# Reactions Involving Electron Transfer. 12. Effects of Solvent and Substituents upon the Ability of Lithium Diorganocuprates to Add to Enones[1]

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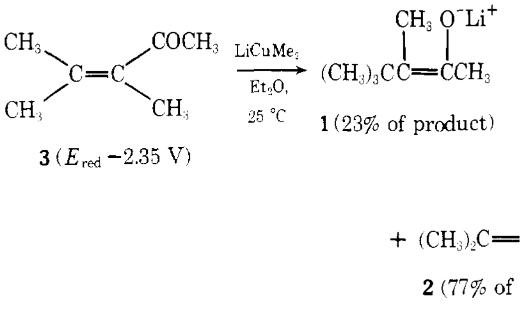
A series of enones, **7**, **8**, and **3**, with progressively more negative reduction potentials has been used to study the effects of solvent (or other donor ligands) and the nature of the substituent R upon the ability of cuprate reagents, $LiCuR_2$, to form conjugate adducts from unsaturated carbonyl compounds. Good donor solvents (THF, DME, DMF) retarded or inhibited conjugate addition; the best yields of conjugate adducts were obtained with mixtures of $Et_2O$–$Me_2S$ or $Et_2O$–pentane as the reaction solvent. The limiting reduction potentials ($E_{red}$) for successful conjugate additions varied with the nature of the cuprate reagent, $LiCuR_2$, in the following way: $E = -2.35$ V, R = *n*-Bu or $CH_2{=}CH-$; $E_{red} = -2.2$ to $-2.3$ V, R = Ph, *sec*-Bu, or Me; $E_{red} = -2.1$ V, R = *t*-Bu; and $E_{red} = -2.0$ to $-2.1$ V, R = $CH_2{=}CHCH_2$. Three side reactions have been observed in reactions of $LiCuR_2$ reagents with enones whose $E_{red}$ values cause conjugate addition to be marginally successful. The most common side reaction was formation of the metal enolate of the starting enone. With *sec*-Bu and *t*-Bu cuprate reagents a second side reaction, resulting from thermal decomposition of the cuprate reagent, produced 1,2 and/or 1,4 reduction products of the starting enone. A third side reaction observed with *t*-Bu and allyl cuprate reagents was the formation of 1,2-addition products. This latter side reaction, also related to decomposition of the cuprate reagents, was significantly enhanced by the use of impure Cu(I) salts to prepare the cuprate reagents. Additional experiments are provided to support the idea that the *soluble* metal enolates from enones and $LiCuMe_2$ are Li enolates and not Cu(I) enolates.

Previous study[2] of the reaction of lithium dimethylcuprate ($LiCuMe_2$)[3] with various $\alpha,\beta$-unsaturated carbonyl compounds in ether solution has demonstrated that the reduction potential ($E_{red}$ vs. SCE in an aprotic solvent) of the unsaturated carbonyl compound should be within the range $-1.3$ to $-2.3$ V in order to obtain the conjugate addition product in good yield. More easily reduced substrates ($E_{red}$ less negative than $-1.3$ V) typically yield reduction products rather than conjugate adducts, while more difficultly reduced substrates ($E_{red}$ more negative than $-2.3$ V) either fail to react or, more commonly, react with $LiCuMe_2$ to form the enolate (e.g., **2**) of the starting material (e.g., **3**). This latter circumstance results in an apparent recovery of "unchanged" starting material after hydrolysis of the reaction mixture. Most unsaturated carbonyl compounds of interest as synthetic intermediates have $E_{red}$ values within the range $-1.8$ to $-2.5$ V.[4] Consequently, it was of interest to extend our study of the upper limit of $E_{red}$ values for successful conjugate addition to include the use of reaction solvents other than $Et_2O$ and the use of cuprates, $LiCuR_2$, where the reagent substituent R is not a methyl group. This paper reports our study of these solvent and substituent effects.

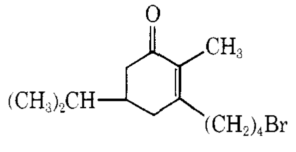


**3** ($E_{red}$ −2.35 V)

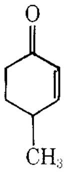
**1** (23% of product)

**2** (77% of product)

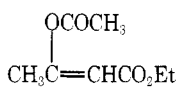
**Choice of Reaction Solvent.** The coupling reaction of $LiCuR_2$ reagents with alkyl halides is accelerated by changing the reaction solvent from $Et_2O$ to a better donor solvent[5] such as THF or an $Et_2O$–HMP [$(Me_2N)_3PO$] mixture,[6] while the mechanistically related coupling of $LiCuR_2$ with alkyl tosylates and epoxides is retarded by the use of THF rather than $Et_2O$.[7] Previous observations relating to the conjugate addition of $LiCuR_2$ reagents to unsaturated carbonyl compounds suggest that the presence of good donor solvents or donor ligands may be deleterious.[8] For example, in the reaction of the enone **4**[8a] (calcd[4] $E_{red} = -2.3$ V) with $LiCuMe_2$ an increasing fraction of the enone was recovered as the solvent was changed from PhH to $Et_2O$ to THF. Similarly, lower yields of conjugate adducts were obtained with THF rather than $Et_2O$ as the solvent for reaction of several enones[8c] (calcd[4] $E_{red} = -2.1$ to $-2.2$ V) with $LiCuMe_2$. The addition of 2–3 molar equiv of the donor ligand, 12-crown-4-polyether, was found[8b] to inhibit the addition of $LiCuMe_2$ to enone **5** (calcd[4] $E_{red} = -2.1$ V) and the addition of $LiCuEt_2$ to ester **6** (calcd[9] $E_{red} = -2.3$ V).



**4**



**5**



$$CH_3\overset{\overset{\displaystyle OCOCH_3}{|}}{C}{=}CHCO_2Et$$

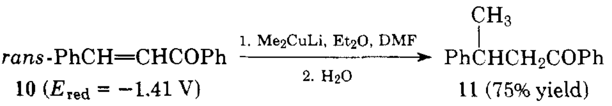
**6**

To examine the effect of solvent on conjugate addition in a more systematic way, the set of enones **7**, **8**, and **3** (Scheme I) with progressively more negative reduction potentials was used. These enones were allowed to react with $LiCuMe_2$ in $Et_2O$ and in mixtures of $Et_2O$ with poorer (pentane, PhH, $CH_2Cl_2$, $Me_2S$) or better (THF, DME) donor solvents. The results, summarized in Table I, demonstrate that for the most difficulty reduced enone **3** there is a clear advantage in using a mixed solvent containing as much pentane as can be added without precipitating the cuprate reagent. Furthermore, there is a clear disadvantage to adding a better donor solvent such as THF or DME. With the more easily reduced enone **8**, use of an $Et_2O$–pentane mixture rather than pure $Et_2O$ as the solvent offered no advantage, but the deleterious effect of

**Scheme I**

$CH_3CH{=}CHCOCH_3$
·**7** ($E_{red}$ = 2.08 V)
$(CH_3)_2C{=}C(CH_3)COCH_3$
**3** ($E_{red} = -2.35$ V)

$(CH_3)_2C{=}CHCOCH_3$
**8** ($E_{red} = -2.21$ V)
$(CH_3)_2C{=}C(CH_3)COCH_2D$
**9**



$$trans\text{-}PhCH{=}CHCOPh \xrightarrow[\text{2. } H_2O]{\text{1. } Me_2CuLi,\ Et_2O,\ DMF} Ph\overset{\overset{\displaystyle CH_3}{|}}{C}HCH_2COPh$$

**10** ($E_{red} = -1.41$ V) **11** (75% yield)

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**Table I. Reaction of $LiCuMe_2$ with the Enones 7, 8, and 3 at 10–30 °C in Various Solvents**

| | Reaction product (% yield) | | |
|---|---|---|---|
| Solvent | *trans*-$CH_3CH{=}CHCOCH_3$ (**7**; $E_{red} = -2.08$ V) | $(CH_3)_2C{=}CHCOCH_3$ (**8**; $E_{red} = -2.21$ V) | $(CH_3)_2C{=}C(CH_3)COCH_3$ (**3**; $E_{red} = -2.35$ V) |
| $Et_2O$–pentane (1:3.4 v/v) | | $(CH_3)_3CCH_2COCH_3$ (**13**; 88%) | $(CH_3)_3CCH(CH_3)COCH_3$ (**12**; 59%) + **3** (26%) |
| $Et_2O$–PhH (1:5 v/v) | | | **12** (37%) + **3** (62%) |
| $Et_2O$–$Me_2S$ (1:5 v/v) | | | **12** (31%) + **3** (62%) |
| $Et_2O$–$CH_2Cl_2$ (1:3.3 v/v) | | | **12** (25%) + **3** (63%) |
| $Et_2O$ | $(CH_3)_2CHCH_2COCH_3$ (**14**; 94%)[a] | **13** (93%) | **12** (21%)[b] + **3** (72%) |
| $Et_2O$–THF (1:5 v/v) | **14** (98%) | **13** (51%) + **8** (39%) | **3** (96%) |
| $Et_2O$–DME (1:5 v/v) | **14** (84%) | **13** (45%) + **8** (45%) | **3** (100%) |

[a] This experiment was described by H. O. House, W. L. Respess, and G. M. Whitesides, *J. Org. Chem.*, **31**, 3128 (1966). [b] This experiment was originally reported in ref 2b; the range of product compositions was 15–30% of **12** and 70–85% of **3**.

adding better donor solvents (THF or DME) was still apparent. In these experiments the recovered starting material (e.g., **3**) resulted from a relatively slow reaction [precipitation of $(CH_3Cu)_n$] to form the enolate **2** that was reconverted to the starting ketone **3** by hydrolysis with $H_2O$ or to the monodeuterio ketone **9** by quenching in a $D_2O$–DOAc mixture.

Since the usual preparative route to $LiCuR_2$ reagents (reaction of CuI or CuBr with 2 molar equiv of RLi) produces a solution containing the cuprate reagent accompanied by an equivalent amount of LiI or LiBr, it might be supposed that the deleterious effect of THF or DME arises from the increased ability of these solvents to complex with $Li^+$ (from LiI or LiBr). If this extra $Li^+$ were a catalyst for the conjugate addition, then coordination of the $Li^+$ with a good donor ligand could retard or inhibit the reaction (cf. ref 7). We were able to disprove this hypothesis by demonstrating that the same amount of conjugate adduct **12** was formed from the enone **3** using either an $Et_2O$ solution of the usual cuprate reagent ($LiCuMe_2$ + LiBr) or an $Et_2O$ solution of $LiCuMe_2$ from which 95% of the LiBr had been removed.[6b,10]

Only with the most easily reduced enone **7** was it possible to demonstrate that addition of one of the donor solvents, THF or DME, had no deleterious effect on conjugate addition. Since stable solutions of $LiCuMe_2$ in mixtures of $Et_2O$ and DMF can be prepared,[2c] it was also possible to examine the effect of a very good[5] donor solvent on the conjugate addition reaction. Using $LiCuMe_2$ in an $Et_2O$–DMF mixture (1:3 v/v) we did not detect the conjugate adduct from any of the enones **7**, **8**, or **3** and only obtained a conjugate adduct **11** in this solvent mixture with the very easily reduced (and difficultly enolizable[11]) enone **10**.

Consideration of these results indicates that the choice of reaction solvent can be a very important factor in obtaining good yields of conjugate adducts from cuprate reagents and unsaturated carbonyl compounds. This is particularly true in the rather common circumstance where the estimated[4] $E_{red}$ value for the unsaturated carbonyl is more negative than −2.1 V. In such cases the presence of good donor solvents (e.g., THF or DME) or good donor additives (e.g., DMF or HMP) may either lower the yield or completely inhibit the formation of a conjugate adduct. In general the best choice of reaction solvent would appear to be either pure $Et_2O$ or an $Et_2O$–$Me_2S$ mixture. Dilution of these cuprate solutions with a hydrocarbon cosolvent (e.g., pentane) before use is clearly desirable whenever the estimated[4] $E_{red}$ value for the unsaturated carbonyl compound is more negative than −2.2 V.

**The Effect of the Substituent R in $LiCuR_2$.** In order to survey the effect of the group R in a cuprate reagent, $LiCuR_2$, upon limiting substrate $E_{red}$ value for successful conjugate addition, we have studied the reactions of the enones **7**, **8**, and **3** with a representative group of cuprate reagents, **15**–**21** (see Table II). In performing these reactions we selected reaction temperatures 5–10 °C below the temperature at which significant thermal decomposition of the cuprate reagent began in order to minimize subsequently discussed side reactions. Although successful conjugate additions require only 1 molar equiv of $LiCuR_2$ reagent for each mole of enone,[2g] we used an excess of $LiCuR_2$ in each of these reactions to minimize the possibility that portions of the starting enones **7**, **8**, or **3** were recovered because of adventitious destruction of a portion of the $LiCuR_2$ reagent. Furthermore, we used reaction times well in excess of those normally needed for complete reaction. Thus, we believe that any unchanged enone found among the reaction products represents the portion of enone that was converted to its enolate (e.g., **2** from **3**) rather than undergoing conjugate addition. In most cases this relatively slow enolate formation was the major side reaction when conjugate addition was retarded or inhibited. Whenever practical, we used mixtures of $Et_2O$ with $Me_2S$ or $Me_2S$ plus a hydrocarbon (pentane, hexane, or cyclohexane) as the reaction solvent in order to optimize the proportion of conjugate adduct **12**–**14** or **22**–**34** (see Table II) in the product.

The results of this series of reactions, summarized in Table II, suggest that the following limiting $E_{red}$ values are appropriate for the various cuprates studied: −2.35 V, LiCu(Bu-*n*)$_2$ and $LiCu(CH{=}CH_2)_2$; −2.2 to −2.3 V, $LiCuPh_2$, LiCu(Bu-*sec*)$_2$, and $LiCuMe_2$; −2.1 V, LiCu(Bu-*t*)$_2$; −2.0 to −2.1 V, $LiCu(CH_2CH{=}CH_2)_2$. This *order of ability* to undergo conjugate addition with an enone having a certain $E_{red}$ value (*n*-Bu ~ $CH_2{=}CH_2$ > Ph ~ *sec*-Bu ~ Me > *t*-Bu > allyl) generally parallels the *order of relative rates* for conjugate addition determined in several sets of competition experiments. When limited amounts of several enones were allowed to react with solutions containing both $LiCuMe_2$ and $LiCu(CH{=}CH_2)_2$, the relative rate of R group transfer was $CH_2{=}CH$ > Me.[2b,12] In competition experiments involving addition to enone **8** the order was *n*-Bu > *sec*-Bu > *t*-Bu and the order *n*-Bu ~ *sec*-Bu > *t*-Bu > Ph was reported for competitive additions to $CH_2{=}CHCOCH_3$.[13,14] These relative rate orders were consistent with our order of reactivity except for the positions of $LiCuPh_2$ and LiCu(Bu-*t*)$_2$, where our data clearly indicated $LiCuPh_2$ to be more reactive, not less reactive, than LiCu(Bu-*t*)$_2$. Although this difference might be interpreted to mean that the reactivity order changed in mixed cuprates such as LiCu(Ph)Bu-*t* [formed from $LiCuPh_2$ and LiCu(Bu-*t*)$_2$], the facts that the earlier relative rate study[13] was performed at a temperature (0 °C) where thermal decomposition of LiCu(Bu-*t*)$_2$ would be extensive and used an enone ($CH_2{=}CHCOCH_3$) that would be a very efficient trap for alkyl radicals led us to reexamine these relative rates. Reaction of the enone **8** (Scheme II) with an excess of an equimolar mixture of $LiCuPh_2$ and LiCu(Bu-*t*)$_2$ indicated that the relative rates of R group transfer were Ph > *t*-Bu, as our previous data suggested.

**Table II. Reaction of $LiCuR_2$ Reagents with the Enones 7, 8, and 3 in $Et_2O$ or $Et_2O$–Hexane Solution**

| | | Reaction products (% yield)[e] | | |
|---|---|---|---|---|
| $LiCuR_2$[d] (solvent) | Reaction temp, °C | *trans*-$CH_3CH{=}CHCOCH_3$ (**7**; $E_{red} = -2.08$ V) | $(CH_3)_2C{=}CHCOCH_3$ (**8**; $E_{red} = -2.21$ V) | $(CH_3)_2C{=}C(CH_3)COCH_3$ (**3**; $E_{red} = -2.35$ V) |
| LiCu(Bu-*n*)$_2$ (**15**) ($Et_2O$–$Me_2S$–hexane, 1:3:3 v/v/v) | −20 to −30 | | *n*-BuC$(CH_3)_2CH_2COCH_3$ (**22**; 83%) | *n*-BuC$(CH_3)_2CH(CH_3)COCH_3$ (**23**; 74%) + **3** (5%) |
| $LiCu(CH{=}CH_2)_2$ (**16**) ($Et_2O$–$Me_2S$–THF, 1:1:1 v/v/v) | −20 to −35 | | $CH_2{=}CHC(CH_3)_2CH_2COCH_3$ (**24**; 72%)[a] | $CH_2{=}CHC(CH_3)_2CH(CH_3)COCH_3$ (**25**; 55%) + **3** (17%)[b] |
| $LiCuPh_2$ (**17**) ($Me_2S$–$Et_2O$, 1:3 v/v) | 10–27 | | $PhC(CH_3)_2CH_2COCH_3$ (**26**; 77%) | $PhC(CH_3)_2CH(CH_3)COCH_3$ (**27**: 48%) + **3** (43%) |
| LiCu(Bu-*sec*)$_2$ (**18**) ($Et_2O$–$Me_2S$–cyclohexane, 1:1:2 v/v/v) | −50 to −55 | *sec*-BuCH$(CH_3)CH_2COCH_3$ (**28**, 87%) | *sec*-BuC$(CH_3)_2CH_2COCH_3$ (**29**; 77%) | *sec*-BuC$(CH_3)_2CH(CH_3)COCH_3$ (**30**; 17–43% + **3** (19–45%) + other products |
| $LiCuMe_2$ (**19**) ($Et_2O$) | 10–30 | $(CH_3)_2CHCH_2COCH_3$ (**14**; 94%)[c] | $(CH_3)_3CCH_2COCH_3$ (**13**; 93%) | $(CH_3)_3CCH(CH_3)COCH_3$ (**12**; 21%) + **3** (72%) |
| LiCu(Bu-*t*)$_2$ (**20**) ($Et_2O$–$Me_2S$–pentane, 1:1:1 v/v) | −55 to −65 | *t*-BuCH$(CH_3)CH_2COCH_3$ (**31**; 74%) | *t*-BuC$(CH_3)_2CH_2COCH_3$ (**32**; 4%) + **8** (59–62%) + other products | |
| $LiCu(CH_2CH{=}CH_2)_2$ (**21**) ($Et_2O$–$Me_2S$, 3:1 v/v) | −30 to −70 | $CH_2{=}CHCH_2CH(CH_3)CH_2COCH_3$ (**33**; 10–16%) + **7** (48–53%) + **35** (12–18%) | $CH_2{=}CHCH_2C(CH_3)_2CH_2COCH_3$ (**34**; 1%) + **8** (6%) + **36** (71%) | |

[a] This experiment is reported in ref 2f. [b] This experiment is described in ref 2b. [c] This experiment is described by H. O. House, W. L. Respess, and G. M. Whitesides, *J. Org. Chem.*, **31,** 3128 (1966). [d] Registry no.: **15**, 24406-16-4; **16,** 22903-99-7; **17**, 23402-69-9; **18**, 23402-73-5; **19,** 15681-48-8; **20**, 23402-75-7; **21**, 21500-57-2. [e] Registry no.: **7**, 3102-33-8; **28**, 21409-93-8; **14**, 108-10-1; **31**, 65995-71-3; **33**, 35194-34-4; **35**, 919-98-2; **8**, 141-79-7; **22**, 49585-97-9; **24**, 1753-37-3; **26**, 7403-42-1; **29**, 66018-00-6; **13**, 590-50-1; **32**, 65995-72-4; **34**, 17123-68-1; **36**, 926-20-5; **3**, 684-94-6; **23**, 58105-39-8; **25**, 54678-05-6; **27**, 1203-12-9; **30**, 65995-73-5; **12**, 5340-45-5.

**Scheme II**

$$\underset{\mathbf{8}}{(CH_3)_2C{=}CHCOCH_3} + \underset{\mathbf{17}}{LiCuPh_2} + \underset{\mathbf{20}}{LiCu(Bu\text{-}t)_2} \xrightarrow[2.\ H_2O]{1.\ Et_2O,\ Me_2S,\ pentane,\ -62\ to\ -72\ ^\circ C} \underset{\mathbf{26}\ (67\%)}{PhC(CH_3)_2CH_2COCH_3} + \underset{\mathbf{32}\ (1.3\%)}{t\text{-}BuC(CH_3)_2CH_2COCH_3} + \text{other products}$$

Thus, with proper attention to reaction conditions, conjugate addition to unsaturated carbonyl substrates having $E_{red}$ values less negative than −2.3 V is likely to be a satisfactory synthetic procedure for $LiCuR_2$ reagents where the group R is primary or secondary alkyl, methyl, vinyl, or aryl. Substrates with $E_{red}$ values less negative than −2.3 V include acetylenic ketones and esters, a fair number of ethylenic ketones, and a limited number of ethylenic esters.[4] However, the number of simple unsaturated carbonyl substrates that are likely to form conjugate adducts in good yield ($E_{red}$ = −2.1 V or less) with $LiCuR_2$ reagents where the group R is tertiary alkyl or allyl is much more limited. In instances where the foregoing data would suggest that a satisfactory conjugate addition is doubtful, it would seem prudent to modify the unsaturated carbonyl substrate in such a way that its reduction potential will be less negative. For example, although unsaturated esters of the type **37** normally fail to give good yields of conjugate adducts with $LiCuMe_2$,[15a] the corresponding more easily reduced alkylidene malonates **38**[15a] or alkylidene cyanoacetates[15b] are satisfactory substrates. Similarly, while the reaction of enone **7** with either $LiCu(CH_2CH{=}CH_2)_2$ or with $CH_2{=}CHCH_2MgBr$ in the presence of a $Me_2SCuBr$ catalyst formed the conjugate adduct **33** in only 10–20% yield, the corresponding reaction with the more easily reduced enone **39** formed the conjugate adduct **40** in 75% yield.[16]

$R_2C{=}CHCO_2Et$ **37** (calcd[4] $E_{red} = -2.4$ V)

$R_2C{=}C(CO_2Et)_2$ **38** ($E_{red} = -2.1$ V)

$CH_3CH{=}CHCOCH_3$ **7** ($E_{red} = -2.08$ V)

$CH_2{=}CHCH_2CH(CH_3)CH_2COCH_3$ **33**

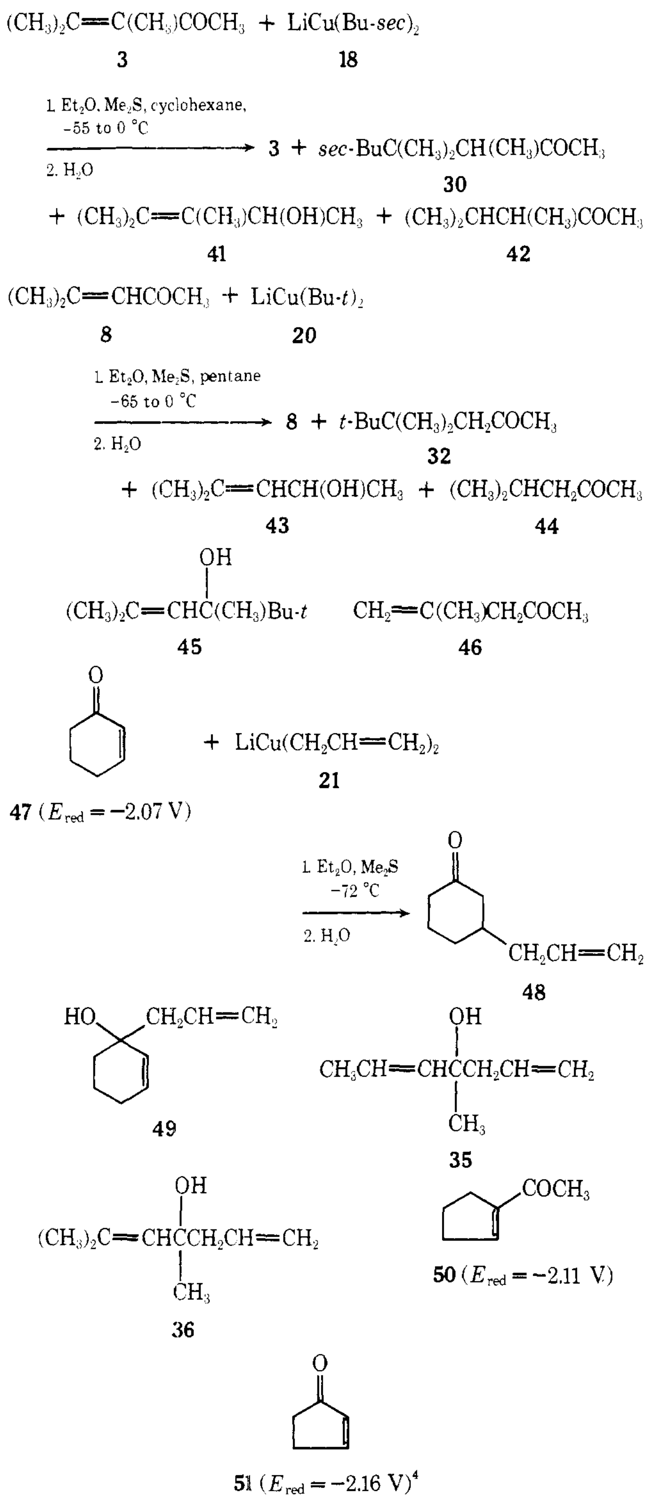
$CH_3CH{=}C(CO_2Bu\text{-}t)COCH_3$ **39** ($E_{red} = -1.8$ V)

$CH_2{=}CHCH_2CH(CH_3)CH(CO_2Bu\text{-}t)COCH_3$ **40**

**Side Reactions with the *sec*-Butyl, *tert*-Butyl, and Allyl Cuprates.** Our study of the reaction of LiCu(Bu-*sec*)$_2$ with the enone **3** (Scheme III) and the reaction of LiCu(Bu-*t*)$_2$ with the enone **8** were both complicated by the formation of reduction products **41**–**44**. The amounts of these byproducts varied from run to run and appeared to be related to the amount of thermal decomposition of the cuprate reagent that occurred during the course of the reaction. Analogous byproducts were not observed in reactions of either of these cuprate reagents with more easily reduced enones where conjugate addition occurred readily. We are, therefore, inclined to believe that these reduction products are formed by partial thermal decomposition of *sec*-alkyl and *tert*-alkyl cuprates to form copper hydride species of the type LiCuH(R) that reduce the enones at a rate competitive with conjugate addition or enolate formation.[17]

A second side reaction, noted in the reaction of LiCu(Bu-*t*)$_2$ (**20**) with the enone **8** and the reaction of LiCu-

Scheme III



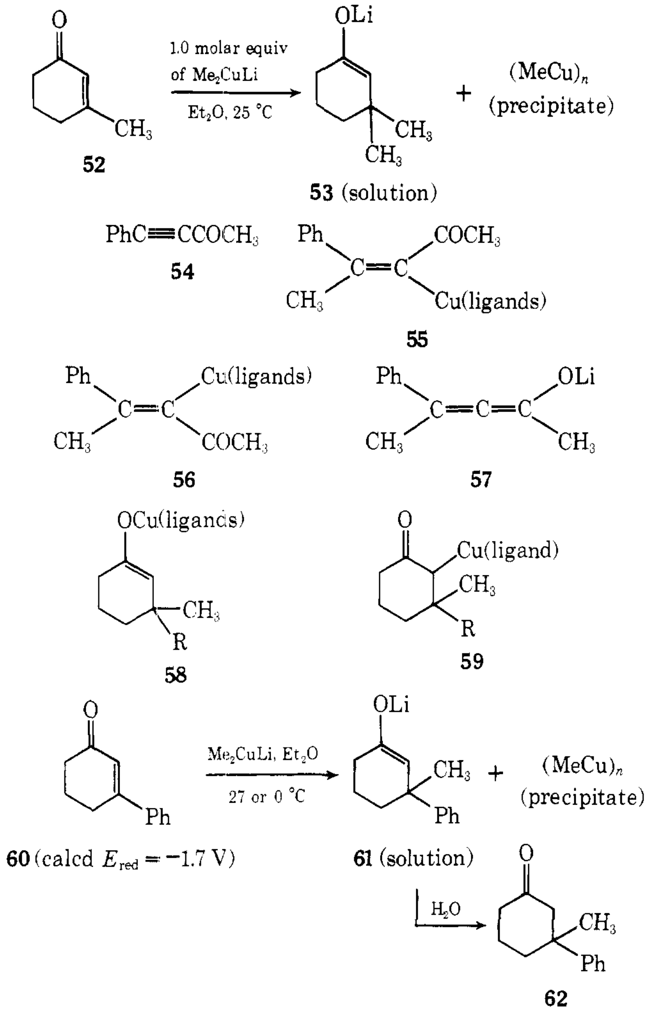
$(CH_2CH{=}CH_2)_2$ (**21**) with the enones **7**, **8**, and **47**, was the formation of 1,2 adducts **35**, **36**, **45**, and **49**. A major cause of this side reaction was the special sensitivity of the cuprates **20** and **21** to thermal decomposition when the Cu(I) salt used to prepare the cuprates contained an impurity [presumably a Cu(II) derivative]. Thus, the $t$-$Bu_2CuLi$ (**20**) generated at −60 to −70 °C from freshly prepared (or freshly recrystallized) $Me_2SCuBr$ was obtained as a pale orange solution that reacted with the enone **8** to form, after hydrolysis, a mixture of the starting enone **8** and the conjugate adduct **32**. However, when the cuprate **20** was prepared from samples of $Me_2SCuBr$ that had been stored for some time before use, partial decomposition of the cuprate **20** was evident (brown-black precipitate) during its formation, even at −70 °C, and a substantial amount (20% or more) of the 1,2-adduct **45** was formed upon addition of the enone **8**. Similarly, repetition of the previously reported[18] addition of $LiCu(CH_2CH{=}CH_2)_2$ (from freshly purified $Me_2SCuBr$) to the enone **47** formed the conjugate adduct **48** in 91% yield, while similar reactions employing $Me_2SCuBr$ that had been stored before use yielded mixtures containing both the ketone **48** and the alcohol **49**. These observations suggest that in the presence of small amounts of a Cu(II) compound the cuprates **20** and **21** are particularly prone to an autocatalytic decomposition[17e] that generates one of the organolithium reagents, $t$-BuLi or $CH_2{=}CHCH_2Li$, and leads to 1,2 addition as a side reaction.

Even with special care to control the reaction temperature and purity of the Cu(I) source, we have found the course of the reaction of $LiCu(CH_2CH{=}CH_2)_2$ with enones having $E_{red}$ values of about 2.1 V to vary significantly with the structure of the enone. While high yields of conjugate adducts have been obtained from reaction of $LiCu(CH_2CH{=}CH_2)_2$ or $LiCu[CH_2C(CH_3){=}CH_2]_2$[19a] with the cyclic enones **47** and **51**,[19b] reaction of $LiCu(CH_2CH{=}CH_2)_2$ with the enones **7** and **50** yielded mixtures containing comparable amounts of the starting enone, the conjugate adduct, and the 1,2 adduct. The yields of 1,4-adduct **33** (10–16%), 1,2-adduct **35** (12–18%), and recovered enone (48–53%) obtained from enone **7** and $LiCu(CH_2CH{=}CH_2)_2$ were not significantly different when the $CH_2{=}CHCH_2Li$ used to prepare the cuprate **21** was obtained from $Sn(CH_2CH{=}CH_2)_4$ and PhLi,[20a] rather than from $PhOCH_2CH{=}CH_2$ and Li,[20b] in spite of the fact that the latter reagent contains an equivalent amount of PhOLi. However, one difference dependent on the source of the $CH_2{=}CHCH_2Li$ was observed. The red precipitate, previously suggested[18,19] to be allylcopper, that resulted either when the allylcuprate solution was treated with a reactive enone or when the Cu(I) salt was treated with only 1 molar equiv of $CH_2{=}CHCH_2Li$ was observed only with the $CH_2{=}CHCH_2Li$ preparation that contained an equimolar amount of PhOLi. In reactions utilizing phenoxide-free $CH_2{=}CHCH_2Li$ [from $(CH_2{=}CHCH_2)_4Sn$], the above circumstances led to the formation of red-orange solutions but no red precipitate. These observations suggest that the above red precipitate may be some mixed cuprate cluster such as (allyl)(PhO)CuLi.

Although an early study[21] had suggested that an added Cu(I) salt was not effective in catalyzing the conjugate addition of an allyl Grignard reagent to the enone **47**, in retrospect this early Cu-catalyzed reaction, performed at 25 °C, could not have succeeded because the allylcopper reagents undergo rapid thermal decomposition at temperatures above −30 °C. When the enone **7** was allowed to react with $CH_2{=}CHCH_2MgBr$ in $Et_2O$ at −40 to −50 °C in the presence of 27 mol % of $Me_2SCuBr$, the yield of 1,4-adduct **33** (13–20%) was similar to that obtained with the allylcuprate **21**. As might be expected, the yield of alcohol **35** (53–60%) was higher and the amount of recovered enone **7** (4–8%) was lower. The more easily reduced derivative (**39**) of enone **7** reacted with $CH_2{=}CHCH_2MgBr$ at −70 °C in the presence of 27 mol % of $Me_2SCuBr$ to yield 75% of the conjugate adduct **40**.[2f] In the absence of a Cu(I) catalyst, each of the enones **7**, **8**, and **47** reacted with $CH_2{=}CHCH_2MgBr$ to give a good yield of 1,2-adduct **35**,[2f] **36**, or **49**. Both this observation and related control experiments with allyllithium indicated the product compositions reported here are not being complicated by a base-catalyzed[22] oxy-Cope rearrangement during the reaction or subsequent product isolation.

We conclude that one may expect satisfactory yields of conjugate adducts from reaction of either $LiCu(CH_2CH{=}CH_2)_2$ or $CH_2{=}CHCH_2MgBr$ accompanied by a soluble Cu(I) catalyst with unsaturated carbonyl compounds if the $E_{red}$ values are −2.0 V or less negative. However, as the substrate $E_{red}$ values become more negative than −2.0 V it is

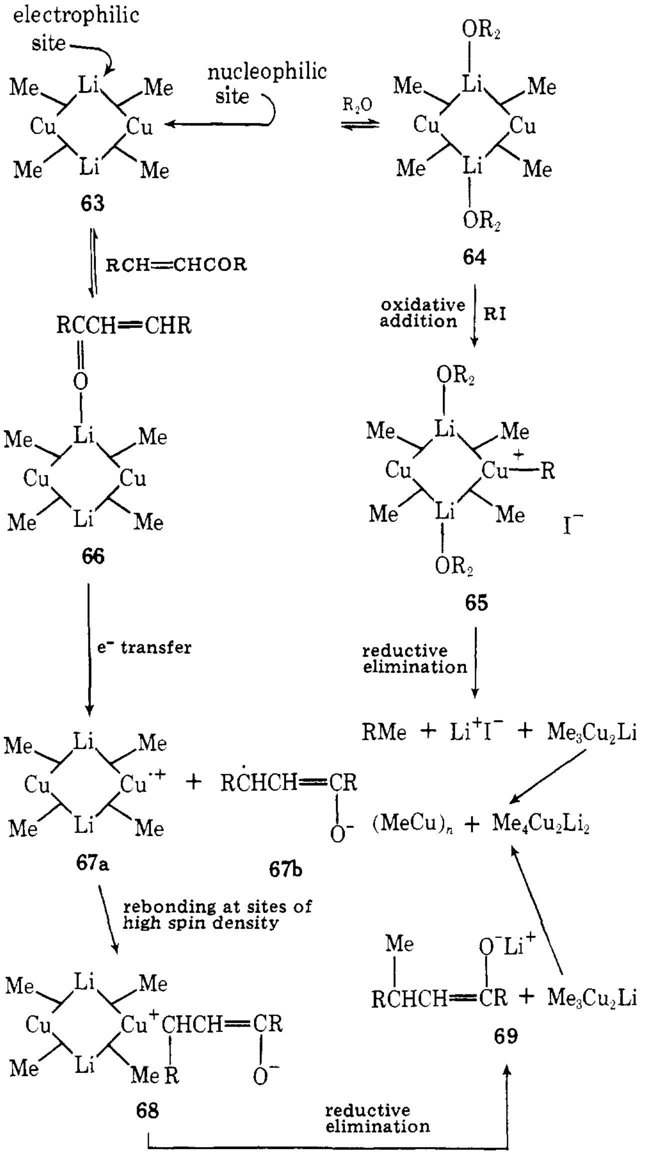
Scheme IV



difficult to predict whether the predominant mode of reaction will be 1,2 addition or conjugate addition.[23] In such cases it appears wise to consider alternative synthetic routes to the conjugate adduct, such as the base-catalyzed oxy-Cope rearrangement[22] or the very efficient reaction of the enone with $CH_2{=}CHCH_2SiMe_3$ and $TiCl_4$.[24]

**The Nature of the Initial Reaction Product.** The reaction of the enone **52** (Scheme IV) with 1 molar equiv of $LiCuMe_2$ at 25 °C formed a suspension in which all of the enolate **53** was in solution and all of the Cu used was in the MeCu precipitate.[2g] This simple observation allows the unambiguous conclusion that the first stable product formed at 25 °C is a lithium enolate and not some type of copper enolate. However, there is clear precedent for the formation of solutions of vinylcopper enolates such as **55** and **56** (confirmed by spectral measurements) by the addition of $LiCuMe_2$ to the acetylenic ester **54**,[25] and the corresponding lithium enolate **57** is formed only upon reaction of **56** with MeLi at 25 °C. Thus, the possibility exists that the reaction of the enone **52** initially formed some type of copper enolate (e.g., **58** or **59**) that dissociated at 25 °C to form the observed lithium enolate **53** and the insoluble MeCu. We have sought more information concerning this possibility by studying the reaction of the more reactive enone **60** with 1 molar equiv of $LiCuMe_2$ at various temperatures. At both 27 and 0 °C the results with enone **60** paralleled the earlier study in forming a suspension with all the enolate **61** in solution and all of the Cu in the MeCu precipitate. Even after reaction at much lower temperatures (−44 and −72 °C) essentially all of the Cu (94–98%) remained in the precipitate along with a significant fraction (20% at −44 °C and 98% at −72 °C) of the conjugate adduct. When these cold solutions were warmed to 0 °C before hydrolysis, the mixture then contained the usual mixture with all the enolate **61** in solution and all the Cu in the precipitate. Thus, we can conclude that at 0 °C or above the conjugate adduct is a lithium enolate and even at −44 °C that portion of the conjugate adduct *in solution* is the lithium enolate. However, we have found no convincing way to decide whether the insoluble conjugate adduct present at low temperatures (−44 or −72 °C) is a lithium enolate or a copper enolate. In any case, it is clear that if a copper enolate such as **59** is formed it is much less stable than the vinylcopper enolate **56** (which was stable in solution at 25 °C).

Scheme V



## Discussion

The effect of donor solvents (or other donor ligands) upon the reactions of $LiCuR_2$ reagents can be understood if the metal atoms in the cuprate cluster **63** (Scheme V) are considered as either electrophilic (Li atoms) or nucleophilic (Cu atoms) sites. The presence of a good donor solvent, $R_2O$, would increase the proportion of the solvated complex **64**. Since this solvation (**63** → **64**) would increase the electron density of the cluster, it should facilitate the oxidative addition[3a,6] of an alkyl halide at the Cu atom (**64** → **65**), leading to an increased rate of formation of coupled product, $RCH_3$. By contrast, the conjugate addition of the cuprate reagent to an enone is believed to proceed by initial coordination of the enone oxygen atom with the cluster (**63** → **66**),[2a,c] followed by inner-sphere electron transfer and subsequent transformations (**66** → **67** → **68** → **69**) leading to the conjugate adduct. A good donor ligand, $R_2O$, would clearly compete with the enone for electrophilic coordination sites on the cuprate cluster and would, consequently, tend to diminish the concentration of the enone–cuprate complex (**66**) needed for electron transfer and subsequent conjugate addition. With difficultly reduced enones, where the electron-transfer step **66** → **67** is not especially favorable, the result of diminishing the concentration of complex **66** would be to decrease the rate of conjugate additions, allowing the usually slower competing enolate formation to become the dominant reaction. Although it is not presently clear what cuprate species is primarily responsible for the conversion of ketones to their metal enolates, it is apparent that this competing reaction is not inhibited by the presence of good donor solvents.

The order of reactivity in conjugate addition of $LiCuR_2$ reagents with various R groups ($n$-Bu ~ $CH_2{=}CH$ > Ph ~ *sec*-Bu ~ Me > $t$-Bu > $CH_2{=}CHCH_2$) differs from the reactivity order in coupling reactions with alkyl halides (*sec*-Bu > $t$-Bu > $n$-Bu > Ph)[13] or alkyl tosylates (*sec*-alkyl and *tert*-alkyl > Ph and Me).[6c] Neither reactivity order suggests any obvious explanation. One possibility is that the size and/or geometry of the cuprate cluster $LiCuR_2$ varies with different R groups, so that the dimeric formulation **63** indicated[3] for $LiCuMe_2$ is not applicable to other cuprate reagents. If this were true then it would not be surprising to find that both the oxidation potential of the cuprate and its steric requirements for bonding with other ligands would vary with changes in the size and geometry of the cuprate cluster.

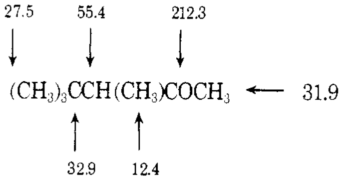
## Experimental Section[26]

**Preparation of Reagents.** All solvents were purified by distillation from $LiAlH_4$ immediately before use. Recrystallized samples of $Me_2SCuBr$[2b] were used to prepare all organocopper(I) derivatives. The $Me_2S$ was purified by distillation from $LiAlH_4$; bp 36–38 °C. Pure samples of enones **7**[27] and **3**[2b] were obtained as previoulsy described and a pure sample of enone **8** was obtained by fractional distillation[28] of commercial mesityl oxide: bp 127–128 °C; $n^{25}{}_D$ 1.4430 (lit.[28] bp 129.8 °C; $n^{20}{}_D$ 1.44575). Solutions of PhLi, obtained by reaction of PhBr with Li wire in $Et_2O$, were standardized by a double titration procedure[29] in which aliquots of the reagent, both before and after reaction with $BrCH_2CH_2Br$, were titrated with standard aqueous acid. The same standardization procedure[29] was used for commercial solutions of $n$-BuLi (Foote Mineral Co.) in hexane, $t$-BuLi (Lithium Corporation of America) in pentane, and *sec*-BuLi (Foote Mineral Co.) in cyclohexane. Ethereal solutions of allylmagnesium bromide, prepared in the usual way,[30] were standardized by titration with *sec*-BuOH employing 2,2′-bipyridyl as the indicator.[31] Ethereal solutions of allyllithium, containing an equivalent amount of PhOLi, were prepared by a modification of a previously described procedure[20b] in which $PhOCH_2CH{=}CH_2$ was allowed to react with Li in $Et_2O$ solution. Alkoxide-free ethereal solutions of allyllithium were prepared by the previously described[20a] reaction of $(CH_2{=}CHCH_2)_4Sn$ with ethereal PhLi. In each case the amounts of allyllithium and residual base in the solutions were determined by the double titration procedure.[29] Solutions of halide-free MeLi, obtained by reaction of MeCl with Li dispersion in $Et_2O$, were standardized by the double titration procedure[29] or by titration with *sec*-BuOH employing 2,2′-bipyridyl as the indicator.[31] Titration for halide ion by the Volhard procedure indicated that the LiCl content of the halide-free MeLi was 5–6 mol %.

Freshly distilled commercial samples of enone **47** were used for electrochemical measurements employing previously described procedures.[16,32] Solutions in anhydrous DMF containing 0.5 M $n$-$Bu_4NBF_4$ and $1.3–4.8 \times 10^{-3}$ M enone **47** exhibited a polarographic $E_{1/2}$ value of −2.07 V vs. SCE ($n$ = 0.9, $i_d$ = 7–19 $\mu$A).

The previously described[33] reaction of 3-ethoxy-2-cyclohexenone with ethereal PhMgBr followed by treatment with dilute aqueous $H_2SO_4$ yielded 14.8 g (78%) of the enone **60** as pale yellow plates: mp 61–62 °C (lit. mp 61–61.5,[34] 64.5–66 °C[33]); IR ($CCl_4$) 1670 cm$^{-1}$ (C=O); NMR ($CCl_4$) $\delta$ 7.1–7.7 (5 H, m, aryl CH), 6.26 (1 H, partially resolved multiplet, vinyl CH), and 1.9–2.9 (6 H, m, aliphatic CH); UV max (95% EtOH) 217.5 ($\epsilon$ 9180) and 283.5 nm ($\epsilon$ 17 000); mass spectrum $m/e$ (relative intensity) 172 ($M^+$, 99), 145 (25), 144 (100), 128 (20), 116 (70), 115 (72), and 102 (21).

**Reactions of $LiCuMe_2$ with Enone 3 in Various Solvents.** Solutions of $LiCuMe_2$, prepared from 411 mg (2.0 mmol) of $Me_2S$–CuBr and 2.4 mL of $Et_2O$ containing 4.0 mmol of halide-free MeLi, were stirred at 10–25 °C for 5 min and then diluted either with 12 mL of $Et_2O$ or with the appropriate volume (see Table I) of one of the purified cosolvents: pentane, PhH, $Me_2S$, $CH_2Cl_2$, THF, or DME. Then weighed samples of the enone **3** (~112 mg or 1 mmol) and $n$-$C_{12}H_{26}$ (~100 mg, internal standard) in 2.0 mL of the cosolvent were added and the reaction mixtures were stirred for 12 h at 25–30 °C. After the mixtures had been treated with a limited amount of $H_2O$ (~0.3 mL) and then filtered, the resulting organic solutions were analyzed by GLC [FFAP (Regis Chemical Co.) on Chromosorb P, apparatus calibrated with known mixtures]; the retention times were: ketone **12**, 8.7 min; enone **3**, 18.6 min; $n$-$C_{12}H_{26}$, 36.8 min. Collected (GLC) samples of the ketones **3** and **12** ($n^{25}{}_D$ 1.4152; lit. $n^{25}{}_D$ 1.4161,[35] 1.4162[2b]) were identified with authentic samples[2b] by comparison of IR, NMR, and mass spectra and GLC retention times. The $^{13}C$ NMR spectrum of the ketone **12** ($CDCl_3$ solution) is summarized in the following structure; the indicated assignments are consistent with off-resonance decoupling measurements. The yields of ketone **12** and recovered enone **3** from the various reactions are summarized in Table I.



$$(\overset{27.5\,\downarrow}{CH_3})_3\underset{\uparrow\,32.9}{C}\overset{55.4\,\downarrow}{C}H(\underset{\uparrow\,12.4}{CH_3})\overset{212.3\,\downarrow}{C}OCH_3 \longleftarrow 31.9$$

A cold (15 °C) solution of $Me_2CuLi$, from 3.717 g (18.1 mmol) of $Me_2SCuBr$, 36.2 mmol of MeLi (halide-free) in 25 mL of $Et_2O$, and 125 mL of THF, was treated with a solution of 1.021 g (9.12 mmol) of the enone **3** in 10 mL of THF. The originally colorless solution progressively turned yellow, pink, and then violet and yellow $(MeCu)_n$ began to precipitate after 10 min. After the reaction mixture had been stirred at 15–20 °C for 1 h, it was added slowly with stirring to a solution of DOAc and $D_2O$ prepared by refluxing a mixture of 7.91 g (77.6 mmol) of freshly distilled $Ac_2O$ and 10 mL of $D_2O$. The resulting mixture was filtered and extracted with three 25-mL portions of $Et_2O$. After the combined ethereal extracts had been washed with aqueous $NaHCO_3$, dried, and concentrated, an aliquot of the crude liquid product (1.92 g) was mixed with a known weight of $n$-$C_{12}H_{26}$ for GLC analysis. The calculated recovery of the enone **9** (or **3**) was 85% and none of the conjugate adduct **12** was detected. Short-path distillation of the remaining crude product separated 686 mg of the enone **9** containing (mass spectral analysis) 15% $d_0$ species, 78% $d_1$ species, and 7% $d_2$ species. The NMR spectrum ($CCl_4$) of this product corresponded to the NMR spectrum of the enone **3**, except that the $CH_3CO$ singlet at $\delta$ 2.10 was largely replaced by a three-line pattern ($J_{HD}$ = 2.2 Hz) at slightly higher field ($\delta$ 2.08),[36] corresponding to the $COCH_2D$ grouping. In a second comparable experiment, the recovered enone **9** (86% yield) contained (mass spectral analysis) 22% $d_0$ species and 78% $d_1$ species and exhibited NMR absorption comparable to that described above. As a control experiment, 755 mg (6.74 mmol) of the enone **3** in 5 mL of THF was added to a solution prepared from 10.1 mmol of $Me_2CuLi$, 78 mL of THF, 43 mmol of $CH_3CO_2D$, and 10 mL of $D_2O$. After the resulting mixture had been stirred at 27 °C for 2 h, the previously described isolation procedure was used to separate 491 mg of the enone **3**, bp 49–50 °C (12 mm), that contained (mass spectral analysis) 99% $d_0$ species and 1% $d_1$ species.

The following experiments were performed to compare the reaction of enone **3** with ethereal $Me_2CuLi$ in the presence and absence of dissolved $Li^+$ salts. A solution of 84 mg (0.75 mmol) of the enone **3** and 60 mg of $n$-$C_{12}H_{26}$ in 4 mL of $Et_2O$ was added to a cold (6 °C) solution of 1.69 mmol of $Me_2CuLi$ and 1.69 mmol of LiBr [from 348 mg (1.69 mmol) of $Me_2SCuBr$ and 3.38 mmol of halide-free MeLi in 8.2 mL of $Et_2O$]. The resulting mixture was allowed to warm from 6 to 22 °C with stirring during 20 min, quenched with $H_2O$, and analyzed (GLC, UCON 50HB 280X on Chromosorb P, apparatus calibrated with known mixtures). The crude product contained ketone **12** (retention time 7.1 min, 19% yield), enone **3** (12.1 min, 80% yield), and $n$-$C_{12}H_{26}$ (28.5 min). In a second comparable reaction the yields were 22% of ketone **12** and 69% of enone **3**.

Reaction of 1.03 g (5.00 mmol) of $Me_2SCuBr$ with 4.96 mmol of halide-free MeLi in 9.2 mL of $Et_2O$ yielded a slurry of yellow $(MeCu)_n$

that was centrifuged. After the supernatant liquid had been separated, the $(MeCu)_n$ precipitate was washed with one 6-mL portion of $Et_2O$ and then treated with 4.65 mmol of halide-free MeLi in 9 mL of $Et_2O$. Aliquots of the resulting $Me_2CuLi$ solution (0.53 M) were quenched in aqueous $H_2SO_4$, filtered, and titrated for halide content by the Volhard procedure; in a series of cuprate preparations, the halide concentration (mainly LiCl) was 0.023–0.030 M (4–6 mol %). After a solution of 2.65 mmol of this halide-free $Me_2CuLi$ in 9 mL of $Et_2O$ had been allowed to react with 84 mg (0.75 mmol) of the enone **3** as previously discribed, the product yields (GLC analysis) were 17% of ketone **12** and 81% of enone **3**. From a second comparable run, the yields were 17% of ketone **12** and 77% of enone **3**. Thus, in all of the reactions of enone **3** with $Me_2CuLi$ in $Et_2O$ solution the product was composed of 18–24% of the conjugate adduct **12** and 76–82% of the enone **3** (from enolate formation) irrespective of whether the solution contained a molar equivalent of LiBr.

**Reaction of $LiCuMe_2$ with the Enones 7 and 8 in Various Solvents.** Solutions of $LiCuMe_2$, from 411 mg (2.0 mmol) of $Me_2S$–CuBr and 2.4 mL of an $Et_2O$ solution containing 4.0 mmol of MeLi, were diluted with 11 mL of either THF or DME and then treated with 2.0 mL of the same cosolvent containing weighed amounts of $n$-$C_{12}H_{26}$ (~80–90 mg, internal standard) and either enone **8** (~98 mg, 1.0 mmol) or **7** (~84 mg, 1.0 mmol). The resulting mixtures were stirred at 25–30 °C for 12 h and then subjected to the previously described isolation and analytical procedures.

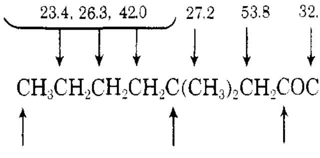
The GLC retention times (Carbowax 20M on Chromosorb P) for reactions with the enone **8** were: ketone **13**, 16.1 min; enone **8**, 29.9 min; $n$-$C_{12}H_{26}$, 58.9 min. The corresponding values for reactions with the enone **7** were: ketone **14**, 13.9 min; $n$-$C_{12}H_{26}$, 55.8 min. Collected (GLC) samples of the ketones **8**, **13**, and **14** were identified with authentic samples[2e] by comparison of GLC retention times and IR and either NMR or mass spectra. Comparable reaction and analysis procedures were used for the reaction of 1.024 mmol of the enone **8** with 2.05 mmol of $Me_2CuLi$ in 8.7 mL of $Et_2O$ and for the reaction of 0.997 mmol of the enone **8** with 2.76 mmol of $Me_2CuLi$ in a mixture of 3.6 ml of $Et_2O$ and 14 mL of pentane. The yields of the ketones **13** and **14** and the recovered enone **8** are summarized in Table I.

**Reaction of $LiCuMe_2$ With the Enone 10 in $Et_2O$–DMF Solution.** A solution of $LiCuMe_2$, prepared from 520 mg (2.53 mmol) of $Me_2SCuBr$ and 4.95 mmol of MeLi (halide-free) in 3 mL of $Et_2O$, was diluted with 15 mL of anhydrous DMF and then a solution of 256 mg (1.23 mmol) of the enone **10** in 2 mL of $Et_2O$ was added dropwise with stirring. The resulting solution, which turned red immediately upon addition of the enone, was stirred at 25 °C for 5 h; during this period the initial red solution turned green within ~10 min, but no further change and no precipitation of $(MeCu)_n$ were evident. The resulting mixture was partitioned between pentane and an aqueous solution of $NH_4Cl$ and $NH_3$. The organic layer was washed with aqueous NaCl, dried, and concentrated to leave 345 mg of crude solid product containing (TLC, silica gel coating with an $Et_2O$–hexane eluent, 1:4 v/v) the adduct **11** ($R_f$ 0.43) and two minor unidentified impurities ($R_f$ 0.10 and 0.26). A 183.8-mg aliquot of the crude product was subjected to preparative TLC to separate 104.1 mg (75% yield) of the adduct **11** as colorless plates, mp 70–72 °C (lit.[18a] mp 70.5–71 °C); the product was identified with an authentic sample by comparison of IR, NMR, and mass spectra.

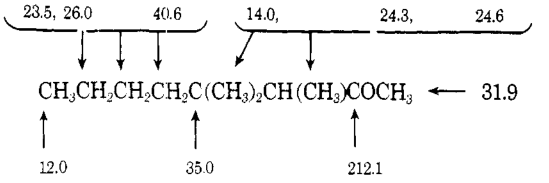
**Reactions of $Ph_2CuLi$. A. With Enone 8.** To a cold (10 °C) solution of 3.46 g (16.9 mmol) of $Me_2SCuBr$ in 15 mL of $Me_2S$ was added, dropwise with stirring and cooling during 20 min, 35.7 mL of an $Et_2O$ solution containing 33.8 mmol of PhLi. To the resulting cold (10 °C) green solution was added 1.10 g (11.3 mmol) of enone **8**. The resulting mixture, which warmed to 34 °C and slowly became a dark green-brown color, was stirred for 1 h at 27 °C and the mixture was then partitioned between $Et_2O$ and an aqueous solution (pH 8) of $NH_3$ and $NH_4Cl$. The organic layer was washed successively with aqueous $NH_3$, aqueous NaCl, and $H_2O$ and then dried and concentrated to leave 2.16 g of crude liquid product. An aliquot was mixed with an internal standard ($n$-$C_{16}H_{34}$) and subjected to GLC analysis (Carbowax 20M on Chromosorb P, apparatus calibrated with known mixtures of authentic samples); the product contained $n$-$C_{16}H_{34}$ (retention time 6.3 min), ketone **26** (77% yield, 19.0 min), and PhPh (26.0 min). In three comparable reactions, the yields of ketone **26** were 76, 77, and 87%. A collected (GLC) sample of PhPh was identified with an authentic sample by comparison of IR and mass spectra and GLC retention times. A collected (GLC) sample of the ketone **26** was obtained as a colorless liquid, $n^{25}{}_D$ 1.5118 [lit. bp 61–62 °C (1 mm),[37a] 134 °C (22 mm);[37b] $n^{20}{}_D$ 1.5115[37a]]; IR ($CCl_4$) 1725 and 1708 $cm^-$ (C=O); NMR ($CCl_4$), $\delta$ 7.0–7.5 (5 H, m, aryl CH), 2.58 (2 H, s, $CH_2CO$), 1.63 (3 H, s, $CH_3CO$), and 1.33 (6 H, s, $CH_3$); UV (95% EtOH) series of weak maxima ($\epsilon$ 60–243) in the region 239–278.5 nm; mass spectrum $m/e$ (rel intensity) 176 ($M^+$, 24), 120 (20), 119 (100), 118 (38), 91 (63), and 43 (58).

**B. With Enone 3.** To a solution (at 20 °C) of $Ph_2CuLi$, prepared from 2.303 g (11.2 mmol) of $Me_2SCuBr$ in 7 mL of $Me_2S$ and 28 mL of $Et_2O$ and 28 mL of an $Et_2O$ solution containing 22.4 mmol of PhLi, was added, dropwise and with stirring, a solution of 896 mg (8.0 mmol) of the enone **3** in 12 mL of $Et_2O$. The reaction mixture, a green solution containing some white solid, was stirred at 27 °C for 1 h and then subjected to the usual isolation procedure. An aliquot of the crude liquid product (1.74 g) was mixed with a known amount of internal standard ($n$-$C_8H_{17}Ph$) for GLC analysis (Carbowax 20 M on Chromosorb P). The product contained (GLC) the enone **3** (retention time 10.2 min, 43% recovery), $n$-$C_8H_{17}Ph$ (34.5 min), the ketone **27** (44.3 min, 48% yield), and PhPh (47.9 min). Collected (GLC) samples of PhPh and the enone **3** were identified with authentic samples by comparison of GLC retention times and IR and mass spectra. A collected (GLC) sample of the ketone **27** was obtained as a colorless liquid, $n^{25}{}_D$ 1.4468 [lit. bp 72–75 °C (0.15 mm),[38a] 129–130 °C (5 mm),[38b] 138.5 °C (18 mm);[38c] $n^{25}{}_D$ 1.4604,[38b] 1.5093[38c]]; IR ($CCl_4$) 1711 $cm^{-1}$ (C=O); NMR ($CCl_4$) $\delta$ 7.1–7.5 (5 H, m, aryl CH), 2.91 (1 H, q, $J$ = 7.5 Hz, CHCO), 1.68 (3 H, s, $CH_3CO$), 1.35 (6 H, s, $CH_3$), and 0.95 (3 H, d, $J$ = 7.5 Hz, $CH_3$); mass spectrum $m/e$ (rel intensity), 190 ($M^+$, 5) 120 (11), 119 (100), 91 (37), 43 (30), and 41 (18); UV (95% EtOH) series of weak maxima ($\epsilon$ 174–248) in the region 246–264 nm with an additional maximum at 289 nm ($\epsilon$ 56).

**Reaction of $n$-$Bu_2CuLi$. A. With Enone 8.** To a cold (−20 to −30 °C) solution of $n$-$Bu_2CuLi$, from 14.35 g (70 mmol) of $Me_2SCuBr$, 75 mL of $Me_2S$, and 77.5 mL of a hexane solution containing 140 mmol of $n$-BuLi, was added, dropwise with stirring and cooling, a solution of 4.9 g (50 mmol) of the enone **8** in 20 mL of $Et_2O$. The resulting dark green-brown mixture was stirred at −20 to −30 °C for 20 min and then allowed to warm to 27 °C with stirring during 15 min. This warming was accompanied by thermal decomposition of the excess cuprate with separation of $Cu^0$ as a black precipitate. The reaction mixture was partitioned between $Et_2O$ and an aqueous solution (pH 8) of $NH_4Cl$ and $NH_3$. The organic phase was filtered, washed successively with aqueous $NH_3$ and with aqueous NaCl, and then dried and concentrated by fractional distillation. The residual yellow liquid (8.046 g) contained (GLC, Carbowax 20 M on Chromosorb P) the ketone **22** (retention time 11.7 min) accompanied by two minor unidentified impurities (4.5 and 5.3 min). A 7.060-g aliquot of the product was fractionally distilled to separate 5.670 g (83%) of the ketone **22** as a colorless liquid: bp 93–95 °C (30 mm); $n^{25}{}_D$ 1.4223. A collected (GLC) sample of the pure ketone **22** was obtained as a colorless liquid, $n^{25}{}_D$ 1.4240 [lit.[39] bp 62–64 °C (7 mm); $n^{20}{}_D$ 1.4250]; IR ($CCl_4$) 1716 $cm^{-1}$ (C=O); UV max (95% EtOH) 284.5 nm ($\epsilon$ 21); NMR ($CCl_4$) $\delta$ 2.25 (2 H, s, $CH_2CO$), 2.04 (3 H, s, $CH_3CO$), and 0.8–1.5 (15 H, m, aliphatic CH including a $CH_3$ singlet at $\delta$ 0.97); mass spectrum $m/e$ (rel. intensity) 156 ($M^+$, <1), 98 (35), 69 (30), 58 (14), 57 (36), 56 (22), 43 (100), and 41 (16). The natural abundance $^{13}C$ NMR spectrum of the ketone **22** ($CDCl_3$) is summarized in the following formula; the indicated assignments are consistent with off-resonance decoupling measurements.


$$CH_3CH_2CH_2CH_2C(CH_3)_2CH_2COCH_3$$

**B. With Enone 3.** To a cold (−25 °C) solution of $n$-$Bu_2CuLi$, from 2.173 g (10.6 mmol) of $Me_2SCuBr$ in 13 mL of $Me_2S$ and 13.9 mL of a hexane solution containing 21.2 mmol of $n$-BuLi, was added, dropwise with stirring and cooling, a solution of 846 mg (7.55 mmol) of the enone **3** in 4 mL of $Et_2O$. After the resulting dark-colored solution had been stirred at −25 °C for 15 min, it was warmed to 27°C during 15 min and then subjected to the previously described isolation procedure. After an aliquot of the crude liquid product (1.94 g) had been mixed with a known weight of internal standard ($n$-BuPh), analysis (GLC, Carbowax 20 M on chromosorb P) indicated the presence of the starting enone **3** (retention time 8.3 min, ~5% recovery), $n$-BuPh (12.0 min), and the adduct **23** (18.9 min, 74% yield). A collected (GLC) sample of the ketone **23** was obtained as a colorless liquid: $n^{25}{}_D$ 1.4336; IR ($CCl_4$) 1711 $cm^{-1}$ (C=O); UV max (95% EtOH) 285.5 nm ($\epsilon$ 17); NMR ($CCl_4$) $\delta$ 2.49 (1 H, q, $J$ = 7 Hz, CHCO), 2.08 (3 H, s, $COCH_3$), and 0.8–1.5 (18 H, m, aliphatic CH including a $CH_3$ singlet at $\delta$ 0.90); mass spectrum $m/e$ (rel intensity) 170 ($M^+$, <1), 98 (19), 72 (100), 71 (15), 57 (50), and 43 (61). The natural abundance $^{13}C$ NMR spectrum of the ketone **23** ($CDCl_3$) is summarized in the following formula; the indicated assignments are consistent with off-resonance decoupling measurements.



$CH_3CH_2CH_2CH_2C(CH_3)_2CH(CH_3)COCH_3$

Anal. Calcd for $C_{11}H_{22}O$: C, 77.58; H, 13.02. Found: C, 77.47; H, 13.04.

**Reaction of *t*-$Bu_2CuLi$. A. With Enone 8.** To a cold (−72 °C) solution of 11.73 g (57.1 mmol) of freshly recrystallized $Me_2SCuBr$ in 50 mL of $Et_2O$ and 62 mL of $Me_2S$ was added, dropwise with stirring and cooling during 45 min, 68.3 mL of a pentane solution containing 114 mmol of *t*-BuLi. The temperature was maintained at −72 to −65 °C during this addition. The yellow to orange precipitate that separated during the initial phase of the addition redissolved as the remainder of the *t*-BuLi was added to give an orange solution of *t*-$Bu_2CuLi$. A solution of 3.83 g (39.1 mmol) of the enone **8** in 10 mL of $Et_2O$ was added, dropwise and with stirring during 10 min, to the cold solution of *t*-$Bu_2CuLi$ while the mixture was maintained at −65 °C. During the addition of the enone **8** the solution turned red and a red precipitate separated. The resulting mixture was stirred at −60 °C for 45 min and then allowed to warm to 0 °C over a period of 20 min. During this warming thermal decomposition (separation of brown-black solid) was evident as the temperature rose above −25 °C. The reaction mixture was partitioned between $Et_2O$ and an aqueous solution of $NH_4Cl$ and $NH_3$. The organic phase was washed with aqueous NaCl, dried, concentrated, and mixed with a known weight of *n*-$C_{14}H_{30}$ (an internal standard). Analysis [GLC, 74 °C with FFAP (a modified Carbowax) on Chromosorb P, apparatus calibrated with known mixtures] indicated the presence of the starting enone **8** (retention time 2.9 min, 51% recovery), the isomerized enone **46** (2.2 min, 11% yield), the alcohol **43** (5.3 min, 10% yield), the ketone **32** (11.6 min, 3.5% yield), and *n*-$C_{14}H_{30}$ (26.2 min). A peak corresponding in retention time (1.8 min) to ketone **44**, the conjugate reduction product of enone **8**, was also observed. Under the conditions used for this analysis the subsequently described alcohol **45** exhibited a GLC peak at 10.1 min. In another comparable experiment employing 1,3,5-(*i*-$Pr)_3C_6H_3$ (retention time 31.0 min) as the internal standard, the yields and retention times of the products were: **8**, 57% (3.0 min); **46**, 1.9% (2.3 min); **43**, 4.5% (5.6 min); and **32**, 4.7% (12.7 min). Collected (GLC) samples of ketones **8** and **46** and alcohol **43** were identified with authentic samples by comparison of GLC retention times and IR and mass spectra. A collected (GLC) sample of the ketone **32** was obtained as a colorless liquid, $n^{25}{}_D$ 1.4416 [lit.[40] bp 196.1 °C; $n^{20}{}_D$ 1.4420]; IR ($CCl_4$) 1715 (sh) and 1708 $cm^{-1}$ (C=O); NMR ($CCl_4$) $\delta$ 2.29 (2 H, s, $CH_2CO$), 2.05 (3 H, s, $CH_3CO$), 0.97 (6 H, s, $CH_3$), and 0.87 (9, H, s, *t*-Bu); mass spectrum *m/e* (rel intensity) 141 (9), 123 (9), 101 (24), 100 (57), 99 (26), 98 (26), 85 (58), 83 (71), 57 (69), 55 (36), 43 (100), 41 (58), and 39 (31).

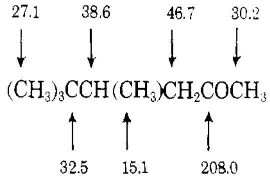
In an experiment where the cuprate reagent was prepared at −57 to −65 °C from 14.65 g (71.5 mmol) of $Me_2SCuBr$ (*not* freshly purified), 60 mL of $Me_2S$, and 72.2 mL of a pentane solution containing 143 mmol of *t*-BuLi, at least partial decomposition of the cuprate occurred during its preparation. After the resulting cold (−65 °C) dark-colored mixture had been treated with a solution of 5.00 g (51.0 mmol) of the enone **8** in 20 mL of $Et_2O$, the resulting mixture was stirred at −60 to −65 °C for 20 min and then allowed to warm to room temperature with stirring during 15 min. After following the usual isolation procedure, the residual crude liquid product (3.63 g) contained (IR and NMR analysis) a mixture of the starting enone **8** and the alcohol **45** with little if any saturated ketone product. A 3.12-g aliquot of this crude product was distilled in a short-path still to separate 1.37 g (20%) of the pure alcohol **45** as a colorless liquid [bp 30–31 °C (0.4 mm); $n^{25}{}_D$ 1.4510–1.4512] that was identified with the subsequently described sample by comparision of IR and NMR spectra. A collected (GLC) sample of the starting enone **8** was identified with an authentic sample by comparison of GLC retention times and IR spectra.

To obtain an authentic sample of the alcohol **45**, a solution of 153 mmol of *t*-BuLi in 135 mL of pentane was cooled to −72 °C and then a solution of 7.497 g (76.5 mmol) of the ketone **8** in 25 mL of $Et_2O$ was added dropwise and with stirring while the temperature of the reaction mixture was maintained at −65 to −72 °C. After the resulting yellow mixture had been stirred at −72 °C for 30 min, it was warmed to −30 °C and siphoned into $H_2O$. This mixture was saturated with NaCl and extracted with $Et_2O$. After the ethereal solution had been dried and concentrated, the residue, 11.89 g of liquid containing (IR and NMR analysis) mainly the alcohol **45**, was fractionally distilled in apparatus that had been washed with aqueous $NH_3$ and dried before use. The alcohol **45** was collected as 3.83 g (33%) of colorless liquid: bp 28–33 °C (0.42 mm); $n^{25}{}_D$ 1.4500–1.4508 [lit. bp 180–185 °C,[40] 46 °C (4 mm);[41a] $n^{20}{}_D$ 1.4502[41b]]; IR ($CCl_4$) 3610, 3500 (OH), and 1665 $cm^{-1}$ (weak, C=C); NMR ($CCl_4$) $\delta$ 5.1–5.4 (1 H, m, vinyl CH), 1.87 (3 H, d, $J$ = 1.5 Hz, allylic $CH_3$), 1.72 (3 H, d, $J$ = 1.5 Hz, allylic $CH_3$), 1.23 (3 H, s, $CH_3$), and 0.92 (9 H, s, *t*-Bu); mass spectrum *m/e* (rel intensity) 138 (13), 123 (84), 81 (85), 79 (20), 67 (34), 57 (59), 55 (42), 53 (30), 43 (55), 42 (100), and 39 (58).

*Reduction of* 1.02 g (10.44 mmol) *of the enone* **8** *with* 564 mg (14.9 mmol) of $LiAlH_4$ in 18 mL of $Et_2O$, followed by hydrolysis with a limited amount (2.2 mL) of aqueous NaOH and the usual isolation procedure, yielded 635 mg (61%) of the alcohol **43** as a colorless liquid: bp 37–45 °C (10 mm); $n^{25}{}_D$ 1.4350 [lit.[41b] bp 63 °C (36 mm); $n^{18}{}_D$ 1.440]; IR ($CCl_4$) 3608, 3420 (br, OH), and 1674 $cm^{-1}$ (C=C); NMR ($CCl_4$) $\delta$ 4.1–5.3 (2 H, m, vinyl CH and CHO), 3.13 (1 H, br, OH), 1.63 (6 H, d, $J$ = 1 Hz, allylic $CH_3$), and 1.11 (3 H, d, $J$ = 6 Hz, $CH_3$); mass spectrum *m/e* (rel intensity) 100 ($M^+$, 7), 85 (100), 82 (20), 67 (73), 55 (21), 45 (25), 43 (57), 41 (77), and 39 (36).

**B. With Enone 7.** To a cold (−55 to −60 °C) red-colored solution of *t*-$Bu_2CuLi$, formed at −60 to −65 °C from 3.73 g (18.2 mmol) of $Me_2SCuBr$ in 15 mL of $Me_2S$ and 20.6 mL of a pentane solution containing 33.4 mmol of *t*-BuLi, was added, dropwise with stirring and cooling, a solution of 1.007 g (12.0 mmol) of the enone **7** in 6 mL of $Et_2O$. After the reaction mixture had been stirred at −55 °C for 30 min, it was allowed to warm to 27 °C during 30 min and then subjected to the usual isolation procedure. An aliquot of the crude liquid product (1.72 g) was mixed with a known amount of internal standard (durene) and analyzed by GLC (silicone $QF_1$ on Chromosorb P). The product contained (GLC) durene (retention time 12.9 min) and the ketone **31** (19.9 min, 74% yield) as well as two minor unidentified volatile by-products (3.9 and 10.8 min).

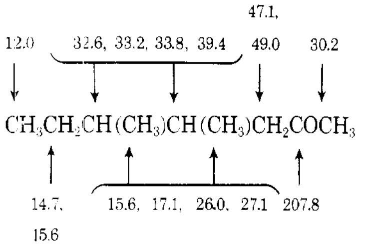
A collected (GLC) sample of the ketone **31** was obtained as a colorless liquid, $n^{25}{}_D$ 1.4227 [lit.[42] bp 162 °C (735 mm), $n^{20}{}_D$ 1.4275]; IR ($CCl_4$) 1718 $cm^{-1}$ (C=O); UV max (95% EtOH) 277.5 nm ($\epsilon$ 34); NMR ($CCl_4$) $\delta$ 1.7–2.7 (6 H, m, aliphatic CH including a $CH_3CO$ singlet at $\delta$ 2.05) and 0.7–0.95 (12 H, *t*-Bu singlet at $\delta$ 0.85 partially resolved from a $CH_3$ doublet); mass spectrum *m/e* (rel intensity) 142 ($M^+$, <1), 127 (7), 86 (32), 71 (36), 57 (65), 43 (100), and 41 (39). The natural abundance $^{13}C$ NMR spectrum ($CDCl_3$) is summarized in the following formula; the indicated assignments are consistent with off-resonance decoupling measurements.



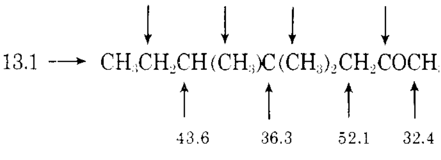
$(CH_3)_3CCH(CH_3)CH_2COCH_3$

**Reaction of the Enone 8 With a Mixture of *t*-$Bu_2CuLi$ and $Ph_2CuLi$.** A cooled (15 °C) solution of 2.02 g (9.82 mmol) of $Me_2SCuBr$ (recrystallized before use) in 8.5 mL of $Et_2O$ and 14.5 mL of $Me_2S$ was treated with 8.85 mL of an $Et_2O$ solution containing 9.82 mmol of PhLi (from PhBr and Li). The resulting greenish yellow slurry was cooled to −72 °C and 5.88 mL of a pentane solution containing 9.82 mmol of *t*-BuLi was added dropwise and with stirring while the temperature was maintained at −65 to −72 °C. After the resulting solution of the cuprates had been stirred at −70 °C for 10 min a solution of 317 mg (3.24 mmol) of the enone **8**, 9.1 mg of *n*-$C_{16}H_{34}$ (internal standard), and 61 mg of 1,3,5-(*i*-$Pr)_3C_6H_3$ (internal standard) in 2 mL of $Et_2O$ was added dropwise and with stirring at −62 to −68 °C. During the addition of the enone a red precipitate $[(t\text{-BuCu})_n]$ separated. The reaction mixture was stirred at −72 °C for 1 h and then was allowed to warm to 25 °C during 45 min. After the mixture had been quenched in an aqueous solution of $NH_4Cl$ and $NH_3$, it was filtered to remove precipitated Cu and then extracted with $Et_2O$. The $Et_2O$ solution was washed with aqueous NaCl, dried, and analyzed by GLC [FFAP (a modified Carbowax) on Chromosorb P, apparatus calibrated with known mixtures]. With the GLC column at 74 °C, the yields and retention times of the components were: enone **46**, 0.4% yield (2.5 min); enone **8**, 6.4% recovery (3.5 min); alcohol **43**, 3.3% yield (5.7 min); alcohol **45**, 0.7% yield (10.5 min); ketone **32**, 1.3% yield (11.7 min); and 1,3,5-(*i*-$Pr)_3C_6H_3$ (32.2 min). With the GLC column at 141 °C the yields and retention times of the components were: *n*-$C_{16}H_{34}$ (7.9 min); ketone **26**, 67% yield (16.7 min); and PhPh (22.7 min). From a second comparable reaction the product yields were: **46**, 3.1%; **8**, 6.4%; **43**, 7.9%; **32**, 1.6%; and **26**, 77%. A collected sample of the major product, ketone **26**, was identified with an authentic sample by comparison of GLC retention times and IR spectra. Thus the ratio of conjugate addition products **32** (*t*-Bu addition) to **26** (Ph addition) was 2:98.

**Reactions of *sec*-Bu$_2$CuLi. A. With Enone 7.** To a cold (−72 °C) mixture of 3.80 g (18.5 mmol) of Me$_2$SCuBr, 10 mL of Me$_2$S, and 10 mL of Et$_2$O was added, dropwise with stirring and cooling, 27.4 mL of a cyclohexane solution containing 36.9 mmol of *sec*-BuLi. After the resulting solution of *sec*-Bu$_2$CuLi had been stirred for 5 min at −55 °C, a solution of 1.108 g (13.2 mmol) of the enone **7** in 4 mL of Et$_2$O was added dropwise with stirring while the mixture was kept at −50 to −55 °C. The resulting reaction mixture was stirred at −50 °C for 20 min and then allowed to warm to 0 °C with stirring during 10 min. After the mixture had been partitioned between Et$_2$O and an aqueous solution of NH$_3$ and NH$_4$Cl, the organic phase was dried, concentrated, and mixed with a known weight of internal standard (tetralin). The crude product contained (GLC, Carbowax 20 M on Chromosorb P, apparatus calibrated with known mixtures) the ketone **28** (retention time 10.9 min, diastereoisomers not resolved, yield 87%), tetralin (32.1 min), and two minor unidentified alcohol (IR analysis) impurities (5.3 min and 21.0 min), but lacked a GLC peak for the starting enone **7** (4.5 min). A collected (GLC) sample of the ketone **28** was obtained as a colorless liquid, $n^{25}{}_D$ 1.4236 [lit.[43] bp 71–73 °C (15 min)]; IR (CCl$_4$) 1720 cm$^{-1}$ (C=O); UV max (95% EtOH) 278 nm (ε 25); NMR (CCl$_4$) δ 1.6–2.8 (6 H, m, aliphatic CH including a CH$_3$CO singlet at δ 2.06) and 0.6–1.1 (12 H, m, aliphatic CH); mass spectrum *m/e* (rel intensity) 142 (M$^+$, <1), 85 (35), 84 (59), 69 (25), 58 (26), 57 (22), 43 (100), and 41 (22). The natural abundance $^{13}$C NMR spectrum (CDCl$_3$) of the ketone **28** is summarized in the following structure. Since two diastereoisomers are present in this sample, two chemical shift values are given for each carbon atom where the two diastereoisomers have different chemical shifts.

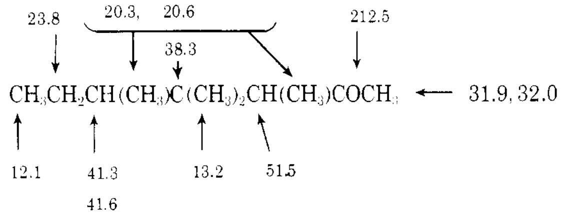


**B. With Enone 8.** To a cold (−50 to −55 °C) solution of *sec*-Bu$_2$CuLi, from 3.38 g (16.4 mmol) of Me$_2$SCuBr, 10 mL of Me$_2$S, 10 mL of Et$_2$O, and 23.2 mL of a cyclohexane solution containing 31.3 mmol of *sec*-BuLi, was added, dropwise with stirring and cooling, a solution of 1.096 g (11.2 mmol) of the enone **8** in 4 mL of Et$_2$O. After the reaction mixture had been stirred for 20 min at −50 °C and for an additional 10 min while it was allowed to warm to 0 °C, the usual isolation procedure was followed and the crude neutral product was mixed with a known amount of internal standard (*sec*-BuPh). The crude product contained (GLC, Carbowax 20 M on Chromosorb P, apparatus calibrated with known mixtures) *sec*-BuPh (retention time 10.9 min), the ketone **29** (18.3 min, yield 77%), and two minor unidentified impurities (5.6 and 35.0 min). A collected (GLC) sample of the ketone **29** was obtained as a colorless liquid: $n^{25}{}_D$ 1.4330; IR (CCl$_4$) 1720 cm$^{-1}$ (C=O); UV max (95% EtOH), 284 nm (ε 25); NMR (CCl$_4$) δ 2.36 (2 H, s, CH$_2$CO), 2.12 (3 H, s, CH$_3$CO), and 0.6–1.8 (15 H, m, aliphatic CH including a CH$_3$ singlet at δ 0.96); mass spectrum *m/e* (rel intensity) 141 (1), 99 (17), 98 (38), 83 (25), 57 (17), 43 (100), and 41 (12). The natural abundance $^{13}$C NMR sepctrum (CDCl$_3$) of the ketone **29** is summarized in the following structure; the indicated assignments are consistent with off-resonance decoupling measurements.



Anal. Calcd for C$_{10}$H$_{20}$O: C, 76.86; H, 12.90. Found: C, 76.60; H, 12.89.

**C. With Enone 3.** To a cold (−68 to −72 °C) solution of *sec*-Bu$_2$CuLi, from 6.80 g (33.1 mmol) of Me$_2$SCuBr, 25 mL of Me$_2$S, 25 mL of Et$_2$O, and 45.3 mL of a cyclohexane solution containing 66.2 mmol of *sec*-BuLi, was added 2.523 g (22.5 mmol) of the enone **3** in 2 mL of Et$_2$O. After the resulting mixture had been stirred at −55 to −60 °C for 30 min and at −45 to −60 °C for 90 min, it was warmed to 0 °C during 10 min and then subjected to the usual isolation procedure. After the crude liquid product had been mixed with an internal standard (1,3,5-triisopropylbenzene), analysis [GLC, FFAP (Regis Chemical Co.) on Chromosorb P] indicated the presence of the ketone **42** (retention time 4.1 min, 5% yield), the starting enone **3** (9.6 min, 20% yield), the alcohol **41** (23.9 min, 13% yield), the ketone **30** (35.6 min, the two diastereoisomers were not resolved, 19% yield), and 1,3,5-(*i*-Pr)$_3$C$_6$H$_3$ (59.5 min). From a number of comparable reactions, the following ranges of yields were observed for the various products: **42**, 5–10%; **3**, 19–45%; **41**, 13–34%; **30**, 17–43%. Collected (GLC) samples of products **3**, **41**, and **42** were identified with authentic samples by comparison of IR and mass spectra and GLC retention times. A collected (GLC) sample of the ketone **30** was obtained as a colorless liquid: $n^{25}{}_D$ 1.4430; IR (CCl$_4$) 1713 cm$^{-1}$ (C=O); UV max (95% EtOH) 288 nm (ε 36); $^1$H NMR (CCl$_4$) δ 2.5–2.9 (1 H, m, CHCO), 2.07 (2 H, s, CH$_3$CO), and 0.7–1.4 (18 H, m, aliphatic CH); mass spectrum *m/e* (rel intensity) 137 (1), 113 (11), 99 (11), 98 (31), 83 (23), 72 (16), 57 (34), 55 (12), 43 (100), and 41 (14). The natural abundance $^{13}$C NMR spectrum (CDCl$_3$) of ketone **30** is summarized in the following structure; the indicated assignments are consistent with off-resonance decoupling measurements. Since the product is a mixture of two diastereoisomers, certain of the $^{13}$C NMR signals appear as two peaks.



Anal. Calcd for C$_{11}$H$_{22}$O: C, 77.58; H, 13.02. Found: C, 77.57; H, 13.02.

To obtain an authentic sample of the alcohol **41**, 1.00 g (8.93 mmol) of the enone **3** was reduced with 177 mg (4.65 mmol) of LiAlH$_4$ in 8 mL of refluxing Et$_2$O for 30 min. After addition of 0.7 mL of H$_2$O and 0.2 mL of aqueous 15% NaOH to precipitate the metal salts, the Et$_2$O solution was dried, concentrated, and distilled to separate the alcohol **41** as a colorless liquid: bp 41–42 °C (12 mm); $n^{25}{}_D$ 1.4508 [lit.[44] bp 65–68 °C (25 mm)]; IR (CCl$_4$) 3615 and 3470 cm$^{-1}$ (OH); NMR (CCl$_4$) δ 4.72 (1 H, q, $J$ = 6.5 Hz, CHO), 2.70 (1 H, s, OH), 1.4–1.8 (9 H, m, allylic CH$_3$), and 1.10 (3 H, d, $J$ = 6.5 Hz, CH$_3$), mass spectrum *m/e* (rel intensity) 114 (M$^+$, 20), 99 (64), 96 (18), 81 (44), 79 (15), 55 (30), 53 (19), 45 (17), 43 (100), 41 (43), and 39 (25).

An authentic sample of the ketone **42** was obtained by hydrogenating a solution of 0.40 g (3.5 mmol) of the enone **3** in 8 mL of EtOH over 30 mg of a 5% Pd/C catalyst at 25 °C and 1 atm of H$_2$. After 8 h the H$_2$ uptake (3.9 mmol) ceased and the mixture was filtered and concentrated. A collected (GLC) sample of the ketone **42**[45] was obtained as a colorless liquid, $n^{25}{}_D$ 1.4070 (lit. bp 135–140,[45a] 136–138 °C[45b]); IR (CCl$_4$) 1713 cm$^{-1}$ (C=O); NMR (CCl$_4$) δ 1.7–2.3 (5 H, m, aliphatic CH including a CH$_3$CO singlet at δ 2.04) and 0.7–1.3 (9 H, m, CH$_3$); mass spectrum *m/e* (rel intensity) 114 (M$^+$, 2), 72 (22), 71 (19), 55 (12), 43 (100), and 41 (20).

**Reaction of (CH$_2$=CHCH$_2$)$_2$CuLi. A. With Enone 47.** To a cold (−72 °C) partial solution of 545 mg (2.65 mmol) of freshly purified Me$_2$SCuBr in 4 mL of Me$_2$S and 4 mL of Et$_2$O was added, dropwise and with stirring, a solution of 5.30 mmol of CH$_2$=CHCH$_2$Li (from PhOCH$_2$CH=CH$_2$) in 6.3 mL of Et$_2$O while the temperature was maintained at −60 to −68 °C. As this addition proceeded the white precipitate (Me$_2$SCuBr) was replaced by a red precipitate (presumably a derivative of allylcopper) and finally a clear red solution of (CH$_2$=CHCH$_2$)$_2$CuLi was obtained. To this solution was added, dropwise and with stirring, a solution 126 mg (1.31 mmol) of the enone **47** and 94 mg of PhC$_8$H$_{17}$-*n* in 4 mL of Et$_2$O. The resulting mixture, from which a red precipitate separated during the addition of the enone, was stirred at −72 °C for 3 h and then allowed to warm to 27 °C overnight. During the warming, decomposition of the excess cuprate reagent was evident (separation of a fine black precipitate) as the temperature of the reaction mixture rose above −30 °C. The final reaction mixture was added, dropwise and with stirring, to an aqueous solution of NH$_4$Cl and NH$_4$OH, and the resulting mixture was extracted with Et$_2$O. After the ethereal solution had been washed successively with aqueous 10% NaOH (to remove PhOH from the PhOCH$_2$CH=CH$_2$) and with aqueous NaCl, it was dried, concentrated, and analyzed [GLC, FFAP (Regis Chemical Co.) on Chromosorb P, apparatus calibrated known mixtures]. The product contained the ketone **48** (retention time 11.1 min, yield 91%), $PhC_8H_{17}$-*n* (22.0 min), and a minor unidentified impurity (3.4 min), but did not exhibit a GLC peak corresponding to the alcohol **49** (9.6 min).

A comparable reaction was run employing the cuprate, from 3.60 g (17.5 mmol) of $Me_2SCuBr$, 35 mmol of $CH_2{=}CHCH_2Li$ (from $PhOCH_2CH{=}CH_2$), 23 mL of $Me_2S$, and 38 mL of $Et_2O$, with a solution of 1.20 g (12.5 mmol) of the enone **47** in 5 mL of $Et_2O$. After the mixture had been stirred at −72 °C for 1 h and then warmed to 0 °C during 15 min, the previously described isolation procedure separated 1.50 g of the crude product as a yellow liquid. Short-path distillation of a 1.39-g aliquot of this product separated 910 mg (57%) of the ketone **48** as a colorless liquid, $n^{25}{}_D$ 1.4720–1.4721, that was identified with the previously described[18] sample by comparison of IR, NMR, and mass spectra.

A solution of 5.00 g (52.1 mmol) of the enone **47** in 10 mL of $Et_2O$ was added, dropwise and with stirring during 20 min, to a solution containing 60 mmol of $CH_2{=}CHCH_2MgBr$ in 68 mL of $Et_2O$. After the resulting mixture had been stirred at 25 °C for 12 h, it was poured into aqueous $NH_4Cl$ and extracted with $Et_2O$. The organic layer was dried and concentrated to leave 6.74 g of the crude alcohol **49**. Fractional distillation afforded 1.01 g of forerun [bp 35–40 °C (0.06 mm); $n^{25}{}_D$ 1.5154] and 3.58 g (50%) of the pure alcohol **49** as a colorless liquid: bp 40–42 °C (0.05 mm); $n^{25}{}_D$ 1.4932; IR ($CCl_4$) 3620, 3480 (OH), 1640 (C=C), and 912 $cm^{-1}$ ($CH{=}CH_2$); NMR ($CCl_4$) $\delta$ 4.7–6.2 (5 H, m, vinyl CH), 2.48 (1 H, s, OH), and 1.0–2.3 (8 H, m, $CH_2$); mass spectrum *m/e* (rel intensity) 120 (6), 97 (100), 79 (32), 55 (37), 41 (33), and 39 (30).

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.18; H, 10.24.

**B. With Enone 8.** To a cold (−65 to −72 °C) solution of $(CH_2{=}CHCH_2)_2CuLi$, from 417 mg (2.03 mmol) of $Me_2SCuBr$, 4.06 mmol of $CH_2{=}CHCH_2Li$ (from $PhOCH_2CH{=}CH_2$), 4 mL of $Me_2S$, and 9.1 mL of $Et_2O$, was added, dropwise and with stirring, a solution of 99 mg (1.01 mmol) of the enone **8** in 4 mL of $Et_2O$. The resulting solution, from which a red precipitate separated within 5 min, was stirred at −72 °C for 2 h and then allowed to warm to 27 °C during 2 h. After following the previously described isolation procedure, an aliquot of the crude product (164 mg of liquid) was mixed with a known weight of dicyclohexyl (an internal standard) for analysis [GLC, FFAP (Regis Chemical Co.) on Chromosorb P, apparatus calibrated with known mixtures]. The crude product contained the enone **8** (retention time 3.2 min, 6% recovery), the ketone **34** (8.4 min, 1% yield), the alcohol **36** (15.1 min, 71% yield), and dicyclohexyl (25.5 min). A comparable reaction of 2.00 g (20.4 mmol) of the enone with a solution of $(CH_2{=}CHCH_2)_2CuLi$ [from 6.30 g (30.7 mmol) of $Me_2SCuBr$ and 61.3 mmol of $CH_2{=}CHCH_2Li$ (from $PhOCH_2CH{=}CH_2$)] in 30 mL of $Me_2S$ and 40 mL of $Et_2O$ produced 3.27 g of crude liquid product containing (GLC) the alcohol **36** accompanied by minor amounts of the enone **8** and the ketone **34**. A collected (GLC) sample of the ketone **34** was identified with an authentic sample by comparison of IR spectra and GLC retention times. Distillation of a 3.14-g aliquot of the curde product separated 1.96 g (72%) of the alcohol **36** [bp 68–74 °C (10 mm); $n^{25}{}_D$ 1.4552–1.4585] that was identified with an authentic sample by comparison of IR and NMR spectra and GLC retention times.

Reaction of 2.76 g (28 mmol) of the enone **8** with 34 mmol of $CH_2{=}CHCH_2MgBr$ in 48 mL of $Et_2O$, followed by the usual isolation procedure, afforded 3.06 g (78%) of the alcohol **36** as a colorless liquid: bp 70–75 °C (10 mm); $n^{25}{}_D$ 1.4570 [lit.[46] bp 72 °C (18 mm); $n^{20}{}_D$ 1.4598]; IR ($CCl_4$) 3600, 3570, 3460 (OH), 1666, 1639 (C=C), and 922 $cm^{-1}$ ($CH{=}CH_2$); NMR ($CCl_4$) $\delta$ 4.7–6.2 (4 H, m, vinyl CH), 2.25 (2 H, d, $J \approx 7$ Hz, allylic $CH_2$), 1.83 (3 H, d, $J$ = 1 Hz, allylic $CH_3$), 1.6–1.8 (1 H, br, OH), 1.66 (3 H, d, $J$ = 1 Hz, allylic $CH_3$), and 1.25 (3 H, s, $CH_3$).

Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 76.96; H 11.55.

Following a previously described[24] procedure, a solution of 1.00 g (8.8 mmol) of $CH_2{=}CHCH_2SiMe_3$ in 10 mL of $CH_2Cl_2$ was added, dropwise and with stirring during 2 min, to a cold (−78 °C) mixture of 0.78 g (8.0 mmol) of the enone **8** and 1.52 g (8.0 mmol) of $TiCl_4$ in 10 mL of $CH_2Cl_2$. The resulting red-brown mixture was allowed to warm to 25 °C with stirring during 40 min and then partitioned between $H_2O$ and $Et_2O$. The organic solution was dried and concentrated to leave 1.60 g of crude liquid product. After an aliquot of the crude product had been mixed with a known amount of 1,3,5-$(i\text{-}Pr)_3C_6H_3$ (an internal standard), analysis (GLC, Carbowax 20 M on Chromosorb P, apparatus calibrated with known mixtures) indicated the presence of the enone **8** (retention time 12.8 min, 13% recovery), the ketone **34** (26.8 min, 85% yield), and 1,3,5-$(i\text{-}Pr)_3C_6H_3$ (108 min). Distillation of a 1.39-g aliquot of the crude product separated 641 mg (66%) of the ketone **34** as a colorless liquid: bp 45–60 °C (10 mm); $n^{25}{}_D$ 1.4330 [lit.[47] bp 167–168 °C; $n^{25}{}_D$ 1.4335]; IR ($CCl_4$) 1720 (C=O), 1639 (C=C), and 922 $cm^{-1}$ ($CH{=}CH_2$); UV max (95% EtOH) 286 nm ($\epsilon$ 21); NMR ($CCl_4$) $\delta$ 4.7–6.2 (3 H, m, vinyl CH), 2.25 (2 H, s, $CH_2CO$), 1.9–2.2 (5 H, m, allylic $CH_2$ and $COCH_3$), and 0.98 (6 H, s, $CH_3$); mass spectrum *m/e* (rel intensity) 125 (7), 99 (46), 82 (75), 67 (33), 55 (28), 43 (100), 41 (36), and 39 (36).

**C. With Enone 7.** To a cold (−72 °C) mixture of 576 mg (2.80 mmol) of $Me_2SCuBr$, 6 mL of $Me_2S$, and 6 mL of $Et_2O$ was added, dropwise with stirring and cooling, a solution of 5.60 mmol of $CH_2{=}CHCH_2Li$ [from $(CH_2{=}CHCH_2)_4Sn$] in 5.2 mL of $Et_2O$. As the lithium reagent was added the white precipitate ($Me_2SCuBr$) dissolved to give an orange-red solution and finally a pale yellow solution when all of the lithium reagent had been added. However, unlike the cuprate preparation using $CH_2{=}CHCH_2Li$ from $PhOCH_2CH{=}CH_2$, no red precipitate was observed when equimolar amounts of $Me_2SCuBr$ and $CH_2{=}CHCH_2Li$ were present. To the cold (−72 °C) solution of the cuprate was added, dropwise and with stirring, a solution of 94.1 mg (1.12 mmol) of the enone **7** and 66.3 mg of *n*-$C_{12}H_{26}$ (an internal standard) in 2 mL of $Et_2O$. During this addition the solution developed a red-orange color, but no red precipitate was observed. The resulting solution was warmed to −50 °C, stirred for 2 h, warmed to −40 °C, and siphoned into a cold (−40 °C), stirred solution of 3 mL of HOAc in 25 mL of $Et_2O$. (In other runs, where the diallylcuprate reagent was allowed to warm to −30 to −35 °C before quenching, some thermal decomposition of the cuprate reagent was evident.) The resulting mixture was warmed to 25 °C and partitioned between $Et_2O$ and aqueous $NaHCO_3$. After the ethereal layer had been washed successively with an aqueous solution (pH 8) of $NH_3$ and $NH_4Cl$ and with aqueous NaCl, it was dried and concentrated for GLC analysis (UCON 50HB 280 X on Chromosorb P, apparatus calibrated with known mixtures). The product contained the enone **7** (retention time 3.4 min, 44% yield), the ketone **33** (7.6 min, 13% yield), the alcohol **35** (10.1 min, 16% yield), and *n*-$C_{12}H_{26}$ (15.1 min). In a second comparable run, where the reaction mixture was stirred at −55 to −60 °C for 45 min and then warmed to 25 °C before quenching, the yields were: 28% of enone **7**, 18% of ketone **33**, and 22% of alcohol **35**. Collected (GLC) samples of ketones **7** and **33** and alcohol **35** were identified with authentic samples[2f] by comparison of GLC retention times and IR spectra.

In an additional set of experiments $CH_2{=}CHCH_2Li$, prepared from $PhOCH_2CH{=}CH_2$, was used to prepare the diallylcuprate reagent. These preparations differed from the preparation described above in that a red precipitate separated when equimolar quantities of $Me_2SCuBr$ and $CH_2{=}CHCH_2Li$ were present and redissolved as the second equivalent of $CH_2{=}CHCH_2Li$ was added to give a cold (−70 to −72 °C) orange solution of the diallylcuprate reagent. From a series of reactions ran for 2–3 h within the temperature range −72 to −30 °C and then quenched in a HOAc–$Et_2O$ mixture at −40 to −30 °C, the product yields were: 48–53% of enone **7**, 10–16% of ketone **33**, and 12–18% of alcohol **35**.

A solution of 1.27 mmol of $CH_2{=}CHCH_2MgBr$ in 1.73 mL of $Et_2O$ was added, dropwise and with stirring, to a cold (−65 °C) suspension of 71.2 mg (0.35 mmol, 28 mol %) of $Me_2SCuBr$ in 3 mL of $Me_2S$ and 3 mL of $Et_2O$ and the resulting pale orange solution was stirred at −60 to −65 °C for 10 min. Then a solution of 95.8 mg (1.14 mmol) of the enone **7** and 74.3 mg of *n*-$C_{12}H_{26}$ (an internal standard) in 3 mL of $Et_2O$ was added dropwise and with stirring during 35 min while the temperature of the mixture was maintained at −48 to −52 °C. The resulting light orange suspension was stirred at −50 °C for 2 h and then warmed to −40 °C, quenched in an HOAc–$Et_2O$ mixture at −40 °C, and subjected to the previously described isolation and analysis procedures. The yields were 8% of enone **7**, 20% of ketone **33**, and 60% of alcohol **35**. Collected (GLC) samples of the products were identified with authentic samples by comparison of IR and mass spectra and GLC retention times. In a similar reaction where an $Et_2O$ solution of $CH_2{=}CHCH_2MgBr$ was added slowly to a cold (−72 °C) mixture of the enone **7** and 27 mol % of $Me_2SCuBr$ the yields were 4% of enone **7**, 13% of ketone **33**, and 53% of the alcohol **35**.

**Reaction of $Me_2CuLi$ With the Enone 60.** To a cold (0 °C) solution of $Me_2CuLi$, from 358 mg (1.74 mmol) of $Me_2SCuBr$, 3.48 mmol of halide-free MeLi, and 12 mL of $Et_2O$, was added, dropwise and with stirring, a solution of 198 mg (1.15 mmol) of the enone **60** in 4 mL of $Et_2O$. After the resulting red-orange solution, from which a yellow precipitate separated rapidly, had been stirred at 0 °C for 1 h, it was siphoned into a vigorously stirred aqueous solution (pH 8) of $NH_4Cl$ and $NH_3$. The resulting solution was extracted with $Et_2O$ and the ethereal extract was dried, concentrated, and mixed with a known weight of *o*-terphenyl (an internal standard) for GLC analysis (silicone

**Table III. Reaction of Enone 60 With $Me_2CuLi$ in $Et_2O$ Solution**

| | Product yields, % | | | | | |
|---|---|---|---|---|---|---|
| | Supernatant solution | | | Precipitate | | |
| Temp, °C | Cu | Enone **60** | Ketone **62** | Cu | Enone **60** | Ketone **62** |
| 27 | 0.5 | 15 | 72 | 99 | | |
| 0 | 1.5 | 17 | 68 | 98 | | |
| −44 | 1.2 | 4 | 67 | 98 | 3 | 17 |
| −72 | 5.3 | 9 | 0.5 | 94 | 59 | 32 |

SE-52 on Chromosorb P, apparatus calibrated with known mixtures). The crude product contained the ketone **62** (retention time 12.8 min, 96% yield) and *o*-terphenyl (37.0 min), but none of the starting enone **60** (17.7 min) was detected. A collected (GLC) sample of the ketone **62** was obtained as a colorless liquid: $n^{25}{}_{D}$ 1.5397 [lit.[48] bp 80–100 °C (0.1 mm)]; IR ($CCl_4$) 1719 $cm^{-1}$ (C=O); NMR ($CCl_4$) $\delta$ 7.0–7.4 (5 H, m, aryl CH), 1.4–3.0 (8 H, m, $CH_2$), and 1.26 (3 H, s, $CH_3$; lit.[32] 1.28); UV (95% EtOH) series of weak maxima ($\epsilon$ 283 or less) in region 247–268 nm with a maximum at 282 nm ($\epsilon$ 87); mass spectrum *m/e* (rel intensity) 188 ($M^+$, 65), 173 (30), 145 (30), 131 (100), 118 (50), 117 (33), 91 (51), 55 (68), and 42 (43).

In a series of similar experiments, solutions of 1.16–1.18 mmol of the enone **60** in 5 mL of $Et_2O$ were added, dropwise and with stirring during a period of 40–45 min, to centrifuge tubes containing 1.22–1.28 mmol of $Me_2CuLi$ in 6.5 mL of $Et_2O$ that were continuously cooled in baths at the temperatures indicated in Table III. In each case a yellow (27, 0, −44 °C) to orange (−72 °C) precipitate separated during the addition of the enone **60**. The resulting mixtures were stirred for 40 min at the bath temperatures indicated in Table III, centrifuged for 1–2 min, and again stored in the cooling baths while the supernatant liquid was separated from each tube with a cannula. In the experiments performed at 27 °C and at 0 °C, the precipitates were washed with two 10-mL portions of $Et_2O$ (at 0 or 27 °C) and these washings were combined with the appropriate supernatant solutions. The separate supernatant solutions and precipitates were each hydrolyzed with water and extracted with $Et_2O$. Each of the $Et_2O$ extracts was dried, concentrated, mixed with a known weight of *o*-terphenyl, and subjected to the previously described GLC analysis. Each aqueous phase was acidified with aqueous $H_2SO_4$ and $HNO_3$, boiled to complete the oxidation of all Cu salts to Cu(II) salts and to expel oxides of nitrogen, and then analyzed for copper by electrodeposition. The yields of Cu, the recovered enone **60**, and the ketone **62**, found in the precipitates and the supernatant solutions are presented in Table III.

To explore the solubility of the lithium enolate **61** at low temperature, the above reaction of $Me_2CuLi$ with the enone **60** was repeated at 27 °C and the supernatnat solution was separated from the $(MeCu)_n$ precipitate by centrifugation. When this supernatant solution was cooled to 0 °C, a small amount of gray-white solid precipitated. This precipitate was separated by centrifugation, hydrolyzed, and subjected to the previously descrbed GLC analysis. The organic material obtained from this precipitate contained the enone **60** (0.4% recovery) and the ketone **62** (0.4% yield). The remaining solution was cooled to −72 °C and centrifuged to separate a white crystalline precipitate (mainly LiBr) from a pale yellow supernatant solution. The organic material obtained from this precipitate contained the enone **60** (1.1% recovery) and the ketone **62** (0.7% yield). The supernatant solution was hydrolyzed to give the enone **60** (22% recovery) and the ketone **62** (55% yield). Thus, we conclude that the lithium enolate **61** is relatively soluble in $Et_2O$ at −72 °C in the concentration range where these experiments were performed.

**Registry No.**—**9,** 65995-74-6; **10,** 614-47-1; **11,** 1533-20-6; **41,** 2747-54-8; **42,** 565-78-6; **43,** 4325-82-0; **44,** 108-10-1; **45,** 65995-75-7; **46,** 3744-02-3; **47,** 930-68-7; 48, 20498-05-9; **49,** 65995-76-8; **60,** 10345-87-6; **62,** 33026-37-8.

## References and Notes

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(2) (a) For a recent review, see H. O. House, *Acc. Chem. Res.*, **9,** 59 (1976); (b) H. O. House, C. Y. Chu, J. M. Wilkins, and M. J. Umen, *J. Org. Chem.*, **40,** 1460 (1975); (c) H. O. House and C. Y. Chu, *ibid.*, **41,** 3083 (1976); (d) H. O. House and K. A. J. Snoble, *ibid.*, **41,** 3076 (1976); (e) H. O. House, A. V. Prabhu, J. M. Wilkins, and L. F. Lee, *ibid.*, **41,** 3067 (1976); (f) H. O. House, C. Y. Chu, W. V. Phillips, T. S. B. Sayer, and C. C. Yau, *ibid.*, **42,** 1709 (1977); (g) H. O. House and J. M. Wilkins, *ibid.*, **41,** 4031 (1976).

(3) Although this reagent is now known to be dimeric ($Li_2Cu_2Me_4$) in $Et_2O$ solution, we will continue to represent this reagent as $LiCuMe_2$ unless clarity of the discussion requires the dimeric formulation. Molecular weight studies of this reagent have been performed by (a) R. G. Pearson and C. D. Gregory, *J. Am. Chem. Soc.*, **98,** 4098 (1976); and (b) E. C. Ashby and J. J. Watkins, *ibid.*, **99,** 5312 (1977).

(4) H. O. House, L. E. Huber, and M. J. Umen, *J. Am. Chem. Soc.*, **94,** 8471 (1972).

(5) M. Szwarc in "Ions and Ion Pairs in Organic Reactions", Vol. 1, M. Szwarc, Ed., Wiley-Interscience, New York, N.Y., 1972, pp 1–6.

(6) (a) For a general review, see G. H. Posner, *Org. React.*, **22,** 253 (1975); (b) G. M. Whitesides, W. F. Fischer, Jr., J. San Filippo, Jr., R. W. Bashe, and H. O. House, *J. Am. Chem. Soc.*, **91,** 4871 (1969); (c) C. R. Johnson and G. A. Dutra, *ibid.*, **95,** 7777, 7783 (1973); (d) G. Linstrumelle, J. K. Krieger, and G. M. Whitesides, *Org. Synth.*, **55,** 103 (1976).

(7) C. R. Johnson, R. W. Herr, and D. M. Wieland, *J. Org. Chem.*, **38,** 4263 (1973).

(8) (a) G. H. Posner, J. J. Sterling, C. E. Whitten, C. M. Lentz, and D. J. Brunelle, *J. Am. Chem. Soc.*, **97,** 107 (1975); G. H. Posner, C. E. Whitten, and J. J. Sterling, *ibid.*, **95,** 7788 (1973); (b) C. Ouannes, G. Dressaire, and Y. Langlois, *Tetrahedron Lett.*, 815 (1977); (c) E. C. Ashby, J. J. Lin, and J. J. Watkins, *J. Org. Chem.*, **42,** 1099 (1977).

(9) Comparison of the reduction potentials for $CH_3CH{=}CHCOCH_3$ (−2.08 V) and $CH_3C(OCOCH_3){=}CHCOCH_3$ (−2.14 V, ref 2b) suggests that a $\beta$-$OCOCH_3$ substituent has about the same effect on the reduction potential as a $\beta$-H substituent. The reduction potential of the unsaturated ester **6** was estimated (see ref 4) on this basis.

(10) H. O. House and W. F. Fischer, Jr., *J. Org. Chem.*, **33,** 949 (1968).

(11) H. O. House and P. D. Weeks, *J. Am. Chem. Soc.*, **97,** 2785 (1975).

(12) G. H. Posner, C. E. Whitten, J. J. Sterling, and D. J. Brunelle, *Tetrahedron Lett.*, 2591 (1974).

(13) W. H. Mandeville and G. M. Whitesides, *J. Org. Chem.*, **39,** 400 (1974).

(14) K. Koosha, J. Berlan, M. L. Capmau, and W. Chodkiewicz [*Bull. Soc. Chim. Fr.*, 1284 (1975)] have reported a very different order of reactivity, *t*-Bu > *i*-Pr > *n*-Bu > Ph > Me, for competitive additions of cuprate mixtures to $CH_2{=}C{=}CHP(O)Ph_2$. The meaning of this observation is not clear.

(15) (a) H. O. House and M. J. Umen, *J. Am. Chem. Soc.*, **94,** 5495 (1972); *J. Org. Chem.*, **38,** 3893 (1973); (b) H. O. House, J. Lubinkowski, and J. J. Good, *ibid.*, **40,** 86 (1975).

(16) H. O. House, W. V. Phillips, T. S. B. Sayer, and C. C. Yau, *J. Org. Chem.*, **43,** 700 (1978).

(17) For recent examples, see (a) H. O. House and J. C. Dubose, *J. Org. Chem.*, **40,** 788 (1975); (b) M. F. Semmelhack and R. D. Stauffer, *ibid.*, **40,** 3619 (1975); (c) T. Yoshida and E. Negishi, *J. Chem. Soc., Chem. Commun.*, **No. 18,** 762 (1974); (d) E. C. Ashby and J. J. Lin, *Tetrahedron Lett.*, **No. 50,** 4453 (1975); E. C. Ashby, J. J. Lin, and R. Kovar, *J. Org. Chem.*, **41,** 1939 (1976); (e) K. Wada, M. Tamura, and J. Kochi, *J. Am. Chem. Soc.*, **92,** 6656 (1970); (f) M. F. Semmelhack, R. D. Stauffer, and A. Yamashita, *J. Org. Chem.*, **42,** 3180 (1977); (g) E. C. Ashby, J. J. Lin, and A. B. Goel, *ibid.*, **43,** 183 (1978).

(18) H. O. House and W. F. Fischer, Jr., *J. Org. Chem.*, **34,** 3615 (1969).

(19) (a) E. S. Binkley and C. H. Heathcock, *J. Org. Chem.*, **40,** 2156 (1975); (b) A. E. Greene and P. Crabbé, *Tetrahedron Lett.*, 4867 (1976); (c) H. O. House, T. S. B. Sayer, and C. C. Yau, *J. Org. Chem.*, in press.

(20) (a) D. Seyferth and M. A. Weiner, "Organic Syntheses", Collect. Vol. 5, Wiley, New York, N.Y., 1973, p 452; (b) J. J. Eisch and A. M. Jacobs, *J. Org. Chem.*, **28,** 2145 (1963).

(21) L. Mandell and J. M. Brodmann, *J. Org. Chem.*, **31,** 591 (1966).

(22) D. A. Evans and A. M. Golob, *J. Am. Chem. Soc.*, **97,** 4765 (1975).

(23) For example, G. Daviaud and Ph. Miginiac [*Tetrahedron Lett.*, 3345 (1973)] have reported the successful conjugate addition of $LiCu(CH_2CH{=}CH_2)_2$ to the ester $CH_3CH{=}CHCO_2Bu$-*sec* (calcd $E_{red} = -2.3$ V) in an $Et_2O$–THF mixture.

(24) A. Hosomi and H. Sakurai, *J. Am. Chem. Soc.*, **99,** 1673 (1977).

(25) J. Klein and R. Levene, *J. Chem. Soc., Perkin Trans. 2*, 1971 (1973), and references cited therein.

(26) All melting points are corrected and all boiling points are uncorrected. Unless otherwise stated, $MgSO_4$ was employed as a drying agent. The IR spectra were determined with a Perkin-Elmer Model 257 infrared recording spectrophotometer fitted with a grating. The UV spectra were determined with a Cary Model 14 or a Perkin Elmer Model 202 recording spectrophotometer. The proton NMR spectra were determined at 60 MHz with a Varian Model A-60 or Model T-60-A NMR spectrometer and the $^{13}C$ NMR spectra were determined at 25 MHz with a JEOL Fourier transform spectrometer, Model PFT-100. The chemical-shift values are expressed in $\delta$ values (ppm) relative to a $Me_4Si$ internal standard. The mass spectra were obtained with a Hitachi (Perkin-Elmer) Model RMU-7 or a Varian Model M-66 mass spectrometer. All reactions involving strong bases or reactive organometallic intermediates were performed under a nitrogen atmosphere.

(27) H. C. Odom and A. R. Pinder, *Org. Synth.*, **51,** 115 (1971).

(28) F. H. Stross, J. M. Monger, and H. de V. Finch, *J. Am. Chem. Soc.*, **69,** 1967 (1947).

(29) G. M. Whitesides, C.P. Casey, and J. K. Krieger, *J. Am. Chem. Soc.*, **93**, 1379 (1971).
(30) (a) O. Grummitt, E. P. Budewitz, and C. C. Chudd, ref 20a, Collect. Vol. 4, 1963, p 748; (b) J. C. H. Hwa, and H. Sims, ref 20a, Collect. Vol. 5, 1973, p 608.
(31) (a) S. C. Watson and J. F. Eastham, *J. Organomet. Chem.*, **9**, 165 (1967); (b) M. Gall and H. O. House, *Org. Synth.*, **52**, 39 (1972).
(32) These measurements were performed in our laboratory by Mr. Ronald Sieloff.
(33) G. F. Woods and I. W. Tucker, *J. Am. Chem. Soc.*, **70**, 2174 (1948).
(34) H. O. House and R. L. Wasson, *J. Am. Chem. Soc.*, **79**, 1488 (1957).
(35) W. H. Saunders, Jr., and G. L. Carges, *J. Am. Chem. Soc.*, **82**, 3582 (1960).
(36) This deuterium isotope effect on the position of an $^1$H NMR signal has been noted previously: G. Van Dyke Tiers, *J. Chem. Phys.*, 963 (1958).
(37) (a) J. W. Wilt and A. Danielzadeh, *J. Org. Chem.*, **23**, 920 (1958); (b) A. Hoffman, *J. Am. Chem. Soc.*, **51**, 2542 (1929).
(38) (a) W. A. Mosher, P. W. Berger, A. P. Foldi, J. E. Gardner, T. J. Kelly, and C. Nebel, *J. Chem. Soc. C*, 121 (1969); (b) A. D. Grebenyuk and N. T. Zaitseva, *Zh. Org. Khim.*, **4**, 302 (1968); (c) J. Colonge and L. Pichat, *Bull. Soc. Chim. Fr.*, 177 (1949).
(39) I. N. Nazarov and Zh. A. Krasnaia, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 870 (1958); *Chem. Abstr.*, **53**, 1124e (1959).
(40) F. C. Witmore, D. P. J. Goldsmith, N. C. Cook, J. C. Yarze, and G. G. Ecke, *J. Am. Chem. Soc.*, **72**, 53 (1950).
(41) (a) A. D. Petrov, V. L. Suchchinsky, and L. D. Konovalchikov, *Zh. Obshch. Khim.*, **25**, 1566 (1955); (b) H. Sliwa and P. Maitte, *Bull. Soc. Chim. Fr.*, 369 (1962).
(42) R. Ya. Levina, V. N. Kostin, P. A. Gembitskii, and E. G. Treshchova, *J. Gen. Chem. USSR*, **30**, 883 (1960).
(43) J. Royer and J. Dreux, *Tetrahedron Lett.*, **No. 53**, 5589 (1968); *Justus Liebigs Ann. Chem.*, **741**, 109 (1970).
(44) H. H. Stechl, *Chem. Ber.*, **97**, 2681 (1964).
(45) (a) R. C. Huston and R. L. Guile, *J. Am. Chem. Soc.*, **61**, 69 (1939); (b) C. D. Nenitzescu and I. Chicos, *Ber. Dtsch. Chem. Ges.*, **68**, 1584 (1935); (c) L. E. Hightower, L. R. Glasgow, K. M. Stone, D. A. Albertson, and H. A. Smith, *J. Org. Chem.*, **35**, 1881 (1970).
(46) H. R. Henze, B. B. Allen, and W. B. Leslie, *J. Org. Chem.*, **7**, 326 (1942).
(47) A. Viola, E. J. Iorio, K. K. Chen, G. M. Glover, U. Nayak, and P. J. Kocienski, *J. Am. Chem. Soc.*, **89**, 3462 (1967).
(48) J. R. Bantick and E. Rothstein, *J. Chem. Soc. C*, 2512 (1971).

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# Palladium-Catalyzed Arylation of Ethylene

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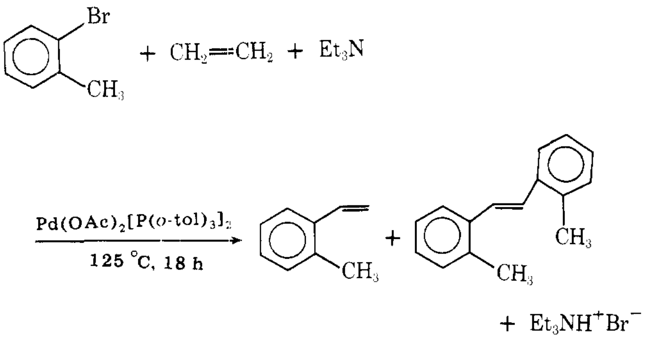
A variety of styrene derivatives and 3-vinylpyridine were prepared in moderate to good yields by the palladium–tri-*o*-tolylphosphine catalyzed reaction of ethylene with aryl bromides or 3-bromopyridine, respectively.

Styrene derivatives are often very useful chemical intermediates. Frequently, the synthesis of many of these derivatives is not trivial. Therefore, we thought it worthwhile to investigate the palladium-catalyzed arylation of ethylene as a simple general route to these compounds. Previously, ethylene had been successfully used in the arylation reaction but the generality of the reaction had not been determined.[1,2] This paper reports a study of the reaction employing a variety of aryl bromides.

## Results and Discussion

Preliminary experiments reacting 2-bromotoluene in acetonitrile solution with ethylene using triethylamine as base and 1 mol % palladium acetate, plus 2 mol % tri-*o*-tolylphosphine (based upon the halide) as catalyst, showed that ethylene pressure was necessary to obtain good yields of *o*-methylstyrene. The yield of 2-methylstyrene in 20 h at 125 °C increased from 54 to 83 to 86% as the pressure of ethylene was increased from 20 to 100 to 120 psi, respectively. The reason for the lower yields at the lower pressures was that (*E*)-2,2′-dimethylstilbene was being formed as a side product by a second arylation of the 2-methylstyrene. The yields of the stilbene decreased from 34 to 10 to 4%, respectively, in the above reactions. At pressures above about 200 psi the reaction rates decreased. At 750 psi only 40% of the styrene was formed in 20 h and 60% of the starting bromide remained unreacted. The high ethylene pressure apparently deactivates the catalyst by coordination probably decreasing the rate of oxidative addition of the 2-bromotoluene.



In one experiment, the use of triphenylphosphine rather than the tri-*o*-tolylphosphine gave product at only half the rate. Therefore, subsequent experiments were carried out with 100–200 psi of ethylene with tri-*o*-tolylphosphine in the catalyst.

Ethylene was arylated with seven different aryl bromides and 3-bromopyridine as shown in Table I. The isolated yields of distilled styrene products ranged from 45 to 86%. The stilbene yields were also obtained by isolation. Unreacted aryl bromides were determined by GLC. These are relatively good yields considering the fact that the reactions were carried out on only a 10–20 mmol scale and some polymerization often occurred. 3-Bromopyridine yielded the 3-vinyl derivative in 52% yield (isolated as the picrate). Styrene derivatives with methyl, nitro, acetamide, amino, formyl, and carboxyl substituents also were prepared. *o*-Divinylbenzene was obtained from *o*-dibromobenzene in 76% (isolated) yield. Thus, the palladium-catalyzed arylation of ethylene appears to be an excellent method for the preparation of a wide variety of styrene derivatives.

## Experimental Section

**Reagents.** All of the aryl bromides were commercial products which were used without further purification. The ethylene, triethylamine, and acetonitrile were reagent grade materials and were used as received. The tri-*o*-tolylphosphine was prepared by the Grignard procedure described previously.[3] The palladium acetate was prepared by the published method.[4]

**General Procedure for the Arylation of Ethylene.** A 45-mL T-303 stainless steel bomb (Parr Instrument Company) containing a Teflon-coated magnetic stirring bar was charged with 20 mmol of