

## The Reaction of the Highly Functionalized Copper Reagents $\text{RCu}(\text{CN})\text{ZnI}\cdot\text{BF}_3$ with Aldehydes

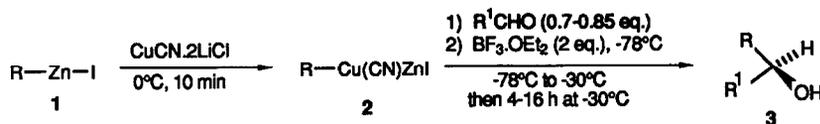
Ming Chang P. Yeh, Paul Knochel\* and Leroy E. Santa

Department of Chemistry, The University of Michigan, Ann Arbor, Michigan 48109

**Summary.** The new copper reagent  $\text{RCu}(\text{CN})\text{ZnI}$  **2**, which may contain important functional groups like the ester, nitrile, enoate or imide group, react in the presence of  $\text{BF}_3\cdot\text{OEt}_2$  with aldehydes to afford polyfunctional secondary alcohols in good yields (68-93%).

Recently we have reported that organozinc iodides<sup>1,2</sup> **1** can be transmetalated into the corresponding copper derivatives  $\text{RCu}(\text{CN})\text{ZnI}$  **2** by using the soluble salt  $\text{CuCN}\cdot 2\text{LiCl}$ . Of special interest is that these copper reagents, unlike the copper compounds prepared from lithium or magnesium organometallics,<sup>3,4</sup> may contain important functional groups like the ester, ketone, nitrile, enoate or imide function. They react readily with enones, acyl chlorides and allylic halides and allow the formation of polyfunctional products in high yields.<sup>1,2</sup> Some time ago,<sup>5</sup> we have reported that alkylzinc halides can also be transmetalated with  $\text{Cl-Ti}(\text{O-i-Pr})_3$  into the corresponding titanium reagents  $\text{RTi}(\text{O-i-Pr})_3$  which react with aldehydes to afford secondary alcohols. However, in this study we have noticed that if functionalized zinc organometallics are used, a large excess of the titanium reagent  $\text{RTi}(\text{OR})_3$  or  $\text{R}_2\text{Ti}(\text{OR})_2$  was required to achieve good conversions.<sup>2</sup>

### Scheme 1

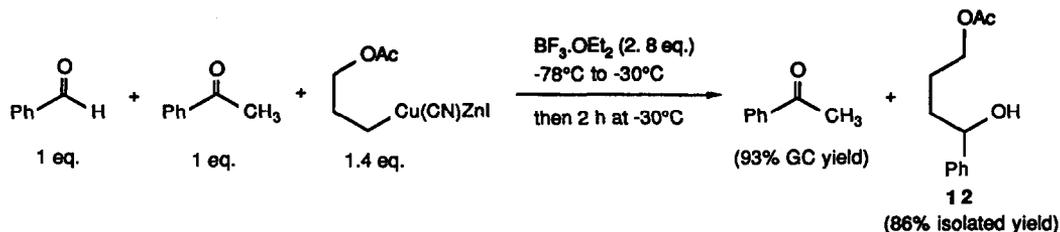


**R** may contain an ester, a nitrile, an enoate or an imide group.

We report now that the polyfunctional copper reagent  $\text{RCu}(\text{CN})\text{ZnI}$  **2** (1 eq.) reacts in the presence of  $\text{BF}_3\cdot\text{OEt}_2$  (2 eq.) with various aldehydes (0.7-0.85 eq.) in THF at  $-30^\circ\text{C}$  (4-16 h) to furnish the highly functionalized secondary alcohols **3** in satisfactory yields (68-93%); see Scheme 1. The  $\text{BF}_3$  activation of the aldehyde is compatible with the presence of various functional groups present in **2** like an ester, a nitrile, an enoate or an imide (see Table I). Benzaldehyde and cinnamaldehyde show the greatest reactivity (4 h at  $-30^\circ\text{C}$ ) and in the case of benzaldehyde the zinc reagent **1** may be used instead of **2** (see entry 1 of Table I). However, for aliphatic aldehydes which require longer reaction times (10-16 h at  $-30^\circ\text{C}$ ),  $\text{RCu}(\text{CN})\text{ZnI}$  is the reagent of choice (a ten-times faster reaction than with  $\text{RZnI}$  is observed and far higher yields are obtained, see entry 2). A chiral aldehyde like 2-phenylpropionaldehyde after the addition of various copper compounds **2** affords the Cram-type products<sup>7</sup> **7a** and **8c** with a fair selectivity

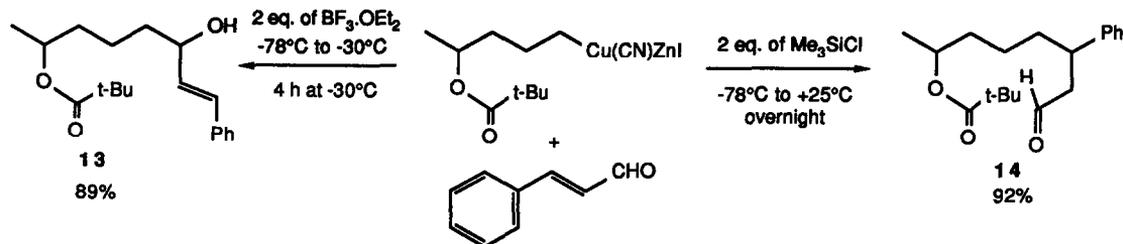
(R\*,R\*/R\*,S\* ratio: 83-85/17-15; see entries 6 and 10). Ketones do not react under our conditions and the treatment of a 1:1 mixture of benzaldehyde and acetophenone with 3-acetoxypropylzinc iodide (2 h at  $-30^{\circ}\text{C}$ ) furnishes the acetoxy-alcohol **12** in 86% yield whereas acetophenone is recovered in 93% yield (see Scheme 2).

Scheme 2



The reactivity of  $\text{RCu}(\text{CN})\text{ZnI}$  depends strongly on the nature of the additives. Thus, cinnamaldehyde leads in the presence of 2 eq. of  $\text{BF}_3\cdot\text{OEt}_2$  to the 1,2-adduct **13** in 89% yield, whereas in the presence of 2 eq. of  $\text{Me}_3\text{SiCl}$ ,<sup>8</sup> the 1,4-adduct **14** is obtained in 92% yield (less than 2% of the 1,2-adduct **13** could be detected); see Scheme 3.

Scheme 3

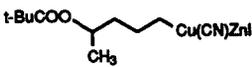
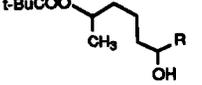
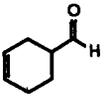
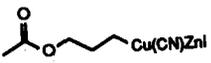
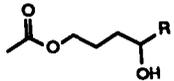
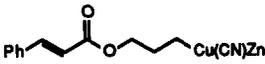
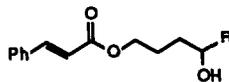
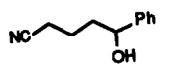
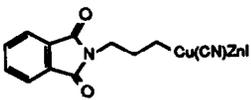
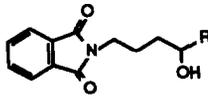
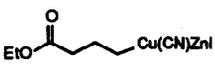
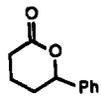


The easy preparation of various highly functionalized zinc iodides<sup>1,2,9</sup> **1** combined with the good reactivity of the corresponding copper reagent  $\text{RCu}(\text{CN})\text{ZnI}$  **2** toward various organic electrophiles should allow applications of this methodology in the synthesis of complex polyfunctional molecules. The reactivity of  $\text{RCu}(\text{CN})\text{ZnI}$  and  $\text{RCu}(\text{CN})\text{ZnI}\cdot\text{BF}_3$  toward other carbon electrophiles is currently being investigated in our laboratory.

**Typical Procedure.** A solution of 14.82 g (65 mmol) of 3-iodopropyl acetate in 21 mL of THF was added within 1.5 h at  $32^{\circ}\text{C}$  to 5.23 g (80 mmol) of cut zinc foil (0.25 x 2 x 5 mm; 99.99% purity) which has been activated,<sup>1</sup> respectively, with 250 mg of 1,2-dibromoethane and 0.15 mL of  $\text{Me}_3\text{SiCl}$ . After 6 h of stirring at  $40^{\circ}\text{C}$ , the zinc reagent was ready to use (over 90% yield by GC analysis).

A THF solution of 10 mmol of 3-acetoxypropylzinc iodide prepared as above was added at  $-20^{\circ}\text{C}$  to a solution of 0.9 g (9 mmol) of  $\text{CuCN}$  and 0.9 g (21 mmol) of  $\text{LiCl}$  in 10 mL of THF. After 5 min of stirring at  $0^{\circ}\text{C}$ , the reaction mixture was cooled to  $-78^{\circ}\text{C}$  and successively 0.89 mL (6.62 mmol) of heptaldehyde and 2.45 mL (20 mmol) of  $\text{BF}_3\cdot\text{OEt}_2$  were added. The reaction mixture was allowed to warm within 1 h to  $-30^{\circ}\text{C}$  and was stirred 16 h at this temperature. After the usual work-up and a flash chromatography of the resulting oil (solvent: hexane/ether), 1.30 g (91% yield) of analytically pure 1-acetoxy-4-decanol was obtained.

Table I. Products 4-11 Obtained by the Addition of the Copper Reagent RCu(CN)ZnI 2 to Aldehydes in the Presence of BF<sub>3</sub>·OEt<sub>2</sub>.

Entry	RCu(CN)ZnI	Aldehyde	Product	Yield(%) <sup>a</sup>
1	i-PrCu(CN)ZnI	PhCHO	i-PrCH(OH)Ph 4	88(85) <sup>b</sup>
2	c-HexCu(CN)ZnI	PrCHO	C <sub>6</sub> H <sub>11</sub> CH(OH)Pr 5	78(50) <sup>b</sup>
3		PhCHO	 6a: R=Ph-	80
4	"		6b: R= 	84 <sup>c</sup>
5	"	HexCHO	6c: R=Hex-	77 <sup>c</sup>
6		PhCH(CH <sub>3</sub> )CHO	 7a: R=CH(CH <sub>3</sub> )Ph	77 <sup>d</sup>
7	"	HexCHO	7b: R=Hex-	91
8		PhCHO	 8a: R=Ph	93
9	"		8b: R=  Ph	79
10	"	PhCH(CH <sub>3</sub> )CHO	8c: R=CH(CH <sub>3</sub> )Ph	73 <sup>c</sup>
11	NC-CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -Cu(CN)ZnI	PhCHO	 9	85
12		PhCHO	 10: R=Ph	89
13	"		10b: R=  Ph	68
14		PhCHO	 11	72 <sup>f</sup>

<sup>a</sup>All indicated yields are isolated yields. Satisfactory spectral data (IR, <sup>1</sup>H and <sup>13</sup>C-NMR, mass spectra) and elemental analyses were obtained for all new compounds.

<sup>b</sup>Yield obtained by using RZnI instead of RCu(CN)ZnI and BF<sub>3</sub>·OEt<sub>2</sub> (2 eq.).

<sup>c</sup>1:1 mixture of diastereoisomers.

<sup>d</sup>Diastereomeric ratio d.r (R\*,R\*/R\*,S\*): 83/17.

<sup>e</sup>d.r. (R\*,R\*/R\*,S\*): 85/15.

<sup>f</sup>The initial mixture of lactone and hydroxy-ester was converted to the lactone 11 by successive saponification, acidification (diluted HCl) and lactonization (5 h, toluene, 110°C); the overall yield of this process is indicated.

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### References

1. Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, in press.
2. Yeh, M. C. P.; Knochel, P. *Tetrahedron Lett.* **1988**, *29*, in press.
3. For excellent reviews see: (a) Posner, G. H. *Org. React.* **1972**, *19*, 1; **1975**, *22*, 253. (b) Normant, J. F. *Synthesis* **1972**, 63. (c) Lipshutz, B. H. *Synthesis* **1987**, 325.
4. Functionalized copper reagents can also be prepared from Cu<sup>0</sup> and an alkyl halide, see: (a) Ebert, G. W.; Rieke, R. D. *J. Org. Chem.* **1984**, *49*, 5280. (b) Wehmeyer, R. M.; Rieke, R. D. *J. Org. Chem.* **1987**, *52*, 5056. (c) Wu, T.-C.; Wehmeyer, R. M.; Rieke, R. D. *J. Org. Chem.* **1987**, *52*, 5057.
5. (a) Knochel, P.; Normant, J. F. *Tetrahedron Lett.* **1986**, *27*, 4431. See also (b) Reetz, M. T.; Steinbach, R.; Wenderoth, B. *Synth. Commun.* **1981**, *11*, 261. (c) For a recent application see Ochiai, H.; Nishihara, T.; Tamaru, Y.; Yoshida, Z. *J. Org. Chem.* **1988**, *53*, 1343.
6. Yamamoto, Y. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 947; *ibid. Angew. Chem.* **1986**, *98*, 945.
7. (a) Reetz, M. T.; Steinbach, R.; Westermann, J.; Peter, R. *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 1011; *ibid. Angew. Chem.* **1980**, *92*, 1044. (b) Reetz, M. T.; Steinbach, R.; Westermann, J.; Urz, R.; Wenderoth, B.; Peter, R. *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 135; *ibid. Angew. Chem.* **1982**, *94*, 133; *Angew. Chem. Supplement* **1982**, 257. (c) The relative stereochemistry of each isomer has been determined by <sup>1</sup>H-NMR; see: Uzawa, J.; Zushi, S.; Kodama, Y.; Fukuda, Y.; Nishihata, K.; Unemura, K.; Nishio, M.; Hirota, M. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 3623.
8. (a) Chuit, C.; Foulon, J. P.; Normant, J. F. *Tetrahedron* **1980**, *36*, 2305. (b) Chuit, C.; Foulon, J. P.; Normant, J. F. *Tetrahedron* **1981**, *37*, 1385. (c) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6019. (d) Horiguchi, Y.; Matsuzawa, S.; Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* **1986**, *27*, 4025.
9. All the alkylzinc iodides described are obtained in over 90% yield (GC yield of the hydrolyzed organometallic). We found in this study that the 3-acetoxypropylzinc iodide is a perfectly stable reagent and has no tendency to form cyclopropane in contrast to 3-chloro-1-iodopropane which could not be converted into the corresponding zinc derivative; also, the zinc derivatives used in entries 8, 9, 10, 12, and 13 represent new classes of functionalized zinc reagents whose properties and synthetic applications are currently being investigated.

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