1468, 1380, 1202 cm^{-1}. Further structure proof of **3f** was carried out by saponification to the known 3-isopropyloxiranecarboxylic acid.

Ethyl 3-isopropyloxiranecarboxylate (**3f**) in ether (50 mL) was treated with 10% NaOH. The resulting biphasic mixture was stirred at room temperature overnight. The aqueous phase was then separated, acidified with 6 N HCl (pH 3), and extracted with ethyl acetate (2 × 50 mL). The combined ethyl acetate extracts were dried ($MgSO_4$) and concentrated to provide an oil (64%) after purification by flash chromatography (hexane/ethyl acetate (50:50)): ^{1}H NMR ($CDCl_3$) δ 0.97 (d, 3 H, J = 6.8 Hz, $CH(CH_3)_2$), 1.14 (d, 3 H, J = 6.6 Hz, $CH(CH_3)_2$), 1.67 (m, 1 H, $CH(CH_3)_2$), 2.94 (dd, 1 H, J = 9.2, 4.8 Hz, $OCHCH(CH_3)_2$), 3.60 (d, 1 H, J = 4.4 Hz, HO_2CCH), 10.3 (br, 1 H, COOH); FTIR(neat) 3687-2218 (br), 2967, 1727, 1468, 1204 cm^{-1}. Spectral data were in good agreement with literature data for 3-isopropyloxiranecarboxylic acid.[7d]

***tert*-Butyl 3-isopropyloxiranecarboxylate (3g)** was prepared from *syn*-**2g** (390 mg, 1.0 mmol) and triethylamine (0.3 mL) as a colorless oil (170 mg, 91%) after bulb to bulb distillation (bath temperature 85-95 °C (38 mmHg)): ^{1}H NMR ($CDCl_3$) δ 0.94 and 1.14 (two d, 6 H, J = 6.8 Hz, $CH(CH_3)_2$), 1.50 (s, 9 H, $C(CH_3)_3$), 1.60 (m, 1 H, $CH(CH_3)_2$), 2.81 (dd, 1 H, J = 4.6, 9.2 Hz, C-3), 3.44 (d, J = 4.6 Hz, cis C-2). ^{1}H NMR was consistent with the cis isomer. GC analysis also showed only a single component: GC/MS (t_R 9.68) m/z 130 (M^+ - *t*-Bu, 11), 85 (20), 59 (17), 57 (100), 56 (88), 55 (46), 53 (14), 51 (10), 50 (13); ^{13}C NMR (100 MHz) δ 18.34, 20.18, 26.99, 28.05, 53.64, 62.92, 82.29, 167.36; FTIR (neat) 2970, 1747, 1472, 1369, 1251, 1159 cm^{-1}. Further structure proof of this compound was confirmed by transformation to 3-isopropyloxiranecarboxylic acid.

tert-Butyl 3-isopropyloxiranecarboxylate (**3g**, 250 mg, 1.35 mmol), was treated with trifluoroacetic acid (2 mL) at room temperature for 2 h. After dilution with ether (100 mL), the solution was washed with H_2O (2 × 100 mL), dried ($MgSO_4$), and purified by bulb to bulb distillation to provide 3-isopropyloxiranecarboxylic acid (170 mg, 97%) as a colorless oil. Spectral data were in good agreement with the literature data.[7d]

Methyl 2-azido-3-hydroxybutanoate (6a) was prepared by a typical procedure for the formation of 2-azido-3-hydroxy esters **6** from 3-hydroxy-2-nosyloxy esters **2**. Nosylate **2a** (2.25 g, syn:anti = 75:25) was prepared from methyl 2-[(*p*-nitrobenzenesulfonyl)oxy]-3-oxobutanoate (**1a**) (10 mmol) and $NaBH_4$ and used without purification. This material was dissolved in DMSO (20 mL) at room temperature and NaN_3 (1.30 g, 20 mmol) was added. The resulting solution was heated at 50 °C for 20 h. After the mixture was cooled to room temperature, H_2O (100 mL) was added, and the solution was extracted with ether (4 × 100 mL), dried ($MgSO_4$), and concentrated to provide a pale yellow oil (850 mg, 56% for two steps from **1a**) after purification by flash chromatography (hexane/ethyl acetate (90:10 to 80:20)): ^{1}H NMR ($CDCl_3$) δ 1.28 (d, 3 H, J = 6.4 Hz, $CHCH_3$), 2.60 (br, 1 H, OH), 3.84 (s, 3 H, OCH_3), 3.98 (d, 1 H, J = 5.6 Hz, anti CHN_3), 4.14 (m, 1 H, J = 6.0 Hz, CHOH); the ^{1}H NMR spectrum was consistent with 38:62 ratio of syn/anti isomers in the product; IR (neat) 3340 (br), 2970, 2100, 1735 cm^{-1}. Anal. Calcd for $C_6H_9N_3O_3$: C, 33.74; H, 5.70; N, 26.40. Found: C, 37.56; H, 5.63; N, 26.19.

Ethyl 2-azido-3-hydroxybutanoate (6b) was prepared from **2b** (3.3 g, 10 mmol, syn:anti = 62:38) and NaN_3 (1.3 g, 20 mmol) as a colorless oil (900 mg, 53% after two steps from **1b**) after purification by flash chromatography (hexane/ethyl acetate (90:10)): ^{1}H NMR ($CDCl_3$) δ 1.34 (set of m, 6 H, OCH_2CH_3 and $CHCH_3$), 2.57 and 2.74 (br, 1 H, OH for two isomers), 3.80 (d, 0.4 H, J = 3.8 Hz, syn CHN_3), 3.96 (d, 0.6 H, J = 5.6 Hz, anti CHN_3), 4.15 (q, 1 H, CHOH), 4.30 (dt, 2 H, OCH_2CH_3); FTIR-(neat) 3442 (br), 2983, 2111, 1731, 1480, 1266, 1196 cm^{-1}. Spectral data were in good agreement with literature data,[20] and the ^{1}H NMR spectrum was consistent with a 36:64 ratio of syn/anti isomers in the product.

Ethyl 2-azido-3-hydroxy-4-methylpentanoate (6f) was prepared from *syn*-**2f** (1.03 g, 2.9 mmol) and NaN_3 (390 mg, 6 mmol) as a colorless oil (280 mg, 49%) after purification by flash chromatography (hexane/ethyl acetate (90:10)): ^{1}H NMR ($CDCl_3$) δ 0.99 (two d, 6 H, J = 4.6, 4.8 Hz, $CH(CH_3)_2$), 1.34 (t, 3 H, OCH_2CH_3), 1.93 (m, 1 H, J = 5.4 Hz, $CH(CH_3)_2$), 1.90 (br, 1 H, OH), 3.69 (dd, 1 H, J = 4.6 Hz, CHOH), 3.90 (d, 0.8 H, J = 6.4 Hz, anti CHN_3), 4.04 (d, 0.2 H, J = 4 Hz, syn CHN_3), 4.49 (q, 2 H, OCH_2CH_3); the ^{1}H NMR spectrum was consistent with a 25:75 ratio of syn/anti isomers in the product; FTIR(neat) 3496 (br), 2965, 2109, 1736, 1372 cm^{-1}. Anal. Calcd for $C_8H_{15}N_3O_3$: C, 47.75; H, 7.51; N, 20.88. Found: C, 47.69; H, 7.44; N, 20.67.

Azido ester **6f** was also prepared from **2f** (syn:anti = 92:8) and 1,1,3,3-tetramethylguanidinium azide[20] (3 equiv) in 63% yield after purification by flash chromatography (hexane:ethyl acetate = 90:10). The ^{1}H NMR spectrum was consistent with a 25:75 ratio of syn/anti isomers in the product.

Acknowledgment. The authors are very grateful to the National Science Foundation (8709853 and 9004980) for financial support of this work. The National Science Foundation (8814575) also provided funds toward the purchase of the high-field NMR used in this work.

(20) Evans, D. A.; Britton, T. C.; Ellman, J. A.; Dorow, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 4011.

Functional Group Hybrids. Reactivity of α'-Nucleofuge α,β-Unsaturated Ketones. 1. Reactions with Organocopper Reagents

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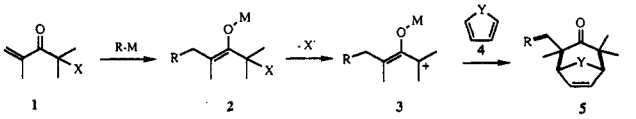
Received May 24, 1991

A series of α-nucleofuge α',β'-unsaturated ketones encompassing a variety of structural types and nucleofuges was prepared. Treatment of these compounds with lithium dimethylcuprate or methylcopper leads primarily to either reductive cleavage of the α-nucleofuge or conjugate addition. Good α-nucleofuges favored the reduction pathway while poorer nucleofuges favored conjugate addition.

Introduction

In recent years, a variety of chemical processes involving sequential C-C bond-forming reactions have been described and were the topic of a recent review by Posner.[1] Most of these multireaction processes involve either sequential pericyclic reactions or sequential conjugate additions and lead to a large increase in molecular complexity[2] in a single step. In an effort to develop efficient polycyclic synthesis methodology, we considered the

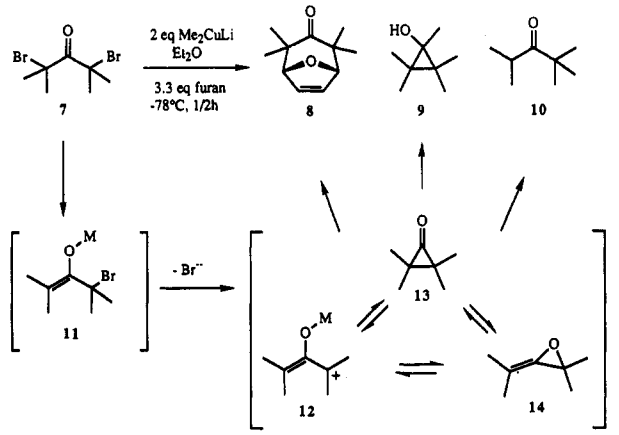
Scheme I. Sequential Conjugate Addition-Cycloaddition Process



(1) Posner, G. H. *Chem. Rev.* **1986**, *86*, 831.

0022-3263/91/1956-6764$02.50/0

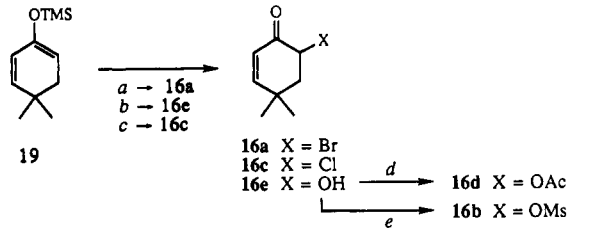
Scheme II. Reaction of 7 with Me_2CuLi in the Presence of a π-Oxyallyl Trap



merging of a conjugate addition process to a pericyclic process as shown in Scheme I. Addition of a metalated species to the β position of an α′-nucleofuge α,β-unsaturated ketone would produce the enolate **2**, which would reasonably be expected to undergo loss of the nucleofuge (X) to generate a π-oxyallyl species **3** which may be trapped in situ to provide an adduct (**5**) in which three new C–C bonds (boldface) had been formed. The novelty of the process lies in the method of π-oxyallyl species generation, which, to our knowledge, is not precedented.

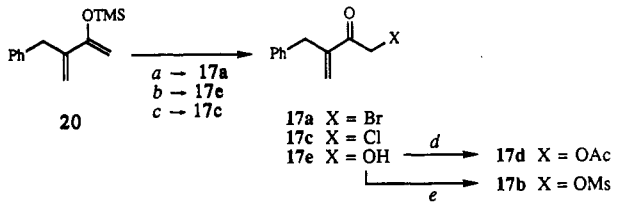
While the chemistry of α,β-unsaturated ketones and of α-nucleofuge ketones[3] has been extensively studied, no systematic studies of the "hybrid" substances (combining both structural features) have appeared.[4] Our interest in such compounds was further heightened during the course of studies related to the chemistry of α-halo and α,α′-dihalo ketones where we observed an interesting result. Treatment of 2,4-dibromo-2,4-dimethyl-3-pentanone (**7**) with 2 equiv of Me_2CuLi at −78 °C in diethyl ether/furan gave the volatile cyclopropanol **9** (44%), 2,2,4-trimethyl-3-pentanone (**10**; 5%), and the bicyclic adduct **8** (6%). The formation of these diverse products can be explained by initial net two-electron reduction of **7** to give **11**, followed by ionization of bromide to enter a manifold of intermediates described by the π-oxyallyl cation **12**[5] and/or cyclopropanone **13**[6] and/or allene oxide **14**,[7] which give rise to the observed products.[8] This observation encouraged us to study the feasibility of the previously described sequential reaction process. Since substances such as **1** possess several sites of reaction with nucleophiles, one can imagine several reactivity modes. As a prelude to the design and study of complex reaction sequences within these systems, it was desirable to study the fundamental reactivity of **1** and allied substances. Previously, only isolated anecdotal reports of the reactions of such substances with electron rich reagents had been reported. In this and the following manuscript, we report the results of our studies of the reaction of such hybrid substances with two organocopper species and dimethyl malonate anion.[9]

Scheme III. Preparation of Substrates 16a–d[a]



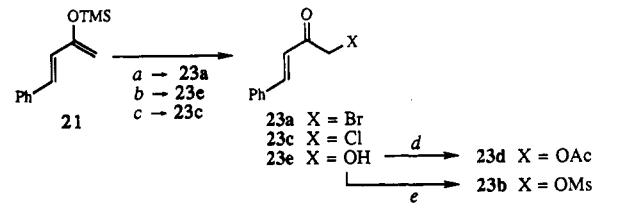
[a] Key: (a) Br_2/CH_2Cl_2, 85%; (b) 1. MCPBA/hexane, 2. MeOH, rt, 2 h, 54%; (c) SO_2Cl_2/CH_2Cl_2, 95%; (d) Ac_2O, Et_3N, CH_2Cl_2, 60%; (e) MsCl, Et_3N, CH_2Cl_2, 80%.

Scheme IV. Preparation of Substrates 17a–d[a]



[a] Key: (a) 1. NBS, 2. aq HF, 53%; (b) 1. MCPBA/hexane, 2. MeOH, rt, 2 h, 94%; (c) SO_2Cl_2/CH_2Cl_2, 97%; (d) Ac_2O, Et_3N, CH_2Cl_2, 65%; (e) MsCl, Et_3N, CH_2Cl_2, 62%.

Scheme V. Preparation of Compounds 23a–d[a]



[a] Key: (a) Br_2, CH_2Cl_2, 74%; (b) 1. MCPBA/hexane, 2. MeOH, rt, 2 h, 74%; (c) SO_2Cl_2/CH_2Cl_2, 81%; (d) Ac_2O, Et_3N, CH_2Cl_2, 35%; (e) MsCl, Et_3N, 71%.

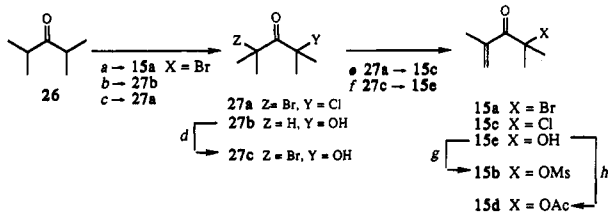
Results and Discussion

Substrate Synthesis. So that a cross-section of information could be obtained about the reactivity of α′-nucleofuge α,β-unsaturated ketones, a series of these compounds was needed representing a variety of nucleofuges and structural features. Compounds ranging structurally from acyclic and cyclic enones to an ynone and possessing nucleofuges at primary, secondary, and tertiary sites were considered. The nucleofuges initially selected included bromide, chloride, mesylate, and acetate, providing a range of synthetically interesting and easily attainable functionality. Ultimately, the substrates **15a–d**, **16a–d**, **17ad**, and **18a,d** were studied.

A search of the literature revealed that few examples of these compounds were known and that no general methods were available for their synthesis. While α,β-unsaturated ketones and α-nucleofuge ketones each can be readily synthesized by a variety of methods, upon combining these subunits into α′-nucleofuge α,β-unsaturated ketones, these methods generally give rise to functional group incom-

(2) Bertz, S. H. *J. Am. Chem. Soc.* **1982**, *104*, 5801.
(3) DeKimpe, N.; Verhe, R. *The Chemistry of α-Haloketones, α-Haloaldehydes and α-Haloimines*; John Wiley and Sons: New York, 1988.
(4) A few anecdotal studies of a single kind of α-leaving group with limited substrates have appeared: (a) Stork, G.; Logusch, E. W. *Tetrahedron Lett.* **1979**, 3361. (b) Bull, J. R.; Lachmann, H. H. *Tetrahedron Lett.* **1973**, 3055. Ruden, R. A.; Litterer, W. E. *Tetrahedron Lett.* **1975**, 2043. Cuprate additions to α-methoxycyclopentenones and 5-acetoxycyclopent-2-en-1-one have been extensively studied by: Smith, A. B., III; Dunlap, N. K.; Sulikowski, G. A. *Tetrahedron Lett.* **1988**, *29*, 439.
(5) (a) Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 1. (b) Mann, J. *Tetrahedron* **1986**, *42*, 4611. (c) Noyori, R.; Hayakawa, Y. *Org. React.* **1983**, *29*, 163.
(6) Turro, N. *Acc. Chem. Res.* **1969**, *2*, 25.
(7) Chan, T. H.; Ong, B. S. *Tetrahedron* **1980**, *36*, 2269.
(8) Posner did not report the isolation of cyclopropanone-containing products in a similar reaction carried out in pentane at −50 °C. See: Posner, G. H.; Sterling, J. J. *J. Am. Chem. Soc.* **1973**, *95*, 3076. Posner, G. H.; Sterling, J. J.; Whitten, C. E.; Lentz, C. M.; Brunelle, D. J. *J. Am. Chem. Soc.* **1974**, *96*, 107.
(9) See the next paper in this issue.

Scheme VI. Preparation of Substrates 15a–d[a]

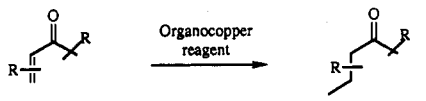


[a] Key: (a) 1.2 equiv Br_2, 2. DBU, DMF, 45%; (b) 1. Br_2, 2. K_2CO_3, $AgNO_3$; (c) 1. SO_2Cl_2, 2. Br_2; (d) Br_2; DBU, DMF, 30% from 26; (f) DBU, DMF, 64% from 26; (g) MsCl, Et_3N, 60%; (h) Ac_2O, Et_3N, 70%.

patibility problems.[10] DeKimpe and Verhé have provided a general review of the synthesis of α-halogenated ketones covering the literature through the first half of 1986.[11] After reviewing the various methods available for the synthesis of α-halo ketones and anticipating incompatibility problems, a common pathway was found for the preparation of a variety of the desired substrates. The connecting thread was the mild and regioselective functionalization of trimethylsilyl dienol ethers. Thus, compounds **19–21** were prepared by reluxing the parent α,β-unsaturated ketones with triethylamine and chlorotrimethylsilane in DMF following the general method of House.[12] These trimethylsilyl dienol ethers were then functionalized as shown in Schemes III–V. Bromination was effected by the reaction of either bromine or *N*-bromosuccinimide[13] with the trimethylsilyl dienol ethers in dichloromethane at low temperature. The chlorination of **19–21** by reaction with 1 equiv of sulfuryl chloride in CH_2Cl_2 at low temperature provided the chloro enones. Epoxidation of **19–21** with MCPBA by the method of Rubottom,[14] followed by rearrangement to α-(trimethylsilyl)oxy enones gave, upon hydrolysis with potassium carbonate in methanol, the α-hydroxy enones **16e**, **17e**, and **23e**. The final functionalization of these substrates was accomplished by reaction of the α-hydroxy enones with triethylamine and either MsCl or Ac_2O to afford α-mesyloxy enones **16b**, **17b**, and **23b** or α-acetoxy enones **16d**, **17d**, and **23d**, respectively. Thus, a general albeit obvious, method for the synthesis of α,β-unsaturated ketones containing an α′-nucleofuge had been developed.

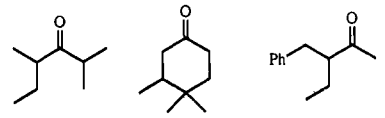
In some of the mesylation reactions, an interesting side reaction was observed. In addition to the expected cyclic mesylate **16b**, the reaction conditions also led to the formation of β-hydroxy γ-sultone **24** and α,β-unsaturated γ-sultone **16h**, respectively. Analogous products were

Table I. Control Reactions of Parent Enones with Me_2CuLi and MeCu[a]

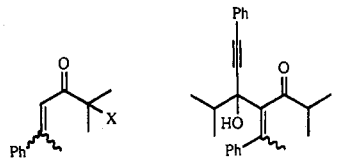


substrate	product[f]	Me_2CuLi	MeCu
15f	**29f**	82	0
16f	**30f**	78	0
17f	**31f**	81	0
18f	**32f**	61[b]	53[d]
18g	**32g**	46[c]	55[e]

[a] Yields represent chromatographically isolated products. [b] *E*/*Z* ratio 1:1.2, 3% **33**. [c] *E*/*Z* ratio 1.3:1. [d] 48% **33**, 5% (*E*)-**32f**. [e] *E*/*Z* ratio 1:1.2. [f] Structures **29f–32f** and **32g** are shown below.



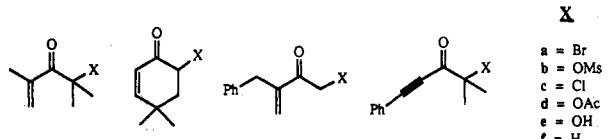
29f 30f 31f



32f,g 33

observed in the formation of **15b** as well. These products presumably arise from the small equilibrium concentration of the mesylate anion reacting with the carbonyl carbon which is further activated by the presence of the α-electron-withdrawing mesylate group. This type of reactivity has recently been observed with an α-mesyloxy nitrile.[15]

The general route just described could not be applied to the preparation of **15a–d** due to the instability of the silyl enol ether derived from **15f**. Instead, independent



15 16 17 18

routes were devised for the preparation of **15a–d** (Scheme VI). The bromo enone **15a** was produced by dibromination of 2,4-dimethyl-3-pentanone (**26**) followed by careful monodehydrohalogenation with DBU in DMF. It proved impossible to prevent double elimination to the dienone; however, **15a** could be separated by chromatography on silica. The chloro enone **15c** was prepared by monochlorination of **26** with sulfuryl chloride yielding the known 2-chloro-2,4-dimethyl-3-pentanone[16] which was then brominated to give 2-bromo-4-chloro-2,4-dimethyl-3-pentanone (**27a**). Dehydrobromination under the reaction conditions previously developed conveniently gave the chloroenone **15c**. The α-hydroxy enone **15e** was prepared from diisopropyl ketone in 64% overall yield by bromination and hydrolysis according to the method of Cologne and Dubin[17] to give α-hydroxy ketone **27b**. Bromination

(10) The reaction of enones with electrophiles has recently been reviewed: Müllen, K.; Wolf, P. In *The Chemistry of Enones*; Patai, S., Rappoport, Z., Ed.; Wiley: 1989; Chapter 12, pp 513–558.

(11) De Kimpe, N.; Verhé, R. *The Chemistry of α-Haloketones, α-Haloaldehydes and α-Haloimines*; Patai, S., Rappoport, Z., Ed.; Wiley: 1988; Chapter 1, pp 3–38; Appendix to Chapter 1, pp 122–148.

(12) House, H. O.; Czuba, L. J.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1969**, *34*, 2324.

(13) NBS was used in the bromination of **20** to avoid overbromination observed with Br_2. However, an aq HF workup was needed to convert the stable succinimide adduct **22** → **17a**. Similar adducts in the reactions of TMS enol ether with NCS have been reported: Hambley, G. F.; Chan, T. H. *Tetrahedron Lett.* **1986**, *27*, 2563.

22 24

(14) Rubottom, G. M.; Vazquez, M. A.; Pelegrina, D. R. *Tetrahedron Lett.* **1974**, 4319. (b) Rubottom, G M.; Gruber, J. M. *J. Org. Chem.* **1978**, *43*, 1599. (c) Hassner, A.; Reuss, R. H.; Pinnick, H. W. *J. Org. Chem.* **1975**, *40*, 3427.

(15) Calvo-Mateo, A.; Camarasa, M.; Díaz-Ortiz, A.; Heras, F. G. *J. Chem. Soc., Chem. Commun.* **1988**, 1114.

(16) (a) Wyman, D. P.; Kaufman, P. R. *J. Org. Chem.* **1964**, *29*, 1956. (b) Delbaere, P. *Bull. Soc. Chim. Belg.* **1942**, *51*, 1. (c) Warnhoff, E. W.; Martin, D. G.; Johnson, W. S. *Org. Synth.* **1957**, *37*, 8.

(17) Cologne, J.; Dubin, J. *Bull. Soc. Chim. Fr.* **1960**, 1180.

gave bromohydroxy ketone **27c** which was then dehydrobrominated to give **15e**. Treatment of **15e** with methanesulfonyl chloride and triethylamine in dichloromethane gave **15b**, while reaction with acetic anhydride, triethylamine, and catalytic DMAP[18] in dichloromethane yielded the acetoxy enone **15d**.

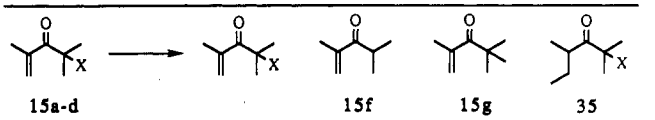
It was subsequently found that the substrates in the **23** series would be unusable because the parent enone **23f** not having an α-substituent would not undergo reaction with either MeCU or Me_2CuLi using the standard conditions. We prepared a fourth substrate series of two compounds (**18a** and **18d**) using known literature procedures.[19] These ynones increased the structural diversity of the study substantially.

Reactions with Organocopper Reagents. To check the validity of the systems under study we treated each of the parent enones **15f–18f** with what eventually became standard reaction conditions to be certain that conjugate addition was a major reaction pathway. Each of the systems exhibited good reactivity with Me_2CuLi, and conjugate adducts were isolated in 46–82% yield (Table I). In a parallel set of experiments, the use of MeCu (generated as was the cuprate utilizing only 1 equiv of methyllithium) in place of the cuprate produced no reaction, except with ynones **18f** and **18g**. With **18f**, the aldol dimer **33** was formed as the major product along with 5% of the expected adduct (*E*)-**32f**. Presumably, **33** was formed by conjugate addition providing an enolate followed by aldol reaction with a second equivalent of the ynone. Increasing the steric bulk around the carbonyl by exchanging the isopropyl group for a *tert*-butyl group (**18g**) allowed conjugate addition to proceed without the subsequent aldol reaction.

When the acyclic substrates **15a–d** with nucleofuges at a tertiary center were treated with organocopper reagents in the presence of furan, the anticipated product of [4 + 3] cycloaddition of the intermediate π-oxyallyl species was not observed. Instead, several alternate reaction modes were observed. The results are summmarized in Table II. In reactions of Me_2CuLi with either the bromide **15a** or the mesylate **15b**, reduction to the parent enone **15f** and coupling with the cuprate to give **15g** were observed. The chloride **15c** was reduced by reaction with Me_2CuLi to **15f** but the coupling product was not observed. Under the same reaction conditions, the tertiary acetate **15d** underwent both reduction to **15f** and conjugate addition to **35d**. The recovery of unchanged starting material in the reactions leading to reduction can be rationalized as the result of the formation of a sterically crowded aldol adduct **36**, which reverts to starting material and **15f** upon workup. Since the parent enone **15f** was essentially unreactive with MeCu, reactions of the functionalized substrates with MeCu were not expected to be very productive. This prediction proved to be correct, with the reaction of each of the substrates **15a–d** with MeCu resulting in the recovery of large amounts of starting material. One interesting result was that both the bromide **15a** and the mesylate **15b** reacted to give the coupled product **15g**.

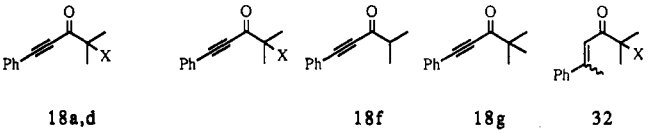
The reaction of ynones with nucleofuges at tertiary sites **18a** and **18d** with organocopper reagents provided more pieces to a pattern that was beginning to emerge. The bromide **18a** reacted with Me_2CuLi to give a mixture of the reduced ynone **18f** and the coupled ynone **18g**, while reaction with MeCu gave only the coupled product **18g**.

Table II. Reaction of 15a–d and 18a,d with Me_2CuLi and MeCu[a]



15a-d **15f** **15g** **35**

substrate	reagent	starting material	reduction	coupling	conjugate addition
15a (Br)	Me_2CuLi	0	40	38	0
b (OMs)		10	16	3	0
c (Cl)		40	42	0	0
d (OAc)		40	10	0	18
15a (Br)	MeCu	70	0	15	0
b (OMs)		60	0	30	0
c (Cl)		72	0	0	0
d (OAc)		84	0	0	0



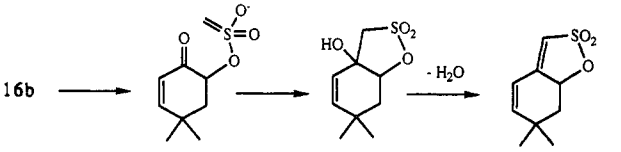
18a,d **18f** **18g** **32**

18a (Br)	Me_2CuLi	0	33	3	0
d (OAc)		0	0	0	69[b]
18a (Br)	MeCu	24	0	5	0
d (OAc)		28	0	0	7[c]

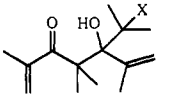
[a] Yields represent chromatographically isolated products. [b] *E*/*Z* ratio 1:1.65. [c] *E*/*Z* ratio 1:1.33.

This result was consistent with the results from the tertiary substrate **15a**. With Me_2CuLi and MeCu, the acetate **18d** gave a slightly different result. Whereas α-acetoxy enone **15d** had given both reduction product and conjugate addition, the α-acetoxy ynone **18d** gave only *E* and *Z* 1,4-conjugate addition products **32d**. The *E* and *Z* isomers were assigned by correlation with the parent adducts, the calculated ^1H NMR chemical shifts for the vinyl protons, and comparison of ^1H and ^{13}C NMR resonances of the vinyl methyl groups with analogous compounds. The chemical shift of the vinyl proton calculated for the *E* isomer is >0.4 ppm downfield of the *Z* isomer, and the enone of each isomer pair with the higher chemical shift was tentatively assigned as the *E* isomer.[20]

In reactions of the cyclic series of enones **16a–d** with Me_2CuLi (Table III) reduction to the cyclohexenone **16f** and coupling with the cuprate to give **16g** were expected from the bromide and mesylate, with conjugate addition competing with the acetate. Indeed, it was found that



16b **24** **16h**

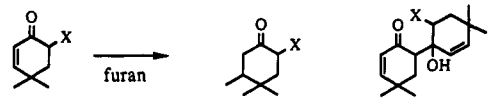


36

with the better nucleofuges (bromide, mesylate, and chloride) reduction was the major mode of reaction. The simple reduced product **16f** was not observed. Instead, reduction was followed by self-condensation to give a

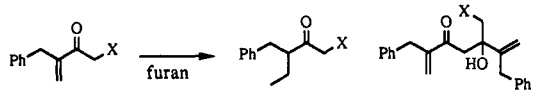
(18) Höfle, G.; Steglich, W.; Vorbrüggen, H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 522.
(19) Jackson, R. S. W.; Raphael, R. A. *J. Chem. Soc., Perkin Trans. 1* **1984**, 535.
(20) Pascual, C.; Meier, J.; Simon, W. *Helv. Chim. Acta* **1966**, *49*, 164.

Table III. Reaction of 16a–d and 17a–d with Me_2CuLi and MeCu[a]



38 39

substrate	reagent	conjugate addition	reduction–aldol
16a (Br)	Me_2CuLi	0	54[b]
b (OMs)		0	21[b]
c (Cl)		0	53[b]
d (OAc)		42	0
16a (Br)	MeCu	0	20[c]
b (OMs)		0	4
c (Cl)		0	19[c]
d (OAc)		5	0



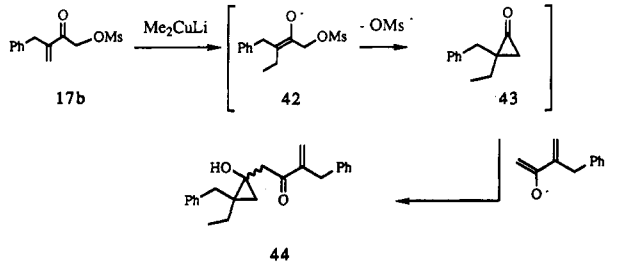
40 41

17a (Br)	Me_2CuLi	0	62
b (OMs)		0	19[f]
c (Cl)		0	56
d (OAc)		65	0
17a (Br)[d,e]	MeCu	0	18
b (OMs)[f]		0	0
c (Cl)		0	6
d (OAc)		6	0

[a] Yields represent chromatographically isolated products. [b] Isolated as a mixture of unassigned diastereomers. [c] Isolated as one unassigned diastereomer. [d] 3% of the simple debromination product (**17f**) was isolated. [e] 10% of the simple iodide displacement product (**17h**, X = I) was isolated. [f] 1% of the simple iodide displacement product was isolated. [g] See text.

mixture of diastereomeric aldol adducts (**39**). Aldol adducts similar to these have previously been observed in the reaction of α-chlorocycloalkanones with cuprates.[21] The acetoxy enone **16d** underwent conjugate addition to give a 1:1 mixture of cis and trans adducts **38d**. Each of these substrates was also treated with MeCu, and as expected, the reaction led predominantly to the recovery of starting material. The reaction that did occur resulted in formation of the reduction–aldol products **39a–c** from the bromide, mesylate, and chloride while the acetate gave small amounts of the conjugate adduct **38d**. The aldol adducts **39a–c** were obtained as mixtures of diastereomers, the relative configurations of which have not been assigned. Gross structural assignment of the individual diastereomers was based on decoupling experiments which confirmed the connectivity of each spin system.

Reaction of the acyclic enone series containing nucleofuges at primary centers (**17a–d**) with Me_2CuLi gave predominantly the reduction–aldol type products **41a–c**



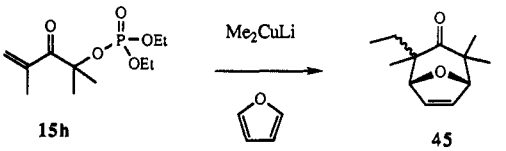
17b 42 43 44

(21) Bull, J. R.; Tuinman, A. *Tetrahedron Lett.* **1973**, 4349.

from the bromide, mesylate, and chloride, while the acetate gave the expected conjugate adduct **40d**. Given the results obtained earlier with the cyclic series, the reduction–aldol reaction mode was not unexpected. By comparison to the cyclic aldol adducts **39**, the structural assignment of the adducts **41a–c** was straightforward. There were, however, a few surprising results in the reactions of this series of substrates. In addition to the aldol product **41b**, the mesylate **17b** also gave rise to the cyclopropanols **44** as a mixture of the two isomers in 5% and 3% yield. Presumably, these cyclopropanols arose from conjugate addition of the cuprate to give an enolate **42**, with subsequent loss of the mesylate leading penultimately to cyclopropanone **43**, which was then trapped by the enolate **42**, with subsequent loss of the mesylate leading penultimately to cyclopropanone **43**, which was then trapped by the enolate generated by reduction of the starting material. This result was quite interesting since it presumably involved entry into the 2-oxyallyl/cyclopropanone/allene oxide reaction manifold.

Returning to the initial idea that conjugate addition would lead to an enolate which could continue on to a π-oxyallyl cation, two problems become obvious. First, with the better nucleofuges, the reduction of the nucleofuge (Br, OMs, and Cl) is too facile and conjugate addition is not observed due to the competing reduction. Second, for the nucleofuges that are not readily reduced (OAc), ionization does not occur. Therefore, the nucleofuge would be required to ionize more readily than an acetate, but at the same time possess a reduction potential no lower than the acetate. This combination of properties appeared to be a severe requirement. It was suggested that a phosphate might meet the stringent requirements.[22] Certainly, the ionizing ability of phosphates was well-known, but a reasonable guess at the reduction potential of an α-phosphoryl ketone was not available.

Substrate **15h** was prepared by phosphorylation of α-hydroxy enone **15e**. Reaction of **15h** with Me_2CuLi under the conditions already described resulted in the formation in about 5% yield of the bicyclic adduct **45** as a mixture



15h 45

of isomers from which only the major isomer could be purified, along with a mixture of nonpolar compounds which could not be separated or further characterized. While the formation of this cycloadduct triggered by the conjugate addition process was encouraging, the low yields initially found could not be improved upon.

Through the reactions of the primary α-mesyloxy enone and the phosphate just described, a fleeting glimpse of the sought after reactivity has been observed but, unfortunately, the major modes of reaction for these hybrid substrates with Me_2CuLi involve either simple reduction of the nucleofuge or simple conjugate addition of the cuprate.

Conclusion

The scope and limitations of the reaction of α′-nucleofuge α,β-unsaturated ketones with nucleophiles as a new methodology for the generation of 2-oxyallyl cations has been examined. Reaction of these substrates when the nucleofuge is halogen or mesylate with Me_2CuLi results

(22) The authors wish to thank Professor Norman A. Lebel for this useful suggestion.

in reduction of the α-nucleofuge to generate an enolate which can undergo subsequent reactions typical of enolates. Reaction of Me_2CuLi with α-acetoxy enones produces the corresponding β-methylated α-acetoxy ketones in good yield except with the tertiary acetoxy group which was competitively reduced.

A companion study of the reactions of the hybrid systems with malonate anion, a reagent which acts via an entirely different mechanism is detailed in the following paper in this issue.

Experimental Section

General Methods. For details, see the corresponding section in ref 28. Evaporation of solvent was accomplished with a rotary evaporator operating at aspirator pressure. Extracts were dried over Na_2SO_4.

2,4-Dimethylpent-1-en-3-one (15f). To a stirred solution of 12.0 g (62.5 mmol) of 2-bromo-2,4-dimethyl-3-pentanone[23] in 75 mL of DMF at room temperature was added over 30 min 9.3 mL (9.5 g, 62.5 mmol) of DBU during which time an exothermic reaction ensued. After stirring for 2 h, the mixture was diluted with 400 mL of 1:1 ether/pentane, extracted twice with 300 mL of 7% aqueous HCl, twice with 300 mL of saturated NaCl, dried and evaporated under reduced pressure to yield 5.8g (83%) of **83f**. This compound exhibited IR, ^1H and ^{13}C NMR spectral properties identical with those previously reported.[24]

4-Bromo-2,4-dimethyl-1-penten-3-one (15a). To a stirred solution of 45.6 mL (81.5 g, 0.3 mol) of 2,4-dibromo-2,4-dimethyl-3-pentanone[25] in 100 mL of DMF at room temperature was added over 30 min 44.9 mL (45.7 g, 0.3 mol) of DBU. After being stirred for 2 h, the mixture was diluted with 400 mL of 1:1 ether/pentane, extracted twice with 300 mL of 7% aqueous HCl and twice with 300 mL of saturated NaCl, dried, and evaporated under reduced pressure to yield a mixture of approximately 1.5:1 **15a**/starting material with a trace of 2,4-dimethyl-1,4-pentadien-3-one. Attempts to optimize the conversion to bromo enone resulted in increased production of the dienone. Pure **15a** was obtained in approximately 45% yield after preparative HPLC, eluent 95% hexane/EtOAc. **15a**: IR (neat) 2979, 2930, 1672, 1630, 1460 cm^{-1}; ^1H NMR (300 MHz) δ 1.94 (s, 6 H), 1.98 (s, 3 H), 5.71 (s, 1 H), 6.09 (s, 1 H); ^{13}C NMR (75 MHz) δ 21.1 31.3, 60.3, 123.9, 140.9, 199.1; HRMS calcd for $C_7H_{11}BrO$ 189.9994, found 189.9997.

4-(Mesyloxy)-2,4-dimethyl-1-penten-3-one (15b). To a stirred solution of 7.0 g (55 mmol) of **15e** in 20 mL CH_2Cl_2 and 16.7 mL (12.1 g, 120 mmol) of Et_3N at 0 °C was added 5.0 mL (7.4 g, 65 mmol) of CH_3SO_2Cl over 20 min. After the addition was complete, the ice bath was removed and the reaction stirred for 10 h. Extractive workup gave 6.8 g (60%) of **15b** and 2.1 g (18%) of **24**. **15b**: IR (neat) 3002, 2943, 1683, 1631, 1342, 1180 cm^{-1}; ^1H NMR (300 MHz) δ 1.71 (s, 6 H), 1.86 (s, 3 H), 2.99 (s, 3 H), 5.84 (s, 1 H), 6.03 (s, 1 H); ^{13}C NMR (75 MHz) δ 19.4, 26.4, 40.6, 91.0, 124.7, 140.8, 199.5; HRMS calcd for $C_8H_{15}SO_4$ 207.0691, found 207.0687 (M^+ + H (self CI's)).

β-Hydroxy δ-sultone 24: mp 75 °C dec; IR (neat) 3506, 3433, 2996, 1725, 1640, 1237, 1176, 1136, 1068 cm^{-1}; ^1H NMR (300 MHz) δ 1.46 (s, 3 H), 1.58 (s, 3 H), 1.86 (d, 3 H, J = 1 Hz), 3.44 (s, 1 H), 3.51 (d, 3 H, J = 14 Hz), 3.96 (d, 3 H, J = 14 Hz), 5.14 (s, 2 H); ^{13}C NMR (75 MHz) δ 20.1, 21.9, 25.3, 55.9, 83.1, 97.6, 116.3, 141.5; HRMS calcd for $C_8H_{15}SO_4$ 207.0691, found 207.0692 (M^+ + H (self CI's)).

Sultone 16: mp 110–111.5 °C; IR (KBr) 3084, 2966, 1740, 1707, 1637, 1590, 1325, 1194 cm^{-1}; ^1H NMR (300 MHz) δ 1.20 (s, 6 H), 1.77 (dd, 1 H, J = 13, 12 Hz), 2.27 (dd, 1 H, J = 12, 5 Hz), 5.32 (ddd, 1 H, J = 13, 5, 2 Hz), 6.11 (d, 1 H, J = 10 Hz), 6.23 (d, 1 H, J = 10 Hz), 6.40 (d, 1 H, J = 2 Hz); ^{13}C NMR (75 MHz) δ 26.9, 30.7, 35.3, 41.4, 78.8, 114.5, 115.7, 147.4, 150.6; HRMS calcd for $C_9H_{12}SO_3$ 200.0507, found 200.0507.

2-Bromo-4-chloro-2,4-dimethyl-3-pentanone (27a). To 18 g (0.12 mol) of 2-chloro-2,4-dimethyl-3-pentanone[26] was added a small portion of Br_2. If the uptake of Br_2 was not complete within 5 min, the mixture was gently warmed with a heat gun. Once the reaction was initiated, as evidenced by the loss of the red color, the reaction was cooled to 5–10 °C and the remainder of 19.4 (0.12 mol) of Br_2 was added at such a rate so as to maintain a slight orange color. After the addition was complete, the reaction was stirred for 1 h, taken up in pentane, washed with water, saturated $NaHCO_3$, and saturated NaCl, dried, and evaporated to give **27a**: IR (neat) 2982, 2936, 1705, 1464, 1115, 1042 cm^{-1}; ^1H NMR (300 MHz) δ 1.90 (s, 6 H), 2.08 (s, 6 H); ^{13}C NMR (75 MHz) δ 32.0, 32.1, 60.7, 69.3, 200.2; MS isobutane chemical ionization 227 (M^+ + H); HRMS calcd for C_4H_6BrO, 148.9603, found 148.9609 (M^+ – $(CH_3)_2CCl$).

4-Chloro-2,4-dimethyl-1-penten-3-one (15c). Dehydrobromination of the bromochloro ketone **27a** as above yielded **15c** in 30% overall yield for three steps from diisopropyl ketone: IR (neat) 2984, 2934, 1677, 1631, 1459, 1057 cm^{-1}; ^1H NMR (300 MHz) δ 1.76 (s, 6 H), 1.94 (s, 3 H), 5.73 (s, 1 H), 6.12 (s, 1 H); ^{13}C NMR (75 MHz) δ 20.6, 30.4, 68.6, 124.6, 140.7, 199.5; HRMS calcd for $C_7H_{11}ClO$ 146.0498, found 146.0493.

4-Acetoxy-2,4-dimethyl-1-penten-3-one (15d). To a stirred solution of 9 g (70 mmol) of **83e** in 20 mL CH_2Cl_2, 12.7 mL (9.2 g, 91 mmol) of Et_3N, and 855 mg (7 mmol) of DMAP at 0 °C was added 8.6 mL (9.3 g, 91 mmol) of Ac_2O over 15 min. Extractive workup after 4 h yielded 8.4 g (70%) of **15d**: IR (neat) 2996, 1739, 1685, 1631, 1257, 1151, 1060 cm^{-1}; ^1H NMR (300 MHz) δ 1.57 (s, 6 H), 1.85 (s, 3 H), 1.99 (s, 3 H), 5.63 (s, 1 H), 5.89 (s, 1 H); ^{13}C NMR (75 MHz) δ 19.0, 21.5, 25.4, 83.6, 121.4, 141.2, 170.3, 201.2; HRMS calcd for $C_9H_{15}O_3$ 171.1021, found 171.1017 (M^+ + H (self CI's)).

4-Bromo-2-hydroxy-2,4-dimethyl-3-pentanone (27c). 2-Hydroxy-2,4-dimethyl-3-pentanone[17] was brominated as described above to yield after recrystallization from pentane **27c**: mp 33–34.5 °C; IR (melt) 3555, 2978, 2934, 1074, 1468, 1369, 1205, 1115 cm^{-1}; ^1H NMR (300 MHz) δ 1.48 (s, 6 H), 1.97 (s, 6 H), 2.93 (br s, 1 H); ^{13}C NMR (75 MHz) δ 29.7, 30.2, 62.6, 79.8, 208.8; HRMS calcd for $C_7H_{14}BrO_2$ 209.0178, found 209.0181 (M^+ + H (self CI's)).

4-Hydroxy-2,4-dimethyl-1-penten-3-one (15e). Dehydrobromination of **27c** as above gave **15e** in 64% overall yield for four steps from diisopropyl ketone: IR (neat) 3473, 2980, 1664, 1465, 1374, 1051 cm^{-1}; ^1H NMR (300 MHz) δ 1.48 (s, 6 H), 1.92 (s, 3 H), 4.05 (br s, 1 H), 5.81 (s, 1 H), 5.95 (s, 1 H); ^{13}C NMR (75 MHz) δ 19.9, 28.3, 76.0, 125.6, 140.4, 206.4; MS isobutane chemical ionization 129 (M^+ + H); HRMS calcd for $C_7H_{11}O$ 111.0810, found 111.0813 (M^+ – OH).

4-(Diethoxyphosphoryl)-2,4-dimethyl-1-penten-3-one (15h). To a slurry of 1.87 g (78 mmol) of NaH in 100 mL of THF was added 10 g (78 mmol) of **15e** at –20 °C. After being warmed to room temperature over 1 h, the mixture was cooled to 0 °C and 11.3 mL (13.5 g, 78 mmol) of diethyl chlorophosphate was added. After the addition was complete, the ice bath was removed and the reaction stirred for 1 h. Extractive workup gave 12.2 g (59%) of **15h**: IR (neat) 2986, 2938, 1682, 1633, 1267, 1032, 985 cm^{-1}; ^1H NMR (300 MHz) δ 1.27 (td, 6 H, J = 7, 1 Hz), 1.64 (d, 6 H, J = 1 Hz), 1.88 (s, 3 H), 4.02 (m, 4 H, J = 7, 1 Hz), 5.76 (s, 1 H), 6.08 (s, 1 H); ^{13}C NMR (75 MHz) δ 15.9 (d, J_{CCOP} = 6 Hz), 19.7, 26.7 (d, J = 4 Hz), 63.6 (d, J = 7 Hz), 86.5 (d, J = 7 Hz); 125.2, 140.7, 201.4 (d, J = 7 Hz); HRMS calcd for $C_{11}H_{22}PO_5$ 265.1205, found 265.1200 (M^+ + H).

6-Bromo-4,4-dimethylcyclohex-2-en-1-one (16a). Prepared by the bromination of a CH_2Cl_2 solution of 5,5-dimethyl-2-[(trimethylsilyl)oxy]-1,3-cyclohexadiene **19** at –20 °C by the method of Conia.[27]

6-(Mesyloxy)-4,4-dimethylcyclohex-2-en-1-one (16b). To a stirred solution of 10.7 g (76 mmol) of **16e** in 100 mL CH_2Cl_2 was added 21.1 mL (15.4 g, 1.52 mmol) of Et_3N at –10 °C. After 10 min, 7.0 mL (10.3 g, 90 mmol) of MsCl was added over 15 min. After 1 h, the reaction was diluted with CH_2Cl_2 and extracted with water, $NaHCO_3$, and saturated NaCl, dried, and evaporated to yield a red-brown oil that can be crystallized after passing through a short silica gel column with 4:1 hexane/EtOAc to give 13.6 g (82%) of **16b**: mp 64–66 °C; IR (melt) 3027, 2965, 2874, 1698, 1615, 1353, 1179 cm^{-1}; ^1H NMR (300 MHz) δ 1.19 (s, 3 H),

(23) Hoffman, H. M. R.; Clemens, K. E.; Schmidt, E. A.; Smithers, R. H. *J. Am. Chem. Soc.* **1972**, *94*, 3201.
(24) Bienvenue, A.; Duchatellier, B. *Tetrahedron* **1972**, *28*, 833.
(25) Mann, J. *Tetrahedron* **1986**, *42*, 4611.
(26) Wyman, D. P.; Kaufman, P. R. *J. Org. Chem.* **1964**, *29*, 1956.
(27) Blanco, L.; Amice, P.; Conia, J. M. *Synthesis* **1976**, 194.

1.26 (s, 3 H), 2.10 (t, 1 H, J = 13 Hz), 2.22 (ddd, 1 H, J = 13, 6, 1 Hz), 3.21 (s, 3 H), 5.22 (dd, 1 H, J = 13, 6 Hz), 5.84 (d, 1 H, J = 10 Hz), 6.68 (dd, 1 H, J = 10, 1 Hz); ^{13}C NMR (75 MHz) δ 25.8, 30.2, 35.5, 39.2, 42.8, 77.7, 124.5, 160.0, 192.7; HRMS calcd for $C_9H_{14}SO_4$ 218.0613, found 218.0616.

6-Chloro-4,4-dimethylcyclohex-2-en-1-one (16c). To a stirred solution of 22.5 mL (19.6 g, 0.1 mol) of **19** in 200 mL CH_2Cl_2 at −20 °C was added 8.0 mL (13.5 g, 0.1 mol) of SO_2Cl_2 in 25 mL of CH_2Cl_2 over 15 min. After 15 min, the reaction was warmed to room temperature over 45 min, evaporated, and recrystallized from hexane at low temperature to give 15 g (94%) of **16c** as a white solid: mp 49–50.5 °C; IR (melt) 2959, 2933, 1689, 1622, 1194, 1110 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.21 (s, 3 H), 1.26 (s, 3 H), 2.22 (t, 1 H, J = 13 Hz), 2.33 (ddd, 1 H, J = 13, 5, 2 Hz), 4.66 (dd, 1 H, J = 13, 5 Hz), 5.93 (d, 1 H, J = 10 Hz), 6.68 (dd, 1 H, J = 10, 2 Hz); ^{13}C NMR (75 MHz) δ 25.8, 29.9, 35.5, 46.7, 58.3, 124.8, 159.3, 191.8; HRMS calcd for $C_8H_{11}ClO$ 158.0498, found 158.0451.

6-Acetoxy-4,4-dimethylcyclohex-2-en-1-one (16d). To a solution of 8.2 g (58.5 mmol) of **6e** in 50 mL of CH_2Cl_2 and 10.6 mL (7.7 g, 76 mmol) of Et_3N at 0 °C was added 7.2 mL (7.7 g, 76 mmol) of Ac_2O over 5 min. After 2 h, the reaction was worked up by extraction with H_2O (4 x), $NaHCO_3$ (until CO_2 evolution ceases) and saturated NaCl (2 x), dried and evaporated to give 6.4 g (60%) of **16d**: IR (neat) 2964, 2871, 1749, 1702, 1616, 1377, 1237, 1118, 1078 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.09 (s, 3 H), 1.18 (s, 3 H), 1.92 (m, 2 H), 2.03 (s, 3 H), 5.37 (dd, 1 H, J = 13, 7 Hz), 5.74 (d, 1 H, J = 10 Hz), 6.54 (dd, 1 H, J = 10, 2 Hz); ^{13}C NMR (75 MHz) δ 20.4, 25.5, 30.2, 34.8, 41.2, 70.6, 124.5, 158.7, 169.6, 193.5; HRMS calcd for $C_{10}H_{14}O_3$ 182.0943, found 182.0946.

6-Hydroxy-4,4-dimethylcyclohex-2-en-1-one (16e). 6-(Trimethylsiloxy)-4,4-dimethylcyclohex-2-en-1-one was prepared from **19** by the procedure of Rubottom[14] and hydrolyzed to **16e** by being stirred in CH_3OH for 2 h at room teperature followed by evaporation. Recrystallization from 1:1 EtOAc/petroleum ether yielded 54% of **16e**: mp 53.5–56 °C; IR (neat) 3475, 3024, 2963, 2870, 1689, 1617, 1470, 1366, 1094 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.20 (s, 3 H), 1.28 (s, 3 H), 1.80 (t, 1 H, J = 13 Hz), 2.22 (ddd, 1 H, J = 13, 5, 2 Hz), 3.56 (s, 1 H, OH), 4.35 (dd, 1 H, J = 13, 5 Hz), 5.94 (d, 1 H, J = 10 Hz), 6.70 (dd, 1 H, J = 10, 2 Hz); ^{13}C NMR (75 MHz) δ 25.6, 30.8, 35.0, 44.1, 69.6, 123.4, 160.8, 200.3; HRMS calcd for $C_8H_{12}O_2$ 140.0837, found 140.0834.

3-Benzyl-3-buten-2-one (17f). A mixture of 8.2 g of 3-benzyl-4-hydroxy-2-butanone[28] (46 mmol), 50 mL of $PhCH_3$, and 100 mg of p-TsOH was heated with azeotropic distillation of water, followed by distillation of pure **17f**, 3.9 g (53%): bp 86–88 °C (1.3 mmHg); IR (neat) 3062, 3028, 2924, 1679, 1627, 1602, 1495, 1365, 945, 700 cm^{-1}; ^{1}H NMR (300 MHz) δ 2.35 (s, 3 H), 3.62 (s, 2 H), 5.66 (s, 1 H), 6.10 (s, 1 H), 7.25 (m, 5 H); ^{13}C NMR (75 MHz) δ 26.1, 36.8, 126.4, 128.6, 129.3, 139.3, 148.8, 205.2; HRMS calcd for $C_{11}H_{12}O$ 160.0888, found 160.0890.

3-Benzyl-2-[(trimethylsilyl)oxy]-1,3-butadiene (20). Following the general method of House,[12] a mixture of 10 g of **17f** (62.5 mmol), 40 mL of Et_3N (28.9 g, 286 mmol), and 23 mL of TMSCl (19.7 g, 181 mmol) in 300 mL of DMF was refluxed for 12 h. Flash chromatography with hexanes as eluent yielded 8.4 g (58%) of pure **20**, and further elution of the column with 70% hexanes/EtOAc returned 3.0 g of **17f** (30%): IR (neat) 3062, 3028, 2958, 1700, 1680, 1590, 1495, 1454, 1253, 847, 700 cm^{-1}; 1H NMR (C_6H_6) (300 MHz) δ 0.15 (s, 9 H), 3.48 (s, 2 H), 4.38 (s, 1 H), 4.55 (s, 1 H), 4.94 (s, 1 H), 5.81 (d, 1 H, J = 2 Hz), 7.25 (m, 5 H); ^{13}C NMR (C_6H_6) (75 MHz) δ 0.0, 39.6, 93.9, 115.6, 126.3, 128.5, 129.0, 140.1, 143.7, 155.8; HRMS calcd for $C_{14}H_{20}SiO$ 232.1283, found 232.1286.

3-Benzyl-1-bromo-3-buten-2-one (17a). To a stirred solution of 3.9 g of **20** (16.9 mmol) in 50 mL of CH_2Cl_2 at 0 °C was added 3.0 g of NBS (16.9 mmol). After 1 h, the reaction was worked up by extraction with saturated NaCl, dried, and evaporated. The resulting oil was dissolved in 50 mL of CH_2Cl_2 and 5 mL of 49% aqueous HF added. After the heat dissipated (1 h), 300 mL of CH_2Cl_2 was added and the mixture neutralized with 15% NaOH, extracted with saturated NaCl, dried, and evaporated to yield 2.1 g of 95% pure **17a** (53%): IR (neat) 3061, 3028, 2946, 1676, 1626, 1602, 1495, 1040, 949, 699 cm^{-1}; ^{1}H NMR (300 MHz) δ 3.66 (s, 2 H), 4.23 (s, 2 H), 5.79 (s, 1 H), 6.16 (s, 1 H), 7.25 (m, 5 H); ^{13}C NMR (75 MHz) δ 30.6, 37.1, 126.4, 127.7, 128.5, 129.0, 138.2, 145.5, 192.1; HRMS calcd for $C_{11}H_{11}BrO$ 237.9994, found 237.9999. If the reaction with HF was omitted, a succinimide adduct **22** was obtained along with the desired **17a** in a ratio of ca 1:1.

3-Benzyl-1-(mesyloxy)-3-buten-2-one (17b). To a stirred solution of 1.0 g of **17e** (5.7 mmol) and 876 μL of Et_3N (632 mg, 6.25 mmol) in 20 mL of CH_2Cl_2 at 0 °C was added 484 μL of CH_3SO_2Cl (716 mg, 6.25 mmol) and the mixture stirred at 0 °C for 1 h then room temperature for 1 h. The reaction was quenched with saturated $NaHCO_3$, washed with saturated NaCl, dried, and evaporated to give 900 mg of **17b** (62%): IR (neat) 3028, 2939, 1700, 1628, 1602, 1356, 1174, 1002, 968, 800, 731, 702 cm^{-1}; ^{1}H NMR (300 MHz) δ 3.18 (s, 3 H), 3.63 (s, 2 H), 5.22 (s, 2 H), 5.77 (s, 1 H), 6.02 (s, 1 H), 7.25 (m, 5 H); ^{13}C NMR (75 MHz) δ 36.7, 39.0, 69.7, 126.6, 126.9, 128.6, 129.0, 137.7, 145.3, 193.0; HRMS calcd for $C_{12}H_{14}SO_4$ 254.0613, found 254.0614.

3-Benzyl-1-chloro-3-buten-2-one (17c). To a stirred solution of 3.8 g of **20** (16.0 mmol) in 50 mL of CH_2Cl_2 at −20 °C was added 1.32 mL of SO_2Cl_2 (2.2 g, 16 mmol). After 30 min, the reaction was quenched with aqueous saturated $NaHCO_3$, extracted with saturated NaCl, dried, and evaporated to yield 3.0 g (95%) of **17c** contaminated with ≅5% of **17f**: IR (neat) 3062, 2942, 1699, 1628, 1603, 1495, 1045, 782, 740, 701 cm^{-1}; ^{1}H NMR (300 MHz) δ 3.66 (s, 2 H), 4.46 (s, 2 H), 5.76 (s, 1 H), 6.09 (s, 1 H), 7.25 (m, 5 H); ^{13}C NMR (75 MHz) δ 37.0, 45.5, 126.4, 127.0, 128.4, 129.0, 138.0, 145.8, 191.8; HRMS calcd for $C_{11}H_{11}ClO$ 194.0498, found 194.0501.

1-Acetoxy-3-benzyl-3-buten-2-one (17d). To a stirred solution of 1.0 g of **17e** (5.7 mmol) and 964 μL of Et_3N (696 mg, 6.8 mmol) in 20 mL of CH_2Cl_2 at 0 °C was added 590 μL of Ac_2O (638 mg, 6.25 mmol) and the mixture stirred at 0 °C for 1 h then room temperature for 1 h. The reaction was quenched with saturated $NaHCO_3$, washed with saturated NaCl, dried, and evaporated to give 800 mg of **17d** (65%): IR (neat) 3062, 3029, 2939, 1750, 1697, 1628, 1603, 1231, 1029, 948, 703 cm^{-1}; ^{1}H NMR (300 MHz) δ 2.18 (s, 3 H), 3.62 (s, 2 H), 5.08 (s, 2 H), 5.70 (t, 1 H, J = 1 Hz), 6.04 (s, 1 H), 7.27 (m, 5 H); ^{13}C NMR (75 MHz) δ 20.3, 36.7, 65.3, 125.8, 126.3, 128.4, 129.0, 138.0, 145.7, 170.2, 192.9; HRMS calcd for $C_{13}H_{14}O_3$ 218.0943, found 218.0947.

3-Benzyl-1-hydroxy-3-buten-2-one (17e). To a stirred solution of 8.4 g of **20** (36.2 mmol) in 200 mL of pentane at −15 °C was added a slurry of 7.83 g of m-chloroperbenzoic acid ("45 mmol" of 80–85%) in 50 mL of pentane. After being warmed to 25 °C over 2 h, the reaction was filtered through a sintered glass funnel and evaporated. The resultant oil was dissolved in 75 mL of CH_2Cl_2 and 10 mL of 49% aq HF added. After 1 h, the mixture was taken up in 100 mL of CH_2Cl_2, neutralized with 15% aq NaOH, washed with saturated NaCl, dried, and evaporated to give 6.0 g of **17e** (94%): IR (neat) 3471, 3062, 3028, 2915, 1683, 1628, 1494, 1022, 749, 702 cm^{-1}; ^{1}H NMR (300 MHz) δ 3.31 (t, 1 H, J = 5 Hz), 3.67 (s, 2 H), 4.58 (d, 2 H, J = 5 Hz), 5.74 (t, 1 H, J = 1 Hz), 6.04 (s, 1 H), 7.29 (m, 5 H); ^{13}C NMR (75 MHz) δ 36.6, 64.6, 126.1, 126.3, 128.3, 128.8, 137.9, 144.8, 199.2; HRMS calcd for $C_{11}H_{12}O_2$ 176.0837, found 176.0841.

Ynones 18a and 18d. These were prepared by coupling of lithium phenylacetylide with the corresponding acid chloride according to literature procedures.[19]

4-Methyl-1-phenyl-1-pentyn-3-one (18f): This was prepared by coupling of lithium phenylacetylide with the corresponding acid chloride in a manner similar to the literature procedures used to prepare **18a** and **18d**. The yield of **18f** was 77%: bp 97–99 °C (2.5 mmHg); IR (neat) 2973, 2934, 2873, 2201, 1670, 1056, 758, 689 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.21 (d, 6 H, J = 7 Hz), 2.69 (m, 1 H, J = 7 Hz), 7.28–7.52 (overlapping m, 5 H); ^{13}C NMR (75 MHz) δ 17.6, 42.7, 86.6, 91.1, 119.8, 128.3, 130.3, 132.6, 191.5; HRMS calcd for $C_{12}H_{12}O$ 172.0888, found 172.0889.

4,4-Dimethyl-1-phenyl-1-pentyn-3-one (18g): This was prepared by coupling of lithium phenylacetylide with the corresponding acid chloride in a manner similar to the literature procedures used to prepare **18a** and **18d**. The yield of **18g** was 78%: bp 104–106 °C (2.5 mmHg); IR (neat) 2934, 2870, 2200, 1664, 1490, 1478, 1287, 1073, 1013 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.26 (s, 9 H), 7.35–7.54 (overlapping m, 5 H); ^{13}C NMR (75 MHz) δ 25.9, 44.6, 85.8, 92.0, 120.0, 128.4, 130.4, 132.7, 193.9; MS iso-

(28) Martin, V. A.; Murray, D. H.; Pratt, N. E.; Zhao, Y.-b.; Albizati, K. F. *J. Am. Chem. Soc.* **1990**, *112*, 6965.
(29) Moriarty, R. M.; Hou, K.-C. *Tetrahedron Lett.* **1984**, *25*, 691.
(30) Kletzke, P. G. *J. Chem. Eng. Data* **1973**, *18*, 93.

butane chemical ionization 187 ($M^+ + H$); HRMS calcd for C_9H_5O, 129.0340, found 129.0345 (M^+ - *tert*-butyl).

4-Bromo-1-phenylbut-1-en-3-one (23a). This compound was prepared analogously to **16a** by low-temperature bromination of *trans*-1-phenyl-3-[(trimethylsilyl)oxy]butadiene (**21**) to give pure **23a** in 74% yield after HPLC (eluent 90% hexane/EtOAc) **23a**: IR (melt) 3060, 2941, 1684, 1609, 1495, 1332, 1067, 977, 687 cm^{-1}; ^1H NMR (300 MHz) δ 4.10 (s, 2 H), 6.93 (d, 1 H, J = 16 Hz), 7.40 (m, 3 H), 7.56 (m, 2 H), 7.68 (d, 1 H, J = 16 Hz); ^{13}C NMR (75 MHz) δ 33.0, 122.1, 128.4, 128.8, 130.9, 133.7, 145.0, 190.7; HRMS calcd for $C_{10}H_9BrO$ 223.9837, found 223.9840.

4-(Mesyloxy)-1-phenylbut-1-en-3-one (23b). This compound was prepared from **23e** in the same manner as **16b**. Following flash chromatography with 65% hexane/EtOAc, the mesylate precipitated giving 71% yield. **23b**: mp 117–118.5 °C; IR (melt) 3034, 2947, 1702, 1614, 1454, 1348, 1174, 1034, 830, 753, 690 cm^{-1}; ^1H NMR (300 MHz) δ 3.22 (s, 3 H), 5.05 (s, 2 H), 6.83 (d, 1 H, J = 16 Hz), 7.42 (m, 3 H), 7.57 (m, 2 H), 7.69 (d, 1 H, J = 16 Hz); ^{13}C NMR (75 MHz) δ 38.8, 71.2, 120.4, 128.7, 129.1, 131.4, 133.7, 145.3, 191.1; HRMS calcd for $C_{11}H_{12}SO_4$ 240.0456, found 240.0458.

4-Chloro-1-phenylbut-1-en-3-one (23c). This compound was prepared from **21** analogously to **16c** in 81% yield after HPLC (eluent 90% hexane/EtOAc) **23c**: mp 57–58.5 °C; IR (melt) 3061, 3028, 2933, 1703, 1690, 1611, 1577, 1496, 1450, 1401, 1334, 1174, 1087, 980, 778, 745, 689 cm^{-1}; ^1H NMR (300 MHz) δ 4.30 (s, 2 H), 6.97 (d, 1 H, J = 16 Hz), 7.41 (m, 3 H), 7.58 (m, 2 H), 7.70 (d, 1 H, J = 16 Hz); ^{13}C NMR (75 MHz) δ 47.3, 121.6, 128.6, 129.0, 131.1, 133.9, 145.2, 191.2; HRMS calcd for $C_{10}H_9ClO$ 180.0342, found 180.0340.

4-Acetoxy-1-phenylbut-1-en-3-one (23d). This compound was prepared by the acetylation of **23e** in the same manner as **16d** from **23e** to give 35% yield after HPLC (eluent 75% hexane/EtOAc) **23d**: IR (neat) 3027, 2937, 1750, 1703, 1683, 1615, 1232, 1051, 750, 690 cm^{-1}; ^1H NMR (300 MHz) δ 2.19 (s, 3 H), 4.93 (s, 2 H), 6.77 (d, 1 H, J = 16 Hz), 7.39 (m, 3 H), 7.53 (m, 2 H), 7.65 (d, 1 H, J = 16 Hz); ^{13}C NMR (75 MHz) 20.4, 67.3, 121.5, 128.4, 128.9, 130.9, 134.0, 144.0, 170.2, 192.3; HRMS calcd for $C_{12}H_{12}O_3$ 204.0786, found 204.0788.

4-Hydroxy-1-phenylbut-1-en-3-one (23e). This compound was prepared in the same manner as **16e** from **21** to give 77% of **23e**. This compound exhibited IR and ^1H and ^{13}C NMR spectral properties identical with those previously reported.[29]

A. Reactions of Enones with Me_2CuLi: General Procedure. To a stirred slurry of 381 mg of CuI (2.0 mmol) in 5.0 mL of ether at −10 °C was added 2.85 mL of MeLi (1.4 M in ether, 4.0 mmol) and this mixture cooled to −78 °C. After 30 min, a solution of the enone (2.0 mmol) in 3.0 mL of furan was added and the mixture stirred for an additional 30 min. The reaction was quenched at −78 °C with 1.0 mL of saturated NH_4Cl poured into 75 mL of CH_2Cl_2 and 75 mL of saturated NH_4Cl and stirred for 30 min, and the layers were separated, washed with saturated aq NH_4Cl (until the blue Cu^{2+} color has dissipated) and saturated NaCl, dried, and evaporated under reduced pressure. In all cases, the mixtures were separated by semipreparative (ca. 100–200-mg scale) HPLC on silica using EtOAc/hexane mixtures as eluants. Yields are quoted in the tables and represent isolated and purified products.

B. Reactions of Enones with MeCu: General Procedure. These reactions were run under identical conditions to the cuprate reactions described above except that only 1 equiv of MeLi was used in the generation of the organocopper reagent. To a slurry of 381 mg CuI (2.0 mmol) in 5.0 mL of ether at −10 °C was added to 1.43 mL of MeLi (1.4 M in ether, 2.0 mmol), and this mixture cooled to −78 °C. After 30 min, a solution of the enone (2.0 mmol) in 3.0 mL of furan was added and the mixture stirred for an additional 30 min. The reaction was quenched at −78 °C with 1.0 mL of saturated aq NH_4Cl, poured into 75 mL of CH_2Cl_2 and 75 mL of saturated NH_4Cl, and stirred for 30 min. The layers were separated, washed with saturated NH_4Cl (until the blue Cu^{2+} color has dissipated), saturated NaCl, dried, and evaporated under reduced pressure. In all cases, the mixtures were separated by semipreparative (ca. 100–200-mg scale) HPLC on silica using EtOAc/hexane mixtures as eluants. Yields are quoted in the tables and represent isolated and purified products.

2,4-Dimethylhexan-3-one (29f). This compound was found to be identical with that reported.[30]

2,4,4-Trimethylpent-1-en-3-one (15g). This compound exhibited IR and ^1H and ^{13}C NMR spectral properties identical with those previously reported.[25]

2-Acetoxy-2,4-dimethylhexan-3-one (35d): IR (neat) 2971, 2878, 1742, 1716, 1251, 1151, 1018 cm^{-1}; ^1H NMR (300 MHz) δ 0.86 (t, 3 H, J = 8 Hz), 1.07 (d, 3 H, J = 7 Hz), 1.35 (m, 1 H), 1.50 (s, 3 H), 1.52 (s, 3 H), 1.65 (m, 1 H), 2.05 (s, 3 H), 2.77 (m, 1 H, J = 7 Hz); ^{13}C NMR (75 MHz) δ 11.6, 17.1, 21.3, 24.0, 26.8, 41.4, 83.8, 170.0, 212.8; HRMS calcd for $C_{10}H_{18}O_3$ 186.1256, found 186.1258.

Reaction of 15h with Me_2CuLi. Reaction of phosphorylenone **15h** with Me_2CuLi yielded after HPLC 90% hexane/EtOAc 3% α-**45** and 2% β-**45** along with other unidentified material which appears to be oligomeric.

2-Ethyl-2,4,4-trimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (α-45): IR (neat) 2972, 2933, 1705, 1070, 937, 923 cm^{-1}; ^1H NMR (300 MHz) δ 0.81 (t, 3 H, J = 7 Hz, 0.89 (s, 3 H), 0.93 (s, 3 H), 0.93 (s, 3 H), 1.48 (m, 1 H, J = 14, 7 Hz), 1.62 (m, 1 H, J = 7 Hz), 1.62 (s, 1 H), 1.62 (s, 2 H); ^{13}C NMR (75 MHz) δ 8.5, 17.4, 21.1, 25.9, 31.2, 51.4, 55.3, 84.8, 86.6, 133.6, 133.9, 216.2; HRMS calcd for $C_{12}H_{18}O_2$ 194.1307, found 194.1310.

4,4,5-Trimethylcyclohexanone (38f): IR (neat) 2961, 2873, 1716 cm^{-1}; ^1H NMR (300 MHz) δ 0.81 (d, 3 H, J = 7 Hz), 0.89 (s, 3 H), 0.93 (s, 3 H), 1.48 (td, 1 H, J = 13, 5 Hz), 1.62 (overlapping m, 2 H), 2.06 (dd, 1 H, J = 14, 12 Hz), 2.16 (overlapping m, 2 H), 2.29 (td, 1 H, J = 12, 6 Hz); ^{13}C NMR (75 MHz) δ 16.3, 18.8, 28.4, 32.4, 38.2, 39.8, 41.3, 45.8, 211.7; HRMS calcd for $C_9H_{16}O$ 140.1201, found 140.1198.

Reaction of 16a with Me_2CuLi. Reaction of **16a** with Me_2CuLi gave after HPLC (90% hexane/EtOAc) two isomeric aldol adducts in 39% (**39a-I**) and 15% (**39a-II**) yield.

Reaction of 16a with MeCu. Reaction of **16a** with methyl copper gave after HPLC 20% **224a-I** and 43% recovered **16a**.

6-(6-Bromo-4,4-dimethyl-1-hydroxycyclohex-2-enyl)-4,4-dimethylcyclohex-2-en-1-one (39a-I): mp 134 °C dec; IR (neat) 3443, 3012, 2963, 2871, 1648, 1217 cm^{-1}; ^1H NMR (300 MHz) δ 1.02 (s, 3 H), 1.06 (s, 3 H), 1.16 (s, 3 H), 1.23 (s, 3 H), 1.52 (t, 1 H, J = 13 Hz), 1.73 (ddd, 1 H, J = 13, 5, 2 Hz), 1.94 (ddd, 1 H, J = 12, 2,2 Hz), 2.60 (t, 1 H, J = 13 Hz), 3.19 (dd, 1 H, J = 15, 5 Hz), 4.38 (dd, 1 H, J = 13, 3 Hz), 5.46 (d, 1 H, J = 10 Hz), 5.54 (s, 1 H, OH), 5.56 (d, 1 H, J = 10 Hz), 5.86 (d, 1 H, J = 10 Hz), 6.71 (dd, 1 H, J = 10, 2 Hz); ^{13}C NMR (75 MHz) δ 25.2, 27.7, 30.0, 30.4, 33.6, 36.2, 37.6, 42.6, 48.7, 54.1, 72.6, 124.9, 127.4, 141.6, 160.5, 203,6; MS isobutane chemical ionization 309 ($M^+ + H - OH$); HRMS calcd for $C_{16}H_{22}BrO$ 309.0855, found 309.0850 ($M^+ - OH$).

6-(6-Bromo-4,4-dimethyl-1-hydroxycyclohex-2-enyl)-4,4-dimethylcyclohex-2-en-1-one (39a-II): mp 137–139 °C; IR (neat) 3461, 3025, 2866, 1646, 1364, 1118, 1086, 1042 cm^{-1}; ^1H NMR (300 MHz) δ 1.06 (s, 3 H), 1.14 (s, 3 H), 1.19 (s, 6 H), 1.83 (t, 1 H, J = 14 Hz), 1.99 (overlapping m, 1 H), 2.42 (t, 1 H, J = 13 Hz), 2.94 (dd, 1 H, J = 14, 4 Hz), 3.65 (s, 1 H, OH), 5.24 (dd, 1 H, J = 13, 3 Hz), 5.42 (d, 1 H, J = 10 Hz), 5.62 (d, 1 H, J = 10 Hz), 5.78 (d, 1 H, J = 10 Hz), 6.63 (dd, 1 H, J = 10, 2 Hz); ^{13}C NMR (75 MHz) δ 24.7, 26.9, 30.1, 30.6, 33.6, 36.3, 36.6, 43.9, 48.5, 59.6, 72.0, 124.4, 127.7, 141.5, 160.0, 200.1; HRMS calcd for $C_{16}H_{23}BrO_2$ 326.0882, found 326.0886.

6-[6-(Mesyloxy)-4,4-dimethyl-1-hydroxycyclohex-2-enyl]-4,4-dimethylcyclohex-2-en-1-one (39b): IR (neat) 3430, 3026, 2964, 2254, 1656, 1333, 1177 cm^{-1}; ^1H NMR (300 MHz) δ 1.08 (s, 6 H), 1.15 (s, 3 H), 1.22 (s, 3 H), 1.52 (t, 1 H, J = 14 Hz), 1.80 (m, 1 H), 1.98 (m, 1 H), 2.34 (t, 1 H, J = 12 Hz), 3.03 (dd, 1 H, J = 14, 5 Hz), 3.08 (s, 3 H), 5.00 (dd, 1 H, J = 13, 4 Hz), 5.42 (d, 1 H, J = 10 Hz), 5.55 (d, 1 H, J = 10 Hz), 5.86 (d, 1 H, J = 10 Hz), 6.72 (dd, 1 H, J = 10, 1 Hz); ^{13}C NMR (75 MHz) δ 25.1, 27.9, 30.3, 30.4, 33.8, 35.1, 37.0, 37.4, 39.4, 45.5, 72.8, 76.6, 125.0, 127.1, 141.4, 161.2, 203.9; MS isobutane chemical ionization 343 ($M^+ + H$); HRMS calcd for $C_{16}H_{23}SO_4$ 325.1473, found 325.1477 ($M^+ - OCH_3$).

Reaction of 16c with Me_2CuLi. Reaction of **16c** with Me_2CuLi yielded after HPLC 90% hexane/EtOAc two isomeric aldol adducts in 30% (**39c-I**) and 23% (**39c-II**) yield.

Reaction of 16 with MeCu. Reaction of **16c** with MeCu gave after HPLC 19% **39c-I** and 48% recovered **16c**.

6-(6-Chloro-4,4-dimethyl-1-hydroxycyclohex-2-enyl)-4,4-dimethylcyclohex-2-en-1-one (39c-I): mp 134 °C dec; IR (neat) 3448, 3023, 2872, 1650, 1472, 1215, 1041 cm^{-1}; ^1H NMR (300 MHz)

δ 1.03 (s, 3 H), 1.06 (s, 3 H), 1.17 (s, 3 H), 1.23 (s, 3 H), 1.55 (t, 1 H, J = 13 Hz), 1.77 (overlapping m, 2 H), 2.44 (t, 1 H, J = 13 Hz), 3.19 (dd, 1 H, J = 14, 5 Hz), 4.23 (dd, 1 H, J = 13, 3 Hz), 5.48 (d, 1 H, J = 10 Hz, 5.50 (s, 1 H, OH), 5.55 (d, 1 H, J = 10 Hz), 5.87 (d, 1 H, J = 10 Hz), 6.72 (dd, 1 H, J = 10, 2 Hz); ^{13}C NMR (75 MHz) δ 25.1, 27.8, 30.1, 30.4, 33.6, 35.4, 37.6, 41.3, 47.1, 59.4, 72.9, 125.5, 127.3, 141.5, 160.4, 203.6; MS isobutane chemical ionization 283 (M^+ + H); HRMS calcd for $C_{16}H_{22}ClO$ 265.1359, found 265.1362 (M^+ - OH).

6-(6-Chloro-4,4-dimethyl-1-hydroxycyclohex-2-enyl)-4,4-dimethylcyclohex-2-en-1-one (39c-II): mp 134–136 °C; IR (neat) 3458, 3025, 2959, 2871, 1696, 1646, 1474, 1378, 1364, 1250, 1118 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.08 (s, 3 H), 1.14 (s, 3 H), 1.21 (s, 6 H), 1.79–1.98 (overlapping m, 3 H), 2.84 (t, 1 H, J = 13 Hz), 2.89 (dd, 1 H, J = 14, 5 Hz), 4.20 (s, 1 H, OH), 4.91 (dd, 1 H, J = 13, 3 Hz), 5.41 (d, 1 H, J = 10 Hz), 5.63 (dd, 1 H, J = 10, 1 Hz), 5.82 (d, 1 H, J = 10 Hz), 6.66 (dd, 1 H, J = 10, 2 Hz); ^{13}C NMR (75 MHz) δ 24.7, 27.0, 30.2, 30.5, 33.6, 35.4, 36.8, 42.5, 47.4, 62.9, 72.7, 125.5, 127.6, 141.6, 159.0, 200.5; HRMS calcd for $C_{16}H_{23}ClO_2$ 282.1387, found 282.1390.

Reaction of 16d with Me_2CuLi. Reaction of **16d** with Me_2CuLi yielded after HPLC (62% hexane/38% EtOAc) 19% *trans*-**38d** and 23% *cis*-**38d**.

Reaction of 16d with MeCu. Reaction of **16d** with MeCu gave after HPLC gave 3% *cis*-**38d**, 2% *trans*-**38d** and 63% recovered **16d**.

***trans*-2-Acetoxy-4,4,5-trimethylcyclohexanone (*trans*-38d)**: IR (neat) 2966, 2940, 2875, 1751, 1731, 1457, 1378, 1233, 1173, 1087, 1042 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.93, (d, 3 H, J = 7 Hz), 1.02 (s, 3 H), 1.09 (s, 3 H), 1.68 (t, 1 H, J = 13 Hz), 1.70 (m, 1 H), 1.96 (dd, 1 H, J = 12, 6 Hz), 2.13 (s, 3 H), 2.29 (overlapping m, 2 H), 5.26 (dd, 1 H, J = 13, 6 Hz); ^{13}C NMR (75 MHz) δ 16.0, 18.7, 20.6, 28.8, 34.3, 42.4, 44.8, 46.5, 74.1, 169.9, 204.0; HRMS calcd for $C_{11}H_{18}O_3$ 198.1256, found 198.1251.

***cis*-2-Acetoxy-4,4,5-trimethylcyclohexanone (*cis*-38d)**: IR (neat) 2964, 2944, 2877, 1754, 1731, 1468, 1378, 1239, 1086, 1065, 1046 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.89, (d, 3 H, J = 7 Hz), 0.97 (s, 3 H), 1.30 (s, 3 H), 1.83–1.92 (overlapping m, 3 H), 2.11 (s, 3 H), 2.18 (dd, 1 H, partly obscured, J = 14, 3 Hz), 2.84 (dd, 1 H, J = 14, 6 Hz), 5.28 (dd, 1 H, J = 12, 8 Hz); ^{13}C NMR (75 MHz) δ 15.8, 20.6, 27.8, 34.1, 40.1, 44.1, 73.7, 169.9, 204.6; HRMS calcd for $C_{11}H_{18}O_3$ 198.1256, found 198.1254.

3-Benzyl-2-pentanone (40f): IR (neat) 3062, 3028, 2964, 2934, 2877, 1712, 1603, 736, 700 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.90 (t, 3 H, J = 7 Hz), 1.5–1.7 (overlapping m, 2 H), 2.01 (s, 3 H), 2.66–2.81 (overlapping m, 2 H), 2.89 (dd, 1 H, J = 12, 7 Hz), 7.25 (m, 5 H); ^{13}C NMR (75 MHz) δ 11.5, 24.4, 30.1, 37.3, 56.0, 126.1 128.4, 128.8, 139.6, 212.3; HRMS calcd for $C_{12}H_{16}O$ 176.1201, found 176.1205.

2,6-Dibenzyl-5-(bromomethyl)-5-hydroxyhepta-1,6-dien-3-one (41a): IR (neat) 3463, 3062, 3028, 2913, 1663, 1602, 1495, 910, 733, 701 cm^{-1}; ^{1}H NMR (300 MHz) δ 3.14 (d, 1 H, J = 17 Hz), 3.5–3.5 (overlapping d, 5 H), 3.58 (s, 2 H), 4.68 (br s, 1 H), 5.22 (s, 1 H), 5.72 (s, 1 H), 6.09 (s, 1 H), 7.25 (m, 10 H); ^{13}C NMR (75 MHz) δ 36.6, 38.6, 41.3, 43.2, 75.7, 115.3, 126.3, 126.4, 127.2, 128.4, 128.5, 129.0, 129.3, 138.4, 138.8, 148.4, 150.0, 201.9; HRMS calcd for $C_{22}H_{23}BrO_2$ 308.0881, found 398.0886.

2,6-Dibenzyl-5-hydroxy-5-[(mesyloxy)methyl]hepta-1,6-dien-3-one (41b): IR (neat) 3494, 3062, 3028, 1665, 1602, 1175, 963, 735, 701 cm^{-1}; ^{1}H NMR (300 MHz) δ 2.99 (d, 1 H, J = 17 Hz), 3.01 (s, 3 H), 3.36 (overlapping d's, 3 H), 3.56 (s, 2 H), 4.03 (d, 1 H, J = 13 Hz), 4.10 (d, 1 H, J = 13 Hz), 4.84 (br s, 1 H), 5.24 (s, 1 H), 5.72 (s, 1 H), 6.07 (s, 1 H), 7.23 (m, 10 H); ^{13}C NMR (75 MHz) δ 36.5, 37.5, 38.9, 41.2, 74.4, 75.9, 115.8, 126.4, 127.5, 128.4, 128.5, 129.0, 129.2, 138.3, 138.6, 148.1, 148.9, 201.9; HRMS calcd for $C_{23}H_{28}SO_5$ 416.1657, found 416.1650.

1-(3-Benzyl-3-buten-2-onyl)-2-benzyl-2-ethylcyclopropanol (44, major isomer): IR (neat) 3518, 3027, 2964, 1669, 1602, 1453, 1048, 946, 700 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.33 (d, 1 H, J = 6 Hz), 0.80 (t, 3 H, J = 7 Hz), 0.85 (d, 1 H, J = 6 Hz), 1.00 (m, 1 H, J = 14, 7 Hz), 1.17 (m, 1 H, J = 14, 7 Hz), 2.90 (d, 1 H, J = 15 Hz), 2.99 (d, 1 H, J = 15 Hz), 3.10 (d, 1 H, J = 18 Hz), 3.18 (d, 1 H, J = 18 Hz), 5.69 (s, 1 H), 6.10 (s, 1 H), 7.30 (m, 10 H); ^{13}C NMR (75 MHz) δ 10.5, 24.3, 25.1, 31.3, 34.8, 36.8, 42.2, 59.3, 125.7, 126.4, 126.5, 128.1, 128.5, 129.0, 129.3, 138.6, 140.7, 148.3, 202.7; HRMS calcd for $C_{23}H_{26}O_2$ 334.1933, found 334.1936.

1-(3-Benzyl-3-buten-2-onyl)-2-benzyl-2-ethylcyclopropanol (44, minor isomer): IR (neat) 3063, 3028, 2966, 1754, 1732, 1604, 1232, 1033, 749, 703 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.92 (t, 3 H, J = 7 Hz), 1.54 (m, 1 H), 2.10 (s, 3 H), 2.73 (m, 2 H), 2.91 (m, 1 H), 4.18 (d, 1 H, J = 17 Hz), 4.61 (d, 1 H, J = 17 Hz), 7.21 (m, 5 H); ^{13}C NMR (75 MHz) δ 11.3, 20.2, 24.6, 37.4, 51.7, 68.6, 126.3, 128.4, 128.6, 139.0, 169.8, 206.7; HRMS calcd for $C_{14}H_{18}O_3$ 234.1256, found 234.1260.

2,6-Dibenzyl-5-(chloromethyl)-5-hydroxyhepta-1,6-dien-3-one (41c): IR (neat) 3474, 3062, 3028, 2917, 1664, 1602, 1495, 911, 735, 700 cm^{-1}; ^{1}H NMR (300 MHz) δ 3.10 (d, 1 H, J = 17 Hz), 3.5–3.5 (overlapping d's, 5 H), 3.58 (s, 2 H), 4.68 (br s, 1 H), 5.22 (s, 1 H), 5.72 (s, 1 H), 6.09 (s, 1 H), 7.25 (m, 10 H); ^{13}C NMR (75 MHz) δ 36.6, 38.7, 42.3, 51.4, 76.5, 115.3, 126.3, 126.4, 127.2, 128.4, 128.5, 129.0, 129.3, 138.4, 138.9, 148.5, 150.0, 202.0; HRMS calcd for $C_{22}H_{24}ClO_2$ 355.1465, found 355.1468 (M^+ + H).

1-Acetoxy-3-benzyl-2-pentanone (40d): IR (neat) 3063, 3028, 2966, 1754, 1732, 1604, 1232, 1033, 749, 703 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.92 (t, 3 H, J = 7 Hz), 1.54 (m, 1 H), 1.72 (m, 1 H), 2.10 (s, 3 H), 2.73 (m, 2 H), 2.91 (m, 1 H), 4.18 (d, 1 H, J = 17 Hz), 4.61 (d, 1 H, J = 17 Hz), 7.21 (m, 5 H); ^{13}C NMR (75 MHz) δ 11.3, 20.2, 24.6, 37.4, 51.7, 68.6, 126.3, 128.4, 128.6, 139.0, 169.8 206.7; HRMS calcd for $C_{14}H_{18}O_3$ 234.1256, found 234.1260.

(*E*)-5-Methyl-2-phenylhex-2-en-4-one ((*E*)-32f): IR (neat) 3060, 2969, 2873, 1683, 1602, 1575, 1446, 1381, 1064, 967, 764, 696 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.17 (d, 6 H, J = 7 Hz), 2.57 (s, 3 H), 2.74 (m, 1 H, J = 7 Hz), 6.57 (s, 1 H), 7.38 (overlapping m, 3 H), 7.50 (overlapping m, 2 H); ^{13}C NMR (75 MHz) δ 18.2, 41.9, 123.1, 126.3, 128.4, 128.8, 142.7 154.1, 204.8; HRMS calcd for $C_{13}H_{16}O$ 188.1201, found 188.1198.

(*Z*)-5-Methyl-2-phenylhex-2-en-4-one ((*Z*)-32f): IR (neat) 3058, 2970, 1692, 1676, 1619, 1599, 1088, 981, 764, 698 cm^{-1}; ^{1}H ^{1}HNMR (300 MHz) δ 1.03 (d, 6 H, J = 7 Hz), 2.21 (s, 3 H), 2.49 (m, 1 H, J = 7 Hz), 6.25 (s, 1 H), 7.21 (dd, 2 H, J = 8, 2 Hz), 7.35 (overlapping m, 3 H); ^{13}C NMR (75 MHz) δ 18.2, 26.8, 40.3, 125.4, 126.9, 127.8, 128.0, 140.9, 151.7, 205.4; HRMS calcd for $C_{13}H_{16}O$ 188.1201, found 188.1198.

Aldol Adduct 33: mp 112.5–114 °C (neat) 3366, 3076, 2970, 1674, 1618, 1490, 1031, 970, 909, 757, 704 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.70 (d, 3 H, J = 7 Hz), 0.95 (d, 3 H, J = 7 Hz), 1.22 (d, 3 H, J = 7 Hz), 1.29 (d, 3 H, J = 7 Hz), 2.14 (m, 1 H, J = 7 Hz), 2.43 (s, 3 H), 2.59 (m, 1 H, J = 7 Hz), 2.74 (br s, 1 H), 7.22–7.54 (overlapping m, 10 H); ^{13}C NMR (75 MHz) δ 16.6, 17.3, 17.7, 18.7, 22.2, 37.9, 42.5, 74.8, 85.4, 90.7, 122.8, 127.8, 128.3, 128.4, 131.6, 138.1, 143.4, 213.4; HRMS calcd for $C_{25}H_{28}O_2$ 360.2089, found 360.2092.

Reaction of 18g with Me_2CuLi. Reaction of **18g** with Me_2CuLi gave after HPLC (90% hexane/10% EtOAc) 26% (*E*)-**32g** and 20% (*Z*)-**32g**.

Reaction of 18g with MeCu. Reaction of **18g** with MeCu yielded after HPLC 25% (*E*)-**32g** and 30% (*Z*)-**32g**.

(*E*)-5,5-Dimethyl-2-phenylhex-2-en-4-one ((*E*)-32g): IR (neat) 3059, 2968, 2870, 1676, 1600, 1090, 960, 766, 732, 696 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.24 (s, 9 H), 2.53 (s, 3 H), 6.77 (s, 1 H), 7.39 (overlapping m, 3 H), 7.51 (overlapping m, 2 H); ^{13}C NMR (75 MHz) δ 18.5, 26.6, 44.1, 120.8, 126.4, 128.4, 128.7, 143.2, 153.9, 206.4; HRMS calcd for $C_{14}H_{18}O$ 202.1358, found 202.1359.

(*Z*)-5,5-Dimethyl-2-phenylhex-2-en-4-one ((*Z*)-32g): IR (neat) 2969, 1687, 1617, 1598, 1100, 972, 763, 697 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.22 (s, 9 H), 2.24 (s, 3 H), 6.55 (s, 1 H), 7.22 (dd, 2 H, J = 8, 2 Hz), 7.36 (overlapping m, 3 H); ^{13}C NMR (75 MHz) δ 26.3, 27.3, 43.3, 121.3, 127.3, 127.7, 128.3, 141.2, 153.0, 204.8; HRMS calcd for $C_{14}H_{18}O$ 202.1358, found 202.1360.

Reaction of 18d with MeCuLi. Reaction of **18d** with Me_2CuLi yielded after HPLC 90% hexane/EtOAc, 26% (*E*)-**32d** and 43% (*Z*)-**32d**.

Reaction of 18d with MeCu. Reaction of **18d** with MeCu yielded after HPLC (90% hexane/10% EtOAc) 3% (*E*)-**32d**, 4% (*Z*)-**32d**, and 28% recovered **18d**.

(*E*)-5-Acetoxy-5-methyl-2-phenylhex-2-en-4-one ((*E*)-32d): IR (neat) 3058, 2984, 1739, 1670, 1605, 1146, 1088, 766, 697 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.57 (s, 6 H), 2.09 (s, 3 H), 2.56 (d, 3 H, J = 1 Hz), 6.64 (d, 1 H, J = 1 Hz), 7.39–7.46 (overlapping m, 5 H); ^{13}C NMR (75 MHz δ 18.6, 21.2, 23.8, 84.1, 118.7, 126.5, 128.5, 129.0, 142.9, 156.4, 170.1, 199.0; HRMS calcd for $C_{15}H_{18}O_3$ 246.1256, found 246.1260.

(Z)-5-Acetoxy-5-methyl-2-phenylhex-2-en-4-one ((Z)-32d): IR (neat) 3058, 2983, 1739, 1700, 1617, 1371, 1099, 815, 764, 699 cm^{-1}; ^1H NMR (300 MHz) δ 1.48 (s, 6 H), 2.13 (s, 3 H), 2.21 (s, 3 H), 6.40 (s, 1 H), 7.27–7.36 (overlapping m, 5 H); ^{13}C NMR (75 MHz) δ 21.3, 23.6, 27.9, 83.8, 118.8, 126.8, 127.7, 128.0, 141.0, 156.5, 170.1, 197.0; HRMS calcd for $C_{15}H_{18}O_3$ 246.1256, found 246.1258.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this work. We also thank the National Institutes of Health for a Biomedical Research Support grant.

Supplementary Material Available: ^1H NMR spectra of all new compounds (52 pages). Ordering information is given on any current masthead page.

Functional Group Hybrids. Reactivity of α'-Nucleofuge α,β-Unsaturated Ketones. 2. Reactions with Malonate Anion. Concerning the Mechanism of the Favorskii Rearrangement

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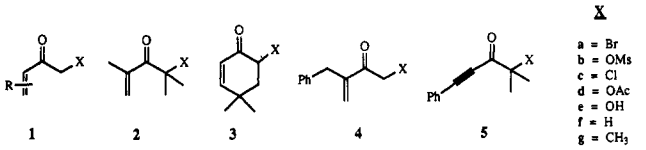
Received May 24, 1991

The scope and limiations of the reaction of α'-nucleofuge α,β-unsaturated ketones with sodium dimethyl malonate has been studied systematically. The substrates with good nucleofuges (halides, mesylate) give cyclopropanols upon reaction with malonate anion by way of a conjugate Favorskii reaction. In reactions with substrates containing the poorer nucleofuge (acetoxy) conjugate addition proceeded without entering the Favorskii manifold. Concerning the mechanism of the Favorskii reaction, it is suggested that the loss of the nucleofuge occurs to give a 2-oxyallyl cation, but that disrotatory ring closure is facile and the only products observed result from nucleophilic trapping of cyclopropanones to yield cyclopropanols in fair to good yield.

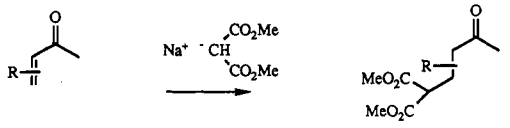
The 1,4-conjugate addition of active methylene compounds to the β-carbon of an α,β-unsaturated ketone is a widely utilized method for the formation of carbon–carbon bonds.[2] In a project designed to develop a sequential conjugate addition–cycloaddition process for carbocycle synthesis (Scheme I, previous paper), we examined the reaction of α'-nucleofuge α,β-unsaturated ketones with a variety of agents which were anticipated to undergo conjugate addition to 1 as the triggering reaction to such a sequential process. In the previous article, we described the synthesis of substrates of general structure 1 in the form of **2–5 (a–d)** and their reactions with Me_2CuLi and MeCu. Herein we present our results of the reactions of **2–5** with dimethyl malonate anion, which should proceed via a different mechanistic pathway than either Me_2CuLi or MeCu.



Results

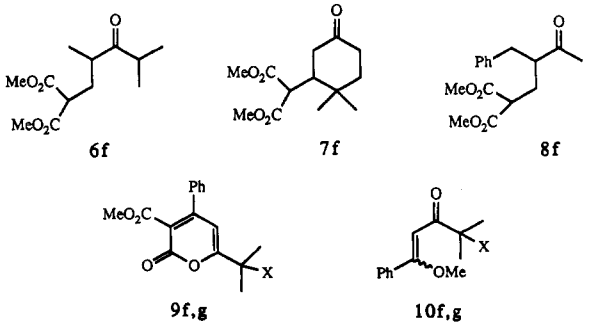
Given the many possible reaction pathways envisioned for the substrates under study, it was necessary to show that "simple" conjugate addition to the enone portion of these substrates was viable. As control experiments, each of the parent α,β-unsaturated ketones **2f–5f** was treated with sodium dimethyl malonate. The dimethyl ester of malonic acid was selected for study since this choice conveniently minimized the number of ^1H and ^{13}C NMR resonances and avoids unnecessary spectral complexity. Two sets of standard reaction conditions were employed for these conjugate additions. Method A involved the generation of the sodium anion of dimethyl malonate with NaH in THF followed by the addition of a solution of the unsaturated ketone in furan. After 2 h, the reaction was quenched and acidified with 1 M HCl. Method B utilized

Scheme I. Reactions of 2f–5f,g with Dimethyl Malonate Anion[a]



Substrate	Product	Method A	Method B
2f	6f	40	52
3f	7f	0	28
4f	8f	70	41
5f	9f	77[b]	24[b,c]
5g	10g	71[b]	19[b,d]

[a] Yields represent chromatographically isolated products; [b] Conjugate addition leads to formation of pyrones **9f** or **g**; [c] Also gives 11% **10f**; [d] Also gives 16% **10g**.



(1) Author to whom correspondence should be addressed concerning the X-ray analyses.

(2) (a) Bergman, E. D.; Ginsburg, D.; Pappo, R. *Org. React.* **1959**, *10*, 179. (b) Oare, D.; Heathcock, C. *Top. Stereochem.* **1991**, *20*, 87.

0022-3263/91/1956-6773$02.50/0