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- (26) Quenching rate constants were calculated using our β values for 2-methylpentene-2 in the appropriate solvent and the following lifetimes of $^1\text{O}_2$: benzene, 24 μsec ; 15 pyridine, 33 (± 15) μsec ; 27 acetonitrile, 30 μsec .¹⁵
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- (42) We attempted to measure polarographic half-wave oxidation potentials of several azomethine dyes in pyridine in order to obtain evidence for or against a CT contribution to the quenching reaction. Dc polarography with a dropping mercury electrode gave oxidation waves for several dyes, but cyclic voltametry (10 V/sec) indicated that the measured half-wave potentials were not thermodynamic since return waves were not obtained. We are indebted to Dr. Eric Brown for assistance in the electrochemical experiments.
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Reactions Involving Electron Transfer. VI. A Stereochemical Test for Anion Radical Intermediates in Additions to Carbonyl Compounds¹

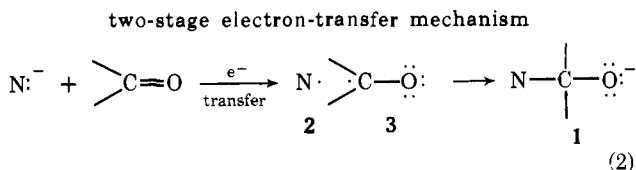
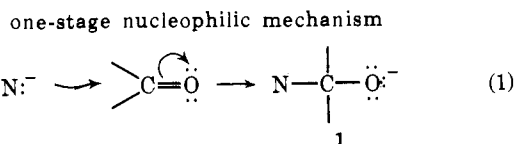
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Abstract: The cis enones **4** and **8**, which undergo rapid electron exchange with the corresponding radical anions resulting in isomerization to the trans isomers **5** and **9**, have been used to test for the presence of radical anions during addition reactions of MeLi, Me₂Mg, and Me₂CuLi and during reduction reactions with LiAlH₄, Cr(en)₂(OAc)₂, and Li and *t*-BuOH in liquid NH₃. In reactions with MeLi, Me₂Mg, and LiAlH₄, both the alcohol products and the recovered excess cis enone used were recovered without appreciable stereochemical isomerization indicating that these reactions occur by direct nucleophilic addition (eq 1). In reactions with Me₂CuLi and Cr(en)₂(OAc)₂, the excess enone recovered was almost completely isomerized to the trans isomer and in reduction with Li and *t*-BuOH in liquid NH₃, the excess enone recovered was partially isomerized. These results are compatible with the presence of an anion radical during reaction either as an intermediate in a two-stage addition process (eq 2) or, possibly, as a by-product formed during reaction (eq 3).

The addition of a nucleophilic reagent, N:⁻, to a carbonyl compound is usually represented (eq 1) as a single stage redistribution of the electron pair of the nucleophile, N:⁻, to form a new N–C bond in the adduct **1**. However, a second two-stage reaction pathway (eq 2) is clearly possible in which the first stage is a transfer of a single electron from the electron-rich nucleophile, N:⁻, to the electrophilic carbonyl group. This initial electron transfer is then followed by a second step in which the intermediate radicals or radical ions **2** and **3** recombine to form the adduct **1**.

Although a distinction between these two mechanistic possibilities may initially appear rather esoteric, upon further reflection several consequences of practical importance in synthesis become apparent. For example, in any reaction where there is a distinct preference in activation energies for the reaction to proceed by the two-stage mechanism (eq 2), one would expect a correlation between the success of the overall reaction and the ease with which the nucleophile, N:⁻, can donate an electron (measured as the oxidation potential of N:⁻) and the carbonyl compound can ac-



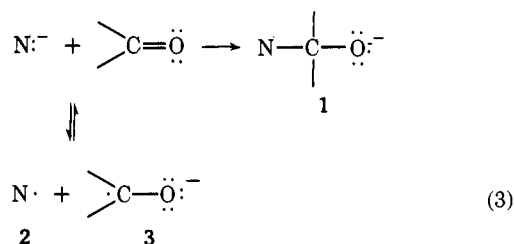
cept an electron (measured as the reduction potential of the carbonyl component). In such cases with a given nucleophile, the success or failure of addition to various carbonyl components could be predicted from either a simple measurement or an estimate² of the reduction potentials of the carbonyl components of interest. An example is provided by a correlation of the ability of lithium dimethylcuprate to add to various unsaturated carbonyl compounds with the reduction potentials of these substrates.³ Such predictive ability is, of course, very helpful in selecting from among various proposed synthetic routes that synthesis with a high probability of success as the route to be studied in the laboratory.

A second reason for distinguishing between the two mechanisms (eq 1 and 2) arises in any case where the lifetimes of the intermediate radicals or radical ions **2** and **3** are sufficient to allow the occurrence of other intramolecular or intermolecular reactions that will compete with the recombination of **2** and **3** to form the expected adduct **1**. Since electron-transfer reactions, such as the first stage in eq 2, are sometimes very rapid processes (rate constants 10^7 to $10^9 \text{ M}^{-1} \text{ sec}^{-1}$),⁴ there is a distinct possibility that intermediates **2** and **3** will have significant lifetimes before reaction with one another allowing the formation of by-products from competing intermolecular or intramolecular reactions. For example, the formation of benzpinacol as significant by-product of the addition of certain Grignard reagents to benzophenone is almost certainly the result of a competing intermolecular dimerization of the intermediate benzophenone ketyl.^{5,6}

Finally, it seems likely that certain reactions commonly regarded as one-stage nucleophilic additions (eq 1) may exhibit a change in mechanism (and perhaps a change in products) to a two-stage process (eq 2) as the nucleophilic reagent, N^- , is treated with a succession of electrophiles having decreasingly negative reduction potentials. Thus, it appears possible that a rather general correlation may exist between the nature of a reaction (e.g., eq 1 or eq 2) and the redox potentials of the nucleophile, N^- (a potential reducing agent), and the electrophile (a potential oxidizing agent). For example, easily reduced substrates such as quinones^{6a,f,7} (typical $E_{1/2}$ values 0.0 to -1.0 V vs. SCE)⁸ and nitro compounds⁹ (typical $E_{1/2}$ values -1.0 to -1.6 V vs. SCE)⁸ generally appear to react with potential nucleophilic reagents such as organometallic reagents and stabilized carbanions by a two-stage electron transfer process. There is no particular reason why the favored positions for bonding of a polydentate nucleophile with a polydentate electrophile need to correspond to the favored positions for coupling between an anion radical and a cation radical. Consequently, a change in mechanism may also be accompanied by a change in product structure with the product structure from a two-stage reaction (eq 2) being best explained by coupling the ion radical intermediates **2** and **3** at their sites of highest spin density.

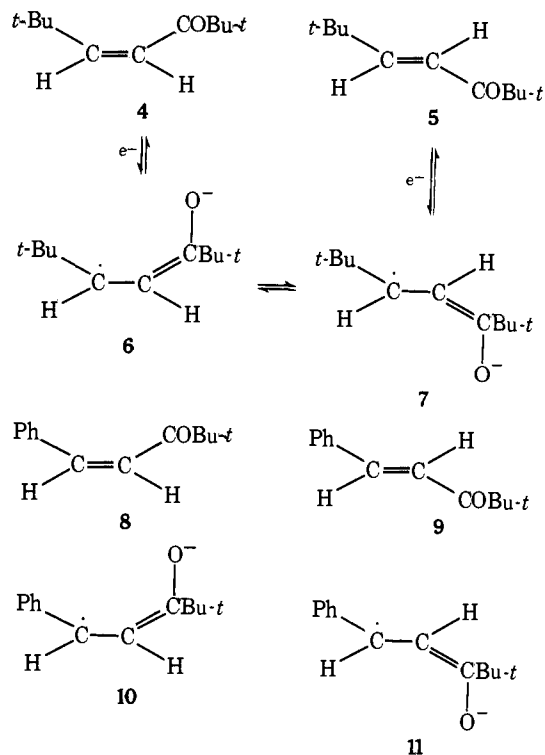
Evidence compatible with the presence of radical or radi-

cal ion intermediates such as **2** and **3** can sometimes be gained from the observation of the EPR signals from reactions run in the cavity of an EPR spectrometer,¹⁰ from the observation of NMR emission signals (CIDNP) from reactions run in the probe of an NMR spectrometer,¹¹ or from the isolation of products derivable from an intermediate radical (e.g., bimolecular reduction products from a ketyl anion radical). Failure to detect radical intermediates by one of these methods is ambiguous since low concentrations of such reaction intermediates would preclude their detection as bimolecular reduction products and either weak signals or broad signals from these intermediates may often prevent their detection by magnetic resonance techniques. Even when such experiments provide positive evidence for radical intermediates, it is often not convincing either because the rather sensitive magnetic resonance techniques may provide evidence pertaining only to a minor side reaction or because the radical intermediates **2** and/or **3** detected may arise from a parasitic equilibrium (eq 3) that does not lie on the reaction path forming the adduct **1**. In this paper and two accompanying papers,¹² we describe several tests based on isolated reaction products that we believe provide useful methods for examining and, in some cases, distinguishing between the two mechanisms (eq 1 and 2).



The criteria described in this paper are based on our earlier observations with the cis enones **4** and **8** (Scheme I).¹³ The enone **4**, obtained from the more stable trans isomer **5** by photochemical irradiation, is stable to the isomerization **4** \rightarrow **5** in several subsequently described chemical reactions. However, when the cis enone **4** [reduction potential -2.21

Scheme I



V (vs. SCE) in DMF^{13j}) is converted to its anion radical **6**, the rotational barrier for conversion of **6** to the trans isomer **7** is much lower so that the rotation **6** → **7** occurs readily even at -78° . Furthermore, the addition of one of the anion radicals **6** or **7** to a solution of the cis enone **4** results in rapid electron exchange¹⁴ between the ion radical **6** or **7** and the neutral enone **4** resulting in a net isomerization of **4** to **5** in reaction mixtures containing one of the free anion radicals **6** or **7**. Related recently reported phenomena include the isomerization of *cis*-stilbene to *trans*-stilbene by the addition of a catalytic amount of sodium anthracenide (suggested to involve successive conversion of the stilbene isomers to their radical ions and their dianions with isomerization occurring at the dianion stage)^{15a} and the isomerization of diethyl maleate to diethyl fumarate by treatment with a mixture of Cu, Cu₂O, and *t*-BuN=C (a process thought to involve electron transfer to the unsaturated diester).^{15b}

Although the properties of the radical anions **10** and **11** derived from the cis enone **8** [reduction potential -1.710 V (vs. SCE) in DMF solution]^{13a} and the trans enone **9** [reduction potential -1.698 V (vs. SCE) in DMF solution]^{13a} have not been investigated extensively, the chemical behavior of these two enones **8** and **9**^{13b} parallel the behavior of enones **4** and **5** indicating the rapid rotation of the cis anion radical **10** to the trans isomer **11**.

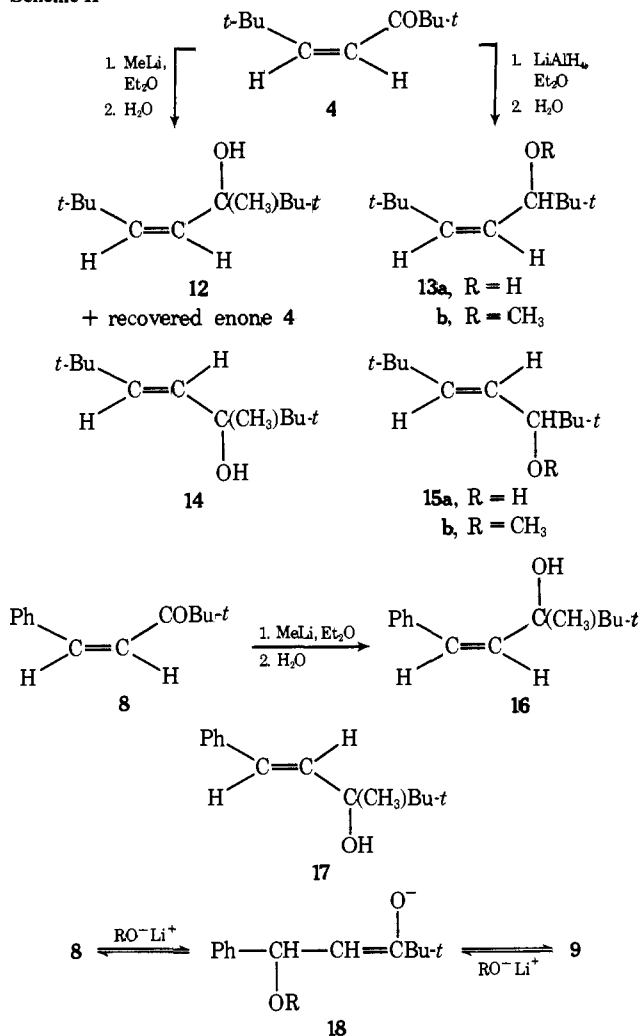
We have utilized these properties of the cis enones **4** and **8** in a series of experiments in which 2 mol equiv of one of these enones has been treated with a series of reagents in amounts (ca. 1 mol equiv) sufficient to consume only half of the starting enone. Three probable results might be obtained in these experiments. In reactions involving a single stage nucleophilic addition (eq 1) to the carbonyl group, both the alcohol products (e.g., **12** and **13**, Scheme II and Tables I and II) and the recovered excess enone would be expected to retain the cis stereochemistry. We have observed this behavior in addition of ethereal MeLi to the enone **4** to form alcohol **12** and in the reduction of the enone **4** with ethereal LiAlH₄ to form alcohol **13a**. Only traces of the isomeric trans alcohols **14** and **15a** (available from the trans enone **5**) were formed in these reactions.

Similarly, the reaction of excess cis enone **8** with ethereal MeLi yielded the cis alcohol **16** contaminated with trace amounts of the trans alcohol **17** (available from the trans enone **9** and MeLi). In this case the recovered excess enone **8** was found to be slowly isomerized to the more stable trans isomer **9** as the reaction mixture was stirred at 25° . Since this enone isomerization **8** → **9** was clearly occurring *after* the rapid consumption of the MeLi, it is apparent that the enone isomerization is attributable not to a process involving MeLi but rather to reaction of the enone **8** with the reaction product, a lithium alkoxide RO⁻Li⁺. The most reasonable path for this isomerization is the reversible conjugate addition of the alkoxide, RO⁻, as illustrated in structure **18**. Although the analogous isomerization **4** → **5** was not observed following reaction of the cis enone **4** with ethereal MeLi, such an isomerization was observed^{13a} when the cis enone **4** was treated with *t*-BuO⁻K⁺ in DMF solution where complete dissociation of the metal alkoxide to ion pairs is probable.

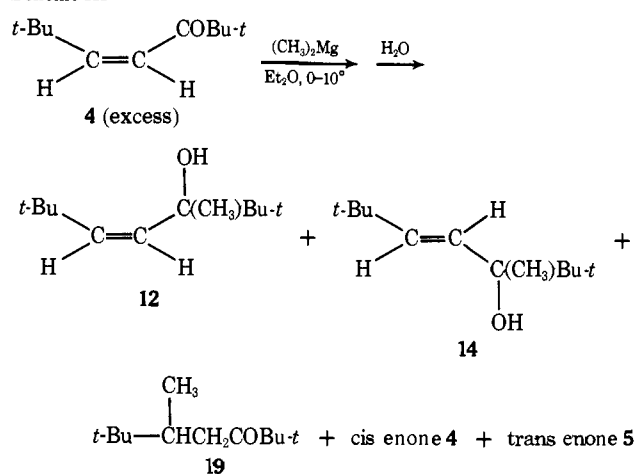
Reaction of excess enone **4** with ethereal Me₂Mg (prepared from doubly sublimed Mg¹⁶) gave results (Scheme III and Table I) similar to those obtained with MeLi, the major products being the cis alcohol **12** and the recovered cis enone **4** along with minor amounts (1–4% yields) of the trans alcohol **14**, the trans enone **5**, and the conjugate addition product **19**.

The results summarized in Schemes II and III provide

Scheme II



Scheme III

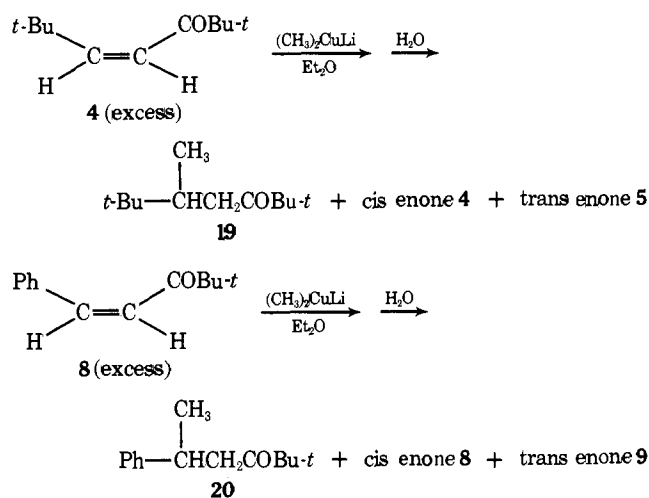


examples of additions to the carbonyl group of the cis enones **4** and **8** without appreciable isomerization being observed either in the products **12**, **13a**, and **16** or in the excess enones **4** or **8** recovered as soon as the addition reaction is complete. These observations are clearly compatible with the description of these reactions as direct nucleophilic additions (eq 1) and could be compatible with a two-step electron-transfer process (eq 2) only if the intermediates **2** and **3** recombined to form products faster than the bond rotation **6** → **7**. Two lines of evidence have led us to discount

this latter possibility. From a study of the reaction of Me_2Mg with the enone **4** for short periods of time, we estimate the half-life for this reaction at the concentrations used in our study to be about 40 sec at 0° . Earlier experiments had shown that the half-life for isomerization of the cis anion radical **6** to the trans isomer **7** was less than 2 sec at -78° .^{13a} If the initial electron-transfer step (eq 2) is rapid as often assumed,⁴ the lifetimes of the intermediates **2** and **3** in this case would certainly be long enough to permit cis \rightarrow trans isomerization. A second line of evidence indicating that this reaction with Me_2Mg does not proceed by an initial electron transfer is provided by a consideration of redox potentials. The reduction potential of the enone **4** (-2.207 V vs. SCE)^{13a} is 1.5 V more negative than the approximate oxidation potential (ca. -0.7 V vs. SCE) determined¹⁷ for dialkylmagnesium compounds. With a potential difference this large, the concentrations of intermediates (e.g., **2** and **3**, eq 2) that would be formed by an initial electron transfer would be negligible ($<10^{-20}$ M).

In marked contrast to the reactions of the enones **4** and **8** with MeLi , Me_2Mg , or LiAlH_4 where both the alcohol products **12**, **13a**, and **16** and the excess enones **4** and **8** were recovered without appreciable isomerization, reaction of Me_2CuLi with either of the enones **4** or **8** (Scheme IV) resulted in the formation of the conjugated adducts **19** and **20** accompanied by the isomerized trans enones **5** and **9**. The essentially complete isomerization of the excess cis enones **4** and **8** in these reactions to the trans isomers is compatible with the idea³ that an anion radical (**6** and **7** or **10** and **11**) is formed in the reaction mixtures and possesses a sufficient lifetime to undergo electron exchange with the excess neutral enone. This electron exchange would, of course, isomerize all of the excess cis enone to the corresponding trans isomer.¹⁸

Scheme IV



To explore the behavior of the cis enones **4** and **8** with reagents that almost certainly react by formation of intermediate radicals or radical anions, we examined the reduction of excess enone **4** with the chromium(II) complex, $\text{Cr}(\text{en})_2(\text{OAc})_2$,¹⁹ and the reduction of each cis enone **4** and **8** with Li and *t*-BuOH in liquid NH_3 (see Scheme V). Reaction of the chromium(II) reagent with excess cis enone **4** resulted in formation of the dihydro ketone **21** and practically complete isomerization of the starting material **4** to the trans enone **5**. This observation is in accord with our earlier studies¹⁹ indicating the formation of a relatively long-lived radical intermediate that could be intercepted with an added mercaptan H atom donor. Reaction of the enones **4**

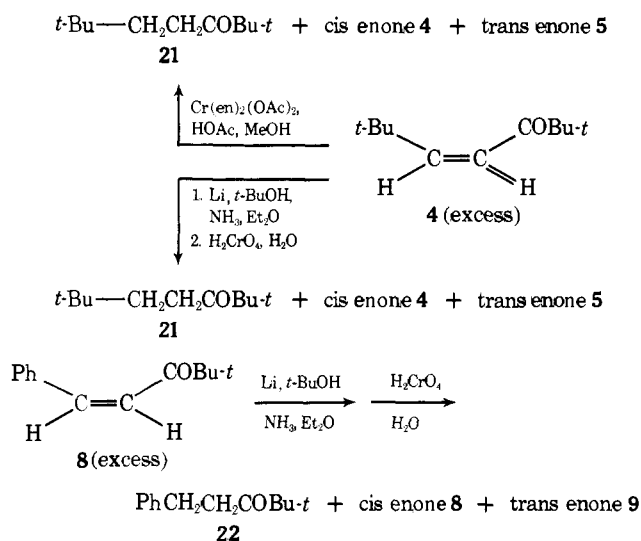
and **8** with Li and *t*-BuOH in liquid NH_3 yielded the expected dihydro products **21** and **22** but resulted in only partial isomerization of the excess cis enones **4** and **8** to their trans isomers **5** and **9**. This incomplete enone isomerization might initially be regarded as peculiar since the Li- NH_3 reductions almost certainly proceed by an initial electron transfer process.¹³ We believe that this experimental result is a consequence of the rapidity with which the intermediate anion radicals formed in metal- NH_3 are protonated at oxygen and then reduced further in the reaction. As noted previously,¹⁸ whenever the lifetime of the radical anion intermediates becomes very short, electron exchange leading to isomerization of the excess enone will be retarded or prevented. An estimate of the minimum time required for trapping of an intermediate radical by further reduction with a metal- NH_3 solution may be obtained from a study of reduction of a *cis*-chloroolefin with excess Na and *t*-BuOH in liquid NH_3 .²⁰ In this reaction, the time required for reduction was comparable to the time required for inversion of an α -alkylvinyl radical. Although a reliable value for rate of inversion of an α -alkylvinyl radical is not available,²¹ a preexchange lifetime longer than 10^{-8} sec seems likely.^{21,22} In an accompanying paper¹² we provide data indicating that protonation and reduction of an enone anion radical with a solution of Li and *t*-BuOH in liquid NH_3 must be significantly faster than 10^{-3} sec under the conditions used in our experiments. Consequently, we believe that the stereochemical test described here is applicable for the detection of anion radical intermediates (e.g., **3** in eq 2) provided these intermediates have a *minimum* lifetime somewhere within the range 10^{-4} to 10^{-7} sec. Whenever data providing either the rate of inversion of an α -alkylvinyl radical or the rate of rotation of an enone anion radical (such as **6** \rightarrow **7**) become available, it should be possible to narrow the limits of this time span substantially.

Finally, it must be noted that the stereochemical tests described here do not allow a clear distinction between the presence of ion radicals as intermediates that lie on the reaction path (eq 2) and the presence of ion radicals formed in a parasitic equilibrium (eq 3). Although a rigorous distinction between these possibilities is difficult, we believe that a subsequently described test¹² involving intramolecular structural rearrangement of ion radical before product formation provides rather convincing evidence that the ion radical is an intermediate on the reaction path to product.

Experimental Section²³

Preparation of the Unsaturated Ketones **4 and **5** and the Saturated Ketones **19** and **21**.** Previously described procedures²⁴ were followed to prepare a pivaldehyde and to condense this aldehyde with the lithium enolate of pinacolone [from the ketone and $\text{LiN}(i\text{-Pr})_2$] to form 2,2,6,6-tetramethyl-5-hydroxy-3-heptanone. A solution of 70 g of this hydroxy ketone and 3.4 g of *p*-TsOH in 1.3 l. of PhH was refluxed for 30 min and then distilled until all the H_2O was removed as the H_2O -PhH azeotrope. The remaining solution was concentrated and the residue was extracted with CCl_4 to leave the insoluble *p*-TsOH. The CCl_4 solution deposited 56.2 g (88%) of the trans ketone **5** as white needles, mp $41\text{--}42^\circ$ (lit.¹³ mp $44\text{--}45^\circ$), that were identified with a previously described¹³ sample by comparison of ir spectra and a mixture melting point determination. A pentane solution of the trans ketone **5** was irradiated (254 μ light) and the resulting mixture, bp $83\text{--}88^\circ$ (20 mm), containing (GLC, TCEP on Chromosorb P) ca. 30% cis ketone **4** (retention time 6.8 min) and ca. 70% trans ketone **5** (10.2 min), was fractionally crystallized¹³ from pentane at Dry Ice temperatures. The mother liquors from a typical low-temperature crystallization contained (glpc) 78% of the cis ketone **4** and 22% of the trans isomer **5**. Since either prolonged storage or the prolonged heating required to separate this mixture by fractional distillation tended to isomerize the cis ketone **4** to the trans isomer **5**, we employed col-

Scheme V



umn chromatography to separate samples of the pure cis ketone **4** as needed. In a typical separation, 3.4 g of the crude mixture of enones **4** and **5** was chromatographed on 190 g of silicagel (Grace 60–200 mesh) employing a pentane–Et₂O mixture (98:2 v/v) as an eluent. After removal of the first 300 ml of eluent, the second 300 ml of eluent contained 1.2 g of the pure (GLC) cis enone **4** and the third 300 ml of eluent contained 1.1 g of mixtures (GLC) of 81–98% of the cis enone **4** accompanied by the trans isomer **5**. The final 500 ml of eluent contained 0.6 g of the pure (GLC) trans enone **5**.

Authentic samples of the saturated ketones **19**²⁵ and **21** (*n*²⁵D 1.4217)^{13a} has been prepared and characterized previously. In the present study collected (GLC) samples of these products from reaction mixtures were identified with the authentic samples by comparison of ir and mass spectra and GLC retention times.

Preparation of the Alcohol Derivatives 13 and 15.²⁶ A solution of 20.0 g (119 mmol) of the trans ketone **5** in 30 ml of Et₂O was added, dropwise and with stirring over 1 hr, to a solution of 4.94 g (130 mmol) of LiAlH₄ in 30 ml of Et₂O. The resulting mixture was stirred at 25° for 5 hr and then treated with 10 ml of H₂O and 2.7 ml of aqueous 15% NaOH. The resulting slurry was filtered and the residual salts were washed with Et₂O. The ethereal filtrates were concentrated and the residual liquid was distilled to separate 18.7 g (91%) of the crude trans alcohol **15a**, bp 94–96° (20 mm), *n*²⁵D 1.4368. A pure sample of the alcohol **15a** was collected (GLC) and redistilled in a short-path still (20 mm and 120° bath) for characterization: ir (CCl₄) 3610, 3490 (free and associated OH), and 975 cm⁻¹ (*trans*-CH=CH); uv (95% EtOH) end absorption with ϵ 60 at 210 m μ ; NMR (CCl₄) δ 5.1–5.8 (2 H, m, vinyl CH), 3.58 (1 H, d, *J* = 6 Hz, CHO), 1.4–1.8 (1 H, m, OH, exchanged with D₂O), 0.98 (9 H, s, *t*-Bu), and 0.82 (9 H, s, *t*-Bu); mass spectrum, *m/e* (rel intensity) 137 (10), 95 (22), 67 (12), 57 (30), 55 (18), 43 (24), 41 (32), 39 (13), 29 (14), and 18 (100).

Anal. Calcd for C₁₁H₂₂O: C, 77.58; H, 13.02. Found: C, 77.78; H, 13.08.

A solution of 7.0 g (40 mmol) of the trans alcohol **15a** in 200 ml of THF was treated with 21.1 ml of a hexane solution containing 50 mmol of *n*-BuLi. To the resulting solution was added 9.31 g (50 mmol) of CH₃OTs. The resulting solution was stirred at 25° for 4 days (during which time a white precipitate separated), and then 30 ml of H₂O was added; stirring was continued for 2 days and then the mixture was partitioned between H₂O and Et₂O. The ether layer was washed with aqueous NaCl, dried, and concentrated. The residual red liquid was distilled to separate 5.6 g (75%) of the crude ether **15b** as a colorless liquid, bp 72–74° (10 mm), *n*²⁵D 4200, that contained (GLC, TCEP on Chromosorb P) several minor impurities. A sample of the pure ether **15b** was collected (GLC) for characterization: ir (CCl₄) 1655 (C=C) and 980 cm⁻¹ (*trans*-CH=CH); NMR (CCl₄) δ 5.60 (1 H, d, *J* = 16 Hz, vinyl CH), 5.15 (1 H, d of d, *J* = 16 and 8 Hz, vinyl CH), 3.15 (3 H, s, OCH₃), 2.96 (1 H, d, *J* = 8 Hz, CHO), 1.07 (9 H, s, *t*-Bu), and 0.82 (9 H, s, *t*-Bu); mass spectrum, *m/e* (rel intensity) 169 (1), 128 (16), 127 (100), 95 (50), 57 (28), and 41 (26).

Anal. Calcd. for C₁₂H₂₄O: C, 78.19; H, 13.13. Found: C, 78.19; H, 12.86.

The GLC (TCEP on Chromosorb P) retention times of the various trans isomers were: ether **15b**, 6.4 min; isobutylbenzene (an internal standard), 12.3 min; ketone **5**, 22.5 min; and alcohol **15a**, 29.3 min.

A comparable reduction was performed with 4.83 g (28.7 mmol) of the cis ketone **4** and 1.25 g (33 mmol) of LiAlH₄ in 30 ml of Et₂O. The crude product, which contained (GLC) mainly the cis alcohol **13a**, was distilled [bp 90–93° (20 mm)], and a sample of the pure alcohol **13a** was collected (GLC) and redistilled in a short-path still (20 mm and 120° bath): ir (CCl₄) 3610 and 3420 cm⁻¹ (free and associated OH); uv (95% EtOH) end absorption with ϵ 61 at 210 m μ ; NMR (CCl₄) δ 5.0–5.6 (2 H, m, vinyl CH), 4.17 (1 H, d, *J* = 8 Hz, CHO), 1.4 (1 H, broad, OH, exchanged with D₂O), 1.12 (9 H, s, *t*-Bu), and 0.84 (9 H, s, *t*-Bu); mass spectrum, *m/e* (rel intensity) 137 (12), 113 (14), 95 (36), 67 (15), 57 (57), 55 (25), 43 (72), 41 (53), 39 (19), 29 (24), and 18 (100).

Anal. Calcd for C₁₁H₂₂O: C, 77.58; H, 13.02. Found: C, 77.84; H, 13.29.

A comparable alkylation was performed by treatment of 480 mg (2.8 mmol) of the cis alcohol **13a** in 15 ml of THF first with 3.7 ml of ether containing 3.4 mmol of MeLi and then 632 mg (3.4 mmol) of CH₃OTs in 5 ml of THF. The mixture, from which a white precipitate separated, was stirred at 25° for 21 hr and then partitioned between Et₂O and aqueous NaCl. The Et₂O layer was dried and concentrated to leave 0.35 g of liquid containing (GLC) the ether **13b**. A pure sample of the ether **13b** was collected (GLC, Apiezon L on Chromosorb P) as a colorless liquid: *n*²⁵D 1.4335; ir (CCl₄) 1645 cm⁻¹ (weak C=C); NMR (CCl₄) δ 5.57 (1 H, d, *J* = 13 Hz, vinyl CH), 4.8–5.3 (1 H, m, vinyl CH), 3.81 (1 H, d, *J* = 11 Hz, CHO), 3.24 (3 H, s, OCH₃), 1.14 (9 H, s, *t*-Bu), and 0.86 (9 H, s, *t*-Bu); mass spectrum, *m/e* (rel intensity) 169 (1), 137 (10), 127 (100), 85 (81), 57 (18), 47 (22), and 45 (20).

Anal. Calcd for C₁₂H₂₄O: C, 78.19; H, 13.13. Found: C, 78.22; H, 13.14.

Preparation of the Alcohols 12 and 14. To a cold (–11 to –20°) solution of 10 mmol of MeLi in 9.6 ml of Et₂O was added, dropwise and with stirring during 5 min, a solution of 1.00 g (6.0 mmol) of a mixture of enones **4** and **5** [36% cis **4** and 64% trans **5**] in 1.0 ml of Et₂O. The resulting solution was stirred at –20° for 1.5 hr and then allowed to warm to –3° and partitioned between Et₂O and an aqueous solution of NH₄Cl and NaCl. The ethereal layer was washed with aqueous NaCl, dried, and concentrated to leave 0.92 g of liquid product containing (GLC, silicone SE-30 on Chromosorb P) the trans alcohol **14** (ca. 63%, ret time 20.0 min), and the cis alcohol **12** (ca. 37%, 24.8 min) and lacking GLC peaks corresponding to either the trans enone **5** (16.0 min) or the cis enone **4** (13.9 min). A pure sample of the trans alcohol **14** was collected as colorless liquid: *n*²⁵D 1.4453; ir (CCl₄) 3610 (OH), 1660 (weak, C=C), and 990 cm⁻¹ (*trans*-CH=CH); NMR (CCl₄) δ 5.58 (2 H, s, vinyl CH), 1.17 (3 H, s, CH₃), 1.10 (1 H, s, exchanged with D₂O), 0.98 (9 H, s, *t*-Bu), and 0.86 (9 H, s, *t*-Bu); mass spectrum, *m/e* (rel intensity) 166 (1), 127 (60), 109 (20), 83 (9), 69 (9), 57 (18), 43 (100), and 41 (15).

Anal. Calcd for C₁₂H₂₄O: C, 78.19; H, 13.13. Found: C, 78.30; H, 13.14.

A pure sample of the cis alcohol **12** was collected (GLC) as a colorless liquid: *n*²⁵D 1.4488; ir (CCl₄) 3620 cm⁻¹ (OH); NMR (CCl₄) δ 5.22 (2 H, partially resolved multiplet, vinyl CH), 1.1–1.4 (13 H, m, OH (exchanged with D₂O) with a CH₃ singlet at 1.26 and a *t*-Bu singlet at 1.20), and 0.97 (9 H, s, *t*-Bu); mass spectrum, *m/e* (rel intensity) 169 (1), 166 (15), 127 (100), 109 (40), 83 (23), 69 (20), 57 (42), 55 (20), and 43 (68).

Anal. Calcd for C₁₂H₂₄O: C, 78.19; H, 13.13. Found: C, 78.22; H, 13.18.

Product Analyses. Before analysis each product mixture was treated with a known weight of *n*-C₁₂H₂₆ as an internal standard and the mixtures were analyzed on GLC equipment that had been calibrated with known mixtures of the internal standard and authentic samples of each of the products. Since certain of the reaction products (particularly alcohols **12** and **14**) were occasionally observed to undergo partial decomposition (presumably acid-catalyzed dehydration in the GLC injection port) to form more rapidly eluted products when injected on untreated GLC apparatus, before each analysis a sample of Et₃N was passed through the GLC appa-

Table I. Reaction of Methyl Organometallic Reagents (Me-M) with Excess Cis Enone 4

Me-M (mmol)	Enone 4, mmol	Et ₂ O, ml	Reaction temp, °C	Reaction time, min	Product yields ^a				
					Enone 4	Enone 5	Alcohol 12	Alcohol 14	Ketone 19
MeLi (0.72)	1.62	10.0	22-25	120	71		28		
Me ₂ CuLi (0.81)	1.85	10.0	0	90	1 ^b	69			23
Me ₂ Mg (1.00)	1.45	10.0	0-10	15 ^c	50	1	38	3	2
			0-10	35 ^c	42	1	40	3	2
			25	65 ^c	34	2	50	3	4
			0	0.67 ^c	60		15	3	2
Me ₂ Mg (0.60)	0.65	11.4	0	7.0 ^c	38		33	7	4
			0	15.0 ^c	37		38	6	3
			0	60.0 ^c	30	1	41	6	3

^a All yields are based on the amount of starting enone 4 employed. ^b In a similar run employing 0.80 mmol of Me₂CuLi and 1.37 mmol of enone 4, the yields were 4% of 4, 50% of 5, 1% of 14, and 23% of 19. ^c These analyses were obtained from successive aliquots removed from the same reaction mixture.

Table II. Reduction with an Excess of One of the Enones 4 or 5

Reducing agent (mmol or mg-atom)	Enone (mmol)	Solvent (ml)	Reaction temp, °C	Reaction time, min	Product yield, % ^a				
					Enone 4	Enone 5	Alcohol 13a	Alcohol 15a	Ketone 21
LiAlH ₄ (0.45)	4 (1.42)	Et ₂ O (10.0)	0-25	135	16		81	2	
LiAlH ₄ (0.68)	5 (2.49)	Et ₂ O (10.0)	0-25	135		5		77	11
Li (2.0) + <i>t</i> -BuOH (2.4)	4 (2.0)	NH ₃ (30) + Et ₂ O (3.0)	-78	5	33	10			33
Cr(en) ₂ (OAc) ₂ (10.5)	4 (1.51)	MeOH (40) + HOAc (1.05)	25	480 ^b	2	55			12
				1080 ^b	1	48			14

^a All yields are based on the amount of starting enone 4 employed. ^b These analyses were obtained from successive aliquots removed from the same reaction mixture.

ratus. Employing this precaution, reproducible response factors were obtained for all products being analyzed. Samples of all of the reaction products were collected (GLC) from representative product mixtures of each reaction and the identities of each collected component with authentic samples were established by comparison of ir and mass spectra as well as GLC retention times. On one GLC column used (3-m, 15% Carbowax 20 M on Chromosorb P at ca. 120°) the retention times were: *n*-C₁₂H₂₆, 8.4 min; cis enone 4, 10.8 min; ketone 21, 11.6 min; trans enone 5, 12.4 min; ketone 19, 15.8 min; trans alcohol 14, 18.1 min; cis alcohol 13a and trans alcohol 15a (not resolved), 21.4 min; and cis alcohol 12, 22.6 min. Since this GLC column was not satisfactory for analysis of mixtures containing both of the secondary alcohols 13a and 15a, a second GLC column was also used for analysis of such mixtures. On the second GLC column (3-m, 12% TCEP on Chromosorb P at ca. 105°), the retention times were: *n*-C₁₂H₂₆, 3.8 min; cis enone 4, 11.6 min; ketone 21, 15.4 min; trans alcohol 15a, 18.2 min; trans enone 5, 18.4 min; and cis alcohol 13a, 21.3 min.

Reaction of the Methyl Organometallic Reagents with an Excess of the Enone 4. Commercial halide-free ethereal MeLi (Foote Mineral Co.) was standardized either by titration with a 2,2-bipyridyl indicator,²⁷ or by a double titration procedure with ethylene dibromide.²⁸ Ethereal solutions of Me₂CuLi were obtained by treating of a cold (0°) ethereal slurry of 1.1 mol equiv of purified CuI with 2.0 mol equiv of ethereal MeLi. An ethereal solution of Me₂Mg was obtained by reaction of neat Me₂Hg with excess doubly sublimed Mg (Dow Chemical Co.) followed by dilution with Et₂O and standardization by a double titration procedure.²⁹ Employing the molar quantities and temperatures summarized in Table I, the cis enone 4 was added to an ethereal solution of Me₂CuLi or ethereal solutions of MeLi or Me₂Mg were added to an ethereal solution of the enone 4. After the reaction times specified in Table I, either aliquots or the entire reaction mixture were partitioned between Et₂O and aqueous NH₄Cl. Each Et₂O layer was separated, mixed with a known weight of *n*-C₁₂H₂₆, washed with aqueous NaCl, dried, concentrated, and subjected to the previously described GLC analysis. In reactions where aliquots were taken, the internal standard, *n*-C₁₂H₂₆, was added to the original reaction mixture. The yields listed in Table I are based on the amount of enone 4 employed. None of the reduction products, ketone 21 or alcohols 13a or 15a, were detected (GLC) in these reaction mixtures.

To obtain an estimate of the half-life for the Me₂Mg-enone 4 reaction, this reaction was repeated at 0° and aliquots were removed and analyzed after short reaction periods to give the results summarized in Table I. These data indicate that the half-life for this reaction is approximately 40 sec.

Reductions with an Excess of One of the Enones 4 or 5. The LiAlH₄ reductions, summarized in Table II, were performed by adding LiAlH₄, in one portion, to cold (0°) ethereal solutions of one of the enones 4 or 5. After the reaction period indicated, the solutions were subjected to the same isolation and analysis procedures used with the previously described organometallic reactions. The Li-NH₃ reduction experiments (Table II) were performed by dissolving the Li in cold (-78°) liquid NH₃ and then adding a solution of the enone 4 and *t*-BuOH in Et₂O. After 5 min, solid NH₄Cl was added and the NH₃ was allowed to evaporate. After the residue had been partitioned between H₂O and Et₂O, the organic solution was concentrated, treated successively with an acetone solution of 8 N H₂CrO₄^{13b} and with Me₂CHOH, and again concentrated and partitioned between H₂O and Et₂O. This final Et₂O solution was mixed with a known weight of *n*-C₁₂H₂₆, dried, concentrated, and subjected to the previously described GLC analysis. The reduction with Cr(en)₂(OAc)₂ (Table II) was performed under an N₂ atmosphere by forming the Cr(II) complex from 2.0 g (10.5 mmol) of Cr(OAc)₂·H₂O and 1.3 mol (16.5 mmol) of H₂NCH₂CH₂NH₂ in 30 ml of degassed MeOH containing 1.05 ml (24.5 mmol) of HOAc and then treating this solution successively with 10 ml of degassed MeOH and with the enone 4 and a known amount of *n*-C₁₂H₂₆. After the reaction period indicated, the reaction mixture was added to 50 ml of an ice-H₂O mixture, acidified to pH 3 with 6 M HCl, and extracted with Et₂O. The Et₂O extract was washed successively with aqueous NaCl, aqueous NaHCO₃, and aqueous NaCl and then dried, concentrated, and analyzed as previously described.

To establish that the rapid isomerization of the excess cis enone 4 to the trans isomer 5 was not caused by components other than the Cr(II) complex in the reaction mixture, a solution of the Cr(III) salts from oxidation of 3.0 g (15.9 mmol) of Cr(OAc)₂·H₂O, 2.3 g (37.9 mmol) of H₂NCH₂CH₂NH₂, 1.52 g (25.3 mmol) of HOAc, and 336 mg (2.0 mmol) of the enone 4 in 30 ml of MeOH was stirred at 25° for 24 hr and then mixed with an internal standard (*n*-C₁₂H₂₆) and subjected to the usual isolation and analysis procedures. No reduction product was formed and the re-

covered enone mixture contained the cis enone **4** (81% recovery) and the trans enone **5** (12% yield).

Preparation of the Unsaturated Ketones 8 and 9 and the Saturated Ketone 22. The preparation and characterization of each of the ketones **8**, **9**, and **22** was described previously.¹³ After photochemical isomerization of a pentane solution of the trans ketone **9** to form a mixture of ketones **8** and **9** followed by fractional crystallization to partially separate the trans ketone **9**, the remaining mixture contained (GLC, silicone gum, SE-52, on Chromosorb P) the cis ketone **8** (ca. 75%, ret time 7.6 min) and the trans ketone **9** (ca. 25%, 10.9 min). Chromatography of 2.5 g of this mixture on 190 g of silica gel (Grace, 60–200 mesh) with relatively large volumes of pentane as an eluent partially separated the enones such that the material (831 mg) in the early fractions contained (GLC) ca. 84% of the cis ketone **8** and ca. 16% of the trans ketone **9** with latter fractions containing progressively more of the trans ketone **9**. Rechromatography of the early fractions afforded 340 mg of pale yellow liquid fractions containing (GLC) ca. 93% of the cis isomer **8** and ca. 7% of the trans ketone **9**.

Preparation of the Ketone 20. To a cold (0°) solution of Me₂CuLi, prepared from 490 mg (2.58 mmol) of CuI and 4.28 mmol of halide-free MeLi (Foote Mineral Co.) in 10 ml of Et₂O, was added a solution of 240 mg (1.28 mmol) of the trans ketone **9** in 5 ml of Et₂O. After the mixture had been stirred at 0° for 1 hr, it was partitioned between Et₂O and aqueous NH₄Cl. The ethereal layer was washed with aqueous NaCl, dried, and concentrated to leave 228 mg (87%) of the crude ketone **20** as a colorless liquid that solidified on standing and exhibited only one GLC peak (silicone, SE-52, on Chromosorb P) at 8.3 min under conditions where the retention time of the starting material **9** was 10.9 min. A pure sample of the ketone **20** was collected (GLC) as a colorless solid, mp 40–41°. Recrystallization from hexane afforded the ketone **20** as colorless plates: mp 40.5–41°; ir (CCl₄) 1710 cm⁻¹ (C=O); uv (95% EtOH) series of weak maxima (ε 204 or less) in the region 241–268 mμ; nmr (CCl₄) δ 6.8–7.4 (5 H, m, aryl CH), 2.9–3.9 (1 H, m, benzylic CH), 2.5–2.8 (2 H, m, CH₂CO), 1.22 (3 H, d, J = 7 Hz, CH₃), and 0.98 (9 H, s, *t*-Bu); mass spectrum, *m/e* (rel intensity) 204 (M⁺, 15), 147 (23), 105 (100), 91 (19), 57 (42), and 41 (21).

Anal. Calcd for C₁₄H₂₀O: C, 82.30; H, 9.87. Found: C, 82.10; H, 9.73.

Preparation of the Alcohols 16 and 17. To a cold (0°) solution of 1.60 g (8.5 mmol) of the enones (ca. 75% of **8** and 25% of **9**) in 20 ml of Et₂O was added, dropwise and with stirring during 5 min, 8.0 ml of an Et₂O solution containing 13.7 mmol of MeLi. After the reaction solution had been stirred at 0° for 1 hr, it was partitioned between Et₂O and aqueous NH₄Cl. The ethereal solution was washed with aqueous NaCl, dried, and concentrated to leave 1.64 g of crude product (a mixture of alcohols **16**, **17**, TLC, and NMR analysis) as a liquid. A 488-mg aliquot of the crude product was subjected to preparative thin-layer chromatography on plates coated with silica gel (E. Merck, No. PF-254) with an Et₂O-hexane mixture (1:20 v/v) as eluent. Elution of the faster moving component (*R*_f 0.5) afforded 270 mg of the crude cis alcohol **16** as a liquid and elution of the slower moving component (*R*_f 0.4) separated 95 mg of the crude trans alcohol **17**. From these data the total yield of alcohols is 71% of a mixture containing ca. 74% of cis alcohol **16** and ca. 26% of trans alcohol **17**. Each crude liquid alcohol was purified by a short-path bulb-to-bulb distillation under reduced pressure. The pure cis alcohol **16** was separated as a colorless liquid; n²⁵_D 1.5213; ir (CCl₄) 3590 cm⁻¹ (OH); uv max (95% EtOH) 243 mμ (ε 5830); NMR (CCl₄) δ 7.1–7.6 (5 H, m, aryl CH), 6.49 (1 H, d, J = 13 Hz, vinyl CH), 5.80 (1 H, d, J = 13 Hz, vinyl CH), 1.23 (3 H, s, CH₃), and 0.95 (10 H, s, *t*-Bu and OH, 1 H exchanged with D₂O); mass spectrum, *m/e* (rel intensity), 204 (M⁺, <1), 186 (6), 147 (20), 129 (100), 128 (27), and 57 (27).

Anal. Calcd for C₁₄H₂₀O: C, 82.30; H, 9.87. Found: C, 82.29; H, 9.89.

The pure trans alcohol **17** was obtained as a colorless liquid; n²⁵_D 1.5267; ir (CCl₄) 3600 cm⁻¹ (OH); uv max (95% EtOH) 250 mμ (ε 6800); NMR (CCl₄) δ 7.0–7.5 (5 H, m, aryl CH), 6.64 (1 H, d, J = 16 Hz, vinyl CH), 6.36 (1 H, d, J = 16 Hz, vinyl CH), 1.6 (1 H, broad, OH, exchanged with D₂O), 1.32 (3 H, s, CH₃), and 0.98 (9 H, s, *t*-Bu); mass spectrum, *m/e* (rel intensity) 204 (M⁺, 3), 186 (11), 130 (18), 129 (100), 128 (29), 105 (76), and 57 (37).

Anal. Calcd for C₁₄H₂₀O: C, 82.30; H, 9.87. Found: C, 82.26; H, 9.89.

When the above procedure was repeated with 1.209 g (6.43 mmol) of the trans ketone **9** and 13.7 mmol of MeLi in Et₂O, the crude product was 866 mg (66%) of the trans alcohol **17** that was identified with the previously described sample by comparison of TLC *R*_f values and NMR spectra.

Quantitative Study of Reactions Employing Excess Cis Enone 8.

A. With Me₂CuLi. A cold (0°) solution containing 0.48 mmol of Me₂CuLi in 20 ml of Et₂O was treated with 204 mg (1.09 mmol) of the cis enone **8** (93% **8** and 7% of the trans isomer **9**). After the mixture had been stirred for 1 hr at 0°, it was subjected to the usual isolation procedure and the crude liquid product was mixed with a known weight of PhC≡CPh (an internal standard). Analysis (GLC, Carbowax 20 M on Chromosorb P, apparatus calibrated with known mixtures of authentic samples) indicated the presence of the saturated ketone **20** (ret time 8.8 min, 30% yield), the cis enone **8** (13.6 min, 1% recovery), the trans enone **9** (23.1 min, 22% yield), and PhC≡CPh (internal standard, 48.0 min). Collected (GLC) samples of the products **9** and **20** were identified with authentic samples by comparison of GLC retention times and ir spectra.

B. Reduction with Li and *t*-BuOH in Liquid NH₃. A solution of 245 mg (1.3 mmol) of the enriched cis enone **8** (ca. 84% **8** and 16% of the trans isomer **9**) and 103 mg (1.4 mmol) of *t*-BuOH in 10 ml of Et₂O was added to a solution of 9.0 mg (1.3 mg-atom) of Li in 25 ml of liquid NH₃. After the resulting mixture had been stirred at reflux for 5 min, excess solid NH₄Cl was added and then the NH₃ was allowed to evaporate and the residue was partitioned between H₂O and Et₂O. The crude organic product, obtained by concentration of the Et₂O solution, was dissolved in cold (0°) acetone and treated with 2 ml of aqueous 8 N H₂CrO₄. The excess oxidant was consumed by addition of *i*-PrOH and the resulting mixture was again partitioned between H₂O and Et₂O. After the ethereal solution has been dried and concentrated, the crude product was mixed with a known weight of PhC≡CPh (an internal standard). Analysis (GLC, Carbowax 20M on Chromosorb P, apparatus calibrated with known mixture of authentic samples) indicated the presence of the saturated ketone **22** (ret time 8.8 min, 29% yield), the cis enone **8** (12.9 min, 38% recovery), the trans enone **9** (20.5 min, 5% yield), and PhC≡CPh (40.2 min, internal standard). Collected (GLC) samples of the products **8**, **9**, and **22** were identified with authentic samples by comparison of GLC retention times and ir spectra.

C. Reaction with MeLi. To a cold (-40°) solution of 340 mg (1.81 mmol) of the cis enone **8** (ca. 93% of **8** and 7% of the trans isomer **9**) in 10 ml of Et₂O was added a solution of 0.93 mmol of MeLi in 5 ml of Et₂O. The resulting solution was stirred at -40° for 1 hr and then warmed to 25°, stirred for 45 min, and partitioned between Et₂O and aqueous NH₄Cl. The Et₂O solution was washed with aqueous NaCl, dried, and concentrated to leave the crude liquid product that was mixed with a known weight of PhC≡CPh (an internal standard). The subsequent GLC analysis was obtained on a column packed with silicone SE-30 on Chromosorb P that was heated to 150° and was "neutralized" by injecting a sample of Et₃N before each analysis. This GLC apparatus was calibrated with known mixtures of authentic samples. The crude product contained (GLC) the cis enone **8** (ret time 14.2 min, 14% recovery), the cis alcohol **16** (18.0 min, 33% yield), the trans enone **9** (20 min, 14% yield), the trans alcohol **17** (25.1 min, 1% yield), and PhC≡CPh (35.6 min, internal standard).

In a second experiment, a cold (-50°) solution of 320 mg (1.70 mmol) of the enones (75% cis enone **8** and 25% trans enone **9**) in 15 ml of Et₂O was treated, dropwise and with stirring, with 0.5 ml of an Et₂O solution containing 0.84 mmol of MeLi. After the reaction times and temperatures indicated below, aliquots of the reaction mixture were removed and subjected to the previously described isolation and analysis procedure to determine the proportion of the various products present: 35 min at -40 to -50°, 10% of **9**, 69% of **8**, 10% of **17**, and 11% of **16**; 35 min at -40 to -50° and 10 min at -40 to +23°, 6% of **9**, 66% of **8**, 15% of **17**, and 13% of **16**; 35 min at -10 to -50°, 10 min at -40 to 23°, and 30 min at 23–25°, 17% of **9**, 52% of **8**, 16% of **17**, and 15% of **16**; 35 min at -40 to -50°, 10 min at -40 to +23°, and 60 min at 23–25°, 25% of **9**, 41% of **8**, 17% of **17**, and 16% of **16**. Collected (GLC) sam-

ples of each of the components **8**, **9**, **16**, and **17** were identified with authentic samples by comparison of GLC retention times and infrared spectra. It is apparent from this experiment that although the proportions of cis alcohol **16** (48–50% of the alcohol mixture) to trans alcohol **17** remain essentially constant as the reaction mixture was warmed from -40 to 25° , the proportion of the excess trans enone **9** to the cis enone **8** changes from the initial value of 8–12% trans enone **9** at low temperature to 38% trans enone **9** after the mixture had been stirred at 25° for 1 hr. Thus, we conclude that the lithium alkoxide product present in the reaction mixture is slowly converting the cis enone **8** to trans enone **9** as the solution is stirred at 25° .

References and Notes

- (1) This research has been supported by Public Health Service Grant RO1-GM-20197 from the National Institute of General Medical Science. The execution of this research was also assisted by Institution Research Grants from the National Science Foundation for the purchase of a mass spectrometer and a Fourier transform NMR spectrometer.
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- (18) Although we have not yet found an example, there is another possible experimental result intermediate between the experimental results obtained with $MeLi$, Me_2Mg , and $LiAlH_4$ and the results obtained with Me_2CuLi . In a case where a reaction proceeds by initial electron transfer (eq 2) but the intermediates **2** and **3** combine to form a product more rapidly than the anion radical **3** undergoes electron exchange with neutral molecules, it might be possible to form an isomerized product of **1,2** addition accompanied by nonisomerized starting enone. For this result to be obtained, the intramolecular isomerization of these anion radical intermediates (e.g., **6** \rightarrow **7**) would have to be more rapid than intermolecular electron exchange.
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