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Reaction of Lithium Dialkylcuprates with Acetoxy Epoxides. Assessment of a Method for Nucleophilic α-Alkylation of Ketones[1]

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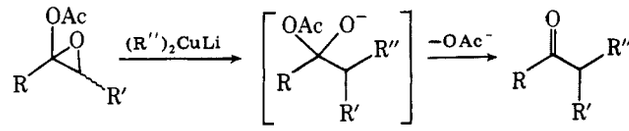
The reaction between acetoxy oxiranes and lithium dialkylcuprates proceeds at low temperatures (−78 °C) to produce the desired α-alkyl ketones in yields which vary greatly with the cuprate and acetoxy oxirane used (2.3–43%). Lithium dimethylcuprate generally gives the best yields, with lithium di-*n*-butyl- and diphenylcuprate giving more complex product mixtures which contain less of the desired substituted ketone. Formation of the nonalkylated ketone is consistently observed and several potential mechanisms for the reaction are considered in light of its formation. The use of cuprates having a nontransferable ligand and also the use of the epoxides of enol pivalates, benzoates, and mesitoates, as substrates, were explored as a means of controlling formation of the unsubstituted ketone.

The alkylation of carbonyl compounds by reaction of enolates with electrophilic alkylating agents is a reaction of fundamental importance in synthetic organic chemistry. However, there are certain cases where such an electrophilic α-alkylation approach is not favorable. For example, the electrophile may be severely hindered and thus subject to facile elimination reactions, or, in the case of sp^2 or sp hybridized centers, the site may not be subject to direct displacement. In considering alternative methods that would avoid difficulties of this nature, we were intrigued by the possibility of achieving a nucleophilic α-alkylation. In such a process the conventional roles of electrophile (alkylating agent) and nucleophile (enolate) are reversed, and, in this sense, the method represents another example of "umpolung" or "charge affinity inversion".[2] The nucleophilic α-alkylation method is particularly appealing for those cases where the substituent to be introduced is alkenyl or aryl.

Several methods have recently been reported that result in the nucleophilic α-alkylation or arylation of ketones; these utilize as reactants or intermediates α-halo ketones,[3] α,α′-dihalo ketones,[4] hydrazones of α,β-epoxy ketones,[5] vinyl nitro[6] or nitroso compounds,[7] or vinyl azo sulfonates.[8,9] While these approaches operate efficiently in the systems examined, we were particularly intrigued by an approach that appeared to involve a minimum of steps in the preparation of the electrophilic analogue of the enolate and in the regeneration of the ketone after nucleophilic addition.

Lithium dialkylcuprates are known to react with epoxides by displacement at the least-substituted carbon. The cuprates appear superior to alkyllithium reagents in this regard, plus they are unreactive toward ester functions.[10] On the basis of this behavior, we considered it likely that the reaction of a lithium dialkylcuprate with an acetoxy epoxide would proceed as illustrated in the scheme below. The acetoxy function places



one carbon at the oxidation state of a carbonyl group; thus, attack of the cuprate at the other, less hindered center, generates a species that should eliminate acetate ion. The overall reaction would produce the alkylated carbonyl compound by a nucleophilic α-alkylation process in which the electrophile is the acetoxy epoxide (ketone precursor) and the nucleophile is the dialkylcuprate.

We have found that the reaction of organocuprates with acetoxy epoxides does indeed proceed in this manner; however, the yield of the desired alkylation product depends greatly upon the nature of the organocuprate, the structure of the acetoxy epoxide, and the reaction conditions.

Results

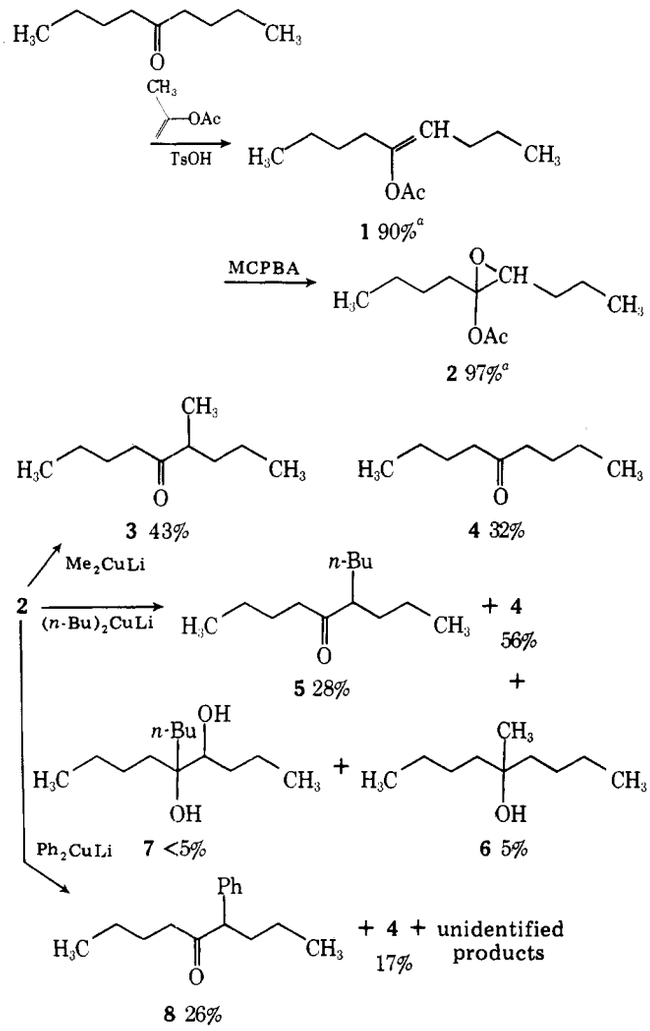
Reaction of Lithium Dialkylcuprates with Acetoxy Epoxides. The enol acetates (1) required for formation of the substituted oxiranes are conveniently prepared from the corresponding ketone and isopropenyl acetate using *p*-toluenesulfonic acid as a catalyst. Epoxidation using *m*-chloroperbenzoic acid yields the desired oxiranes (2) in generally high yields. This class of compounds exhibits a well-known[11] intramolecular thermal or acid-catalyzed isomerization to the corresponding α-acetoxy ketones, but with reasonable care the compounds can be readily prepared. They are stored at

−20 °C and are generally used shortly after their preparation.

5-Acetoxynonane 4,5-oxide (2) reacts with lithium dimethylcuprate (twofold excess in ether at −78 °C) to give the desired 4-methyl-5-nonanone (3) in 43% yield. Unexpectedly, a substantial amount of 5-nonanone (32%) (4) is also produced. The formation of the unsubstituted ketone, a product that results from a formal reduction of the acetoxy epoxide, is observed quite consistently throughout these reactions, and we shall consider its possible sources later.

As shown in Scheme I, compound 2 also reacts with lithium

Scheme I



[a] The olefin and oxirane are a mixture of cis and trans isomers.

di-*n*-butylcuprate to give the desired 4-butyl-5-nonanone (5), as well as the reduction product 5-nonanone (4). In addition, two other products were formed: the tertiary carbinol 6 and the vicinal diol 7, which was characterized by oxidative cleavage using periodic acid and identification of the carbonyl fragments as their 2,4-DNP derivatives. The amounts of these products formed are highly variable, and in an initial study the isolated yields were 13%:34%:30%:26% for 5:4:6:7, respectively.

Alcohol 6 could arise from the addition of two butyl groups to an acetyl group, and diol 7, from the addition of one butyl group to the α-hydroxyl ketone (formed from 2 by acetyl cleavage). Thus, it seemed likely that these alcohols were originating from reactions of free *n*-butyllithium with 2. To confirm this fact, a series of reactions was run with 2 in which the CuI:*n*-BuLi ratio was varied, and the product was analyzed to determine the relative amounts of ketone and alcohol components.

Table I. Dependence of Ketone vs. Alcohol Product Ratio upon Organocopper Composition in Reaction with 5-Acetoxynonane 4,5-Oxide (2)

CuI:*n*-BuLi	Ketones (4 + 5):alcohols (6 + 7)[a]
1:1.0	No reaction
1:1.5	100:0
1:2.0	90:10
1:2.5	25:75
n-BuLi alone	0:100

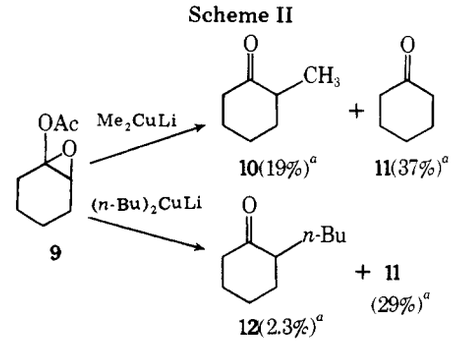
[a] Approximate molar % based on GLC data.

As shown in Table I, the alkyl copper itself is nonreactive toward the epoxide. In the case of the 1:1.5 ratio, which should contain both butylcopper and di-*n*-butylcuprate, only ketone products were observed (along with some unconsumed starting material). The 1:2.0 ratio frequently shows the formation of some alcohol products, but the amounts produced are highly variable. Apparently, the reaction is very sensitive to slight excesses of *n*-butyllithium, potentially caused by errors in the amount of alkyllithium added, impurities in the cuprous salt, or decomposition of the cuprate during formation.[12,18] The 1:2.5 ratio demonstrates that even a small excess of *n*-butyllithium competes very effectively with the cuprate complex, as the ratio of products is shifted heavily in favor of the alcohols. Finally, the alkyllithium alone shows no formation of ketone products, thus confirming the essential role of copper in directing attack at the oxirane rather than the ester function. In light of these results, we have been able to achieve yields of 28 and 56% for 5 and 4, respectively (Scheme I), with only small amounts of the alcohol products by avoiding excess *n*-butyllithium.

Compound 2 also reacts with lithium diphenylcuprate to give 4-phenyl-5-nonanone (8), but in widely varying yields. The use of commercial phenyllithium for generation of the cuprate reagent gave extremely poor yields, ca. 0.5% isolated. The use of freshly prepared phenyllithium affords better yields of 8 (best 26%), but still shows formation of several as yet unidentified products. One positive aspect to this particular reaction is the formation of somewhat smaller amounts of 4 compared to the other cuprates (best case: 26% of 8, 17% of 4).

The results of dialkylcuprate reactions with 1-acetoxycyclohexane 1,2-oxide (9) were similar to those in the nonane system, but the yields of alkylated ketone were uniformly lower (see Scheme II). Treatment with lithium dimethylcu-

Scheme II



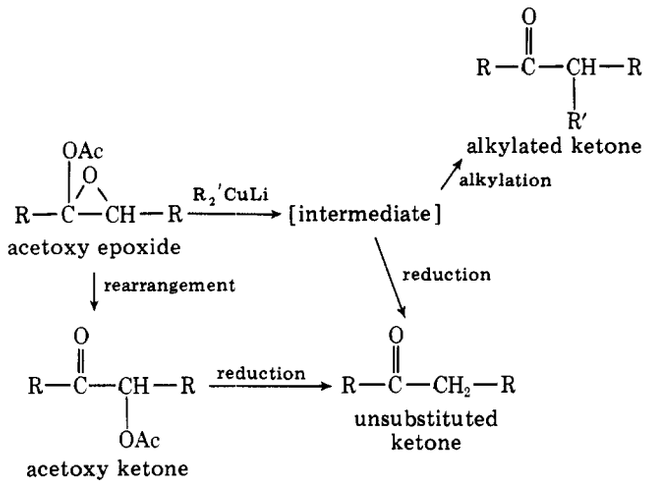
[a] Isolated yields.

prate gave 10 and 11 in yields of 19 and 37%, respectively; reaction of 9 with lithium di-*n*-butylcuprate gave a rather disappointing 2.3% yield of 12, along with considerable amounts (29%) of 11. A substantial portion of the products from the reactions of 9 consisted of material that was polar and rela-

tively nonvolatile (presumed to be condensation products) and was not further characterized. As in the nonane series, the formation of alcohol products can be controlled by avoiding any excess alkyllithium.

Source of Unsubstituted Ketone By-product. As the formation of the unsubstituted ketone is obviously detrimental to the overall yield of the desired product, its possible origins are of considerable interest. Two potential sources that appear likely are shown in Scheme III. The first route would

Scheme III



involve formation of some type of intermediate by reaction of the epoxide with the cuprate reagent (oxidative addition; see Discussion). This intermediate could then undergo further conversion to give either the alkylated ketone or the unsubstituted ketone, in a ratio that might be influenced by a number of factors: leaving group, the R′ group on the cuprate, counterions present, reaction conditions, etc. The second route involves a rearrangement of the acetoxy oxirane to an α-acetoxy ketone followed with attack by the cuprate reagent to give the unsubstituted ketone. The reductive cleavage of some α-acetoxy ketones using lithium dimethylcuprate has been reported and has been further investigated by us.[13]

As mentioned previously, the rearrangements of acetoxy epoxides have been reported to occur under both thermal and acid-catalyzed conditions.[11] However, the temperatures used in the cuprate reactions (−78 to 0 °C) are not sufficient to induce rearrangement, and the solutions certainly are not acidic. Metal cations have been shown[14] to catalyze rearrangements in some epoxides; however, treatment of **9** with a homogeneous mixture of CuI and LiCl in THF at 0 °C and of **2** with a heterogeneous mixture of CuI and LiCl in Et_2O at 0 °C failed to show any evidence of rearrangement. These findings favor the route involving formation of an intermediate (although it is still possible that the rearrangement is catalyzed by some as yet unknown agent).

It is possible in the reactions using lithium di-*n*-butylcuprate that a portion of the unalkylated ketone arises from the reaction of copper hydride (generated by thermal decomposition of the cuprate) with the acetoxy epoxide; however, in most of the butylation reactions, reagent generation, reaction, and quenching were performed below −40 °C, conditions that minimize copper hydride formation. Furthermore, such a copper hydride mechanism cannot be invoked to explain the formation of unalkylated product in the methylation and phenylation reactions.

In an effort to minimize the production of the unsubstituted ketone by-product, we have explored several reaction parameters: the use of mixed cuprates, alteration of the form of the copper salt, and the use of leaving groups other than acetate. The results of these studies are summarized in Tables

Table II. Effect of Organocuprate Composition on Relative Yield of Alkylated Ketone

		Alkylated ketone as mol % of total ketone[a,b]	
Registry no.	Cuprate	System 2	System 9
53128-68-0	*n*-Bu(PhS)CuLi	30	
62197-73-3	*n*-Bu($C_4H_9C{\equiv}C$)CuLi	30	
24406-16-4	*n*-Bu_2CuLi (from CuI)	28[c]	7
	n-Bu_2CuLi (from Me_2S–CuBr)	31	14
15681-48-8	Me_2CuLi (from CuI)	57[c]	46
	Me_2CuLi (from Me_2S–CuBr)	48	41

[a] Percentages are not actual yields but rather the fraction of total ketone content that is the desired alkylation product. [b] Unless otherwise indicated, yield data were determined by GLC analysis. [c] Yield data are based on isolated products.

Table III. Effect of Ester Structure on Relative Yield of Alkylated Ketone

	Alkylated ketone as mol % of total ketone[a,b]					
Cuprate	9[e]	18	19	2	24	25
Me_2CuLi	34[c]	30	32	57[c]	42	39
n-Bu_2CuLi	6[c]	4		28[c]	19	18
Ph_2CuLi[d]					60[c]	

[a] Percentages are not actual yields but the fraction of total ketone content that is desired alkylation product. [b] Unless otherwise indicated, yield data were determined by GLC analysis. [c] Isolated products. [d] Registry no., 23402-69-9. [e] System.

II and III. The amount of alkylated ketone formed in each case is presented as a mol % of total ketone in the crude reaction product; this permits a direct evaluation of whether the alkylation/reduction ratio is being influenced favorably or not.

Alteration in the Nature of the Cuprate Reagent. The use of mixed cuprates in which one of the ligands bound to copper is nontransferable has been finding increasing use because their reaction characteristics are improved and the R group to be donated is conserved, of value particularly when R is difficult to prepare. One such class contains compounds possessing a heteroatom bonded to copper.[15] We chose to study the phenylthio group because its stability is reported to be superior to that of other hetero ligands. Thus, lithium phenylthio(*n*-butyl)cuprate was reacted with **2** to produce both **4** and **5**; however, the product ratio was not significantly different from the lithium di-*n*-butylcuprate (Table II). Acetylenic groups have also been used as nontransferable ligands in cuprates.[16] Formation of the lithium *n*-butyl(*n*-butylethynyl)cuprate by addition of *n*-butyllithium to *n*-butylethynylcopper[17] followed by reaction with **2** again gave **5** as 30% of the total ketone content of the crude product. Thus, it was apparent that use of these mixed cuprates does not produce any significant improvement in the product ratio.

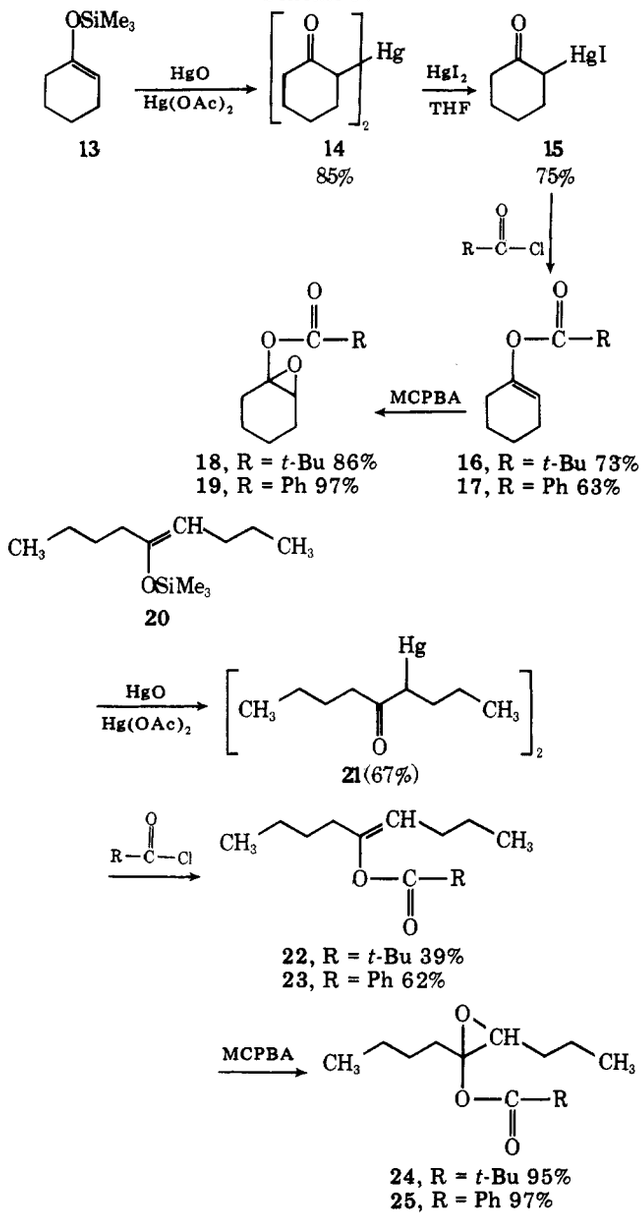
One of the major problems involved in the generation of cuprate reagents is the presence of impurities in the commercially available cuprous salts, and the resulting decomposition of the organocopper that they induce. House has recently described[18] a procedure in which a complex between CuBr or CuCl and dimethyl sulfide is generated, allowing removal of cupric salts as well as other impurities. To investigate

the effect that the nature of the cuprous salt might have on the product ratios, we chose to use the cuprous bromide–dimethyl sulfide complex to purify the salt and to prepare the cuprate reagent.

As indicated in Table II, the methylation reactions with **2** and **9** (using this reagent) showed a small decrease in the amount of alkylated product; the significance of this difference is not clear, since replicate experiments occasionally show variations of this magnitude. In the case of the butylation of **2** and **9**, the trend is in the opposite direction, toward more alkylation product, but again appears to be of marginal significance.

Alteration of the Acyloxy Oxirane. If the alkylation and reduction products originate from a common intermediate (see Scheme III), one might expect that the use of leaving groups other than acetate might have a substantial effect upon the ratio of products. Toward this end, we prepared a number of acyloxy oxiranes that differed in the ester portion, as shown in Scheme IV. We were not able to achieve satisfactory yields

Scheme IV



of the enol esters using classical O-acylation conditions: enolate (formed by either sodium hydride or lithium diisopropylamide) addition to a large excess of acylating agent (benzoyl chloride) in a dipolar aprotic solvent (DMF); however, a method described by House was utilized successfully.[19]

Mercuration of the trimethylsilyl enol ethers **13** and **20** gives the bisketomercurials **14** and **21**. Compound **14** was first converted to the α-iodomercuri ketone derivative **15** and then O-acylated; compound **21** was O-acylated directly, but in somewhat lower yield. The enol esters were epoxidized with *m*-chloroperbenzoic acid and stored at −20 °C to prevent thermal rearrangement.

Treatment of these epoxide derivatives with lithium dimethylcuprate and lithium di-*n*-butylcuprate gave the results shown in Table III. It can be readily seen that both the pivalate and benzoate derivatives gave somewhat lower percentages of the alkylation product compared to the acetates, particularly in the case of the nonane compounds.

In a related study, we also prepared 5-nonanone enol mesitoate (2,4,6-trimethylbenzoate) in the same manner as the pivalates and benzoates. The derivative was then treated with *n*-butyllithium instead of the cuprate in hopes of further defining the role of copper in the reaction. However, this compound was reactive only in the presence of a large excess of the alkyllithium, and attack occurred almost exclusively at the relatively inert ester function, with only traces of the α-alkylation product resulting from attack at the epoxide. These results suggest that the use of the ester function may have only limited use as a potential leaving group in the nucleophilic alkylation of oxygen-substituted epoxides.

Silyl enol ethers would appear to hold promise, since the silyl group would be inert to attack by cuprate reagents, and reacts with alkyllithiums only slowly (at 25 °C), thus allowing more versatility in the organometallic chosen. However, the oxirane formed by reaction of trimethylsilyl enol ethers with *m*-chloroperbenzoic acid rapidly rearranges to the α-trimethylsiloxy ketone, a process that may be catalyzed by the organic acid generated during the epoxidation.[20]

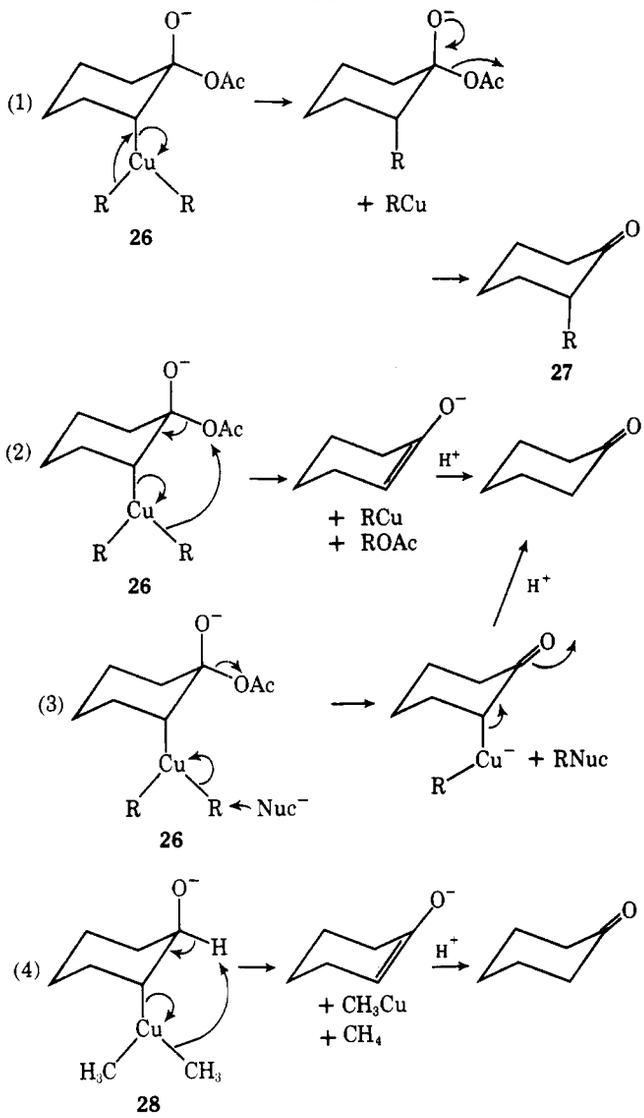
In the hope that steric bulk might retard this rearrangement, we prepared the *tert*-butyldimethylsilyl enol ether of 5-nonanone. However, it too underwent rearrangement upon epoxidation with *m*-chloroperbenzoic acid, despite attempts to remove the benzoic acid during the reaction by extraction into aqueous sodium bicarbonate solution. The rearranged α-siloxy ketone was also formed when epoxidation was attempted with ($Mo(CO)_6$, *t*-BuOOH)[21] or basic benzonitrile–H_2O_2.[22] We were also unable to prepare the epoxide of the triphenylsilyl enol ether[23] of 5-nonanone.

Discussion

The organocoppers differ substantially from alkyllithiums in their reactivity and the sites at which they attack the acyloxy epoxides and related systems. Johnson has proposed[10a] that these differences can be explained by stating that an alkyl carbon is the nucleophile in the case of the alkyllithiums, whereas the copper atom is the nucleophile in the cuprate reagents. The dramatic difference in the sites of attack of the two nucleophiles is readily observed in the reaction of **2** with *n*-butyllithium to give exclusively products (**6** and **7**) resulting from attack at the ester carbonyl, and none of the product (**5**) arising from attack at the oxirane carbon. The cuprate reagent, in contrast, appears to attack exclusively at the latter, since none of the alcohol products (**6** and **7**) are produced when care is taken to exclude any slight excesses of *n*-butyllithium. The fact that metal atoms can act as nucleophiles has been demonstrated by Kochi.[24] He found that lithium dialkylaurates react with alkyl halides to produce a relatively stable gold(III) complex, which, upon thermally induced elimination, gives the coupling product.

If indeed the copper atom is acting as the nucleophile, we could then propose **26** as a possible structure for our postu-

Scheme V



lated intermediate. As shown in the first reaction in Scheme V, alkylated ketone **27** would be produced by a normal type of alkyl donation to the cyclohexane ring with a simultaneous loss of the copper(I) alkyl followed by expulsion of acetate. The copper(I) alkyl is readily observed in the case of the lithium dimethylcuprate as a rapid formation of insoluble yellow polymeric methyl copper. A second alternative (2), which would produce the unsubstituted ketone, would involve a β-elimination of the copper(I) alkyl from **26** with transfer of the remaining R group to acetate. A similar type of mechanism (4) has been proposed by Johnson[10a] to explain the formation of ketones as the major by-products in the addition of cuprates to unsubstituted epoxides: intermediate **28** undergoes the β-elimination to give both the alkyl copper and methane. One other alternative (3) would have an R group from copper undergo a reductive displacement (by acetate or another nucleophile in the reaction medium), to give the enolate.

Mechanisms 2 and 3 would predict the formation of RNuc in amounts equal to the unsubstituted ketone. Thus far we have been unable to demonstrate the presence of any *n*-butyl acetate resulting from attack by acetate in the reaction of **2** with lithium di-*n*-butylcuprate. Work is continuing on isolation of other products due to attack by other potential nucleophiles, namely the alkyl halide or, more likely, the hydrocarbon dimer.

It would appear that the fate of the proposed intermediate **26** could be influenced by changing either the R group on the cuprate or the leaving group on the epoxide. In fact, the influence of the R group is quite significant, with *n*-butyl usually giving the least favorable ratios of alkylated to nonalkylated product, and phenyl the most favorable. Of course, in this case we are limited by the R group we desire to add to the ketone. The other alternative, the use of groups other than acetate, would not be placed under such a restriction. Unfortunately, in the two cases examined thus far, the enol pivalates and benzoates, the ratio of ketone products was shifted away from the desired alkylation product.

While alteration of the steric bulk of the leaving group did not have a favorable effect on the extent of ketone alkylation, it is possible that changes in the electronic nature of the group (i.e., leaving groups other than esters) might have a more desired effect. Two points should be raised in this regard: the derivative should be relatively easy to prepare from the carbonyl compound, since the desired net effect is a nucleophilic α-alkylation of a ketone, and, secondly, the epoxide derivative must be stable. We were fortunate in that the ester epoxides are relatively stable compared to other functionalized epoxides. For example, chloro olefins can be epoxidized using peracids, but the intermediate chloro epoxides are frequently unstable and undergo a facile rearrangement to the corresponding α-chloro ketones.[25] Although some enol ethers can be epoxidized without rearrangement, others, including the silyl ether that we investigated, undergo further reaction rapidly.[26]

While the reaction of an organocuprate with an acyloxy-epoxide produces substituted ketone in which the substituent group is derived from a nucleophile, the relatively modest yields and the concomitant production of the unsubstituted ketone mar this approach to nucleophilic ketone alkylation. We are currently in the process of examining other systems that may enable this process to be carried out more efficiently.

Experimental Section

Melting points were determined on a Fisher-Johns hot-stage apparatus and are corrected. ^{1}H NMR spectra were recorded on Varian T-60 or A-60 spectrometers; chemical shifts are reported in ppm downfield from a tetramethylsilane internal standard (δ scale). Infrared spectra were recorded on a Perkin-Elmer Model 137 spectrometer. Mass spectra were obtained from either a Varian MAT CH-5 or SM-112 spectrometer and were at 70 eV, unless otherwise noted. Elemental analyses were provided by the microanalytical service lab of the University of Illinois.

Analytical gas-chromatographic work utilized a Hewlett-Packard 5750 instrument equipped with flame-ionization detectors. Columns used were either a 10 ft × 0.125 in. SE-30, 5% on Gas-Chrom Q, 80/100; or a 5 ft × 0.125 in. OV-17, 3% on Supelcoport, 100/120. Preparative gas chromatography was performed using a Varian 90-P instrument with a 10 ft × 0.375 in. SE-30, 5% on Chromosorb W, 60/80 column.

Glassware for reactions involving organometallic reagents was dried for a minimum of 2 h at 120 °C, and such reactions were run under a N_2 atmosphere. THF and DME were dried by distillation from sodium naphthalide; anhydrous diethyl ether (Mallinckrodt) was used as received. All other reagents were used as commercially available unless otherwise noted. The organolithium reagents (ventron) were titrated before use, utilizing either the double-titration method[27] or the single-titration method using 1,10-phenanthroline as an indicator.[28]

The phenyllithium,[29] the silyl enol ethers **13** and **20**,[30] *n*-butylethynylcopper,[17] and the cuprous bromide–dimethyl sulfide complex[18] were all prepared by literature methods.

Cyclohexanone Enol Acetate. Cyclohexanone, 24.5 g (0.25 mol), was mixed with 50 mL of benzene and 60 mL (0.55 mol) of isopropenyl acetate, followed by 2.0 g of *p*-toluenesulfonic acid as a catalyst. The mixture was heated on an oil bath so as to maintain a slow distillation of acetone through a 12-in. glass-helices column. When GLPC analysis showed the reaction to be complete (ca. 6 h), the reaction mixture was diluted with ether, washed several times with saturated $NaHCO_3$, and

dried over $MgSO_4$. Distillation afforded 21.1 g (60%) of a colorless liquid: bp 87–90 °C at 28 mm Hg, lit.[31a] 180–182 °C at 760 mmHg; ^1H NMR (CCl_4) δ 5.20 (m, 1 H), 2.00 (s, 3 H), 1.95–2.25 (m, 4 H), 1.50–1.80 (m, 4 H).

5-Nonanone Enol Acetate (1). The above procedure was followed using 21.3 g (0.15 mol) of 5-nonanone, 50 mL (0.45 mol) of isopropenyl acetate, and 25 mL of benzene. An additional 25 mL of isopropenyl acetate was added later when GLC analysis showed the reaction to be incomplete. Work-up as before afforded 24.7 g (90%) of a colorless liquid; bp 41–42 °C at 2.0 mmHg; ^1H NMR (CCl_4) δ 4.98, 4.87 (t, J = 7 Hz, 1 H, cis and trans isomers), 2.05, 2.00 (s, 3 H, cis and trans isomers), 1.60–2.30 (m, 4 H), 1.10–1.60 (m, 6 H), 0.75–1.10 (m, 6 H).

Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.70; H, 10.94. Found: C, 71.71; H, 10.85.

Cyclopentanone Enol Acetate. The above procedure was followed using 21.0 g (0.25 mol) of cyclopentanone, 60 mL (0.55 mol) of isopropenyl acetate, and 0.6 g of p-toluenesulfonic acid. No benzene was used as a cosolvent. Work-up as before gave 19.8 g (63%) of a colorless liquid; bp 153–156 °C, lit.[31b] 156–158 °C; ^1H NMR (CCl_4) δ 5.20–5.35 (m, 1 H), 2.15–2.60 (m, 4 H), 2.05 (s, 3 H), 1.60–2.15 (m, 2 H).

1-Acetoxycyclohexane 1,2-Oxide (9). A mixture of cyclohexanone enol acetate, 5.6 g (40 mmol), in 75 mL of CH_2Cl_2 was cooled on an ice bath. m-Chloroperbenzoic acid, 9.70 g (48 mmol at 85% purity), was dissolved in 200 mL of CH_2Cl_2 and added to the above solution over a 2-h period. The mixture was stirred for 2–6 h at 0 °C and then gradually allowed to warm to room temperature while following the reaction progress by GLC. Care should be taken to avoid excessive reaction times at the higher temperatures. When the starting material was consumed, the excess peracid was removed by washing with saturated Na_2SO_3. Extracts were washed with saturated $NaHCO_3$ and dried over $MgSO_4$. The solvent was removed under reduced pressure to give 5.97 g (96%) of a colorless liquid. The purity of the product was usually high, and further purification was generally avoided due to the lability of the compound. The neat liquid was stored at −20 °C at all times. ^1H NMR (CCl_4) δ 3.08 (t, J = 2 Hz, 1 H), 1.70–2.25 (m, 4 H), 1.97 (s, 3 H), 1.25–1.70 (m, 4 H).

Anal. Calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.74. Found: C, 61.54; H, 7.90.

5-Acetoxynonane 4,5-Oxide (2). The above procedure was followed using 9.2 g (50 mmol) of 5-nonanone enol acetate (1) in 50 mL of CH_2Cl_2 and 12.2 g (60 mmol at 85% purity) of m-chloroperbenzoic acid in 200 mL of CH_2Cl_2. Work-up as before yielded 9.65 g (97%) of a colorless liquid purified by silica gel chromatography (5% ether/hexane). ^1H NMR (CCl_4) δ 2.65–2.90 (m, 1 H), 2.00 (s, 3 H), 1.15–1.70 (m, 10 H), 0.70–1.15 (m, 6 H).

Anal. Calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07. Found: C, 66.09; H, 10.22.

1-Acetoxycyclopentane 1,2-Oxide. The above procedure was followed using 9.45 g (75 mmol) of cyclopentanone enol acetate and 15.3 g (115 mmol at 85% purity) of m-chloroperbenzoic acid. Work-up as before afforded a colorless liquid which could be distilled (without apparent rearrangement) to give 8.95 g (84%) of the product; bp 39–42 °C at 0.7 mm Hg; ^1H NMR (CCl_4) δ 3.46 (broad s, 1 H), 2.01 (s, 3 H), 1.35–2.40 (m, 6 H).

Anal. Calcd for $C_7H_{10}O_3$: C, 59.14; H, 7.09. Found: C, 59.03; H, 6.89.

Reactions with 5-Acetoxynonane 4,5-Oxide (2). (A) Lithium Dimethylcuprate. Cuprous iodide, 7.62 g (40.0 mmol), was slurried with 50 mL of anhydrous ether and cooled to −20 °C. Methyllithium, 48.5 mL of a 1.65 M solution in ether (80.0 mmol), was added to give a nearly colorless solution. Further cooling to −78 °C was followed by the addition of 4.0 g (20.0 mmol) of 2 in 15 mL of ether over a 10-min period. The yellow solution was stirred for 2.5 h at −78 °C and then gradually warmed to 0 °C for an additional 1 h. The mixture was quenched with 5 mL of saturated NH_4Cl, filtered, and dried over $MgSO_4$. GLC analysis showed only two major components. Silica gel chromatography (solvent gradient 3–80% ether/hexane) gave the pure compounds along with some mixed fractions. Small amounts of polar products were also isolated but not characterized.

(1) 5-Nonanone (4): 0.91 g (32%); ^1H NMR (CCl_4) δ 2.15–2.50 (broad t, J = 6.5 Hz, 4 H), 1.05–1.80 (m, 8 H), 0.70–1.05 (m, 6 H); 2,4-DNP derivative mp 39–39.5 °C, lit. 41 °C;[32] mass spectrum (2,4-DNP) m/e (rel intensity) 322 (M^+, 49).

(2) 4-Methyl-5-nonanone (3): 1.35 g (43%); ^1H NMR (CCl_4) δ 2.20–2.65 (m, 3 H), 1.02 (d, J = 7 Hz, 3 H), 0.70–1.80 (m, 14 H); mass spectrum m/e (rel intensity) 156 (M^+, 5), 114 (29), 99 (12), 85 (95), 72 (45), 71 (69), 57 (100). n^{20}_D 1.4219.

Anal. Calcd for $C_{10}H_{20}O$: C, 76.86; H, 12.90. Found: C, 76.88; H, 12.73.

(B) Lithium Di-n-butylcuprate. Cuprous iodide, 7.62 g (40 mmol), was slurried with 60 mL of anhydrous ether and cooled to −45 °C. n-Butyllithium, 39.0 mL of a 2.05 M solution in hexane (80 mmol), was added to give a dark solution. Cooling to −78 °C was followed by the addition of 4.0 g (20 mmol) of 2 in 10 mL of ether over a 10-min period. After stirring for an additional 3 h at −78 °C, the mixture was quenched with 5 mL of saturated NH_4Cl, filtered, and dried over $MgSO_4$. GLC analysis showed four major components which were separated by silica gel chromatography using an ether/hexane solvent gradient (5–80%).

(1) 5-Nonanone (4): 0.96 g (34%); ^1H NMR (CCl_4) δ 2.15–2.50 (broad t, J = 6.5 Hz, 4 H), 1.05–1.80 (m, 8 H), 0.70–1.05 (m, 6 H); mass spectrum m/e (rel intensity) 142 (M^+, 13), 85 (88), 58 (70), 57 (100).

Anal. Calcd for $C_9H_{18}O$: C, 76.00; H, 12.76. Found: 76.06; H, 12.72.

(2) 5-Methyl-5-nonanol (6): 0.96 g (30%); ^1H NMR (CCl_4) δ 2.02 (s, 1 H, exchangeable with D_2O), 1.15–1.60 (m, 12 H), 1.08 (s, 3 H), 0.70–1.15 (m, 6 H). An authentic sample was prepared by reaction of 5-nonanone with methyllithium. This product showed identical GLC retention time and mass spectrum with the isolated reaction product. Mass spectrum m/e (rel intensity) 143 (10), 101 (10), 83 (17), 57 (17). n^{20}_D 1.4314.

(3) 4-Butyl-5-nonanone (5): 0.53 g (13%); ^1H NMR (CCl_4) δ 2.10–2.50 (m, 3 H), 1.05–1.80 (m, 14 H), 0.70–1.05 (m, 9 H); mass spectrum m/e (rel intensity) 198 (M^+, 1), 142 (20), 141 (4), 113 (22), 100 (27), 85 (59), 57 (100); n^{20}_D 1.4320.

Anal. Calcd for $C_{13}H_{26}O$: C, 78.72; H, 13.21. Found: C, 78.60; H, 13.12.

(4) 5-Butyl-4,5-nonanediol (7): 1.14 g (26%); mp 74–75 °C; ^1H NMR (CCl_4) δ 3.20–3.50 (m, 1 H), 2.21 (s, 2 H, exchangeable with D_2O), 1.10–1.70 (m, 16 H), 0.70–1.10 (m, 9 H); IR (Nujol) 3380, 1470, 1380 cm^{-1}; mass spectrum (10 eV) m/e (rel intensity) 199 (0.2), 159 (19), 144 (10), 143 (100), 85 (8).

Anal. Calcd for $C_{13}H_{28}O_2$: C, 72.17; H, 13.04. Found: C, 72.08; H, 13.11.

A later run, using the above procedure but with care to avoid any excess of n-butyllithium, gave GLC yields of 56 and 28% for 4 and 5, respectively, with only very small amounts of 6 and 7.

(C) Lithium Diphenylcuprate. Cuprous iodide, 0.95 g (5 mmol), was slurried with 25 mL of anhydrous ether and cooled to −45 °C. Phenyllithium, 8.85 mL of a 0.96 M solution in ether (8.5 mmol), was then added to give a dark solution. Further cooling to −78 °C was followed by a rapid addition of 0.5 g (2.5 mmol) of 2 in 5 mL of ether. The mixture was stirred at −78 °C for 4 h and an additional 18 h at −25 °C. Following addition of 2 mL of saturated NH_4Cl, the product was filtered and dried over $MgSO_4$. GLC analysis revealed a complex mixture of products and only the ketone components were isolated using silica gel chromatography (3% ether/hexane).

(1) 4-Phenyl-5-nonanone (8): 0.14 g (26%); ^1H NMR (CCl_4) δ 7.21 (s, 5 H), 3.56 (t, J = 7 Hz, 1 H), 2.28 (t, J = 6.5 Hz, 2 H), 0.60–2.10 (m, 14 H); IR (neat) 1720, 755, 700 cm^{-1}; mass spectrum m/e (rel intensity) 218 (M^+, 2), 176 (13), 133 (16), 91 (100), 85 (83), 57 (53); n^{20}_D 1.4738.

Anal. Calcd for $C_{15}H_{22}O$: C, 82.52; H, 10.16. Found: C, 82.53; H, 10.09.

(2) 5-Nonanone (4): 0.06 g (17%); product was identical in all respects to previously isolated samples.

Oxidative Cleavage of 7. To verify the structure of diol 7, a periodate oxidation was performed. The diol, 0.11 g (0.5 mmol), was dissolved in 10 mL of ether, and the mixture was added slowly to a solution of 0.14 g (0.6 mmol) of H_5IO_6 in 40 mL of ether. The mixture was stirred for 2 h at 0 °C, during which time a white precipitate of HIO_3 formed. The mixture was then neutralized with saturated $NaHCO_3$ and the organic layer was separated and dried over $MgSO_4$. The product was diluted with 10 mL of absolute ethanol and the two carbonyl fragments were separated by distillation (the lighter one distilling with the ethanol) and derivatized.

(1) 5-Nonanone: 2,4-DNP mp 41–42 °C, lit.[32] 41 °C; mass spectrum (2,4-DNP) m/e (rel intensity) 322 (M^+, 36).

(2) Butanal: 2,4-DNP mp 122–123 °C, lit.[33] 123 °C; mass spectrum (2,4-DNP) m/e (rel intensity) 252 (M^+, 100).

Reaction with 1-Acetoxycyclohexane 1,2-Oxide (9). (A) Lithium Dimethylcuprate. Cuprous iodide, 3.81 g (20 mmol), was slurried with 25 mL of anhydrous ether and cooled to −10 °C. Methyllithium, 24.2 mL of a 1.65 M solution in ether (40 mmol), was added to give a colorless solution. Further cooling to −78 °C was followed by the addition of 1.56 g (10 mmol) of 9 in 10 mL of ether. The mixture was stirred for 3 h at −78 °C and then gradually warmed to 0 °C. After quenching with 5 mL of saturated NH_4Cl, the product was filtered and dried over $MgSO_4$. GLC analysis showed only two major

products. These ketone components were separated from the polar residues by silica gel chromatography (3–10% ether/hexane solvent gradient). Since the chromatography failed to give a clean separation of the two ketones, the yields were determined by GLC, and pure samples for derivative preparation were obtained by preparative GLC.

(1) Cyclohexanone (**11**): 0.36 g (37%); 2,4-DNP mp 158–161 °C, lit.[33] 162 °C; mass spectrum (2,4-DNP) *m/e* (rel intensity) 278 (M^+, 92).

(2) 2-Methylcyclohexanone (**10**): 0.21 g (19%); 2,4-DNP mp 137–138 °C, lit.[33] 137 °C; mass spectrum (2,4-DNP) *m/e* (rel intensity) 292 (M^+, 78).

(B) Lithium Di-*n*-butylcuprate. Cuprous iodide, 11.43 g (60 mmol), was slurried with 50 mL of anhydrous ether and cooled to −45 °C. *n*-Butyllithium, 50.0 mL of a 2.40 M solution in hexane (120 mmol), was added to give a dark solution. Further cooling to −78 °C was followed by the addition of 4.68 g (30 mmol) of **9** in 20 mL of ether. The mixture was stirred for 3.5 h at −78 °C and then quenched with 5 mL of saturated NH_4Cl. Separation of the products was achieved by silica gel chromatography (3–80% ether/hexane solvent gradient). Some difficulty was encountered in separating **6** and **11** cleanly, so their yield was determined by GLC.

(1) Cyclohexanone (**11**): 0.84 g (29%); 2,4-DNP mp 158–161 °C, lit.[33] 162 °C; mass spectrum (2,4-DNP) *m/e* (rel intensity) 278 (M^+, 58).

(2) 5-Methyl-5-nonanol (**6**): 1.35 g (29%); identified by coinjection with an authentic sample on GLC.

(3) 2-Butylcyclohexanone (**12**): 0.09 g (2%); 2,4-DNP mp 107–109 °C, lit.[34] 109–110 °C; semicarbazone mp 146–148 °C, lit.[35] 150 °C; mass spectrum (2,4-DNP) *m/e* (rel intensity) 334 (M^+, 24).

A substantial amount of polar material remained (1.55 g) but no attempt was made to characterize each component present.

α-Mercuricyclohexanone Derivatives 14 and 15. Using the procedure described by House,[19] 7.58 g (35 mmol) of HgO and 0.27 g (0.84 mmol) of $Hg(OAc)_2$ were slurried with 1.5 mL of water and 5.5 mL of ethanol. Compound **13**, 11.91 g (70 mmol), was added over a 10-min period with evolution of heat and disappearance of the red coloration. An additional 25 mL of ethanol was added to keep the solution fluid during the addition. After stirring for 1 h at 25 °C, the mixture was diluted with 150 mL of warm $CHCl_3$, dried over $MgSO_4$, and filtered while still warm. The chloroform was reduced to ca. 30 mL and dilution with hexane gave 11.67 g (85%) of white crystals of **14**, collected by suction filtration.

Without further purification, 11.06 g (28 mmol) of **14** was added to a solution of 12.74 g (28 mmol) of HgI_2 in 100 mL of THF to produce a cloudy white solution. After stirring for 1 h, the mixture was diluted with 50 mL of hexane and 50 mL of $CHCl_3$. Cooling on ice afforded white crystals, which were filtered and recrystallized from $CHCl_3$/hexane to give 17.5 g (75%) of **15**, mp 117–119 °C, lit.[19] 115–117 °C.

Bisketomercurial Derivative 21. The procedure for the preparation of **14** was followed using 14.99 g (70 mmol) of **20**. Work-up followed by recrystallization from hexane gave 11.17 g (67%) of **21**, mp 151–152 °C. ^1H NMR ($CDCl_3$) δ 3.01 (t, J = 7 Hz, 2 H), 1.85–2.50 (m, 4 H), 0.70–1.85 (m, 28 H).

Anal. Calcd for $C_{18}H_{34}O_2Hg$: C, 44.75; H, 7.09. Found: C, 44.43; H, 6.98.

Cyclohexanone Enol Pivalate (16). Compound **15**, 8.31 g (20 mmol), was suspended in 30 mL of DME, followed by the addition at 25 °C of 4.82 g (40 mmol) of pivaloyl chloride in 12 mL of DME. The solution became homogeneous within 5–10 min and was stirred for an additional 2 h. Saturated $NaHCO_3$ (5 mL) was added and the DME was removed under reduced pressure. The product was extracted with ether and washed several times with $NaHCO_3$ to remove the excess acid chloride. After drying briefly over $MgSO_4$, silica gel chromatography (5% ether/hexane) gave 2.65 g (73%) of a colorless liquid. ^1H NMR (CCl_4) δ 5.05–5.20 (m, 1 H), 1.85–2.20 (m, 4 H), 1.50–1.80 (m, 4 H), 1.17 (s, 9 H); mass spectrum *m/e* (rel intensity) 182 (M^+, 7), 98 (72), 97 (13), 85 (18), 83 (17), 70 (25), 57 (100); n^{20}_D 1.4517.

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.69; H, 9.90.

Cyclohexanone Enol Benzoate (17). Compound **15**, 6.63 g (16 mmol), was slurried with 30 mL of DME, followed by the addition at 25 °C of 4.50 g (32 mmol) of benzoyl chloride in 15 mL of DME. The solution became homogeneous within 30 min and was stirred an additional 4 h. Work-up as above followed by silica gel chromatography (15% ether/hexane) gave 2.03 g (63%) of a colorless liquid. ^1H NMR (CCl_4) δ 7.75–8.05 (m, 2 H), 7.10–7.45 (m, 3 H), 5.25–5.45 (m, 1 H), 1.95–2.40 (m, 4 H), 1.50–1.95 (m, 4 H); mass spectrum *m/e* (rel intensity) 202 (M^+, 4), 105 (100), 77 (38); n^{20}_D 1.5403.

Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 76.94; H, 6.93.

5-Nonanone Enol Pivalate (22). Compound **21**, 4.83 g (10 mmol), was slurried with 30 mL of DME, followed by the addition at 25 °C of pivaloyl chloride, 4.82 g (40 mmol), in 15 mL of DME. The solution was homogeneous after 15 min and was stirred for an additional 2 h. Work-up as above followed by silica gel chromatography (4% ether/hexane) gave 1.78 g (39%) of a colorless liquid. ^1H NMR (CCl_4) δ 4.86, 4.80 (t, J = 7 Hz, 1 H, cis and trans isomers), 1.10–2.30 (m, 10 H), 1.22 and 1.18 (s, 9 H, cis and trans isomers), 0.70–1.10 (m, 6 H); mass spectrum *m/e* (rel intensity) 226 (M^+, 3), 142 (8), 113 (18), 101 (1), 100 (18), 85 (21), 57 (100); n^{20}_D 1.4330.

Anal. Calcd for $C_{14}H_{26}O_2$: C, 74.29; H, 11.58. Found: C, 74.58; H, 11.36.

5-Nonanone Enol Benzoate (23). Compound **21**, 4.83 g (10 mmol), was slurried with 30 mL of DME, followed by the addition at 25 °C of 5.62 g (40 mmol) of benzoyl chloride in 15 mL of DME. When the reaction failed to become homogeneous within 0.5 h, the mixture was warmed to 50 °C and stirred at that temperature for 16 h. Work-up as above followed by silica gel chromatography (10% ether/hexane) afforded 3.05 g (62%) of a colorless liquid. ^1H NMR (CCl_4) δ 7.75–8.05 (m, 2 H), 7.10–7.45 (m, 3 H), 5.08, 4.90 (t, J = 7 Hz, 1 H, cis and trans isomers), 1.65–2.45 (m, 4 H), 1.10–1.65 (m, 6 H), 0.70–1.10 (m, 6 H); mass spectrum *m/e* (rel intensity) 246 (M^+, 5), 105 (100), 77 (24); n^{20}_D 1.4980.

Anal. Calcd for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 78.01; H, 9.12.

Epoxidation of the Enol Pivalate and Benzoate Derivatives. (A) 1-Pivaloyloxycyclohexane 1,2-Oxide (18). The *m*-chloroperbenzoic acid, 1.22 g (6.0 mmol at 85% purity), was dissolved in 25 mL of CH_2Cl_2 and then added slowly (1 h) at 0 °C to a solution of 0.91 g (5 mmol) of **16** in 25 mL of CH_2Cl_2. The solution was stirred for 6 h at 0 °C and then stored overnight at −20 °C. If necessary to complete the reaction, the mixture can be warmed to room temperature and monitored by GLC, taking care to avoid excessive time at the higher temperatures. The product was washed with 2 × 25 mL of saturated Na_2SO_3, and with 3 × 25 mL of saturated $NaHCO_3$. After drying over $MgSO_4$, the solvent was stripped at low temperature, <25 °C, and the last traces were removed under vacuum, <1 mm Hg. A colorless liquid (0.85 g; 86%) was isolated and used without further purification. ^1H NMR (CCl_4) δ 3.02 (t, J = 2 Hz, 1 H), 1.70–2.20 (m, 4 H), 1.20–1.60 (m, 4 H), 1.15 (s, 9 H); mass spectrum *m/e* (rel intensity) 198 (M^+, 6), 114 (7), 113 (29), 85 (31), 57 (100).

Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.89; H, 8.92.

(B) 1-Benzoyloxycyclohexane 1,2-Oxide (19). The above procedure was followed using 1.01 g (5 mmol) of **17**. Product (1.06 g; 97%) was isolated and purified by silica gel chromatography (10% ether/hexane). ^1H NMR (CCl_4) δ 7.90–8.20 (m, 2 H), 7.25–7.65 (m, 3 H), 3.26 (t, J = 2 Hz, 1 H), 1.80–2.40 (m, 4 H), 1.25–1.80 (m, 4 H); mass spectrum (10 eV) *m/e* (rel intensity) 218 (M^+, 2), 113 (17), 105 (100), 97 (1), 96 (4), 77 (1).

Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.62; H, 6.46.

(C) 5-Pivaloyloxynonane 4,5-Oxide (24). The above procedure was followed using 1.13 g (5 mmol) of **22**. A colorless liquid (1.15 g; 95%) was isolated and used without further purification. ^1H NMR (CCl_4) δ 2.73 (t, J = 6 Hz, 1 H), 0.70–2.20 (m, 16 H), 1.15 and 1.17 (s, 9 H, derived from cis and trans enol pivalates); mass spectrum (10 eV) *m/e* (rel intensity) 242 (M^+, 0.4), 226 (3), 170 (2), 157 (2), 142 (4), 141 (3), 85 (100), 57 (56).

Anal. Calcd for $C_{14}H_{26}O_3$: C, 69.38; H, 10.81. Found: C, 69.51; H, 10.61.

(D) 5-Benzoyloxynonane 4,5-Oxide (25). The above procedure was followed using 1.23 g (5 mmol) of **23**. A colorless liquid (1.27 g; 97%) was isolated and purified by silica gel chromatography (3% ether/hexane). ^1H NMR (CCl_4) δ 7.90–8.20 (m, 2 H), 7.25–7.65 (m, 3 H), 2.85–3.15 (m, 1 H), 1.20–2.40 (m, 10 H), 0.70–1.20 (m, 6 H); mass spectrum *m/e* (rel intensity) 105 (100), 85 (37), 77 (20), 57 (28).

Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.37; H, 8.51.

Compound **18** showed a substantial amount of rearrangement after 11 days at room temperature, whereas **19** and **25** showed no evidence (^1H NMR) of such a reaction after 14 days. As a precaution, however, the epoxides were stored at −20 °C.

Reactions of Enol Pivalate and Benzoate Epoxides. (A) With Lithium Dimethylcuprate. Cuprous iodide, 0.38 g (2 mmol), was suspended in 20 mL of ether and cooled to −20 °C. Methyllithium was then added until the yellow precipitate initially formed disappeared to give a colorless and homogeneous solution. Following further cooling to −78 °C, 1 mmol of the appropriate epoxide (0.20 g of **18**, 0.22 g of **19**, 0.24 g of **24**, and 0.26 g of **25**) in 5 mL of ether was added. After stirring the resulting yellow solution for 3 h at −78 °C, it was

then quenched with 1–2 mL of saturated NH_4Cl. The product was filtered and dried over $MgSO_4$. The ratio of alkylated to nonalkylated ketone was then determined by GLC analysis and the results are summarized in Table III.

(B) With Lithium Di-*n*-butylcuprate. Cuprous iodide, 0.38 g (2 mmol), was suspended in 20 mL of ether and cooled to −45 °C. *n*-Butyllithium, 1.69 mL of a 2.13 M solution in hexane (3.6 mmol to avoid any excess of alkyllithium), was then added to give a dark solution. After further cooling to −78 °C, 1 mmol of the appropriate epoxide (0.20 g of **18**, 0.24 g of **24**, and 0.26 g of **25**) in 5 mL of ether was added. After stirring the dark solution for 3 h at −78 °C, it was quenched with 1–2 mL of saturated NH_4Cl, filtered, and dried over $MgSO_4$. The ratio of alkylated to nonalkylated ketone was determined by GLC analysis and the results are summarized in Table III.

Reaction of 2 with the Mixed Alkynyl Cuprate. The *n*-butylethynylcopper, 0.72 g (5 mmol), was suspended in 20 mL of anhydrous ether and cooled to −50 °C. *n*-Butyllithium, 2.30 mL of a 2.13 M solution in hexane (4.9 mmol), was added with no apparent change in color or solubility of the yellow suspension. After stirring for an additional 30 min, the mixture was cooled to −78 °C and 0.5 g (2.5 mmol) of **2** in 5 mL of ether was added. After 2.5 h at −78 °C, the dark-green solution was quenched with saturated NH_4Cl, filtered, extracted, and dried over $MgSO_4$. Although the reaction was only ca. 60% complete, it was possible to determine by GLC the amount of alkylation product relative to the total ketone content, and it was not found to be significantly different from the di-*n*-butylcuprate reaction (30 and 28%, respectively).

Lithium Phenylthio(*n*-butyl)cuprate. Preparation and Reaction with 2. Following a previously described procedure,[15] thiophenol, 0.41 g (3.75 mmol), was added to 15 mL of anhydrous ether and cooled to 0 °C. *n*-Butyllithium, 2.26 mL of a 1.66 M solution in hexane (3.75 mmol), was added to generate the thiophenoxide anion. Cuprous iodide, 0.71 g (3.75 mmol), was slurried with 10 mL of ether, and the above solution was added at 25 °C to give a dark solution. After cooling to −78 °C, 2.26 mL of 1.66 M *n*-butyllithium (3.75 mmol) was added, followed by 0.5 g (2.5 mmol) of **2** in 5 mL of ether. After stirring for 1 h at −78 °C, the mixture was allowed to warm slowly to 0 °C. The reaction was quenched with saturated NH_4Cl after 3-h total time, and was washed with 2 × 30 mL of 3 N NaOH to remove the thiophenol. The extracts were dried over $MgSO_4$. The amount of alkylated product relative to total ketone was determined by GLC and was not found to be significantly different from the di-*n*-butylcuprate reaction (30 and 28%, respectively).

Reaction of 2 and 9 with Cuprous Bromide–Dimethyl Sulfide Derived Cuprates. (A) Lithium Dimethylcuprate. The cuprous bromide–dimethyl sulfide complex, 1.03 g (5 mmol), was dissolved in 10 mL of Me_2S and 10 mL of anhydrous ether. After cooling to 0 °C, methyllithium was added until the initially formed yellow precipitate just disappeared. The mixture was cooled to −78 °C and 2.5 mmol of the appropriate epoxide (0.39 g of **9** and 0.5 g of **2**) in 5 mL of ether was added rapidly. The resulting yellow solution was stirred for 3 h at −78 °C and then quenched with 1–2 mL of saturated NH_4Cl. The product was filtered, washed with dilute NH_4OH to remove the Cu complex, and dried over $MgSO_4$. Although the reactions were not complete under these conditions, it was possible to get the alkylated to nonalkylated ketone ratios by GLC and the results are summarized in Table II. Reactions can be forced to completion by a gradual warming to 0 °C.

(B) Lithium Di-*n*-butylcuprate. The cuprous bromide–dimethyl sulfide complex, 1.03 g (5 mmol), was dissolved in 10 mL of Me_2S and 10 mL of anhydrous ether. After cooling to −45 °C, 4.17 mL of 2.28 M *n*-butyllithium (9.5 mmol) was added to give a dark solution. The mixture was cooled further to −78 °C and 2.5 mmol of the appropriate epoxide (0.39 g of **9** and 0.5 g of **2**) in 5 mL of ether was added rapidly. After stirring for 4 h at −78 °C, the reactions were worked up as described above. The product ratios are indicated in Table II.

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Registry No.—*cis*-**1**, 62183-26-0; *trans*-**1**, 62183-39-5; *trans*-**2**, 62183-27-1; *cis*-**2**, 62183-40-8; **3**, 35900-26-6; **4**, 502-56-7; **4**, DNP, 3657-08-7; **5**, 40239-44-9; **6**, 33933-78-7; **7**, 62183-28-2; **8**, 41718-52-9; **9**, 14161-46-7; **10** DNP, 5138-30-7; **11**, 108-94-1; **11** DNP, 1589-62-4; **12** DNP, 1166-09-2; **15**, 37160-47-7; **16**, 62183-29-3; **17**, 13163-64-9; **18**, 62183-30-6; **19**, 62183-31-7; **20**, 62183-32-8; **21**, 62183-33-9; **22**, 62183-34-0; **23**, 62183-35-1; **24**, 62183-36-2; **25**, 62183-37-3; isopropenyl acetate, 108-22-5; cyclohexanone enol acetate, 1424-22-2; cyclopentanone enol acetate, 933-06-2; cyclopentanone, 120-92-3; 1-acetoxycyclopentane 1,2-oxide, 62183-38-4; butanal 2,4-DNP, 1527-98-6; pivaloyl chloride, 3282-30-2; benzoyl chloride, 98-88-4.

References and Notes

(1) Presented in part at the 170th National Meeting (Chicago, Ill., Aug 1975) and the 11th Midwest Regional Meeting (Carbondale, Ill., Oct 1975) of the American Chemical Society.
(2) For a discussion of these terms, see, respectively, D. Seebach and M. Kolb, *Chem. Ind. (London)*, 687 (1974); D. A. Evans and G. C. Andrews, *Acc. Chem. Res.*, **7**, 147 (1974).
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2-Methoxyallyl Bromide. A Superior Acetonyl Alkylating Agent

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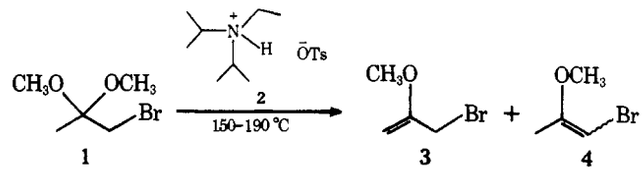
Heating 1-bromo-2,2-dimethoxypropane (1) in the presence of a catalytic amount of diisopropylethylammonium *p*-toluenesulfonate (2) gives 3-bromo-2-methoxy-1-propene (3) in greatly improved yield. Bromide 3 is a good alkylating agent monoalkylating acids, nitriles, esters, ketones, dialkylamides, enamines, and imines in yields of 44–96%. Alkylation of the lithium salt of imines with 3 followed by hydrolysis leads to α-acetonyl ketones which can be cyclized to 3,4-disubstituted cyclopentenones.

In our attempts to extend the Robinson annelation[1] to the formation of cyclopentenones via a three-carbon annelating agent, we desired an effective method of adding an acetonyl side chain to the α carbon of ketones or their equivalents. Several possible reagents for addition of this side chain have been described previously; however, each has problems in its use. The direct alkylation with haloacetones is useful only with the most acidic carbons due to the predominance of side reactions.[2,3] Alkylations with 2,3-dichloro-1-propene have been successful, but difficulties occur in that the vigorous conditions necessary for the unmasking of the vinyl chloride usually lead to the isolation of furans.[4] Lansbury has developed a nongeneral method of electrophilic cyclization to cyclopent*an*ones from these alkylated intermediates, requiring solvolytic conditions.[5] Alkylations with propargyl bromide are troubled by allene formation.[6] Better results have been obtained with the use of the protected 3-bromo-1-trimethylsilyl-1-propyne,[6] but, again, rather stringent conditions are required for conversion of the silylated alkyne to the acetonyl group. The use of methallyl halides as alkylating agents has also been described, but conditions for the subsequent conversion to the acetonyl side chain, ozonolysis or treatment with osmium tetroxide/periodate, are undesirable in many cases.[7] Yoshikoshi and co-workers have recently described the successful addition of an acetonyl side chain synthon to trimethylsilyl enol ethers via a $SnCl_4$-catalyzed Michael addition to 2-nitropropene.[8] Jung has reported the use of 2-trimethylsilyl-3-iodo-1-propene as an acetonyl synthon but unmasking of the ketone requires epoxidation followed by strong acid again limiting the applicability of the reagent.[9] Ketals such as 1-bromo-2,2-dimethoxypropane (1) are, of course, extremely poor alkylating agents.

Results and Discussion

Our solution to the problem of alkylating with a masked acetonyl side chain was found in the use of 2-methoxyallyl bromide (3). The 2-methoxyallyl halides have been synthesized by three groups.[10–12] The alkylation chemistry of 2-methoxyallyl bromide and the analogous 2-tetrahydropyranyloxyallyl bromide have been briefly studied by Bruce and Ban[10] and by Horning et al.[11] We felt that a further investigation of their alkylation chemistry was in order.

Access to the 2-methoxyallyl halides previously has been obtained by the reaction of *N*-halosuccinimides with 2-methoxypropene, or by the pyrolysis of 1-halo-2,2-dimethoxypropanes.[10,12] The former method resulted in a carbon tetrachloride solution of the 2-methoxyallyl halide contaminated with products resulting from the addition of succinimide to the enol ether double bond. The latter method resulted in only 10–20% conversion to the desired 2-methoxyallyl halide. We have found that pyrolytic cracking of 1-bromo-2,2-dimethoxypropane[12] (1) in the presence of diisopropylethylammonium tosylate (2) leads to a mixture, **5**, of 2-methoxyallyl bromide (3), 1-bromo-2-methoxy-1-propene (4), and starting material 1 (in an average ratio of 65:21:14).[13] Attempts to separate this mixture by distillation, even through spinning band columns, failed due to decomposition, but direct use of the product mixture in alkylation reactions was found to be satisfactory. The cracking is best accomplished by heating the 1-bromo-2,2-dimethoxypropane (1) and 0.016 equiv of the ammonium salt 2 to 150–190 °C while distilling off the methanol formed through a 12-in. fractionating column. After all of the methanol has been removed, quick distillation of the remaining liquid through a short-path distillation apparatus yields the product mixture, crude **3 ≡ 5**. Best results are obtained if the cracking time is kept to less than 90 min, i.e., retaining a small amount of starting material, as 2-methoxyallyl bromide (3) will polymerize slowly under these conditions. The product mixture, which contains less than 1% protic impurities, is stable for long periods of time if stored below 0 °C; samples stored at 25 °C darken after a month or so. Mass recoveries via this method are in the range of 85–90%. This procedure works well on a scale of 30 g but scaling up of the reaction size much beyond this point results in a decrease in the yield, probably due to polymerization of the 2-methoxyallyl bromide. This polymerization results from the increased time necessary for conversion to products if the size of the reaction is increased.



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Several tertiary alkylammonium salts were investigated for use as cracking catalysts, including the *p*-toluenesulfonate salts of dicyclohexylethylamine, diisopropylethylamine, benzyldiisopropylamine, tributylamine, and quinaldine.[12] Other acidic catalysts included H_2SO_4, *p*-toluenesulfonic acid,