Tetrahedron Vol. 40, No. 24, pp. 5005 to 5038, 1984
Printed in the U.S.A.

0040–4020/84 $03.00+.00
Pergamon Press Ltd.

TETRAHEDRON REPORT NUMBER 176

THE CHEMISTRY OF HIGHER ORDER ORGANOCUPRATES

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(*Received in USA* 1 *February* 1984)

CONTENTS

I. INTRODUCTION

Developments in organometallic chemistry through the decades have come with exponential growth, yet it is the organic chemistry of Cu which has emerged as the most heralded and widely used among the transition metals in organic synthesis.[1] The pivotal role played by Cu-complexes composed of transferrable ligands is attested to by the frequent reviews which strive to keep abreast of the constantly expanding methodological advances, as well as the many applications which appear each year.[2,3] An appreciation for their vast domain may be quickly gained upon inspection of the numerous C–C bond forming transformations which these reagents effect. Thus, the category of substitution reactions encompasses primary, secondary, tertiary, vinylic, acyl, aryl, acetylenic and epoxide centers. Displacements following an S_N2' course include propargylic and allylic systems. Addition processes across both unconjugated acetylenes and Michael acceptors comprise the second major classification of reaction type, the latter commonly involving enones, enoates, or ynoates as educts. Substrate reductions have also been accomplished using organocopper reagents.[3]

The "ate" complexes of Cu which have been developed over the years since Gilmans' initial report[4] on the formation of Me_2CuLi are as varied as the chemistry they engender. Reactivity profiles may be altered by controlling several parameters: the source of Cu(I) (CuX, where X = halide, nitrile, thiocyanate, etc.); the ratio of CuX to R–M (being either stoichiometric or catalytic in CuX); the gegenion involved (usually M = MgX or Li); the presence of additives (oftentimes as solubilizing, stabilizing or activating groups, such as sulfides, phosphines, and Lewis acids); and lastly, the choice of solvent (almost always ethereal).

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

Clearly then, the number of possible combinations and permutations bespeaks the complexity of the subject. While an updated review summarizing the extent of progress in the field would certainly be helpful,[5] the purpose of this Report is to address, for the first time, a subject of most recent arrival to the sphere of Cu reagents: the "higher order" organocuprates. It is interesting to note, in light of the developments in this new area, that much of the very early studies (as well as ongoing work!) wherein catalytic Cu(I)/RM systems were used can now be appreciated to have involved "higher order" reagents. These species are differentiated from "lower order" or Gilman-like cuprates, R_2CuLi, in that the Cu-cluster contains an additional ligand (originally negatively charged). Hence, they are formally Cu(I) dianionic salts. For the sake of completeness, also included are discussions of other stoichiometric mixes of CuX:RM which do not technically adhere to the above requirements. These latter complexes are generally more highly aggregated, each with a constitutionally unique make-up and consequently, with individual properties and potential in synthetic situations.

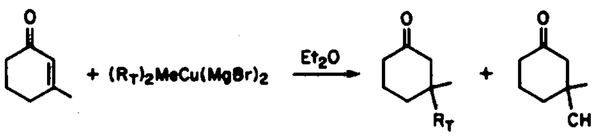
Higher Order Cuprates:	R_3CuLi_2	$R_3Cu(MgX)_2$
	$R_2Cu(CN)Li_2$	$R_2R'Cu(MgX)_2$
	$R\,R'Cu(CN)Li_2$	
Highly Aggregated Cuprates:	$R_5Cu_3Li_2$	$R_5Cu_3(MgX)_2$
	R_3Cu_2Li	

(X = halide)

II. HIGHER ORDER ORGANOCUPRATES, FROM:

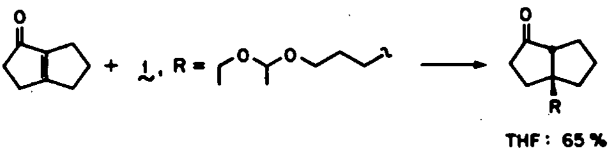
(A) *Copper(I) halides plus Grignard reagents*

In 1978, Drouin *et al.*[6] recognized the potential for generating higher order, mixed magnesio homocuprates $(R_T)_nMeCu(MgBr)_n$ from MeCu and n equivalents of R_TMgBr. In evaluating the propensity of these reagents to deliver R_T in a conjugate sense, 3-methylcyclohexenone served as a model system. With n = 2, excellent selectivities were observed for transfer of primary (89:11) and secondary (99:1) alkyl, and vinyl (92:8) ligands, R_T, over the methyl group in good yields (62–83%). With n = 3, better ratios were obtained, although not sufficiently so to warrant investment of another equivalent of Grignard reagent. Quite unexpectedly, with the intended R_T = t-Bu, 100% selective transfer of the Me ligand occurred, just the opposite selectivity being known to ensue from lower order cuprates.[7] By virtue of a positive Gilman test,[8] free R_TMgBr was determined to be present in the medium, suggesting an equilibrium between, at the very least, the higher order species and $[R_T(Me)CuMgBr + R_TMgBr]$. Whether MeMgBr is present in solution is not known, however, as only 1,2-addition of R_TMgBr to the enone was observed in tests which gave a positive response.



The same authors have also prepared the higher aggregates $R_4(Me)Cu_3(MgBr)_2$, **1**, and again analyzed their synthetic potential as Michael donors of "R^-".[9] These reagents are selective for

$$MeLi + 3CuI + 4RMgBr \longrightarrow \underset{\mathbf{1}}{R_4(Me)Cu_3(MgBr)_2} + 2MgBrI + LiI$$



THF: 65 %
Et₂O: 70 %

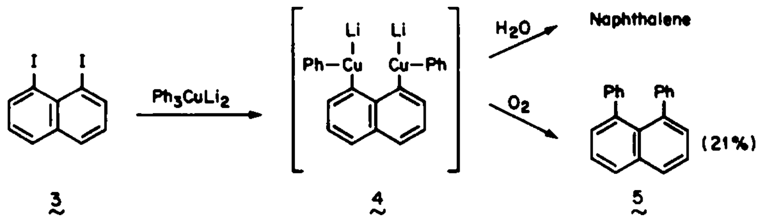
transfer of R_T, and only require 1.3 equiv of R_TMgBr per equivalent of ketone for total consumption of starting material. Thus, for the transfer of R_T, as in the example above, it is likely that a series of unique yet interrelated cuprates are involved, each with different kinetic reactivities and equilibrium concentrations under the reaction conditions. Surprisingly, whereas $(t\text{-Bu})_n\text{-}MeCu(MgBr)_n$ ($n = 2, 3$) delivered the Me group exclusively,[6] $(t\text{-Bu})_4MeCu_3(MgBr)_2$ transferred only the t-Bu group.[9]

(B) *Copper(I) halides plus organolithium reagents*

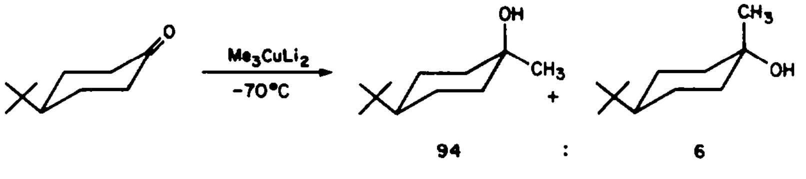
In 1972, House *et al.*[10] noticed that when CuBr was treated with greater than two equivalents of PhLi, a reagent more reactive than Ph_2CuLi was formed corresponding to the stoichiometry

$$3\ \mathrm{PhLi} + \mathrm{CuBr} \xrightarrow{\mathrm{Et_2O}} \underset{\mathbf{2}}{\mathrm{Ph_3CuLi_2}}$$

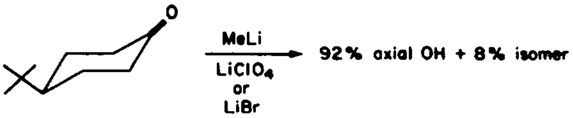
Ph_3CuLi_2, **2**. Solutions of **2** reacted with diiodide **3** affording, after oxidative workup, the product of a double substitution reaction, **5**, albeit in low yield. The *bis*-cuprate **4** was suggested as an intermediate since hydrolysis formed mainly naphthalene.



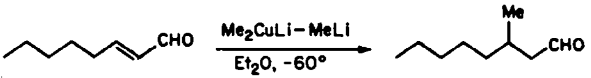
A few years later, Macdonald and Still discovered that a solution composed of Me_2CuLi and one equivalent MeLi adds to conformationally rigid ketones (e.g. 4-t-butylcyclohexanone) at low temperatures in a stereoselective manner.[11] In the case illustrated below, predominant equatorial attack was observed at −70°, where a 94:6 ratio of epimeric alcohols was realized. Comparison data with MeMgI, Me_2Mg and MeLi at various temperatures led to ratios between 51–79:49:21. Hence, this combination of reagents appears to alter the nature of the individual reagents present, as Me_2CuLi itself is relatively inert at these low temperatures. Similar results were seen utilizing both n-BuLi- and s-BuLi-derived cuprates. The authors proposed that low concentrations of a "bulky, highly reactive" cuprate might account for the stereochemical outcome.



Shortly after this work appeared, Ashby *et al.*[12] provided evidence to the effect that the stereochemistry of the above addition could be rationalized on the basis of ketone complexation with Me_2CuLi followed by rapid 1,2-addition of MeLi, predominantly from the less congested equatorial face. Either $LiClO_4$ or LiBr in the presence of an equivalent of MeLi gave products with ratios very similar to those seen employing the Me_2CuLi–MeLi mixture (i.e. "Me_3CuLi_2").



Attention was then turned to probing the synthetic potential of "higher order" cuprates. In a follow-up paper, Still and Macdonald also considered conjugate addition reactions of ethereal Me_3CuLi_2 with α,β-unsaturated systems.[13] They found that exclusive 1,4-delivery of Me took place at −60° with both cyclohexenone and isophorone in excellent yields (85–90%). Surprisingly,[3a] 2-octenal likewise acted as a Michael acceptor, leading to 3-methyloctanal in 81% yield.



In a subsequent, far more extensive study by the Ashby group,[14] the prognosis for "R_3CuLi_2" as reagents in Michael additions was not quite as encouraging. Methylation reactions (R = Me) with relatively unhindered cases, which were conducted at room temperature in THF as solvent, did afford high yields of products. Di- and trisubstituted systems (e.g. mesityl oxide, isophorone), however, led to little, if any 1,4-adduct. These seems to be a slight discrepancy between these reports,[13,14] with respect to the reaction solvent of choice (Et_2O vs THF), as well as one substrate common to both, isophorone. It should be noted, however, that other reaction parameters involved were undoubtedly different (e.g. temperatures, concentrations, presence of Li salts, etc.), and these may explain the divergence in experimental findings.

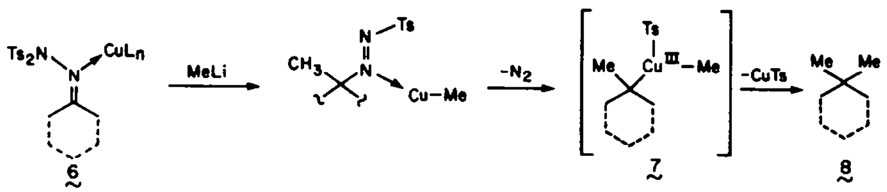
Concurrent with these studies on enones, Ashby and Lin[15] carried out coupling experiments using not only Me_3CuLi_2, but also Me_3Cu_2Li, and $Me_5Cu_3Li_2$ with primary, secondary, allylic, vinylic, and aryl halides. In general, Me_3CuLi_2 was found superior not only to the latter two aggregates, but to both Me_2CuLi and MeLi as well. As examples, 1-chlorodecane, upon treatment with Me_2CuLi in THF for 12 h at room temperature, gave n-undecane in only 22% yield, while

$$\underset{(22\%)}{\underline{n}\text{-}C_{11}H_{24}} \xleftarrow[THF]{Me_2CuLi} \underline{n}\text{-}C_{10}H_{21}Cl \xrightarrow[THF]{Me_3CuLi_2} \underset{(\text{quant.})}{\underline{n}\text{-}C_{11}H_{24}}$$

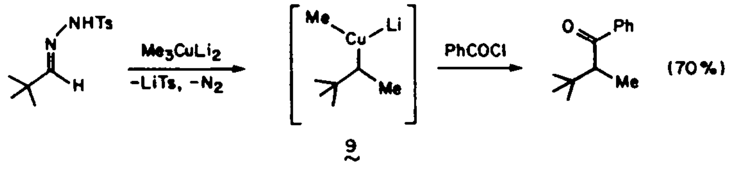
$$\underset{(45\%)}{Ph\text{-}CH_3} \xleftarrow[THF]{Me_2CuLi} Ph\text{-}Br \xrightarrow[THF]{Me_3CuLi_2} \underset{(\text{quant.})}{Ph\text{-}CH_3}$$

Me_3CuLi_2 afforded the same hydrocarbon quantitatively. Likewise, reaction with bromobenzene (in THF, rt, 24 h) led to toluene to the extent of 45%, whereas the higher order reagent again gave the product in quantitative yield.

R_3CuLi_2 has also been shown by Bertz to provide a source of Cu(I) which activates the C–N bond in hydrazones toward nucleophilic attack by lithio reagents (e.g. MeLi).[16] Interestingly, whereas Li salts are powerful Lewis acids in reactions of carbonyl compounds (*vide supra*), they have a negligible effect in this case. The preferred solvent is Et_2O, as THF, presumably, competitively complexes with copper ions in solution. It has been observed that hydrazone derivative **6** ultimately forms 1,1-dimethylcyclohexane **8**, as one of several products. Hydrocarbon **8** appears to be the first reported case of a *gem*-dialkylated product formed directly from such reagents. The proposed mechanism involves a Cu(III) intermediate **7**, as shown.

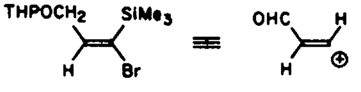


In a related paper concerning similar substrates,[17] tosylhydrazones are converted *via* reactions with Me_3CuLi_2 into hindered cuprates which undergo subsequent alkylation. The entire process may be conducted in a single pot, and gives quite good isolated yields of *gem*-disubstituted products. Unfortunately, only α-di- and trisubstituted aldehyde tosylhydrazones lead to synthetically useful results. The proposed reactive species is **9**, formed from the initial 1,2-addition of a Me group to the C=N. Presumably, mixed cuprate **9** delivers the secondary (or tertiary) ligand on Cu preferentially over Me, as no mention is made of the selectivity of ligand transfer. This

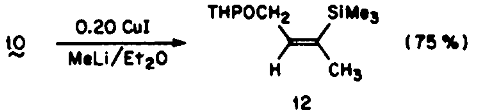


preference for alkyl group transfer, also noted by Whitesides,[18] has been used to advantage in our studies on the chemistry of higher order cuprates derived from CuCN (*vide infra*).

In a recent report[19] describing use of vinyl bromide **10** as a synthon for vinyl cation **11**, treatment of **10** with MeLi and 20 mol% CuI in Et_2O gave **12** in 75% yield. Undoubtedly, the reaction medium contained Me_2CuLi, Me_3CuLi_2, and perhaps, higher aggregates. Assignment as to which species was responsible for effecting the coupling is difficult to make, although in view of the consistently greater reactivity of higher order reagents, it is likely that Me_2CuLi played a minimal role.

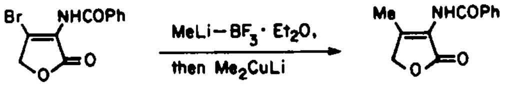


10 11



12

In an attempt to prepare 2,3-diamino carboxylic acids, alkylated γ-lactones of type **14** were envisioned as arising *via* a cuprate-mediated net substitution process on bromide **13**. All efforts[20] using Me_2CuLi gave low yields of **14**. However, by premixing MeLi with $BF_3 \cdot Et_2O$ and **13** at 0°, followed by introduction of Me_2CuLi, a 78% yield of product resulted. Me_3CuLi_2 alone gave a complex mixture, while use of preformed $Me_3CuLi_2{-}BF_3 \cdot Et_2O$ decreased the yield to 57%. Thus, B-activation seems to be necessary, a phenomenon previously witnessed in other Cu-directed conjugate addition schemes.[21] Since two equivalents of all reagents were employed, the amide is most likely in the form of its anion, leaving a full equivalent of MeLi to react with the incoming Gilman cuprate. The higher order species, being formed in relatively low concentrations due to the mode of addition, may see only pre-complexed substrate with which to react. Having a full equivalent of Me_3CuLi_2, or some other Cu-complex in the pot prior to substrate addition apparently encourages alternative, competitive reaction pathways.



13 14

Larock and Leach[22] have presented the details of extensive cross-coupling reactions between organomercurials and organocuprates. With PhHgCl as a model system, methylation studies leading

$$ArHgCl + 5Li_2CuMe_3 \xrightarrow{x\text{'s MeI}} \xrightarrow{O_2} \xrightarrow{NH_4Cl} Ar{-}CH_3$$

to toluene formation pointed to the higher order species Me_3CuLi_2 as the reagent of choice (60–65%), as compared with Me_2CuLi (45%). Mixed heterocuprates Me(L)CuLi gave inferior results (11–31%, L = CN, O-t-Bu, SPh, etc.). It was found beneficial to add excess MeI to the reaction to account for a postulated metal–halogen exchange,[23] followed by exposure to oxygen prior to workup.[24] In this way, the yield was increased dramatically to 92%. Other arylmercuric halides were also examined, and while phenyl-substituted cases generally coupled reasonably well, heteroaromatics gave poor yields. Other substrate types were also considered, the order of reaction efficiency being aryl > vinyl > primary alkyl > secondary alkyl. Trends were also noted as a function of R in R_3CuLi_2, with yields decreasing according to the scheme Me > vinyl > primary alkyl > secondary alkyl. The data obtained was rationalized according to the following events:

$$RHgCl + LiCuR'_2 \rightarrow RHgR' + CuR' + LiCl$$

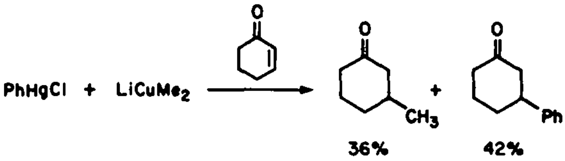
$$RHgR' + CuR' + LiCl \rightarrow LiCuRR' + R'HgCl$$

$$RHgR' + LiCuR'_2 \rightarrow LiCuRR' + HgR'_2$$

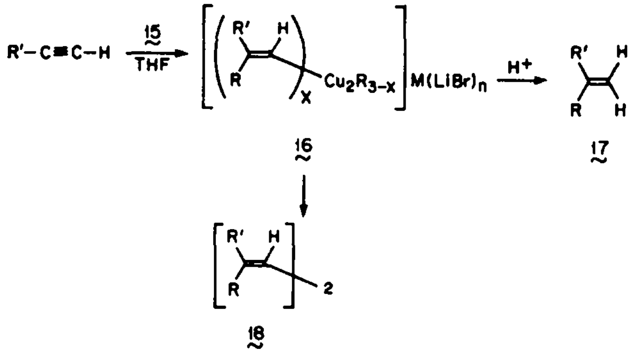
$$LiCuRR' \xrightarrow{O_2} R{-}R'$$

$$LiCuRR' + R'I \rightarrow R{-}R'.$$

The involvement of the mixed reagent LiCuRR′ is supported by the fact that addition of cyclohexenone to a mixture of PhHgCl and Me_2CuLi affords both 3-methyl- and 3-phenylcyclohexanone. Unfortunately, the control reaction using Me(Ph)CuLi on this enone was not done. Moreover, the mechanism suggested, however, does not take into account the role of R_3CuLi_2 in these couplings.

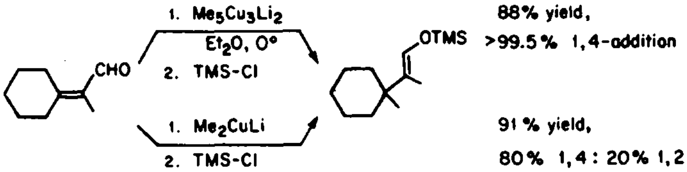


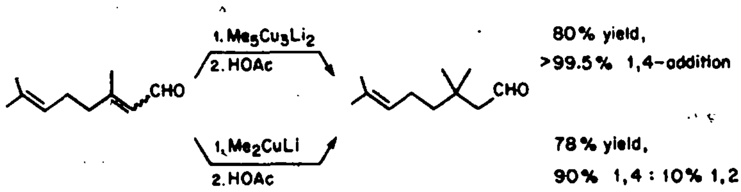
The Cu-complexes $R_3Cu_2M(LiBr)_n$, **15**, R = Me, Et, M = MgCl, MgBr, Li, have been found to be very effective for converting 1-alkynes into 1-alkenes.[25] Both Ph—C≡CH and 1-octyne served as typical substrates with yields for these additions usually being impressively close to quantitative. Some interesting aspects noted by the authors include: (1) the presence of LiBr (~6 equiv) encourages conversion of **16** to **17**, essentially surpressing "decomposition"[25] of **16** to **18**; (2) when M = Li, none of **18** is formed; (3) only a single regioisomer resulting from *syn*-addition is seen, as verified by ^1H NMR analysis of **16** following deuterolysis; (4) these reagents are more powerful



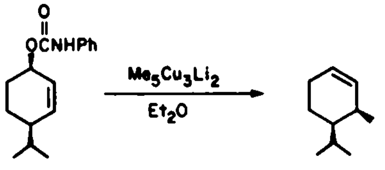
in reactions of this type than either [RCuX]M or R_2CuM, both in terms of efficiency and equivalents of RM.

Work describing aggregate $Me_5Cu_3Li_2$ has recently appeared by Clive *et al.*, this complex being an excellent species for delivering a Me group in a Michael sense to enals.[26] Although in highly hindered cases yields tend to be low, comparison experiments with Me_2CuLi demonstrated its superiority. The possibility of extending this method, which calls for the combination of 5 MeLi + 3 CuI, to other RLi was not touched on. The following examples are illustrative.





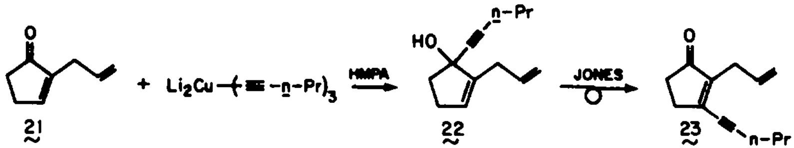
Gallina[27] has also employed this reagent in reactions of allylic acetates and carbamates. For example, urethane **19**, upon treatment with $Me_5Cu_3Li_2$, undergoes displacement with both regio- and stereospecificity to afford **20**, the product of *syn*-substitution in 82% yield. The results suggest an initial rapid proton abstraction from the carbamate followed by fast cuprate equilibration and



19 20

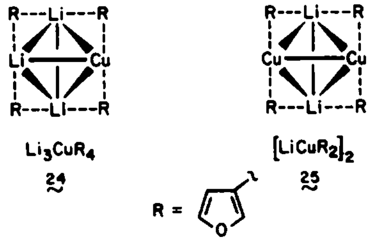
finally, a slower coupling between substrate and reagent. A concerted process involving coordination between the lithiated leaving group and Me$_5$Cu$_3$Li$_2$ within a cyclic transition state is hypothesized to account for the selectivity observed.

The regiospecific 1,2-addition of dilithium trialkynylcuprates to cyclic enones can be effected in the presence of HMPA as co-solvent (*ca* 20%).[28] Without this additive, reagents of this nature are rather unreactive toward either 1,2- or 1,4-modes of addition. In the case shown below, reaction of **21** with dilithium tris(pent-1-ynyl)cuprate gave, *via* tertiary carbinol **22**, the rearranged cyclopentenone **23** after an acidic, oxidative workup with Jones reagent.



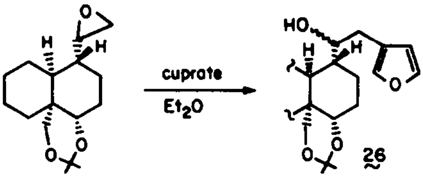
21 22 23
(~quant.)

Furans continue to attract interest both as ligands in cuprate reagents and as educts for synthetic goals. Kojima and Kato[29] reported in 1980 on the benefits ascribed to the combination of lithium di(3-furyl)cuprate with an "extra" two equivalents of 3-furyllithium. Only this stoichiometry (i.e. "Li$_3$Cu(3-furyl)$_4$") in Et$_2$O significantly raised the yields of substitution reactions of epoxides, as compared with both the R$_3$CuLi$_2$ and R$_2$CuLi counterparts. In some cases, introduction of Me$_2$S was found advantageous. The authors propose structure **24** for this reactive copper cluster, which is analogous to the dimeric form **25** proposed for Gilman reagents.[3g,30]



Li$_3$CuR$_4$ 24
[LiCuR$_2$]$_2$ 25

Cuprate **24** was of particular value in maximizing formation of product **26**, an intermediate *en route* to a Clerodin homolog, the synthesis of which was deemed necessary for elucidating structure-activity relationships for this antifeeding diterpene.[31]

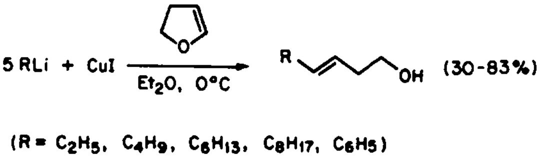


26

LiCu(3-furyl)$_2$	20 %
Li$_3$Cu(3-furyl)$_4$	67 %
Li$_3$Cu(3-furyl)$_4$ · SMe$_2$	77 %

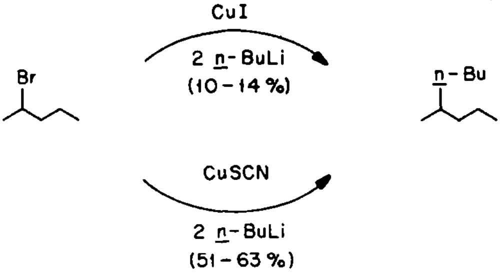
Dihydrofuran itself is susceptible to nucleophilic attack by the mixture of five equivalents of an organolithium and one equivalent of CuI.[32] The product is an (*E*)-3-alken-1-ol, obtained in good yields as the only geometrical isomer produced. Other reagents, including n-BuLi (7%), n-Bu$_2$CuLi

(15%), and n-Bu_3CuLi_2 (70%) were less satisfactory. Both secondary and tertiary alkyllithium-derived cuprates did not effect this transformation.



(C) *Cuprous thiocyanate plus organolithium reagents*

In Gilman's original paper[4] discussing the admixture of various Cu salts with two equivalents of an organolithium RLi, both Cu(I) halides and cuprous thiocyanate (CuSCN) were believed to give cuprates R_2CuLi. This presumption stood intact and, indeed, encouraged researchers to employ either source of Cu(I) for over 30 years.[33] Recently, however, we have reinvestigated the nature of the species formed from CuSCN.[34] It was shown, from side-by-side reactions, that in certain situations, reagents formed from CuI + 2RLi behave in a remarkably different manner from those prepared from CuSCN + 2RLi. The distinctions were most vivid in comparison runs involving substitution reactions on secondary, unactivated bromides. For example, while 2-bromopentane reacted with CuI/2 n-BuLi in THF at 0° for 3 h to afford 4-methyloctane to the extent of only 10–14%, treatment of this halide with CuSCN/2 n-BuLi under identical conditions consistently gave the hydrocarbon in *ca* five times the yield (51–63%). This trend held as well in the case of bromocyclopentane (14–24 vs 44–56%).

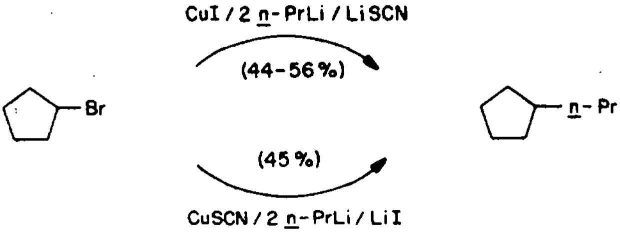


Although these reactions provided major clues in distinguishing between reagents, additional evidence of a visual, chemical and spectroscopic nature further attested to their apparent dissimilarities. While addition of 2 RLi (e.g. R = n-Bu) to CuI routinely leads to dark mixtures even at low temperatures,[3a] by contrast, reagents formed from CuSCN remained a translucent tan, very much akin to those originating from CuCN (*vide infra*). Moreover, comparison experiments were conducted where the identical composition of each solution was insured by the addition of the required salts (eqns 1 and 2). Obviously, the initial makeup must be different due to the anion associated with Cu(I). In principle, adding LiSCN to the pot containing CuI/2 RLi, and LiI to the CuSCN/2 RLi combination, should result in the same chemical blend. One test of this

$$CuI + 2\,RLi \rightarrow R_2CuLi + LiI \qquad \therefore \text{ add LiSCN} \qquad (1)$$

$$CuSCN + 2\,RLi \rightarrow R_2CuLi + LiSCN \qquad \therefore \text{ add LiI} \qquad (2)$$

hypothesis would be an observable increase in product yield in the reaction of [CuI/2 RLi + LiSCN] over that witnessed for CuI/2 RLi alone. In the event, treatment of bromocyclopentane with CuI/2 n-PrLi/LiSCN did, in fact, raise the yield of coupling product from that seen with CuI/2 n-PrLi (14–24%) to that obtained with either CuSCN/2 n-PrLi (44–56%) or CuSCN/2 n-PrLi/LiI (45%).



IR spectroscopic analysis, using 1,4-dicyanobenzene as a standard according to the method of Burmeister,[35] likewise revealed the similarity of solutions prepared as indicated in eqns (1) and (2). Both showed (ν_{CN} = 2065 cm^{-1} of similar intensity at identical concentrations. By virtue of this technique, it was also suggested that the ambident $[SCN]^-$ ligand is most likely bound via S to Cu.

The explanation proposed,[34] which accounts for all of the data accrued, invokes generation of a higher order, mixed organocuprate, which forms directly from CuSCN and 2 RLi according to eqn (3). While interesting in their own right, reactions of these reagents are not, in general, as

$$CuSCN + 2\,RLi \rightarrow \text{“}R_2Cu(SCN)Li_2\text{”} \tag{3}$$

efficient as those which rely on "$R_2Cu(CN)Li_2$" (*vide infra*). Perhaps the key point here is that many pieces of work which have relied on the chemistry of "R_2CuLi" over the past 10–15 years have not specified the source of the Cu(I) salt. Hence, this study serves as a caveat with respect to future interpretations of and/or expectations from earlier reports. Clearly, cuprates prepared from CuSCN have properties oftentimes decidedly superior to those of lower order reagents R_2CuLi, commonly prepared today from CuBr or CuI.

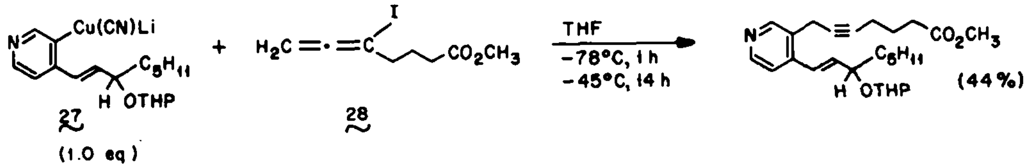
(D) *Cuprous cyanide plus organolithium reagents*

1. *Introduction.* Cuprous cyanide continues to be used as a source of Cu(I) in the formation of lower order organocuprates with the advantage that only one equivalent of an organolithium is required to form an active reagent. This was first demonstrated in 1973 by Levisalles' group[36] in their efforts to develop an unsymmetrical lithium cuprate which would transfer one ligand preferentially.[37] There had been precedent[18] (*vide supra*) for incorporation of a non-transferrable group into a cuprate cluster with the intent of conserving precious ligands which would be selectively transferred from Cu to C. Formation of a homocuprate requires at least two equivalents of an organolithium, with the consequence that upon reaction where one R group is consumed, one is left with a relatively unreactive, oftentimes polymeric species, RCu. By using a non-transferrable, or "dummy" ligand, R_R, only a 1:1 stoichiometry (R_TLi:R_RCu) is needed to form R_TR_RCuLi. Alkynyl groups such as 1-pentynyl,[38] t-butylacetylide,[39] and 3-methoxy-3-methyl-1-butynyl,[40] exemplify the characteristics necessary for a useful residual ligand R_R. Since a nitrile is electronically similar to an alkyne, cuprous cyanide appeared quite promising as a readily available alternative. CuCN is not only an excellent substitute for cuprous halides (both in terms of stability and expense),[41] but it also already contains an R_R (i.e. CN^-) attached to Cu eliminating any need for a preliminary lithiation (R_RLi)/metal–metal exchange process. These mixed, lower order cyanocuprates have been found satisfactory for displacement of primary halides and in 1,4-additions to α,β-unsaturated enones.[36] More recently, Acker has described their potential in epoxide openings.[42] Marino *et al.* have also examined their use in opening cyclic allylic epoxides[43] as well as in 1,4-additions to enol silyl ethers,[44] and enol phosphates derived from α,β-epoxy cyclohexanones.[45]

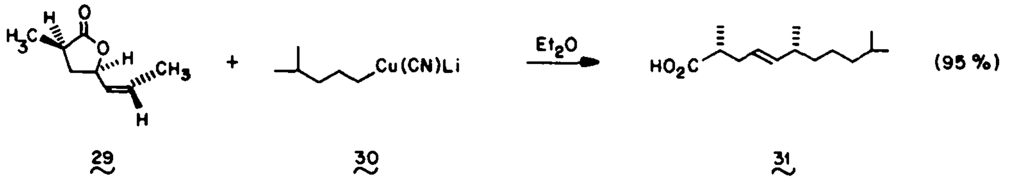
$$H-\equiv-R \xrightarrow{RLi} Li-\equiv-R \xrightarrow{Cu(I)} Cu-\equiv-R \xrightarrow{R_TLi} R_TCu(\equiv-R)Li$$

$$CuCN + R_TLi \longrightarrow R_TCu(CN)Li$$

The value of this type of cuprate can best be appreciated by citing recent applications in total syntheses where conservation of ligands is an important consideration during a multi-step sequence. In a synthesis of various pyridino prostanoids (effective inhibitors of the biosynthesis of thromboxane A_2), Corey[46] utilized the ability of a mixed cyanocuprate to effect 1,3-substitution on an iodoallene. One equivalent of a 3-lithio pyridine derivative was added to 1.1 equiv of CuCN to form the mixed cyanocuprate **27**, which when treated with iodoallene **28**, gave the alkynyl ester.



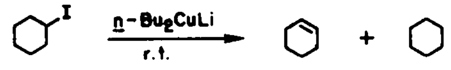
Trost[47] has also made use of cyanocuprates *en route* to the side-chain of vitamin E. In developing a method for effecting chirality transfer in acyclic systems, it was shown that use of alkylcyanocuprates represents a stereochemical complement to the analogous Pd-induced process. Whereas the combination of catalytic Pd(0) and the appropriately stabilized nucleophile reacted with lactone **29** to produce an acyclic product corresponding to a net retention of configuration,[48] addition of **29** to cyanocuprate **30** proceeded via an S_N2' mode to give the corresponding material **31** with inversion of configuration.[47] These two cases[46,47] highlight some of the benefits associated with CuCN-derived organocuprates, exemplifying both a conservation of valuable ligands as well as elements of regio- and stereochemical predictability.



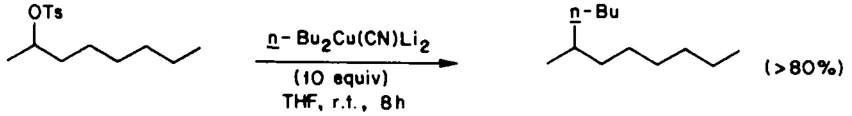
In spite of these attractive features, there are serious disadvantages to these reagents, not the least of which, as Whitesides[18] has pointed out, is that "the reactivity of organometallic groups in mixed cuprates is qualitatively intermediate between the reactivity of the constituent components". That is, a diorgano homocuprate is expected to be considerably more reactive than the corresponding mixed cuprate containing one transferrable group and one residual ligand. In going to dilithium dianions characteristic of higher order organocuprates (R_3CuLi_2), greater reactivity might be observed (*vide supra*) relative to their lower order predecessors (R_2CuLi). By combining the merits of both CuCN-based and higher order reagents, it was anticipated that a reactive hybrid species should result from the combination of two equivalents of RLi and one equivalent of CuCN. It was this hypothesis which prompted investigation by our group into the nature, synthetic potential, and scope of these higher order, mixed organocuprate reagents, "$R_2Cu(CN)Li_2$".

$$2RLi + CuCN \rightarrow \text{“}R_2Cu(CN)Li_2\text{”}$$

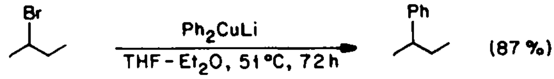
2. *Substitution reactions*—(a) *Unactivated secondary halides and sulfonates*. Our initial efforts tested the ability of higher order cyanocuprates to displace unactivated secondary halides,[41] a reaction rarely contemplated in planning synthetic strategy. An early paper[23] examining the scope and limitations of Gilman-type reagents in coupling reactions had shown that displacement in primary systems was facile, whereas substitution of secondary unactivated halides was not a synthetically useful operation. For example, the attempted coupling of cyclohexyl iodide with lithium di-n-butylcuprate gave none of the desired n-butylcyclohexane, producing instead only products of reduction and elimination. In a more exhaustive examination[24] of these events, it was reported that when 2-bromopentane was treated with the same cuprate, only 12% of the expected hydrocarbon resulted. Failure to couple secondary unactivated *iodides* with organocuprates, we have since determined,[49] may partially be attributed to the reaction conditions chosen (*vide infra*). In general, however, an efficient displacement of a secondary iodide or bromide with a lower order cuprate is not considered viable.[50]



In contrast, most higher order cyanocuprates, $R_2Cu(CN)Li_2$, **32**, were shown to be very effective in coupling reactions with these same substrates.[41,51] For example, treatment of cyclohexyl iodide with **32**, R = n-Bu, under extremely mild conditions provides the desired n-butylcyclohexane in greater than 90% yield. Use of this same cuprate with 2-bromopentane gave 4-methyloctane (94%). Iodides and bromides of cyclic and acyclic systems illustrate the potential of this method, and the results are summarized in Table 1. Iodides appear to be "displaced" more easily than bromides, while chlorides are relatively sluggish under the conditions indicated. Cyclohexyl bromide gives disappointingly low yields, although the literature[52] substantiates a general reluctance on the part of this specific substrate in other substitution reactions, presumably due to steric factors. In this particular instance, the discrepancy between reactions of cyclohexyl iodide and cyclohexyl bromide might reflect an innate difference in reduction potentials[53] and, hence, a difference in mechanism (*vide infra*). Sulfonates, including mesylates and tosylates, also react in a surprising manner in that they afford, at best, moderate yields of product under "standard" conditions (1–2 equiv of cuprate). This is ironic when one recalls the work of Johnson and Dutra[54a,b] on the reactivity patterns of primary systems with lower order cuprates, where they discovered that tosylates are *more* easily displaced than iodides. This reversal in reactivity trend has yet to be adequately explained. Possible factors which might be considered include competing acidity of a proton on the sulfonate, steric encumbrance to the approach of the cuprate, or alternative modes of sulfonate cleavage due to differences in reduction potentials (i.e. S–O vs C–O cleavage).[53] It should be noted, however, that reaction of 2-octyl tosylate with a large excess (10 equiv) of the higher order reagents does allow for a dramatic increase in yield.[51]

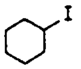
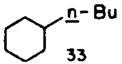
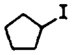
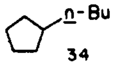
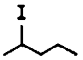
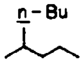
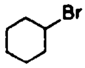
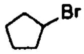
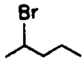
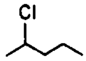
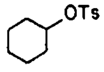
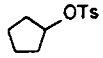
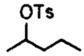
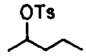
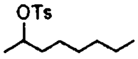
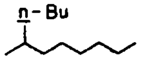
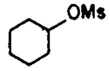
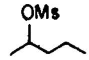


The scope of this methodology involving higher order cyanocuprates is given further extension by varying the nature of the organolithium used to form the reagent (Table 2). It can be seen that n-alkyllithiums all give reactive cuprates; vinyllithium- and allyllithium-based reagents are also quite effective. The phenyllithium-derived cuprate $Ph_2Cu(CN)Li_2$, however, seems to exhibit anomalous behavior compared to that of the similarly hybridized vinyllithium-derived species, as well as that of its copper halide-derived analog. For example, when 2-bromobutane is treated with diphenylcopperlithium, albeit under atypical cuprate conditions, sec-butylbenzene is produced in greater than 85% yield.[24] The explanation for the inconsistent behavior of $Ph_2Cu(CN)Li_2$ relative to Ph_2CuLi toward secondary halides is further obscured by the discovery that this same higher order reagent is very effective in opening epoxides,[55] as well as in displacements of primary halides[56] (*vide infra*). Unsatisfactory results were also obtained from the higher order cyanocuprate derived from sec-BuLi, as attempted coupling with secondary halides led to low yields of desired material. Hence, it appears that substitution reactions at secondary centers are limited to those cuprates prepared from either n-alkyl or vinyllithium precursors.



(b) ***Primary halides and sulfonates.*** Although displacement of primary halides (**37**, X = I, Br, Cl) and sulfonates (**37**, X = OSO_2Ar) with lower order cuprates had been shown some time ago to be a useful process,[24,54a] it was felt that the enhanced reactivity of higher order, mixed cuprates might provide a valuable alternative if fewer equivalents of reagent would be required. Moreover, primary chlorides, though relatively unreactive toward Gilman-type reagents, might prove to be compatible

Table 1. Reactions of secondary halides and sulfonates with n-$Bu_2Cu(CN)Li_2$

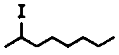
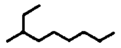
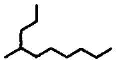
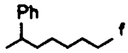
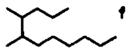
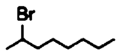
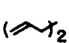
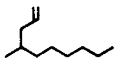
Halides	Conditions[a]	Product[b]	Yield (%)[c]
	−78°, 1 h	 33	>90
	−78°, 2 h	 34	82
	−50°, 2 h	 35	99
	rt, 2 h	33	22[d]
	0°, 6 h	34	86
	0°, 2h → rt, 1 h	35	94
	rt, 11 h	35	28
Sulfonates			
	rt, 3 h	33	5[e]
	0°, 5 h	34	35[e]
	−25°, 24 h[f]	35	40
	rt, 7 h	35	58
	rt, 8 h[g]		>80
	0°, 2 h	h	—
	0°, 2 h → rt, 1 h	h	—

[a] All reactions were conducted in THF using 1.5 - 2.0 equiv of reagent unless specified otherwise. [b] Identified by comparison with an authentic sample. [c] By quantitative VPC. [d] 52% starting material remained. [e] Starting material still observed by TLC. [f] Reaction was run in Et_2O. [g] 10 equivalents were used. [h] None of the desired product was formed.

coupling partners with these cyanocuprates. Thus, primary systems were also evaluated[5b] and our data is presented in Table 3. In light of the fact that secondary iodides react between −50 and −78°, it was not unreasonable to find that primary iodides were reactive at extremely low temperatures (−100°). However, reduction was a competing side process. It was felt that lower temperatures would prove more difficult to obtain than worthwhile, and therefore the investigation concentrated on primary bromides, chlorides, and sulfonates.

Treatment of primary bromides with $R_2Cu(CN)Li_2$ (as in Table 3) revealed that very mild conditions (*ca* −50°) suffice, in most cases, for an efficient displacement utilizing less than two equivalents of reagent. Lower order cuprates generally require temperatures around 0° with larger quantities of reagent.[3d] With the sterically encumbered norbornene-containing bromide, somewhat

Table 2. Reactions of secondary halides with $R_2Cu(CN)Li_2$

Substrate	Cuprate	Conditions[a]	Product[b]	Yield (%)[c]
 36	$Me_2Cu(CN)Li_2$	0°C, 6h		85
36	$Et_2Cu(CN)Li_2$	-78°C, 1.5 h		100
36	$\underline{n}$-$Pr_2Cu(CN)Li_2$	-78°C, 1 h		90[d]
36	()$_2$Cu(CN)Li$_2$	0°C, 6h		90[e]
36	$(Ph)_2Cu(CN)Li_2$	0°C, 6 h		7[g]
36	$\underline{s}$-$Bu_2Cu(CN)Li_2$	-50°C, 1 h		19
	()$_2$Cu(CN)Li$_2$	-22°C, 1.5 h		>90[h]

[a] Reactions performed in THF as solvent. [b] Products verified by comparison with authentic sample unless stated otherwise. [c] By quantitative VPC. [d] 10% starting material observed in addition to 90% product. [e] VPC indicates 6% starting material remains. [f] Product was not compared with an authentic sample. [g] Major product resulted from reduction (i.e. octane). [h] Product identified by comparison of spectral data with literature values.

higher temperatures were essential. Even the least reactive of the reagents which we have tested to date, $Ph_2Cu(CN)Li_2$, participates in these substitution reactions with bromides and tosylates, and gave yields for both in excess of 90%!

Primary chlorides likewise reacted with these cuprates. Although the chloro ketal in Table 3 led to a modest 58% of the corresponding masked ω-unsaturated ketone, exposure of the same substrate to the Gilman-like reagent (i.e. vinyl$_2$CuLi) under otherwise identical conditions produced only 2% of this product. Chemospecificity was illustrated in the case of 1-bromo-3-chloropropane. The lower reactivity of the chloride enabled the 100% selective displacement at carbon bearing bromine. Furthermore, this example demonstrates that secondary alkyllithium-derived cuprates may now be employed with primary halides as substrates.

The reluctance of the primary tosylate of the norbornene derivative to undergo substitution can be explained by steric hindrance. The mesylate gave no product corresponding to breakage of the C–O bond, but gives rise instead only to the alcohol resulting from S–O bond cleavage, presumably due to β-elimination initiated by the basic cuprate reagent.

The results of this brief study on the reactivity of primary, unactivated halides towards "$R_2Cu(CN)Li_2$" raise two key points worthy of mention: (1) by using CuCN-based cuprates, the reactivity of an iodide toward R_2CuLi can be mimicked using primary bromides, and (2) substitution of a bromide in place of an iodide obviates the occasional extreme levels of caution which are exercised in dealing with (light, heat, chromatography) sensitive materials.

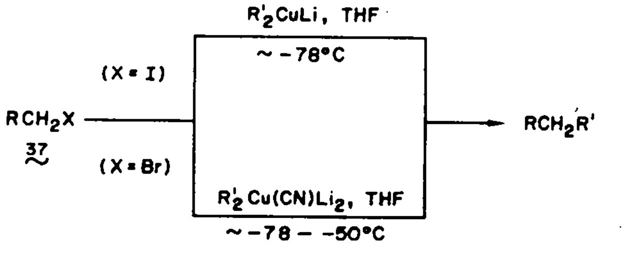
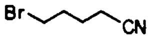
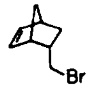
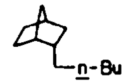
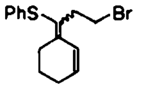
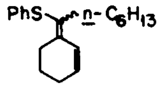
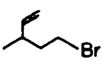
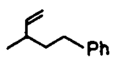
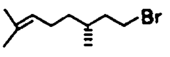
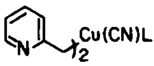
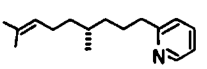
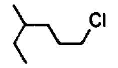
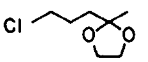
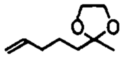
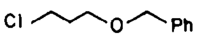
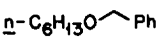
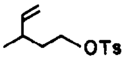
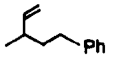
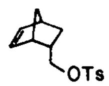
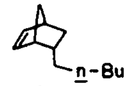
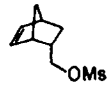
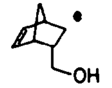
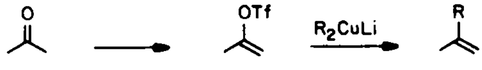


Table 3. Reactions of $R_2Cu(CN)Li_2$ with primary halides/sulfonates

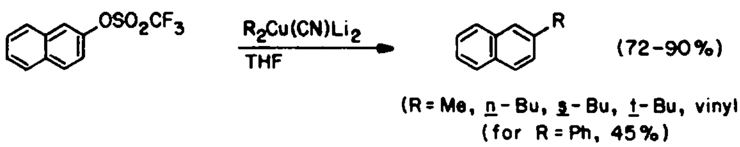
Substrate	Cuprate/(equivalents)	Conditions[a]	Product	Yield (%)
	n-$Bu_2Cu(CN)Li_2$ (2.0) **38**	-100°C, 30 min	n-$C_{11}H_{24}$[b]	50[c]
	**38** (2.0)	- 50°C, 2.5 h	n-$C_{11}H_{24}$	95[c]
	**38** (1.3)	- 50°C, 2.5 h	n-$C_8H_{17}CN$	92[d]
	**38** (1.7)	0°C, 3.5 h		91[c]
	**38** (2.0)	- 35°C, 20 h		74[d]
	$Ph_2Cu(CN)Li_2$ (2.0) **39**	r.t., 24 h		91[c]
	 Cu(CN)Li₂ (1.4)	- 50°C, 3 h		93[d]
	s-$BuCu(CN)Li_2$ (1.1)	- 78°C, 0.75h		89[c]
	 Cu(CN)Li₂ (4.0)	r.t., 24 h		58[c]
	n-$Pr_2Cu(CN)Li_2$ (2.0)	0°C, 21 h		81[d]
	**39** (2.0)	r.t., 24 h		95[c]
	**38** (2.0)	0°C, 21 h		30[c]
	**38** (2.0)	r.t., 7 h		>90[c]

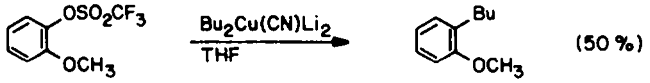
[a] All reactions performed in THF. [b] 20% starting material, 30% reduction product remaining. [c] By quantitative VPC, product verified by comparison with authentic sample. [d] Isolated yield of chromatographically pure product. [e] Only the alcohol was isolated.

(c) *Displacements at vinylic centers.* The utility of lower order cuprates for substituting C–C for C–X bonds at sp^2 carbons is widely recognized.[3d] Vinyl halide and enolic derivatives are typical substrates. One recent example involves a new method of olefin synthesis from ketones.[57,58] Here, McMurry found that enol triflates can be replaced by R in a regio- and stereoselective manner through the agency of R_2CuLi. Yet, when analogous reactions were attempted with structurally

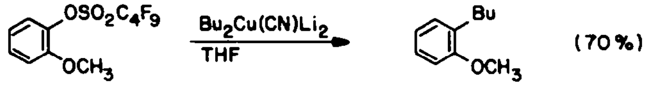


similar phenolic triflates, appreciable substitution did not occur under the influence of conventional diorganocuprates. Instead, only products arising from S–O bond cleavage were obtained. The desired reaction, however, is successful employing higher order, mixed cyanocuprates.[59] This observation has virtue in that methodology is therefore now available for converting a phenol into a substituted arene regiospecifically. As illustrated below, naphthyl triflates are displaced in high yields with a variety of cuprates $R_2Cu(CN)Li_2$. The less reactive higher order cuprate from





phenyllithium, in contrast to alkyl- and vinyllithium-based reagents, afforded only modest yields. Substituted phenyltriflates were also reactive, but apparently to a lesser extent. The more reactive nonaflates (nonafluorobutane sulfonates) were also examined and found to give marginally better results.



(d) *Epoxides*. The opening of an epoxide ring using various organocopper reagents can be accomplished with good success.[3d] Reactions of higher order cyanocuprates toward oxirane cleavage have also been found to proceed efficiently,[51,55] and fare quite favorably in many respects when compared with those of lower order Gilman cuprates. High yields of desired products are obtained using only a slight excess of reagent under mild conditions (Table 4). Moreover, mono-, di-, and trisubstituted epoxides are found to react with predictable regio- and stereochemistry (*vide infra*).

Nucleophilic attack at the least hindered carbon of the epoxide, as with R_2CuLi, is preferred. For example, styrene oxide, when treated with the higher order di-n-butylcyanocuprate shows a selectivity preference (85/8) for attack at the more accessible rather than more electrophilic carbon. In the case of an α-substituted styrene oxide, nucleophilic attack occurs exclusively at the least substituted position. Trisubstituted epoxides also provide good yields of the desired alcohols, again proceeding in a regiospecific manner as seen with both the cyclohexene and cyclopentene oxides (**41** and **42**, respectively). Tetrasubstituted and sterically encumbered epoxides do not react in the desired sense, exhibiting either limited reactivity or, where possible, behavior resulting in generation of an allylic alcohol(s) *via* β-elimination.

Again, there appear to be few limitations on the variety of organolithium-derived reagents which have been found effective. The diphenylcyanocuprate **39**, although reactive in a nonproductive manner where secondary halides are concerned (*vide supra*), show C—C bond forming ability with epoxides. For example, in the reaction of cyclopentene oxide, **43**, $Ph_2Cu(CN)Li_2$ was established as a stereochemical descriptor of this ring opening process, as C—C bond formation occurred with inversion of configuration giving *trans*-2-phenylcyclopentanol. Allylic epoxide **44** was opened in an S_N2' fashion with the same cuprate to afford a mixture of *E* and *Z* isomers, the former predominating to the extent of 3.4:1. The divinylcyanocuprate may also be utilized efficaciously. In the specific case of monosubstituted epoxide **45**, however, the regioselectivity is not impressive. Steric effects related to reagent size (cf. reaction of styrene oxide with n-$Bu_2Cu(CN)Li_2$) may be the controlling factor. The final entry in Table 4 illustrates that heteroatom-containing ligands do not preclude cuprate generation and subsequent coupling.

These results cover our initial study in this area where THF had been employed as solvent.[55] The choice of this reaction medium was based on our original successes with secondary halides.[41] We have recently found,[51] however, that Et_2O affords enhanced rates of epoxide openings. These differences were manifested in side-by-side reactions of *cis*-2-butene oxide with di-n-butylcyanocuprate **38**. Under the conditions shown, the reaction of **46** in Et_2O was found to give

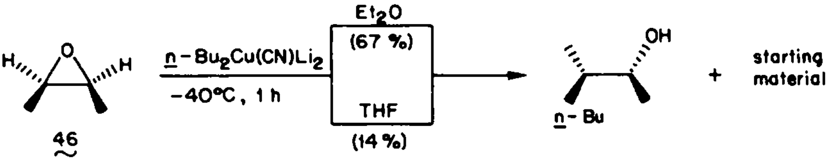
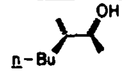
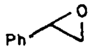
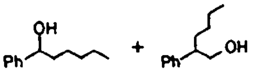
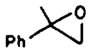
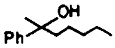
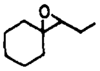
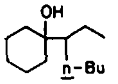
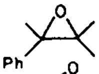
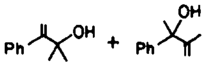
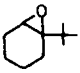
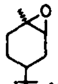
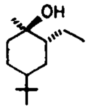
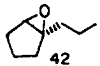
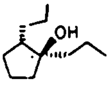
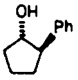
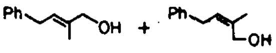
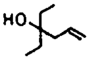
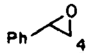
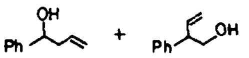
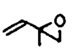
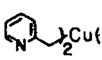
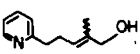


Table 4. Reactions of epoxides with $R_2Cu(CN)Li_2$

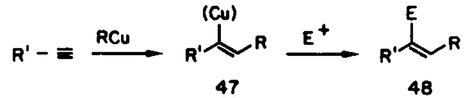
Epoxide	Cuprate/(equiv.)	Conditions[a]	Product(s)	Ratio	Yield(%)[b]
	n-$Bu_2Cu(CN)Li_2$ (1.1) 38	-20°C, 2 h		—	95[c]
	38 (1.3)	-40°C, 2 h		85 : 8	93
	38 (1.3)	-20°C, 2 h		—	96
	38 (2.0)	0°C, 6 h		—	74[c,d]
	38 (1.3)	0°C, 3 h		1 : 1	61
	38 (3.0)	0°C, 6 h	—	—	[e]
 41	$Et_2Cu(CN)Li_2$ (2.0)	0°C, 6 h		—	98
 42	n-$Pr_2Cu(CN)Li_2$ (2.0)	0°C, 8 h		—	86[c]
 43	$Ph_2Cu(CN)Li_2$ (2.0) 39	r.t. 10 h		—	98
 44	39 (1.1)	-45°C, 1.5 h		3.4 : 1[f]	96
	($)_2Cu(CN)Li_2$ (1.3) 40	0°C, 5 h		—	94
 45	40 (2.3)	-10°C, 2.5 h		57 : 35	92
	$_2Cu(CN)Li_2$ (1.7)	-40°C, 1.5 h		7 : 2[g]	73[h]

[a] Reactions performed in THF. [b] Isolated yield unless stated otherwise. [c] By quantitative VPC. [d] The remaining mass is starting material. [e] No reaction occurred under these conditions. [f] Determined by NMR analysis. [g] Determined by VPC analysis. [h] 15% of 1,2-adduct at methylene site also isolated.

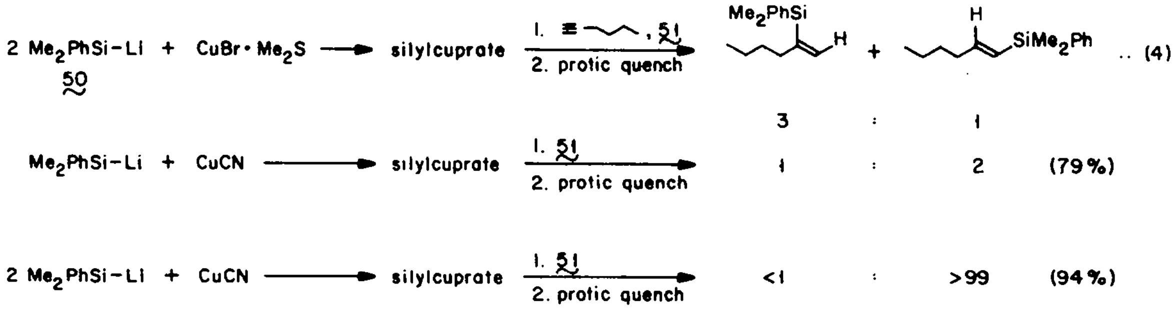
67% product, while in THF only 14% of the same alcohol had accrued. Thus, it appears that, as with lower order cuprates,[54c] Et_2O is the preferred solvent in terms of reaction rate, although both solvents give clean products of oxirane opening.

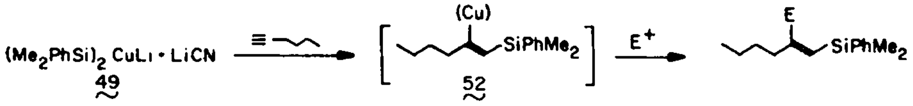
3. *Addition reactions.* The versatility of higher order cyanocuprates, $R_2Cu(CN)Li_2$, is further illustrated by their ability to undergo addition processes, both across acetylenes[3f] and in a Michael fashion.[3a] Notwithstanding the fact that diorganocuprates have a strong record of successful applications involving each of these reaction pathways, the higher order reagents merit attention on several counts: (1) they are easily prepared; (2) they do not necessitate additives or complexing ligands, thereby facilitating workup; (3) in some cases, they may result in enhanced regioselectivity; and (4) yields tend to be excellent.

(a) *Terminal acetylenes.* In methodology directed toward preparation of substituted vinylsilanes, Fleming *et al.*,[60,61] illustrated the unique behavior of a higher order silyl cyanocuprate toward addition across terminal acetylenes. While these additions may be achieved with some facility using organocopper reagents RCu,[3f,62] diorganocuprates tend only to abstract a proton from the acidic carbon without further reaction.[3f,63] The regioselectivity which accompanies organocopper additions across terminal acetylenes is usually such that the branched chain product **48** obtains, presumably *via* an intermediate **47** derived from *syn*-addition.[64] Westmijze and Vermeer[65] have shown that this



regioselectivity can be reversed by increasing the size of the substituents present. However, when the higher order disilylcyanocuprate, $(Me_2PhSi)_2CuLi{\cdot}LiCN$, **49**,[66] is added to a terminal acetylene, the stereochemical outcome is altogether different from that realized using Gilman-like silylcuprates. The regioselectivity noted is not simply a function of silylcupration versus carbocupration. For example, when $CuBr{\cdot}Me_2S$ was treated with two equivalents of dimethylphenylsilyllithium, **50**, followed by addition of 1-hexyne **51**, *syn*-addition runs slightly in favor of the branched chain product (eqn 4). Similarly, when either copper cyanide or copper iodide is treated with an equivalent of dimethylphenylsilyllithium to form the silylcyanocuprate or silylcopper, regioselectivity is now altered, with the terminal silane being favored, but again only in modest proportions. However, when copper cyanide was treated with two equivalents of dimethylphenylsilyllithium thereby forming the higher order cyanocuprate **49**, and this in turn was treated with **51**, an exceptionally high ratio of the *E*-vinylsilane to 1,1-disubstituted isomer was observed in excellent yield.



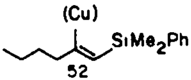
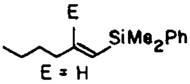
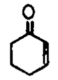
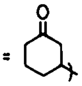
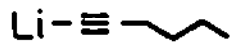
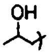


The vinyl Cu adduct, intermediate **52**, may be treated with a variety of electrophiles to afford 1,2-disubstituted vinylsilanes in good overall yields (Table 5). Even less reactive electrophiles can be employed provided that either HMPT [hexamethylphosphorous(III) triamide] or 1-lithiohexyne is present to accentuate vinylcopper reactivity. In this way, weak electrophiles such as n-butyl iodide, cyclohexenone, and propylene oxide afford coupling products.

Fleming's group also examined the silylcupration *via* **49** of several other acetylenes and found that addition likewise occurs in a regio- and stereoselective manner. Some adducts, such as **52** for example, were shown to remain configurationally stable for hours at 0°. Addition across an internal, symmetrical acetylene was also successful (E = H; 69%; $E = CH_3$; 45%).[61]

(b) α,β-*Unsaturated ketones*. Cu-promoted conjugate addition reactions have evolved steadily since an initial report in 1941 by Kharasch and Tawney.[67] This early work described the use of catalytic quantities of CuCl in the presence of MeMgBr for effecting 1,4-addition of a Me group to isophorone (>82% yield). The presence of excess strong base in the reaction medium, however, has encouraged development of reagents derived from stoichiometric ratios of Cu(I) salts to R-Metal. These more recent, stoichiometrically well-defined organocuprates, have also been used occasionally in conjunction with a Lewis acid or heteroatom ligand. Consequently, a number of reviews[3] which feature these species as Michael donors have highlighted the ability of organocopper

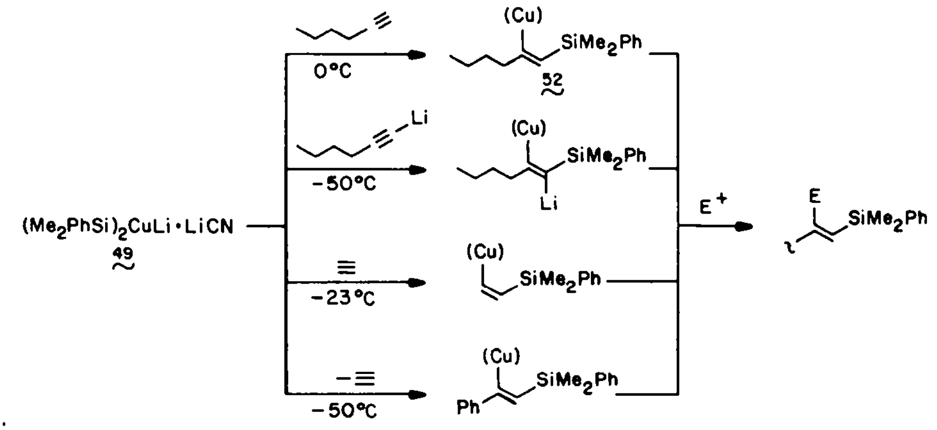
Table 5. Reaction of vinylcopper reagent 52 with various electrophiles

Vinylcopper	E^+	Conditions[a]	Product	Yield (%)[b]
 52	NH_4Cl	0°C, 5 min	 E = H	94
52	I_2	0°C, 2 h	E = I	88
52	CO_2	0°C, 1 h	$E = CO_2H$	69
52	$CH_3CH_2\overset{O}{\overset{\parallel}{C}}Cl$	0°C, 3 h	$E = CH_3CH_2\overset{O}{\overset{\parallel}{C}}-$	78
52	CH_3I	0°C, 40min	$E = CH_3$	71
52		HMPT -23°C, 80min	E = 	54
52		 -78°C, 20 min -8°C, 68 h	E = 	89

[a] All reactions performed in THF. [b] Isolated yields.

reagents to serve in this capacity. It is oftentimes implied, however, that any one combination of Cu(I) salt and organometallic may not be applicable, in a general sense, to all Michael acceptors. The nature of R-Metal (Metal = MgX, Li), the choice of organocopper vs organocuprate, solvent, and the need for additives all contribute to the complexity of determining which reagent is best suited for the substrate in question.

With these concepts in mind, we explored the potential of higher order cyanocuprates to engage in 1,4-additions[68,69] so as to compare and contrast them with, in particular, the highly popular Gilman cuprates. Initially, this work was approached with guarded optimism as we were uncertain as to the structural integrity of the higher order cyanocuprates. That is, based on spectroscopic work performed by Ashby[70] on Me_3CuLi_2, an equilibrium exists between free methyllithium and the Gilman reagent. Whether such an equilibrium could also be established for higher order cyanocuprates had yet to be determined. Should free organolithium exist in solution, then competing 1,2-addition might jeopardize their use in this context.



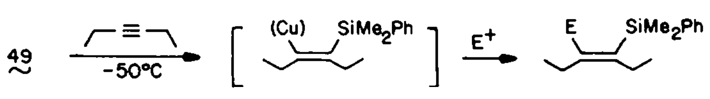
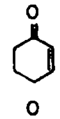
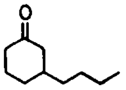
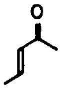
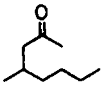
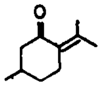
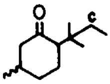
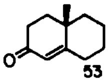
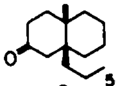
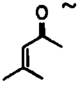
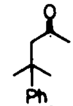
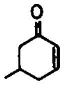
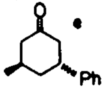
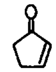
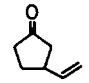
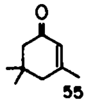
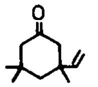
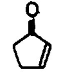
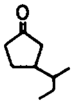


Table 6. Reactions of $R_2Cu(CN)Li_2$ with α,β-unsaturated ketones

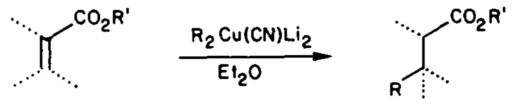
Substrate	Cuprate	Conditions[a]	Product	Yield (%)[b]
	n-$Bu_2Cu(CN)Li_2$ 38	−78°C, 0.5 h		86
	38	−78°C, 1 h		84
	$Et_2Cu(CN)Li_2$	−25°C, 3h	 [c]	81 (99)[d]
 53	n-$Pr_2Cu(CN)Li_2$	−25°C, 2h	 54	85
	$Ph_2Cu(CN)Li_2$ 39	−78°C, 1 h		83
	39	−78°C, 1 h	 [e]	82
	 $_2Cu(CN)Li_2$[f] 40	−78°C, 0.75 h		83[d]
 55	40	−50°C, 2 h		88
	s-Bu(Me)Cu(CN)Li_2	−78°C, 0.5 h[g]		97[h]

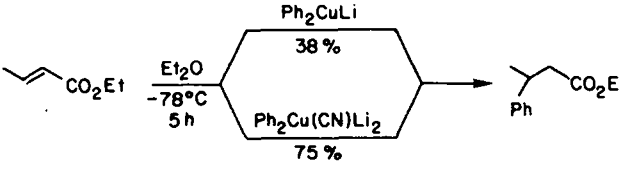
[a] All reactions performed in Et_2O unless stated otherwise. [b] Isolated yields. [c] 3.5:1 ratio of isomers. [d] VPC yield. [e] Major isomer: see text. [f] Vinyllithium is purchased commercially as a THF solution. [g] Reaction performed in THF. [h] No product of methyl transfer observed.

As evidenced by the examples in Table 6, introduction of α,β-unsaturated ketones, of varying levels of olefin substitution, to solutions containing higher order cyanocuprates 32, afforded products of conjugate addition in good to excellent yields. The procedure is general for cyclic and acyclic enones using alkyl, aryl, or vinyllithium-derived reagents. Octalone 53 was felt to be a particularly challenging example, as structurally similar bicyclic molecules have been reported to give significant amounts of 1,2-adducts in reactions with dialkylcuprates.[71] Here, treatment of 10-methyl-1-(9)-octal-2-one, 53, with n-$Pr_2Cu(CN)Li_2$ at −25° for 2 h gave the *cis*-fused 2-decalone 54[72] in 85% yield. Both phenyl and vinyllithium-based cyanocuprates are also quite reactive, for which temperatures usually in the −78° to −50° range suffice. The reaction of isophorone 55 with (vinyl)$_2$Cu(CN)Li_2 provided an excellent opportunity to highlight several advantages of higher vs lower order cuprates in conjugate addition schemes. In 1970, Hooz had shown[73] that addition of a vinyl group to isophorone using a Gilman homocuprate took place at 0° in the presence of n-Bu_3P as a stabilizing and solubilizing ligand. After the required chromatographic separation from tri-n-butylphosphine, the isolated yield was 60%. By contrast, the cyanocuprate not only performed this task at −50°, indicative of appreciably enhanced reactivity, but the overall efficiency was dramatically improved (88%). Moreover, no additives whatsoever are required, a practical consideration which should not be underestimated.

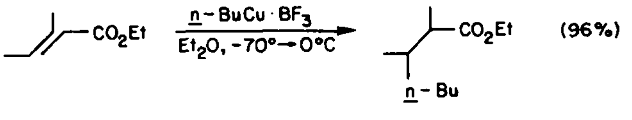
The last example in Table 6 demonstrates this method's ability to add branched alkyl groups to enones in a 1,4-sense. The reagent formed from two equivalents of s-BuLi plus one CuCN, initially used in Et_2O, is apparently indiscriminant in its activity, as severe competition from numerous reaction pathways led to only poor yields of the desired product. The reagent, however, may be tempered by altering either the cuprate or the reaction medium, or both, so as to maximize conjugate addition. Although 1,4-additions performed in THF as solvent are notoriously sluggish,[3g,74] in the case of these extremely reactive Cu(I) dianions, THF can oftentimes be used with impunity, the effect of which in this case is presumably to retard the reactive nature of the cuprate, thereby allowing 1,4-addition to become the favored process. Incorporation of a Me group as a second ligand on Cu, rather than utilizing two equivalents of a s-Bu group relates to a concept which will be discussed in detail in a subsequent section (i.e. Section 6; selectivity of ligand transfer). Suffice it to say for now that under these conditions the Me group acts, in essence, as a non-transferrable ligand (as does the nitrile group), with the combined net effect being that reactivity of the cuprate is moderated, resulting in a high yield of the desired 1,4-product with 100% selectivity of transfer.

(c) *α,β-Unsaturated esters.* The conjugate addition of conventional diorganocuprates to α,β-unsaturated esters has met with limited success owing to competitive reaction at the carbonyl center.[3a] Recently, Yamamoto's group[75] described the Lewis acid-activated organocopper reagent ($n\text{-BuCu·BF}_3$) which represents a valuable alternative to $n\text{-Bu}_2CuLi$ for inducing 1,4-addition to enoates. The conjugate addition of higher order cyanocuprates has also been evaluated in this context,[76] and the results of this study are shown in Table 7. Insofar as β-substituted examples are concerned, short reaction times, low temperatures, and only a slight excess of reagent again highlight their appeal. Differences in reactivity between Gilman reagents and $R_2Cu(CN)Li_2$ were manifested in side-by-side reactions of Ph_2CuLi and $Ph_2Cu(CN)Li_2$. Although to each of these cuprates, under identical conditions, had been added equal quantities of ethyl crotonate, the higher order reagent afforded *ca.* twice the yield of conjugate adduct.



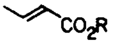
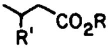
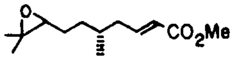
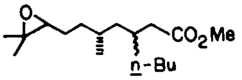
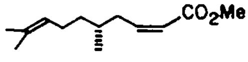
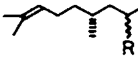
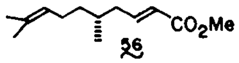
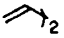
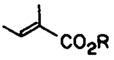
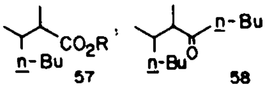
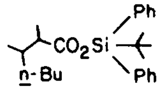
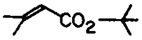
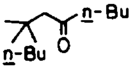


While $R_2Cu(CN)Li_2$ performed well on β-monosubstituted enoate esters, it was discovered that increasing substitution about the olefin resulted in not only decreasing yields, but substantial numbers of undesired side-products. Thus, α,β- and β,β-disubstituted esters led to disappointing results, principally due to contamination arising from a 1,2-addition/1,4-addition sequence. For example, the ethyl ester of tiglic acid, when treated with $n\text{-Bu}_2Cu(CN)Li_2$ afforded only dialkylated ketone **58**. In contrast, the same substrate, upon exposure to $n\text{-BuCu·BF}_3$, is reported to give a 96% yield of the desired saturated ester **57**. Thus, while cyanocuprates appear to be the reagents of choice for enoates bearing solely β-substitution,[76] the Yamamoto reagent[75] is superior for reactions of more highly branched educts.



(4) *Stereochemistry.* The stereochemical course followed by these higher order cyanocopper reagents has already been described for their substitution reactions with epoxides and in their additions across terminal or symmetrical acetylenes (*vide supra*). Thus, opening of cyclopentene

Table 7. Reactions of unsaturated esters with $R_2Cu(CN)Li_2$

Substrate	Cuprate /(equivalents)	Conditions[a]	Product(s)		Yield (%)[b]
					
R = Et	$\underline{n}$-$Bu_2Cu(CN)Li_2$ **38** (1.1)	−78°C → −25°C 45 min	R' = $\underline{n}$-Bu, R = Et		94[c]
R = $SiMe_2\underline{t}$-Bu	**38** (1.25)	−78°C → −25°C 2.5 h	R' = $\underline{n}$-Bu, R = $SiMe_2\underline{t}$-Bu		92[c]
R = $SiPh_2\underline{t}$-Bu	**38** (1.25)	−78°C → −25°C 45 min	R' = $\underline{n}$-Bu, R = $SiPh_2\underline{t}$-Bu		23
R = Et	$Ph_2Cu(CN)Li_2$ (1.1)	−78°C, 6 h	R' = Ph, R = Et		75[c]
	**38** (1.1)	−78°C → −25°C 1 h			95
	**38** (1.0)	−78°C → −10°C 50 min	 R = $\underline{n}$-Bu		92
 **56**	**38** (1.0)	−78°C → −10°C 1.5 h	R = $\underline{n}$-Bu		88
56	 $_2Cu(CN)Li_2$ (1.0)	−78°C → −10°C 1.25 h	R = vinyl		65
56	$\underline{n}$-$Pr_2Cu(CN)Li_2$ (1.1)	−78°C → −25°C 1.5 h	R = $\underline{n}$-Pr		87
			 **57**	**58**	
R = Et	**38** (1.0)	−78°C → 0°C 3h	0	1	d
R = $\underline{t}$-Bu	**38** (1.1)	−78°C, 4h	3-4	1	d
R = $SiMe_2\underline{t}$-Bu	**38** (3.1)	−78°C, 3h	1	2	d
R = $SiPh_2\underline{t}$-Bu	**38** (3.1)	−78°C, 1h			50-65
R = Si($\underline{i}$-Pr)$_3$	**38** (1.1)	−78°C → 0°C 1 h	—		e
	**38** (2.9)	−78°C → 0°C 1 h			d

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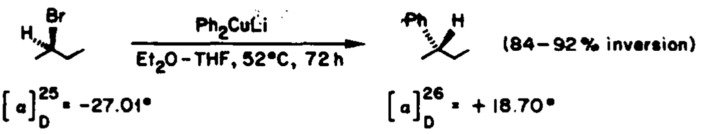
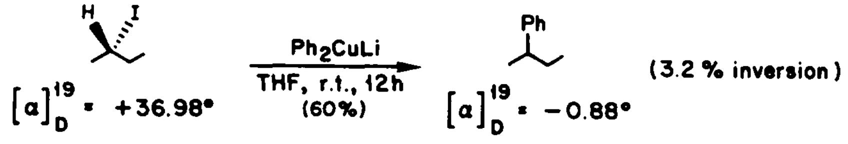
[a] All reactions performed in Et_2O. [b] Isolated yields unless otherwise stated. [c] Yield determined by quantitative VPC. [d] Yield not determined. [e] At least five products detected by VPC.

oxide with $Ph_2Cu(CN)Li_2$ proceeds *via* backside displacement giving *trans*-2-phenylcyclopentanol,[55] while the higher order silylcyanocuprate adds across acetylenes affording products stereospecifically resulting from an initial *syn*-addition.[60,61] In both instances, the outcome parallels that seen with lower order homocuprates on oxiranes and disubstituted alkynes.[34] The stereochemical consequences which result from displacement of halide ion by organocuprates, however, merits special attention. An early paper, detailing substitution reactions of R_2CuLi, sought to illustrate the resulting chirality at carbon following coupling with a secondary unactivated halide.[24] Described was the reaction of Ph_2CuLi with (*R*)-(−)-2-bromobutane which led to (*S*)-(+)-2-phenylbutane. Analysis of the rotations of each indicated 84–92% inversion had occurred. An outgrowth of this single experiment is the commonly held view[1,3d] that secondary halides, *in general*, react via a net S_N2-like process. To establish that higher order mixed cuprates **32** behave similarly, displacement

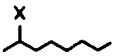


processes were carried out on optically active 2-iodooctane. Addition of (*R*)-(−)-2-iodooctane to $Et_2Cu(CN)Li_2$ in THF at −78° provided the expected 3-methylnonane, but as a *racemic mixture!* Uncertain as to why secondary iodides, upon treatment with higher order reagents, should behave differently from their reactions with lower order cuprates, attention was next focused on the coupling of this same substrate with Et_2CuLi. Again, the *racemate* of 3-methylnonane was obtained (see Table 8). This preliminary data indicated that the stereochemical outcome might be a function of the substrate rather than the reagent. To further test this hypothesis, (*S*)-(+)-2-bromooctane was treated with the more highly mixed cuprate, $Et(Me)Cu(CN)Li_2$,[51] (Section II.D.6) providing in good yield 3-methylnonane, the rotation on which signified that complete Walden inversion had occurred. This experimental value, determined in the usual way, is actually the highest rotation reported thus far for 3-methylnonane.[77] Even when compared with rotations based on extrapolation,[78] nearly 100% inversion is implied. The coupling of Et(Me)CuLi with optically active 2-bromooctane also provided the same hydrocarbon with an essentially identical optical rotation. Finally, to unequivocally verify stereochemical dependence on the halide, (*S*)-(+)-2-iodobutane was treated with Ph_2CuLi. As stated earlier, optically active 2-bromobutane reacts with this Gilman-type cuprate providing the product of inversion.[24] Yet in this instance, the optically active *iodo*butane afforded *racemic* sec-butylbenzene. The common misconception then, that clean inversion results from substitution reactions on secondary halides, in general, has now been clarified,[79] as summarized in Table 8.



The implication from these results is that iodides and bromides, both of which may lead to the desired products of coupling, do so via different mechanistic avenues. Iodides presumably react via radical intermediates, although a single electron transfer (SET) route to a Cu(III) derivative is also not precluded. Bromides likewise retain the option of involving either Cu(III) species,[80] or

Table 8. Reactions of optically active halides with higher and lower order organocuprates

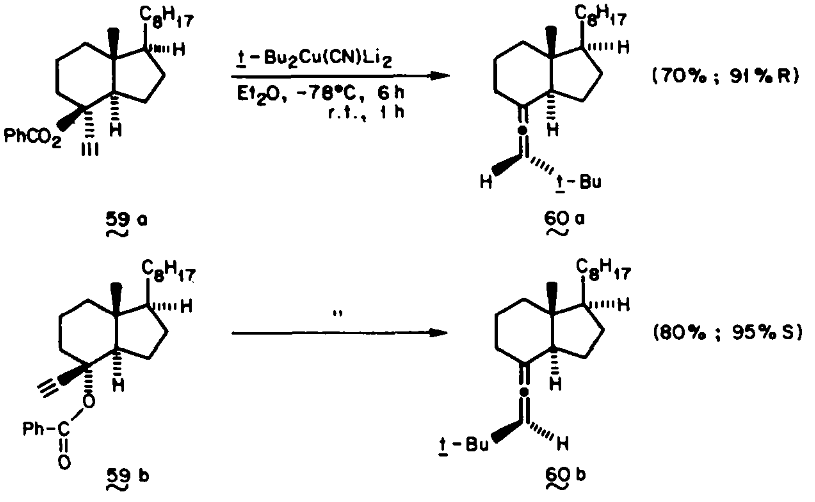
, $[\alpha]_D$, deg[a]	Cuprate/Conditions	, $[\alpha]_D$, deg[a]	Percent Inversion[b]
X = I, $[\alpha]^{19}_D$ = −50.98°	$Et_2Cu(CN)Li_2$ THF, −78°C, 2h (92%)	$[\alpha]^{22}_D$ = −0.11°	1.1−1.2
X = I, $[\alpha]^{19}_D$ = −50.31°	Et_2CuLi THF, −50°C, 3h (82%)	$[\alpha]^{22}_D$ = 0.00°	0
X = Br, $[\alpha]^{19}_D$ = +35.78°	$Et(Me)Cu(CN)Li_2$ THF, 0°C → r.t., 2h (72%)	$[\alpha]^{19}_D$ = +9.60°	97 − 103
X = Br, $[\alpha]^{19}_D$ = +35.94°	Et(Me)CuLi THF, 0°C, 10h (59%)	$[\alpha]^{19}_D$ = +9.53°	97 − 102

[a] Corrected rotation; based on specific rotation of starting material. [b] Range due to reported values for 3-methylnonane.[77,78]

short-lived radicals,[81] or perhaps both. Our findings are also in agreement with work recently reported by Ashby.[82] Precisely how these remarkable events take place still poses one of the most complex yet fundamental problems in organocopper chemistry.

One further consequence of this study (Table 8) concerns the observation that lower order cuprates can be induced to displace secondary halides in fair yields under the appropriate experimental conditions. With iodides in particular, reduction and elimination pathways become prominent at higher temperatures thereby drastically lowering yields.

The stereochemistry which accompanies 1,3-substitution reactions of higher order cyanocuprates with propargylic derivatives has also been examined recently. Okamura *et al.*, as part of their intensive studies on vitamin D chemistry,[83] found the reaction of the functionalized hydrindane **59** to proceed with *anti*-selectivity,[84] in consonance with the actions of other organocuprates on related structures.[85] Each isomer of propargyl benzoate **59** was treated with t-Bu$_2$Cu(CN)Li$_2$ to provide an allene **60** as shown, signifying *anti* attack, with yields and diastereomeric purities as indicated.



5. *Thermal stability.* One of the major commonly acknowledged limitations of most lower order cuprates concerns their thermal instability, a parameter which usually varies as a function of the number and type of ligands on Cu. Decomposition of Cu(I) species, at least in the specific case of n-BuCu·P(*n*-Bu)$_3$, has been shown to proceed via elimination of CuH giving equal amounts of 1-butene and butane.[86] The latter hydrocarbon is formed from the reaction of the CuH produced with the starting alkyl copper. To discourage breakdown, both mixed and hetero ligand-containing reagents have been developed over the past decade or so. Their use in isolated synthetic operations, however, does not allow a true evaluation of their stability, as differences in reactivity (vs homocuprates) cannot be easily factored out. In what can only be interpreted as an "eye-opening" investigation of this issue, Bertz and Dabbagh devised a protocol for testing most of the established, as well as recently introduced, organocopper reagents.[87] Measurements were made at −50, 0 and 25°, which consisted of quenching each sample with excess PhCOCl. This quantitative comparison is effective owing to the rapidity of reaction between cuprate and substrate, thus negating any misinterpretation of stability for reactivity. Their results, summarized in part in Table 9, are most enlightening and imply that a number of ligands reputed to impart thermal longevity are actually deleterious at certain temperatures.[88] While development of both novel and highly stable lower order heterocuprates (e.g. Li(Ph$_2$P)CuR and Li[(c-C$_6$H$_{11}$)$_2$N]CuR) provided the impetus for this study, the higher order, mixed species n-Bu$_2$Cu(CN)Li$_2$ was also tabulated. As we had suspected earlier,[41] n-Bu$_2$Cu(CN)Li$_2$ is more stable, particularly at ambient temperatures, than e.g. n-Bu(CN)Li, n-BuCu·Ligand, and even n-BuCu(SPh)Li. Thus, these cyanocuprates of recent vintage, R$_2$Cu(CN)Li$_2$, enjoy the enviable position of possessing seemingly conflicting physical properties: excellent stability *and* reactivity. As yet, no other organocopper reagent as an agent for effecting *both* substitution and addition reactions in high yields can make this claim.

Table 9. Thermal stability of n-butylcopper reagents. Yield (%)[a] of PhCOBu after 0.50 h at temperature T(°C)

Reagent	-50	0	25
Li(CN)CuBu$_2$	99	95	84
Li(CN)CuBu	97	92	60
CuBu [b]	94	5	0
LiCuBu$_2$ [b]	96	89	82
Li(*t*-BuCC)CuBu	100	92	89
(Bu$_3$P)CuBu	100	92	0
Li(PhS)CuBu	100	19	0
Li(Ph$_2$P)CuBu [c]	90	99	95

[a] Measured by glc calibrated with n-dodecane as internal standard after quenching the reagent with excess PhCOCl.

[b] Also present was 1 equiv. of LiI.

[c] Also present was 1 equiv. LiBr.

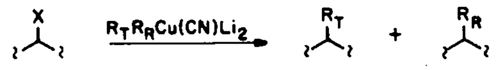
(6) *Selectivity of ligand transfer*. Quite often the merit of a reaction in organic synthesis is based on yield. In reactions of organocuprates, yield optimization may not only be dependent on substrate, but may reflect the quantity of reagent required as well. Lower order homocuprates, in most cases, would necessarily suffer in this regard as one of the ligands R$_T$ is usually not transferred from the unreactive organocopper by-product (R$_T$Cu) and is ultimately lost upon work-up, presumably as R$_T$H. Such wasting of (potentially valuable) ligands may be averted by forming a mixed cuprate R$_T$R$_R$CuLi where a residual ligand, R$_R$, replaces one equivalent of R$_T$. Common residual or "dummy" ligands are those of metalated acetylenes, or are anions of heteroatom-containing species where backbonding or strong sigma bonding to Cu is present. As stated earlier (*vide supra*), a primary advantage for using lower order reagents formed from cuprous cyanide is that the CN moiety (an R$_R$) is already attached to copper. This concept of R$_T$ preservation has also been extended to higher order reagents where a means of ligand conservation would also be of significant impact. The hope, of course, is that the synthetic advantage gained from utilization of a more highly mixed, higher order cyanocuprate (eqn 5), would not be compromised by severely diminished reactivity or competitive transfer of the intended residual ligand.

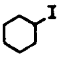
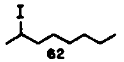
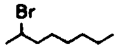
$$\left.\begin{array}{l} \mathrm{R_RLi + Cu(I) \longrightarrow R_RCu \xrightarrow{R_TLi} R_TR_RCuLi} \\ \mathrm{R_TLi + CuCN \longrightarrow R_TCu(CN)Li} \end{array}\right\} \text{lower order cuprates}$$

$$\begin{array}{l} \mathrm{2\,R_TLi + CuCN \longrightarrow R_{T_2}Cu(CN)Li_2} \\ \mathrm{R_RLi + CuCN \longrightarrow R_RCu(CN)Li \xrightarrow{R_TLi} \underset{\mathbf{61}}{R_TR_RCu(CN)Li_2}} \quad \cdots\cdots(5) \end{array}$$

With this goal in mind, we first directed our efforts toward finding a suitable non-transferrable ligand for reactions of **61** with secondary halides (Table 10). Since a phenyl group shows little tendency to transfer from Ph$_2$Cu(CN)Li$_2$ in these reactions (*vide supra*), it was reasonable to postulate that it might function as a residual ligand. Hence, treatment of cyclohexyl iodide with n-Bu(Ph)Cu(CN)Li$_2$ indeed showed a selectivity (21 : 1) favoring n-Bu transfer. A Me group was also thought to have potential as R$_R$ due to its reluctance to transfer at low temperatures. Exposure of iodocyclohexane to n-Bu(Me)Cu(CN)Li$_2$ showed excellent selectivity of 60 : 1, delivering an n-Bu over methyl ligand. Acyclic substrates were also examined. For the reaction of 2-iodooctane with Et(Me)Cu(CN)Li$_2$, exclusive delivery of "Et$^-$" was observed within the limits of VPC detection. With 2-bromooctane, Me transfer was more competitive since this coupling requires higher reaction temperatures. Unfortunately, all attempts to find an R$_R$ such that R$_T$ = a vinyl ligand would be selectively released from Cu have not been successful to date.[114] Both vinyl(Me)Cu(CN)Li$_2$ and

Table 10. Selectivity of transfer; reactions of $R_TR_RCu(CN)Li_2$ with secondary haldies



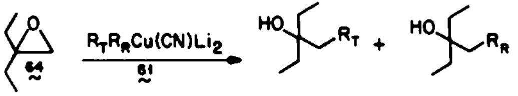
Substrate	R_T	R_R	Conditions	Ratio R_T : R_R
	n-Bu	Ph	THF, -50°C, 1 h	21 : 1
"	n-Bu	Me	THF, -50°C, 2.5	60 : 1
 **62**	Et	Me	THF, -78°C, 1 h	1 : 0
62		Me	THF, 0°C, 6 h	1 : 5.6
62		Me	Et_2O, 0°C, 6 h	1 : 3.9
62		Ph	THF, 0°C, 6 h	2.4 : 1
	Et	Me	THF, 0°C, 12 h	10-12 : 1

vinyl(Ph)Cu(CN)Li_2 are unsatisfactory reagents, the former preferring Me over vinyl transfer (5.6 : 1), the latter affording extensive amounts of the product of reduction. Table 10 summarizes these results which suggest that a simple Me ligand is a suitable R_R for all cases of primary alkyl group transfer. Most reactions of R_T(Me)Cu(CN)Li_2, **63**, involved preparing this reagent by admixture of R_TLi, MeLi and CuCN in THF initially at −78° followed by warming until a solution was formed. In cases where R_TLi is unstable to temperatures > −78°, one may chose to solubilize the CuCN by first forming MeCu(CN)Li, which stays in solution at −78°, to which is then added R_TLi.

As for epoxides (e.g. **64**, Table 11), the selectivity of transfer in $R_TR_RCu(CN)Li_2$ was variable, depending upon the nature of cuprate **61**. Interestingly, a phenyllithium derived cuprate R_T(Ph)Cu(CN)Li_2 gave better ratios of R_T : Ph transfer than were observed with **63**. As the reactivity of $R_TR_RCu(CN)Li_2$ increases, as with R_T = s-Bu, a greater preference for R_T transfer is observed. Although a vinyl group is released over phenyl from vinyl(Ph)Cu(CN)Li_2, the modest 1.5:1 ratio is obviously of little synthetic promise. Thus, a phenyl moiety seems to be the R_R of choice for most substitution reactions of **61** with oxiranes, although $R_R = CH_3$ may give comparable results in some cases (compare entries 2 vs 6).

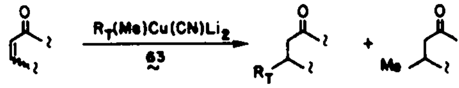
In searching for the appropriate ligand R_R such that selective transfer of R_T from **61** to enones would be encouraged, it was clear from Table 6 that both phenyl and vinyl groups would not be wise choices, as both undergo 1,4-addition at low temperatures. A quick look at cyclohexenone, where R_R = Me, R_T = n-Bu revealed that not an overly impressive 11–12:1 ratio of n-Bu:Me transfer took place even at −85°. Since yields for these conjugate additions are generally high, this result certainly seemed tolerable and a more thorough study with R_R = Me was undertaken. From the seven cases outlined in Table 12, several features deserve comment. Reactions of **63**, (R_T = a primary alkyl group) with simple cyclic and acyclic enones give similar ratios. As the steric bulk of R_T increases from a primary to either a secondary or tertiary alkyl ligand, 100% selectivity of R_T transfer is witnessed. As alluded to earlier (Section II.D.3.b), the reaction of cyclopentenone with s-Bu(Me)Cu(CN)Li_2 required THF as solvent rather than the usually preferred Et_2O medium. This modification significantly reduced the activity of the reagent, an essential feature for directing exclusive 1,4-addition. All attempts at using s-Bu(Me)Cu(CN)Li_2 in Et_2O at −78° led instantaneously to a multitude of products, as judged by TLC. However, the combination of a second "R_R" and competition by THF for complexation of Li^+ led to a

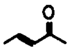
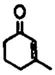
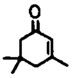
Table 11. Selectivity of transfer; reactions of $R_TR_RCu(CN)Li_2$ with 1,1-diethyl ethylene oxide, 64



R_T	R_R	Conditions	Ratio R_T: R_R
Et	Me	THF, -40°C, 4.5h	5.5 : 1
n-Bu	Me	THF, -40°C, 2 h	8 : 1
s-Bu	Me	THF, -50°C, 1.5 h	27 : 1
Ph	Me	THF, 0°C, 3.5h	1 : 2.2
vinyl	Me	THF, 0°C, 2 h	1 : 2.6
n-Bu	Ph	THF, -20°C, 2 h	14 : 1
vinyl	Ph	THF, 0°C, 5h	1.5 : 1

Table 12. Selectivity of transfer; reactions of $R_T(Me)Cu(CN)Li_2$ with enones

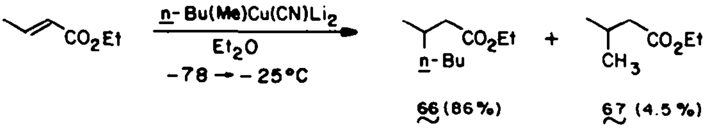


Substrate	R_T	Conditions	Ratio R_T : Me
	*n*-Bu	Et_2O, -85°C, 1 h	11-12 : 1
	*n*-Bu	Et_2O, -78°C, 3 h	12 : 1
	*t*-Bu	Et_2O, -25°C, 0.25 h	1 : 0
 65	*s*-Bu	THF, -78°C, 0.5 h	1 : 0
65		THF, -78°C, 1 h	142 : 1
65		Et_2O, -78°C, 0.3h	31.5 : 1
		Et_2O, -50°C, 3.5h	37 : 1

successful outcome. The implication of this particular example is that there exists considerable latitude for "fine tuning" of the experimental conditions which best accommodate both substrate and reagent.

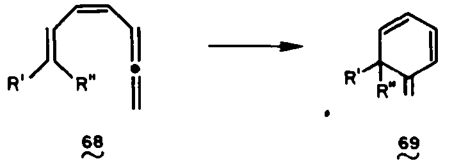
Both entries 5 and 7 in Table 12 are also especially noteworthy in several contexts. The ability to deliver a vinyl residue with such a degree of selectivity is unsurpassed in mixed cuprate chemistry. Posner has observed a similar trend for vinyl(Me)CuLi where a 25:1 vinyl:Me ratio was noted.[89] The excellent reaction efficiency, taken together with this new potential for ligand conservation, should have immediate impact in synthesis. Perhaps even more intriguing is the curious switch in ligand release (i.e. vinyl over Me) upon going from substitution to conjugate addition processes. We had hoped, somewhat naively, that differences in aggregation state as a function of solvent might be responsible for this turnabout.[90] However, the observed preference for Me over vinyl in displacement reactions, while the reverse is observed for 1,4-additions, is independent of solvent (Table 10, entry 4 vs 5; Table 12, entry 5 vs 6). In fact, vinyl(Me)Cu(CN)Li_2 gives a remarkable 142:1 vinyl:Me transfer *in THF!* The corresponding reaction in Et_2O afforded a 31.5:1 ratio under similar conditions.

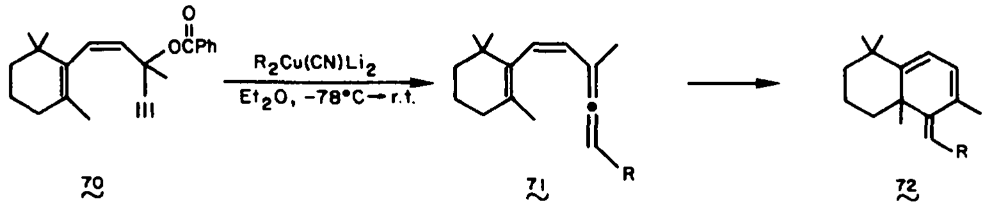
A single experiment, designed to gauge the generality of R_T(Me)Cu(CN)Li_2 as an effective means of limiting the number of equivalents of R_T needed in reactions with enoates, was conducted on ethyl crotonate. As shown below, a useful 19:1 ratio of n-Bu:Me transfer (**66**:**67**, respectively) was seen, even better than that described for simple enones (cf. Table 12, entries 1 and 2).



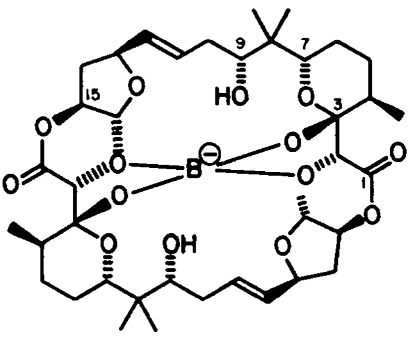
7. *Applications in Synthesis.* Although methodology based on higher order, mixed cuprates has only recently appeared in print, already it is of proven value in synthesis. The appeal derives from the simplicity of reagent formation, their increased reactivity relative to traditional cuprates, and in most circumstances, predictable regio- and stereochemistry. Quite often, these reagents have had the opportunity to demonstrate their potential only after more customary organocuprates failed to give satisfactory results. Yet R_2Cu(CN)Li_2 may be prepared as or more easily than R_2CuLi or its many analogs, and their reactions usually require fewer equivalents per substrate.

Okamura *et al.* have used higher order cuprates in 1,3-substitution reactions on propargylic systems.[91] As part of a synthetic strategy directed towards preparation of vitamin D analogs and 11-*cis*-retinoids, vinylallenes **68** were envisioned as potential intermediates. Interestingly, they undergo spontaneous electrocyclization to trienes **69**, rather than the expected product of a [1,7]sigmatropic shift. For example, treatment of 7-*cis*-propargyl benzoate **70** with a cuprate, as shown below, provides the substituted vinyl allene **71** (R = n-Bu, 77%; R = t-Bu, 79%; R = Ph, 60%). A subsequent six-electron electrocyclization yielded drimatriene **72**.



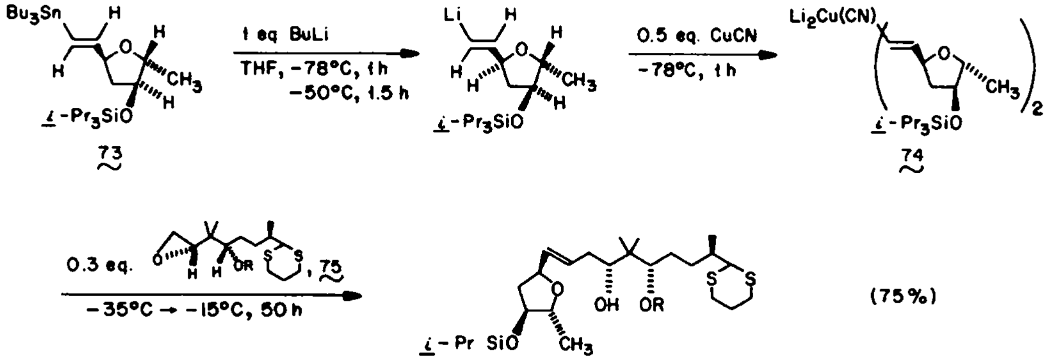


In a recent total synthesis of the antibiotic (+)-Aplasmomycin, Corey *et al.*[92] described a convergent and stereocontrolled construction of the C(3)–C(17) fragment, in chiral form, involving



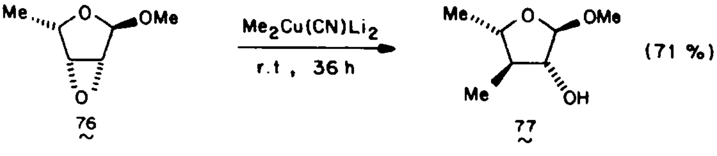
Aplasmomycin

as a key step epoxide opening *via* a higher order cyanocuprate. The vinylstannane 73, following lithiation with one equivalent of n-BuLi, was added to 0.5 equiv of cuprous cyanide affording cyanocuprate 74. Exposure of this reagent to epoxide 75 gave the functional equivalent of the C(3)–C(17) segment of Aplasmomycin in 75% yield (89% based on recovered epoxide).



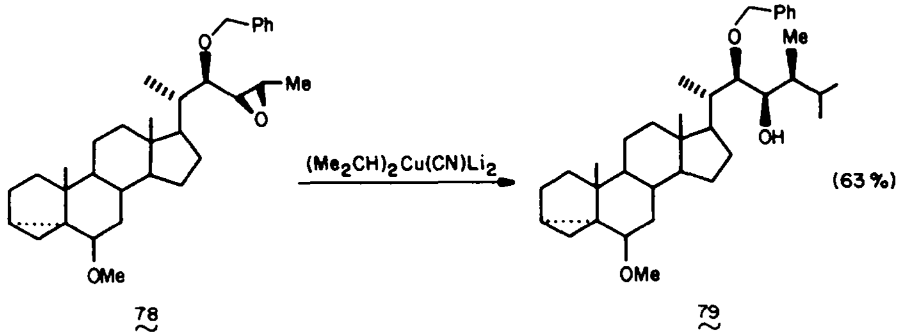
R= methylthiomethyl

In a formal total synthesis of Pseudomonic Acid C, Fleet and Shin take advantage of the regio- and stereospecificity associated with higher order cyanocuprate-induced epoxide openings for construction of the requisite chiral side-chain.[93] The chiral epoxide 76, prepared from methyl-α-L-arabinofuranoside in three steps, gave disappointing yields when treated with the Gilman reagent, Me_2CuLi. However, when the dimethylcyano cuprate was used, regiospecific ring opening to the C-3-methyl alcohol 77 occurred in 71% yield.



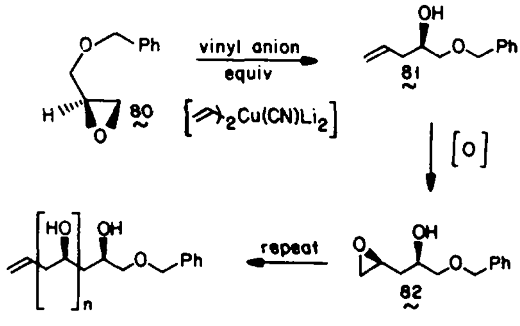
Another example of epoxide opening utilizing $R_2Cu(CN)Li_2$ is provided by Oshima's group in their approach to a stereoselective synthesis of the side-chain of Brassinolide, a plant growth steroidal hormone.[94] Treatment of epoxide 78 with the cyanocuprate derived form i-PrLi produced alcohol 79 in a regio- and stereoselective manner.

In our group, we have recently completed development of a reiterative, two-step sequence using higher order cuprates for construction of chiral all *syn*-1,3-polyols, characteristic segments of the polyene macrolides.[95] These natural products, typified by Amphotericin B,[96] Roflamycoin,[97] and the Mycoticins,[98] are potent antifungal agents of considerable synthetic interest.[95] Our contribution

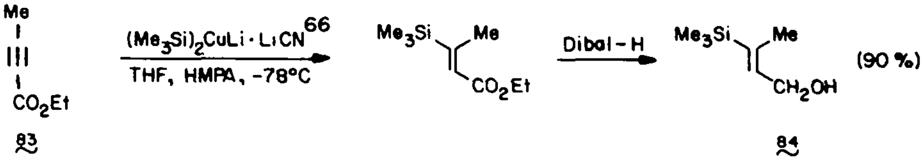


has at its foundation an efficient preparation of homoallylic alcohols by virtue of oxirane cleavage using close to a stoichiometric amount of the appropriate vinyllithium-based cuprate. Hence, opening of optically pure epoxide **80**[99] with $(vinyl)_2Cu(CN)Li_2$ led to homoallylic alcohol **81** in >86% isolated yield. Epoxidation *via* a cyclic carbonate (a modification of the Cardillo procedure[100]) led predominantly (10–14:1) to **82**, which is now suitable for repetition of the sequence as summarized in Scheme 1. Thus, in principle, any number of *syn*-1,3-hydroxyl residues, in optically pure form, can be realized.

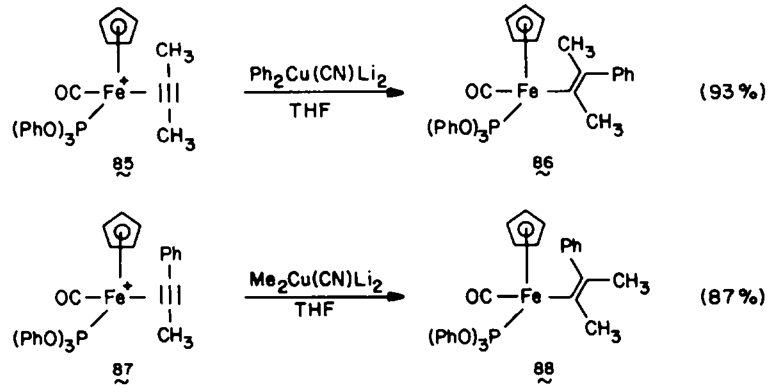
Scheme 1.



A recent paper by Marshall[101] cites an improved synthesis of (*E*)-3-trimethylsilyl-2-buten-1-ol **84**, using methodology first introduced by Fleming (*vide supra*).[60,61] As organocopper reagents are well known to add across acetylenes,[36f] Marshall felt that one approach might entail the reaction of a silylcuprate with ethyl tetrolate **83**. Several organocopper reagents, however, failed to give satisfactory results. For example, $Me_3SiCu{\cdot}LiBr{\cdot}Me_2S$ showed insufficient reactivity at low temperatures and formed a mixture of stereoisomers upon warming. Likewise, $Me_3SiCu(CN)Li$ and $Me_3SiCu{\cdot}LiI{\cdot}Me_2S$ gave undesirable *E*:*Z* mixtures. Yet, when the higher order disilylcyanocuprate, formed by addition of two Me_3SiLi to one CuCN, was reacted with ethyl tetrolate at −78°, the kinetic addition product (*E* isomer) was obtained as the only isomer. Reduction of the enoate so formed using diisobutylaluminum hydride produced the allylic alcohol in 90% overall yield from **83**.

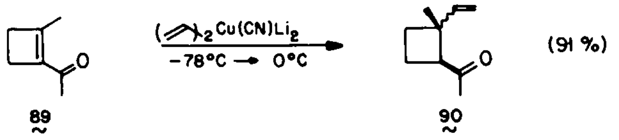


In an investigation on nucleophilic additions to unsaturated organic ligands π-coordinated to iron, Reger *et al.* found that higher order mixed cyanocuprates gave significantly better yields than "normal" organocuprate reagents.[102] The product results from a *trans*-addition to the alkynyl complex, as determined by independent syntheses of both isomers. Thus, treatment of **85** with $Ph_2Cu(CN)Li_2$ gave (*E*)-**86**, whereas introduction of **87** to $Me_2Cu(CN)Li_2$ produced the *Z*-isomer

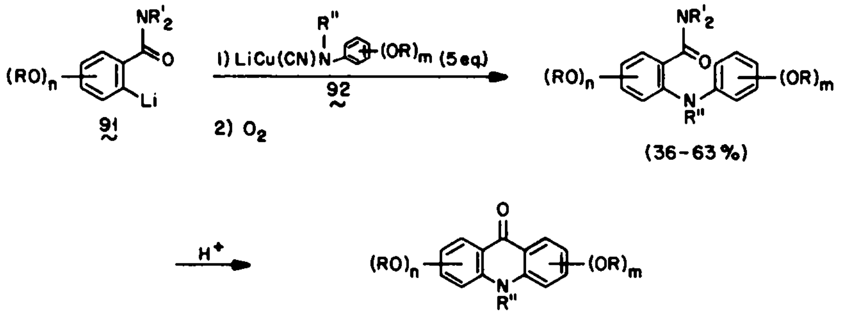


88, both reactions proceeding with excellent efficiency. The latter product was characterized by X-ray crystallography.

Negishi's recently completed synthesis of grandisol relied heavily on the conjugate addition of "vinyl$^-$" to an α,β-unsaturated ketone.[103] Numerous attempts to reach product **90** using lower order cuprates gave disappointing results. Treatment of **89** with $(\text{vinyl})_2\text{Cu(CN)Li}_2$, however, gave the 1,4-product in high yield, albeit as a 2:1 mixture of *cis* and *trans* isomers.



A series of acridone alkaloids have been synthesized by Snieckus *et al.*[104] via oxidative coupling of ortho-lithiated benzamides **91** with cyanocuprates **92**. We interpret this process as involving the intermediacy of a higher order, highly mixed cuprate composed of at least three unique ligands. Yields obtained are significantly better using CuCN rather than CuCl as the source of Cu(I). The latter salt would give rise to a lower order cuprate, which perhaps accounts for the observed differences in efficiency. A non-trivial finding pointed out by these authors is that, with ligands reluctant to couple during the oxidative exchange, cyano ligand transfer can occur, although in low yield. The impressively rapid architectural buildup associated with this approach provides one of the first examples of C–N coupling using higher order cuprates, and is perhaps indicative of future advances to be made with reagents of related novel composition (i.e. $[\text{R}_1\text{Cu(XR}_2\text{)(CN)Li}_2]$, X = heteroatom).



(E) *Copper hydrides*

The facility with which ligands attached to Cu are transferred to organic substrates has encouraged examination of their potential to effectively deliver hydride in an analogous fashion. Various types of hydrido copper complexes have been prepared, including CuH itself, usually in complexed form (with pyridine[105] or Ph_3P[106]). Monnier[107] has published a preparation of CuAlH_4, however, its utility is quite limited by its thermal instability above −80°. More recently, reagents of general formula LiCuHR have become popular,[108] where R = O-t-Bu, SPh, and 1-pentynyl, for purposes of effecting conjugate addition of "H^-" to enones. Masamune *et al.*,[109] likewise depolyed similar cuprates (R = alkyl, alkynyl) for reduction of halides and mesylates as part of their synthesis of the macrolide aglycone Methynolide. Semmelhack[110] subsequently found that another useful combination of either $LiAl(OCH_3)_3H$ or $NaAlH_2(OCH_2CH_2OCH_3)_2$ with CuBr will deliver hydride in a conjugate sense to α,β-unsaturated carbonyl compounds.

All of the above studies, relate as well to Ashby's disclosure in 1974 on the preparation of the first stable complex metal hydride of Cu, $LiCuH_2$.[111] Its attainment follows from treatment of Gilman's Me_2CuLi with LAH in Et_2O, initially at low temperatures, to afford the desired

$$LiCuMe_2 + LiAlH_4 \xrightarrow[-78 \rightarrow rt]{Et_2O} LiCuH_2 + LiAlMe_2H_2$$

material as a relatively stable yellow solid. Subsequent to this early disclosure, the same school described a series of complexes of empirical formula $Li_nCu_mH_{(n+m)}$ by applying the same basic, yet successful approach.[112] Thus, both lower and higher order species corresponding to $LiCu_2H_3$, $Li_2Cu_3H_5$, $LiCuH_2$, Li_2CuH_3, Li_3CuH_4, Li_4CuH_5, Li_5CuH_6 were all characterized, the data on which

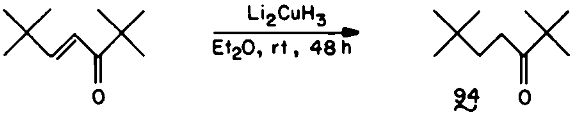
$$(n+1)CH_3Li + (m)CuI \xrightarrow{Et_2O} Li_nCu_mH_{(n+m)} + LiI$$

included determinations of their relative thermal stabilities. That these hydrides are indeed individual discrete reagents, as opposed to simply mixtures of either [$CuH + LiCuH_2$] or [$LiH + LiCuH_2$], follows from the findings that (a) should CuH be present, it would decompose above −80°; (b) DTA–TGA measurements indicated that each reagent decomposes at a different temperature ($LiCu_2H_3$ and $Li_2Cu_3H_5$, ~0°; $LiCuH_2$, 70°; Li_2CuH_3, 90°; Li_3CuH_4, 110°; Li_4CuH_5, 120°; Li_5CuH_6, 140°); (c) the presence of LiH was not detected in the X-ray analyses of these hydrides; (d) the solubility properties of each are unlike those of CuH and LiH in ethereal media, and (e) the reducing power of each in substitution or Michael addition processes is unique (*vide infra*).

In their full account of this work, which included an assessment of the synthetic potential of the various reagents $Li_nCu_mH_{(n+m)}$, Ashby *et al.*[113] detail the virtues, in particular, of Li_4CuH_5 and Li_2CuH_3. The former is an excellent choice for halide reductions, apparently being even more reactive than LAH in this regard, while the latter is a valuable Michael donor of hydride (**93**→**94**). The following examples illustrate the potential of these complexes.

$$\underline{n}\text{-}C_8H_{17}\text{-}X \xrightarrow[THF,\ rt]{Li_4CuH_5} \underline{n}\text{-octane } (\%)$$

X = OTs	99
X = Cl	99
X = Br	100
X = I	100



93

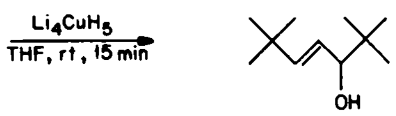
94

93% 1,4

(6% 1,2)

In addition, Li_4CuH_5 represents a powerful carbonyl reducing agent. In reactions of 4-t-butylcyclohexanone, introduction of this hydride source as a slurry in THF affords a product

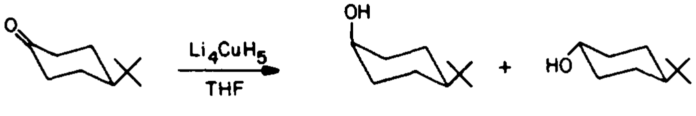
93



95 % 1,2

(5 % 1,4)

mixture rich in the diequatorial isomer. When employed as a solution in the same solvent, considerable erosion in selectivity is noted. The authors suggest that differences in THF solubility are due to the manner in which Li_4CuH_5 was prepared. Rigorous removal of complexed Et_2O imparts limited solubility properties, while simple filtration of the originally heterogeneous mixture in Et_2O followed by addition of THF results in complete dissolution.



slurry	15	85
solution	45	55

III. CONCLUDING REMARKS

It is hoped that by having highlighted this relatively new branch of organocopper chemistry, the potential of higher order organocuprates to augment prior art in a meaningful way is evident. We would claim, however, that the concept of "higher order" organocuprates is still at an early stage of development. Many challenging, complex problems both in this area and that of lower order cuprate reagents remain, especially concerning the issues of structure and mechanism. We suspect, in light of the continuing popularity of cuprate chemistry, that our present boundaries of knowledge in this field are surely temporary, and many fascinating contributions have yet to be made.

Note Added in Proof. As a result of publication delays at Pergamon Press, the timely appearance of recently submitted contributions to Tetrahedron Reports has been slowed considerably. During the intervening months, however, we have completed a study of copper(I) halide derived organocuprates *via* ^7Li NMR spectroscopy. Using various MeLi:MeCu ratios as a model, this analytical technique has quite unexpectedly demonstrated that "R_3CuLi_2" is not a discrete species, its composition being a function of solubilized lithium salts and solvent(s). In *all* cases examined (i.e. with and without LiI present, in either THF or Et_2O), a very healthy percentage of free MeLi is present. From these spectroscopic observations, as well as chemical tests, it now appears that the chemistry of a "higher order" cuprate originating from a copper halide, in reality, is due to that of a "lower order" cuprate plus free organolithium. Hence, the interpretational remarks offered within Section (B) of this overview must be considered in light of these recent findings; cf. B. H. Lipshutz, J. A. Kozlowski, C. M. Breneman, submitted for publication.

Acknowledgements—We are pleased to acknowledge financial support for work carried out in the laboratories of BHL, as cited in the text and references, by grants from the National Science Foundation (CHE-83-02421), and the donors of the Petroleum Research Fund, administered by the American Chemical Society. Our thanks go to Prof. E. C. Ashby (Georgia Institute of Technology), and W. H. Okamura (UC Riverside), Drs. D. M. Floyd (Squibb) and S. H. Bertz (AT and T. Bell Laboratories) for most helpful comments and valuable suggestions regarding this review.

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the reaction is low (20%), the product 9-(2-octyl)-9,10-dihydroanthracene has been isolated with 54% ee, which corresponds to 68–70% inversion. This result appears to be contrary to our findings; it has been reported that allyl- and benzyl*lithium* to proceed with inversion on secondary halides. See E.-I. Negishi, *Organometallics in Organic Synthesis*, Vol. 1, p. 110. Wiley, New York (1980).

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