The Chemistry of Carbanions. XXVI. The Synthesis of Certain γ-Alkenyl α,β-Unsaturated Ketones[1]

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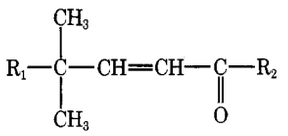
Alkylation of the α-carbon atom of isobutyraldehyde (**3**) was best accomplished by reaction of an alkyl halide with the corresponding lithium salt **8a** of the imine **7** rather than with the lithium enolate **6**. Reaction of the resulting alkylated aldehydes **16** with the ketone lithium enolate **20** afforded good yields of the aldols **21** which underwent acid-catalyzed dehydration to form the enones **22**. The enone **22d** was cyclized to the cyclopentane derivatives **23–25** under very mild conditions.

Our interest in the possible utilization of anion radicals **2** derived from unsaturated carbonyl compounds **1** as synthetic intermediates in carbon–carbon bond forming reactions led us to explore synthetic routes to enones of the type **1**. To examine possible synthetic applications involving intramolecular cyclization, we wanted enones **1** in which the γ substituent, R_1, contained unsaturation. Since



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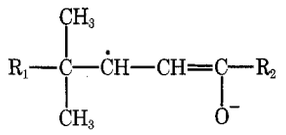

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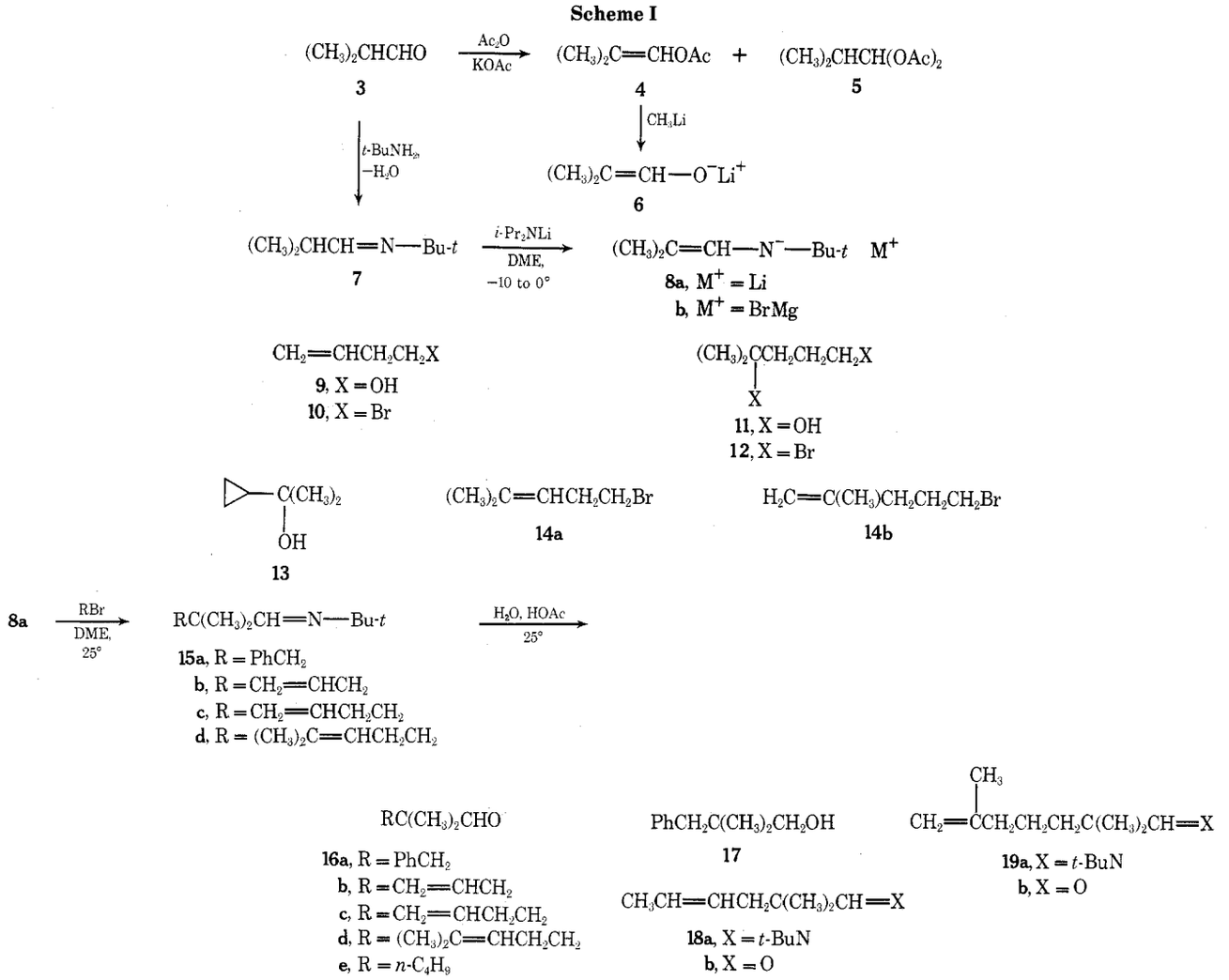
earlier studies[2] had indicated that relatively stable anion radicals **2** could be obtained from enones **1** when no hydrogen atoms were present at either the γ position (*i.e.*, $R_1 \neq H$) or the α′ position [*e.g.*, $R_2 = C(CH_3)_3$], we directed our attention to the synthesis of a series of enones **1** in which R_1 was an alkenyl group and R_2 was a *tert*-butyl group. This paper describes a satisfactory synthetic route to these substances.

Our synthetic plan required the alkylation of isobutyraldehyde (**3**) to form the aldehydes **16** (Scheme I) containing the desired alkenyl substituent R. Although isobutyraldehyde (**3**) has been successfully alkylated in moderate yields (15–75%) by treatment with a mixture of an alkyl ha-

Scheme I

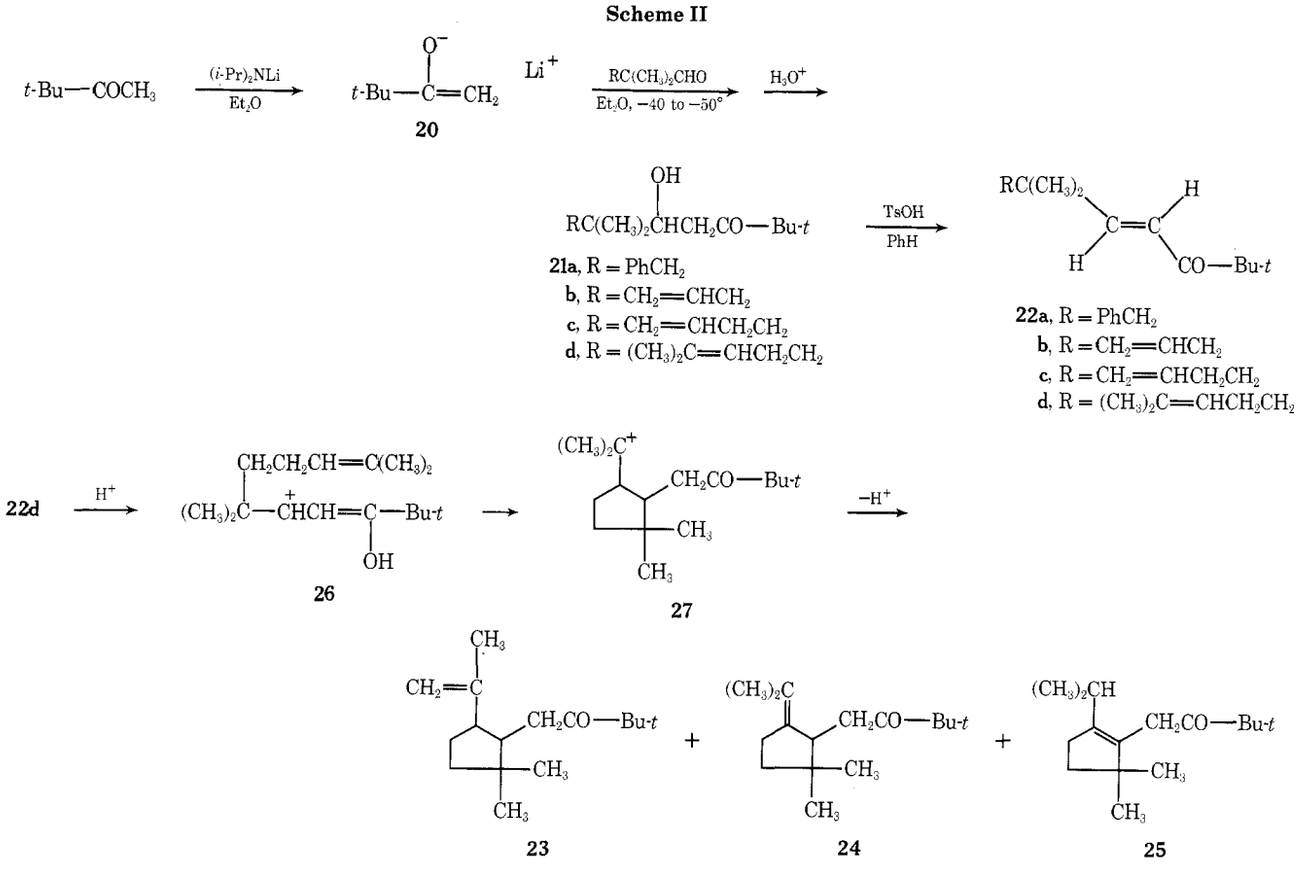


lide, aqueous 50% NaOH, and a tetrabutylammonium salt, this process was satisfactory only with very reactive alkyl halides such as methyl iodide or allylic or benzylic halides.[3] With less reactive alkyl halides, competing aldol condensation predominated.[3] We expected that competing aldol condensation might be minimized or eliminated if the aldehyde **3** was converted completely to its enolate anion **6** in an aprotic solvent before alkylation. Therefore, the lithium enolate **6** was generated in 1,2-dimethoxyethane (DME) solution either by adding the enol acetate **4** to 2 equiv of MeLi or by adding the aldehyde **3** to a cold (0–2°) solution of *i*-Pr_2NLi.[4] In each case, when the solution of the enolate **6** was treated with benzyl bromide, the desired alkylated product **16a** was accompanied by significant amounts of the alcohol **17** as well as higher boiling material. Alcohol and ester by-products were also produced along with the aldehyde **16b** when the lithium enolate **6** (from **4**) was treated with allyl bromide. Thus, we conclude that although the lithium enolates of aldehydes (*e.g.*, **6**) can be prepared in suitable aprotic media, the alkylation of these enolates is complicated by reaction of the alkylated aldehyde products **16** with the various bases (*e.g.*, **6**, *t*-BuO^-Li^+, *i*-$Pr_2N^-Li^+$) present in the reaction mixture to give the products of a Cannizzaro or a Tishchenko reaction.[5]

$$\underset{\mathbf{16}}{RC(CH_3)_2CHO} \xrightarrow{\text{base}} RC(CH_3)_2CH_2OH + RC(CH_3)_2CO_2^- + RC(CH_3)_2CH_2OCOC(CH_3)_2R$$

We, therefore, turned our attention to an alternative synthesis for the aldehydes **16** in which the imine **7** was converted to its anion **8** which would serve as the nucleophile in alkylation reactions. This alkylation procedure, as originally introduced by Stork and Dowd,[6] involved reaction of imines, such as **7**, with EtMgBr to form bromomagnesium salts (*e.g.*, **8b**). Subsequently, many workers have generated anions analogous to **8** employing various lithium salts as bases to form lithium salts such as **8a**.[7] In the present study we have compared the ease of converting the imine **7** to salt **8b** with EtMgBr in THF to the ease of converting it to the salt **8a** by reaction with *i*-Pr_2NLi in DME. The latter procedure, which forms the lithium salt **8a**, was clearly preferable. In the course of examining the formation of solutions of salt **8a** we also observed that this lithium salt **8a** attacks the solvent, DME, at temperatures above 30° to form the starting imine **7**, CH_3OLi, and $CH_2{=}CHOCH_3$. This same type of cleavage of DME with *i*-Pr_2NLi has been observed in the temperature range 0–10°.[4] Because of this solvent cleavage, the generation and use of the lithium salt **8a** was best accomplished by treatment of a cold (−10 to 0°) solution of *i*-Pr_2NLi in DME with the imine **7** followed by warming the solution to 10–20°. During the subsequent addition of alkyl halide the temperature of the exothermic reaction mixture was maintained in the range 20–30° to achieve reasonably rapid alkylation while avoiding extensive solvent cleavage. When the reaction mixture was hydrolyzed by addition of H_2O, the corresponding imines **15** could easily be isolated from the aqueous alkaline solutions. The imines **15** were best hydrolyzed to form the aldehydes **16** by stirring with a mixture of hexane and excess aqueous 1 *M* HOAc at 25°. The conditions, which give an aqueous medium of pH ~4 corresponding to the maximum rate of imine hydrolysis,[8] are to

Scheme II



EXPERIMENTAL SECTION[10]

Preparation of the Enol Acetate 4.[11] -- A solution of 216 g (3.00 mol) of isobutyraldehyde and 36 g (0.38 mol) of KOAc in 535.5 g (4.5 mol) of Ac_2O was refluxed for 12 hr, diluted with 1 l. of pentane, and washed with three 500-ml portions of water. The pentane solution was stirred at 25° with 250 ml of saturated aqueous $NaHCO_3$ solution containing excess $NaHCO_3$ for approximately 1 hr at which time all the excess Ac_2O had been hydrolyzed (ir analysis). The organic layer was dried, concentrated, and distilled to separate 146.7 g (42.8%) of the pure (glpc) enol acetate 4 as a colorless liquid, bp 124-126°, $n^{25}D$ 1.4201 [lit. bp 124-126°, $n^{25}D$ 1.4178;[12] bp 126°, $n^{20}D$ 1.4226[13]; ir (CCl_4), 1750 (ester C=O) and 1690 cm^{-1} (enol C=C); nmr (CCl_4), δ 6.83 (1H, septuplet, J = 1.5 Hz, vinyl CH), 2.05 (3H, s, $COCH_3$), and 1.66 (6H, d, J = 1.5 Hz, CH_3); mass spectrum, m/e (relative intensity), 114 (M^+, 87), 72 (88), 57 (100), 43 (85), 41 (25), and 39 (27).

In an attempt to form the enol acetate 4 in an acid-catalyzed process,[14] a solution of 14.4 g (0.20 mol) of isobutyraldehyde and 50 ml (0.54 mol) of Ac_2O in 240 ml of CCl_4 was treated with 0.14 ml (ca. 0.8 mmol) of aqueous 70% $HClO_4$ and the resulting solution was allowed to stand at 25° for 3 hr. The orange-brown reaction solution was diluted with 160 ml of pentane and stirred at 25° with 160 ml of saturated aqueous $NaHCO_3$ containing excess $NaHCO_3$ until the excess Ac_2O had been hydrolyzed. The resulting organic layer was dried, concentrated, and distilled to separate 21.8 g (63%) of the pure (glpc) acetate 5 as a colorless liquid, bp 89-90.5° (16 mm), $n^{25}D$ 1.4092 [lit.[15] bp 189°]; ir (CCl_4), 1765 cm^{-1} (ester C=O); nmr (CCl_4) δ 6.51 (1H, d, J = 5.0 Hz, CH(OAc)$_2$), 1.7-2.2 (7H, m, CH including a $COCH_3$ singlet at 2.01), and 0.95 (6H, d, J = 6.8 Hz, CH_3); mass spectrum, m/e (relative intensity), 131 (8), 115 (78), 103 (43), 71 (35), 58 (59), 44 (29), 43 (100), 42 (39), 41 (22), and 39 (22).

Preparation of the Imine 7.[6,16] -- Isobutyraldehyde (72 g or 1.0 mol), was added, dropwise and with stirring during 2 hr, to 73 g (1.0 mol) of t-$BuNH_2$. During the addition the temperature rose from 25° to 40° and an aqueous layer separated near the end of the addition. The organic layer was treated with 15 g of anhydrous K_2CO_3, stirred at 25° for 17 hr, and then decanted onto 12 g of BaO. After this mixture had been stirred at 25° for 10 hr, it was filtered and the organic filtrate was distilled to separate 88.3 g (70%) of the imine 7 as a colorless liquid, bp 56° (75 mm) [lit[16] bp 51-53° (85 mm), $n^{20}D$ 1.4078]; ir (CCl_4), 1675 cm^{-1} (C=N); nmr (CCl_4), δ 7.49 (1H, d, J = 4.5 Hz, CH=N), 2.0-2.6 (1H, m, CH), 1.10 (9H, s, t-Bu), and 1.03 (6H, d, J = 7 Hz, CH_3); mass spectrum, m/e (relative intensity), 127 (M^+, 6), 112 (25), 72 (16), 57 (100), 56 (15), 55 (18), and 41 (27).

Preparation of the Bromide 10. -- An ethereal solution of allylmagnesium bromide, from 242 g (2.00 mol) of allyl bromide, 53.5 g (2.2 g-atom) of Mg, and 1500 ml of Et_2O, was mixed with a slurry of 60.0 g (2.00 mol) of dry paraformaldehyde in 100 ml of Et_2O and the resulting mixture was refluxed with stirring for 6 hr.[17] After the usual isolation procedure, fractional distillation of the residual liquid through a 40-cm. spinning-band column separated 65.5 g (45.5%) of the unsaturated alcohol 9 as a colorless liquid, bp 112-113°, $n^{25}D$ 1.4195 [lit[18] bp 115° (770 mm), $n^{25}D$ 1.4182]; ir (CCl_4), 3620, 3360 (OH) and 1640 cm^{-1} (C=C); nmr (CCl_4), δ 4.8-6.2 (3H, m, vinyl CH), 3.97 (1H, broad, OH), 3.60 (2H, t, J = 7 Hz. CH_2-O), and 2.0-2.5 (2H, m, allylic CH_2); mass spectrum, m/e (relative intensity), 72 (M^+, 6), 57 (7), 43 (17), 42 (100), 41 (34), 39 (24), and 31 (74). The product exhibited a single glpc peak (silicone gum, No. SE-30, on Chromosorb P). To 24.0 g (89 mmol) of cold (-15°) PBr_3 was added, dropwise and with stirring during 2 hr with continuous cooling, a mixture of 12.2 g (170 mmol) of the alcohol 9 and 8.3 g (67 mmol) of pyridine. The resulting mixture, an orange slurry, was stirred at 25° for 2 hr and then distilled to separate 17.05 g (74.5%) of the bromide 10 as a colorless liquid, bp 96-99°, $n^{25}D$ 1.4665 [lit.[19] bp 99°, $n^{25}D$ 1.4625]; ir (CCl_4), 1640 cm^{-1} (C=C); nmr (CCl_4), δ 4.0-6.2 (3H, m, vinyl CH), 3.34 (2H, t, J = 6 Hz, addition long-range coupling also apparent, CH_2Br), and 2.3-2.8 (2H, m, allylic CH_2); mass spectrum, m/e (relative intensity), 137 (2), 136 (M^+, 4), 135 (2), 134 (M^+, 4), 55 (100), 41 (15), and 39 (18). Comparison of the nmr spectrum of this product with the spectrum of crotyl bromide established the absence of the isomeric bromide in our product.

Preparation of the Bromide 14a. -- A cold (-5°) solution of 0.29 mol of MeLi in 130 ml of Et_2O was treated, dropwise and with stirring during 1 hr, with 18.3 g (0.22 mol) of methylcyclopropyl ketone. The reaction mixture was stirred at 25° for 14 hr and then subjected to the usual isolation procedure to separate 13.4 g (61%) of the crude alcohol 13, bp 120-122°, that contained (glpc, Carbowax 20 M on Chromosorb P) the alcohol 13 (15.3 min, ca. 94%) accompanied by the starting ketone (9.3 min, ca. 6%). A solution of 13.4 g (0.134 mol) of the crude alcohol 13 in 30 ml of olefin-free pentane was stirred at 25° with 250 ml of aqueous 46% HBr for 25 min. Then an additional 100 ml of pentane was added and the organic layer was separated, washed successively with aqueous NaCl and aqueous $NaHCO_3$, and then dried and concentrated. Distillation of the residual liquid afforded 12.2 g (56%) of the bromo olefin 14, bp 91-93° (100 mm), $n^{25}D$ 1.4763 [lit.[20] bp 84-85° (84 mm), $n^{20}D$ 1.4758]; containing (nmr analysis) ca. 96% of olefin 14a and ca. 4% of olefin 14b.

To explore an alternative synthesis of the bromide 14a,[11] a cold (-5°) solution of 0.94 mol of MeLi in 500 ml of Et_2O was treated with 37.02 g (0.430 mol) of δ-butyrolactone and the resulting solution was allowed to warm to room temperature during 1 hr with stirring. Water (16.9 g or 0.94 mol) was added, dropwise and with stirring, the ethereal solution was decanted, and the residual semisolid was extracted with five 100-ml portions of Et_2O. The residual semisolid (containing most of the diol) was dissolved in 500 ml of H_2O and continuously extracted with Et_2O for 7 days. All of the Et_2O solutions were combined, dried, concentrated, and distilled to separate 26.12 g (51.3%) of the diol 11 as a colorless liquid, bp 97-98° (3 mm), $n^{25}D$ 1.4503 [lit.[21] bp 127-128° (22 mm), $n^{20}D$ 1.4449]; ir (CCl_4), 3600, and 3320 cm^{-1} (O-H); nmr (pyridine), δ 5.42 (2H, broad, OH), 3.7-4.0 (2H, m, CH_2O), 1.4-2.3 (4H, m, CH_2), and 1.33 (6H, s, CH_3); mass spectrum, m/e (relative intensity), 103 (1), 85 (20), 59 (100), 43 (62), 42 (8), 41 (14), and 31 (17).

A solution of 11.8g (100 mmol) of the diol 11 in 5.4 g (68 mmol) of pyridine was added, dropwise with stirring and cooling, to 21.7 g (80 mmol) of cold (-5°) PBr_3. The reaction mixture was allowed to warm to 25°, diluted with 200 ml of Et_2O, and then treated with ice to destroy the excess PBr_3. The organic layer was washed successively with H_2O and with aqueous NaCl and then dried and concentrated. Distillation of the residual liquid (26.8 g) separated 19.1 g (78%) of the crude dibromide 12 as a colorless liquid, bp 98-104° (60 mm), $n^{25}D$ 1.4895 [lit.[22] bp 95° (20 mm), $n^{23}D$ 1.4990]. Although the product lacked ir absorption (CCl_4) in the 3- or 6-μ regions attributable to OH or C=O functions, the nmr spectrum (CCl_4) of the product exhibited weak nmr absorption in the region δ 4.6-5.3 attributable to the vinyl CH of unsaturated bromides 14 as well as nmr absorption attributable to the dibromide 12: δ 3.1-3.6 (2H, m, CH_2Br) and 1.5-2.8 (10H, m, CH_2 and a CH_3 singlet at 1.75). A mixture of 10.9 g (45 mmol) of the crude dibromide 12 and 3.6 g (46 mmol) of pyridine was slowly warmed to 100° and then heated at 100° for 20 min.[22] The mixture was distilled to separate 5.56 g (77%) of a fraction, bp 78-87° (90 mm), $n^{25}D$ 1.4758. An Et_2O solution of this fraction was washed successively with aqueous Na_2CO_3, with H_2O, and with aqueous NaCl, and then dried and concentrated. Distillation of the residual liquid (4.64 g) afforded 3.27 g (55%) of a mixture of the bromo olefins 14, bp 83.5-84.5° (85 mm), [lit.[20] for olefin 14a, bp 84-85° (84 mm), $n^{20}D$ 1.4758]. The nmr spectrum (CCl_4) of this mixture indicated the presence of ca. 67% of the olefin 14a (vinyl multiplet at δ 5.0-5.3) and ca. 33% of the olefin 14b (vinyl multiplet at δ 4.7-4.9). Our efforts to obtain a relatively pure sample of the bromo olefin 14a from this mixture were not successful.

Preparation of the Imine Salts 8. -- A cold (-55 to -57°) solution of i-Pr_2NLi, prepared from 57.8 mmol of MeLi, 5.85 g (57.8 mmol) of i-Pr_2NH, 3 mg of 2,2'-bipyridyl, and 30 ml of DME,[23] was treated with 6.60 g (52 mmol) of the imine 7. An aliquot of this cold solution was withdrawn and the nmr spectra of the aliquot was determined successively at temperatures of -10°, 0°, 25°, and 50°. The solution exhibited an nmr doublet (J = 4.5 Hz) at δ 7.55 characteristic of the imine 7 and a broad singlet at δ 6.38 attributable to the lithium derivative 8a. In addition, the solution at -10°, 0°, and 25° exhibited weak nmr peaks at δ 6.69, 6.57, and 6.45 that we attribute to part of the vinyl CH absorption of $CH_3OCH=CH_2$ from reaction of i-Pr_2NLi with the solvent.[24] The conversion of the imine 7 to the lithium derivative 8a was incomplete (nmr analysis) at -10° but was essentially complete at 0° and at 25°. As the solution was warmed to 50°, the extra nmr peaks, attributable to $CH_2=CHOCH_3$, increased in size with a corresponding decrease in the nmr peak attributable to the lithium reagent 8a. This observation indicates that attack of the lithium derivative 8a on DME becomes a serious competing reaction at temperatures above ca. 30° and suggests that reaction solutions in DME employing the derivative 8a are best used within the temperature range 0 to 30°. When the remaining solution of i-Pr_2NLi in DME was warmed to 50° for 5 min and then stirred overnight at 25°, 1.0 g of CH_3OLi separated as a white precipitate. A solution of this precipitate in D_2O exhibited an nmr singlet at δ 3.37 (CH_3O) as well as weak singlets at δ 5.14 (OH) and 1.16.

To verify the location of the nmr peaks attributable to $CH_3OCH=CH_2$, a cold (-35 to -40°) solution of 50 mmol of i-Pr_2NLi in 50 ml of DME was warmed to 23° and allowed to stand for 15 hr. At this time the color of the 2,2-bipyridyl indicator was discharged indicating complete distruction of the i-Pr_2NLi. The nmr spectrum of this DME solution exhibited four low-field peaks at δ 6.69, 6.57, 6.45, and 6.33 attributable to the α-vinyl proton of $CH_3OCH=CH_2$.

To examine the formation of the bromomagnesium salt 8b,[6] a solution of 6.35 g (50 mmol) of the imine 7 and 50 mmol of EtMgBr in 44 ml of tetrahydrofuran (THF) was refluxed for 12 hr. However, the amount of EtH evolved (ca. 100 ml) indicated that salt formation was incomplete. The nmr spectrum of this THF solution exhibited peaks of comparable intensity at δ 7.57 (doublet, J = 4Hz, CH=N of the imine 7) and at δ 6.30 (broad, singlet, CH=C of the BrMg salt 8b) also indicating that formation of the salt 8b was incomplete. The ratio of areas for these nmr peaks did not change after the solution had been kept at 25° for an additional three days.

Preparation of the Aldehyde 16a. A. From the Imine 7. -- A cold (-35°) solution of 50 mmol of i-Pr_2NLi in 35 ml of DME was treated with 6.36 g (50 mmol) of the imine 7. The resulting solution of the lithio imine 8a was warmed to 20° over a period of 1.3 hr and then treated, dropwise and with stirring during 12 min, with 8.55 g (50 mmol) of $PhCH_2Br$ while the temperature of the reaction mixture was kept in the range 20-40° by external cooling. When the addition was complete, the reaction mixture (a slurry containing solid LiBr) was stirred at 25° for 3.5 hr and then partitioned between aqueous NaCl and Et_2O. The ethereal solution was dried and then concentrated under reduced pressure. Distillation of the residual liquid (14.6 g) separated 1.25 g of forerun, bp 35-64° (0.45 mm), $n^{25}D$ 1.5292, and 8.25 g (ca. 76%) of fractions, bp 65-69° (0.39-0.40 mm), $n^{25}D$ 1.4873-1.4883, containing (glpc, silicone fluid, SE-30, on Chromosorb P) primarily the imine 15a (ret. time 11.4 min) accompanied by several minor impurities (3.9 min, 4.9 min). A collected (glpc) sample of the imine 15a was obtained as a colorless liquid, $n^{25}D$ 1.4875; ir (CCl_4), 1665 and 1655 cm^{-1} (C=N); nmr (CCl_4), δ 7.47 (1H, s, CH=N), 7.0-7.2 (5H, m, aryl CH), 2.69 (2H, s, benzylic CH_2), 1.10 (9H, s, t-Bu), and 1.00 (6H, s, CH_3); mass spectrum, m/e (relative intensity), 217 (M^+, 19), 202 (46), 147 (34), 91 (61), 57 (100), and 41 (23).

Anal. Calcd for $C_{16}H_{23}N$: C, 82.89; H, 10.67; N, 6.45. Found: C, 83.01; H, 10.90; N, 6.04.

The optimum conditions for hydrolysis of the imine 15a were studied by stirring a mixture of a hexane solution of the imine 15a with various concentrations of aqueous HOAc.[25] After various reaction times and temperatures the organic solution was separated, washed successively with aqueous $NaHCO_3$, H_2O, and aqueous NaCl, and then dried and concentrated. Analysis (glpc, silicone gum, SE-30, on Chromosorb P) of the residual liquid determined the relative amounts of the imine 15a (retention time 7.2 min) and the aldehyde 16a (4.7 min) present. The following procedure was found to result in complete hydrolysis. A mixture of 16.33 g (75.2 mmol) of the imine 15a, 200 ml (200 mmol) of aqueous 1 M HOAc, and 80 ml of hexane was stirred at 22° under a nitrogen atmosphere for 2 hr and then saturated with NaCl and extracted with Et_2O. The organic solution was washed successively with aqueous $NaHCO_3$ and aqueous NaCl and then dried and concentrated. Distillation of the residual liquid (15.27 g) separated 11.4 g (ca. 93%) of fractions, bp 56-59° (0.3-0.4 mm), containing (glpc, silicone gum, SE-30, on Chromosorb P) 96% or more of the aldehyde 16a (7.7 min) accompanied by a minor unidentified impurity (5.0 min).

A collected (glpc) sample of the pure aldehyde 16a was obtained as a colorless liquid, $n^{24}D$ 1.5072 [lit.[26] bp 87-88° (1 mm), $n^{20}D$ 1.5097], ir (CCl_4), 2800, 2770, 2690 (aldehyde, C-H), 1725 (strong), and 1700 cm^{-1}, (weak, C=O); uv (95% EtOH), a series of weak maxima (ε 157-227) in the region 242-267 mμ with a maximum at 293 mμ (ε 42); nmr (CCl_4), δ 9.48 (1H, s, CHO), 6.8-7.3 (5H, m, aryl CH), 2.70 (2H, s, benzylic CH), and 0.97 (6H, s, CH_3); mass spectrum, m/e (relative intensity), 162 (M^+, 17), 92 (13), 91 (100), 65 (8), 55 (6), and 39 (6).

In an experiment where the intermediate imine 15a was not isolated, a solution of 50 mmol of the salt 8a in 40 ml of DME was treated with 8.54 g (50 mmol) of $PhCH_2Br$ (temperature of the mixture 7-60°). After the reaction mixture had been stirred at 24° for 21 hr, it was diluted with 60 ml of aqueous 10% HCl, refluxed for 2 hr and then cooled, saturated with NaCl and extracted with Et_2O. The ethereal solution was washed with aqueous NaCl, dried, and concentrated. Distillation of the residual liquid (9.83 g) afforded 5.56 (69%) of the aldehyde 16a, bp 55-57° (0.4-0.6 mm), $n^{25}D$ 1.5066, containing (glpc) one minor (ca. 1%) lower boiling impurity. In a comparable experiment involving hydrolysis of the imine 15a for 1 hr, the initial neutral product isolated, bp 53-60° (0.3-0.4 mm), $n^{25}D$ 1.5083, amounted to only 2.73 g (34%). When the acidic aqueous layer was made basic (NaOH) and extracted with Et_2O, distillation of the organic extract afforded an additional 2.65 g (ca. 32%) of product, bp 55-64° (0.8 mm), $n^{25}D$ 1.4986-1.5002, containing (glpc) mixtures of the aldehyde 16a and the unchanged imine 15a as well as minor amounts of lower boiling materials.

B. From the Lithium Enolate 6. -- To a cold (5-10°) solution of 50 mmol of MeLi and 3 mg of 2,2'-bipyridyl (an indicator) in 40 ml of DME was added, dropwise and with stirring during 25 min, 2.71 g (23.7 mmol) of the enol acetate 4.[25] The resulting pink (slight excess of MeLi) solution of the lithium enolate 6 was warmed to 25° and then treated with 8.55 g (50 mmol) of benzyl bromide. The reaction mixture was stirred at 30-40° (external cooling required initially) for 45 min and then a 25-ml aliquot of the mixture (total volume 67 ml) was partitioned between saturated aqueous $NaHCO_3$ and hexane. The remaining aqueous phase was extracted with ether and the combined organic extracts were dried and concentrated. Distillation of the residual liquid (3.20 g) separated 1.21 g of fractions, bp 88-96° (3 mm), and 0.49 of fractions, bp 61-89° (0.4 mm). The early fractions contained (glpc, silicone gum, SE-30, on Chromosorb P) varying amounts of $PhCH_2Br$ (5.3 min) and the aldehyde

16a (8.6 min) and later fractions contained these two components accompanied by the alcohol 17 (11.4 min) and bibenzyl (23.6 min). The estimated yields were: aldehyde 16a, 19%; alcohol 17, 7%; bibenzyl, 9%; and $PhCH_2Br$, 29% recovery. When the remainder of the reaction mixture was stirred for 20 hr at 25° and then subjected to the same isolation procedure, the crude product contained (ir and nmr analysis) none of the desired aldehyde 16a. From a comparable reaction employing a reaction time of 1 hr at 25-41°, and an additional 30 min at reflux, the estimated yields were: aldehyde 16a, 12%; alcohol 17, 20%; bibenzyl, 23%; and $PhCH_2Br$, 32% recovery. When the reaction time was shortened to 2.5 min at 10-25°, only $PhCH_2Br$ (ca. 80% recovery) and bibenzyl (ca. 10%) were found. Collected (glpc) samples of bibenzyl and the aldehyde 16a were identified with authentic samples by comparison of ir and nmr spectra and glpc retention times. A collected (glpc) sample of the alcohol 17 was obtained as a colorless liquid [lit.[27] mp 33-35°, bp 126-124° (14 mm)]: ir (CCl_4), 3630 and 3390 cm^{-1} (OH); nmr (CCl_4), δ 7.0-7.4 (5H, m, aryl CH), 3.27 (2H, s, CH_2O), 2.93 (1H, s, OH), 2.55 (2H, s, benzylic CH_2), and 0.84 (6H, s, CH_3); mass spectrum, m/e (relative intensity), 164 (M^+, 13), 92 (92), 91 (100), 73 (25), 55 (22), and 43 (19).

Since the major difficulty in this reaction appeared to arise from a Cannizzaro reaction of the initially formed aldehyde 16a caused by the bases (t-BuOLi and 5) present in the reaction mixture, we also examined the preparation of the lithium enolate by direct reaction of isobutyraldehyde with i-Pr_2NLi. To a cold (0-2°) solution of 50 mmol of i-Pr_2NH in 40 ml of DME was added, dropwise and with stirring and cooling during 20 min, a solution of 6.10 g (63 mmol) of isobutyraldehyde in 5 ml of DME.[23] The resulting pink (slight excess of i-Pr_2NLi) solution was warmed to 21°, stirred at 21-23° for 30 min, and then treated with 8.54 g (50 mmol) of $PhCH_2Br$. The resulting mixture was stirred at 23-35° for 30 min and then poured into 40 ml of cold aqueous 10% HCl, saturated with NaCl, and extracted with Et_2O. The organic solution was washed successively with aqueous 5% HCl and with aqueous NaCl and then dried and concentrated. Distillation of the residual liquid (10.5 g) separated 7.50 g of fractions, bp 35-98° (0.3-0.4 mm), containing (glpc) various amounts of $PhCH_2Br$, aldehyde 16a, and alcohol 17 as well as other minor unidentified products. The estimated yields were: aldehyde 16a, 40%; alcohol 17, 5%; and $PhCH_2Br$, 31% recovery.

Preparation of the Aldehyde 16b. A. From the Enamine.[11] Following a previous procedure,[28] the pyrrolidine enamine of isobutyraldehyde was prepared in 71% yield: bp 93-95° (100 mm), $n^{25}D$ 1.4724 [lit. 43-44° (12 mm),[28a] $n^{25}D$ 1.4741[28b]]. Reaction of 15.1 g (125 mmol) of allyl bromide (bp 67-70°) with 18.6 g (125 mmol) of this enamine for 20 hr at ambient temperature followed by hydrolysis with aqueous 2 M HCl afforded 4.112 g (29%) of the unsaturated aldehyde 16b as a colorless liquid, bp 123-125°, $n^{25}D$ 1.4189-1.4190 [lit.[28] bp 124-125°, $n^{20}D$ 1.4203]; ir (CCl_4), 2800, 2700 (aldehyde CH), 1730 (C=O), 1640 (C=C), 995 and 920 cm^{-1} (CH=CH_2); nmr (CCl_4), δ 9.47 (1H, s, CHO), 4.8-6.1 (3H, m, vinyl CH), 2.19 (2H, d of t, J = 7.2 and 0.6 Hz, allylic CH_2), and 1.03 (6H, s, CH_3); mass spectrum m/e (relative intensity), 112 (M^+, 4), 97 (32), 94 (41), 84 (25), 83 (75), 70 (75), 69 (64), 67 (27), 55 (91), 55 (100), 53 (30), 43 (79), 42 (31), 41 (79), and 39 (61).

An attempt to prepare the aldehyde 16b by reaction of the lithium enolate 5 (from enol acetate 4) with allyl bromide in DME afforded a complex mixture that contained (ir and glpc) the aldehyde 16b accompanied by alcohol and ester products as well as other unidentified materials.

B. From the Imine 7. -- A solution of 100 mmol of the salt 8a in 90 ml of DME was treated with 12.1 g (100 mmol) of allyl bromide during 25 min while the temperature was maintained in the range 19-40° by use of external cooling. After the mixture had been stirred at 23° for 12 hr and then subjected to the previously described isolation procedure, distillation separated 12.5 g (75%) of the crude imine 15b as colorless liquid fractions, bp 24-56° (10-14 mm), $n^{25}D$ 1.4210-1.4265. The later fractions from the distillation, bp 53-56° (14 mm), $n^{25}D$ 1.4260-1.4265, contained (glpc, TCEP on Chromosorb P) the pure imine 15b (ret. time 10.4 min). An analytical sample of the imine 15b was collected (glpc); ir (CCl_4), 1665 (C=N), 1640 (C=C), 1000, and 925 cm^{-1} (CH=CH_2); nmr (CCl_4), δ 7.42 (1H, s, CH=N), 4.8-6.0 (3H, m, vinyl CH), 2.12 (2H, d, J = 7 Hz, allylic CH_2), 1.10 (9H, s, t-Bu), and 0.96 (6H, s, CH_3); mass spectrum m/e (rel. intensity), 167 (M^+, 2), 152 (16), 112 (40), 111 (15), 96 (38), 84 (11), 70 (17), 57 (100), 55 (27), and 41 (32).

Anal. Calcd for $C_{11}H_{21}N$: C, 78.97; H, 12.65; N, 8.37. Found: C, 78.96; H, 12.65; N, 8.38.

Use of the previously described hydrolysis procedure with 6.68 g (40 mmol) of the imine 15b, 30 ml of hexane, and 100 ml (30 mmol) of aqueous 1 M HOAc afforded 7.35 g of low-boiling fractions, bp 30-42° (135 mm), and 5.61 g (80%) of the crude aldehyde 16b as a colorless liquid, bp 79-81° (135 mm), $n^{25}D$ 1.4140. This product exhibited one major glpc peak (TCEP on Chromosorb P) corresponding to the aldehyde 16b (ca. 86%, 20.2 min) accompanied by minor unidentified components (9.6 min, 23.8 min). The product was identified with the previously described sample of the aldehyde 16b by comparison of ir spectra.

Preparation of the Aldehyde 16c. -- A solution of 50 mmol of the salt 8a in 35 ml of DME was treated with 6.75 g (50 mmol) of the bromo olefin 10 during 15 min while the reaction temperature was kept at 25-39°. The resulting mixture was stirred at 25° for 16 hr and then subjected to the previously described isolation procedure to separate 6.50 g (72%) of the crude imine 15c as colorless liquid fractions, bp 63-69° (15 mm), $n^{25}D$ 1.4308-1.4310. Analysis (glpc, TCEP on Chromosorb P) of this crude product indicated the presence of the imine 15c (ret. time 11.4 min) accompanied by minor amounts of two impurities (10.8 and 12.6 min) believed to be isomeric imines 16a. These impurities were partially removed by collection (glpc, TCEP column) to give a sample of the partially purified imine 15c as a colorless liquid, $n^{25}D$ 1.4310; ir (CCl_4), 1665 (C=N), 1638 (C=C), 995 and 920 cm^{-1} (CH=CH_2); nmr (CCl_4), δ 7.40 (1H, s, CH=N), 4.7-6.1 (3H, m, vinyl CH), 1.2-2.2 (4H, m, CH_2), 1.10 (9H, s, t-Bu), and 1.00 (6H, s, CH_3); mass spectrum, m/e (relative intensity), 181 (M^+, 0.5), 166 (5), 127 (33), 112 (31), 71 (28), 57 (100), 55 (32), and 41 (32).

Hydrolysis of 5.70 g (31.4 mmol) of the crude imine 15c with 30 ml of hexane and 100 ml of aqueous 1 M HOAc yielded 2.96 g (75%) of the crude aldehyde 16c as a colorless liquid, bp 63-64° (17 mm), $n^{25}D$ 1.4230. This product contained (glpc, TCEP on Chromosorb P, primarily the aldehyde 16c (ret. time 33.8 min) accompanied by a minor impurity (ca. 10%, 29.0 min) thought to be the isomeric aldehyde 18b. A collected (glpc sample of the product thought to be aldehyde 18b was obtained as a colorless liquid: ir (CCl_4), 2810, 2780, 2700 (aldehyde CH), 1720 (C=O), and 982 cm^{-1} (trans CH=CH); mass spectrum, m/e (relative intensity), 126 (M^+, 73), 111 (55), 108 (53), 97 (37), 93 (52), 72 (75), 72 (90), 69 (70), 57 (75), 56 (80), 55 (100), 54 (42), 53 (37), 43 (34), 41 (75), and 39 (58).

A collected (glpc) sample of the aldehyde 16c was obtained as a colorless liquid, $n^{25}D$ 1.4235; ir (CCl_4), 2810, 2780, 2700 (aldehyde CH), 1725 (C=O), 1640 (C=C), 1000 and 925 cm^{-1} (CH=CH_2); nmr (CCl_4), δ 9.43 (1H, s, CHO), 4.7-5.2 (3H, m, vinyl CH), 1.3-2.2 (4H, m, CH_2), and 1.04 (6H, s, CH_3); mass spectrum m/e (relative intensity), 126 (M^+, <1), 97 (9), 82 (13), 72 (33), 69 (9), 57 (15), 56 (15), 55 (100), 43 (24), 41 (36), and 39 (13).

Anal. Calcd for $C_7H_{14}O$: C, 76.14; H, 11.18. Found: C, 76.14; H, 11.20.

Preparation of the Aldehyde 16d. -- A solution of 50 mmol of the salt 8a in 50 ml of DME was treated with 8.2 g (50 mmol) of the bromide 16d during 15 min and the resulting mixture was stirred at 25° for 15 hr. After following the previously described isolation procedure, distillation separated 1.2 g of a low-boiling fraction, bp 30-59° (15 mm), containing (glpc, TCEP on Chromosorb P) the bromide 16d (ca. 73%, ret. time 18.5 min), the imine 15d (ca. 9%, 20.1 min), and several minor unidentified components (5-6 min). Subsequent distillation fractions amounted to 1.4 g, bp 61-108° (15 mm), containing (glpc) the bromide 16d (ca. 42%) and the imine 15d (ca. 58%) and 5.9 g, bp 109-110° (15 mm), consisting (glpc) the bromide 16d (ca. 5%) and the imine 15d (ca. 95%). Thus, the total yield of imine 15d was ca. 59%. A pure sample of the imine 15d was collected (glpc) as a colorless liquid, $n^{25}D$ 1.4421; ir (CCl_4), 1665 cm^{-1} (C=N); nmr (CCl_4), δ 7.40 (1H, s, CH=N), 4.6-5.3 (1H, m, vinyl CH), 1.2-2.2 (10H, m, CH_2 and allylic CH_2), 1.12 (9H, s, t-Bu), and 0.98 (6H, s, CH_3); mass spectrum, m/e (rel. intensity), 208 (M^+, 1), 194 (2), 127 (100), 112 (57), 71 (54), and 49 (36).

Anal. Calcd for $C_{14}H_{25}N$: C, 80.31; H, 13.00; N, 6.69. Found: C, 80.28; H, 12.96; N, 6.73.

Hydrolysis of 4.65 g (22 mmol) of the imine 15d with 25 ml of hexane and 75 ml of aqueous 1 M HOAc yielded 2.87 g (82%) of the aldehyde 16d, bp 81-84° (15 mm), which showed a single glpc peak (silicone SE-30 on Chromosorb P, ret. time 15.2 min). A collected (glpc) sample of the aldehyde 16d was obtained as a colorless liquid, $n^{25}D$ 1.4417; ir (CCl_4), 2810, 2785, 2705 (aldehyde CH) and 1727 cm^{-1} (C=O); nmr (CCl_4), δ 9.43 (1H, s, CHO), 4.8-5.3 (1H, m, vinyl CH), 1.2-2.2 (10H, m, CH_2 and allylic CH_2), and 1.02 (6H, s, CH_3); mass spectrum, m/e (rel. intensity), 154 (M^+, 1), 83 (81), 82 (82), 72 (56), 69 (75), 67 (48), 56 (33), 55 (47), and 41 (100).

Anal. Calcd for $C_{10}H_{18}O$: C, 77.86; H, 11.76. Found: C, 77.88; H, 11.76.

Preparation of the Aldehyde 16e. -- A cold (5°) solution of 50 mmol of the lithio derivative 8a in 40 ml of DME was treated with 6.85 g (50 mmol) of n-BuBr and the resulting mixture, which initially warmed to ca. 50°, was stirred at 23° for 19 hr. The mixture was diluted with 60 ml of aqueous 10% HCl, refluxed for 1.5 hr, and then subjected to the previous isolation procedure to separate 2.94 g of distillate, bp 40-92° (20-80 mm), that contained (glpc, silicone gum, SE-30, on Chromosorb P) the desired aldehyde 16e (10.6 min, estimated yield 43%) accompanied by several minor, more rapidly eluted components. A collected (glpc) sample of the pure aldehyde 16e was obtained as a colorless liquid, $n^{25}D$ 1.4121 [lit.[30] bp 49° (5 mm), $n^{25}D$ 1.4140]; ir (CCl_4), 2805, 2790, 2700 (aldehyde CH), and 1725 cm^{-1} (C=O); nmr (CCl_4), δ 9.38 (1H, s, CHO), 1.1-1.5 (6H, m, CH_2), and 0.8-1.1 (9H, m, CH_3

including a singlet at 1.00); mass spectrum m/e (relative intensity), 128 (M^+, <1), 99 (48), 7 (100), 57 (97), 55 (57), 43 (94), 41 (97), and 39 (55).

Preparation of the Keols 21a,b. A. Ketol 21a. -- To a cold (-30°) solution of i-Pr_2NLi, from 10.0 mmol of MeLi, 1.11 g (11 mmol) of i-Pr_2NH, 3 mg of 2,2'-bipyridyl, and 10 ml of Et_2O, was added dropwise and with stirring during 1 min, 1.00 g (10 mmol) of pinacolone. The resulting brown solution was stirred at -50 to -60° for 0.5 hr and then 1.62 g (10 mmol) of the aldehyde 16a was added, dropwise and with stirring during 1 min. The resulting light yellow solution was stirred at -35° for 15 min and then 40 ml of ice cold aqueous 1 M HCl was added. The mixture was saturated with NaCl and extracted with Et_2O. The ethereal extract was washed successively with aqueous $NaHCO_3$ and with aqueous NaCl and then dried and concentrated. The residual crude ketol 21a amounted to 2.30 g (95%) of white solid, mp 59.5-65°, which exhibited a single spot (R_f 0.68) on tlc analysis [silica coating with Et_2O-hexane (1:1 v/v) as eluent]. Recrystallization from hexane afforded the pure ketol 21a as white leaflets, mp 70-70.5°; ir (CCl_4), 3450 (associated OH) and 1690 cm^{-1} (C=O, H-bonded); uv [95% EtOH), a series of weak maxima (ε 261 or less) in the region 242-268 mμ with a maximum at 285 mμ (ε 39); nmr (CCl_4), δ 7.0-7.3 (5H, m, aryl CH), 3.62 (1H, d of d, J = 8.6 and 3 Hz, CH-O), 3.25 (1H, broad, OH, exchanged with D_2O), 2.3-3.0 (4H, m, CH_2CO and benzylic CH_2), 1.10 (9H, s, t-Bu), 0.89 (3H, s, CH_3), and 0.50 (3H, s, CH_3); mass spectrum, m/e (relative intensity), 244 (27), 187 (68), 163 (63), 162 (92), 159 (55), 147 (70), 145 (62), 133 (54), 119 (67), 117 (56), 103 (74), 100 (51), 92 (66), 91 (100), 69 (64), 57 (73), and 43 (61).

Anal. Calcd for $C_{18}H_{28}O_2$: C, 77.82; H, 9.99. Found: C, 77.90; H, 9.97.

B. Ketol 21b. -- When the same procedure was followed with 23.9 mmol of i-Pr_2NLi, 15 ml of Et_2O, 2.39 g (23.9 mmol) of pinacolone, and 3.13 g of the crude aldehyde 16b (containing 23.5 mmol of 16b), the residual colorless liquid product (4.96 g) contained (tlc, silica coating, eluent Et_2O-hexane (1:1 v/v), primarily the aldol 21b (R_f 0.32) accompanied by a minor unidentified component (R_f 0.22). A 20.6-mg portion was chromatographed (acid-washed silicic acid, Et_2O-hexane (1:4 v/v) eluent) to separate 19.2 mg of the major component, the ketol 21b, as a colorless liquid, $n^{25}D$ 1.4523; ir (CCl_4), 3540 (associated OH), 1695 (C=O, H-bonded), 1635 (C=C), 1005, and 925 cm^{-1} (CH=CH_2); nmr (CCl_4), δ 4.8-6.2 (3H, m, vinyl CH), 3.68 (1H, d of d, J = 9 and 3 Hz, CH-O), 2.95 (1H, broad, exchanged with D_2O, OH), 1.9-2.7 (4H, m, CH_2CO, and allylic CH_2), 1.13 (9H, s, t-Bu), 0.89 (3H, s, CH_3), and 0.86 (3H, s, CH_3); mass spectrum m/e (relative intensity), 194 (<1), 153 (2), 137 (8), 100 (17), 85 (10), 57 (100), 56 (20), 55 (70), 43 (38), 41 (90), and 39 (22).

Anal. Calcd for $C_{15}H_{26}O_2$: C, 73.33; H, 11.39. Found: C, 73.37; H, 11.43.

An attempt to purify the crude ketol 21b by short-path distillation afforded a colorless liquid, bp 35-42° (15 mm), $n^{25}D$ 1.4319, which contained (tlc) primarily the ketol 21b (R_f 0.64), accompanied by two minor unidentified materials (R_f 0.50 and 0.12).

C. Ketol 21c. -- The same procedure with 10 mmol of i-Pr_2NLi, 10 ml of Et_2O, 1.00 g (10 mmol) of pinacolone, and 1.26 g (10 mmol) of the aldehyde 16c yielded 2.08 g (92%) of the crude ketol 21c as a colorless liquid. This crude product contained (tlc, silica gel coating with an Et_2O-hexane eluent (1:1 v/v)] primarily the ketol 21c (R_f 0.66) accompanied by several minor unidentified components (R_f 0.77, 0.43, and 0.16). A 1.268-g sample of this crude product was chromatographed on 100 g of acid-washed silicic acid employing an ether-hexane mixture (1:5 v/v) as the eluent. The intermediate fractions contained (tlc) the partially purified ketol 21c isolated as a colorless liquid, $n^{25}D$ 1.4537; ir (CCl_4), 3620 (shoulder), 3540 (OH), 1695 (H-bonded C=O), 1640 (C=C), 1000, and 920 cm^{-1} (CH=CH_2); nmr (CCl_4), δ 4.7-6.2 (3H, m, vinyl CH), 3.71 (1H, d of d, J = 9 and 3 Hz, CH-O), 3.11 (1H, broad, OH), 1.2-2.6 (6H, m, CH_2), 1.12 (9H, s, t-Bu), 0.89 (3H, s, CH_3), and 0.87 (3H, s, CH_3).

D. Ketol 21d. -- Use of this procedure with 17.5 mmol of i-Pr_2NLi, 10 ml of Et_2O, 1.75 g (17.5 mmol) of pinacolone, and 2.70 g (17.5 mmol) of the aldehyde 16d yielded 4.3 g (97%) of the crude ketol 21d as a white solid. The nmr spectrum (CCl_4) of this crude product exhibited a multiplet at δ 4.8-5.3 (vinyl CH of 21d) as well as a weak multiplet at δ 4.8-4.8 probably attributable to some of the isomer 28 with a terminal double bond. Repeated recrystallization from hexane separated the pure ketol 21d as white needles, mp 36-36.5°; ir (CCl_4), 3540 (broad, OH) and 1690 cm^{-1} (H-bonded C=O); nmr (CCl_4), δ 4.8-5.3 (1H, m, vinyl CH), 4.68 (1H, d of D, J = 3.8 and 8.2 Hz, carbinol CH), 3.12 (1H, broad, OH), 2.3-2.8 (2H, m, CH_2CO), 1.8-2.2 (2H, m, allylic CH_2), 1.66 (3H, broad, s, allylic CH_3), 1.62 (3H, broad s, allylic CH_3), 1.2-1.6 (2H, m, CH_2), 1.14 (9H, s, t-Bu), 0.99 and 0.96 (6H, two partially resolved singlets, CH_3); mass spectrum, m/e (rel. intensity), 166 (16), 165 (21), 100 (18), 83 (57), 82 (56), 72 (34), 69 (70), 67 (40), 57 (100), 56 (30), 55 (36), 43 (36), and 41 (25).

Anal. Calcd for $C_{15}H_{28}O_2$: C, 75.53; H, 11.89. Found: C, 75.63; H, 11.92

19

Preparation of the Enones 22. A. Enone 22a. -- A solution of 2.50 g (9.5 mmol) of the crude ketol 21a and 131 mg (0.67 mmol) of p-TsOH in 45 ml of PhH was boiled until 2 ml of the PhH-H_2O azeotrope had been distilled and then the solution was cooled and washed successively with aqueous NaCl, with aqueous $NaHCO_3$, and with aqueous NaCl. After the organic solution had been dried and concentrated, the residual liquid (2.37 g) was distilled under reduced pressure in a short-path still to separate 1.90 g (*ca* 90%) of the crude trans-enone 22a as a colorless liquid, $n^{25}D$ 1.5052, bp 162-164° (8 mm), which exhibited one major glpc (silicone gum, SE-30, on Chromosorb P) peak corresponding to the enone 22a (7.8 min) accompanied by a minor, more rapidly eluted impurity (1.1 min). A collected (glpc) sample of the pure enone 22a was obtained as a colorless liquid, $n^{25}D$ 1.5055. The product was also purified by crystallization from hexane at Dry Ice temperature to separate the enone 22a as white needles, mp 34-34.5°; ir (CCl_4), 1685 (conjugated C=O), 1620 (C=C), and 980 cm^{-1} (trans CH=CH); uv max (95% EtOH), 230 mμ (ε 11,200); nmr (CCl_4), δ 6.7-7.3 (5H, m, aryl CH and 1 vinyl CH), 6.13 (1H, d, J = 15.5 Hz, vinyl CH), 2.63 (2H, s, benzylic CH_2), and 1.04 (15H, s, t-Bu and CH_3); mass spectrum, m/e (relative intensity), 244 (M^+, 32), 187 (91), 159 (90), 145 (94), 91 (100), 69 (59), 57 (74), and 43 (40).

Anal. Calcd for $C_{17}H_{24}O$: C, 83.55; H, 9.90. Found: C, 83.67; H, 9.86.

B. Enone 22b. -- After a solution of 2.12 g (10 mmol) of the crude ketol 21b and 132 mg (0.7 mmol) of p-TsOH in 90 ml of PhH was boiled for 10 min, during which time 15 ml of distillate was removed, application of the usual isolation procedure separated 2.46 g of residual colorless liquid. A 963-mg portion of the crude product was distilled to separate 733 mg (96%) of colorless liquid, bp 44° (25 mm), $n^{25}D$ 1.4617. This material exhibited one major

20

glpc peak (silicone gum, SE-30, on Chromosorb P) corresponding to the enone 22b (13.2 min). A collected (glpc) sample of the pure enone 22b was obtained as a colorless liquid, $n^{25}D$ 1.4567; ir (CCl_4), 1688 (conjugated C=O), 1640 (C=C), 1620 (conjugated C=C), 990, and 900 cm^{-1} ($CH=CH_2$ and trans CH=CH); uv max (95% EtOH), 230 mμ (ε 11,800), and 321 mμ (ε 65); nmr (CCl_4), δ 6.81 (1H, d, J = 15.5 Hz, vinyl CH), 6.32 (1H, d, J = 15.5 Hz, vinyl CH), 4.7-6.0 (3H, m, vinyl CH), 2.15 (2H, d, J = 6.5 Hz, further partially resolved splitting apparent, allylic CH_2), 1.14 (9H, s, t-Bu), and 1.09 (6H, s, CH_3); mass spectrum, m/e (relative intensity), 194 (M^+, 1), 153 (22), 137 (60), 109 (55), 95 (32), 85 (18), 69 (28), 67 (37), 57 (100), and 41 (48).

Anal. Calcd for $C_{13}H_{22}O$: C, 80.35; H, 11.41. Found: C, 80.49; H, 11.43.

C. Enone 22c. -- A solution of 717 mg (3.2 mmol) of the crude ketol 21c and 44.8 mg (0.24 mmol) of p-TsOH in 30 ml of PhH was refluxed for 10 min and then subjected to the usual isolation procedure. Distillation of the crude liquid product (710 mg) in a short-path still separated 578 mg (87%) of the enone 22c as a colorless liquid, bp 31-50° (8 mm) that contained (glpc, silicone SE-30 on Chromosorb P) primarily the enone 22c (rel. time 19.1 min) accompanied by a minor unidentified impurity (4.7 min). A collected (glpc) sample of the enone 22c, $n^{25}D$ 1.4589, was used for characterization: ir (CCl_4), 1685 (conjugated C=O), 1640 (C=C), 1620 (conjugated C=C), 995 and 925 cm^{-1} ($CH=CH_2$ and trans CH=CH); nmr (CCl_4), δ 6.80 (1H, d, J = 15.5 Hz, vinyl CH), 6.32 (1H, d, J = 15.5 Hz, vinyl CH), 5.7-6.1 (3H, m, $CH=CH_2$), 1.2-2.3 (4H, m, CH_2), 1.12 (9H, s, t-Bu), and 1.08 (6H, s, CH_3); uv max (95% EtOH), 230 mμ (ε 11,800), and 321 mμ (ε 64); mass spectrum, m/e (rel. intensity), 208 (M^+, 12), 193 (5), 151 (100), 123 (31), 109 (90), 107 (41), 95 (25), 81 (71), 69 (68), 67 (46), 57 (95), 55 (47), 43 (24), 41 (85), and 39 (20).

21

Anal. Calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 81.06; H, 11.80

In an alternative purification procedure, 500 mg of the crude enone 22c was repeatedly crystallized from hexane at Dry Ice temperatures to separate the enone 22c as a colorless crystalline solid that remained solid when stored at -8°.

D. Enone 22d. -- A solution of 0.54 g (2.1 mmol) of the crude aldol 21d and 5 mg (0.003 mmol) of TsOH in 20 ml of PhH was refluxed for 10 min and then subjected to the usual isolation procedure. The nmr spectrum (CCl_4) of the crude product indicated the presence of both the desired enone 22d (*ca* 84%, vinyl CH at δ 4.8-5.3) and a second minor component believed to be the double bond isomer 28 (*ca* 16%, vinyl CH at δ 4.3-4.8; ir (CCl_4), 1680 (conjugated C=O), 1620 (C=C), and 900 cm^{-1} ($C=CH_2$)]. When the same reaction was repeated with 230 mg of the pure aldol 21d, the crude enone product (204 mg) again contained (nmr analysis) a mixture of *ca* 83% of the enone 22d and *ca* 17% of a contaminant believed to be enone 28. A 200-mg sample of the crude enone was partially purified by preparative tlc employing a silica gel GF-254 coating with an Et_2O-hexane mixture (3:97 v/v) as the eluent. This procedure separated 130 mg of a fraction (R_f 0.5) of colorless liquid that contained (nmr analysis) primarily the enone 22d accompanied by a small amount of the double bond isomer 28. Repeated recrystallization of this material from hexane at Dry Ice temperatures separated 80 mg of the pure enone 22d as white needles, mp 22°; ir (CCl_4), 1690 (conjugated C=O), 1620 (conjugated C=C), and 985 cm^{-1} (trans CH=CH); uv max (95% EtOH), 229 mμ (ε 13,300) and 323 mμ (ε 68); nmr (CCl_4), δ 6.84, 6.39 (2H, AB pattern with J = 16 Hz, trans CH=CH), 4.8-5.3 (1H, m, vinyl CH), 1.2-2.2 (10H, m, including two broad peaks at 1.68 and 1.58, CH_2 and allylic CH_3), 1.14 (9H, s, t-Bu), and 1.08 (6H, s, CH_3); mass spectrum, m/e (rel. intensity), 236 (M^+, 12), 221 (45), 179 (32), 153 (26), 123 (26), 121 (30), 109 (30),

22

97 (71), 81 (26), 69 (91), 57 (100), 55 (42), 43 (32), and 41 (84).

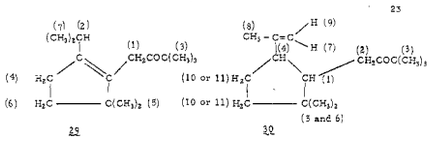
Anal. Calcd for $C_{16}H_{28}O$: C, 81.29; H, 11.94. Found: C, 81.52; H, 12.10.

When the reaction time or the amount of TsOH catalyst used in this dehydration procedure was increased, the crude product contained (glpc, silicone SE-30 on Chromosorb P) various mixtures of the cyclized products 23 (rel. time 18.0 min), 24 (23.4 min), and 25 (21.8 min) as well as the enone 22d (28.0 min) and a component thought to be enone 28 (26.2 min). When a PhH solution of 6.1 mmol of the aldol 21d and 0.2 mmol of TsOH was refluxed for 60 min before product isolation, the product yields were estimated (glpc and nmr analysis) to be 59% of 25, 5% of 24, and 3% of 23. From a comparable reaction employing a reflux period of only 10 min, the estimated yields were 1% of 25, 8% of 24, 60% of 23, 3% of 22d and 4% of 28.

A collected (glpc) sample of the ketone 25 was obtained as white needles, mp 31°; ir (CCl_4), 1710 cm^{-1} (C=O); uv (95% EtOH), end absorption with ε 2700 at 210 mμ; mass spectrum, m/e (rel. intensity), 236 (M^+, 3), 95 (16), 57 (100), 43 (25), and 41 (19); nmr (CCl_4), δ 3.10 (2H, broad, CH_2CO), 2.0-2.5 (3H, m, CH and allylic CH_2), 1.3-1.8 (2H, m, CH_2), 1.16 (9H, s, t-Bu), 0.95 (6H, d, J = 7 Hz, CH_3), and 0.86 (6H, s, CH_3). When a CCl_4 solution of the ketone 25 was treated with successive increments of the nmr shift reagent Eu (dpm)$_3$, the relative shifts, Δδ, for the various protons followed the order indicated in the structure 29 (where No. 1 represents the largest shift and No. 7 the smallest).

Anal. Calcd for $C_{16}H_{28}O$: C, 81.29; H, 11.94. Found: C, 81.33; H, 11.97.

23



A collected (glpc) sample of the minor cyclized product 24 was obtained as a liquid: ir (CCl_4), 1705 cm^{-1} (C=O); nmr (CCl_4), δ 1.8-3.1 (5H, m, allylic CH and CH_2 and CH_2CO), 1.58 (6H, broad, s, allylic CH_3), 1.1-1.5 (2H, m, CH_2), 1.07 (9H, s, t-Bu), 0.92 (3H, s, CH_3), and 0.83 (3H, s, CH_3); mass spectrum, m/e (rel. intensity), 236 (M^+, 5), 221 (5), 137 (18), 121 (18), 95 (20), 85 (15), 57 (100), and 41 (20).

Anal. Calcd for $C_{16}H_{28}O$: C, 81.29; H, 11.94. Found: C, 81.29; H, 11.97.

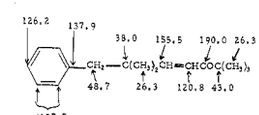
A collected (glpc) sample of ketone 23 was obtained as a liquid that solidified at 15°; ir (CCl_4), 1705 (C=O), 1640 (C=C), and 900 cm^{-1} ($C=CH_2$); mass spectrum, m/e (rel. intensity), 236 (M^+, 3), 221 (10), 136 (27), 121 (89), 109 (26), 95 (70), 91 (25), 87 (24), 57 (100), and 41 (61); nmr (CCl_4), δ 4.5-4.7 (2H, m, vinyl CH), 2.1-2.4 (3H, m, allylic CH and CH_2CO), 1.3-1.8 (7H, m, CH_2 and allylic CH_3), 1.10 (9H, s, t-Bu), 0.98 (3H, s, CH_3), and 0.82 (3H, s, CH_3). When a CCl_4 solution of the ketone 23 was treated with successive increments of the nmr shift reagent, Eu(fod)$_3$, the relative shifts, Δδ, for the various protons followed the order indicated in structure 30 (where No. 1 is the largest shift).

Anal. Calcd for $C_{16}H_{28}O$: C, 81.29; H, 11.94. Found: C, 81.48; H, 12.09.

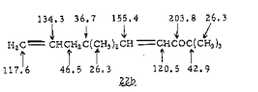
^{13}C NMR Spectra of the Enones 22. -- The natural abundance ^{13}C nmr spectrum of each of these enones was measured in $CDCl_3$ solution with added TMS as an internal standard. In each case the spectrum was

24

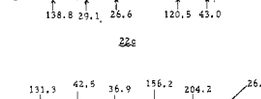
measured both with broadband proton decoupling and with off-resonance decoupling. The chemical shift assignments, indicated in ppm in the accompanying structures, are compatible both with the off-resonance decoupling experiments and with expected chemical shift values for carbon atoms in similar environments.[31]



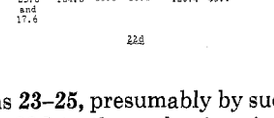
22a



22b



22c



22d

be preferred over the original procedure (refluxing aqueous 10% mineral acid)[6] since the hydrolysis is *faster* and acid-catalyzed side reactions (*e.g.*, double-bond isomerization) are largely avoided. By attention to the foregoing details, each of the desired aldehydes **16** was synthesized in good yield and contamination of aldehydes **16c** and **16d** with their double-bond isomers **18b** and **19b** was minimized.

With the aldehydes **16** in hand, application of a previously described[9] aldol condensation procedure in which each aldehyde **16** was added to a *cold* (−40 to −50°) *ether solution* of the lithium enolate **20** (Scheme II) produced the aldol products **21** in high yield. Subsequent dehydration of the aldols **21** with a catalytic amount of TsOH in PhH afforded the indicated trans enones **22,** three of which could be isolated as low-melting crystalline materials.

Although the conditions used for the acid-catalyzed dehydration of the aldols **21a, 21b,** and **21c** to the corresponding enones **22** were not particularly critical (*ca* 0.1 molar equiv of TsOH in boiling PhH), the enone **22d** proved to be especially prone to subsequent acid-catalyzed cyclization. Thus, attempts to dehydrate the aldol **21d** with 0.1 molar equiv of TsOH in boiling PhH formed primarily the cyclic keto olefins **23–25,** presumably by successive conversion of the enone **22d** to the carbonium ion intermediates **26** and **27.** With much less acid catalyst (*ca* 0.001 molar equiv) and a short reaction time, the dehydration reaction could be stopped at the desired stage to form the enone **22d.** The ease of this acid-catalyzed cyclization **22a** → **23–25** is, of course, gratifying support for our expectation that cyclization of electron-deficient intermediates derived from the enone **22d** will be a favorable process.

Registry No.—**3,** 78-84-2; **4,** 14498-14-9; **5,** 6283-77-8; **6,** 32970-42-6; **7,** 6852-60-4; **8a,** 52278-93-0; **9,** 627-27-0; **10,** 5162-44-7; **11,** 1462-10-8; **12,** 52278-94-1; **13,** 930-39-2; **14a,** 2270-59-9; **15a,** 52278-95-2; **15b,** 52278-96-3; **15c,** 52278-97-4; **15d,** 52278-98-5; **16a,** 1009-62-7; **16b,** 5497-67-6; **16c,** 52278-99-6; **16d,** 52279-00-2; **16e,** 996-12-3; **17,** 13351-61-6; **18b,** 52341-50-1; **21a,** 52279-01-3; **21b,** 52279-02-4; **21c,** 52279-03-5; **21d,** 52279-04-6; **22a,** 52279-05-7; **22b,** 52279-06-8; **22c,** 52279-07-9; **22d,** 52279-08-0; **23,** 52279-09-1; **24,** 52279-01-4; **25,** 52279-11-5; **28,** 52279-12-6; allyl bromide, 106-95-6; methyl cyclopropyl ketone, 765-43-5.

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References and Notes

(1) This research has been supported by Public Health Service Grant RO1-GM-20197 from the National Institute of General Medical Sciences. The execution of this research was also assisted by Institutional Research Grants from the National Science Foundation for the purchase of a mass spectrometer and a Fourier transform nmr spectrometer.
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(10) All melting points are corrected and all boiling points are uncorrected. Unless otherwise stated $MgSO_4$ was employed as a drying agent. The ir spectra were determined with a Perkin-Elmer Model 237 or Model 257 infrared recording spectrophotometer fitter with a grating. The uv spectra were determined with a Cary Model 14 or a Perkin-Elmer Model 202 recording spectrophotometer. The proton nmr spectra were determined at 60 MHz with a Varian Model A-60 or Model T-60 nmr spectrometer and the ^{13}C nmr spectra were obtained at 100 MHz with a JEOL Fourier transform spectrometer, Model PFT-100. The chemical shifts are expressed in δ values (parts per million) relative to a Me_4Si internal standard. The mass spectra were obtained with an Hitachi Perkin-Elmer Model RMU-7, or a Varian Model M-66, mass spectrometer. All reactions involving strong bases or reactive organometallic intermediates were performed under a nitrogen atmosphere.
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Reduction of Phenyl Trifluoromethyl Ketone with Halomagnesium Alkoxides. An Almost Irreversible Meerwein–Ponndorf–Verley-Type System

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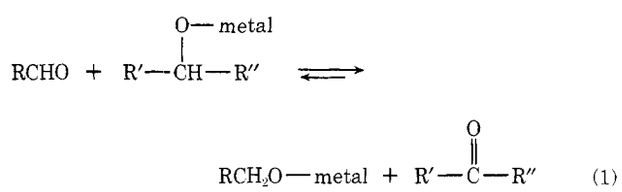
Phenyl trifluoromethyl ketone is reduced rapidly by both primary and secondary bromomagnesium alkoxides to phenyltrifluoromethylcarbinol (as the bromomagnesium salt). Using deuterium-labled alkoxides and chiral alkoxides it was shown that whereas Meerwein–Ponndorf–Verley-type reduction of phenyl trifluoromethyl ketone is facile, the alkoxide produced has little tendency to transfer its hydride to acceptor carbonyl compounds present in the reaction mixture. The electron-withdrawing inductive effect of the trifluoromethyl group is believed to be responsible for this behavior.

Meerwein–Ponndorf–Verley-type reductions (MPV reductions) are equilibrium reactions[1,2] which show a strong preference for the formation of primary alcoholate and ketone in equilibria involving primary and secondary alcoholates[3] (eq 1). A few examples of reductions of ketones by



primary alcoholates have been reported[4] but in these cases the reaction was forced to completion by distillation of the aldehyde as it was formed.

In agreement with the above view of the MPV-type reaction we found that treatment of isopropyl phenyl ketone with 2-phenyl-1-butoxymagnesium bromide in ether–benzene at room temperature for 3 days gave no detectable (glpc) amount of isopropylphenylcarbinol after hydrolysis (eq 2). In contrast, we found that phenyl trifluoromethyl