Tetrahedron Vol. 45, No. 2, pp. 425 to 434, 1989
Printed in Great Britain.

0040-4020/89 \$3.00+.00

ORGANOCOPPER REAGENTS IN DIMETHYL SULFIDE[1]

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(*Received in USA* 13 *June* 1988)

Abstract: Organocopper(I) reagents, RCu, are both more stable and more reactive when prepared in dimethyl sulfide instead of ether or tetrahydrofuran. A wide range of Li reagents has been investigated with good results, as has a selection of Grignard reagents. Excellent yields of products are observed with typical substrates such as α,β-unsaturated ketones and acid chlorides.

Historical Introduction

Corey and Carney prepared divinylcopper lithium from CuI in diisopropyl sulfide, diluted the solution with tetrahydrofuran (THF), and added an enone dissolved in diethyl ether.[2] In a similar manner Clark and Heathcock prepared divinylcopper lithium by adding a THF solution of vinyllithium to a solution of CuI in 2 : 1 diethyl ether/dimethyl sulfide (ether/DMS).[3] They reported that "the use of dimethyl sulfide in place of diisopropyl sulfide gives a considerably easier work-up procedure."[3]

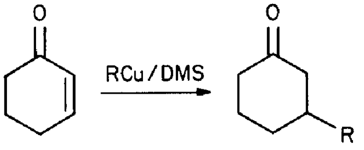
House and coworkers investigated the DMS complexes of CuCl, CuBr, and CuI and found that, while they were insoluble in a typical organic solvent such as ether, solutions were obtained when additional DMS was present.[4] Their precursor of choice was $CuBr \cdot SMe_2$, and cuprates were prepared in ether/DMS. Substrates were added in ether so that the final solutions were about one-third DMS. Following this work, a number of groups have used CuI/DMS in combination with ether or THF.[5–9] In some cases one equiv of alkyllithium was used[5–7] and in some cases two.[5,8,9] In all cases DMS was the minor component of the solvent system, sometimes <1%.

Before our work the properties of organocopper reagents in neat (or nearly neat) DMS had not been studied. In the course of our investigation of the effects of solvent on asymmetric induction with amidocuprates,[10] we added a DMS solution of PhLi to an equimolar solution of CuI in DMS and obtained a light yellow solution, rather than the dark gray suspension observed when PhLi was added to a suspension of CuI in ether. Intrigued by this result, we decided to survey RCu/DMS reagents in order to study their properties and ascertain their potential for usefulness.

Results and Discussion

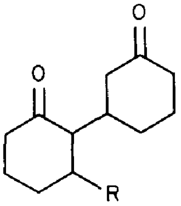
Choice of Precursor

We have shown that the preparation of organocopper reagents as well as their subsequent reactivity depends upon the precursor Cu(I) salt and the solvent (ether *vs.* THF).[11] Table 1 summarizes the results of experiments in which 2-cyclohexenone (**1**) was treated with BuCu reagents, prepared from equimolar amounts of BuLi and various Cu(I) salts in DMS, THF or ether at –50 °C (0.25 h). The yields of 3-butylcyclohexanone (**2a**) and other products were measured after 1 h at –78 °C. For the reactions run in ether or THF, yields were also measured after a further 1 h at 0 °C, as substantial starting material remained after 1 h at –78 °C in these solvents. In DMS significant **1** was recovered in only one case (CuOTf, see footnote *c*). With $CuBr \cdot SMe_2$ or CuOTf in DMS, substantial amounts of "double Michael reaction"[12–14] product **3a** were observed (*ca.* 40% based on **1**, 1 : 10 ratio of stereoisomers[15]). Traces of **3a** with a 1 : 2 ratio of the same isomers were observed for BuCu/LiI in some experiments. With CuCN a significant amount (21%) of 1,2-adduct, 1-butylcyclohex-2-en-1-ol, contaminated the product. Annealation of the CuCN/DMS reagent at 0 °C for 0.1 h before the addition of **1** at –78 °C eliminated the 1,2-adduct; however, the yield of **2a** (76%) was approximately the same. To within ±1%, CuBr gave the same results as $CuBr \cdot SMe_2$ in DMS. Surprisingly, after 1 h at 0 °C in ether, BuCu/LiI gave a 95% yield of **2a**.



1

2a, R = nBu
b, R = tBu
c, R = Ph
d, R = Me
e, R = Pe
f, R = Cy
g, R = Allyl



3a, R = nBu
b, R = Ph

Table 1. The Reaction of BuCu Reagents from Various Precursors with 2-Cyclohexenone.

	Yields (%)[a] of 2a [or 3a]					
Cu(I) Salt	DMS		THF		ether	
	−78 °C	[%3a][b]	−78 °C	0 °C	−78 °C	0 °C
CuI	99	[<1]	24	40	71	95
$CuBr \cdot SMe_2$	63	[37]	14	38	36	65
CuOTf	21[c]	[38]	3	2	1	<1
CuCN	79	[<1]	4	60	76	73

[a] Measured by glc using the internal standard method. Reaction time was 1 h at each temperature. 2a = 3-butylcyclohexanone. [b] Product from conjugate addition of 3-butylcyclohexanone enolate to 1 at −78 °C. [c] A 34% yield of recovered 1 was also present.

The solubility properties of the Cu(I) salts were important in the preparation of the *t*BuCu/DMS reagent. While all those examined (*cf.* Table 1) except CuCN were soluble in DMS (0.1 M) at room temperature, only CuI remained in solution at −50 °C. Fortunately, a 0.1 M solution of CuI in DMS was homogeneous at −78 °C. This property facilitated the preparation of *t*BuCu at −78 °C, a temperature where it was stable. When 1 was added to the *t*BuCu reagent after 1.0 min at −78 °C, a small amount of 1,2-adduct was observed along with 1,4-adduct 3-*t*-butylcyclohexanone (2b), which indicated that the reagent was not completely formed in this time. At least 1.5 min (usually 0.1 h) was allowed in subsequent experiments, and no 1,2-adduct was observed.

Thermal Stability Studies

The thermal stabilities of *n*Bu and *t*Bu copper reagents prepared from CuI in DMS, THF, or ether can be compared by using the data in Table 2. In each case the Li reagent was added to CuI in 10 mL of the specified solvent at −75 °C. After 30 min at −75 °C, the reaction mixture was sampled (dry ice-cooled syringe), and then the reaction vessel was placed in a −50 °C bath. The sampling procedure was repeated after 30 min at −50 °C and again after 30 min at 0 °C. The samples (2 mL) were added to 2 equiv of benzoyl chloride in THF (2 mL) at −78 °C (30 min). After slowly warming to ~0 °C (15 min) and stirring at 0 °C (15 min), the samples were quenched with 3 M aqueous ammonium chloride. The amount of *n*-butylphenylketone (4a) or *t*-butylphenylketone (4b) in a sample represents the amount of viable copper reagent present in the reaction mixture.

Table 2. Thermal Stabilities of *n*-Butyl and *t*-Butyl Organocopper Reagents.

	Yields (%)[a,b] at Temp.:		
Reagent	−75 °C	−50 °C	0 °C
*n*BuCu/DMS	97	100	96
*n*BuCu/THF	76	79	65
*n*BuCu/ether	83	92	7
*t*BuCu/DMS	95	<1	<1
*t*BuCu/THF	66	73	<1
*t*BuCu/ether	17	9	<1

[a] 4a (from *n*BuCu) or 4b (from *t*BuCu), measured by glc.
[b] Reaction time was 30 min at each temperature.

Table 3. Thermal Stabilities of Phenyl Organocopper Reagents.

	Yields (%)[a,b] at Temp.:		
Reagent	−50 °C	0 °C	25 °C
PhCu/DMS	100	99	98 (71)[c]
PhCu/THF	86	97	95 (53)[c]
PhCu/ether	57	42	58 (24)[c]

[a] Benzophenone, measured by glc using the internal standard method. [b] Reaction time was 30 min at each temperature, except for parenthetical values. [c] Reaction time was 20 h.

This method is based upon the assumption that the yields from the reagents and excess PhCOCl are quantitative. In light of the yields in the first entries of Tables 2 and 3 and our previous studies,[16] this appears to be a useful assumption (*vide infra*, Table 4 in *Scope and Limitations of the Reagents*). When the yields improved upon warming from −75 °C to −50 °C, the reagents had not been completely formed at −75 °C. The *n*BuCu / DMS reagent had remarkable thermal stability: only 4% of it decomposed during 30 min at 0 °C. While it was not stable at −50 °C, *t*BuCu / DMS gave the best yield (95%) of **4b** at −75 °C.

Whitesides *et al.* have shown that *n*-butylcopper(I) decomposes by a β-hydride elimination mechanism.[17–19] The order of stability of the *n*BuCu reagents (note 0 °C data) according to solvent is DMS > THF > ether, which can be rationalized by the observation that this is also the expected order of ligand-Cu bond strength (*vide infra, The Nature of the Reagents*). The coordination of solvent molecules blocks sites that must be vacant in order for H to be transferred from the β-carbon to the Cu. A similar stabilizing effect has been observed for phosphines.[20] In every solvent studied, the *t*-butyl copper reagent is less stable than the corresponding *n*-butyl reagent, a consequence of the greater number of β-H atoms in the *t*-butyl group. Curiously, both *S*-heterocuprates and *N*-heterocuprates exhibited the opposite order of stability, *viz.*, the *t*-butyl heterocuprates were *more* stable than the corresponding *n*-butyl reagents.[16]

The thermal stabilities of the PhCu reagents prepared from CuI were assayed in a similar manner with the yields of benzophenone (**4c**) summarized in Table 3. By comparing the data for 0 °C with the corresponding data in Table 2, it is clear that the order of thermal stability in all three solvents is Ph > *n*Bu > *t*Bu. The Ph reagent is more stable than the Bu ones because it has no β-H atoms, which provide a decomposition pathway with a relatively low activation energy.[17–19] Again, the reagent in DMS is formed completely at low temperature, whereas in THF it is not. Nevertheless, once it is formed, the reagent in THF has comparable thermal stability at 0 °C. After 20 h at 25 °C, however, the superiority of the PhCu · LiI / DMS reagent is established. The non-monotonic nature of the yields in ether may be a consequence of the non-homogeneity of the reagent, which makes representative sampling difficult. In contrast, homogeneous solutions are obtained in DMS and THF. (The BuCu reagents are all non-homogeneous.)

Negligible biphenyl (0.5% or less) was produced during the preparation of PhCu in DMS or THF; however, a substantial amount (33%) resulted from the preparation in ether, which accounts for the low initial yield of **4c** upon treatment with PhCOCl. Even if the initial yield of PhCu in ether is taken into account, the thermal stability is still lowest in this solvent. After 20 h at 25 °C, the yields of additional biphenyl were 6% in DMS, 11% in THF and 20% in ether. The preparation of *n*BuCu in DMS or ether produced a small amount of octane (~5%) as a side-product; however, in THF a significant amount (15%) resulted. During the course of the thermal stability study, a further 10% of octane was observed in THF, whereas trivial amounts were observed in DMS (<1%) or ether (3%). A caveat: adventitious oxygen can never be completely ruled out as the source of the coupling product.[21] Nevertheless, in several studies we have observed more octane from butyl cuprates in THF than in ether[11,22] and more biphenyl from phenyl cuprates in ether.[22] Consequently, we believe they are the result of a fundamental process.

Scope and Limitations of the Reagents

The examples in Table 4 help to delineate the scope of the RCu / DMS reagent. Two of the most important reactions of organocopper reagents are conjugate addition and alkylation, and we have focused on these in our choice of substrates: cyclic and acyclic α-enones (as well as an α-enal) and an aromatic and an aliphatic acid chloride. Unactivated alkyl halides (*e.g.*, 1-iodoheptane, iodocyclohexane) were not alkylated by BuCu / LiI in DMS, and the yield from an activated epoxide was low (*vide infra*). A variety of reagents RCu (R = Me, *n*Bu, *t*Bu, Pe, Cy, Ph, allyl), including primary, secondary, and tertiary alkyl and also aryl, can be prepared in DMS from lithium reagents or Grignard reagents. In all cases the ratio of RCu to substrate was 1.0.

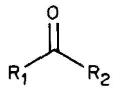
With one exception, the reactions of the RCu / DMS reagents with acid chlorides gave yields of ketones in the range 90-100%. The yields of **4a** and **4c** from PhCOCl and *n*BuCu or PhCu, respectively, were quantitative and the yield of **4b** from PhCOCl and *t*BuCu was nearly so, confirming the assumption underlying the thermal stability studies (*vide supra*). The yield of cyclohexylphenyl ketone (**4d**) from CyCu · MgICl and PhCOCl was limited to 80% by the formation of dicyclohexyl. With pivaloyl chloride, the yield of **4b** from PhCu · LiI was quantitative and the yields of **4e** and **4f** from *n*BuCu / LiI and *t*BuCu / LiI were 93% and 90%, respectively. The yields of ketones from acid chlorides and RCu reagents in other solvents are often significantly lower, and additives may be required.[23]

Two poor yields were encountered among the conjugate additions, *viz.*, the reactions of MeCu/LiI with 2-cyclopenten-1-one and with mesityl oxide. The yields of 3-methylcyclopentanone (**5a**) and 2,2-dimethylpentan-4-one (**4i**), respectively, were improved into the useful range by the inclusion of 2 equiv of chlorotrimethylsilane (TMSCl) and hexamethylphosphoramide (HMPA) (parenthetical values). In those cases where the yields were already good (60-80%), TMSCl/HMPA usually made them quantitative. PhCu·LiI did not alkylate 3,5,5-trimethylcyclohex-2-en-1-one under conditions where it did **1**, thus selective reactions should be possible.

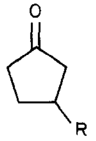
Table 4. Typical Reactions of Organocopper Reagents in DMS.

Reagent	Substrate	Product	Yield (%)[a]	
MeCu / LiI	2-Cyclohexenone (**1**)	**2d**	91[b]	
	2-Cyclopentenone	**5a**	26[c]	(92)[c]
	Mesityloxide	**4i**	33[d]	(81)[c]
	Methacrolein	**4g**	74[b]	(100)[b]
MeCu / MgI_2	**1**	**2d**	92[b]	
*n*BuCu / LiI	**1**	**2a**	100[e]	
	2-Cyclopentenone	**5b**	77[b]	(100)[e]
	Mesityloxide	**4j**	97[c]	
	PhCOCl	**4a**	100[f]	
	*t*BuCOCl	**4e**	93[g]	
*n*BuCu / MgBrI	**1**	**2a**	97[c]	
PeCu / LiI	**1**	**2e**	96[b]	
	Methacrolein	**4h**	63[e]	(100)[e]
CyCu·MgICl	**1**	**2f**	72[e]	(78)[e]
	PhCOCl	**4d**	80[h]	
*t*BuCu / LiI	**1**	**2b**	77[b]	(100)[e]
	2-Cyclopentenone	**5c**	91[b]	
	PhCOCl	**4b**	98[b]	
	*t*BuCOCl	**4f**	90[g]	
PhCu·LiI	**1**	**2c**	90[c]	(100)[i]
	PhCOCl	**4c**	100[f]	
	*t*BuCOCl	**4b**	100[g]	

[a] Measured by glc. Parenthetical yields for reactions run in the presence of TMSCl/HMPA. [b] −78 °C/1 h. [c] −78 °C/1 h, 0 °C/0.1 h. [d] 0 °C/2 h. [e] −78 °C/0.1 h. [f] −78 °C/0.5 h, 0 °C/0.5 h. [g] −78 °C/1 h, −78 °C to 0 °C/1 h. [h] −78 °C to 0 °C/1.5 h. [i] −78 °C/1 h, 0 °C/1 h.



4a, R_1 = nBu, R_2 = Ph
b, R_1 = tBu, R_2 = Ph
c, R_1 = R_2 = Ph
d, R_1 = Cy, R_2 = Ph
e, R_1 = nBu, R_2 = tBu
f, R_1 = R_2 = tBu
g, R_1 = H, R_2 = sBu
h, R_1 = H, R_2 = 2-Octyl
i, R_1 = Me, R_2 = neoPe
j, R_1 = Me,
R_2 = 2,2-Dimethylhexyl



5a, R = Me
b, R = nBu
c, R = tBu

In the reaction of PhCu·LiI with **1**, addition of HMPA or TMSCl alone[24] resulted in diminished yields of 3-phenylcyclohexanone (**2c**) (44% and 81% yields, respectively). The maximum yields we observed without additives (~90%) were limited by the formation of two products (3 : 1 ratio[15]) of "double-Michael addition."[12-14] Both of these products were isolated by HPLC and had NMR and MS properties consistent with structure **3b**, although which two of the eight possible stereoisomers we isolated has not been determined. This side-reaction did not take place with TMSCl/HMPA present, but it did with either additive alone.

Whereas PhCu·LiI afforded 70% of **2c** upon treatment with **1** at −78 °C for 1 h, PhCu/LiBr yielded only 1% of **2c** under the same conditions. PhCu prepared from CuBr in DMS is virtually "halide-free", due to the precipitation of LiBr (*vide infra The Nature of the Reagents*). These experiments demonstrate an important activating effect of Li halide on the conjugate addition of PhCu to **1**. Addition of TMSCl/HMPA (2 equiv each) to the PhCu/LiBr reagent made the yield of **2c** quantitative after 1 h at −78 °C and 0.1 h at 0 °C.

The reaction mixtures containing TMSCl or TMSCl/HMPA in DMS yielded ketones directly upon being quenched with ammonium chloride or sodium bicarbonate solutions. Authentic samples of the TMS enol ether derivatives of **2c**, *prepared in THF* either *via* the conjugate addition procedure or the lithium diisopropylamide (LDA) method,[25] were not hydrolyzed by these quenching agents. Apparently, enolates are not readily silylated by TMSCl in DMS. In fact, the reaction mixture from **2c** and LDA in DMS was not silylated until THF was added. The minor isomer in the 3 : 7 mixture of TMS enol ethers from the LDA procedure was identical to the product from the conjugate addition procedure. No interaction between PhCu·LiI and TMSCl in DMS at −78 °C was detectable by ^{13}C or ^{29}Si NMR. When the NMR sample of PhCu·LiI in DMS was treated with **1**, the spectrum became very broad and indistinct. In contrast, treatment of Ph_2CuLi·LiI with **1** gave a well-resolved spectrum which was a superposition of the spectra of

PhCu · LiI and the Li enolate ($\Delta^{1,2}$) of 3-phenylcyclohexanone.

As in the Ph case, **1** did not yield TMS enol ether when treated with BuCu/2TMSCl/2HMPA in DMS. Addition of an equal volume of THF to a DMS solution of the enolate from BuCu/LiI and **1** followed by TMSCl/HMPA (~3 equiv each) induced formation of the corresponding TMS enol ether and a small amount of the regioisomeric TMS enol ether. Addition of an equal volume of HMPA and 2 equiv of TMSCl to a DMS solution of enolate resulted in an ~1 : 1 mixture of the two possible regioisomeric TMS enol ethers. Boeckman has reported that Cu enolates are not alkylated by iodomethane or allyl iodide unless THF and HMPA are added.[26]

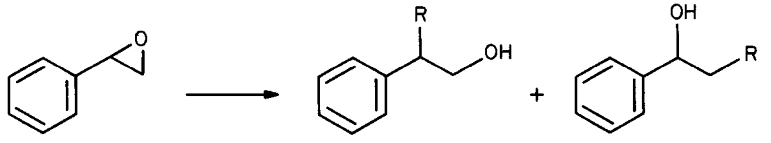
Reactions with Epoxides

The reaction of epoxides with organocuprates is a well-established method for the stereospecific and regioselective preparation of alcohols.[27,28] Pairing one of the more reactive RCu/DMS reagents (BuCu/LiI) with an activated oxirane (styrene oxide, **6**) resulted in low yields of 2-phenyl-1-hexanol (**7a**) and 1-phenyl-1-hexanol (**7b**) (see Table 5, entry 1). Thus, it was not surprising that a less reactive reagent (PhCu · LiI) and an unactivated oxirane (cyclohexene oxide, **8**) afforded no alcohol (entry 13).

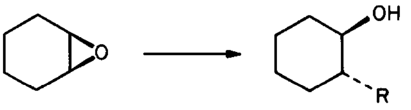
Table 5. Selected Reactions of Organocopper Reagents with Epoxides.

Entry	Reagent	Solvent	Substrate	Product(s)[a]	Yield(s) (%)[a]
1	BuCu/LiI	DMS	Styrene oxide (**6**)	**7a** : **7b**	9 : 3[b]
2		ether	**6**	**7a** : **7b**	11 : 19[b]
3		THF	**6**	**7a** : **7b**	3 : 10[b]
4	BuCu(CN)Li	DMS	**6**	**7a** : **7b**	28 : 17[b]
5		ether	**6**	**7a** : **7b**	28 : 4[b]
6		THF	**6**	**7a** : **7b**	0 : 0[b]
7	$Bu_2CuLi \cdot LiI$	DMS	**6**	**7a** : **7b**	70 : 30[b]
8		ether	**6**	**7a** : **7b**	32 : 48[b]
9		THF	**6**	**7a** : **7b**	7 : 79[b]
10	$Bu_2Cu(CN)Li_2$	DMS	**6**	**7a** : **7b**	34 : 32[b]
11		ether	**6**	**7a** : **7b**	29 : 40[b]
12		THF	**6**	**7a** : **7b**	7 : 84[b]
13	PhCu · LiI	DMS	Cyclohexene oxide (**8**)	**9**	0[c]
14		ether	**8**	**9**	0[c]
15		THF	**8**	**9**	0[c]
16	$Ph_2CuLi \cdot LiI$	DMS	**8**	**9**	24[c]
17		ether	**8**	**9**	89[c]
18		THF	**8**	**9**	22[c]
19	Ph_2CuLi / LiBr	DMS	**8**	**9**	62[c]
20		ether	**8**	**9**	78[c]
21		THF	**8**	**9**	28[c]
22	$Ph_2Cu(CN)Li_2$	DMS	**8**	**9**	47[c]
23		ether	**8**	**9**	59[c]
24		THF	**8**	**9**	12[c]

[a] Absolute yields of 2-phenylhexanol (**7a**), 1-phenyl-1-hexanol (**7b**), and *trans*-2-phenylcyclohexan-1-ol (**9**), measured by glc (internal standard method). [b] −78 °C/1 h, 0 °C/1 h. [c] 0 °C/6 h, 20 °C/18 h.



6 **7a**, R = Bu **7b**, R = Bu



8 **9**, R = Ph

The relative ratios of **7a**:**7b** were the same after 1 h at −78 °C as they were after an additional 1 h at 0 °C (data used in Table 5), except for the reagents BuCu(CN)Li/DMS and $Bu_2Cu(CN)Li_2$/DMS (**7a**:**7b** = 8:11 and 12:21, respectively). The yields were significantly lower before warming to 0 °C and in several cases (reagents in entries 1, 3, 5 and 6) no products were observed. For all reagents but BuCu(CN)Li, the product distributions (Table 5) shifted from **7a** to **7b** upon going from DMS to ether, and the proportion of **7b** increased further in THF. The product distributions can be explained by the interplay between Lewis acidity and nucleophilicity, *e.g.*, a relatively higher Lewis acidity for $Bu_2CuLi \cdot LiI$/DMS (or BuCu(CN)Li/ether) and a relatively higher nucleophilicity for $Bu_2CuLi \cdot LiI$ and $Bu_2Cu(CN)Li_2$ in ethereal solvents, especially in THF. THF is known to compete more effectively than ether for metal coordination sites,[27] thus damping their Lewis acidity. The yield of **7b** from $Bu_2CuLi \cdot LiI$/THF is only slightly lower than that from $Bu_2Cu(CN)Li_2$/THF, due to the formation of a black precipitate ("colloidal Cu") and octane (14%) during the preparation of the former reagent. $Bu_2CuLi \cdot LiI$/DMS is homogeneous and low in octane.

Based upon the yields of *trans*-2-phenylcyclohexan-1-ol (**9**), the best phenyl reagent for opening the unactivated epoxide **8** is $Ph_2CuLi \cdot LiI$/ether. The "higher order" cyanocuprates have been proposed to be superior reagents for epoxide alkylation;[28] however, side-by-side comparisons with other cuprates were not made.

Allylcopper and Lithium Diallylcuprate

House and Fischer prepared lithium diallylcuprate from $CuI(SBu_2)_2$ and allyllithium in ether and reported 90-94% yields of 3-allylcyclohexanone (**2g**) upon treating it with **1**.[29] No 1-allylcyclohex-2-en-1-ol (**10**) was reported to be in the reaction mixture, which was analyzed by glc. In contrast, the reagent prepared from 1 equiv each of allyllithium and $CuI \cdot PBu_3$ in ether yielded only 10-15% of **2g** along with "a number of more rapidly eluted materials thought to be various dienes from 1,2-addition and dehydration."[29] In a later study, House and Wilkins treated **1** with lithium diallylcuprate prepared from $CuBr \cdot SMe_2$ and allyllithium in DMS/ether.[30] The product contained 91% of **2g**, but **10** was not detected by glc. It has been speculated that impurities (*e.g.*, Cu(II) salts) are responsible for the 1,2-product; however, Corey and Boaz found that "even with carefully purified CuI a mixture of 1,4- and 1,2-adducts (ratio 82:18) was obtained from the reaction of lithium diallylcuprate and 2-cyclohexenone at −78 °C in THF."[31] Majetich *et al.* have also reported mixtures of 1,2- and 1,4-adducts from $allyl_2CuLi$.[32]

Table 6. The Reaction of Allyl Reagents with 1 or Mixtures of 1 and 11 in Dimethyl Sulfide.[a]

Reagent	Substrate[b]	%2g[c]	%10[d]	(%12)[e]	$\frac{2g}{2g+10}$	$\frac{12}{2g+10+12}$
AllylLi	**1**	5.73	53.8	—	0.096	—
	1+11	2.50	25.8	(38.7)	0.088	0.58
$AllylCu \cdot LiI$	**1**	18.5	16.4	—	0.53	—
	1+11	6.83	6.41	(22.1)	0.52	0.63
$Allyl_2CuLi \cdot LiI$	**1**	27.5	24.7	—	0.53	—
	1+11	10.5	8.03	(35.2)	0.57	0.66

[a] Reaction conditions: 0.1 h at −78 °C. [b] Cyclohex-2-en-1-one (**1**) or cyclohexanone (**11**). [c] 3-Allylcyclohexanone. [d] 1-Allylcyclohex-2-en-1-ol. [e] 1-Allylcyclohexanol.

We observed mixtures of **2g** and **10** (Table 6) from **1** and allylcopper or lithium diallylcuprate prepared in DMS from purified CuI.[33] The fractions of 1,4-adduct **2g** in the product mixtures (column 6) were the same (within experimental uncertainty) when cyclohexanone (**11**) was present in equimolar amounts to the 2-cyclohexenone (10% excess of each over allyl). For this reason we believe that free allyllithium is not responsible for the 1,2-adduct from allylcopper(I) or lithium diallylcuprate(I). Inverse additions (reagents to substrates) were used for the experiments summarized in Table 6. For comparison, allyllithium itself was added to **1** and to (**1**+**11**), and *ca.* 10% of 1,4-adduct **2g** was observed, along with the expected 1,2-adduct, **10**. Treatment of **1** with BuLi or PhLi in DMS yielded 2% or 0.2% of the respective 1,4-adducts (along with 93% and 80%, respectively, of 1,2-adducts). Thus, not only do allyl copper reagents yield exceptional amounts of 1,2-adduct, allyllithium yields an exceptional amount of 1,4-adduct. As judged by the yields of **2g** and **10** from **1** and the yield of 1-allylcyclohexan-1-ol (**12**) from **11** in the competition experiments, **11** is more reactive than **1** towards all of the allyl reagents (see last column of Table 6).

Hutchinson and Fuchs did a competition experiment between a vinyl sulfone and acetophenone, and they also came to the conclusion that free allyllithium was not involved.[34] They attributed the "abnormal" reactivity of lithium diallylcuprate to a dimeric structure for this compound which contains π-allyl ligands and thus has an 18-electron configuration. "This species is coordinatively saturated and would not be expected to undergo the oxidative insertion reactions associated with normal 14-electron cuprate reagents .... Such a species could, however, undergo direct allylation reactions with ketones, enones, and vinyl sulfones."[34]

Table 7. The Reaction of Selected Allylcopper Reagents with 1.[a,b]

Entry	Precursor	Solvent	equiv AllylLi	% **2g**[c]	% **10**[d]	$\frac{\mathbf{2g}}{\mathbf{2g+10}}$
1	CuI	DMS	1	29	17	0.63
2			2	52	21	0.71
3	CuI	ether	1	28	23	0.55
4			2	64	10	0.86
5	CuI	THF	1	6.6	59	0.10
6			2	16	57	0.22
7	CuBr	DMS	1	24	25	0.49
8			2	72	19	0.79
9	CuBr	ether	1	0.09	0.41	0.18
10			2	9.6	46	0.17
11	CuBr	THF	1	7.5	27	0.22
12			2	18	39	0.32
13	$CuBr \cdot SMe_2$	ether	1	31	5.9	0.84
14			2	67	14	0.83

[a] Reaction conditions: 1 h at −78 °C. [b] Cyclohex-2-en-1-one = **1**. [c] 3-Allylcyclohexanone. [d] 1-Allylcyclohex-2-en-1-ol.

Considering the results in Table 7, mixtures of 1,2- and 1,4-addition products appear to be a general phenomenon. The fraction of 1,4-adduct **2g** in the various product mixtures varies between 0.1 and 0.9, the lower limit being close to the value for allyllithium itself (*cf.* Table 6). Comparison of entries 9 and 10 with 13 and 14 illustrates the dramatic effect 1 equiv of DMS can have on reactivity: CuBr/ether gave fractions of 1,4-addition *ca.* 0.2, whereas $CuBr \cdot SMe_2$/ether gave values *ca.* 0.8. The simple structure proposed for $allyl_2CuLi$ (*vide supra*)[34] is not sufficient to explain the dependence of our results upon the precursor Cu(I) halide.

While the formation of 1,2-adduct has been blamed on impurities in the Cu(I) salt (*vide supra*), we point out that impurities in the Li reagent (*e.g.*, residual base) might be at fault. For this reason we always specify the residual base as well as the active titer (see *Experimental Section*). We note that House *et al.*'s residual base (1 equiv of phenoxide) was also high.[30] Residual Sn (from the preparation of the allyllithium) may also modify the reactivity.

The Nature of the Reagents

DMS and THF are complementary as far as the solubility properties of CuI and LiI are concerned, *i.e.*, CuI is very soluble and LiI is relatively insoluble in DMS, whereas LiI is quite soluble and CuI is very insoluble in THF.[35] These solubility properties can be understood in terms of the solvation of the metal ions. The Cu-S and Li-O interactions are stronger than the respective Cu-O and Li-S interactions.[36,37] Molecular orbital calculations[38] indicate that the $4a_1$ orbital of DMS is the σ-donor to the Cu(I) $3d_{z^2}$ orbital, and the DMS $3b_1$ orbital is a (weak) π-donor to the Cu $3d_{xz}$ orbital. There are also small but significant dπ−dπ back-bonding interactions, which delocalize electron density from the filled Cu 3d orbitals into the empty sulfur 3d orbitals.

The ^{13}C NMR spectrum of $PhCu \cdot LiI$ in DMS contains eight lines (δ 147.5, 143,7, 127.2, 127.1; 149.8, 143.1, 126.6, 125.9 ppm), which indicate two kinds of Ph groups are present. These Ph groups belong to two distinct species, the relative proportions of which vary with concentration and temperature. The same two sets of Ph groups are present in PhCu prepared from CuBr, thus the halide does not play a major role in the solution structure. ^6Li NMR detects a single peak for $PhCu \cdot LiI$ which is within experimental error at the position of free LiI (δ 2.3 ppm).[1] Nevertheless, some interaction between the PhCu and the LiI must occur, as 0.3 M $PhCu \cdot LiI$/DMS is homogeneous, whereas the solubility of LiI in DMS is <0.1 M.[35] Therefore, we denote PhCu prepared from PhLi and CuI as PhCu·LiI to indicate a weak interaction between PhCu and LiI. No ^{6}Li spectrum is observed for the reagent prepared from CuBr, owing to the precipitation of LiBr from the solution. Preliminary results suggest that the PhCu/DMS reagent is an equilibrium mixture of trimer and tetramer. Tetrameric organocopper compounds have substantial precedent.[39–42] There is only one report of a monomeric PhCu(I) complex, which contains the tridentate triphos ligand.[43] PhLi is tetrameric in DMS,[1] an equilibrium mixture of tetramer and dimer in ether, and a mixture of dimer and monomer in THF.[44]

MeCu prepared in DMS is a yellow precipitate, as it is in ether or THF; likewise, the other *n*-alkylcopper reagents are also insoluble. We propose RCu/LiX to symbolize those reagents in which the copper species and the Li halide are not directly associated, *e.g.*, MeCu/LiI or PhCu/LiBr. Even in cases where there is no interaction between RCu and LiX, the Li ion may have an important activating role; therefore, it is necessary to include it in the specification of the reagent. The same principles apply to the *ate* complexes, *e.g.*, the reagent prepared from CuI and 2 equiv of PhLi in DMS may be symbolized as $Ph_2CuLi \cdot LiI$ or $Ph_2Cu(I)Li_2$. The former retains the classic cuprate representation R_2CuLi; however, the latter may be closer to the truth, since ^{6}Li NMR proves that no free LiI is present.[1]

We believe that organocopper reagents are more reactive in DMS than in ethers for several reasons. In some cases solubility differences may be important, *e.g.*, PhCu·LiI in DMS is homogeneous, whereas PhCu in ether is not. In other cases the structure of the reagent may be different, *e.g.*, there are clear differences in reactivity between allyl copper reagents which may be due to differences in structure. In some cases the solvation of the lithium cation may be the controlling factor. The Li ion present in organocopper reagents has been shown by a number of studies to have an important activating effect,[45–47] as we observed in the reaction of 1 with PhCu·LiI *vs.* "halide-free" PhCu (prepared from CuBr in DMS). DMS does not compete as effectively as ethers for Li-coordination sites, making it easier for an enone or oxirane O to coordinate Li in DMS. The enhanced Lewis acidity of $Bu_2CuLi \cdot LiI$ in DMS was noted above in the discussion of its reaction with styrene oxide. Thus, dilution of DMS solutions of Cu reagents with ether or THF, as has been standard practice, may tend to negate the beneficial aspects of its use in some cases.

Perspective and Conclusions

Organocopper reagents are valuable synthetic intermediates because of the variety of C-C bond-forming reactions they mediate with good yields *based on substrate*. In most of their reactions, organocuprates—R_2CuLi—transfer but one of the organic residues (R) to a substrate,[48] as the organocopper(I) species—RCu—that remains is generally much less reactive under the same conditions. Under forcing conditions decomposition often results.[17–19,49]

One strategy for improving the economy of copper reagents has been the replacement of one of the R groups with a ligand such as acetylide,[50] mercaptide,[51] phosphide,[16,45b,52] or thienyl,[53] which are not transferred under the reaction conditions. Some of these auxiliaries improve stability while maintaining reactivity;[52] others sacrifice reactivity[50,53] or stability.[16,51] Another strategy has been the activation of RCu by additives such as tributylphosphine,[54] HMPA/TMSCl,[55,56] 4-dimethylaminopyridine/TMSCl,[56] or TMEDA/TMSCl.[57]

We have found that dimethyl sulfide provides a reaction medium in which organocopper(I) compounds are not only much more thermally stable but also much more reactive than they are in the traditional solvents, ether and tetrahydrofuran. The yields obtained with 1 equiv of RCu/DMS and typical substrates are generally excellent. On the other hand, there are also many substrates that do not react with RCu/DMS, which should enable chemoselective reactions to be performed. DMS also provides a unique medium for spectroscopic studies, which we have begun in order to explore the solution structures of these reagents.[1]

Acknowledgment: We thank A. M. Mujsce for GC-MS analyses and P. Mirau for 500 MHz NMR spectra.

Experimental Section

Li and Mg Reagents. PhLi was prepared by the procedure of Schlosser and Ladenberger;[58] it was recrystallized by adding the minimum amount of ether required for homogeneity to a hexane suspension and cooling the resulting solution to −40 °C in a refrigerator in a dry box. The remaining Li reagents were obtained from commercial sources: "low halide" MeLi (1.58 M in ether, 0.06 M residual base), *n*BuLi (2.62 M in hexanes, 0.10 M residual), and *t*BuLi (1.81 M in pentane, 0.05 M residual) from Aldrich; *n*-pentyllithium, PeLi (1.43 M in hexane, 0.05 M residual) from Lithco; and allyllithium (0.449 M in ether, 0.381 M residual) from Organometallics, Inc. The solvent was removed from the allyllithium by rotary evaporation in a dry box and the residue was extracted with less than one-half the volume of hexane (1.16 M, 0.68 M residual). (The remaining solid was active and care was required in its disposal.)

Analysis (glc and GC-MS) of reaction mixtures in which this material was added to **1** indicated that it contained ~4% PhLi, presumably a starting material in its preparation. We have also detected *ca.* 1% of *n*BuLi in the commercial *t*BuLi. All Li reagents were standardized by using the Gilman double-titration (water quench for total base, 1,2-dibromoethane quench for residual base; RLi = total − residual).[59]

The Grignard reagents, MeMgI (2.63 M in ether, Aldrich), *n*BuMgBr (3.10 M in ether, ROC/RIC), CyMgCl (2.30 M in ether, Aldrich), allylMgBr (1.19 M in ether, Aldrich), were standardized by the Gilman back-titration procedure (addition to a measured excess of acid, back-titration with standard base).[60]

Cu(I) Salts. CuI (Aldrich, 99.999%), CuBr (Aldrich, 99.999%), $CuBr \cdot SMe_2$ (Aldrich, 99%), $(CuOTf)_2 \cdot C_6H_6$ (Strem), and CuCN (Baker) were used unless otherwise noted.

Exploratory Reactions (Typical Procedure). A 4-dram vial (borosilicate glass, *e.g.*, Wheaton #224806 or 224886) was charged with 190.7±0.1 mg (1.001-1.002 mmol) of CuI, a magnetic stirbar (1/2″×5/16″) was added, and the vial was sealed with a septum (Aldrich, 13 mm o.d., white rubber) under Ar in a dry box. The vial was removed from the drybox and 8 mL of dimethyl sulfide (freshly distilled from Na/benzophenone) was added *via* syringe. The vial was connected to a static nitrogen atmosphere with a syringe needle, and it was cooled to −50±3 °C in a dry ice/2-propanol bath. A 1.00-mmol quantity of lithium reagent or Grignard reagent was added, and after 0.1-0.5 h (0.1 h for *t*BuLi, 0.5 h for the allyl reagents, 0.25±0.05 h for the rest), the reaction mixture was cooled to −78 °C. Reagents prepared from CuCN in DMS were warmed to 0 °C for 0.1 h before they were cooled to −78 °C. Substrate (1.00 mmol, distilled before use) and internal standard (decane, undecane or dodecane, 50 μL, weighed to the nearest 0.1 mg) dissolved in 2 mL of dimethyl sulfide were added *via* syringe (5 mL, Becton-Dickinson), which was cooled with dry ice held in a thickly insulated glove. (The liquid should be drawn into the syringe before cooling it, so that the syringe needle does not condense moisture, which happens if the vial containing the liquid is cooled. A syringe with a *double* seal on the plunger *must* be used to avoid leakage.) The reaction mixture was stirred rapidly with a large motor (Sybron Thermolyne Type 25500) and typically sampled after 0.1 h and 1 h at −78 °C and 0.1 h and 1 h at 0 °C. The large stirrer allowed 6-12 reactions to be run simultaneously in a large bath fitted with a vial rack.

3-Phenylcyclohexanone (Typical Large-Scale Procedure). A 500-mL recovery flask was charged with 20.00 g of CuI (105.0 mmol, Alfa "ultrapure") which was dissolved in 40 mL of deoxygenated (Ar sparge) dimethyl sulfide (Aldrich, gold label) at 25 °C under nitrogen. Upon cooling the solution to −50 °C, a white solid precipitated; therefore, an additional 120-mL volume of dimethyl sulfide was added to the cold suspension in order to redissolve the CuI. A 55.5-mL volume of 1.86 M PhLi (103 mmol, 0.17 M residual base, Aldrich) solution (ether/cyclohexane) was added *via* syringe over ~0.1 h. The dark greenish-yellow solution was stirred at −50 °C for 0.5 h. Then it was cooled to −75 °C (~0.25 h) and 9.630 g of 2-cyclohexenone (100.2 mmol, Aldrich, freshly opened bottle) dissolved in 15-mL of dimethyl sulfide was added to the rapidly stirred solution over ~3 min *via* cannula from a 50-mL strawberry-shaped flask cooled in a dry ice/2-propanol bath. After 1 h at −75 °C, a 1.00-mL aliquot of the non-homogeneous reaction mixture was removed *via* cooled syringe and quenched with 3 M NH_4Cl. Samples were also taken after an additional 1 h at −75 °C and 0.5 h at 0 °C, where the reaction went to completion. They were analyzed by glc after weighed amounts of internal standard (decane) were added.

Work-up consisted of the addition of 100 mL of 3 M NH_4Cl (sparged with nitrogen), separation of phases, and extraction of the organic phase with 4×100 mL of 3 M NH_4Cl. The combined aqueous phases were back-extracted with 100 mL of ether. The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was removed by rotary evaporation. (A dry ice trap was inserted between the rotary evaporator and the aspirator to which it was connected.) The residue was treated with 100 mL of hexane and filtered; the filter cake was washed with a total of 75 mL of fresh hexane. The hexane was removed (rotary evaporation) and the residue, which still contained some solid, was dissolved in 100 mL of ether, which was extracted with 2×100 mL of 0.5 M sodium thiosulfate. The combined thiosulfate layers were back-extracted with 100 mL of ether and the combined ether layers were dried over anhydrous Na_2SO_4. Rotary evaporation left 16.8 g of crude 3-phenylcyclohexanone (94% pure by glc). Flash chromatography on a 30 mm×60 mm column of basic alumina (50 g, Woelm act. I) eluted with hexane afforded 13.7 g of product in the first four 50 mL fractions. Further elution with 200 mL of ether yielded 2.3 g of product. The purity was not improved by this chromatography; therefore, 15.9 g of the chromatographed material was distilled at 0.01 torr. Three fractions were collected: 0.8 g (65-88 °C, 49% pure by glc), 3.0 g (88-92 °C, 91% pure), and 8.3 g (92-94 °C, 99% pure). The main impurity was biphenyl from the commercial PhLi solution. (Little biphenyl was observed in the small-scale reactions, which employed solid PhLi free of biphenyl.[58])

^{1}H NMR ($CDCl_3$/TMS): δ 1.82 (2H), 2.10 (2H), 2.40 (2H), 2.55 (2H), 3.01 (1H), 7.20 (3H), 7.30 (2H) ppm, (all *m*). ^{13}C NMR ($CDCl_3$/TMS): δ 25.5, 32.8, 41.2, 44.7, 48.9, 126.6 (2C), 126.7, 128.7 (2C), 144.3, 211.0 ppm. MS (70 eV) *m/e* (% base peak): 27 (16), 28 (7), 29 (6), 39 (38), 40 (6), 41 (22), 42 (55), 50 (14), 51 (35), 52 (11), 53 (6), 55 (10), 63 (17), 65 (19), 70 (12), 74 (6), 75 (6), 76 (9), 77 (50), 78 (57), 79 (7), 82 (5), 83 (15), 89 (9), 91 (50), 92 (7), 102 (12), 103 (52), 104 (97), 105 (20), 115 (39), 116 (10), 117 (100), 118 (33), 128 (7), 129 (7), 131 (78), 132 (11), 145 (5), 146 (6), 174 (87), 175 (11).

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