# Stereospecific Umpolung $\alpha'$ Substitution of Ketones via Reactions of Organocuprates with Enol Ethers of $\alpha,\beta$-Epoxycyclohexanones

**J. P. Marino* and Juan Carlos Jaén**

*Contribution from the Department of Chemistry, The University of Michigan, Ann Arbor, Michigan 48109.* *Received September 21, 1981*

**Abstract:** The silyl enol ethers of substituted 2,3-epoxycyclohexanones react with alkyl- and phenylcyanocuprate reagents in a regio- and stereospecific manner to yield, in most cases, the 1,4-trans adducts. Vinylic cuprates show a regioselectivity that is dependent on the substitution pattern of each particular substrate. The stereochemistry of the adducts obtained in these reactions was determined, as well as their conformational preferences, by $^1H$ and $^{13}C$ NMR analyses. Mild acidic hydrolysis of the 1,4 adducts provides $\alpha'$-mono- and disubstituted 2-cyclohexenones with complete stereospecificity. Other interesting uses of the adducts involve the stereospecific synthesis of 6-substituted 3-hydroxycyclohexanones and the formation of highly functionalized open-chain compounds. The use of organocuprate reagents to introduce a substituent $\alpha$ to a ketone represents a new strategy involving an umpolung reactivity for carbon atoms $\alpha$ to the carbonyl group.

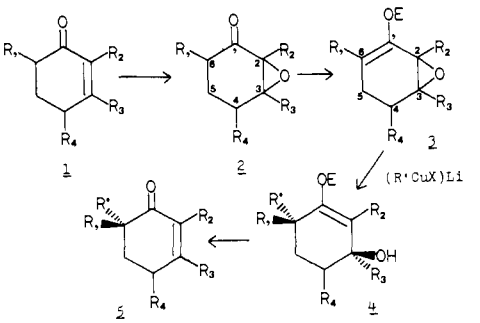
The $\alpha$ substitution of ketones and other carbonyl compounds is most directly accomplished by the alkylation of enolates with electrophiles.[1] This general approach fails with highly substituted and nonaliphatic electrophiles. Furthermore, when the $\alpha$-carbon is tertiary, further alkylation at that position proves to be very difficult, even with some of the most reactive electrophiles.[2] As a solution to this problem, several groups[3] have chosen to study the use of silyl enol ethers as the nucleophile rather than the enolates. In this way, highly substituted groups can be introduced $\alpha$ to a carbonyl group. Albeit, when direct alkylation of the enolate or enol ether takes place effectively, stereospecific introduction of the incoming group is usually difficult to predict and control, often depending on conformational and steric effects of the rest of the molecule. Furthermore, $\alpha'$ alkylation of $\alpha,\beta$-unsaturated ketones can be complicated by the existence of multiple sites for deprotonation.

In 1979, we reported a new strategy for the $\alpha'$ substitution of $\alpha,\beta$-epoxy ketones.[4] This new approach is based on the stereospecific 1,4 addition of organocuprates to enol ethers of $\alpha,\beta$-epoxy ketones and represents an umpolung reactivity for the carbon atom $\alpha$ to a ketone functionality (see Scheme I). Since the organocopper reagents are not subject to the steric requirements of electrophiles or the reactivity profiles of nucleophiles, they provide a unique route for the introduction of vinyl, aryl, and highly substituted alkyl groups $\alpha$ to the ketone group. The organocopper method also allows the stereochemical control of the newly introduced $\alpha'$ substituent.

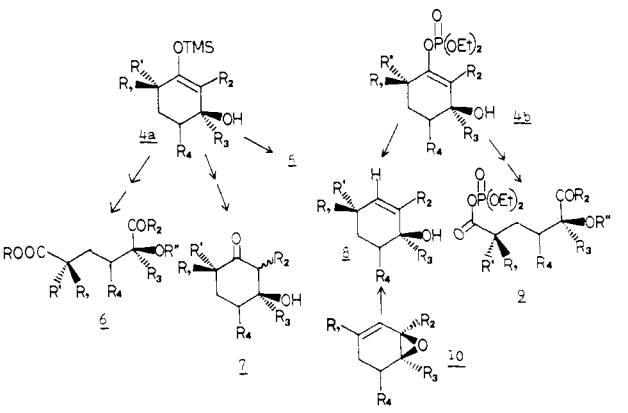
In this report, we wish to describe the scope and stereochemical consequences of this synthetic methodology. In exploring the general applicability of this umpolung $\alpha$ substitution of ketones, we were particularly concerned with variations in enol ethers, in substitution patterns of the epoxy enol ether system, and in the type of organocuprate reagent.

We have focused our attention mainly on enol silyl ethers (**3a**, E = $SiR_3$) and enol phosphates [**3b**, E = $P(O)(OR)_2$]. The choice of one group or the other is not at all arbitrary; rather, it is determined by the further chemical transformations that await adduct **4** (see Scheme II).

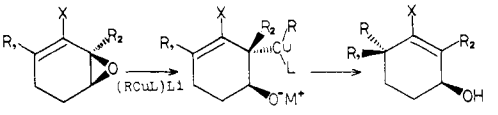
Scheme I



Scheme II



Scheme III



Thus, adducts **4a** can be transformed into open-chain compounds represented by **6**,[4] highly functionalized synthons that have potential as intermediates in the synthesis of a number of natural products, such as the macrolide antibiotics. Also available from adducts **4a** are $\alpha'$-substituted, $\beta$-hydroxy ketones **7**,[4] and $\alpha'$-substituted 2-cyclohexenones **5**, which are produced under mild conditions that do not promote the epimerization of the $\alpha'$-carbon (vide infra), thus effecting a stereospecific $\alpha'$ substitution from **1** to **5**.

On the other hand, the enol phosphate adducts represented by **4b** can be reduced to allylic alcohols **8**,[5] thus providing an al-

(1) Stowell, J. C. "Carbanions in Organic Synthesis"; Wiley: New York, 1979; p 128.
(2) (a) House, H. O.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1971**, *36*, 2361. (b) Stork, G.; Hudrlik, P. F. *J. Am. Chem. Soc.* **1968**, *90*, 4462, 4464.
(3) (a) Chan, T. H.; Paterson, I.; Pinsonnault, J. *Tetrahedron Lett.* **1977**, 4183. (b) Reetz, M. T.; Maier, W. F. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 48. (c) Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503. (d) Paterson, I.; Fleming, I. *Tetrahedron Lett.* **1979**, 2175. (e) Reetz, M. T.; Chatzüosifidis, I.; Löwe, U.; Maier, W. F. *Tetrahedron Lett.* **1979**, 1427. (f) Caine, D. "Carbon-Carbon Bond Formation"; Augustine, R., Ed.; Marcel Dekker: New York, 1979; Vol. 1, p 292. (g) See also: Fleming, I. *Chimia* **1980**, *34*, 265.
(4) Marino, J. P.; Hatanaka, N. *J. Org. Chem.* **1979**, *44*, 4467.
(5) Marino, J. P.; Abe, H. *J. Org. Chem.* **1981**, *46*, 5379.

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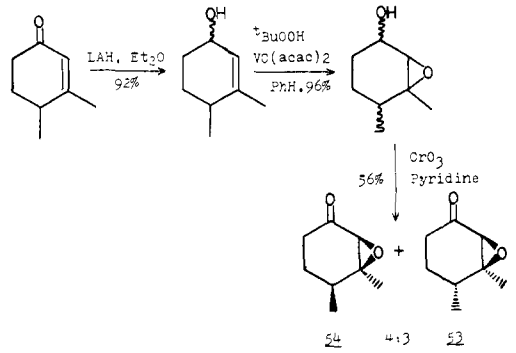
Scheme IV

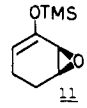
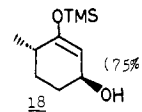
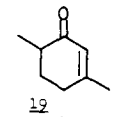
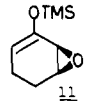
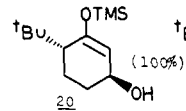
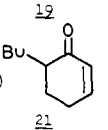
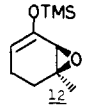
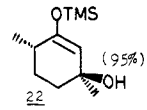
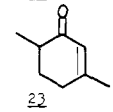
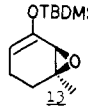
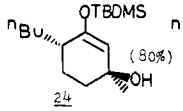
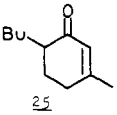
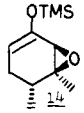
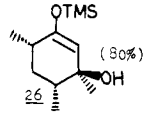
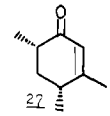
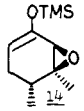
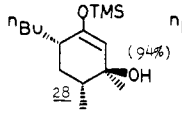
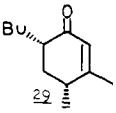
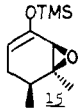
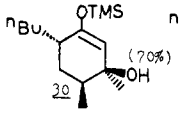
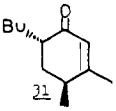
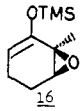
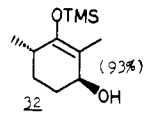
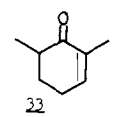
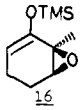
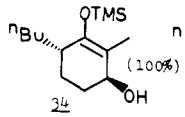
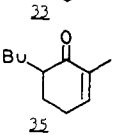
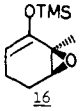
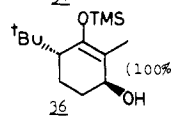
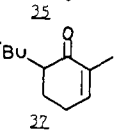
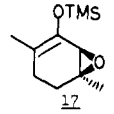
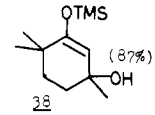
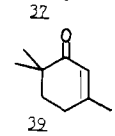
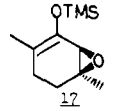
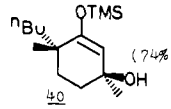
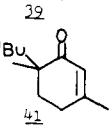
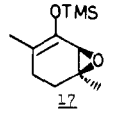
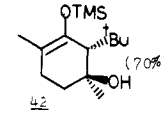
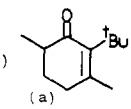



ternative route to a class of compounds previously obtained by the addition of cyanocuprates to diene monoepoxide systems[6] (**10** → **8**). Furthermore, an oxidative cleavage of **4b** will generate an open-chain product such as **9**, which differs from **6** in that one end of the chain is in the form of an unusual mixed anhydride rather than an ester.[7] This mixed anhydride is stable in mild aqueous basic and acidic media.

After our initial report[4,8] on the synthetic utility of the reaction between organocopper reagents and enol ethers of $\alpha,\beta$-epoxy ketones, we explored the generality of the method. The presence of carbon substituents at positions 2 and 6 of the six-membered ring was considered to be of the utmost importance, for several reasons. First, it has repeatedly been proposed[9,10] that the $S_N2'$ reaction of organocopper reagents with allylic epoxides and other reactive allylic groups proceeds with direct displacement of the allylic group by copper, followed by a reductive coupling involving migration of the double bond and delivery of the ligand group to the C-6 position of the ring (see Scheme III). It has also been shown[10] that, when steric effects preclude this attack, an alternative cis addition can predominate, with formation of the product that originates from the cis-$S_N2'$ displacement of the leaving group. (Other possible mechanisms have also been proposed; vide infra.) In light of this, we thought that the presence of a substituent on C2 of our epoxy enol ether system **3** ($R_2 \neq H$) should render that site too hindered for attack by copper, and one might expect to find either a lack of reactivity or the formation of mixtures of isomers arising from more than one of the proposed mechanisms.[10,11] In the second place, the substitution at the C6 position of **3** ($R_1 \neq H$) would allow us to determine the feasibility of our method for the stereospecific formation of $\alpha'$-gem disubstituted ketones **5** and **7**, by the sequential introduction of both substituents.

All our previous work on simple diene monoepoxides had indicated that mixed cyanocuprates were the most selective of all organocopper reagents for the 1,4-trans addition to these systems.[4,6] Furthermore, the use of a mixed reagent represents an economy of potentially valuable ligands in more complicated systems, as compared with homocuprates $R_2CuLi$. Our study includes those organocuprates that could be easily prepared from commercial alkyllithium compounds (RCuCNLi, R = Me, *n*-Bu, *t*-Bu), as well as the $sp^2$ cuprates derived from vinyllithium and phenylmagnesium bromide (RCuCNLi, R = vinyl; RCuCNMgBr, R = Ph).

Table I. Reactions of Alkylcyanocuprates with Substituted Epoxy Enol Ethers

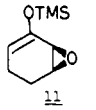
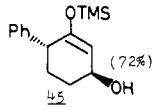
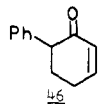
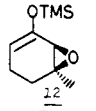
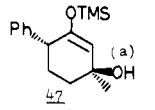
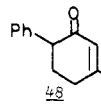
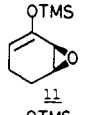
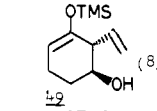
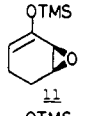
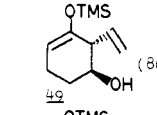
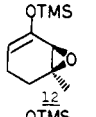
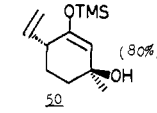
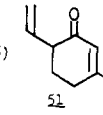
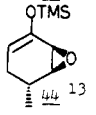
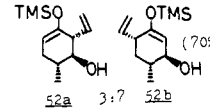
| No. | Substrate | Cuprate | Product (Crude yield) | Enone [c] |
|---|---|---|---|---|
| 1 |  11 | (MeCuCN)Li |  (75%) 18 |  19 |
| 2 |  11 | ($^t$BuCuCN)Li |  (100%) 20 |  21 |
| 3 |  12 | (MeCuCN)Li |  (95%) 22 |  23 |
| 4 |  13 | ($^n$BuCuCN)Li |  (80%) 24 |  25 |
| 5 |  14 | (MeCuCN)Li |  (80%) 26 |  27 |
| 6 |  14 | ($^n$BuCuCN)Li |  (94%) 28 |  29 |
| 7 |  15 | ($^n$BuCuCN)Li |  (70%) 30 |  31 |
| 8 |  16 | (MeCuCN)Li |  (93%) 32 |  33 |
| 9 |  16 | ($^n$BuCuCN)Li |  (100%) 34 |  35 |
| 10 |  16 | ($^t$BuCuCN)Li |  (100%) 36 |  37 |
| 11 |  17 | (MeCuCN)Li |  (87%) 38 |  39 |
| 12 |  17 | ($^n$BuCuCN)Li |  (74%) 40 |  41 |
| 13 |  17 | ($^t$BuCuCN)Li |  (70%) 42 |  (a) |
| | | |  (5%) [b] 43 |  |

[a] Enone not obtainable by the standard mild hydrolysis described in the Experimental Section. [b] Compound not isolated; only detected by 360-MHz $^1$H NMR. [c] The conversion from the 1,4 adduct to the enone is essentially quantitative in most cases.

Epoxy enol ethers **11–17** (Table I) were prepared from the corresponding $\alpha,\beta$-epoxycyclohexanones, which were in turn obtained by direct base-catalyzed epoxidation of the respective

(6) Marino, J. P.; Floyd, D. M. *Tetrahedron Lett.* **1979**, 675.
(7) Marino, J. P.; Jaen, J. C., unpublished results.
(8) For a recent modification of our original methodology, reacting homocuprates $R_2CuLi$ with the enolates of $\alpha,\beta$-epoxy ketones, rather than with their enol ethers, see: Wender, P. A.; Erhardt, J. M.; Letendre, L. J. *J. Am. Chem. Soc.* **1981**, *103*, 2114.
(9) (a) Teutsch, G.; Belanger, A. *Tetrahedron Lett.* **1979**, 2051. (b) For the involvement of copper in the reaction of homocuprates with alkyl halides, see: Pearson, R. G.; Gregory, C. D. *J. Am. Chem. Soc.* **1976**, *98*, 4098.
(10) (a) Chapleo, C. B.; Finch, M. A. W.; Lee, T. V.; Roberts, S. M. *J. Chem. Soc., Chem. Commun.* **1979**, 676. (b) Steric effects are also revealed in the results obtained by: Corey, E. J.; Mann, J. *J. Am. Chem. Soc.* **1973**, *95*, 6832.
(11) (a) Goering, H. L.; Singleton, V. D., Jr. *J. Am. Chem. Soc.* **1976**, *98*, 7854. (b) Gallina, C.; Ciattini, P. G. *Ibid.* **1979**, *101*, 1035. (c) Kreft, A. *Tetrahedron Lett.* **1977**, 1035. (d) Claesson, A.; Olsson, L.-I. *J. Chem. Soc., Chem. Commun.* **1978**, 621.

Table II. Reactions of Vinyl- and Phenylcyanocuprates with Substituted Epoxy Enol Ethers

| No. | Substrate | Cuprate | Product (Crude yield) | Enone |
|---|---|---|---|---|
| 1 |  11 | (PhCuCN)MgBr |  (72%) 45 |  46 |
| 2 |  12 | (PhCuCN)MgBr |  (a) 47 |  (86%) 48 |
| 3 |  11 | $(C_2H_3CuCN)MgBr$ |  (85%) 49 | (b) |
| 4 |  11 | $(C_2H_3CuCN)Li$ |  (80%) 49 | (b) |
| 5 |  12 | $(C_2H_3CuCN)Li$ |  (80%) 50 |  51 |
| 6 |  44 13 | $(C_2H_3CuCN)Li$ |  (70%)[c] 52a 3:7 52b | (d) |

[a] The original 1,4-adduct 47 was not isolated. Enone 48 was obtained directly after workup, in 86% yield. [b] Enone not obtained by the method described in the Experimental Section. [c] Product 52b was not isolated. Separated assignments were made by analysis of the 360-MHz $^1H$ NMR of the crude. See Experimental Section. [d] See Experimental Section.

2-cyclohexenones, with the exception of 2,3-epoxy-3,4-*trans*-dimethylcyclohexanone (**54**); when 3,4-dimethyl-2-cyclohexenone was treated with *t*-BuOOH/Triton B in benzene, 2,3-epoxy-3,4-*cis*-dimethylcyclohexanone (**53**) was formed exclusively. Use of $H_2O_2$/NaOH in methanol provided a 9:1 mixture of epoxy ketones **53**:**54**. The steric interaction between the C-3 and C-4 methyl substituents of the enone causes the C-4 methyl to adopt a pseudoaxial conformation[12] that forces the peroxide reagent to approach the molecule from the opposite side. The *trans*-dimethyl isomer **54** was isolated in better yield by chromatographic separation from the reaction mixture product of the sequence seen in Scheme IV.

The reaction of substrates **11**–**17** with alkylcyanocuprates was studied, and the results are shown in Table I. Table II contains the reactions performed with $sp^2$-hybridized cuprates. Each reaction was run several times with amounts of organocopper reagent ranging from 1 to 4 equiv. In general, 1 equiv of cuprate is sufficient to bring the reaction to completion. Occasionally, with (MeCuCN)Li, some excess of the reagent is required. We believe this is due to the presence of an undetermined amount of inorganic salts in the starting methyllithium ether solution, decreasing the solubility of the organocuprate, thus leading to lower yields.

The crude reaction products were routinely analyzed by $^{13}C$ NMR and 360-MHz $^1H$ NMR. In most cases, the presence of only one product could be clearly determined by these techniques. When alkylcyanocuprates were used, trans-1,4 adducts were obtained, with the exception of entry 13, in yields ranging from 70 to 100%. The unstable alcohol adducts can be isolated, even after an aqueous ammonium chloride workup, if sodium sulfate is used as the drying agent for the isolation procedure. The purity of the crude products is usually very high, as determined by $^{13}C$ NMR and 360-MHz $^1H$ NMR. When the products are stored in solution, hydrolysis to the enone system usually occurs within 2–3 days. If carefully dried and kept without solvent, they can be stored at −10 °C for longer periods of time. Purification of the adducts can occasionally be achieved by flash column chromatography on silica gel, but more often this leads to decomposition to the cyclohexenone.

As shown in Table II, phenylcyanocuprate showed regio- and stereospecificity similar to the alkylcyanocuprates, while vinylcyanocuprate showed a marked dependence on the substitution pattern of the epoxy enol ether system. We have observed a similar "anomalous" behavior with other vinylic cyanocuprates in our laboratory.

The stereochemical elucidation of the 1,4 adducts was not straightforward. We found that the traditional half-chair representation of cyclohexene rings was inconsistent with our spectroscopic data. It has been reported[14] that when $sp^2$-substituted cyclohexenes have α substituents, steric effects can cause these α substituents to deviate from the otherwise preferred pseudoequatorial direction. Instead, deformed half-chair conformations exist, thus minimizing repulsion between vicinal substituents. A complete analysis of the stereochemistry and conformational preferences of the 1,4 adducts and other key compounds, based on spectroscopic and chemical evidence, can be found in the supplementary material accompanying this paper.

We had a certain amount of chemical evidence that was useful in assigning stereochemistry to the adducts. Firstly, we found that mild hydrolysis of the 1,4 adducts, under conditions detailed in the Experimental Section, provided the corresponding 2-cyclohexenones without epimerization at either the α′- or γ-carbons. Hydrolysis of compounds **26**, **28**, and **30** yielded *cis*-3,4,6-trimethyl-2-cyclohexenone (**27**), *cis*-6-*n*-butyl-3,4-dimethyl-2-cyclohexenone (**29**) and *trans*-6-*n*-butyl-3,4-dimethyl-2-cyclohexenone (**31**), respectively. The 360-MHz $^1H$ NMR spectrum of cis enone **27**[12] showed the α-olefinic proton as a broad singlet at 5.799 ppm ($W_{1/2}$ = 5.13 Hz). A sample of the trans isomer[15] of **27** showed its α proton at 5.72 ppm ($W_{1/2}$ = 2.66 Hz). These values of chemical shifts and width of the signals are consistent with those reported in ref 12. In a similar fashion, the new enones **29** and **31** were obtained pure (no epimerizaiton during hydrolysis). As expected, cis enone **29** showed an olefinic signal in its 60-MHz $^1H$ NMR spectrum at 5.6 ppm, with a $W_{1/2}$ = ca. 5 Hz, while the trans enone **31** presented a signal at 5.63 ppm, with a $W_{1/2}$ = ca. 3 Hz. In this way, the trans nature of the cuprate addition that leads to **26**, **28**, and **30** was established, and these compounds were assigned the stereochemistry indicated.

## Discussion

The synthetic method described herein proved to be highly efficient for the stereospecific introduction of alkyl groups α to a ketone functionality. The key features of the methodology are facile introduction of highly substituted alkyl groups, as shown by the ready introduction of *tert*-butyl into systems such as **11** and **16**, formation of gem-disubstituted centers α to the ketone, where the stereochemistry of this center can be strictly controlled by sequential introduction of both alkyl chains, and, finally, the initial 1,4-trans adducts from the cyanocuprate reaction are useful intermediates in themselves, allowing a number of chemical transformations into synthetically interesting compounds.

There are limitations to the use of this method, as shown by the failure to introduce a *tert*-butyl group into an already substituted position (entry 13, Table I). This was indeed an extreme case, but it clearly defines the limits of our method.

The introduction of a phenyl substituent seemed to follow the same characteristics as alkyl groups, and in all the systems ex-

(12) Arnaud, C.; Huet, J. *Bull. Soc. Chim. Fr.* **1971**, *12*, 4525.

(13) The preparation of **44** was previously described in ref 4. Its spectroscopic characteristics are as follows: NMR ($CCl_4$, 60 MHz) 0.22 (9 H, s), 0.91 (3 H, d, $J$ = 6.6 Hz), 1.43–1.90 (1 H, m), 1.96–2.46 (2 H, m), 2.80–2.99 (1 H, m), 3.02–3.20 (1 H, m), 4.52–4.77 (1 H, m); IR (neat) 840, 900, 1190, 1230, 1250, 1670, 2960 $cm^{-1}$; mass spectrum, $m/z$ 198 (M), 183, 165, 156, 142, 127, 84, 75, 73 (100%). Anal. Calcd for $C_{10}H_{18}O_2Si$: C, 60.56; H, 9.15. Found: C, 60.42; H, 9.02.

(14) Senda, Y.; Imaizumi, S.; Ochai, S.; Fujita, K. *Tetrahedron* **1974**, *30*, 539.

(15) The trans enone was obtained by direct alkylation (MeI, THF, −78 °C) of the enolate (1.2 equiv of LDA, THF, −78 °C) of 3,4-dimethyl-2-cyclohexenone. No cis isomer was detected in the crude product mixture.

amined, 1,4 addition took place very effectively. The successful use of an organomagnesium compound, instead of an organolithium, as a precursor to the cyanocuprate is of interest, since Grignard reagents are, in general, easier to obtain than organolithium compounds.

To our surprise, the reaction between epoxy enol ethers and lithium vinylcyanocuprate seems to be highly dependent on the specific substrate used, and particularly its substitution pattern. We have observed (see Table II) that when there is a methyl substituent on C-3 of the ring (see Scheme I for numbering), as in substrate **12**, (vinyl–CuCN)Li adds exclusively in a 1,4-trans fashion (entry 5, Table II). On the other hand, when the ring has no substituents, such as compound **11**, the reaction proceeds with 1,2-trans opening of the epoxide (entries 3 and 4, Table II), and no 1,4 adduct is detectable by inspection of the 360-MHz $^1$H NMR spectrum of the crude reaction mixtures. The result is independent of the use of vinyllithium or vinylmagnesium bromide as the precursor for the cuprate. Finally, an intermediate situation is encountered when the epoxy enol ether substrate is C4 substituted, such as **44**. In this case (entry 6, Table II), both 1,2 and 1,4 additions take place in a 3:7 ratio. At this point, the results seem hard to integrate with the almost complete regio- and stereospecificity of the alkyl- and arylcuprates.

We have also studied the cuprate derived from (Z)-2-ethoxyvinyllithium,[7] and there seems to be complete agreement between the results obtained with this substituted reagent and the parent vinylcuprate. In all cases, the presence of a substituent on C3 of the ring system directs the 1,4 regiospecificity, while a substituent on C4 directs the reaction to yield a mixture of regioisomers. We might point out the trans relationship between the methyl group on C4 and the oxirane ring in **44**. It is conceivable that if the C4 methyl group were cis to the epoxide, the regiochemistry of the reaction would likely be different. Finally, if no ring substitution is present, vinylic cyanocuprates seem to have a preference for 1,2 addition.

Over the years, authors have proposed a number of possible mechanisms for the substitution reactions of organocuprates and allylic systems.[18] We have counted at least five different mechanisms in the literature, although the differences between some of them are often a matter of degree rather than one of concept.[9-11,19-21]

The stereochemical and regiochemical outcome of this type of substitution reaction usually dictates the mechanistic rationale. While most organocopper reactions may be interpreted as involving sequential 1-electron processes,[22] there still exists the possibility for a 2-electron process in highly reactive and polarized allylic systems. It is generally accepted[23] that an oxidative addition of the Cu(I) reagent occurs initially to generate either a radical pair or a Cu(III) intermediate.[24] The real controversy and dilemma lie in the details for this oxidative addition process. It seems reasonable to expect that the chemical behavior of Cu(I) reagents would resemble that for Co(I) and Au(I) and that intermediate Cu(III) species would be possible.[25,26]

We conclude this paper with a discussion of two mechanisms for the reactions of organocuprates with cyclohexenyl epoxides.

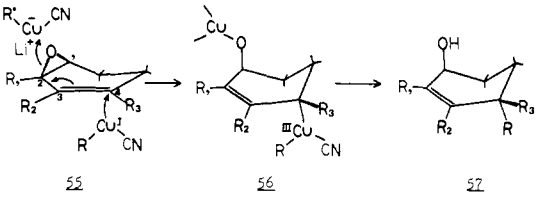


**Figure 1.** One mechanistic rationale for the reaction of cyanocuprates with cyclohexenyl epoxides.

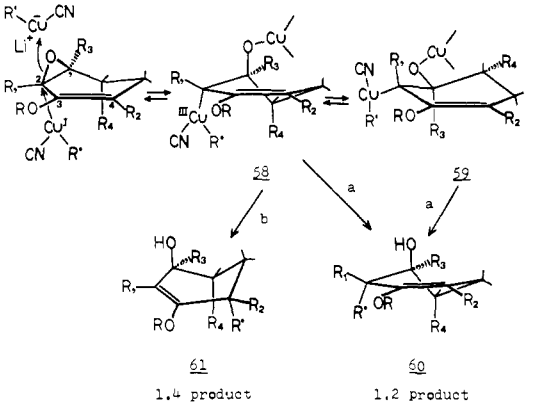


**Figure 2.** An alternative mechanism for the reaction of cyanocuprates with cyclohexenyl epoxides, involving 1,2 opening of the epoxide by copper.

One of the first reports of the reaction of lithium dimethylcuprate with cyclohexa-1,3-diene monoepoxide[27] envisaged the reaction as a concerted nucleophilic process. Since that time, very little commentary on the mechanism of the reaction of vinylic epoxides with organocuprates has appeared. From our initial results[6] with simple epoxycycloalkenes, it was clear that the electron-withdrawing cyano ligand directed the reaction exclusively in a trans-1,4 fashion.[28] One possible explanation (Figure 1) for the effect of the cyano ligand involves the increased Lewis acid character of the copper atom in the cuprate complex. If one envisages an initial coordination of copper(I)[29] to the epoxide oxygen atom, sufficient polarization of the allylic system should result, and the oxidative addition of another cuprate complex in a trans-1,4 manner could ensue, followed by the reductive elimination of CuCN.

The high degree of regioselectivity (1,4 vs. 1,2) could be attributed to the greater accessibility of C4 of the alkene to the bulky cuprate aggregate. The electron-donating properties of the enol ether functionality[8] do not seem to inhibit the addition of the electron-donating cuprate reagent.

An alternative mechanism for the trans-1,4 opening of cyclic vinyl epoxides is depicted in Figure 2. In this case, a kinetic 1,2 opening of the vinyl epoxide system to generate the Cu(III) intermediate **58** is envisaged. This step would necessitate a trans-diaxial opening of the epoxide, aided by previous complexation of the epoxide to another cuprate complex.

Compound **16** ($R_1$ = Me) reacts well with the cyanocuprates, suggesting that the transition state leading to **58** might not resemble that for an $S_N2$ displacement. Reductive elimination of CuCN from **58** would lead directly to a trans-1,2 product, **60** (path a). An allylic transposition of the double bond with concomitant transfer of the R group could explain the trans-1,4 products **61** (path b). This interpretation implies that the 1,4 adducts are the result of an energetically more favorable process from conformer **58** when R is alkyl (except *tert*-butyl) than the reductive elimination process that leads to **60**. The "anomalous" behavior of the

(16) Jackman, L. M.; Sternhell, S. "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd ed.; Pergamon Press: Oxford, London, 1969; pp 280–298.
(17) Garbisch, E. W., Jr. *J. Org. Chem.* **1962**, *27*, 4249.
(18) For a review of organometallic displacement reactions of allylic compounds, see: Magid, R. M. *Tetrahedron* **1980**, *36*, 1901.
(19) Ziegler, F. E.; Cody, M. A. *J. Org. Chem.* **1981**, *46*, 122.
(20) Vermeer, P.; Meijer, J.; Brandsma, L. *Recl. Trav. Chim. Pays-Bas* **1975**, *94*, 112.
(21) Anderson, R. J.; Henrick, C. A.; Siddall, J. B. *J. Am. Chem. Soc.* **1970**, *92*, 735.
(22) Kochi, J. K. *Acc. Chem. Res.* **1974**, *7*, 351.
(23) Posner, G. *Org. React.* **1975**, *22*, 259.
(24) (a) Lewin, A. R.; Goldberg, N. L. *Tetrahedron Lett.* **1972**, 491. (b) Johnson, C. R.; Dutra, G. A. *J. Am. Chem. Soc.* **1973**, *95*, 7783. (c) Corey, E. J.; Kuwajima, I. *Ibid.* **1970**, *92*, 395.
(25) Tamaki, A.; Kochi, J. K. *J. Organomet. Chem.* **1973**, *51*, C39.
(26) (a) Schrauzer, G. N.; Deutch, E. *J. Am. Chem. Soc.* **1969**, *91*, 3341. (b) Jensen, F. R.; Madan, V.; Buchanan, H. *Ibid.* **1970**, *92*, 1414. (c) Tada, M.; Ogawa, H. *Tetrahedron Lett.* **1973**, 2639.
(27) Wieland, D. M.; Johnson, C. R. *J. Am. Chem. Soc.* **1971**, *93*, 3047.
(28) See also: Levisalles, J.; Rudler-Chauvin, M.; Rudler, H. *J. Organomet. Chem.* **1977**, *136*, 103.
(29) The copper(I) species could be either a cuprate aggregate or the cuprous cyanide released from reductive elimination of a Cu(III) intermediate.

vinyl cuprate could be attributed to a greater stability for the Cu(III) species **58** and a diminished propensity for the migration of a vinyl group. A further consequence of a more stable Cu(III) intermediate would be conformational changes to species such as **59**, in which the copper atom is less axial and the R group is too far from C4. This unfavorable conformation (i.e., **59**) would promote 1,2-reductive elimination to **60** (path a). In fact, when vinylcuprate reacts with compounds **11**, **12**, and **44**, the relative amounts of 1,2 and 1,4 adducts could reflect the relative preferences for conformers **58** and **59**. The reactions with **12** have yielded exclusively a 1,4 adduct, suggesting that conformer **58** predominated and collapsed via pathway b to the observed product.

The mechanisms presented in Figures 1 and 2 are not intended to be an absolute, either/or, picture. While we have no direct evidence for an initial 1,2 opening followed by a rearrangement, we believe that this possibility exists, and further efforts to detect this phenomenon are being made. It is also appropriate to point out that any mechanistic discussion is dependent on the exact structure and size of the cuprate reagent. Our lack of knowledge on this aspect of organocopper reagents certainly compromises a complete mechanistic picture. It is always possible that the different organic ligands ($sp^3$ vs. $sp^2$) on copper lead to significantly different structures and hence are responsible for the differences in regiochemistry.

## Experimental Section

Infrared spectra were obtained on a Perkin-Elmer 727B or 457 grating spectrophotometer. $^1H$ NMR spectra were obtained on a Varian T-60A, JEOL-FX90Q, or Brüker 360-MHz spectrometer, with tetramethylsilane as the standard. $^{13}C$ NMR spectra were obtained on a JEOL-FX90Q spectrometer, with $CDCl_3$ as standard ($CDCl_3 \equiv 77.00$ ppm). Mass spectra were obtained on a Finnigan automated GC/MS-E1C1 system mass spectrometer at 70 eV. Elemental analyses were performed by Spang Microanalytical Laboratory, Eagle Harbor, MI, or Galbraith Laboratories, Knoxville, TN. Column chromatography was carried out on EM Reagents silica gel (230–400 mesh ASTM). All chromatography solvents were distilled before use. Commercial MeLi (low halide in ether), *n*-BuLi (in hexane), and *t*-BuLi (in hexane) were purchased from Alfa and titrated[30] prior to use. Vinyllithium was prepared (ether solution) according to Seyferth and Weiner.[31] Organometallic reactions were carried out in flame-dried glassware, under an inert atmosphere of dry nitrogen. NMR chemical shifts are given in ppm downfield from $Me_4Si$.

**Synthesis of α,β-Epoxycyclohexanones.** 2,3-Epoxycyclohexanone, 2,3-epoxy-3-methylcyclohexanone, 2,3-epoxy-3,4-*cis*-dimethylcyclohexanone, 2,3-epoxy-2-methylcyclohexanone, and 2,3-epoxy-3,6-dimethylcyclohexanone were all prepared by House's method[32a] from the corresponding 2-cyclohexenones. Epoxidation of 3,4-dimethyl-2-cyclohexenone with *t*-BuOOH/Triton B in benzene afforded exclusively 2,3-epoxy-3,4-*cis*-dimethylcyclohexanone (**53**), while House's method ($H_2O_2$/NaOH in MeOH) gave a 9:1 mixture of **53**:**54**. The pseudoaxial methyl group at C4[12] hinders attack by the peroxide from the same face, to a degree dependent on the size of the peroxide. Epoxy ketone **54** was better prepared by the sequence shown in Scheme IV.

3,6-Dimethyl-2-cyclohexenone[33] was synthesized by methylation of 3-methyl-2-cyclohexenone (LDA, THF, −78 °C; MeI, −78 °C → room temperature). 2-Cyclohexenone, 3-methyl-2-cyclohexenone, 2-methyl-2-cyclohexenone, and 3,4-dimethyl-2-cyclohexenone were all prepared by standard literature methods.[34]

**2,3-Epoxy-3,4-*cis*-dimethylcyclohexanone (53).** 3,4-Dimethyl-2-cyclohexenone (4.32 g, 34.8 mmol) was dissolved in 50 mL of benzene, and to this solution was added[32b] 4.52 g of 90% *t*-BuOOH (45.2 mmol, 1.3 equiv) followed by 0.48 g of 35% Triton B in methanol (1 mmol, 0.028 equiv). The slightly pink solution was then stirred at room temperature for 48 h. At this point, 50 mL of water was added, and the aqueous layer was extracted with ether. The organic layers were combined and washed several times with a $Na_2SO_3$ solution and brine, after which they were dried over anhydrous $MgSO_4$. Most of the solvent was evaporated in vacuo and the residue distilled to obtain 3.40 g (24.2 mmol, 69%) of a colorless liquid: bp 60–64 °C (1 mmHg) or 25–30 °C (0.05 mmHg); IR ($CCl_4$) 1245, 1400, 1705, 2875, 2960 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 360 MHz) 1.050 (3 H, d, $J$ = 6.84 Hz), 1.413 (3 H, s), 2.135–2.400 (5 H, m), 3.075 (1 H, s); $^{13}C$ NMR ($CDCl_3$) 15.62 (q), 19.90 (q), 23.31 (t), 31.49 (t), 31.98 (d), 61.99 (d), 66.11 (s), 206.69 (s); mass spectrum, $m/z$ 141 (M − 1), 123, 113, 95 (100%). Anal. Calcd for $C_8H_{12}O_2$: C, 68.54; H, 8.62. Found: C, 68.30; H, 8.80.

**2,3-Epoxy-3,4-*trans*-dimethylcyclohexanone (54) (See Scheme II).** Commercial $LiAlH_4$ (600 mg, 20.0 mmol) was suspended in 30 mL of dry ethyl ether and slowly added to a solution of 2.48 g (20 mmol) of 3,4-dimethyl-2-cyclohexenone in 200 mL of ether (0 °C). After addition was complete, stirring was continued at 0 °C for 3 h. The reaction was then quenched with 20 mL of water and 50 mL of $NH_4Cl$ aqueous solution and the mixture extracted with ether. The organic phase was dried over anhydrous $MgSO_4$ and was then evaporated in vacuo to yield 2.35 g (18.65 mmol, 92% crude yield) of crude 3,4-dimethyl-2-cyclohexenol as a mixture of cis and trans isomers that was used directly in the next step without purification. IR 1660, 3350, 3620 $cm^{-1}$; NMR 0.98 (3 H, d, $J$ = 7 Hz), 1.07 (3 H, d, $J$ = 7 Hz, other isomer), 1.3–2.3 (5 H + 5 H, m), 1.65 (3 H + 3 H, brs), 4.13 (1 H + 1 H, m), 5.43 (1 H + 1 H, m).

3,4-Dimethyl-2-cyclohexenol (2.35 g, 18.65 mmol, crude) was dissolved in 50 mL of dry benzene,[35] along with 25 mg (0.5% mol) of $VO(acac)_2$ under nitrogen. Then 2.0 g (20.0 mmol) of *t*-BuOOH (90%), dissolved in 10 mL of dry benzene, was added, and the solution was stirred at room temperature, under nitrogen, for 30 h. The reaction mixture was quenched with 40 mL of $Na_2SO_3$ solution, extracted with ether, and dried over anhydrous $MgSO_4$. Evaporation in vacuo yielded 2.55 g of a yellowish oil, containing three isomeric epoxy alcohols, as shown in Scheme IV. NMR (crude) 1.00 (3 H, d, $J$ = 7 Hz), 1.17 (3 H, s), 1.2–2.5 (5 H, m), 3.0 (1 H, d, $J$ = 3.5 Hz), 3.77 (1 H, m); IR ($CCl_4$) 1210, 1220, 1445, 3450, 3570 $cm^{-1}$.

The crude epoxy alcohol (2.55 g, 18 mmol) was oxidized with a $CrO_3$–pyridine complex; 14.22 g (180 mmol) of dry pyridine was dissolved in 150 mL of $CH_2Cl_2$ and the solution cooled to 0 °C. At this point, 9.0 g (90 mmol) of $CrO_3$ was added, and the mixture was stirred at 0 °C for 15 min. Crude epoxy alcohol (2.55 g) was dissolved in 10 mL of $CH_2Cl_2$ and slowly added to the oxidizing mixture, which was stirred for 1 additional h at 0 °C. The solution was then decanted from a gummy residue, which was rinsed exhaustively with $CH_2Cl_2$. The whole organic solution was washed with an aqueous $NaHCO_3$ solution and then with a NaCl solution and finally dried over anhydrous $MgSO_4$. After concentration in vacuo, the residue was chromatographed on silica gel (cyclohexane:ether, 3:1) to yield 800 mg of epoxy ketone **54** and 600 mg of isomeric **53**.

**54**: IR ($CHCl_3$) 1010, 1215, 1260, 1705, 2875, 2930, 2960 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 360 MHz) 1.42 (3 H, d, $J$ = 6.83 Hz), 1.381 (3 H, s), 1.556–1.724 (2 H, m), 1.996–2.105 (i H, m), 2.452–2.502 (1 H, ddd, $J$ = 4.45, 5.06, 18.06), 3.004 (1 H, s); $^{13}C$ NMR ($CDCl_3$) 16.05 (q), 20.01 (q), 25.80 (t), 32.30 (t), 35.61 (d), 62.40 (d), 64.37 (s), 206.42 (s); mass spectrum, $m/z$ 141 (M − 1), 125, 123, 113, 95, 85 (100%). Anal. Calcd for $C_8H_{12}O_2$: C, 68.54; H, 8.62. Found: C, 68.26; H, 8.88.

**Synthesis of Epoxy Enol Ethers.** Epoxy enol ethers **11**–**17** were all synthesized from the corresponding 2,3-epoxycyclohexanones by formation of the enolates with LDA and trapping of the enolates with trimethylsilyl chloride or *tert*-butyldimethylsilyl chloride.

In a typical run, 4.75 g (47 mmol) of dry diisopropylamine was dissolved in 100 mL of dry THF and cooled to 0 °C under nitrogen. To the cooled solution was slowly added 20.87 mL of *n*-butyllithium–hexane solution (1.71 M, 35.7 mmol). After being stirred at 0 °C for 15 min, the solution was cooled to −78 °C (acetone–dry ice bath), and 3.00 g (23.8 mmol) of 3-methyl-2,3-epoxycyclohexanone, dissolved in 5 mL of THF, was slowly added dropwise. About 30 min was allowed for enolate formation, and then 5.10 g (47 mmol) of neat trimethylsilyl chloride was added. The reaction mixture was allowed to warm up from −78 °C to room temperature over 4 h.

Workup consisted of removing the solvent under reduced pressure, taking the residue up into ether, filtering the salts through a short pad of Celite, and concentrating the ether solution. The residue consisted of 4.65 g of a slightly yellowish oil, determined to be quite pure by IR and NMR spectroscopy. Distillation of the oil afforded 2.50 g of highly pure epoxy enol ether **12** (bp 33–35 °C (0.05 mmHg)) (98% crude yield, 53% after distillation).

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(35) Itoh, T.; Jitsukawa, .; Kaneda, K.; Teranishi, S. *J. Am. Chem .Soc.* **1979**, *101*, 159.

In most cases, crude epoxy enol ethers were pure enough for further reactions, including reaction with alkylcyanocuprates.

**2,3-Epoxy-1-(trimethylsiloxy)-6-cyclohexene (11)**: colorless liquid, bp 50–60 °C (0.6–1.0 mmHg); 86% yield; IR (neat) 1190, 1250, 1655 $cm^{-1}$; $^1H$ NMR ($CCl_4$, 60 MHz) 0.15 (9 H, s), 1.40–2.25 (4 H, m), 2.80–3.00 (1 H, dd, $J$ = 3 Hz, 4 Hz), 3.20–3.40 (1 H, m), 4.60–4.87 (1 H, m); $^{13}C$ NMR ($CDCl_3$) −0.080, 17.959, 21.209, 51.276, 55.447, 104.636, 147.054; mass spectrum, $m/z$ 184 (M), 167, 156, 151, 141, 127, 75, 73 (100%).

**2,3-Epoxy-3-methyl-1-(trimethylsiloxy)-6-cyclohexene (12)**: colorless liquid, bp 90–100 °C (12–15 mmHg); 60% yield; IR (neat) 1170, 1220, 1250, 1655 $cm^{-1}$; $^1H$ NMR ($CCl_4$, 60 MHz) 0.20 (9 H, s), 1.33 (3 H, s), 1.50–2.13 (4 H, m), 2.92 (1 H, d, $J$ = 2 Hz), 4.58–4.93 (1 H, m); $^{13}C$ NMR ($CDCl_3$) −0.134, 19.151, 21.534, 27.114, 58.589, 61.352, 104.040, 147.704; mass spectrum, $m/z$ 198 (M), 183, 170, 165, 155, 142, 127, 73 (100%).

**2,3-Epoxy-3-methyl-1-(*tert*-butyldimethylsiloxy)-6-cyclohexene (13)**: colorless liquid, bp 85–95 °C (ca. 1.0 mmHg); 70% yield; IR (neat) 1170, 1220, 1250, 1655 $cm^{-1}$; $^1H$ NMR ($CCl_4$, 60 MHz) 0.00 (3 H, s), 0.02 (3 H, s), 0.70 (9 H, s), 1.10 (3 H, s), 1.20–1.90 (4 H, m), 2.45 (1 H, d, $J$ = 3 Hz), 4.40–4.60 (1 H, m); $^{13}C$ NMR ($CDCl_3$) −4.685, 17.905, 19.096, 21.643, 25.543, 26.952, 58.643, 61.677, 104.095, 147.704; mass spectrum, $m/z$ 240 (M), 225, 183, 165, 156, 139, 75 (100%), 73.

**2,3-Epoxy-3α,4α-dimethyl-1-(trimethylsiloxy)-6-cyclohexene (14)**: colorless liquid, bp 39 °C (0.2 mmHg); bp 48–50 °C (0.35 mmHg); 94% yield; IR ($CHCl_3$) 845, 1180, 1225, 1255, 1660, 2965 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 60 MHz) 0.03 (9 H, s), 0.83 (3 H, d, $J$ = 7 Hz), 1.26 (3 H, s), 1.33–1.80 (2 H, m), 1.96–2.30 (1 H, m), 2.75 (1 H, d, $J$ = 2 Hz), 4.43–4.76 (1 H, m); $^{13}C$ NMR ($CDCl_3$) 0.02, 16.59, 19.79, 27.26, 30.95, 58.36, 64.48, 101.59, 146.94; mass spectrum, $m/z$ 213 (M + 1), 197 (100%), 185, 123, 95.

**2,3-Epoxy-4β,3α-dimethyl-1-(trimethylsiloxy)-6-cyclohexene (15)**: purified by column chromatography on silica gel (cyclohexane:ether, 3:1); 100% yield; IR ($CCl_4$) 1185, 1220, 1255, 1660, 2950 $cm^{-1}$; $^1H$ NMR ($CCl_4$, 60 MHz) 0.10 (9 H, s), 0.83 (3 H, d, $J$ = 7 Hz), 1.10 (3 H, s), 1.30–1.70 (3 H, m), 2.50 (1 H, d, $J$ = 2.5 Hz), 1.10 (3 H, s), 1.30–1.70 (3 H, m), 2.50 (1 H, d, $J$ = 2.5 Hz), 4.33–4.60 (1 H, m); $^{13}C$ NMR ($CDCl_3$) 0.02, 16.32, 20.01, 28.51, 31.38, 60.36, 63.72, 104.62, 136.90; mass spectrum, $m/z$ 213 (M + 1), 197, 195, 185, 170, 141, 123 (100%).

**2,3-Epoxy-2-methyl-1-(trimethylsiloxy)-6-cyclohexene (16)**: colorless liquid, bp 51–59 °C (0.5–1.2 mmHg); 60% yield; IR (neat) 840, 900, 1170, 1250, 1650, 2850, 2925, 2955, 3045 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 60 MHz) 0.00 (9 H, s), 1.16 (3 H, s), 1.40–2.20 (4 H, m), 3.07 (1 H, m), 4.50–4.73 (1 H, m); $^{13}C$ NMR ($CDCl_3$) 0.02, 17.96, 18.93, 21.86, 55.23, 62.70, 103.88, 148.84; mass spectrum, $m/z$ 198 (M), 183, 170, 156, 141, 127, 75 (100%), 73.

**2,3-Epoxy-3,6-dimethyl-1-(trimethylsiloxy)-6-cyclohexene (17)**: lightly yellowish liquid (coloration probably due to small amount of decomposition during distillation), bp 50 °C (0.2 mmHg); 76% yield; IR (neat) 845, 915, 1185, 1255, 1680, 2920, 2955 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 90 MHz) 0.17 (9 H, s), 1.36 (3 H, s), 1.55 (3 H, bs), 1.50–2.20 (4 H, m), 2.88 (1 H, s); $^{13}C$ NMR ($CDCl_3$) 0.29, 16.33, 21.64, 25.49, 27.27, 58.96, 61.56, 114.82, 140.06; mass spectrum, $m/z$ 212 (M), 197, 194, 179, 147, 105, 73 (100%).

**Reaction of Epoxy Enol Ethers with Alkyl-, Aryl-, and Vinylcyanocuprates.** All cuprates were prepared in situ by reaction of organolithium or organomagnesium compounds with copper(I) cyanide in diethyl ether. We have observed that cyanocuprates take the form of very fine suspensions in ether. The salt content of the starting alkyllithium or organomagnesium solution is very important, especially in the case of methyllithium (ether solution). A common ion effect seems to cause the cyanocuprate to be quite insoluble, to the extent that reaction with the epoxy enol ether may not take place at all when the solutions are not salt free. This effect does not seem to be so important in the case of reagents other than methylcyanocuprate.

Ether solutions of (MeCuCN)Li appear as an intense yellow color, while (*n*-BuCuCN)Li and (*t*-BuCuCN)Li are dark brown-black in color. Other alkyl-, vinyl-, and arylcyanocuprates prepared in our laboratories range in color from light beige to black. No change of color is usually observed when the substrate is added to the cuprate reagent, but the reactions invariably turn black upon warming to room temperature, sometimes with formation of a small film of metallic copper metal covering the walls of the flask.

**General Procedure for the Reaction of Epoxy Enol Ethers with Mixed Cyanocuprates.** In all cases, a suspension of 1–4 equiv of CuCN in ether was cooled to −40 °C, under nitrogen, and an equimolar amount of the organolithium or organomagnesium solution was slowly added. The suspension would then be stirred at −40 °C until no CuCN remained visible (15–60 min). (In some runs, alkylcyanocuprates were allowed to warm up to 0 °C for 1 h, without any lowering of the yield of the reaction.) After the solution was cooled to −78 °C (acetone–dry ice bath), an ether solution of the epoxy enol ether was added, and the mixture was allowed to slowly warm up to room temperature.

In a typical run, 720 mg (8 mmol) of technical-grade CuCN was weighed under nitrogen into a flame-dried round-bottom flask, which was then filled with ca. 40 mL of dry ether and cooled to −40 °C under nitrogen. Then 4.67 mL of methyllithium–ether solution (1.71 M, 8 mmol) was added and the yellowish suspension stirred for ca. 30 min at −40 °C, until no CuCN was visible at the bottom of the flask. After cooling to −78 °C, a solution of 400 mg (2.0 mmol) epoxy enol ether **6** in 5 mL of dry ether was added dropwise, with an intensification of the yellow color. The mixture was allowed to warm up to room temperature over 5 h and then quenched with 30 mL of a saturated $NH_4Cl$ solution. After filtration through a Celite pad and washing of the ether layer with brine solution, the organic phase was dried over sodium sulfate and concentrated in vacuo to yield 390 mg (93%) of adduct **22**.

The crude reaction product was of high purity, as determined by 360-MHz $^1H$ NMR and $^{13}C$ NMR. Only one product was detectable by the aforementioned spectroscopic techniques.

**General Procedure for Hydrolysis of 1,4 Adducts to the Cyclohexenones.** The 1,4 adducts from the cuprate additions could be easily hydrolyzed to the 2-cyclohexenones by one of two ways: running the compound through a short path of silica gel or stirring of an ether solution of the compound with an equal volume of 2% HCl for 5 min without any epimerization of the resulting enones. The conversion is essentially quantitative.

***trans*-3-Hydroxy-6-methyl-1-(trimethylsiloxy)-1-cyclohexene (18)**: IR ($CCl_4$) 1185, 1255, 1680, 2955, 3350 $cm^{-1}$; $^1H$ NMR ($CCl_4$, 60 MHz) 0.00 (9 H, s), 0.76 (3 H, d, $J$ = 7 Hz), 0.8–2.2 (6 H, m), 3.90 (1 H, m), 4.50 (1 H, d, $J$ = 3.5 Hz); mass spectrum, $m/z$ 202 (M), 201, 185 (M + 1 − $H_2O$), 183, 171, 152, 77 (100%), 51.

**6-Methyl-2-cyclohexenone (19)**.[36] A sample of hydroxy enol ether **18** was chromatographed on silica gel (hexane:ether, 3:1) and hydrolyzed on the column, yielding enone **18**, almost quantitative: IR ($CCl_4$) 1680, 2950 $cm^{-1}$; $^1H$ NMR ($CCl_4$, 60 MHz) 1.10 (3 H, d, $J$ = 7 Hz), 1.2–2.35 (5 H, m), 5.75 (1 H, dt, $J$ = 10 Hz, $J$ = 1.5 Hz), 6.50–6.85 (1 H, m). 2,4-Dinitrophenylhydrazone (EtOH) mp 158–159 °C (lit.[36] mp 161–162 °C, 156–157 °C); mass spectrum, $m/z$ 110 (M), 95, 68 (100%), 53.

***trans*-3-Hydroxy-6-*tert*-butyl-1-(trimethylsiloxy)-1-cyclohexene (20)**: IR (neat) 845, 1190, 1250, 1640, 2940, 3350 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 60 MHz) 0.20 (9 H, s), 0.95 (9 H, s), 1.10–2.10 (6 H, m), 3.97–4.32 (1 H, m), 4.75–4.85 (1 H, bd); $^{13}C$ NMR ($CDCl_3$) 0.136, 22.347, 28.902, 31.990, 33.452, 47.538, 66.769, 110.162; mass spectrum, $m/z$ 224 (M − $H_2O$), 209, 168, 151, 147, 137, 96, 75 (100%), 73, 68, 57.

**6-*tert*-Butyl-2-cyclohexenone[37] (21)**. A sample of alcohol **20** was dissolved in 10 mL of ether and stirred at room temperature with 10 mL of 2% HCl for 20 min. At this time the organic layer was separated and concentrated in vacuo, and the residue was purified by preparative TLC on silica gel (hexanes:ether, 1:1), thus yielding enone **21**: IR ($CCl_4$) 1120, 1220, 1365, 1385, 1680, 2950, 3040 $cm^{-1}$; $^1H$ NMR ($CCl_4$, 60 MHz) 1.00 (9 H, s), 1.65–2.60 (5 H, m), 5.77 (1 H, dt, $J$ = 10 Hz, $J$ = 1.5 Hz), 6.53–6.87 (1 H, m); mass spectrum, $m/z$ 152 (M), 137, 109, 96 (100% McLafferty), 81, 68. Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 78.49; H, 10.29

**3β-Hydroxy-3α,6α-dimethyl-1-(trimethylsiloxy)-1-cyclohexene (22)**: IR (neat) 840, 890, 1200, 1255, 1655, 3400 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 90 MHz) 0.07 (9 H, s), 0.89 (3 H, d, $J$ = 7 Hz), 1.16 (3 H, s), 1.20–2.39 (5 H, m), 4.65 (1 H, br s); $^{13}C$ NMR ($CDCl_3$) 0.027, 17.31, 27.06, 29.93, 32.96, 34.32, 69.48, 110.59, 156.32; mass spectrum, $m/z$ 214 (M), 199, 196, 181, 171, 165, 156, 144, 141, 127, 75 (100%), 73.

**3,6-Dimethyl-2-cyclohexenone[33] (23)**. A sample of crude alcohol **22** was hydrolyzed on silica gel (hexane:ether, 3:1) to give a pure sample of enone **23**. This enone was also prepared by alkylation of 3-methyl-2-cyclohexenone (1.2 equiv of LDA, THF, −78 °C, MeI) in 93% yield: bp 96–100 °C (21 mmHg); IR (neat) 870, 1215, 1380, 1440, 1640, 1675, 2870, 2940, 3035 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 90 MHz) 1.12 (3 H, d, $J$ = 6.6 Hz), 1.94 (3 H, d, $J$ = 1 Hz), 1.2–2.4 (5 H, m), 5.84 (1 H, brs); $^{13}C$ NMR ($CDCl_3$) 14.925, 23.972, 30.473, 40.278, 125.927, 161.302, 201.824; mass spectrum, $m/z$ 124 (M), 109, 82 (100%), 67, 54. Anal. Calcd for $C_8H_{12}O$: C, 77.37; H, 9.74. Found: C, 77.36; H, 9.65.

**6α-*n*-Butyl-3β-hydroxy-3α-methyl-1-(*tert*-butyldimethylsiloxy)-1-cyclohexene (24)**: IR ($CCl_4$) 835, 1215, 1255, 1645, 2850, 2925, 3580 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 90 MHz) 0.11 (s, 6 H), 0.87 (9 H, s), 1.23 (3 H, s), 0.80–2.20 (15 H, m), 4.74 (1 H, brs); $^{13}C$ NMR ($CDCl_3$) −4.50, 13.896, 17.905, 22.672, 23.430, 25.543, 29.498, 29.931, 30.365, 34.428, 38.436, 69.586, 110.758, 156.372; mass spectrum, $m/z$ 280 (M − $H_2O$),

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265 (280 − $CH_3$), 223 (280 − $C_4H_9$), 167, 75 (100%), 73.

**6-*n*-Butyl-3-methyl-2-cyclohexenone**[38] **(25).** A sample of **24** was chromatographed on silica gel (hexane:ether, 3:1), producing a pure sample of **25**: IR ($CCl_4$) 1220, 1260, 1380, 1438, 1470, 1640, 1675, 2870, 2955 $cm^{-1}$; $^1H$ NMR ($CCl_4$, 60 MHz) 0.90 (3 H, t), 1.10–1.57 (6 H, m), 1.57–2.45 (5 H, m), 1.93 (3 H, brs), 5.66 (1 H, q, $J$ = 1 Hz); mass spectrum, $m/z$ 166 (M), 123, 110 (100%, McLafferty), 95, 82, 67, 54.

**3β-Hydroxy-3α,4α,6α-trimethyl-1-(trimethylsiloxy)-1-cyclohexene (26).** (In entry 5, Table I, epoxy enol ether **14** was purposely contaminated by 10% of diastereomer **15**. The crude alcohol **26** was in turn contaminated with 10% of isomeric **26b**. $^1H$ NMR spectroscopy (360 MHz) of the crude allows the assignment of signals.) IR ($CCl_4$) 845, 1205, 1250, 1660, 2995, 3460, 3600 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 360 MHz) 0.134 (9 H, s), 0.897 (3 H, d, $J$ = 6.8 Hz), 0.908 (3 H, d, $J$ = 6.8 Hz), 0.96–1.02 (1 H, m), 1.043 (3 H, s), 1.58–1.70 (2 H, m), 2.17–2.24 (1 H, m), 4.742 (1 H, d, $J$ = 1.7 Hz); mass spectrum, $m/z$ 228 (M), 210, 195, 156, 144, 127, 75 (100%), 73.

***cis*-3,4,6-Trimethyl-2-cyclohexenone**[12] **(27).** A sample of alcohol **26** was treated with 2% HCl as described in the general procedure; since **26** was contaminated with a small amount of **26b**, enone **27** was also contaminated with ca. 10% of the trans isomer. IR (mixture of ca. 90% enone **17** and 10% of its epimer) ($CCl_4$) 1218, 1380, 1440, 1460, 1630, 1680, 2970 $cm^{-1}$; $^1H$ NMR, see explanation of 360-MHz $^1H$ NMR spectra in the supplementary material; mass spectra (mass spectra of each isomer obtained by GC–MS), $m/z$ cis (**27**) (longer retention time) 138 (17, M), 124 (29), 119 (11), 117 (12), 95 (8), 82 (83), 67 (100), 55 (18); trans enone (shorter retention time) 138 (19, M), 96 (100), 95 (22), 81 (24), 67 (20), 53 (12).

**6α-*n*-Butyl-3β-hydroxy-3α,4α-dimethyl-1-(trimethylsiloxy)-1-cyclohexene (28):** IR ($CHCl_3$) 1115, 1255, 1655, 2865, 2925, 2960, 3430, 3580 $cm^{-1}$; $^1H$ NMR ($CCl_4$, 60 MHz) 0.00 (9 H, s), 0.70 (3 H, d, $J$ = 7 Hz), 0.80 (3 H, s), 0.60–2.20 (14 H, m), 4.43 (1 H, d, $J$ = 1.5 Hz); $^{13}C$ NMR ($CDCl_3$) 0.08, 13.89, 14.76, 22.78, 22.79, 28.25, 31.88, 34.86, 39.14, 40.60, 72.78, 114.06, 153.44; mass spectrum, $m/z$ 252 (M − $H_2O$), 237, 209, 124, 109, 96, 73 (100%).

***cis*-6-*n*-Butyl-3,4-dimethyl-2-cyclohexenone (29).** A sample of crude adduct **28** was treated with 2% HCl, according to the general procedure, thus producing a quantitative yield of cis enone **29**; no epimerization was observed. The enone was purified by column chromatography on silica gel (petroleum ether:ether, 3:1): IR ($CCl_4$) 1675, 2860, 2935, 2955 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 60 MHz) 1.05 (3 H, d, $J$ = 7 Hz), 1.83 (3 H, d, $J$ = 1 Hz), 0.65–2.50 (13 H, m), 5.66 (1 H, m); $^{13}C$ NMR ($CDCl_3$) 13.35, 18.33, 20.99, 22.40, 28.25, 28.57, 34.91, 37.02, 45.85, 126.52, 163.03, 200.14; mass spectrum, $m/z$ 180 (M), 124 (100%), 109, 96, 81. Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 79.82; H, 11.27.

**6α-*n*-Butyl-3β-hydroxy-3α,4β-dimethyl-1-(trimethylsiloxy)-1-cyclohexene (30):** IR ($CHCl_3$) 1255, 1655, 2865, 2925, 2960, 3600 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 60 MHz) 0.00 (9 H, s), 1.00 (3 H, s), 0.45–1.95 (17 H, m), 4.55 (1 H, s); $^{13}C$ NMR ($CDCl_3$) 0.19, 13.84, 14.60, 22.61, 28.30, 29.93, 30.74, 31.17, 33.83, 38.54, 70.40, 111.51, 156.53.

***trans*-6-*n*-Butyl-3,4-dimethyl-2-cyclohexenone (31).** A sample of crude alcohol **30** was hydrolyzed quantitatively to enone **31** by treatment with 2% HCl, according to the general procedure. The enone was purified by column chromatography on silica gel (petroleum ether:ether, 3:1): IR ($CCl_4$) 1675, 2860, 2930, 2960 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 60 MHz) 1.85 (3 H, brs), 0.70–2.60 (16 H, m), 5.63 (1 H, m); $^{13}C$ NMR ($CDCl_3$) 13.84, 17.58, 22.29, 22.61, 29.06, 33.18, 35.24, 41.68, 125.65, 164.82, 201.50; mass spectrum, $m/z$ 181 (M + 1), 165, 124 (100%), 109, 96, 81, 67. Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 79.74; H, 11.01.

***trans*-3-Hydroxy-2,6-dimethyl-1-(trimethylsiloxy)-1-cyclohexene (32):** IR (neat) 840, 920, 1180, 1250, 1670, 2950, 3350 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 60 MHz) 0.15 (9 H, s), 1.00 (3 H, d,, $J$ = 7 Hz), 1.63 (3 H, d, $J$ = 1 Hz), 1.0–2.3 (6 H, m); $^{13}C$ NMR ($CDCl_3$) 0.515, 13.679, 17.688, 26.139, 28.414, 33.777, 72.251; mass spectrum, $m/z$ 214 (M), 199, 197, 181, 172, 157, 82, 75, 73 (100%).

**2,6-Dimethyl-2-cyclohexenone**[39] **(33).** A sample of crude alcohol **32** was hydrolyzed with 2% HCl, according to the general procedure, yielding enone **33** quantitatively: IR ($CCl_4$) 1640, 1675 $cm^{-1}$; $^1H$ NMR ($CCl_4$, 60 MHz) 1.10 (3 H, d, $J$ = 7 Hz), 1.80 (3 H, brs), 1.5–2.5 (5 H, m), 6.60 (1 H, m).

***trans*-6-*n*-Butyl-3-hydroxy-2-methyl-1-(trimetylsiloxy)-1-cyclohexene (34):** IR (neat) 845, 925, 1185, 1255, 1675, 2870, 2950, 3360 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 60 MHz) 0.00 (9 H, s), 1.53 (3 H, bs), 0.75–2.20 (15 H, m), 3.75–4.00 (1 H, m); $^{13}C$ NMR ($CDCl_3$) 0.51, 13.95, 22.02, 22.78, 28.25, 29.77, 30.36, 39.19, 70.02, 114.33, 150.68 (one of the signals must correspond to two carbons); mass spectrum, $m/z$ (SP) 239 (M − OH), 183 (M − $Me_3Si$), 165, 154, 105 (100%), 77.

**6-*n*-Butyl-2-methyl-2-cyclohexenone (35).** A sample of crude alcohol **34** was hydrolyzed to enone **35** while being chromatographed on silica gel (hexane:ether, 3:1), thus yielding a pure sample of **35**: IR ($CCl_4$) 1090, 1190, 1370, 1460, 1680, 2870, 2940 $cm^{-1}$; $^1H$ NMR ($CCl_4$, 60 MHz) 0.90 (3 H, poorly defined triplet, $J$ = 5 Hz), 1.1–2.4 (11 H, m), 1.70 (3 H, d, $J$ = 2 Hz), 6.33–6.60 (1 H, m); mass spectrum, $m/z$ 166 (M), 137, 123, 110 (100% M − $C_4H_8$, McLafferty), 95, 82, 67, 54. Anal. Calcd for $C_{12}H_{20}O$: C, 79.46; H, 10.91. Found: C, 79.30; H, 11.06.

***trans*-6-*tert*-Butyl-3-hydroxy-2-methyl-1-(trimethylsiloxy)-1-cyclohexene (36):** IR ($CCl_4$) 850, 920, 1175, 1257, 1665, 2960, 3470, 3620 $cm^{-1}$; $^1H$ NMR ($CCl_4$, 60 MHz) 0.00 (9 H, s), 0.80 (9 H, s), 1.60 (3 H, brs), 1.10–2.20 (6 H, m), 4.0 (1 H, m); $^{13}C$ NMR ($CDCl_3$) 0.786, 14.167, 21.534, 29.877, 30.094, 34.157, 47.808, 70.074, 117.313, 149.492; mass spectrum, $m/z$ 257 (M + 1), 238, 181, 165, 147, 110, 91, 75, 73 (100%), 57.

**6-*tert*-Butyl-2-methyl-2-cyclohexenone (37).** A sample of crude alcohol **36** was chromatographed on silica gel (hexane:ether, 3:1), hydrolyzing in the process and yielding a pure sample of enone **37**: IR (neat) 830, 860, 1080, 1180, 1360, 1670, 2940 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 60 MHz) 1.00 (9 H, s), 1.70 (3 H, d, $J$ = 1 Hz), 1.60–2.46 (5 H, m), 6.56 (1 H, m); $^{13}C$ NMR ($CDCl_3$) 16.063, 25.110, 25.976, 28.252, 32.640, 55.555, 136.599, 142.612, 201.499; mass spectrum, $m/z$ 166 (M), 151, 123, 100, (100%, McLafferty), 95, 82, 69, 57. Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.36; H, 10.66.

**3-Hydroxy-3,6,6-trimethyl-1-(trimethylsiloxy)-1-cyclohexene (38):** IR (neat) 850, 890, 1100, 1195, 1250, 1645, 2950, 3400 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 60 MHz), 0.00 (9 H, s), 0.75 (3 H, s), 0.80 (3 H, s), 1.05 (3 H, s), 0.9–2.0 (5 H, m), 4.37 (1 H, s); $^{13}C$ NMR ($CDCl_3$) 0.136, 23.972, 25.326, 28.306, 30.039, 34.536, 34.861, 70.074, 109.079, 124.951; mass spectrum, $m/z$ 228 (M), 210, 195, 170, 155, 141, 119, 95, 75, 93 (100%).

**3,6,6-Trimethyl-2-cyclohexenone**[40] **(39).** A sample of crude alcohol **38** was hydrolyzed to enone **39** on silica gel (petroleum ether:ether, 2:1), yielding a pure sample of the enone. 2,4-Dinitrophenylhydrazone: mp 198–200 °C (EtOH) (lit.[40] mp 203–204 °C (EtOH)); IR ($CCl_4$) 875, 1180, 1218, 1390, 1645, 1675, 2940, 2975 $cm^{-1}$; $^1H$ NMR ($CCl_4$, 60 MHz) 1.05 (6 H, s), 1.90 (3 H, bs), 1.70–2.40 (4 H, m), 5.65 (1 H, m).

**6α-*n*-Butyl-3β-hydroxy-3α,6β-dimethyl-1-(trimethylsiloxy)-1-cyclohexene (40):** IR (neat) 840, 1210, 1250, 1660, 2930, 3400 $cm^{-1}$; $^1H$ NMR ($CCl_4$, 60 MHz) 0.00 (9 H, s), 0.75 (3 H, s), 1.00 (3 H, s), 0.55–1.85 (14 H, m), 4.30 (1 H, s); $^{13}C$ NMR ($CDCl_3$) 0.190, 13.950, 23.376, 24.730, 26.247, 29.769, 31.340, 34.861, 37.678, 37.840, 70.345, 109.674, 158.810; mass spectrum, $m/z$ 252 (M − $H_2O$), 196, 181, 179, 124, 82 (100%), 73.

**6-*n*-Butyl-3,6-dimethyl-2-cyclohexenone (41).** A sample of crude alcohol **40** was treated with 2% HCl, following the general procedure, yielding enone **41** in nearly quantitative yield, purified by preparative TLC (silica gel; hexane:ether, 3:1). IR ($CCl_4$) 860, 1120, 1210, 1375, 1640, 1675, 2865, 2940, 2955 $cm^{-1}$; $^1H$ NMR ($CCl_4$, 60 MHz) 0.97 (3 H, s), 0.80–1.60 (9 H, m, *n*-Bu), 1.60–2.60 (4 H, m, ring $CH_2$), 5.63 (1 H, m); mass spectrum, $m/z$ 180 (M), 165, 124 (M − $C_4H_8$, McLafferty), 109, 82 (100%). Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 79.68; H, 10.96.

**6α-*tert*-Butyl-5β-hydroxy-2,5α-dimethyl-1-(trimethylsiloxy)-1-cyclohexene (42).** Epoxy enol ether **17** (424 mg, 2.0 mmol) was treated with 4 equiv of (*t*-BuCuCN)Li in the standard way, yielding 380 mg (70% total crude yield) of a mixture containing mainly the 1,2 adduct, with less than 5% of the 1,4 adduct (as estimated by 360-MHz $^1H$ NMR spectroscopy of the crude). When the mixture was chromatographed on silica gel (petroleum ether:ether, 3:1), the small amount of 1,4 adduct hydrolyzed to the corresponding enone **43**, while the 1,2 adduct **42** did not hydrolyze. Although **42** was purified without problem, it decomposed upon standing. **42**: IR ($CCl_4$) 845, 1175, 1255, 1680, 2950, 3610 $cm^{-1}$; $^1H$ NMR ($CCl_4$, 60 MHz) 0.13 (9 H, s), 1.03 (9 H, s), 1.20 (3 H, s), 1.55 (3 H, bs), 1.20–2.20 (6 H, m); $^{13}C$ NMR ($CDCl_3$) 1.16, 16.60, 27.49, 29.55, 31.72, 32.04, 32.31, 36.05, 59.18, 111.03, 144.29; mass spectrum, $m/z$ 270, 214, 196, 181, 123, 95, 73 (100%), 57.

**6-*tert*-Butyl-3,6-dimethyl-2-cyclohexenone (43).** As mentioned above, in the reaction between **17** and (*t*-BuCuCN)Li, less than 5% of the 1,4 adduct was formed, which hydrolyzed on silica gel to enone **43**: IR ($CCl_4$) 840, 1210, 1650 (shoulder), 1660, 2950 $cm^{-1}$; $^1H$ NMR ($CCl_4$, 60 MHz) 1.00 (9 H, s), 1.05 (3 H, s), 1.92 (3 H, brs), 1.50–2.33 (4 H, m); $^{13}C$ NMR ($CDCl_3$) 17.959, 23.593, 26.464, 28.523, 30.527, 35.836, 47.375, 127.714, 158.647, 204.316; mass spectrum, $m/z$ 180 (M), 165, 124 °(100%, M − $C_4H_8$, McLafferty), 109, 82. Anal. Calcd for $C_{12}H_{20}O$: C, 779.94; H, 11.18. Found: C, 79.84; H, 11.31.

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*trans*-3-Hydroxy-6-phenyl-1-(trimethylsiloxy)-1-cyclohexene (**45**): IR ($CCl_4$) 850, 910, 1260, 1605, 1655, 2950, 3045, 3600 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 360 MHz) 0.11 (9 H, s), 1.3 (s, 1 H, OH), 1.51-1.58 (1 H, m), 1.61-1.72 (1 H, m), 1.80-1.88 (1 H, m), 2.19-2.30 (1 H, m), 3.416 (1 H, dd, $J$ = 5.37, 5.61 Hz), 4.454 (1 H, dt, $J$ = 3.9, 4.64 Hz), 5.212 (d, $J$ = 3.9 Hz); $^{13}C$ NMR ($CDCl_3$) 0.073, 27.810, 28.568, 45.687, 65.840, 108.528, 126.081, 127.056, 128.085, 128.627, 154.522; mass spectrum, $m/z$ 244 (84%, M - $H_2O$), 229 (10), 211 (11), 167 (5), 153 (36), 73 (100).

**6-Phenyl-2-cyclohexenone**[41] (**46**). HCl (2%) was used to hydrolyze a sample of crude alcohol **45** to enone **46**, purified by column chromatography (silica gel, petroleum ether:ether, 3:1): IR ($CCl_4$) 1240, 1680, 2925, 3025 $cm^{-1}$; $^1H$ NMR ($CCl_4$, 60 MHz) 1.9-2.4 (4 H, m), 3.42 (1 H, br t, $J$ = 7 Hz), 5.95 (1 H, dt, $J$ = 10, 1.5 Hz), 6.7-7.3 (6 H, m); mass spectrum, $m/z$ 172 (67, M), 104 (100%), 68 (95, M - 104).

**3-Methyl-6-phenyl-2-cyclohexenone**[42] (**48**): IR ($CCl_4$) 1675, 2935, 3035, 3070 $cm^{-1}$; $^1H$ NMR ($CCl_4$, 60 MHz) 1.70-2.30 (7 H, m), 3.00-3.45 (1 H, m), 5.63-5.80 (1 H, m), 6.80-7.35 (5 H, m); mass spectrum, $m/z$ 186 (70%, M), 141 (2), 128 (3), 115 (8), 104 (33), 82 (100), 78 (11).

*trans*-5-Hydroxy-1-(trimethylsiloxy)-6-vinyl-1-cyclohexene (**49**). 1,2-Adduct **49** was obtained by reaction of 184 mg (1 mmol) of epoxy enol ether **11** with 5 equiv of ($CH_2$=CHCuCN)MgBr as 180 mg (85%) of a lightly colored oil. Compound **49** could also be obtained by reaction of 184 mg (1 mmol) of **11** with 3 equiv of ($CH_2$=CHCuCN)Li, yielding 170 mg (80%) of crude adduct, which could be purified by column chromatography on silica gel (hexane:ether, 3:1) but soon decomposed upon standing neat at room temperature. **49**: IR ($CCl_4$) 855, 1255, 1655, 2965, 3620 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 360 MHz) 0.105 (9 H, s), 1.462-1.561 (1 H, m), 1.764-1.840 (1 H, m), 2.009-2.089 (2 H, m), 2.11 (br s, OH), 2.640 (1 H, br t, $J$ = 6.9 Hz), 3.622 (1 H, ddd, $J$ = 6.2, 2.9 Hz), 4.832 (1 H, m), 5.097-5.155 (2 H, m), 5.535-5.635 (1 H, m); $^{13}C$ NMR ($CDCl_3$) 0.236, 20.172, 27.377, 53.813, 70.661, 103.545, 117.955, 137.836, 148.400; mass spectrum, $m/z$ 226 (14, M), 168 (45), 153 (7), 143 (38), 73 (100).

3$\beta$-Hydroxy-3$\alpha$-methyl-1-(trimethylsiloxy)-6$\alpha$-vinyl-1-cyclohexene (**50**): IR ($CCl_4$) 855, 1255, 1655, 2965, 3620 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 360 MHz) 0.132 (9 H, s), 1.237 (3 H, s), 1.51-1.65 (2 H, m), 1.82 (br, OH), 1.889-1.985 (2 H, m), 2.649 (br, $W_{1/2}$ = 14 Hz), 4.810 (1 H, s), 4.960-5.009 (2 H, m), 5.641-5.736 (1 H, m); $^{13}C$ NMR ($CDCl_3$) 0.236, 25.101, 30.240, 33.932, 42.979, 69.469, 111.887, 115.192, 138.107, 153.547; mass spectrum, $m/z$ 226 (14, M), 168 (45), 153 (7), 143 (38), 73 (100).

**3-Methyl-6-vinyl-2-cyclohexenone** (**51**). A sample of crude alcohol **50** was hydrolyzed with 2% HCl in the usual way, giving a nearly quantitative yield of enone **51**, which was purified by column chromatography on silica gel (AcOEt:hexane, 1:3) but quickly decomposed upon standing, even in solution. $^1H$ NMR ($CCl_4$, 60 MHz) 1.93 (3 H, br s), 1.6-2.4 (4 H, m), 2.6-3.0 (1 H, m), 4.8-5.2 (2 H, m), 5.7-6.3 (2 H, m); mass spectrum, $m/z$ 136 (24, M), 121 (4), 108 (2), 82 (100), 54 (22).

5$\beta$-Hydroxy-4$\alpha$-methyl-1-(trimethylsiloxy)-6$\alpha$-vinyl-1-cyclohexene (**52a**). Epoxy enol ether **44** (198 mg, 1 mmol), containing ca. 40% of its C4 epimer, was treated with 3 equiv of ($CH_2$=CHCuCN)Li in the usual way, yielding 160 mg (70%) of a mixture of 1,2 and 1,4 adducts. Assignment of the signals in the 360-MHz $^1H$ NMR spectrum of the crude mixture was facilitated by hydrolyzing the mixture with 10% HCl (5 min, room temperature); from this new crude mixture, the only compound that could be completely separated (silica gel, petroleum ether: ether, 3:1) was the 1,2-adduct **52a**. Nevertheless, this allowed the assignment of the 360-MHz $^1H$ NMR spectrum of the original crude mixtures: the ratio of 1,4 to 1,2 addition was estimated to be 7:3. **52a**: IR ($CCl_4$) 1255, 1655, 2965, 3620 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 360 MHz) 0.121 (9 H, s), 1.044 (3 H, d, $J$ = 6.12 Hz), 1.608-1.705 (1 H, m), 1.734-1.780 (1 H, ddd, $J$ = 2.2, 5.8, 10.9 Hz), 2.040-2.111 (1 H, m), 2.675 (1 H, br t), 3.108 (1 H, dd, $J$ = 9.77, 8.79 Hz), 4.813 (1 H, ddd, $J$ = 5.61, 2.19, 1.95 Hz), 5.157-5.246 (2 H, m), 5.569-5.670 (1 H, m); $^{13}C$ NMR ($CDCl_3$) 0.182, 15.188, 30.627, 34.582, 55.005, 65.786, 103.653, 118.821, 138.432, 142.766; mass spectrum, $m/z$ 226 (9, M), 208 (5), 193 (3), 168 (39), 156 (9), 75 (41), 73 (100).

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**Supplementary Material Available:** A complete NMR analysis (360 MHz $^1H$ and $^{13}C$) of the stereochemistry of the adducts from cuprate reactions and chemical evidence for stereochemistry and experimental section for several enones and epoxides (19 pages). Ordering information is given on any current masthead page.

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# Motion at the Active Site of Tosylchymotrypsin

**M. E. Ando, J. T. Gerig,* and E. F. Weigand**

*Contribution from the Department of Chemistry, University of California, Santa Barbara, California 93106.* *Received August 6, 1981*

**Abstract:** Tosylchymotrypsin, deuterium or carbon-13 labeled in the tosyl group, has been prepared and examined by deuterium or carbon NMR spectroscopy. Analysis of spectral line widths indicates that rotation of both the methyl group and the aromatic ring of this moiety is rapid, although aromatic ring motion may be slowed slightly in the associated protein. The chemical shift of the methyl carbon is essentially invariant to sample pH or to denaturation of the protein. When considered in light of the structure of the crystalline protein and the effect of solvents on carbon chemical shifts, our collective observations suggest that the local structure of the active site in tosylchymotrypsin in solution is rather "loose", such that the tosyl group rotates freely and resides in an environment that is solvent rich.

Covalent, substate-derived intermediates are often formed during enzyme catalysis. The presence of the covalently linked group which originated in the substate can stabilize the protein against structural changes induced by pH variation[1] or addition

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