Tetrahedron Letters No. 8, pp 675 - 678.
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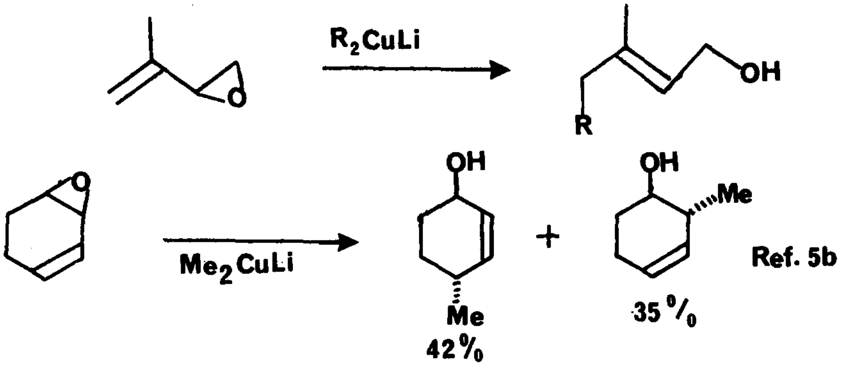
0040-4039/79/0215-0675$02.00/0

# REGIOSELECTIVE REACTIONS OF ORGANOCUPRATES WITH CYCLOALKENE EPOXIDES

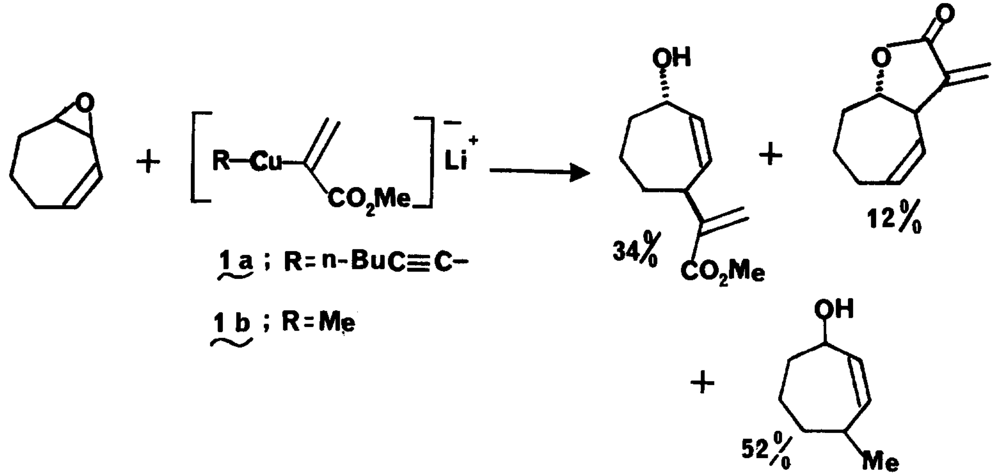
J. P. Marino* and D. M. Floyd[1]
Department of Chemistry, The University of Michigan,
Ann Arbor, Michigan 48109

A recent report[2] on the regiospecific reactions of diepoxides with cyanocuprates and the synthetic potential for regiospecific reactions in cycloheptenes prompted us to describe our recent observations on mixed cyanocuprates. Acker[2] has reported that mixed cyanoalkyl cuprates regiospecifically open the less substituted and pendant epoxide of diepoxides from substituted 4-vinylcyclohexenes. Presumably the cyano ligand is exerting an unusual effect on the reactivity of organocuprates with different epoxides.

During the course of our investigations of the chemistry of α-carboalkoxyvinylcuprates,[3] we observed a very useful regiospecific reaction for the monoepoxides of 1,3-cyclohexadiene and 1,3-cycloheptadiene. It is well known[4] that the reactions of dialkylcuprates with acyclic 1,3-diene monoepoxides proceed regiospecifically and stereospecifically to yield the 1,4-adducts. In direct contrast to this specificity is the observed mixture of 1,2 and 1,4-adducts from the reactions of dialkylcuprates with monoepoxy-1,3-cyclohexadiene.[5] The unfortunate lack of regiospecificity in the cyclohexene epoxide system renders this approach to substituted cyclohexenols synthetically impractical.



As part of our program to develop stereospecific methods for the synthesis of hydroxy-α-methylene-γ-butyrolactones,[6] we reacted the mixed acetylenic cuprate **1a**[3] with the monoepoxide of 1,3-cycloheptadiene[7] in ether at -78°C. After the reaction mixture was quenched with an aqueous ammonium chloride solution, the ether extract was chromatographed on silica gel. Two of the isolated products were the expected 1,2 and 1,4-acrylate adducts, while the predominant product was 4-methyl-2-cyclohepten-1-ol.[8] The 1,2-acrylate product spontaneously cyclized to the *trans*-γ-butyrolactone.[6]



**1a** ; R=n-BuC≡C-

**1b** ; R=Me

While the low yield of acrylate adducts was disappointing, the regiospecific production of the 4-methyl-2-cyclohepten-1-ol was significant. We attributed the transfer of the methyl ligand to the cycloheptene epoxide to the incomplete formation of the desired acetylenic cuprate **1a** and the presence of the mixed methyl cuprate **1b** (R=Me). In fact, when the mixed methyl cuprate **1b** was intentionally prepared from one equivalent of dimethyl copper lithium and methyl α-bromoacrylate and reacted with the cycloheptenyl epoxide, a 98% yield of the methyl transfer product was obtained. G.C. separation of the 4-methyl and 2-methyl isomers was easily achieved and the ratio of 1,4-methyl adduct to 1,2-methyl adduct was found to be 97:3. A control reaction involving the cycloheptene epoxide and dimethyl copper lithium revealed that the ratio of 1,4 to 1,2-methyl adducts was 7:3. Since no previous studies on the reactions of dialkylcuprates with seven-membered ring epoxyalkenes were reported, we took the 7:3 ratio as our reference point for the regioselectivity.

From these results we felt that the strongly electron-withdrawing acrylate ligand was responsible for the high specificity for 1,4-addition. If in fact electron-withdrawing ligands exert an influence on the regiochemistry, this could be examined further. To this end, we prepared several mixed cuprates which contained a methyl ligand and an electron-withdrawing ligand. The results for the reactions of these cuprates with the monoepoxide of 1,3-cycloheptadiene are summarized in Table I.

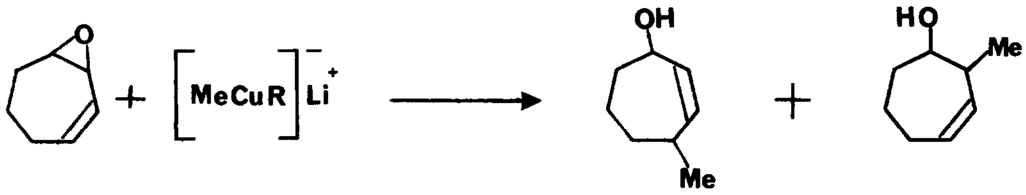


Table I[a]

| R | Total Yield[b] | Yield of 1,4[c] | Yield of 1,2 |
|---|---|---|---|
| Me | 91% | 70% | 30% |
| n-Bu-C≡C- | 95% | 85% | 15% |
| CN | 95% | 90% | 10% |
| $CH_2=C\genfrac{}{}{0pt}{}{\diagup}{\diagdown CO_2Me}$ | 98% | 97% | 3% |
| $[MeCu]_n$ | 90% | 80% | 20% |

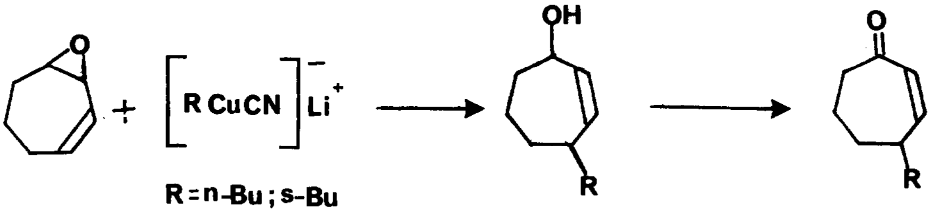
[a] All reactions were carried out in ether at -78°C. Reaction times varied between one hour to three hours.

[b] Total yields of cyclohepten-ols were calculated by nmr using an internal standard.

[c] Ratio of 1,4/1,2-product was determined by vpc analysis using a 3% OV-225 or 5% Carbowax 20M column.

There is a progression of increasing regiospecificity in going from the homocuprate (R=Me) to the acrylate mixed cuprate. From a practical standpoint, the cyanomethylcuprate (R=CN) is the most convenient to prepare. Addition of an alkyl lithium solution to a suspension of anhydrous cuprous cyanide in ether at -78°C generates the mixed alkyl cyano cuprate. While the acrylate ligand exerts the greatest influence on the regiospecificity, its use is limited to the methyl case.[9]

We have extended the use of the cyano ligand to the n-butyl and s-butyl organocuprates. When these mixed cuprates were reacted with the monoepoxide of 1,3-cycloheptadiene, high yields of the corresponding 4-alkyl-2-cyclohepten-1-ols were obtained. In the case of the butyl cyanocuprates, no 1,2-product could be detected by nmr or v.p.c. analysis. Oxidation of these allylic alcohols with chromium trioxide-pyridine complex yields the 4-alkylcyclohepten-1-ol which are not readily available from cycloheptenone or simple precursors.



As a final control for the unusual ligand effect of the cyano group, we investigated the reaction of methyl cyanocuprate with the monoepoxide of 1,3-cyclohexadiene for comparison to previous work.[5] We found that reactions carried out at -78°C or at 0°C only produced the previously known[5] trans-4-methyl-2-cyclohexen-1-ol in high yield. This last result confirms the effect of the cyano ligand, and also rules out any temperature effects (-78°C *vs* 0°C) for the regiospecificity. We thus feel that the use of the cyano ligand in reactions of mixed cuprates with cycloalkene epoxides provides for a simple route to 4-alkylcycloalkenols of six and seven-membered rings. Work is continuing in our laboratories on the control of the stereochemistry of the cycloheptene epoxide reactions and on synthetic applications.

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8. The *trans*-stereochemistry for the 1,4-acrylate adduct was assigned by analysis of the 100 Hz proton magnetic resonance spectrum of the corresponding iodolactone. The 4-methyl-2-cyclohepten-1-ol was a mixture of *cis/trans* isomers which could not be separated by v.p.c., but the 100 Hz pmr spectrum of the mixture suggested a *trans/cis* ratio of 7/3.
9. Several attempts to prepare the n-butyl-acrylate reagent from di-n-butyl copper lithium and methyl α-bromoacrylate failed to yield a reagent which transferred either ligand to an epoxide.

(Received in USA 12 December 1978)