

centration and the remaining terms are already defined.

$$\phi_F^{EC} = I_{\infty}^{EC} / k_{\text{obsd}}[4]_0 \quad (6)$$

The singlet (ϕ^S) and triplet (ϕ^T) excitation yields were calculated from eq 7, where ϕ_{ET} is the quantum yield for energy transfer

$$\phi^{S,T} = \phi_F^{EC} / \phi_{ET}\phi_F^n \quad (7)$$

from the chemienergized excited ketone to fluorophor, ϕ_F^n the fluorescence yield of the fluorophor (F), and the ϕ_F^{EC} term as already defined. For the singlet excitation yields (ϕ^S), 9,10-diphenylanthracene (DPA) was used as fluorophor, for which $\phi_{DPA}^n = 1.00^{23}$ and $\phi_{ET} = \phi_{DPA}^{SS} = 1.00$. For the triplet excitation yields (ϕ^T) 9,10-dibromoanthracene (DBA) was used as fluorophor, for which $\phi_{DBA}^n = 0.10^{24}$ and $\phi_{ET} = \phi_{DBA}^{TS} = 0.25^{25}$. The enhanced chemiluminescence data were processed on a Tektronix 4051 Computer and the results are summarized in Table II.

X-ray Crystallography. The orientation matrix and the cell parameters were determined from all clear colorless crystals of given dimensions on a SYNTHEX-P3 four circle diffractometer. Measurement of intensities: ω scan, 1° range, Mo K α , 2θ maximum = 55° . The structures were solved by direct-phase determination. Positional and thermal parameters could be refined by anisotropic least-squares cycles to the given R values. The positions of the hydrogen atoms were calculated geometrically

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and considered isotropically in all refinements. Perspective drawings are given in Figures 1-4.

Acknowledgment. We are grateful to the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie for generous financial support. We thank Dr. D. Scheutzw for measuring the 400-MHz ^1H NMR and the 100.61-MHz ^{13}C NMR spectra and Dr. G. Lange for measuring the mass spectra.

Registry No. **3a**, 255-37-8; **3b**, 4345-55-5; **3c**, 82912-44-5; **3d**, 82912-45-6; **3e**, 5770-58-1; **3e** (alcohol), 5770-68-3; **3f**, 79792-92-0; **3g**, 82912-48-9; **3h**, 82912-49-0; **3i**, 79792-91-9; **3j**, 75694-46-1; **3j** (alcohol), 91201-75-1; **3k**, 91201-56-8; **3l**, 91201-57-9; **3l** (alcohol), 91201-76-2; **4e**, 91201-58-0; **4f**, 91201-59-1; **4g**, 91201-60-4; **4h**, 91201-61-5; **4i**, 91201-62-6; **4j**, 91201-63-7; **4k**, 91201-64-8; **4l**, 91201-65-9; **5a**, 91201-66-0; **5e**, 79792-93-1; **5f**, 635-67-6; **5g**, 91201-67-1; **5h**, 91201-68-2; **5i**, 79792-94-2; **5j**, 643-94-7; **5k**, 91201-69-3; **5l**, 91201-70-6; **6**, 91201-71-7; **7f**, 91201-72-8; **7g**, 91201-73-9; **7h**, 91201-74-0; $\text{Br}(\text{CH}_2)_2\text{Br}$, 106-93-4; $\text{Br}(\text{CH}_2)_3\text{Br}$, 109-64-8; $\text{Br}(\text{CH}_2)_4\text{Br}$, 110-52-1; PhCOCH_2Br , 70-11-1; PhCHBrCOPh , 1484-50-0; 1,2-dihydroxybenzene, 120-80-9; 2,3-dihydroxy-1-methoxybenzene, 934-00-9; naphthalene-2,3-diol, 92-44-4.

Supplementary Material Available: Positional and thermal parameters of the atoms of the dioxetanes **4g**, **4h**, and **4j**, diester **5h**, and dioxane **6** are given in Tables I-X; details of the crystallographic parameters in Table XI; perspective drawing of diester **5h**; labeling of the atoms in the Figures 1-4 corresponds to that given in Tables I-X (13 pages). Ordering information is given on any current masthead page.

Substitution Reactions of Secondary Halides and Epoxides with Higher Order, Mixed Organocuprates, $\text{R}_2\text{Cu}(\text{CN})\text{Li}_2$: Synthetic, Stereochemical, and Mechanistic Aspects

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Higher order cuprates, represented by the general formula $\text{R}_2\text{Cu}(\text{CN})\text{Li}_2$, are readily prepared from copper cyanide and 2 equiv of an organolithium. These novel reagents react readily and efficiently with secondary unactivated iodides and bromides affording products of substitution. Likewise, mono-, di-, and trisubstituted epoxides undergo ring opening leading to the corresponding alcohols in excellent yields. The effects of solvent, temperature, gegenion, and variations in ligands are discussed. Replacement of the second equivalent of RLi by CH_3Li strongly encourages transfer of R over CH_3 in $\text{R}(\text{CH}_3)\text{Cu}(\text{CN})\text{Li}_2$ with halides. Use of PhLi as $\text{R}_\text{R}\text{Li}$ in place of one $\text{R}_\text{T}\text{Li}$ (i.e., $\text{R}_\text{T}(\text{Ph})\text{Cu}(\text{CN})\text{Li}_2$) is suggested for oxirane cleavage. The stereochemical implications associated with both couplings are also addressed.

Introduction

Among the vast array of methodologies available to the organic chemist, organocopper based reagents have provided one of the most consistently popular tools for carbon-carbon bond construction.¹ This is not surprising as copper salts are available in quantity, and reactions of reagents derived therefrom tend to be efficient and conditions mild.² As with most useful methodologies, however, there are limitations which require alternative strategies for effecting the same net overall synthetic transformation. Thus, in the case of organocuprates R_2CuLi , 1, displacement processes at secondary unactivated centers bearing halogen are quite rare due to highly competitive

reduction and elimination pathways.^{2,3} Likewise, substitution reactions of these "lower order" species **1** with, in particular, di- and trisubstituted epoxides are oftentimes problematic as both products of rearrangement and elimination are commonly encountered.^{2,4} These pitfalls notwithstanding, interest in the applications of cuprate chemistry have continued unabated.⁵

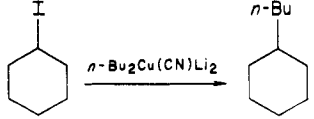
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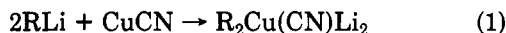
* A. P. Sloan Foundation Fellow, 1984-1986.

Table I. Effects of Solvent on Substitution Reactions of $R_2Cu(CN)Li_2$ with Cyclohexyl Iodide


solvent	conditn	yield, ^a %
THF	1.9 equiv, -78 °C, 1 h	>90
Et ₂ O	1.5 equiv, -50 °C, 1 h	74 ^b
PhCH ₃	1.9 equiv, -50 °C, 1 h	0 ^c
1:1 THF/Et ₂ O	1.5 equiv, -50 °C, 1 h	69 ^d
1:1 THF/PhCH ₃	1.5 equiv, -50 °C, 1 h	61 ^d
DME	2.0 equiv, -78 °C, 1 h	>90

^a By VPC. ^b 26% starting material recovered. ^c All starting material recovered. ^d Essentially all the starting iodide was consumed.

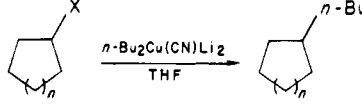
Recently, the concept of "higher order, mixed" copper reagents $R_2Cu(CN)Li_2$, **2**, was introduced wherein Cu(I) dilithium salts are formed in an ethereal solvent from copper cyanide and 2 equiv of an organolithium according to eq 1.⁶ These species display remarkably different



chemical (and spectroscopic⁷) properties relative to Gilman reagents **1**, allowing coupling between one of a variety of ligand types R affixed to copper and either secondary halides⁶ or substituted epoxides⁸ in excellent yields. In a full account of this subject, we now describe (1) the details of our preliminary reports,^{6,8} (2) the role of solvent, gegenion(s), and temperature, (3) the selectivity of ligand transfer from copper to carbon, and (4) in light of some preliminary stereochemical results obtained,⁹ additional experiments aimed at gaining insight into the mechanistic features of the coupling process.

Results and Discussion

Reactions of Secondary Unactivated Halides. At the time that this initial work was begun,⁶ there were numerous literature reports attesting to the inefficiency associated with the coupling between a secondary unactivated center bearing halogen and a Gilman cuprate.^{2,3} Yields were rarely considered synthetically useful. In light of Ashby's extensive studies on substitution reactions of the higher order reagent Me_3CuLi_2 ,¹⁰ which clearly demonstrate that a unique species of considerable synthetic potential is formed from CuI and 3 equiv of MeLi, we set out to prepare the mixed analogue substituting CuCN for CuX (X = I, Br). The reagents resulting from the combination of CuCN plus 2RLi¹¹ are always colored, being a function of the CuCN employed, and usually are formed at temperatures between -78 and -25 °C. Such solutions of $R_2Cu(CN)Li_2$ react rapidly with secondary iodides at very low temperatures (-78 to -50 °C) whereas the corresponding bromides usually require ca. 0 °C. Using cyclohexyl iodide as a model substrate, the solvent of choice

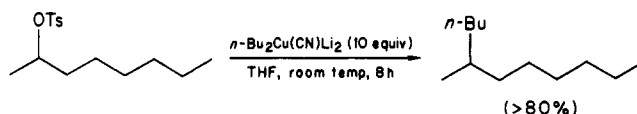
Table II. Coupling Reactions of $n-Bu_2Cu(CN)Li_2$ with Secondary Halides


n	X	conditn	yield, %
1	I	-78 °C, 2 h	82
1	Br	0 °C, 6 h	86
2	I	-78 °C, 1 h	100
2	Br	rt, ^a 6 h	41

X	conditn	yield, %
I	-50 °C, 2 h	99
Br	0 °C, 2 h; rt, ^a 1 h	94
Cl	rt, ^a 11 h	28

^a rt = room temperature.

for mediating the coupling (with **2**, R = *n*-Bu) appears to be THF. Although dimethoxyethane (DME) and Et₂O are also acceptable, large percentages of toluene should be avoided (Table I). In the cyclic series, both cyclohexyl and cyclopentyl iodides and bromides were investigated, along with 2-halopentanes as representative acyclic model systems, chosen for comparison purposes with the classical work³ on lower order reagents. In the former class, all lead to good yields of the anticipated product, with bromocyclohexane being the only problematic case. This is to be expected³ based on the nature of the coupling process (vide infra). Secondary chlorides are also poor reaction partners. Table II summarizes this initial brief study, the results listed being quite striking by comparison with existing literature data.^{2,3,12} In contrast to the remarkable proclivity of reagents **2** toward displacement of secondary iodides and bromides, secondary sulfonates (mesylates, tosylates, and trisylates) are far less prone toward substitution and generally do not lead to acceptable yields of product. It should be mentioned at this juncture that only ca. 1.5 equiv of **2** are routinely used. When, however, the ratio of cuprate to, e.g., tosylate is increased significantly (e.g., 10 equiv), the efficiency of the process improves markedly, as in the case shown below. These observations



are surprising in view of the well-established reactivity of secondary tosylates toward lower order reagents, although yields for these reactions are also in the moderate range.¹³

Variation in RLi. When 2-iodooctane was used as the substrate, ligand transfer from copper to carbon as a function of the nature of the organolithium was next examined. While primary alkylolithium derived reagents lead to very efficient carbon-carbon bond formation, cuprates **2** formed from a secondary or aryllithium (e.g., *s*-BuLi or PhLi) reacted to afford essentially products resulting from competing reduction and (some) elimination. It is particularly noteworthy that vinyl ligands are readily delivered in the case of secondary iodides. However, yields for the same coupling with a bromide dropped considerably (35–40%), even in the presence of a 4-fold excess of **2**, R

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Table III. Variation of RLi in Reactions of $R_2Cu(CN)Li_2$ with Secondary Halides

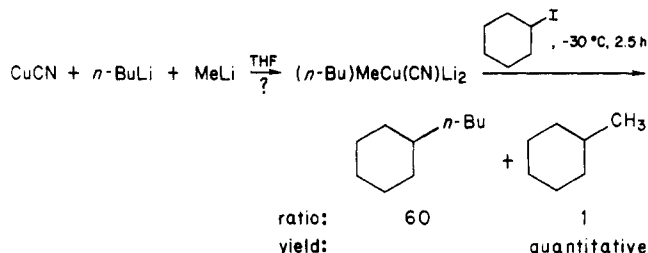
X	R	yield, %
Br	$CH_2=CHCH_2$	>90 ^b
I	$CH_2=CH$	90 ^c
I	CH_3	89
I	CH_3CH_2	>95
I	$CH_3CH_2CH_2$	90 ^d
I	C_6H_5	<7 ^e
I	$CH_3(CH_2CH_2)CH$	19 ^e
I ^f	$CH_2=CH$	70–80 ^{g,h}

^a By VPC analysis. ^b Product identified by comparison of spectral data with literature values; see ref 14. ^c Some starting material remained (6%). ^d 10% starting material recovered. ^e Product was not compared with an authentic sample. ^f Reactant was 1-phenyl-3-iodoheptane. ^g Product was 1-phenyl-3-vinylheptane. ^h Isolated yield.

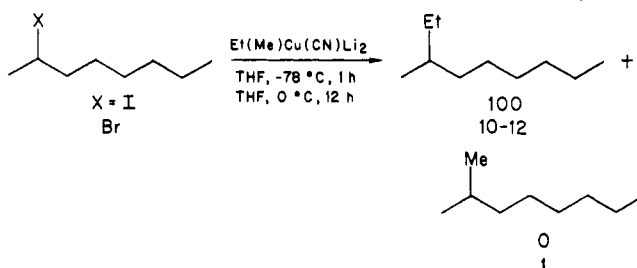
= vinyl. Generation of the allyllithium derived species (i.e., 2, R = allyl, 1.6 equiv) coupled nicely (>90%) with 2-bromooctane. Although it is known that allyllithium,^{14a} as well as allylmagnesium bromide^{14b} and allylsodium,^{14b} will displace secondary bromides, use of a milder organo-copper reagent is usually preferred. Not surprisingly, in side by side comparison runs with both (allyl)₂CuLi (2 equiv) and (allyl)Cu(CN)Li (2 equiv) at -22 °C in THF for 1.5 h only 3% and 2% 4-methyl-1-decene,¹⁵ respectively, were realized. The remainder of the mass was starting bromide, which again reflects the remarkable differences in reactivity between lower and higher order cuprates. A summary of these results is given in Table III.

Selectivity of Ligand Transfer. In our preliminary report⁶ on these reagents we alluded to the possibility of forming still more highly mixed, higher order reagents $R_T R_R Cu(CN)Li_2$, 3, (where R_R is a residual, nontransferable, or "dummy" ligand) which might enable conservation of valuable $R_T X$, the precursor of $R_T Li$ in forming 3. Judging from Table III, a phenyl moiety was an obvious choice since it apparently does not readily couple with secondary centers. Returning to iodocyclohexane as substrate, a solution of (*n*-Bu)PhCu(CN)Li₂, 4 (2.5 equiv), was prepared by sequential addition of PhLi and *n*-BuLi to CuCN, the order being of no consequence whatsoever, followed by introduction of the iodide. After 2.5 h at -45 to -50 °C, a 63% yield (VPC) of *n*-butylcyclohexane was realized, along with 3% phenylcyclohexane (the remainder being starting material). Thus, an *n*-Bu ligand had been transferred in preference to a phenyl group with a selectivity of ca. 21:1.¹⁶

Methylolithium was looked at next [i.e., (*n*-Bu)MeCu(CN)Li₂, 5] as it forms cuprates 2, R = CH₃, which are also noticeably less reactive than all of the other allyllithium derived reagents seen thus far. Although this reaction on the same substrate required a somewhat longer time (2.5 h) relative to the use of 2, R = *n*-Bu (<1 h), at -50 °C, the yield remained unchanged (≈ quantitative) while the ratio of *n*-Bu to Me delivery was satisfyingly 60:1. Switching to 2-iodooctane, the highly mixed species Et(Me)Cu-

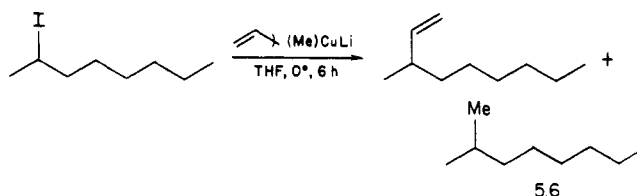


(CN)Li₂ gave, in close to quantitative yield, the product derived *exclusively* from ethyl transfer, in spite of the relative similarity in size of the two ligands (as compared to the *n*-Bu, Me case). 2-Bromooctane, however, afforded ca. a 10–12:1 ratio of Et:Me transfer. Presumably, this



large selectivity dependence on the halide reflects the differences in mechanism of ligand transfer (vide infra). It thus appears that simply substituting 1 equiv of MeLi for the second equivalent of $R_T Li$ (where R_T = a primary alkyl group) is sufficient to maintain reactivity without compromising efficiency.

Although the selective delivery of R_T from 3 looks very promising wherein primary alkyl residues are called for, it was not clear that similar results with R_T = vinyl would be forthcoming. Competition studies with $R(vinyl)Cu(CN)Li_2$, 6 (R = Ph), on 2-iodooctane in THF led to only 24% 3-methylnonene, along with a 23% yield of octane (i.e., reduction), and 36% starting material after 6 h at 0 °C. Replacement of phenyl by methyl (i.e., 6, R = Me) afforded a much cleaner reaction, which was not pursued, as a preference for Me over vinyl transfer of 5.6:1 was observed. The same cuprate in Et₂O, which favors vinyl



transfer over methyl with enones,^{13,17} still gave an undesirable ratio of 3.9:1. Thus, we were forced to look elsewhere for that elusive second ligand which would not significantly decrease reagent reactivity yet would encourage selective loss of the vinyl group from the copper center. Numerous R_R were investigated, relying on either steric or electronic properties as the controlling factor, some of which include *s*-Bu, *t*-Bu, *i*-Pr₂N,¹⁸ Ph₂P,¹⁸ (C-H₃)₂CHCH₂, *t*-BuO,¹⁹ PhS,¹⁹ (EtO)₃P,²⁰ CH₂CN, cyclopentadienyl, CF₃CF₂CF₂, CH₃OC(CH₃)₂C≡C,²¹ and inde-

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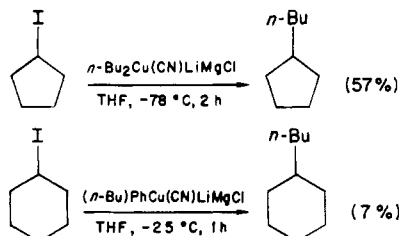
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nyl. Unfortunately, none of these ligands afforded a product of vinyl transfer in acceptable yields, the competing pathways being reduction and elimination. The search continues.

Role of the Gegenion(s). To determine the importance of lithium ions in solutions of cuprates **2**, CuCN was treated with 1 equiv of a Grignard reagent as a substitute for the second equivalent of RLi. For the cases shown below, addition of PhLi and *n*-BuMgCl to CuCN in THF afforded a homogeneous solution into which was added iodocyclohexane (0.5 equiv). After stirring at -25°C for



1 h, only 7% *n*-butylcyclohexane (vs. 100% with **2**, R = *n*-Bu, at -78°C) resulted. Even the more reactive di-*n*-butyl analogue with iodocyclopentane led to only 57% product after 2 h at -78°C (vs. 82% with **2**, R = *n*-Bu, see Table II). The remainder of the mass in each reaction was accounted for in starting material. Thus, replacement of an organolithium with an organomagnesium reagent dramatically decreases the rate of reaction. Attempts to supply additional lithium ions in the form of solubilized LiBr²² led to no effect on either yield or rate.

Effect of Temperature. This particular parameter can play a pivotal role in determining the outcome of halide displacements under the influence of reagents **2**. In general, it is critical that temperatures significantly above those needed for reactions of iodides be avoided, as such conditions, while increasing reaction rates, usually tend to encourage substrate reduction at the expense of the desired coupling. For example, although **2**, R = *n*-Bu, reacts with iodocyclohexane in DME at -50°C to afford *n*-butylcyclohexane in 76% yield (Table I), the remainder of the material presumably being a combination of cyclohexane and cyclohexene, conducting the reaction at -78°C gives the hydrocarbon in essentially quantitative yield. Similar observations have been made with $n\text{-Pr}_2\text{Cu}(\text{CN})\text{Li}_2$ on 2-iodooctane to afford 4-methyldecane (-78°C , 2 h, >90%, <2% octane; -50°C , 1 h, >90%, >4% octane; -78°C , 0.5 h, >80%, >15% octane). With 2-bromooctane, however, these reactions appear to work well at 0°C to room temperature, little (<5%) octane being formed, e.g., at ambient temperature, over 2.5 h (>90% yield of product). This remarkable difference in mode of reactivity perhaps reflects the variation in reduction potentials between the two substrates.²³ Such couplings with secondary bromides, therefore, may well be realizable due to the stability of the higher order cuprates **2**, presumably resulting from the influence of the cyano ligand.²⁴

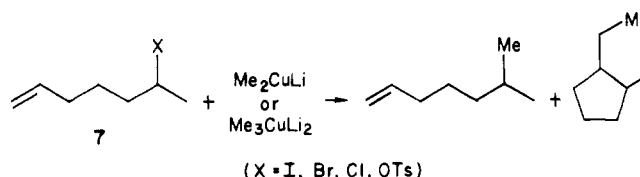
Stereochemistry and Mechanism. The common conception that secondary halides, in general, react with

Table IV. Reactions of Higher and Lower Order Cuprates with Optically Active Substrates

X	reagent	% inversion
I	$\text{Et}_2\text{Cu}(\text{CN})\text{Li}_2$	1.1–1.2 ^a
I	Et_2CuLi	0
Br	$\text{Et}(\text{Me})\text{Cu}(\text{CN})\text{Li}_2$	97–103 ^a
Br	$\text{Et}(\text{Me})\text{CuLi}$	97–102 ^a

^a This percentage varies depending upon the choice of rotation chosen from literature values (9.30–9.86 $^{\circ}\text{C}$). See ref 14b and 15.

Gilman cuprates by way of a net $\text{S}_{\text{N}}2$ process^{1,3} suggested that a similar stereochemical outcome at carbon would be found by using higher order cuprates. Thus, it was unsettling to find that treatment of optically active 2-iodooctane with **2**, R = Et afforded racemic 3-methylnonane.⁹ It was not until this same reaction employing Et_2CuLi had been performed, also affording optically inactive material, that a pattern indicative of a dependence of stereochemistry and (most likely) mechanism on the nature of the halide as opposed to the reagent, emerged. Indeed, repeating these experiments on the corresponding bromides, using $\text{Et}(\text{Me})\text{Cu}(\text{CN})\text{Li}_2$ and $\text{Et}(\text{Me})\text{CuLi}$, now led to the desired hydrocarbon with essentially complete inversion of stereochemistry at the original C-2 center, as summarized in Table IV. The important implication of this study is that an iodide reacts via its radical which couples very efficiently with a ligand delivered from either side of the intermediate. Bromides, by contrast, may react in a more traditional $\text{S}_{\text{N}}2$ -type sense. Recently, reported work from Ashby's laboratory,²⁵ where 6-halo-1-heptenes, **7**, were



treated with both lower and higher order (Me_3CuLi_2) cuprates, demonstrates the intermediacy of radicals in the coupling with iodides, whereas bromides give products of substitution. These studies, however, do not eliminate the presence of radicals in both cases where radical cages, certainly of a different nature between iodides and bromides, may be involved. In the latter substrates, coupling with R_{T} solely from a direction opposite the departing halide ion may result from a radical anion pair where $\text{Br}^{\cdot-}$, in effect, blocks one face of the radical (i.e., $\text{R}^{\cdot}\text{Br}^{\cdot-}$). A similar explanation has been offered to account for stereochemical consequences in reactions of Me_3SnNa , **8**, with related substrates.²⁶ That is, reaction of **8** with 6-bromo-1-heptene (**7**, X = Br) gives predominantly cyclized material yet effects inversion at carbon in the saturated analogue. Hence, although cuprates afford only products of substitution most likely by way of an oxidative addition, reductive elimination sequence in both bromide cases, the possibility that coupling between a radical anion ($\text{R}^{\cdot}\text{Br}^{\cdot-}$) and a copper species $\text{R}_{\text{T}}\text{CuLi}_3$ occurs competitively with cyclization (in the haloheptene series) cannot be ruled out.²⁶ Electrochemical measurements on secondary iodides and bromides in THF point to large differences in reduction potentials (E_{p} , RI more anodic than RBr) between

(22) Ashby, E. C.; Noding, S. A. *J. Am. Chem. Soc.* **1979**, *101*, 4371. Ashby, E. C.; Lin, J. J.; Watkins, J. J. *Tetrahedron Lett.* **1977**, 1709.

(23) Lipshutz, B. H.; Wilhelm, R. S.; Nugent, S. T.; Little, R. D.; Baizer, M. M. *J. Org. Chem.* **1983**, *48*, 3306.

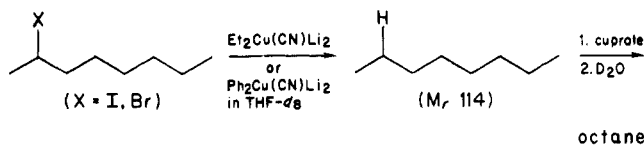
(24) Unfortunately, reactions of secondary bromides (other than bromocyclohexene) with R_2CuLi_2 have not been reported to date. Thermal stability studies on R_2CuLi_2 have been done (S. Bertz, private communication) and gave results which are "close to" those obtained with R_2CuLi . Unsaturated ligands are well-known² to have both a stabilizing and deactivating effect on lower order reagents, which should apply similarly to **2**.

(25) Ashby, E. C.; DePriest, R. N.; Tuncay, A.; Srivastava, S. *Tetrahedron Lett.* **1982**, *23*, 5251.

(26) Ashby, E. C.; DePriest, R. *J. Am. Chem. Soc.* **1982**, *104*, 6144. See also: Kuivila, H.; Alnajjar, M. S. *Ibid.* **1982**, *104*, 6146.

these electrophiles.²³ Iodides show two distinct waves indicative of a stepwise reduction to an anion via a radical. Bromides gave only a single wave suggesting a minimal difference between the first and second reduction potential. Hence, it may be, in the case of bromides, that two successive steps are involved: an initial electron transfer followed by a very rapid coupling. As tosylates are known to give products exclusively of inversion at carbon,²⁷ they may react via a mechanism similar to that of bromides, or, perhaps, by a third type of coupling process. In this vein, it should be recognized that the observed order of reactivity with **2** is $RI > RBr > ROTs$, which contrasts with that of lower order cuprates **1** ($OTs > I > Br$).^{12,27} Since both **1** and **2** couple with iodides and bromides under somewhat similar conditions (although with different levels of efficiency), such a turnabout in the case of tosylates is most curious.

In displacement reactions which lead to side products of reduction, it is interesting to consider the source of hydrogen. Two most likely candidates include (a) the solvent and (b) the workup. Hence, treatment of 2-bromooctane with $Et_2Cu(CN)Li_2$ both in THF- d_8 and in protio THF with a D_2O quench were carried out under conditions which encourage reduction over substitution (i.e., adjustment in reaction temperatures, vide supra).



GC-MS analysis²⁸ of the octane formed in each experiment unequivocally demonstrated that *no deuterium incorporation had occurred in either case!* These are puzzling results, especially in the former reaction as one might anticipate radical formation followed by H• (or D•) abstraction from THF. Still, we point out that the product of reduction is usually a minor component, and hence there are other locations in the medium which can supply hydrogen, including the substrate and reagent. Whitesides et al.²⁹ have shown that the complexed alkyl copper n -BuCu•P(n -Bu)₃ undergoes decomposition to 1-butene and an equivalent amount of n -butane via an intermediate copper hydride (CuH•P(n -Bu)₃). While formation of this hydride source from $Et_2Cu(CN)Li_2$ cannot be ruled out, it is most unlikely that this mechanism is accounting for the octane produced. It is well-known that CuH, in uncomplexed form, is unstable above $-80^\circ C$,³⁰ and Ashby³¹ has used this information in characterizing a variety of hydrido cuprates of general formula $Li_nCu_mH_{n+m}$. Moreover, the fact that $Ph_2Cu(CN)Li_2$ is more effective at encouraging reduction precludes hydride formation via the same β -elimination pathway. These two experiments, while unexpectedly inconclusive insofar as revealing the actual species responsible for donating a hydrogen atom, do provide additional clues to what must still be considered a very complex phenomenon.

Reactions of Epoxides. The quality of substitution processes effected by reagents **2** on oxiranes was next investigated.⁸ Of paramount concern was the extent to which typical competing modes of reaction would occur, mainly

in both di- and trisubstituted examples.³² A general study, therefore, was conducted and several representative examples are shown in Table V. It is apparent that *mono*-, *di*-, and most notably, *trisubstituted* epoxides are receptive toward ring opening to afford good to excellent yields of the corresponding alcohols. In highly hindered cases of tri- (entry 11) and tetraderivatized epoxides (entry 12), either no reaction was observed, or alternative processes ensued to consume starting material. Alkyl, vinyl, heterocyclic, and aryllithium derived reagents reacted smoothly in THF under mild conditions without relying on large excesses for driving each reaction to completion. It should be recalled (vide supra) that cuprates **2**, $R = Ph$ do not lead to products of substitution where secondary halides are involved. Some additional salient features include the following: (1) The regiochemical outcome in unactivated epoxides is such that attack predictably takes place at the least hindered site. (2) Carbon-carbon bond formation occurs with inversion of configuration as demonstrated in the case of cyclopentene oxide (entry 8) with $Ph_2Cu(CN)Li_2$, thereby generating the same material employing Ph_2CuLi , a result formally of an S_N2 process.² (3) Heteroatom-containing ligands are readily incorporated in cuprate formation, where ultimately, for example (entry 7), a substituted pyridine results. (4) Homoallylic alcohols may be realized from the delivery of a vinyl ligand, as in entry 2.

Ligand Transferability. As with secondary unactivated halides, the selectivity of ligand transfer was established by treating a common substrate (1,1-diethylethylene oxide, **11**) with more highly mixed systems **3**. Table VI shows the results of several trials. It suggests that an aryl ligand is least prone to transfer relative to alkyl and vinyl groups, although a 1.5:1 ratio for vinyl:Ph in the last entry is not impressive. A methyl moiety is again satisfactory as a second "dummy" ligand where other alkyl residues are of interest,¹⁶ especially as the steric bulk of R_T increases (compare entries 2 and 3). It is also worthy of note that secondary alkyl lithium derived reagents may now participate, while such is not the case with secondary halides.⁶

The explanation behind the observed selectivity of ligand and transfer in **3** is an interesting problem. Preferential release of one group from a copper center undoubtedly relies on several factors, such as aggregation state, extent of backbonding between a ligand and copper, and stability of both **3** and the lower order cuprate resulting from loss of R_T in **3**.⁷ It appears, for alkyl ligands, that the group to be transferred depends upon the relative basicity of the original RLi .³³ Since those RLi employed in our studies are all stronger bases than $MeLi$, $R_TMeCu(CN)Li_2$ may deliver R over Me thereby affording a more stable species, $MeCu(CN)Li$, relative to $R_TCu(CN)Li$. Unfortunately, further comments of a more substantive nature, as was pointed out close to a decade ago^{16a} with regard to mixed lower order cuprates (i.e., R_1R_2CuLi),³⁴ must await more

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(28) Analyzed by Dr. Robert Petty of the Marine Institute, UCSB, with a Hewlett-Packard Model 5992 A.

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

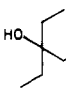






















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

(34) For cases of selected transfer of a methyl group or a residue derived from a hindered tosylhydrazide, see: Marino, J. P.; Floyd, D. M. *Tetrahedron Lett.* **1979**, 675. Bertz, S. H. *Ibid.* **1980**, *21*, 3151, respectively.

Table V. Reactions of Epoxides with $R_2Cu(CN)Li_2$

entry	epoxide	cuprate	product (s)	ratio	yield, %
1		$(n-Bu)_2Cu(CN)Li_2$			95 ^b
2		$(H_2C=CH)_2Cu(CN)Li_2$			94
3		$(n-Bu)_2Cu(CN)Li_2$		85:8	93
4		$(H_2C=CH)_2Cu(CN)Li_2$		57:35	92
5		$(n-Bu)_2Cu(CN)Li_2$			96
6		$Ph_2Cu(CN)Li_2$		3.4:1 ^c	96
7		$(2-C_6H_5NCH_2)_2Cu(CN)Li_2$		7:2 ^d	73 ^e
8		$Ph_2Cu(CN)Li_2$			98
9		$(n-Pr)_2Cu(CN)Li_2$			86 ^b
10		$Et_2Cu(CN)Li_2$			98
11		$(n-Bu)_2Cu(CN)Li_2$			g
12		$(n-Bu)_2Cu(CN)Li_2^h$		1:1	31, 30
13		$(n-Bu)_2Cu(CN)Li_2$			74 ^{b,i}

^a Yields of isolated products unless stated otherwise. ^b By quantitative VPC. ^c Determined by NMR analysis. ^d Determined by VPC analysis. ^e 15% of the 1,2-adduct at the methylene site also isolated. ^f No cyclopentanone was detected by VPC. ^g No reaction occurred after 5 h at 0 °C. ^h 36% starting epoxide was also recovered upon quenching after 3 h at 0 °C. ⁱ The remaining mass is starting material.

Table VI. Selectivity of Ligand Transfer. Reaction of Epoxides


 $\xrightarrow[\text{THF}]{R_1R_2Cu(CN)Li_2}$

+


11
12
13

entry	R ₁	R ₂	conditn	ratio R ₁ :R ₂
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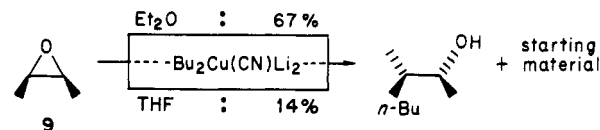
1	Et	Me	-40 °C, 4.5 h	5.5:1
2	<i>n</i> -Bu	Me	-40 °C, 2 h	8:1
3	<i>s</i> -Bu	Me	-50 °C, 1.5 h	27:1
4	Ph	Me	0 °C, 3.5 h	1:2.2
5	vinyl	Me	0 °C, 2 h	1:2.6
6	<i>n</i> -Bu	Ph	-20 °C, 2 h	14:1
7	vinyl	Ph	0 °C, 5 h	1.5:1

^a Relative order: *s*-Bu > *n*-Bu ≥ Et > Me > vinyl > phenyl.

precise information on the exact composition of the reagents themselves.

Solvent Effects. In our preliminary studies on the ring-opening reactions of oxiranes with 2,⁸ THF had been chosen as solvent due to our early success with this me-

dium for halide displacements.⁶ This is in contrast to the well-known preference for Et_2O as solvent where reagents 1 are involved.³² Hence, we decided to briefly investigate the effects of using Et_2O in place of THF. As originally reported, *cis*-2-butene oxide (9), upon treatment with 2, $R = n-Bu$, in THF at -20 °C for 2 h affords 10 in 95% (VPC) yield. Performing the same coupling, in separate



experiments, comparing THF and Et_2O , but at -40 °C for 1.5 h, vividly demonstrate the differences in relative rates of reaction which can occur as influenced by solvent. Likewise, treatment of epoxide 11 (Table V) with 2, $R = vinyl$, in Et_2O led to the expected homoallylic alcohol (>87% yield) in ca. half the time required for the same reaction run in THF.

Summary

It has been demonstrated, albeit in relatively simple

model systems, that higher order, mixed cuprates **2** and their second generation, more highly mixed analogues $R_T R_R Cu(CN)Li_2$, **3**, are superior to their lower order predecessors **1** in effecting substitution reactions of epoxides and unactivated halides. Secondary iodides generally couple between -78 and -50 °C, while bromides require between 0 °C and room temperature. THF appears to be the preferred solvent, although other ethereal media may also be utilized. Both lithium cations in solutions of **2** play a dramatic role in accelerating the coupling process, relative to Grignard derived reagents. The selectivity of ligand transfer is such that a methyl group can oftentimes successfully replace the second equivalent of $R_T Li$, permitting conservation of potentially valuable organic ligands. This does not apply, however, to olefin formation via (vinyl)MeCu(CN)Li₂, as a methyl group is derived preferentially over a vinyl residue. The stereochemistry of the substitution process at carbon has been elucidated; secondary iodides afford racemic products, while bromides react with inversion of configuration. This outcome is dependent upon the nature of the substrate rather than the reagent, as essentially identical observations have been made from reactions with Gilman reagents **1**.

Epoxides couple with a variety of cuprates **2**, the conditions required being a function of degree of substitution on the ring. Displacement occurs with control of both regio- and stereochemistry, the least hindered site in unactivated cases undergoing backside attack. An aryl ligand, which does not undergo transfer from copper to carbon in reactions of halides, will participate in opening epoxides. Relative to an alkyl group, however, it is sluggish and, hence, in more highly mixed species **3**, $R_R = Ph$, may permit selective transfer of R_T . As with halides, this is limited to $R_T = alkyl$, as poor selectivity is seen with $R_T = vinyl$.

Experimental Section

NMR spectra were recorded with a Varian T-60, FT-80, XL-100, or Nicolet NT 300 spectrometer in $CDCl_3$ and are reported in δ values. IR spectra were measured on a Perkin-Elmer Model 283 spectrophotometer. Mass spectra were obtained on a ZAB-2F instrument.

VPC analyses were performed on a Hewlett-Packard Model 5880A gas chromatograph using a 6 ft \times 1/8 in. column packed with 20% SE 30 on Chromosorb W.

Thin-layer chromatographic determinations employed 0.25-mm glass plates coated with silica gel purchased from Baker. Column chromatography was carried out by using Silica Gel-60 from Merck, 70–230 mesh.

All syringes and glassware were oven-dried at 120 °C overnight prior to use. Et_2O and THF were freshly distilled from sodium/benzophenone ketyl, while toluene was dried over CaH_2 . All reactions were run under a blanket of argon.

Cuprous cyanide was obtained from MCB and used as received. It was generally stored over KOH in an Abderhalden at 56 °C (refluxing acetone). Methyllithium (low halide) was purchased from Aldrich, phenyllithium, *n*-butyllithium, and *n*-butylmagnesium chloride were obtained from Ventron, and vinylolithium was bought from Organometallics. Allyllithium was prepared from allyltriphenyltin.³⁵ Ethyllithium was prepared from ethyl chloride (Matheson), and *n*-propyllithium from *n*-propyl chloride, both as described below. All lithium reagents were titrated by the method of Watson and Eastham.³⁶ *n*-Butylcyclohexane was obtained from Aldrich, *n*-butylcyclopentane from Sigma, 4-methylnonane and 4-methyldecane from Pfaltz and Bauer, and 2-methyloctane and 3-methylnonane from Fluka. An authentic sample of 3-methyl-1-nonene was prepared via displacement of

the tosylate of 3-methylpent-4-en-1-ol (the alcohol being purchased from Albany International, Columbus, OH) with *n*-Bu₂Cu(CN)Li₂ in Et_2O ($-78 \rightarrow 0$ °C) in >90% yield.³⁷ 3-Iodo-*n*-heptylbenzene was prepared from 1-phenyl-3-heptanol by using 47% HI.³⁸ Styrene oxide and cyclopentene oxide were obtained from Aldrich. 1-*tert*-Butylcyclohexene oxide,³⁹ 1,1-diethylethylene oxide,⁴⁰ isoprene epoxide,⁴⁰ and *cis*-1-methyl-4-*tert*-butylcyclohexene oxide⁴¹ were prepared by literature procedures. *cis*-2-Butene oxide and α -methylstyrene oxide were prepared as described by Kissel.⁴² 1-*n*-Propylcyclopentene oxide was obtained as discussed by Thummel.⁴³ Elemental analyses were performed by MicAnal, Tucson, AZ.

Preparation of Ethyllithium. Lithium dispersion (30% in mineral oil, 1% sodium, 18 g, 0.77 mol) is placed in a 500-mL three-neck round-bottom flask containing a stir bar and kept under an Argon atmosphere. The lithium is washed with dry hexane (4×20 mL) and then 20 mL of dry hexane is added to the lithium and the temperature lowered to -5 °C. A dry ice condenser is attached and ethyl chloride (12 mL, 167 mmol), which had been previously condensed in a separate 2-neck pear flask, is diluted with 20 mL of dry hexane and added via cannula over a 3-h period to the lithium maintained at -5 °C. After addition is complete, the mixture is allowed to come to room temperature very slowly.⁴⁴ After stirring 3 h at room temperature the slurry takes on a purplish tint. Filtration through a sintered glass funnel is achieved via cannula (maintaining an inert atmosphere). The flask is rinsed with an additional 10 mL of dry Et_2O . The resulting solution is colorless. The solvent is then removed by using a vacuum pump and dry ice trap. Ethyllithium is present as a clean white solid. The solvent is then replaced with 21 mL of dry Et_2O . Titration³⁶ indicates the solution to be 3.80 M (79.8 mmol). The ethyllithium is then stored in the freezer and used within the next few weeks.

Preparation of *n*-Propyllithium. Lithium dispersion (30% in mineral oil, 1% Na, 14 g, 0.6-mol) was placed in a 250-mL two-neck round-bottom flask containing a stir bar, all under an Argon atmosphere. The lithium is washed with dry hexane (5×20 mL) followed by addition of 15 mL of dry hexane. The slurry is cooled to -10 °C and *n*-PrCl, distilled previously from CaH_2 , is placed in a pressure equalizing dropping funnel, dissolved in 30 mL dry hexane, and added slowly over 1.5 h while maintaining the pot temperature at -10 °C. After addition is complete, the reaction is warmed to room temperature and stirring is continued for 5 h. The solution becomes purplish-brown in color. Filtration via cannula through a sintered glass funnel afforded a clear solution which is titrated and stored in the refrigerator.

Typical Procedure for Reagent Preparation. In a dry two-necked flask is placed CuCN. The vessel is flushed with argon and then evacuated under high vacuum, the process being repeated three times leaving the CuCN under argon. Dry THF (1 mL/mmol CuCN) is introduced via syringe and the slurry is cooled to -78 °C. To this slowly stirring suspension is added the organolithium species (2 equiv relative to CuCN) dropwise. The heterogeneous mixture is allowed to warm gradually until complete dissolution results (may require 0 °C) and is then recooled to -78 °C (may get turbid at high concentrations). The substrate is then introduced either as a solution in THF, or as a neat liquid and stirred at the appropriate temperature until starting material is consumed. Reactions were routinely followed by TLC or VPC or both. Following completion, the reaction is quenched with a mixture composed of 10% concentrated NH_4OH /saturated

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aqueous NH_4Cl solution and allowed to stir at room temperature for 5–30 min. Standard extractive workup followed by VPC analysis, distillation, or chromatographic purification afforded the results indicated in the text.

***n*-Butylcyclohexane.** The cuprate $n\text{-Bu}_2\text{Cu}(\text{CN})\text{Li}_2$ was prepared from CuCN (70 mg, 0.78 mmol) in 1.0 mL THF, to which was added $n\text{-BuLi}$ (0.65 mL, 1.41 mmol). The resulting solution was a tan-brown in color; however, at higher concentrations and at low temperatures (-78°C), a cloudy, emulsion-like mixture may be observed. Cyclohexyl iodide (65 μL , 0.50 mmol) was added at -78°C , stirred at that temperature for 1 h, and then quenched. VPC analysis indicated essentially quantitative formation of the product as determined by using *tert*-butylcyclohexane as an internal standard.

Generation of $n\text{-Bu}_2\text{Cu}(\text{CN})\text{Li}_2$ in either Et_2O or DME, as above, provides a slightly turbid solution between -75 and 0°C . In toluene, however, the cuprate appeared to precipitate as a brownish solid, even at 0°C . In 1:1 THF: Et_2O , as with 1:1 THF:toluene, a pale yellow solution forms.

***n*-Butylcyclohexane from Cyclohexyl Bromide.** The cuprate $n\text{-Bu}_2\text{Cu}(\text{CN})\text{Li}_2$ was prepared as described above with CuCN (92 mg, 1.02 mmol), 1.1 mL THF, and $n\text{-BuLi}$ (0.92 mL, 1.95 mmol). The bromide (62 μL , 0.50 mmol) was introduced at -78°C , and the solution was warmed to room temperature for 6 h and then quenched. Quantitative VPC analysis indicated 41% product.

***n*-Butylcyclopentane from Cyclopentyl Iodide.** The cuprate was formed as above from CuCN (82 mg, 0.91 mmol), THF (1.1 mL), and $n\text{-BuLi}$ (0.79 mL, 1.72 mmol). The starting iodide (58 μL , 0.50 mmol) was added neat via syringe to the cold (-78°C) cuprate where it was stirred for 2 h and then quenched. Analysis by VPC indicated an 82% yield of product.

***n*-Butylcyclopentane from Cyclopentyl Bromide.** The cuprate, $n\text{-Bu}_2\text{Cu}(\text{CN})\text{Li}_2$, was formed as above from CuCN (86 mg, 0.96 mmol), 1.0 mL THF, and $n\text{-BuLi}$ (0.88 mL, 1.85 mmol). To the tan solution, maintained at -78°C , was added bromocyclopentane (54 μL , 0.50 mmol) and the solution warmed to 0°C for 6 h and then quenched. Quantitative VPC indicated an 86% yield of product.

4-Methyloctane from 2-Iodopentane. Cuprate $n\text{-Bu}_2\text{Cu}(\text{CN})\text{Li}_2$ was prepared as above from CuCN (83 mg, 0.93 mmol), 1.0 mL THF, and $n\text{-BuLi}$ (0.86 mL, 1.81 mmol). Introduction of 2-iodopentane (66 μL , 0.50 mmol) to the cold (-78°C) solution was followed by stirring at -50°C for 2 h and then quenching in the usual fashion. VPC analysis showed a 99% yield of the desired hydrocarbon.

4-Methyloctane from 2-Bromopentane. Preparation of $n\text{-Bu}_2\text{Cu}(\text{CN})\text{Li}_2$ followed the procedures above by using CuCN (71 mg, 0.79 mmol), 1.2 mL THF, and $n\text{-BuLi}$ (0.73 mL, 1.53 mmol). To this solution at -78°C was added the bromide (62 μL , 0.50 mmol), and the solution was warmed to 0°C for 2 h and then to room temperature for 1 h and then quenched. VPC analysis showed a 94% yield of 4-methyloctane.

4-Methyldecene^{14b} from 2-Bromooctane. The cuprate, $(\text{allyl})_2\text{Cu}(\text{CN})\text{Li}_2$, was formed from CuCN (101 mg, 1.13 mmol) in 1.2 mL THF, to which was added allyllithium (1.26 mL, 2.25 mmol). To this rust red solution was added 2-bromooctane (100 μL , 0.56 mmol) at -78°C , and the solution was warmed to -22°C for 1.5 h and then quenched. VPC analysis showed greater than 90% product.

3-Methylnonene from 2-Iodoctane. The cuprate, $(\text{vinyl})_2\text{Cu}(\text{CN})\text{Li}_2$, was prepared from CuCN (89 mg, 1.0 mmol) in 1.0 mL of THF and vinylolithium (1.05 mL, 2.0 mmol) as a tan-brown solution. Cooling to -78°C was followed by addition of the iodide (91 μL , 0.50 mmol) and the mixture was warmed to 0°C for 6 h and then quenched. VPC indicated a 90% yield of product, along with ca. 6% of starting material.

2-Methyloctane from 2-Iodoctane. $\text{Me}_2\text{Cu}(\text{CN})\text{Li}_2$ was prepared from CuCN (89 mg, 1.0 mmol) in 1.0 mL of THF and 1.48 mL (2.0 mmol) of MeLi (in Et_2O , low halide). Cooling the cuprate to -78°C gave a turbid, somewhat viscous reagent to which was introduced the iodide (91 μL , 0.50 mmol). After 5 min at -78°C , the mixture was warmed to 0°C for 2 h and then quenched. VPC analysis indicated an 89% yield of product.

3-Methylnonane from 2-Iodoctane. $\text{Et}_2\text{Cu}(\text{CN})\text{Li}_2$ was formed from CuCN (55 mg, 0.62 mmol) in 1.3 mL of THF and

EtLi (1.12 mL, 1.16 mmol) as a light tan solution. 2-Iodoctane was added to the solution, the solution was precooled to -78°C where stirring was continued for 1.5 h, and then the reaction was quenched. VPC indicated a quantitative yield of the desired hydrocarbon.

4-Methyldecane from 2-Iodoctane. The cuprate $n\text{-Pr}_2\text{Cu}(\text{CN})\text{Li}_2$ was prepared from CuCN (43 mg, 0.48 mmol) in 0.50 mL of THF and $n\text{-PrLi}$ (0.48 mL, 0.94 mmol). The tan solution was cooled to -78°C to which was added the iodide (46 μL , 0.25 mmol) and the temperature maintained for 1 h. Quenching followed by VPC analysis showed a 90% yield of product along with 10% starting material remaining.

1-Phenyl-3-vinylheptane from 1-Phenyl-3-iodoheptane. The vinyl cuprate $(\text{vinyl})_2\text{Cu}(\text{CN})\text{Li}_2$ was prepared as above from CuCN (42 mg, 0.46 mmol) and 0.48 mL (0.92 mmol) of vinylolithium in 0.25 mL of THF. The iodide (70 mg, 0.23 mmol) in 0.3 mL of THF was added to the cold reagent (-78°C) and then warmed to 0°C for 7.5 h. Quenching, an extractive workup, and filtration of the crude product through SiO_2 (hexanes) gave 32.4 mg (70%) of a colorless oil: IR (neat) cm^{-1} 1640; ^1H NMR, δ 1.25 (12 H, m), 2.52 (2 H, m), 4.85 (1 H, dd, $J = 2.7$ Hz), 5.0 (1 H, d, $J = 1$ Hz), 5.55 (1 H, m), 7.15 (5 H, s, br); mass spectrum, m/e (relative intensity) 202 (M^+ , 4.7), 160 (4.0), 145 (4.7), 131 (4.7), 118 (3.4), 117 (8.1), 105 (34.9), 104 (100); high-resolution MS, calcd for $\text{C}_{15}\text{H}_{22}$ 202.1720, found 202.1728.

3-Methylnonane from (*R*)-(-)-2-Iodoctane. The cuprate, $\text{Et}_2\text{Cu}(\text{CN})\text{Li}_2$, was prepared as above from CuCN (2.0 g, 22.3 mmol), 37 mL of THF, and EtLi (8.3 mL, 44.2 mmol). To the cold (-96°C) solution was added the chiral iodide (2.7 mL, 14.9 mmol, 87% optically pure) and the solution was stirred at this temperature for 25 min. Warming to -78°C for 1.5 h was followed by quenching (slowly!), extractive workup (Et_2O), and isolation by distillation.^{14b} A rotation on neat material of 99+% (VPC) purity indicated at most 1.1–1.2% inversion had occurred.

3-Methylnonane from (*R*)-(-)-2-Iodoctane via Et_2CuLi . The lower order cuprate was formed from CuI (1.6 g, 8.6 mmol) in 9 mL of THF to which was added EtLi (6.8 mL, 17.0 mmol). The cuprate was cooled to -78°C where the iodide (0.73 mL, 4.0 mmol, 86% optically pure) was added, followed by warming to -50°C for 3 h, and was then quenched at this temperature. Workup, isolation by distillation,^{14b} and then preparative VPC (2 m, 10% Apiezon N on Chromosorb W, 60/80 mesh) gave material of >99% purity, which gave no rotation.

3-Methylnonane from (*S*)-(+)-2-Bromooctane. The mixed cuprate $\text{Et}(\text{Me})\text{Cu}(\text{CN})\text{Li}_2$ was formed from CuCN (2.72 g, 30.3 mmol) in 25 mL of THF, to which was added at -78°C MeLi (19.1 mL, 30.2 mmol) and EtLi (10.90 mL, 30.2 mmol), and the mixture was warmed until a brownish solution resulted (usually $<0^\circ\text{C}$). The bromide (3.5 mL, 19.7 mmol, 87% optically pure) was added to the cold (-78°C) cuprate, and the solution was warmed to 0°C for 6 h and then to room temperature for 2 h. Quenching at -78°C followed by extractive workup and isolation by preparative VPC (10% Apiezon N on Chromosorb W, 60/80 mesh) gave material of 98.7% purity which showed a rotation ($[\alpha]_D$ 9.60° (neat)) indicative of complete Walden inversion.^{14b,15}

3-Methylnonane from (*S*)-(+)-2-Bromooctane via $\text{Et}(\text{Me})\text{CuLi}$. The cuprate was prepared from CuI (5.47 g, 28.79 mmol) in 20 mL of THF, MeLi (15.6 mL, 28.7 mmol) and EtLi (13.5 mL, 28.6 mmol) as described for the higher order analogue. The dark solution was cooled to -78°C where the bromide (3.0 mL, 16.9 mmol, 87% optical purity) was introduced. The mixture was warmed to 0°C for 10 h and then quenched. Extractive workup followed by preparative VPC (10% Apiezon N on Chromosorb W, 60/80 mesh) afforded the hydrocarbon of >98% purity. The rotation ($[\alpha]_D$ +9.53° (neat)) indicated essentially 100% inversion had taken place.

threo-3-Methyl-2-heptanol. To $n\text{-Bu}_2\text{Cu}(\text{CN})\text{Li}_2$ maintained at -78°C , prepared from CuCN (100 mg, 1.10 mmol) and $n\text{-BuLi}$ (1.0 mL, 2.2 mmol) in 3.0 mL of THF was added *cis*-2-butene oxide (90 μL , 1.0 mmol). The solution was warmed to -20°C for 2 h. Quenching followed by an extractive workup with Et_2O and VPC analysis indicated a 95% yield of product: IR (neat) cm^{-1} 3360, 1375, 1100, 1060, 920; ^1H NMR δ 0.8–1.1 (6 H, m), 1.15 (3 H, d, $J = 6$ Hz), 1.2–1.6 (7 H, m), 1.9 (1 H, s), 3.7 (1 H, m); mass spectrum, m/e (relative intensity) 129 (M^+ , 0.6), 113 (2.2), 97 (10.8), 84 (18.5), 69 (11.1), 55 (36.5), 45 (100); high-resolution MS

calcd for $C_8H_{18}OH$ 129.1279, found 129.1288.

3-Ethylhex-5-en-3-ol. To $(\text{vinyl})_2\text{Cu}(\text{CN})\text{Li}_2$ at 0°C , formed via addition of vinyl lithium (0.96 mL, 2.0 mmol) to CuCN (89 mg, 1.0 mmol) in 1.5 mL of THF, was added 92 μL (0.77 mmol) of epoxide 11. The solution was stirred at 0°C for 5 h, then quenched, and worked up in the usual fashion. Chromatographic purification on SiO_2 with 10% Et_2O /pentane yielded 92.3 mg (94%) as a clear oil: R_f (1:1 Et_2O -pentane) 0.73; IR (neat) cm^{-1} 3400, 3080, 1640, 1150, 960, 910; ^1H NMR δ 0.85 (6 H, t, $J = 9$ Hz), 1.35 (1 H, s), 1.47 (4 H, q, $J = 9$ Hz), 2.20 (2 H, d, $J = 7.5$ Hz), 5.10 (2 H, m), 5.80 (1 H, m); mass spectrum, m/e (relative intensity) 113 (3.0), 99 (5.1), 87 (52.8), 81 (27.6), 67 (38.7), 57 (100), 41 (52.8); high-resolution MS calcd for $C_8H_{18}O \cdot \text{CH}_3$ 113.0938, found 113.0952. Combustion Anal. Calcd for C, 74.27; H, 13.34. Found: C, 73.98; H, 13.51.

1-Phenylhexanol.⁴⁵ To $n\text{-Bu}_2\text{Cu}(\text{CN})\text{Li}_2$ at -78°C , derived from CuCN (116 mg, 1.3 mmol) in 2.5 mL of THF and $n\text{-BuLi}$ (1.2 mL, 2.6 mmol) as described above, was added styrene oxide (114 μL , 1.0 mmol). The solution was warmed to -40°C for 1.5 h and then quenched. The crude material was purified after an Et_2O extractive workup on SiO_2 with 70% pentane/25% CHCl_3 /5% EtOAc to afford 151 mg (85%) of 1-phenylhexanol and 14 mg (8%) of 2-phenylhexanol, each as a clear oil.

1-Phenylhexanol: R_f (5:3:2 pentane- CHCl_3 - EtOAc) 0.63; IR (neat) cm^{-1} 3350, 3080, 3060, 1050, 1025, 750, 700; ^1H NMR δ 0.85 (3 H, t, $J = 7$ Hz), 1.1-1.8 (8 H, m), 2.1 (1 H, s), 4.6 (1 H, t, $J = 6$ Hz), 7.35 (5 H, s); mass spectrum, m/e (relative intensity) 178 (M^+ , 5.8), 161 (1.6), 107 (100), 79 (71.8), 77 (30.7); high-resolution MS calcd for $\text{C}_{12}\text{H}_{18}\text{O}$ 178.1357, found, 178.1371.

2-Phenylhexanol: R_f (5:3:2 pentane- CHCl_3 - EtOAc) 0.50; IR (neat) cm^{-1} 3350, 3080, 3060, 1600, 1050, 750, 700; ^1H NMR δ 0.8 (3 H, t, $J = 7$ Hz), 1.0-1.8 (6 H, m), 2.8 (1 H, m), 3.7 (2 H, t, $J = 6$ Hz), 7.3 (5 H, m); mass spectrum, m/e (relative intensity) 178 (M^+ , 6.2), 147 (19.8), 103 (5.9), 91 (100), 77 (5.1). An authentic sample was prepared from ethyl phenylacetate via the sequence (i) LDA and $n\text{-BuLi}$ and (ii) LAH/ Et_2O .

1-Phenylbut-3-en-1-ol. The vinyl cuprate $(\text{vinyl})_2\text{Cu}(\text{CN})\text{Li}_2$ was prepared at $-78 \rightarrow 0^\circ\text{C}$ from CuCN (206 mg, 2.3 mmol) and vinyl lithium (2.42 mL, 4.6 mmol) in 3.3 mL of THF. After the solution was recooled to -78°C , styrene oxide (104 μL , 1.0 mmol) was added via syringe and the reaction was warmed to -40°C for 30 min, then to -30°C for 1 h, and then to -20°C for 30 min. Quenching, extractive workup, and chromatography on SiO_2 with 1:1 Et_2O /pentane afforded 84.5 mg (57%) of 1-phenylbut-3-en-1-ol and 52.5 mg (35%) of 2-phenylbut-3-en-1-ol, as clear oils.

1-Phenylbut-3-en-1-ol: R_f (1:1 Et_2O -pentane) 0.50; IR (neat) cm^{-1} 3380, 3065, 3025, 1640, 1050, 920, 760, 700; ^1H NMR δ 2.05 (1 H, d, $J = 5$ Hz), 2.5 (2 H, t, $J = 7$ Hz), 4.75 (1 H, m), 5.2 (2 H, m), 5.8 (1 H, m), 7.45 (5 H, s); mass spectrum, m/e (relative intensity) 148 (M^+ , 0.5), 131 (2.3), 107 (100), 79 (76.2), 77 (36.8), 51 (11.5), high-resolution MS calcd for $\text{C}_{10}\text{H}_{12}\text{O}$ 148.0888, found 148.0887.

2-Phenylbut-3-en-1-ol: R_f (1:1 Et_2O -pentane) 0.32; IR (neat) cm^{-1} 3380, 3080, 3060, 3025, 1640, 1600, 1050, 1030, 940, 760, 700; ^1H NMR δ 3.5 (1 H, m), 3.8 (2 H, t, $J = 6$ Hz), 5.2 (2 H, t, $J = 8$ Hz), 6.0 (1 H, m), 7.3 (5 H, s); mass spectrum, m/e (relative intensity) 148 (M^+ , 1.4), 118 (58.4), 117 (100), 115 (46), 91 (22.3); high-resolution MS calcd for $\text{C}_{10}\text{H}_{12}\text{O}$ 148.0888, found 148.0875.

2-Phenylheptan-2-ol. To CuCN (89.6 mg, 1.0 mmol) in 2.0 mL of cold (-78°C) THF was added $n\text{-BuLi}$ (1.0 mL, 2.0 mmol) and the mixture was warmed to 0°C . After recooling to -78°C , α -methylstyrene oxide (100 mg, 0.75 mmol) in 1.0 mL THF was added via syringe. Warming to -20°C for 2 h was followed by quenching and an extractive (Et_2O) workup. Chromatography on silica gel (40% Et_2O /hexane) afforded 139 mg (96%) of the desired product: R_f (3:2 hexane- Et_2O) 0.53; IR (neat) cm^{-1} 3420, 3080, 3060, 3020, 1600, 1375, 1030, 760, 700; ^1H NMR δ 0.80 (3 H, t, $J = 5$ Hz), 1.0-1.4 (8 H, m), 1.5 (3 H, s), 1.75 (1 H, s), 7.3 (5 H, m); mass spectrum, m/e (relative intensity) 192 (M^+ , 0.8), 175 (57.2), 121 (100), 105 (43.9), 91 (23.5), 77 (27.5); high-resolution MS calcd for $\text{C}_{13}\text{H}_{20}\text{O}$ 192.1514, found 192.1500.

(E,Z)-2-Methyl-4-phenylbut-2-en-1-ol. To CuCN (206 mg, 2.2 mmol) in 4.0 mL of cold (-78°C) THF was added PhLi (2.5

mL, 4.4 mmol) and the mixture was warmed to 0°C . After the solution was recooled to -78°C , 1,2-epoxy-2-methyl-1,3-butadiene (220 μL , 2.0 mmol) was added neat via syringe. Warming to -45°C for 1.5 h was followed by quenching and an extractive (Et_2O) workup. Chromatography on silica gel (1:1 pentane- Et_2O) afforded 312 mg (96%) of the product: R_f (1:1 pentane- Et_2O) 0.37; IR (neat) cm^{-1} 3340, 3060, 3025, 1600, 1000, 740, 690; ^1H NMR δ 1.75 (3 H, s), 3.4 (2 H, d, $J = 7$ Hz), 4.05 and 4.26 (2 H, d, $J = 4$ Hz), 5.6 (1 H, m), 7.25 (5 H, m); mass spectrum, m/e (relative intensity) 162 (M^+ , 10.2), 144 (33.2), 131 (100), 129 (94.5), 104 (26.7), 91 (83.1), 71 (23.6); high-resolution MS (chemical ionization) calcd for $\text{C}_{11}\text{H}_{14}\text{O}$ 162.1044, found 162.1041.

(E,Z)-2-Methyl-5-(2-pyridyl)pent-2-en-1-ol. The cuprate was prepared by the initial metalation of 2-picoline (99 μL , 1 mmol) with $n\text{-BuLi}$ (0.45 mL, 1.0 mmol) in 1.5 mL of THF (deep red anion). Inverse addition of 2-(lithiomethyl)pyridine via cannula to CuCN (45 mg, 0.50 mmol) in 0.5 mL of THF at -78°C was followed by warming to 0°C . The homogeneous, deep red solution was recooled to -78°C and the epoxide (32 μL , 0.30 mmol) was added. The solution immediately turned to a heterogeneous, orange mixture. After warming to -40°C for 1.5 h, the reaction was quenched and worked up in the usual way. Chromatography on SiO_2 with Et_2O , then 3:1 Et_2O /THF, afforded 8 mg (15%) of a product tentatively identified as the 1,2-adduct (R_f 0.33 (Et_2O)) and 39 mg (73%) of a water-white oil, as a mixture of geometrical isomers; VPC analysis indicated a ratio of 7:2 $E:Z$; R_f 0.20 (Et_2O); IR (neat) cm^{-1} 3300, 3090, 3085, 3040, 1590, 1570, 1000, 750, 670; ^1H NMR (partial) δ 1.61 (s, CH_3), 3.98 and 4.06 (3 H, s), 5.31 and 5.47 (1 H total, t, $J = 8$ Hz), 7.13 (2 H, m), 7.58 (1 H, t, $J = 9$ Hz), 8.51 (1 H, m); mass spectrum, m/e (relative intensity) 177 (M^+ , 1.8), 160 (72.9), 146 (33.4), 144 (37.9), 118 (59.5), 117 (24.5), 106 (18.5), 93 (100); high-resolution MS calcd for $\text{C}_{11}\text{H}_{15}\text{NO}$ 177.1154, found 177.1121.

trans-2-Phenylcyclopentanol.² To $\text{Ph}_2\text{Cu}(\text{CN})\text{Li}_2$ at -78°C , prepared from CuCN (175 mg, 1.95 mmol) and PhLi (2.15 mL, 3.76 mmol) in 2.0 mL of THF, was added cyclopentene oxide (88 μL , 1.0 mmol). The solution was warmed to room temperature for 10 h, then quenched, and worked up in the usual fashion. Chromatographic purification on SiO_2 with 1:1 Et_2O /pentane yielded 160 mg (99%) product as a colorless oil: R_f (1:1 Et_2O -pentane) 0.38; IR (neat) cm^{-1} 3360, 3025, 1600; ^1H NMR δ 1.55-2.25 (7 H, m), 2.70-2.95 (1 H, m), 4.0-4.25 (1 H, m), 7.23 (5 H, s); mass spectrum, m/e (relative intensity) 162 (M^+ , 75.5), 144 (23.2), 129 (44.3), 118 (54.4), 104 (38.5), 91 (100).

cis-1,2-Di-*n*-propylcyclopentanol. To $n\text{-Pr}_2\text{Cu}(\text{CN})\text{Li}_2$ at -78°C , prepared from CuCN (84 mg, 0.94 mmol) and $n\text{-PrLi}$ (0.92 mL, 1.80 mmol) in 4.0 mL of THF, was added 1-*n*-propylcyclopentene oxide (65 μL , 0.5 mmol). The solution was warmed to 0°C for 8 h. Quenching, followed by an extractive workup with Et_2O and VPC analysis indicated an 87% yield of product: IR (neat) cm^{-1} 3360, 1140, 955; ^1H NMR δ 0.77-1.72 (22 H, m); mass spectrum, m/e (relative intensity) 170 (M^+ , 3), 127 (53), 109 (30), 99 (100), 86 (43), 71 (49); high-resolution MS calcd for $\text{C}_{11}\text{H}_{22}\text{O}$ 170.1671, found 170.1681.

4 β -tert-Butyl-1 α -methyl-2 α -ethylcyclohexanol. To $\text{Et}_2\text{Cu}(\text{CN})\text{Li}_2$ at -78°C , prepared from CuCN (200 mg, 2.23 mmol) and EtLi (4.20 mL, 4.37 mmol) in 4.0 mL of THF, was added 4 β -tert-butyl-1 α -methylcyclohexene oxide (186 μL , 1.0 mmol). The solution was warmed to 0°C for 6 h, then quenched, and worked up in the usual fashion. Chromatographic purification on SiO_2 with 1:1 Et_2O /pentane (R_f 0.55) yielded 185.4 mg (94%) of product, 98% yield based on recovered starting material: R_f (1:1 Et_2O -pentane) 0.55; IR (neat) cm^{-1} 3370, 1460, 1182; ^1H NMR δ 0.7-1.6 (m br) within which is 0.87 (9 H, s), 1.14 (3 H, s); mass spectrum, m/e (relative intensity) 198 (M^+ , 5), 141 (17), 123 (16), 71 (100), 57 (59); high-resolution MS calcd for $\text{C}_{13}\text{H}_{26}\text{O}$ 198.1996, found 198.1984. Combustion Anal. Calcd for C, 78.71; H, 13.22. Found: C, 78.62; H, 13.39.

2-Methyl-3-phenylbut-3-en-2-ol. To CuCN (134 mg, 1.50 mmol) in 2.5 mL of cold (-78°C) THF was added $n\text{-BuLi}$ (1.38 mL, 3.0 mmol) and the mixture was warmed to 0°C . α,β,β -Trimethylstyrene oxide (171 μL , 1.0 mmol) was added neat via syringe with stirring continued for 10 h followed by quenching and an extractive (Et_2O) workup. Chromatography on silica gel (1:1 pentane- Et_2O) afforded 0.049 g (30%) of 3-methyl-2-phenylbut-3-en-2-ol and 0.0503 g (31%) of 3-methyl-2-phenyl-

but-1-en-2-ol as clear oils: R_f (1:1 Et₂O-pentane) 0.58; IR (neat) cm^{-1} 3390, 3080, 3060, 3020, 1360, 1160, 960, 920, 770, 700; ¹H NMR δ 1.4 (6 H, s), 4.9 (1 H, d, $J = 2$ Hz), 5.4 (1 H, d, $J = 2$ Hz), 7.29 (5 H, s); mass spectrum, m/e (relative intensity) 162 (M^+ , 3.8), 147 (11.1), 104 (100), 91 (13.5) 8 59 (33.6).

3-Methyl-2-phenylbut-3-en-2-ol: R_f (1:1 Et₂O-pentane) 0.41; IR (neat) cm^{-1} 3450, 3080, 3060, 3020, 1370, 1100, 1060, 900, 760, 700; ¹H NMR δ 1.6 (3 H, s), 1.65 (3 H, s), 2.0 (1 H, s), 4.9 (1 H, m), 5.2 (1 H, s), 7.2-7.5 (5 H, m); mass spectrum, m/e (relative intensity) 162 (M^+ , 8.5), 148 (11.6), 147 (100), 129 (22.3), 121 (63.6), 119 (11.2), 104 (23.2), 91 (20.3), 77 (15.4).

1-(3-Heptyl)cyclohexanol. To CuCN (44.8 mg, 0.50 mmol) in 1.0 mL of cold (-78 °C) THF was added *n*-BuLi (0.40 mL, 1.0 mmol) and the mixture was warmed to 0 °C. Propylidene-cyclohexane oxide (38.5 μ L, 0.25 mmol) was added neat via syringe, followed by stirring for 6 h and quenching with an extractive (Et₂O) workup. VPC analysis indicated formation of the product⁴⁶ in 74% yield: R_f (1:1 pentane-Et₂O) 0.72.

Reactions of 11 with $R_1R_2\text{Cu}(\text{CN})\text{Li}_2$: Table VI, Entry 1. **Reaction of Et(Me)Cu(CN)Li₂.** To CuCN (89.6 mg, 1.0 mmol) in 1.0 mL of cold (-78 °C) THF was added MeLi (0.48 mL, 1.0 mmol) and the mixture was warmed to 0 °C. After the solution was recooled to -78 °C, EtLi (0.57 mL, 1.0 mmol) was introduced followed by the epoxide (89 μ L, 0.75 mmol). Warming to -40 °C for 4.5 h followed by quenching and VPC analysis indicated that a 5.5:1 ratio of 12, $R_1 = \text{Et}$, to 13, $R_2 = \text{CH}_3$, had formed.

Spectral data for 12, $R_1 = \text{Et}$ (3-ethylhexan-3-ol): IR (neat) cm^{-1} 3400, 1150, 950, 850; ¹H NMR δ 0.7-1.6 (22 H, m); mass spectrum, m/e (relative intensity) 101 (67.2), 98 (18.8), 97 (23.6), 87 (96.2), 68 (91.4), 57 (68.8), 43 (100). Material was compared with a sample prepared by addition of *n*-PrLi to 3-pentanone.

Spectral data for 13, $R_2 = \text{CH}_3$ (3-ethylpentan-3-ol): IR (neat) cm^{-1} 3400, 1155, 950, 920, 785; ¹H NMR δ 0.85 (9 H, t, $J = 8$ Hz), 1.15 (1 H, s), 1.45 (6 H, q, $J = 8$ Hz); mass spectrum, m/e (relative intensity) 99 (100), 87 (15.6), 81 (40.8), 71 (49.9), 58 (36); high-resolution MS calcd for C₇H₁₆O-C₂H₅ 87.0808, found 87.0797.

Entry 2. Reaction of *n*-Bu(Me)Cu(CN)Li₂. To CuCN (44.8 mg, 0.50 mmol) in 1.0 mL of cold (-78 °C) THF was added MeLi (0.32 mL, 0.50 mmol) and the mixture was warmed to 0 °C. After the solution was recooled to -78 °C, *n*-BuLi (0.20 mL, 0.50 mmol) was introduced followed by the epoxide (59 μ L, 0.50 mmol). Warming to -40 °C for 2 h followed by quenching and VPC analysis indicated that an 8:1 ratio of 12 $R_1 = n\text{-Bu}$, to 13, $R_2 = \text{CH}_3$, had formed.

Spectral data for 12, $R_1 = n\text{-Bu}$ (3-ethyloctan-3-ol): IR (neat) cm^{-1} 3415, 1150, 975, 945, 930; ¹H NMR δ 0.8-1.6 (22 H, m); mass spectrum, m/e (relative intensity) 129 (55.5), 110 (9.7), 98 (31.4), 87 (100), 71 (9.9), 69 (51.2), 55 (38.1); high-resolution MS calcd for C₁₀H₂₂O - C₂H₅ 129.1278, found 129.1260.

Entry 3. Reaction of *sec*-Bu(Me)Cu(CN)Li₂. To CuCN (89.6 mg, 1.0 mmol) in cold (-78 °C) THF (1.5 mL) was added MeLi (0.64 mL, 1.0 mmol) and the mixture was warmed to 0 °C. After the solution was recooled to -78 °C, *s*-BuLi (0.82 mL, 1.0 mmol) was introduced followed by the epoxide (95 μ L, 0.80 mmol). Warming to -50 °C for 1.5 h followed by quenching and VPC analysis indicated that a 27:1 ratio of 12, $R_1 = s\text{-Bu}$, to 13, $R_2 = \text{CH}_3$ had formed.

Spectral data for 12, $R_1 = s\text{-Bu}$ (3-ethyl-5-methylheptan-3-ol): IR (neat) cm^{-1} 3470, 1375, 1150, 950; ¹H NMR δ 0.8-1.7 (22 H, m); mass spectrum, m/e (relative intensity) 129 (44.2), 111 (15.7), 87 (96.4), 71 (57.1), 69 (76.6), 57 (100); high-resolution MS calcd for C₁₀H₂₂O - C₂H₅ 129.1279, found 129.1296.

Entry 4. Reaction of Ph(Me)Cu(CN)Li₂. To CuCN (89.6 mg, 1.0 mmol) in cold (-78 °C) THF (1.0 mL) was added MeLi (0.48 mL, 1.0 mmol) and the mixture was warmed to 0 °C. After the solution was recooled to -78 °C, PhLi (0.47 mL, 1.0 mmol) was introduced followed by the epoxide (89 μ L, 0.75 mmol). Warming to 0 °C for 3.5 h followed by quenching and VPC analysis indicated that a 1:2.2 ratio of 12, $R_1 = \text{Ph}$, to 13, $R_2 = \text{CH}_3$, had formed.

Spectral data for 12, $R_1 = \text{Ph}$ (2-ethyl-1-phenylbutan-2-ol): IR (neat) cm^{-1} 3450, 3080, 3060, 3020, 1600, 1500, 1375, 1120, 970, 760, 710; ¹H NMR δ 0.95 (6 H, t, $J = 9$ Hz), 1.45 (4 H, q, $J = 9$

Hz), 2.75 (2 H, s), 7.25 (5 H, s); mass spectrum, m/e (relative intensity) 149 (28.6), 131 (14.9), 91 (100), 87 (67.9), 69 (21.5), 57 (32.3); high-resolution MS calcd for C₁₂H₁₈OC₂H₅ 149.0966, found 149.0955. Combustion Anal. Calcd for C, 80.84; H, 10.18. Found: C, 80.57; H, 10.02.

Entry 5. Reaction of Me(CH₂CH)Cu(CN)Li₂. To CuCN (44.8 mg, 0.5 mmol) in cold (-78 °C) THF (1 mL) was added MeLi (0.32 mL, 0.50 mmol) and the mixture was warmed to 0 °C. After the solution was recooled to -78 °C, vinyl lithium (0.24 mL, 0.50 mmol) was introduced followed by warming to 0 °C and addition to the epoxide (59 μ L, 0.50 mmol). Stirring for 2 h and quenching followed by VPC analysis indicated that a 1:2.6 ratio of 12, $R_1 = \text{vinyl}$, to 13, $R_2 = \text{Me}$, had formed.

Spectral data for 12, $R_1 = \text{vinyl}$, as listed above for 3-ethylhex-5-en-3-ol.

Entry 6. Reaction of *n*-Bu(Ph)Cu(CN)Li₂. To CuCN (89.6 mg, 1.0 mmol) in 1.0 mL of cold (-78 °C) THF was added PhLi (0.47 mL, 1.0 mmol) and the mixture was warmed to 0 °C. After the solution was recooled to -78 °C, *n*-BuLi (0.42 mL, 1.0 mmol) was introduced followed by warming to -20 °C and addition of the epoxide (89 μ L, 0.75 mmol). Stirring for 2 h and quenching followed by VPC analysis indicated that a 14:1 ratio of 12, $R_1 = n\text{-Bu}$, to 13 $R_2 = \text{Ph}$, had formed.

Entry 7. Reaction of Ph(vinyl)Cu(CN)Li₂. To CuCN (89.6 mg, 1.0 mmol) in 1.0 mL of cold (-78 °C) THF was added PhLi (0.47 mL, 1.0 mmol) and the mixture was warmed to 0 °C. After the solution was recooled to -78 °C, vinyl lithium (0.48 mL, 1.0 mmol) was introduced followed by warming to 0 °C and addition of the epoxide (89 μ L, 0.75 mmol). Stirring for 5 h and quenching followed by VPC analysis indicated that a 1.5:1 ratio of 12, $R_1 = \text{vinyl}$, to 13, $R_2 = \text{Ph}$, had formed.

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Registry No. 2 ($R = \text{Me}$), 80473-70-7; 2 ($R = \text{Et}$), 80473-71-8; 2 ($R = n\text{-Pr}$), 80473-72-9; 2 ($R = n\text{-Bu}$), 80473-69-4; 2 ($R = \text{vinyl}$), 80473-65-0; 2 ($R = \text{allyl}$), 91328-60-8; 2 ($R = \text{Ph}$), 80473-66-1; 4, 91328-64-2; 5, 86250-96-6; 6 ($R = \text{Me}$), 91328-63-1; 6 ($R = \text{Ph}$), 91328-65-3; 9, 1758-33-4; 10, 81120-76-5; 11, 1192-17-2; 12 ($R = \text{Et}$), 597-76-2; 12 ($R = n\text{-Bu}$), 2051-32-3; 12 ($R = \text{sec-Bu}$), 91328-44-8; 12 ($R^1 = \text{Ph}$), 34577-40-7; 12 ($R^1 = \text{vinyl}$), 1907-46-6; 13 ($R^2 = \text{Me}$), 597-49-9; Et(Me)CuCNLi₂, 82352-24-7; *sec*-Bu(Me)CuCNLi₂, 91328-61-9; Ph(Me)CuCNLi₂, 91328-62-0; Et(Me)CuLi, 82352-23-6; EtLi, 811-49-4; Li, 7439-93-2; EtCl, 75-00-3; *n*-PrLi, 2417-93-8; *n*-PrCl, 540-54-5; CuCN, 544-92-3; *n*-BuLi, 109-72-8; MeLi, 917-54-4; CuI, 7681-65-4; PhLi, 591-51-5; *sec*-BuLi, 598-30-1; *n*-butylcyclohexane, 1678-93-9; cyclohexyl iodide, 626-62-0; cyclohexyl bromide, 108-85-0; *n*-butylcyclopentane, 2040-95-1; cyclopentyl iodide, 1556-18-9; cyclopentyl bromide, 137-43-9; 4-methyloctane, 2216-34-4; 2-iodopentane, 637-97-8; 2-bromopentane, 107-81-3; 4-methyl-1-decene, 13151-29-6; 2-bromooctane, 557-35-7; allyllithium, 3052-45-7; 3-methyl-1-nonene, 18435-35-3; 2-iodooctane, 557-36-8; vinyl lithium, 917-57-7; 2-methyloctane, 3221-61-2; 4-methyldecane, 2847-72-5; 1-phenyl-3-vinylheptane, 80471-70-1; 1-phenyl-3-heptane, 80471-71-2; (\pm)-3-methylnonane, 82373-57-7; (*S*)-3-methylnonane, 53213-47-1; (*R*)-(-)-2-iodooctane, 29117-48-4; (*S*)-(+)-2-bromooctane, 1191-24-8; 3-ethylhex-5-en-3-ol, 1907-46-6; 1-phenylhexanol, 4471-05-0; styrene oxide, 96-09-3; 2-phenylhexanol, 25755-73-1; 1-phenylbut-3-en-1-ol, 936-58-3; 2-phenylbut-3-en-1-ol, 6052-63-7; 2-phenylheptan-2-ol, 4436-90-2; α -methylstyrene oxide, 2085-88-3; (*E*)-2-methyl-4-phenylbut-2-en-1-ol, 52497-56-0; (*Z*)-2-methyl-4-phenylbut-2-en-1-ol, 58732-17-5; 1,2-epoxy-2-methyl-1,3-butadiene, 1838-94-4; (*E*)-2-methyl-5-(2-pyridyl)pent-2-en-1-ol, 91328-41-5; (*Z*)-2-methyl-5-(2-pyridyl)pent-2-en-1-ol, 91328-42-6; 2-picoline, 109-06-8; *trans*-2-phenylcyclopentanol, 42086-64-6; cyclopentene oxide, 285-67-6; *cis*-1,2-di-*n*-propyl cyclopentanol, 38338-76-0; 1-*n*-propylcyclopentene oxide, 30762-73-3; 4 β -*tert*-butyl-1 α -methyl-2 α -ethylcyclohexanol, 91328-43-7; 4 β -*tert*-butyl-1 α -methylcyclohexene oxide, 22823-71-8; 2-methyl-3-phenylbut-3-en-2-ol, 25982-72-3; α,β,β -trimethylstyrene oxide, 21578-99-4; 3-methyl-

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2-phenylbut-3-en-2-ol, 29290-99-1; 1-(3-heptyl)cyclohexanol, 84370-47-8; propylidenecyclohexane oxide, 28256-59-9; 2-chloropentane, 625-29-6; 2-bromoheptane, 1974-04-5; 2-iodoheptane, 18589-29-2; 4-methyl-1-nonene, 26741-20-8; 3-methyl-1-octene,

13151-08-1; 2-methylheptane, 592-27-8; 3-methyloctane, 2216-33-3; 4-methylnonane, 17301-94-9; 2-phenylheptane, 2132-84-5; 3,4-dimethylnonane, 17302-22-6; 1-*tert*-butylcyclohexene oxide, 7583-74-6.

Conjugate Addition Reactions of α,β -Unsaturated Ketones with Higher Order, Mixed Organocuprate Reagents, $R_2Cu(CN)Li_2$

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Conjugate addition reactions of mixed cuprates $R_2Cu(CN)Li_2$ with α,β -unsaturated ketones are reported. These reagents, in most cases, react extremely rapidly affording the corresponding alkylated ketones in high yields. Attempts at trapping the intermediate enolates appeared to be successful using MeI as electrophile; however, the method is not general and was, therefore, not pursued. The effects of solvent and ligand composition on $R_2Cu(CN)Li_2$ as well as on the more highly mixed species $R_1R_2Cu(CN)Li_2$ have been examined. The selectivity of ligand transfer in these latter, second generation organocuprates is also discussed.

Introduction

The facility with which organocuprates R_2CuM , 1 ($M = Li$ or MgX), add to α,β -unsaturated ketones¹ forming carbon-carbon bonds exclusively at the β -position has afforded them the distinction of being the reagents of choice for effecting such transformations. The original procedure, which dates back over forty years and relies upon a CuCl-catalyzed addition of a Grignard reagent ($MeMgBr$) to an enone,² has been modified and refined considerably over time. Indeed, today one has myriad literature examples from which to choose in deciding upon reaction parameters.³ Most commonly sought are lithium-based cuprates 1, $M = Li$, prepared stoichiometrically from CuX and 2 RLi , thus obviating use of (large) excesses of strong base in the reaction medium.^{1,3} While lower order Gilman reagents R_2CuLi , 2, continue to serve admirably, they are not without drawbacks, such as thermal instability which necessitates use of additional stabilizing and solubilizing ligands.¹ Hence, the continuing evolution of synthetic methodology, having made extraordinary gains over the past decade, encourages realization of new and improved reagents for molecular elaboration. In this paper we present an extensive accounting of our investigation on the development of novel higher order, mixed organocuprates $R_2Cu(CN)Li_2$, 3. These species are highly reactive toward conjugated ketones transferring ligands very efficiently in a Michael sense.⁴ The scope and limitations of the procedure have been examined, including the effects of variation in the substrate, ligands on copper, and solvent. Moreover, the selectivity of ligand transfer in still more highly mixed systems, $R_1R_2Cu(CN)Li_2$, has also been determined.

Results and Discussion

Although a variety of cuprates 3 are readily prepared, their efficient coupling with secondary halides^{5,6} and epoxides^{6,7} in no way guaranteed their successful application as formal Michael donors. Both chemical⁸ and spectroscopic⁹ evidence has accrued suggesting that higher order homocuprates, generalized by Me_3CuLi_2 , 4, may not be synthetically useful in this regard due to competing 1,2-

addition. Our concurrent detailed studies on the more highly mixed reagents, $R(CH_3)Cu(CN)Li_2$, 5, have revealed the presence of free MeLi in Et_2O solution,¹⁰ as previously observed with 4.⁹ These concerns notwithstanding, a preliminary study, reported previously,⁴ was undertaken which clearly demonstrated that a variety of substrates, both cyclic and acyclic, participate in the coupling. Moreover, cuprates derived from primary, secondary, tertiary, vinyl, and aryllithium reagents may be employed.

Of practical importance, it should be noted that it is a common occurrence for many lower order cuprate additions to enones¹ to rely on the presence of solubilizing or stabilizing ligands (e.g., HMPA,¹² $(EtO)_3P$,¹³ Me_2S ,¹⁴ $LiBr$,¹⁵ $n-Bu_3P$ ¹⁶). Such a requirement not only introduces another variable into an already complex scheme but also mandates care in handling (e.g., $n-Bu_3P$ is pyrophoric) and chromatographic separation after workup. To date, we

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