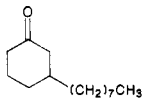
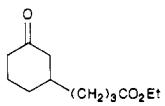
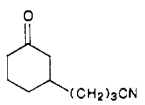
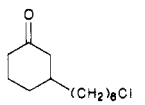
Table I. Reaction of Activated Copper with Primary Alkyl Halides

alkyl halide	equiv[a]	Cu*[b]	conditions[c,d] temp, °C	conditions[c,d] time	product yields, %[e] RH[f]	RX	RR
$CH_3(CH_2)_7Br$	0.40	A	−50	1 h 50 min	71	<3	30
	0.40	B	−78	20 min	65	5	25
	0.41	C[g]	−78	15 min	68	6	21
	0.41	D	−78	20 min	70	0	25
$Br(CH_2)_3CO_2Et$	0.41	B	−78	15 min	64	14	17
			−50	1 h	62	9	20
$Br(CH_2)_3CN$	0.39	B	−78	15 min	58	3	17
$Br(CH_2)_6Cl$	0.40	B	−78	20 min	63	*h*	10

[a] Based on equivalents of CuI. [b] Active copper prepared by reduction of one of the following CuI complexes. A: Preformed $CuIPBu_3$.[14] B: Preformed $CuIPBu_3$[14] plus excess PBu_3 (1.3–1.5 equiv). C: Unpurified CuI[14] plus HMPT (2.3–2.5 equiv). D: Unpurified CuI[14] plus $P(Cy)_3$ (2.3–2.5 equiv.). E: Unpurified CuI[14] plus PBu_3 (2.3–2.5 equiv). [c] Solvent was THF. [d] Alkyl halide plus GC internal standard in THF (5–10 mL) were added rapidly to the Cu* at the specified temperature. [e] GC yields with *n*-decane as internal standard. [f] Yield of alkane product (no alkene) presumably from aqueous quench of organocopper intermediate. [g] This copper species, unlike the others listed, gradually yields more homocoupled product and less reduced product upon continued reaction. [h] Unconsumed alkyl halide GC peak could not be quantitated due to overlap with the naphthalene peak.

Table II. Reaction of 2-Cyclohexen-1-one with Organocopper Reagents

product[a]	alkyl halide	equiv[b]	Cu*[c,d]	equiv of enone[b]	% yield[e]
	$CH_3(CH_2)_7Br$	0.50	B	0.21	94
		0.40	A	0.19	62
		0.41	C	0.15	64
		0.41	D	0.13	78
	$Br(CH_2)_3CO_2Et$	0.41	B	0.19	90
		0.50	E	0.19	90
	$Br(CH_2)_3CN$	0.44	B	0.15	71
	$Br(CH_2)_6Cl$	0.40	B	0.15	52

[a] All products gave consistent IR, ^1H and ^{13}C NMR, and high-resolution mass spectral data. [b] Based on equivalents of CuI. [c] Refer to Table I for methods of Cu* preparation. [d] Solvent was THF unless otherwise specified. [e] GC yields based on calibrated chromatographically pure isolated samples.

from these complexes readily react with 1-bromooctane. Subsequent 1,4-addition reactions with 2-cyclohexen-1-one give 3-*n*-octylcyclohexanone in moderate to good yields, which have not been optimized at this point. HMPT has the advantage of water solubility, thus the phosphine-containing impurities can be removed by simple dilute acid extraction making product isolation much easier. The $P(Cy)_3$ complex with CuI is relatively insoluble in THF; however, the Cu* obtained from this complex is very reactive toward alkyl halides. This supports the idea that donation rather than mere solubility is the important role of the ligand.

In summary, using activated copper a variety of highly functionalized organocopper species have been prepared which exhibit significant reactivity toward conjugate addition chemistry with 2-cyclohexen-1-one. Studies are continuing to determine the effects of solvent, complexing ligand, temperature, stoichiometry, and various other factors which have been shown to contribute to the reactivity of the active copper and to the reactivity of the derived organocopper species in subsequent reactions.

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(13) The complex is formed by the reaction of CuI[14] with an excess (2.3–2.5 equiv) of the appropriate phosphine in THF under argon. The complex is then directly reduced by transferring the solution into a THF solution of lithium naphthalide. Thus, the need for isolation and purification of the CuI complex prior to reduction can be avoided.

(14) Kauffman, G.; Teter, L. *Inorg. Synth.* **1963**, *7*, 9. The preparation of $CuIPBu_3$ as well as a method for purification of CuI is given. $CuIPR_3$ complexes prepared from unpurified CuI are very dark in solution, while those prepared from purified CuI give clear solutions.

Novel Functionalized Organocopper Compounds by Direct Oxidative Addition of Zerovalent Copper to Organic Halides and Some of Their Reactions with Epoxides

Summary: Reactions of epoxides with some unusually functionalized organocopper compounds generated from direct addition of zerovalent copper to organic halides are described. Organocopper reagents containing esters, nitriles, chlorides, and epoxides have been prepared. The first intramolecular cyclization via an epoxide cleavage process using the activated copper is also described.

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Sir: Organocopper reagents have been extensively used in organic synthesis due to their high regio-, stereo-, and chemoselectivity.[1-3] In most cases, organocopper compounds are prepared from organomagnesium[4] or organolithium[5] precursors, along with an appropriate copper(I) salt. It has been difficult to incorporate functionalities in the organocopper reagent via these two basic approaches.[6] In connection with our previous reports[7-9] on the direct formation of organocopper compounds by oxidative addition of highly reactive zerovalent copper to organic halides, we became interested in developing a new class of stable organocopper compounds[10] which not only would have similar regio-, stereo-, and chemoselectivity but would also tolerate a wide variety of functionalities.

We demonstrate here the epoxide-opening reactions of the organocopper intermediates using the activated copper. The procedure involves the direct oxidative addition of highly reactive zerovalent copper to organic halides. The highly reactive zerovalent copper is typically prepared by direct reduction of copper(I) iodide–tributylphosphine complex and an excess of tributylphosphine in THF with preformed lithium naphthalide under an argon atmosphere.[11] The resulting zerovalent copper will oxidatively add to alkyl halides under very mild conditions to form stable alkylcopper compounds at −60 °C or lower.[10] These stable alkylcopper species have enabled us to accomplish a regioselective oxirane cleavage reaction. Table I presents a summary of some of the epoxide-opening reactions which we have attempted to date.

It is significant that the organic halides can contain a wide variety of functional groups (Table I).[7,10] Reactions of the alkylcopper compounds with 1,2-epoxybutane produce a single regioisomer for all cases in high yields. The typical reaction temperature is around −15 °C or lower. The epoxides were found to be reasonably stable in the presence of activated copper under these conditions. The alkylcopper compounds decompose giving elimination products[12] above −15 °C. Also, a small amount of homocoupling of the alkyl halides has been observed, while the aryl halides do not give any homocoupled products under these conditions.[7,10] It is noteworthy that THF is successfully used as the solvent for all epoxide-opening reactions.[13] Diethyl ether is usually reported to be the best solvent for epoxide-cleavage reactions with organocuprate reagents whereas THF is reported to retard this reaction.[14] Ethyl 4-bromobutyrate (entry 2) gave a relatively low yield due to decomposition of both the organocopper compound and the coupled product above −40 °C. The reaction can be improved by employing a bulky ester. For example, the *tert*-butyl ester (entry 3), which produces a relatively stable organocopper reagent, gives a superior yield (87% vs 20–30%). This reaction is quenched at low temperature, since the organocopper and coupled product will decompose if the reaction temperature is increased above −20 °C.

Nearly all the aryl halides (entry 6–9) form arylcopper compounds at 25 °C or lower.[7] These arylcopper species are generally quite stable at room temperature or even in refluxing THF. Treatment of the arylcopper compounds with 1,2-epoxybutane forms β-hydroxyphenylbutanes in high yields at room temperature or with moderate heating. Also of note is the exclusive regioselective substitution at the less-hindered position. The strongly donating group, OCH_3 (entry 8), was observed to accelerate the substitution reaction presumably due to the enhanced nucleophilicity of the arylcopper. Conversely, arylcopper species with strongly withdrawing groups in the ortho or para position are very unreactive because of their poor nucleophilicities. Aryl bromides (entry 9) undergo oxidative addition less rapidly than the corresponding iodides. The resulting arylcopper reagents also show less reactivity toward the epoxide substitutions and give lower yields compared to those derived from aryl iodides (entry 7).

In summary, highly reactive zerovalent copper can ef-

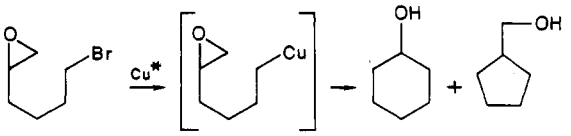
Table I. Reactions of Alkylcoppers or Arylcoppers with 1,2-Epoxybutane

entry	halide	product[a]	% yield[b]
1	$Br(CH_2)_7CH_3$	3-decanol[c]	77
2	$Br(CH_2)_3COOEt$	$CH_3CH_2CH(OH)$-$(CH_2)_4COOEt$	20–30
3	$Br(CH_2)_3COO$-*t*-Bu	$CH_3CH_2CH(OH)$-$(CH_2)_4COO$-*t*-Bu	87
4	$Br(CH_2)_3CN$	$CH_3CH_2CH(OH)(CH_2)_4CN$	88
5	$Br(CH_2)_6Cl$	$CH_3CH_2CH(OH)(CH_2)_7Cl$	81 (78)
6	PhI	$CH_3CH_2CH(OH)CH_2Ph$[d]	*e* (81)
7	*p*-$CH_3C_6H_4I$	$CH_3CH_2CH(OH)CH_2C_6H_4$-(*p*-CH_3)	76
8	*p*-$CH_3OC_6H_4I$	$CH_3CH_2CH(OH)CH_2C_6H_4$-*p*-OCH_3	71 (73)
9	*p*-$CH_3C_6H_4Br$	$CH_3CH_2CH(OH)CH_2C_6H_4$-*p*-CH_3	58

[a] All the synthesized compounds have characteristic spectral data. [b] Yields reported were mostly determined by gas chromatography analysis. Isolated yields are shown in parentheses. [c] 3-Decanol is commercially available. The spectral data of synthesized compounds are identical with those obtained from commercial 3-decanol which was purchased from Wiley Organics, Inc. [d] 1-Phenyl-2-butanol is a known compound previously reported in the literature. The ^{13}C NMR chemical shifts are all within 0.1 ppm of those reported by: Zushi, S.; Kodama, Y.; Fukuda, Y.; Nishihata, K.; Nishio, M.; Hirota, M.; Uzawa, J. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 2113. [e] The GC yield could not be determined due to overlap of the product peak with the naphthalene peak.

(1) Posner, G. H. *An Introduction to Synthesis Using Organocopper Reagents*; Wiley: New York, 1980.
(2) Posner, G. H. *Org. React. (N.Y.)* **1975**, *22*, 253.
(3) Posner, G. H. *Org. React. (N.Y.)* **1972**, *19*, 1.
(4) Kharasch, M. S.; Tawney, P. O. *J. Am. Chem. Soc.* **1941**, *63*, 2308.
(5) Gilman, H.; Jones, R. G.; Woods, L. A. *J. Org. Chem.* **1952**, *17*, 1630.
(6) Nitriles, esters, ketones, and even halides cannot be present in Grignard and organolithium reagents, see ref 1–3.
(7) Ebert, G. W.; Rieke, R. D. *J. Org. Chem.* **1984**, *49*, 5280.
(8) Rieke, R. D.; Rhyne, L. D. *J. Org. Chem.* **1979**, *44*, 3445.
(9) Rieke, R. D.; Burns, T. P.; Wehmeyer, R. M.; Kahn, B. E. *High-Energy Processes in Organometallic Chemistry*, ACS Symposium Series 333; American Chemical Society: Washington, DC, 1987; Chapter 14, p 223.
(10) Wehmeyer, R. M.; Rieke, R. D. *J. Org. Chem.*, in press.
(11) Typically Li^0 (10 mmol) and naphthalene (11 mmol) in 5 mL of freshly distilled THF are stirred at room temperature for 2 h under argon. Then a solution of $CuIP(n\text{-}Bu)_3$ (9.1 mmol) and $P(n\text{-}Bu)_3$ (13.7 mmol) in 7 mL of THF is transferred into the lithium naphthalide via cannula and stirred for 1 h at 0 °C. For the alkyl halides, the alkyl halide (4.5 mmol) in 7 mL of THF is rapidly added to the zerovalent copper (9.1 mmol) which has been precooled to −78 °C. The epoxide (2.2 mmol) in 7 mL of THF is added dropwise at −78 °C and is then allowed to warm slowly to −15 °C. Formation of stable arylcopper compounds is accomplished by stirring the aryl halide (5 mmol) in 7 mL of THF with activated copper (9.1 mmol) at 0 °C for 1 h. The epoxide (3 mmol) in 7 mL of THF is added dropwise and stirred at 0 °C for 1 h. Maximum yield is achieved at room temperature or with moderate heat (ca. 45 °C).
(12) Whitesides, G. M.; Stedrousky, E. R.; Casey, C. P.; Filippo, J. S., Jr. *J. Am. Chem. Soc.* **1970**, *92*, 1426.
(13) The use of THF as solvent for the epoxide opening reactions by higher order organocuprates has been reported by Lipshutz et al.: (a) Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A.; Parker, D. *J. Org. Chem.* **1984**, *49*, 3928. (b) Lipshutz, B. H.; Kozlowski, J.; Wilhelm, R. S. *J. Am. Chem. Soc.* **1982**, *104*, 2305.
(14) Herr, R. W.; Wieland, D. M.; Johnson, C. R. *J. Am. Chem. Soc.* **1970**, *92*, 3813.

ficiently add to organic halides to form organocopper reagents under very mild conditions. Remarkably, the organic halides can contain a variety of functional groups. These unusual organocopper species can undergo nucleophilic opening of epoxides at the less sterically hindered position. Yields are high and reaction conditions are extremely mild. These results have clearly shown that various functionalities can be tolerated by the activated copper. This, in turn, suggests a number of interesting potentials for use of the highly reactive copper. For example, intramolecular cyclizations via an epoxide cleavage process may be readily carried out using this activated copper under very mild conditions with high regio-, stereo-, and chemoselectivity. Preliminary results show that



(1)

5,6-epoxyhexylcopper generated directly from 5,6-epoxyhexyl bromide and the activated copper will undergo intramolecular epoxide opening at low temperature to give a 55% yield of a mixture of cyclohexanol and cyclopentylmethanol in a 6:1 ratio (eq 1). Further results are forthcoming.

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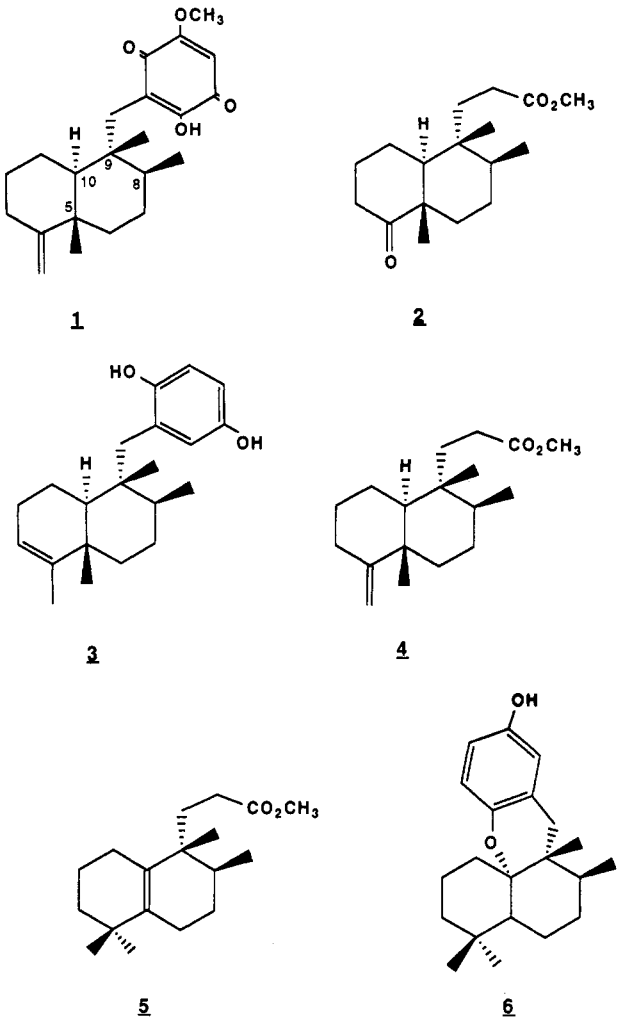
A Revision of the Absolute Stereochemistry of Ilimaquinone

Summary: The absolute stereochemistry of ilimaquinone (1) has been revised following correlation with aureol (6) through a common degradation product.

Sir: During the course of our studies on a number of marine norsesterterpene cyclic peroxides[1] we became aware that CD measurements on 4-keto-5-methyl-*trans*-decalins, obtained as degradation products, were unreliable with respect to assigning absolute stereochemistry, due to their low values.[2] A review of the literature revealed instances[3,4] where the sign of the CD effect, in similar systems of known absolute stereochemistry, was opposite to that predicted. In each case the magnitude of the CD effect was very low. This prompted us to reexamine other assignments of absolute stereochemistry made on related systems.

Ilimaquinone (1) (Chart I) is representative of a class of compounds common to marine sponges. Although the relative stereostructure of 1 was secured by X-ray analysis,[5] an absolute stereochemistry of 5*R*,8*R*,9*S*,10*R* was assigned

Chart I



by interpretation of a weak positive CD measurement ($\Delta\epsilon_{298}$ +0.14) on the 4-keto-5-methyl-*trans*-decalin degradation product **2**.[5] Such an assignment implied that ilimaquinone (1) was "enantiomeric" to avarol (3), a related sponge metabolite whose absolute stereochemistry had been established[6] as 5*S*,8*S*,9*R*,10*S* by interpretation of strong CD effects on two degradation products. Subsequent correlations have resulted in a significant number of marine natural products[7-12] being represented with absolute stereochemistries based on that assigned[5] to ilimaquinone (1). In many of these cases no attempt was made to chemically interrelate the absolute stereochemistry of the natural product under investigation to that of ilimaquinone (1), although the implication was that they had the same absolute stereochemistry. This has resulted in a situation where the majority of sponge metabolites structurally related to ilimaquinone (1) are, without ade-

(1) Capon, R. J.; MacLeod, J. K. *Tetrahedron* **1985**, *41*, 3391.
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(3) San Feliciano, A.; Barrero, A. F.; Miguel del Corral, J. M.; Gordaliza, M.; Medarde, M. *Tetrahedron* **1985**, *41*, 671.
(4) Kitagawa, I.; Kamigauchi, T.; Yonetani, K.; Yashihara, M. *Chem. Pharm. Bull.* **1980**, *28*, 2403.
(5) Luibrand, R. T.; Erdman, T. R.; Vollmer, J. J.; Scheuer, P. J.; Finer, J.; Clardy, J. *Tetrahedron* **1979**, *35*, 609.
(6) de Rosa, S.; Minale, L.; Riccio, R.; Sodano, G. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1408.
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(8) Sullivan, B.; Faulkner, D. J. *Tetrahedron Lett.* **1982**, *23*, 907.
(9) Schmitz, F. J.; Lakshmi, V.; Powell, D. R.; Van der Helm, D. *J. Org. Chem.* **1984**, *49*, 241.
(10) Carté, B.; Rose, C. B.; Faulkner, D. J. *J. Org. Chem.* **1985**, *50*, 2785.
(11) Nakamura, H.; Deng, S.; Kobayashi, J.; Ohizumi, Y.; Hirata, Y. *Tetrahedron* **1986**, *42*, 4197.
(12) Sullivan, B.; Faulkner, D. J.; Matsumoto, G.; Cun-heng, H.; Clardy, J. *J. Org. Chem.* **1986**, *51*, 4568.

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