*-butylphosphine complex was further indicated by comparison of the esr spectra⁵⁷ of the two ether solutions. Our efforts to analyze these esr spectra have thus far been unsuccessful; consequently, it has not been established that the esr spectrum observed corresponds to the lithium fluorenone radical anion in ether solution.⁵⁷

(54) The color (and the visible spectrum) of the fluorene ketyl **33** is dependent on the solvent and associated cation. The sodium ketyl is green in ether,^{24b} and brown in dioxane.^{24c} In tetrahydrofuran, the sodium ketyl is reported^{24c} to have maxima at 450 and 520 $\text{m}\mu$ with the shorter wavelength absorption attributed to the ketyl dimer and the longer wavelength absorption attributed to the monomeric ketyl.

(55) Determined as a solution in perfluorooctanone.

(56) A gas chromatography column packed with Carbowax 20 M suspended on Chromosorb P was employed for this analysis.

(57) The esr spectra of this radical anion in solvents more polar than ether have been thoroughly studied. In dimethylformamide solution, the hyperfine coupling constants are reported as 3.08, 1.96, 0.65, and 0.03 gauss;²⁴ⁱ in 1,2-dimethoxyethane with a sodium counterion, values of 3.01, 2.01, 0.67, and 0.17 gauss are reported as well as a coupling constant of 0.35 gauss from the sodium ion.²⁴ⁱ

(51) The analysis was performed on a thin layer chromatography plate coated with a silicic acid and eluted with a cyclohexane (10 volumes)-ethyl acetate (1 volume) mixture.

(52) H. Pan and T. L. Fletcher, *J. Org. Chem.*, **23**, 799 (1958).

(53) J. L. Kice, *J. Am. Chem. Soc.*, **80**, 348 (1958).