Communications

Direct Formation of Functionalized Alkylcopper Reagents from Alkyl Halides Using Activated Copper. Conjugate Addition Reactions with 2-Cyclohexen-1-one

Summary: Activated copper, prepared by the lithium naphthalide reduction of $CuIPR_3$ complexes, has been shown to readily form stable alkylcopper compounds at low temperatures by direct insertion into carbon–halogen bonds. Alkylcopper reagents containing ester, nitrile, and chloride functionalities have been prepared directly from the corresponding alkyl bromides. These alkylcopper reagents have been used effectively in conjugate additions to 2-cyclohexen-1-one, giving functionalized 3-alkylcyclohexanones in good to excellent yields. This approach allows for functionality previously unavailable in organocopper and cuprate reagents.

Sir: Organocopper and lithium cuprate reagents have seen increased usage in synthetic chemistry in recent years.[1-3] In general, however, these reagents are derived from the reaction of an organolithium or Grignard reagent with an appropriate copper(I) salt. Thus, the functionality which can be present in the copper reagent is severely limited.

Previous reports[4-6] from our laboratory have shown the use of lithium or Grignard reagents can be circumvented by using highly reactive zerovalent copper prepared by the lithium naphthalide reduction of a $CuIPEt_3$ complex in THF under an argon atmosphere. Stable aryl-, alkenyl-, and alkynylcopper reagents have been prepared by the direct insertion of activated copper into the appropriate carbon–halogen bond at 0 °C and above. However, primary alkyl iodides were found to yield primarily the homocoupled product as well as some reduced alkane plus 1-alkene. A stable primary alkylcopper reagent could not be produced by this approach.

In this paper, we wish to report the direct formation of stable, functionalized primary alkylcopper reagents in moderate yields by the reaction of activated copper with the appropriately functionalized primary alkyl halide (Table I). These functionalized organocopper reagents, in turn, have been shown to undergo 1,4-additions with 2-cyclohexen-1-one, giving the functionalized 3-alkylcyclohexanones in good yields (Table II).

Rapid, low-temperature addition of a solution of the alkyl bromide to the activated copper leads to less homocoupling and a higher yield of the organocopper species. The use of PBu_3 is preferred to PEt_3 as the complexing ligand since PBu_3 is considerably less expensive and promotes a higher yield of organocopper species relative to homocoupled product. While the exact nature of the active copper or of the subsequent organocopper species is unknown, the complexing ligand appears to play a significant role in the reactivity of the zerovalent copper. Other ligands such as $P(OEt)_3$, $S(Me)_2$, and NEt_3, while forming soluble CuI complexes, give copper solutions which are relatively inert toward primary alkyl halides. We believe the reactivity of the activated copper can be qualitatively correlated with the electron-donating ability of the complexing ligand.

Primary alkyl bromides containing remote ester, nitrile, and chloride functionalities react rapidly and nearly quantitatively with the active copper solution within 15 min at −78 °C. GC analysis of reaction quenches indicates the formation of the reduced alkane product, typically in yields of 60–70%, as well as the homocoupled product in yields of 15–30%. The organocopper species appears to be very stable below −30 °C; however, they decompose between −30 and 0 °C, giving roughly a 1:1 mixture (GC) of alkane plus 1-alkene.[7] Organocopper reagents prepared by our method have been found to be effective in promoting 1,4-additions to 2-cyclohexen-1-one. The 1,4-additions proceed to a large degree at −78 °C and are essentially complete at −50 °C.[8] The nitrile and chloride functionalities appear to be quite stable in solution with only very slight 1,4-addition product decomposition, even after the mixture was stirred overnight at room temperature. The ester-substituted 1,4-addition product, however, appears to decompose at higher temperatures and therefore the reaction with this substrate is quenched at −50 °C. Low-temperature addition of chlorotrimethylsilane[9-11] to the organocopper reagent followed by addition of the enone gives the 1,4-adduct in excellent yield. GC data from reaction quenches (saturated aqueous NH_4Cl) strongly suggests the presence of the trimethylsilyl enol ether of the 1,4-adduct which is readily hydrolyzed under more acidic conditions (3% HCl).

The use of excess phosphine[12] is important in the conjugate addition reaction with 2-cyclohexen-1-one. Reaction of the *n*-octylcopper species prepared by using 1 equiv tri-*n*-butylphosphine gives the 1,4-adduct in only 62% yield, whereas a separate reaction using an extra 1.53 equiv of tri-*n*-butylphosphine gave a yield of 94%.

Tris(dimethylamino)phosphine (HMPT) and tricyclohexylphosphine ($P(Cy)_3$) have also been used as complexing ligands for CuI.[13] Active copper solutions derived

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[1] Posner, G. H. *Org. React. (N.Y.)* **1975**, *22*, 253.

[2] Posner, G. H. *Org. React. (N.Y.)* **1972**, *19*, 1.

[3] Posner, G. H. *An Introduction to Synthesis Using Organocopper Reagents*; Wiley: New York, 1980.

[4] Rieke, R. D.; Rhyne, L. D. *J. Org. Chem.* **1979**, *44*, 3445.

[5] Ebert, G. W.; Rieke, R. D. *J. Org. Chem.* **1984**, *49*, 5280.

[6] Rieke, R. D.; Burns, T. P.; Wehmeyer, R. M.; Kahn, B. E. In *High Energy Processes in Organometallic Chemistry*; Suslick, K. S., Ed.; ACS Symposium Series 333; American Chemical Society: Washington, DC, 1987; pp 223–245.

[7] Whitesides, G. M.; Stedronsky, E. R.; Casey, C. P.; Filippo, J. S., Jr. *J. Am. Chem. Soc.* **1970**, *92*, 1426.

[8] In a typical reaction, Li (10.3 mmol) and naphthalene (12.4 mmol) in freshly distilled THF (10 mL) were stirred under argon until the Li was consumed (ca. 2 h). A solution of $CuIPBu_3$[14] (9.33 mmol) and PBu_3 (14.3 mmol) in THF (5 mL) was added via cannula to the dark-green lithium naphthalide solution at 0 °C and the resultant reddish black active copper solution stirred for 20 min. 1-Bromooctane (4.68 mmol) and GC internal standard *n*-decane (1.21 mmol) in THF (5 mL) were added rapidly via cannula to the active copper solution at −78 °C. The organocopper formation was typically complete within 20 min at −78 °C. 2-Cyclohexen-1-one (1.95 mmol) in THF (10 mL) was added slowly dropwise over 20 min to the organocopper species at −78 °C. The reaction was allowed to react at −78, −50, and −30 °C and room temperature for 1 h each. GC analysis of reaction quenches (saturated aqueous NH_4Cl) showed the 1,4-adduct, 3-*n*-octylcyclohexanone, produced in 94% yield.

[9] Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, 6015.

[10] Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, 6019.

[11] Alexakis, A.; Berlan, J.; Besace, Y. *Tetrahedron Lett.* **1986**, 1047.

[12] Suzuki, M.; Suzuki, T.; Kawagishi, T.; Noyori, R. *Tetrahedron Lett.* **1980**, 1247.

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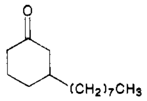
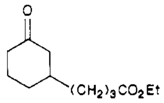
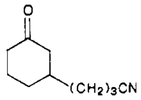
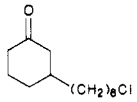
Table I. Reaction of Activated Copper with Primary Alkyl Halides

			conditions[c,d]		product yields, %[e]		
alkyl halide	equiv[a]	Cu*[b]	temp, °C	time	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.