

## Selective Multiple Methylene Insertion Reactions Mediated by Iodomethylzinc Iodide:

### Mechanistic Considerations and Synthetic Applications

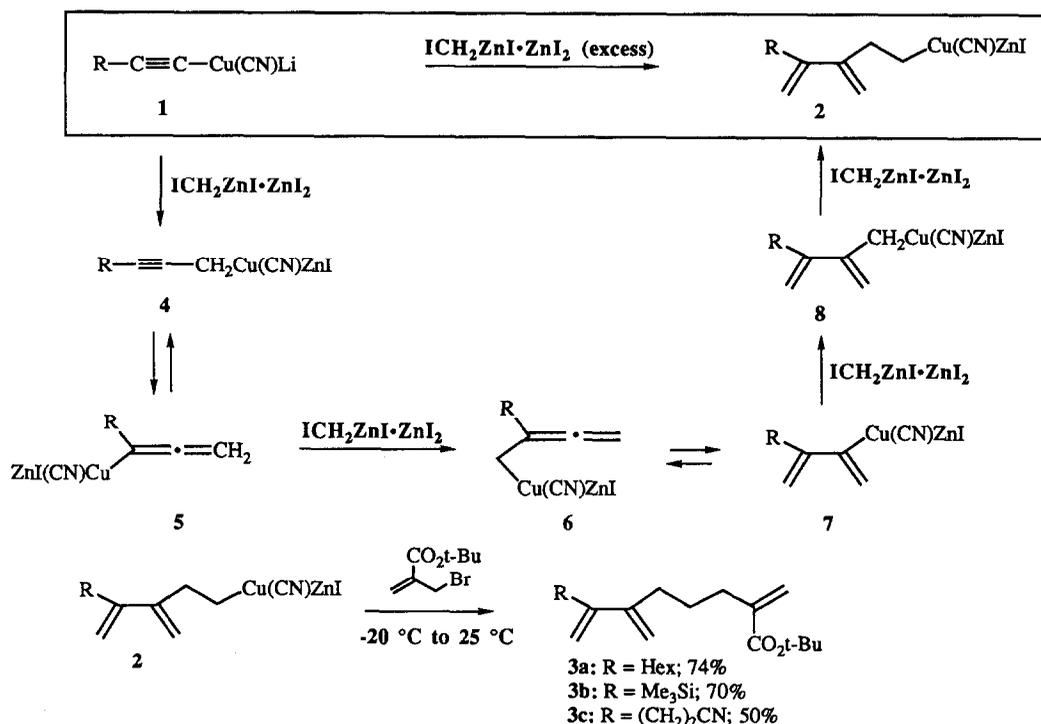
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**Summary:** The reaction of alkynylcoppers **1** with an excess of iodomethylzinc iodide selectively furnishes the quadruple methylene insertion copper organometallics **2** in fair to good yields. The mechanism of the reaction has been investigated and postulated intermediates such as **4** or **8** have been trapped with electrophiles like aldehydes or ketones in excellent yields. A new *in situ* preparation of propargylic copper derivatives **4** starting from readily available alkynylcopper compounds has been developed leading to homopropargylic alcohols in 80-95% yield.

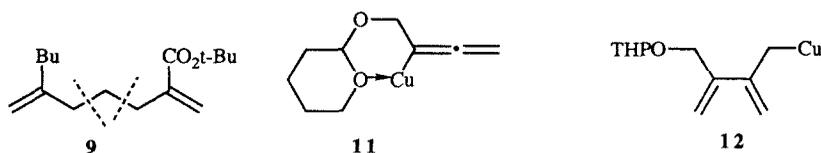
Halomethylzinc organometallics have been used in organic chemistry primarily as cyclopropanation reagents.<sup>1</sup> However, we reported recently that these zinc carbenoids could also serve as very selective monomethylene homologation reagents for

Scheme I



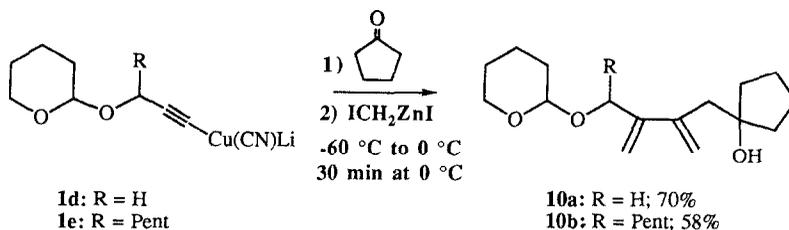
organocopper compounds.<sup>2</sup> We now report that *multiple methylene insertions* can also be performed in a very selective manner (Scheme I). The treatment of an alkynylcopper **1** (1.0 equiv.) with an excess of iodomethylzinc iodide (5 equiv.) affords a dienylcopper derivative of type **2** which, after allylation with tert-butyl  $\alpha$ -(bromomethyl)acrylate<sup>3</sup> (0.6 equiv.), furnishes the acrylic esters **3** in 50-74% isolated yields based on the allylating reagent.<sup>4</sup> In this reaction sequence, the alkynylcopper **1** is first homo- logated to the propargylic copper compound **4**, which is in equilibrium with the allenylcopper **5**. This copper derivative is reactive enough to insert another methylene unit giving the allylcopper **6**, which is in equilibrium with the dienylcopper **7**. A further reaction with iodomethylzinc iodide<sup>5</sup> converts **7** to a new allylic copper compound of type **8** which inserts a fourth methylene group affording the copper organometallic **2**. The reagent **2** does not undergo further insertions under our reaction conditions, and is trapped by an allylic bromide.<sup>4</sup>

This proposed reaction pathway of the quadruple methylene insertion has been confirmed by the following experiments. A propargyl copper intermediate<sup>6</sup> **4a** (R = Hex), prepared from 1-bromo-2-nonyne<sup>7</sup> (i) Zn (1.5 equiv.), THF, 0 °C, 1 h, > 85% yield; (ii) CuCN·2 LiCl<sup>8</sup> (1 equiv.) -60 °C to 0 °C, 1 h), gives after methylene homologation (ICH<sub>2</sub>ZnI (3.5 equiv.)), and allylation with tert-butyl  $\alpha$ -(bromomethyl)acrylate, the ester **3a** in 70% yield. To demonstrate that allylic organometallics such as **6** or **8** can insert a methylene unit, we treated 2-butyl-2-propenylzinc bromide<sup>7b</sup> with ICH<sub>2</sub>ZnI (ca. 4 equiv.; 0 °C to 25 °C, 1 h). After the addition of CuCN·2 LiCl (1 equiv.) and tert-butyl  $\alpha$ -(bromomethyl)acrylate (0.6 equiv.) the ester **9** is obtained in 78% yield. Also, depending on the structure of the starting alkynylcopper, a *selective*



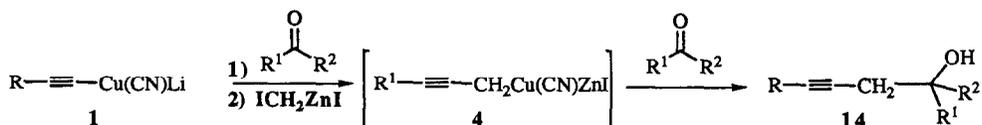
*triple methylene insertion* can be achieved. Thus, the addition of iodomethylzinc iodide (3.5 equiv.; -60 °C to 0 °C, 30 min. at 0 °C) to a mixture of tetrahydropyranyl (THP) protected alkynylcopper compounds of type **1d-e** and a ketone such as cyclopentanone or a sterically hindered aldehyde<sup>8</sup> affords triple methylene insertion products of type **10** in 58-70% yields (Scheme II). The intermediate organometallic of type **11** stabilized by chelation is not reactive enough to add to the ketone present, however, the further homologated allylic reagent **12** reacts with this ketone before undergoing another methylene insertion. With more reactive carbonyl compounds or with less sterically hindered alkynylcopper reagents, the intermediate propargylcopper is reactive

Scheme II



enough to be trapped by these electrophiles. This reaction has been developed to a new efficient *in situ* generation of propargylic copper reagents<sup>9</sup> of type 4. Readily available alkynylcoppers can be homologated by  $\text{ICH}_2\text{ZnI}$  and quenched *in situ* by a carbonyl compound present providing regiospecifically<sup>10</sup> the homopropargylic alcohols of type 14 in good to excellent yields<sup>4</sup> (Scheme III and Table I).

Scheme III



**Table I.** Homopropargylic alcohols 14a-e obtained by the reaction of an alkynylcopper with (iodomethyl)zinc iodide in the presence of a carbonyl compound.

Alkynyl copper	Carbonyl compound	Product	Yield(%) <sup>11</sup>
$\text{Me}_3\text{Si}-\text{C}\equiv\text{C}-\text{Cu}(\text{CN})\text{Li}$ <b>1b</b>	PhCHO	$\text{Me}_3\text{Si}-\text{C}\equiv\text{C}-\text{CH}_2\text{CH}(\text{OH})\text{Ph}$ <b>14a</b>	95
<b>1b</b>	PhCOCH <sub>3</sub>	$\text{Me}_3\text{Si}-\text{C}\equiv\text{C}-\text{CH}_2\text{CH}(\text{OH})(\text{CH}_3)\text{Ph}$ <b>14b</b>	89
<b>1b</b>	cyclohexanone	$\text{Me}_3\text{Si}-\text{C}\equiv\text{C}-\text{CH}_2-\text{C}(\text{OH})$ 	90
$\text{THPOCH}_2-\text{C}\equiv\text{C}-\text{Cu}(\text{CN})\text{Li}$ <b>1d</b>	PhCHO	$\text{THPOCH}_2-\text{C}\equiv\text{C}-\text{CH}_2-\text{CH}(\text{OH})\text{Ph}$ <b>14d</b>	80
 <b>1f</b>	PhCHO	 <b>14e</b>	95

In summary, the nature of the alkynylcopper substituent (R) and the choice of the electrophile (aldehyde or ketone) provides either mono or triple methylene insertion products, whereas in the absence of an electrophile a clean quadruple methylene insertion is observed. The study of the scope of these unique multiple methylene homologation reactions is currently underway in our laboratories.

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  - Typical procedures: (a) Preparation of tert-butyl 2,6,7-trimethylenetridecanoate (**3a**). A solution of butyllithium (5 mmol, 1.6 M in hexane) was added at -60 °C to octyne (5 mmol in 5 mL of THF). The reaction mixture was warmed to 0 °C, cooled back to -60 °C and a solution of CuCN·2 LiCl (5 mmol in 10 mL of THF) was added. The reaction mixture was warmed to 0 °C. After 5 min. it was cooled to -60 °C and a solution of ICH<sub>2</sub>ZnI<sup>2,5</sup> (10 mL, 2.5 M solution in THF) was added at such a rate that the temperature remained below -60 °C. The reaction mixture was warmed carefully to 0 °C (a very exothermic reaction starts at -40 °C) and a cooling bath was necessary to avoid the temperature rising above 0 °C. After 1 h at 0 °C, the reaction mixture was cooled to -60 °C and tert-butyl α-(bromomethyl)acrylate (660 mg, 3 mmol) was added. After 2 h at 0 °C, the reaction was worked up as usual and the resulting crude oil was purified by flash chromatography (ethyl acetate/hexane: 0.5/99.5) affording **3a** as a colorless oil (679 mg; 74%).  
(b) Preparation of 4-trimethylsilyl-1-phenyl-3-butyn-1-ol **14a**. The same procedure described above was performed using trimethylsilylacetylene (490 mg, 5 mmol), benzaldehyde (318 mg, 3 mmol), butyllithium (5 mmol), CuCN·2 LiCl (5 mmol) and ICH<sub>2</sub>ZnI (20 mmol, ca. 2.5 M solution in THF). After workup, the crude oil was purified by flash chromatography affording analytically pure alcohol **14a** (627 mg, 95% yield) as a colorless oil.
  - (a) Seyferth, D.; Andrews, S.B. *J. Organomet. Chem.* **1971**, *30*, 151; (b) Seyferth, D.; Dertouzos, H.; Todd, L.J. *J. Organomet. Chem.* **1965**, *4*, 18.
  - The propargylic copper derivatives prepared under our conditions are stable reagents. They show no tendency to dimerize. This is in strong contrast with allylic copper compounds: (a) Lipshutz, B.H.; Crow, R.; Dimock, S.H.; Ellsworth, E.L.; Smith, R.A.J.; Behling, J.R. *J. Am. Chem. Soc.* **1990**, *112*, 4063; (b) Lipshutz, B.H.; Ellsworth, E.L.; Dimock, S.H.; Smith, R.A.J. *J. Org. Chem.* **1989**, *54*, 4977; (c) Lipshutz, B.H.; Ellsworth, E.L.; Dimock, S.H.; Smith, R.A.J. *J. Am. Chem. Soc.* **1990**, *112*, 4404; (d) Lipshutz, B.H.; Ung, C.; Elworthy, T.R.; Reuter, D.C. *Tetrahedron Lett.* **1990**, *31*, 4539. A detailed study of the reactivity of these propargylic copper derivatives is currently underway.
  - This propargyl bromide has been prepared according to (a) Brandsma, L. *Preparative Acetylenic Chemistry (Second Edition)*, Elsevier **1988**, p. 81 and 247. It has been converted to the propargylic zinc bromide in THF according to; (b) Gaudemar, M. *Bull. Soc. Chim. Fr.* **1962**, 974.
  - The reaction of the alkynylcopper **1d** with a hindered aldehyde like 4,4-diethyl-5-oxopentanenitrile or a ketone such as acetophenone leads to the triple methylene homologation product respectively **13a** (52% yield) and **13b** (76% yield). Similarly, the reaction of the propargylic ether **1f** with cyclopentanone in the presence of an excess of ICH<sub>2</sub>ZnI afforded the diene **15** in 63% yield.
  - Propargylic organometallics are generally prepared from propargylic halides which are obtained in moderate yields from the corresponding alkyne (see reference 7a). Thus, the direct synthesis outlined in Scheme III saves at least two reaction steps.
  - Starting from the alkynyl copper **1b**, **1d** and **1f** only homopropargylic alcohols of type **14** were obtained. However by using the alkynylcopper **1a**, a mixture of allenic and homopropargylic alcohols was isolated. Compare with: (a) Zweifel, G.; Hahn, G. *J. Org. Chem.* **1984**, *49*, 4565; (b) Pansard, J.; Gaudemar, M. *Bull. Soc. Chim. Fr.* **1968**, 3332; (c) Gaudemar, M.; Moreau, J.L. *Bull. Soc. Chim. Fr.* **1968**, 5037; (d) Moreau, J.L.; Gaudemar, M. *Bull. Soc. Chim. Fr.* **1970**, 2171, 2175; (e) Moreau, J.L. *Bull. Soc. Chim. Fr.* **1975**, 1248.
  - All indicated yields refer to isolated yields of analytically pure products (> 95% pure by capillary GC analysis). Satisfactory spectral data (IR, <sup>1</sup>H and <sup>13</sup>C NMR, mass spectra and high resolution mass spectra) were obtained for all new compounds.

