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Nucleophilic reactivity of zinc and copper carbenoids. Part II

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The nitro olefin **3** is typically¹³ added at $-78\text{ }^{\circ}\text{C}$ to a THF solution of the copper organometallic **2** (1.3 equiv) and is then allowed to warm up. In the case of nitro olefins **3a,b,d** the reaction is complete after a few hours at $0\text{ }^{\circ}\text{C}$ (0.5–4 h). For the more reactive 3-acetoxy-2-nitro-1-propene^{4a} (**3c**), the reaction is performed in the presence of 1 equiv of Me_3SiCl (in order to avoid the polymerization of the β -unsubstituted nitro olefins formed **5a–c**), and is completed at $-55\text{ }^{\circ}\text{C}$ after 10 min. The reaction is quenched at this temperature with aqueous NH_4Cl (entries 12–14). These additions to 3-acetoxy-2-nitro-1-propene (**3c**) and to 3-acetoxy-2-nitro-1-cyclohexene (**3d**) occur with excellent chemoselectivity, since the nitro olefins of type **5** formed (entries 12–15) do not react at the reaction temperature ($-55\text{ }^{\circ}\text{C}$ to $-60\text{ }^{\circ}\text{C}$ for **3c** and $0\text{ }^{\circ}\text{C}$ for **3d**) with the excess copper reagent to afford an undesired diadduct.^{4a,b} Various functionalized copper organometallics **2** containing a functional group such as an ester, a nitrile, a chloride, or an alkyne undergo the addition reaction efficiently, as shown in Table I. We noticed also that nitrogen-containing copper reagents like the organocopper compound **2c**¹⁴ derived from (3-cyanopropyl)zinc iodide

react significantly slower than the other organocopper compounds. Besides alkylcopper derivatives, the benzylic reagent **2h** and the heterocyclic organocopper compounds¹⁵ **2f** and **2g** were found to react in a satisfactory way with 1-nitropentene **3b** (75–96%). All these reactions were quenched with acetic acid at $-30\text{ }^{\circ}\text{C}$ and furnished exclusively the nitro compounds **4**. In the case of α -substituted nitro olefins such as **3e** (Scheme II) a mixture of nitroalkanes and ketones (Nef reaction) is formed after quenching with acetic acid; however, by stirring the reaction mixture after the Michael addition in aqueous acidic medium or simply with aqueous NH_4Cl (in the case of **6a** and **6c**),¹⁶ we were able to convert the intermediate nitronate into the corresponding methyl ketone in good yields; see Scheme II.

Further extensions and synthetic applications are currently underway in our laboratories.

Acknowledgment. We thank the National Institutes of Health (Grant GM 41908) for the generous support of this work.

Supplementary Material Available: Full characterization data for all new compounds (5 pages). Ordering information is given on any masthead page.

(13) **Typical Procedure for the Michael Addition to a Nitro Olefin.** The addition of the (4-chlorobutyl)copper derivative **2i** to 1-nitropentene **3b** (entry 11 of Table I). 1-Nitropentene **3b** (7.5 mmol, 0.86 g) was added dropwise at $-78\text{ }^{\circ}\text{C}$ to a THF solution of the (4-chlorobutyl)copper derivative **2i** (10 mmol) prepared as previously reported.¹² The reaction mixture was warmed up to $0\text{ }^{\circ}\text{C}$ and allowed to react for 4 h. The reaction was monitored by GLPC analysis of aliquots. After completion, the reaction mixture was then cooled to $-78\text{ }^{\circ}\text{C}$, quenched by the addition of an acetic acid solution (2 mL in 5 mL of THF), warmed up to $0\text{ }^{\circ}\text{C}$, and worked up as usual. The crude oil obtained after evaporation of the solvents was purified by SiO_2 flash chromatography (20:1 hexane/ Et_2O) giving 1.40 g of 1-chloro-5-(nitromethyl)octane (**4k**) (90% yield). Analytical data for the product is included in the supplementary material.

(14) Due to its low reactivity, $\text{NCCH}_2\text{CH}_2\text{CH}_2\text{Cu}(\text{CN})\text{ZnI}$ (**2c**) does not react cleanly with the sensitive 3-acetoxy-2-nitropropene (**3c**); the rate of the Michael addition is obviously very similar to the polymerization rate of the product.

(15) A report on the preparation and reactivities of new heterocyclic "benzylic" zinc and copper organometallics is in preparation: Chen, H. G.; Knochel, P., Ann Arbor, 1989.

(16) **Typical Procedure for the One-Pot Michael Addition–Nef Reaction.** The addition of the (3-cyanopropyl)copper derivative **2c** to 2-nitro-2-hexene (**3e**). 2-Nitro-2-hexene (**3e**) (7.5 mmol, 0.97 g) was allowed to react with a THF solution of the (3-cyanopropyl)copper derivative **2c** (10 mmol) as previously described.¹³ Under these conditions, a mixture of ketone and oxime was obtained. The mixture was further stirred overnight in a 10% HCl solution (20 mL) and worked up. The desired ketone **6b** was obtained as the exclusive product (0.95 g, 76% yield) after flash chromatography (4:1 to 2:1 hexane/ethyl acetate). Analytical data for the product is included in the supplementary material.

Nucleophilic Reactivity of Zinc and Copper Carbenoids. 2

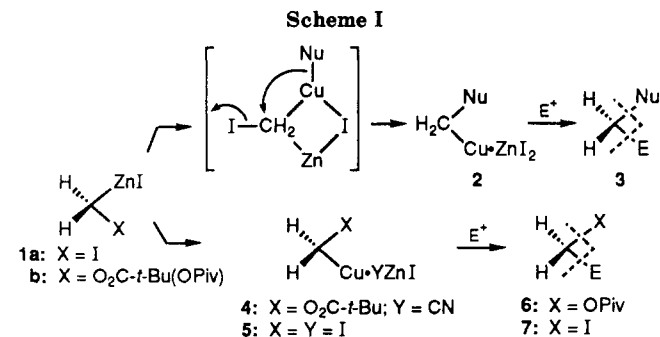
Paul Knochel,* Tso-Sheng Chou, Huai Gu Chen, Ming Chang P. Yeh, and Michael J. Rozema

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Summary: The reactivity of the new zinc and copper carbenoids $\text{PivOCH}_2\text{Cu}(\text{CN})\text{ZnI}$ (**4**) and $\text{ICH}_2\text{Cu}\cdot\text{ZnI}_2$ (**5**) toward various electrophiles has been investigated. Of special interest is the direct and highly stereoselective conversion of allylic bromides to the corresponding homoallylic iodides by using the reagent $\text{ICH}_2\text{Cu}\cdot\text{ZnI}_2$ (**5**).

Sir: The zinc carbenoids of type **1** are excellent carbene precursors and as such have found several synthetic applications.¹ We found recently that the reagent **1a** ($\text{X} = \text{I}$) undergoes a rapid 1,2-rearrangement in the presence of

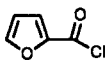
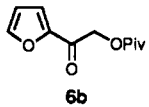

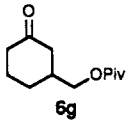
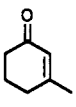
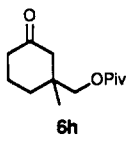
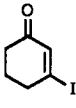
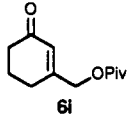

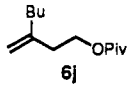

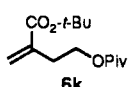


copper nucleophiles NuCu ($\text{Nu} = \text{CN}, \text{SR}, \text{NR}_2, \text{CH(R)CN}$, heteroaryl) leading to the methylene homologated organocopper **2**, which after reaction with various electrophiles **E** affords products of type **3** (Scheme I).²

(2) Knochel, P.; Jeong, N.; Rozema, M. J.; Yeh, M. C. P. *J. Am. Chem. Soc.* 1989, 111, 6474.

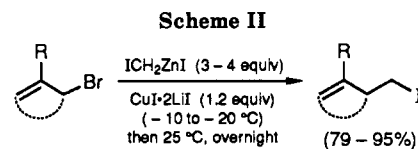
(1) (a) Simmons, H. E.; Smith, R. D. *J. Am. Chem. Soc.* 1959, 81, 4256. (b) Blanchard, E. P.; Simmons, H. E. *J. Am. Chem. Soc.* 1964, 86, 1337. (c) Simmons, H. E.; Blanchard, E. P.; Smith, R. D. *J. Am. Chem. Soc.* 1964, 86, 1347. (d) Wittig, G.; Winkler, F. *Justus Liebig's Ann. Chem.* 1962, 656, 18. (e) Wittig, G.; Winkler, F. *Chem. Ber.* 1964, 97, 2139 and 2146. (f) Wittig, G.; Jautelat, M. *Justus Liebig's Ann. Chem.* 1967, 702, 24. (g) Jautelat, M.; Schwarz, V. *Tetrahedron Lett.* 1966, 5101. (h) Furukawa, J.; Kawabata, N. *Adv. Organomet. Chem.* 1974, 12, 83. (i) Miyano, S.; Hashimoto, H. *Bull. Soc. Chem. Jpn.* 1974, 47, 1500.

Table I. Products 6a-m Obtained by the Reaction of the Zinc (or Cadmium) and Copper Carbenoids 4 and 8 with Electrophiles

entry	copper carbenoid	electrophile	products 6a-m	yield, ^a %
1	PivOCH ₂ Cu(CN)ZnI, 4	PhCOCl	PhCOCH ₂ OPiv 6a	86
2	4		 6b	95
3	4	c-HexCOCl	c-HexCOCH ₂ OPiv, 6c	66
4	4	Cl(CH ₂) ₃ COCl	Cl(CH ₂) ₃ COCH ₂ OPiv, 6d	42
5	PivOCH ₂ Cu(CN)CdI, 8	Cl(CH ₂) ₃ COCl	Cl(CH ₂) ₃ COCH ₂ OPiv, 6d	68
6	4	PhCHO	PhCH(OH)CH ₂ OPiv, 6e	89
7	4	HexCHO	HexCH(OH)CH ₂ OPiv, 6f	73
8	4		 6g	59 ^b
9	4		 6h	71
10	4		 6i	97
11	4		 6j	95
12	4		 6k	94
13	4	Bu ₃ SnCl	PivOCH ₂ SnBu ₃ 6l	93
14	4	Br—Hex	Hex—CH ₂ OPiv 6m	72

^a All yields refer to isolated yields of analytical pure products. Satisfactory spectral data (IR, ¹H and ¹³C NMR, mass spectra and high-resolution mass spectra) were obtained for all new compounds (supplementary material). ^b The intermediate trimethylsilyl enol ether was converted into the ketone 6g by treatment with Bu₄NF (1.1 equiv; THF, 5 °C, 5 min).

We now report the preparation of the new zinc and copper carbenoids 4 (X = OPiv, Y = CN) and 5 (X = Y = I) and their reactivity toward electrophiles leading to products 6 and 7, respectively. Thus the treatment of iodomethyl pivalate³ with activated cut zinc foil⁴ (THF, 12–13 °C, 1 h) produces the corresponding zinc reagent PivOCH₂ZnI 1b in over 85% yield. The addition of 1b to a THF solution of CuCN·2LiCl (–30 °C, 5 min) gives a cloudy white-green solution of the copper derivative PivOCH₂Cu(CN)ZnI (4). This organometallic reacts in fair to good yields with several classes of electrophiles (see Table I) but shows a reduced reactivity compared to other functionalized copper compounds RCu(CN)ZnI.⁴ Its reaction with aromatic acid chlorides proceeds smoothly giving α-(pivaloyloxy)methyl ketones (entries 1, 2 of Table I); however, aliphatic acid chlorides react less efficiently (entries 3 and 4). We found, after much experimentation, that the corresponding cadmium reagent PivOCH₂Cu(CN)CdI (8), prepared in a similar way as 4, displays a higher reactivity leading to the pivaloyloxy ketone 6d in significantly better yields (compare entries 4 and 5). Al-



dehydes such as benzaldehyde or heptaldehyde furnish in the presence of BF₃·OEt₂ (2 equiv, –30 °C to –20 °C, 12 h) the monoesterified diols 6e and 6f in 89% and 73% yield, respectively (entries 6 and 7). The reaction of 4 with cyclohexenone in the presence of Me₃SiCl⁵ (1.1 equiv, –78 °C to 25 °C, 12 h) gives, after a treatment of the intermediate silyl enol ether with Bu₄NF (1.1 equiv, 25 °C, 5 min), the 1,4-addition product 6g in 59% yield (entry 8). The use of more than 1.1 equiv of Me₃SiCl leads to the formation of considerable amounts of Me₃SiCH₂OPiv. The addition of 4 to 3-methylcyclohexenone is best performed in the presence of an excess of BF₃·OEt₂^{4,6} (4 equiv, –30 °C, 3 days), affording the keto ester 6h in 71% yield (entry 9). 3-Iodocyclohexenone⁷ reacts readily with 4, leading to

(3) Bodor, N.; Sloan, K. B.; Kaminski, J. J.; Shih, C.; Pogany, S. *J. Org. Chem.* 1983, 48, 5280.

(4) The zinc foil used was purchased from Alfa (0.62-mm thick, purity m3N; ca. \$16.00 for 500 g); see: (a) Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* 1988, 53, 2390. (b) Yeh, M. C. P.; Knochel, P. *Tetrahedron Lett.* 1988, 29, 2395. (c) Yeh, M. C. P.; Knochel, P.; Santa, L. E. *Tetrahedron Lett.* 1988, 29, 3887. (d) Yeh, M. C. P.; Knochel, P.; Butler, W. M.; Berk, S. C. *Tetrahedron Lett.* 1988, 29, 6693. (e) Berk, S. C.; Knochel, P.; Yeh, M. C. P. *J. Org. Chem.* 1988, 53, 5789.

(5) (a) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* 1985, 26, 6015 and 6019. (b) Alexakis, A.; Berlan, J.; Besace, Y. *Tetrahedron Lett.* 1986, 27, 1047. (c) Horiguchi, Y.; Matsuzawa, S.; Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* 1986, 27, 4025. (d) Nakamura, E.; Matsuzawa, S.; Horiguchi, Y.; Kuwajima, I. *Tetrahedron Lett.* 1986, 27, 4029.

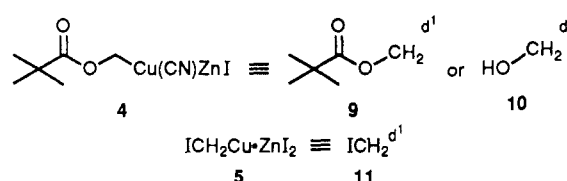
(6) (a) Yamamoto, Y. *Angew. Chem., Int. Ed. Engl.* 1986, 25, 947; *Angew. Chem.* 1986, 98, 945. (b) Lipshutz, B. H. *Synthesis* 1987, 325. See also: Lipshutz, B. H.; Ellsworth, E. L.; Siahaan, T. J. *J. Am. Chem. Soc.* 1989, 111, 1351.

Table II. Products 7a-f Obtained by the Reaction of the in Situ Generated Copper Carbenoid 5 with Allylic Bromides

entry	allylic bromide	homoallylic iodides 7a-f	yield, ^a %
1			90
2			89
3			95
4			96
5			79 ^b
6			90 ^c

^a All yields refer to isolated yields of analytically pure products. Satisfactory spectral data (IR, ¹H and ¹³C NMR, mass spectra and high-resolution mass spectra) were obtained for all new compounds (supplementary material). ^b After addition of ICH₂ZnI, the reaction mixture was warmed up to 5 °C and stirred overnight at this temperature. ^c The iodide 7f is formed in over 90% regioselectivity; 2–3% of (Z)-4,8-dimethyl-3,7-nonadiene (isomerized S_N2 substitution product) and 6–8% of 3,7-dimethyl-3-iodomethyl-1,6-octadiene (S_N2' substitution product) have also been detected in the crude reaction mixture.

the enone 6i in almost quantitative yield (15 °C to –5 °C, overnight; see entry 10). The copper derivative 4 is allylated by allylic bromides such as (2-bromomethyl)hexene and *tert*-butyl bromomethylacrylate and stannylated with Bu₃SnCl in excellent yields (entries 11, 12, and 13). Finally its reaction with a bromoalkyne affords a new direct approach to propargylic esters such as 6m (entry 14). Contrary to the copper carbenoid 4, the reagent ICH₂Cu·ZnI₂ (5) shows only a limited stability and the deep red color of its solution disappears rapidly (15 min) even at –78 °C. To be used for synthetic applications, the carbenoid 5 has to be generated in the presence of an electrophile (Barbier conditions⁸) and at a temperature where it reacts with this electrophile. Thus the addition of ICH₂ZnI⁹ (3–4 equiv) to a THF solution of CuI·2LiI (1.2 equiv) and an allylic bromide between –10 °C and –20 °C furnish the iodomethyl allylated products 7a–f in good to excellent yields (Scheme II and Table II). Various functionalized allylic bromides undergo the iodomethyl homologation reaction furnishing highly functionalized homoallylic iodides (en-

Scheme III

tries 1–3 of Table II). 1,3-Disubstituted allylic bromides such as 2-cyclohexenyl bromide and 2-cyclooctenyl bromide react smoothly (entries 3 and 4). However in the last case, the reaction must not be warmed over 0 °C, in order to avoid the decomposition of the product 3-iodomethyl-1-cyclooctene (7e) to 3-methylene-1-cyclooctene. Of special interest is the highly stereoselective reaction of geranyl bromide with 5 leading in over 90% stereoselectivity to the S_N2 substitution iodide 7f.¹⁰ This product is accompanied by 2–3% of the isomeric S_N2 substitution product ((Z)-4,8-dimethyl-3,7-nonadiene) and by 6–8% of the S_N2' product (3,7-dimethyl-3-iodomethyl-1,6-octadiene) if the addition of ICH₂ZnI to geranyl bromide and CuI·2LiI is performed between –20 and –25 °C. Other electrophiles such as enones, aldehydes (in the presence of BF₃·OEt₂ or ClTi(OiPr)₃ or acyl chlorides do not react with 5 under our reaction conditions showing the relatively low reactivity of this copper species.

In conclusion, we described the preparation and the nucleophilic reactivity of two new d¹ reagents,¹¹ which are synthetically equivalent to the synthons 9 or 10^{12,13} and 11,¹⁴ respectively (Scheme III). Further extensions of this work to more substituted derivatives and to nitrogen and sulfur analogues are currently being investigated in our laboratories.

Acknowledgment. We thank the National Science Foundation for its generous support of this work, and acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research.

Supplementary Material Available: Typical experimental procedures and spectral data for new compounds (5 pages). Ordering information is given on any current masthead page.

(10) The S_N2 regioselectivity observed is in contrast with the S_N2' selectivity observed with other zinc reagents (RZnX⁴ or R₂Zn), see: (a) Nakamura, E.; Aoki, S.; Sekiya, K.; Oshino, H.; Kuwajima, I. *J. Am. Chem. Soc.* 1987, 109, 8056. (b) Sekiya, K.; Nakamura, E. *Tetrahedron Lett.* 1988, 29, 5155. (c) Goering, H. L.; Kanter, S. S. *J. Org. Chem.* 1983, 48, 721. (d) Underiner, T. L.; Paisley, S. D.; Schmitter, J.; Lesheski, L.; Goering, H. L. *J. Org. Chem.* 1989, 54, 2369.

(11) Seebach, D. *Angew. Chem.* 1979, 91, 259; *Angew. Chem., Int. Ed. Engl.* 1979, 18, 239.

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