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1,*n*-Heterobimetallic Reagents of Zinc and Copper: A New Class of Multicoupling Reagents

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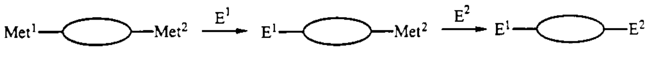
Summary: Various primary 1,*n*-diiodides (*n* = 4–6) were converted to 1,*n*-heterobimetallics of zinc and copper by insertion of zinc followed by a transmetalation with CuCN·2LiCl. These new reagents react with high selectivity with two different electrophiles E^1 and E^2 affording highly polyfunctional molecules of type **6** in good yields.

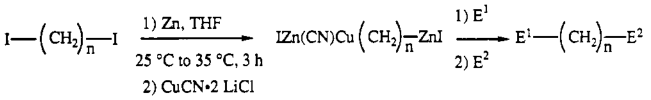
Organometallics bearing two carbon–metal bonds have unique synthetic applications.[1] If the two carbon–metal bonds are in close proximity,[2] their mutual interactions will modify the chemical properties of each carbon–metal bond and unique reactivity patterns will be observed for these reagents. On the other hand, if the two carbon–metal bonds are separated by several carbon atoms, then a chemical behavior typical of each carbon–metal bond will usually be observed. Of special interest as multicoupling reagents[3] are heterobimetallic compounds of type **1** which contain two different metals, Met^1 and Met^2. This type of reagent can, in principle, undergo a selective monocoupling with a first electrophile E^1, affording a functionalized intermediate organometallic **2**. In a second step, the compound **2** can react with a different electrophile E^2 and produce polyfunctional molecules of type **3** (Scheme I). The synthetic utility of this reaction scheme will depend on the chemoselectivity observed in the first reaction step. Herein we report our first results demonstrating that various zinc and copper bimetallic compounds **4** can act as efficient multicoupling reagents, reacting selectively with a variety of electrophiles E^1 such as aldehydes (entries 1, 2, 9, 10 of Table I), iodoalkynes (entry 3), enones (entries 4, 5, 8, 13), nitro olefins (entries 6, 12, 14) and alkylidenemalonates (entries 7, 15) affording highly functionalized organometallics of zinc and copper **5** (Table I).[4] These intermediates can undergo a second bond formation with a different second electrophile E^2 such as an enone (entry 8), iodine (entry 1), an allylic halide (entries 2, 4, 6, 9–13, 15), an aldehyde (entry 3), water (entry 14), or chlorotrimethylstannane (entries 5, 7) leading to the polyfunctional molecules **6** (Scheme II and Table I). The overall yields of this one-pot procedure based on the first electrophile (0.7 equiv) fall between 59% and 81%, which correspond to 75–90% per reaction step.[5]

Scheme I



1 **2** **3**

Scheme II



7: n = 4-6 **4**: n = 4-6 **6**: n = 4-6

The heterobimetallics of zinc and copper **4** were readily prepared by reacting the diiodoalkane **7** (*n* = 4–6) with zinc dust[6] in THF (Zn (2 equiv), 25–40 °C, 3 h, >85% yield), followed by the addition of CuCN·2LiCl (1.0 equiv) and of pentane (ca. 30 volume %).[5] The electrophile E^1 (0.7

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[1] For a review, see: (a) Bickelhaupt, F. *Angew. Chem.* **1987**, *99*, 1020; *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 990. See also: (b) Fujita, K.; Ohnuma, Y.; Yasuda, H.; Tani, H. J. *Organomet. Chem.* **1976**, *113*, 201. (c) Yasuda, H.; Tatsumi, K.; Nakamura, A. *Acc. Chem. Res.* **1985**, *18*, 120. (d) Boudjouk, P.; Sooriyakumaran, R.; Kapfer, C. A. *J. Organomet. Chem.* **1985**, *281*, C21. (e) Hart, H.; Harada, K.; Frank Du, C. J. *J. Org. Chem.* **1985**, *50*, 3104. (f) Xiong, H.; Rieke, R. D. *J. Org. Chem.* **1989**, *54*, 3247. (g) Murty, Y. V. S. N.; Pillai, C. N. *Tetrahedron Lett.* **1990**, *31*, 6067. (h) Harvey, S.; Junk, P. C.; Raston, C. L.; Salem, G. *J. Org. Chem.* **1988**, *53*, 3134. (i) Alonso, T.; Harvey, S.; Junk, P. C.; Raston, C. L.; Skelton, B. W.; White, A. H. *Organometallics* **1987**, *6*, 2110. (j) Bogdanovic, B. *Acc. Chem. Res.* **1988**, *21*, 261. (k) Holtkamp, H. C.; Schat, G.; Blomberg, C.; Bickelhaupt, F. *J. Organomet. Chem.* **1982**, *240*, 1. (l) Freijee, F. J. M.; Schat, G.; Akkerman, O. S.; Bickelhaupt, F. *J. Organomet. Chem.* **1982**, *240*, 217. (m) Seetz, J. W. F. L.; Schat, G.; Akkerman, O. S.; Bickelhaupt, F. *Angew. Chem.* **1983**, *95*, 242; *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 248. (n) Seetz, J. W. F. L.; Schat, G.; Akkerman, O. S.; Bickelhaupt, F. *J. Am. Chem. Soc.* **1982**, *104*, 6848. (o) Seetz, J. W. F. L.; Schat, G.; Akkerman, O. S.; Bickelhaupt, F. *J. Am. Chem. Soc.* **1983**, *105*, 3336. (p) Seetz, J. W. F. L.; Tol, R.; Akkerman, O. S.; Bickelhaupt, F. *Synthesis* **1983**, 721. (q) Canonne, P.; Foscolos, G. B.; Belanger, D. *J. Org. Chem.* **1980**, *45*, 1828. (r) Canonne, P.; Bernatchez, M. *J. Org. Chem.* **1986**, *51*, 2147. (s) Canonne, P.; Bernatchez, M. *J. Org. Chem.* **1987**, *52*, 4025. (t) Canonne, P.; Boulanger, R.; Bernatchez, M. *Tetrahedron Lett.* **1987**, *28*, 4997. (u) Yasuda, H.; Nakamura, A. *Angew. Chem.* **1987**, *99*, 745; *Angew. Chem. Int., Ed. Engl.* **1987**, *26*, 723.

[2] For the reactivity of 1,1-heterobimetallics see: (a) Knochel, P.; Normant, J. F. *Tetrahedron Lett.* **1986**, *27*, 1039, 1043, 4427, 4431, and 5727. (b) Tucker, C. E.; Rao, S. A.; Knochel, P. *J. Org. Chem.* **1990**, *55*, 5446. (c) Eisch, J. J.; Piotrowski, A. *Tetrahedron Lett.* **1983**, *24*, 2043. (d) Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 3611. (e) Pine, S. H.; Zahler, R.; Evans, P. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **1980**, *102*, 3270. (f) Pine, S. H.; Shen, G. S.; Hoang, H. *Synthesis* **1991**, 165.

[3] (a) Seebach, D.; Knochel, P. *Helv. Chim. Acta* **1984**, *67*, 261. (c) Auvray, P.; Knochel, P.; Normant, J. F. *Tetrahedron Lett.* **1985**, *26*, 2329.

[4] For a discussion of the carbon–metal bond nature of compounds **5** and for another approach to polyfunctional zinc and copper organometallics see: (a) Knochel, P.; Jeong, N.; Rozema, M. J.; Yeh, M. C. P. *J. Am. Chem. Soc.* **1989**, *111*, 6474. (b) Knochel, P.; Achyutha Rao, S. *J. Am. Chem. Soc.* **1990**, *112*, 6146.

[5] Typical procedure: Preparation of the diketone **6h** (entry 8 of Table I): A dry 100 mL, three-necked flask was equipped with a magnetic stirring bar, a 25-mL pressure equilizing addition funnel bearing a rubber septum, a three-way stopcock, and a thermometer. The flask was charged with zinc dust (2.6 g, 40 mmol) and flushed with argon. After the addition of 1,2-dibromoethane (400 mg, 2.1 mmol) in 3 mL of dry THF, the resulting zinc suspension was heated gently with a heat gun until the ebullition of the solvent was observed. The reaction mixture was stirred for 1 min, and the heating process was repeated twice. Chlorotrimethylsilane (0.15 mL, 1.2 mmol) was added, and the dark gray zinc suspension was stirred for 2 min. A THF solution of 1,4-diiodobutane (3.10 g, 10 mmol) in 10 mL of dry THF was then added dropwise, and the temperature increased to 40 °C. After 3 h at 40 °C, the formation of 1,4-bis-zinc reagent was complete. The progress of the reaction was monitored by GLC analysis of hydrolyzed reaction aliquots. The excess zinc was allowed to settle, and the resulting clear solution of the zinc reagent was transferred via syringe to a solution of CuCN (0.90 g, 10 mmol) and LiCl (0.84 g, 20 mmol) in 10 mL of THF at –60 °C. The reaction mixture was allowed to warm to 0 °C, affording a yellow-greenish solution, which was cooled back to –60 °C. Pentane (10 mL) was added, followed by 2-cyclohexenone (676 mg, 7 mmol) and chlorotrimethylsilane (1.62 g, 15 mmol). The reaction mixture was allowed to warm to –25 °C and was stirred for 12 h at this temperature. Then 3-iodo-2-cyclohexenone (3.3 g, 15 mmol) was added at –70 °C, and the reaction mixture was allowed to warm to room temperature and was stirred for 15 h. The reaction was diluted with ether (250 mL) and washed with an aqueous ammonium chloride solution (2 × 30 mL). The layers were separated, and the aqueous phase was extracted with ether (2 × 50 mL). The combined organic layer was washed with brine solution (30 mL), dried over $MgSO_4$, and filtered, and the solvent was evaporated. The resulting crude oil was dissolved in 10 mL of THF and treated with a 1 M THF solution of Bu_4NF (15 mL, 15 mmol). After 0.5 h the reaction was worked up and the residue was purified by flash column chromatography (solvent: hexane/ethyl acetate, 70:30), affording 1.11 g of analytically pure diketone **6h** (64% yield).

[6] Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390.

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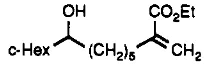
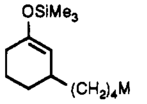
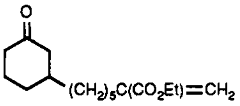
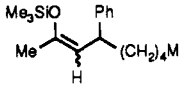
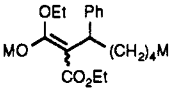
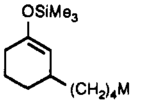
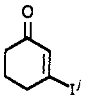
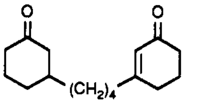
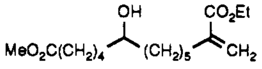
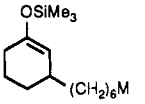
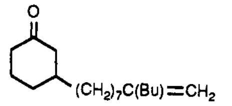
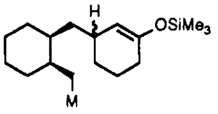
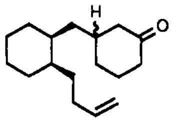
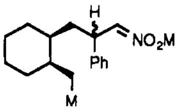
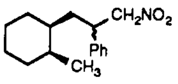
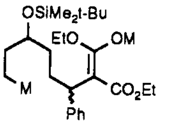
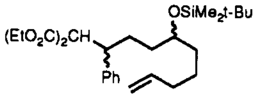
Table I. Intermediate Zinc and Copper Organometallics 5 Obtained by the Selective Addition of an Electrophile E^1 to the Heterobimetallics of Type 4 and Products 6 Obtained by the Additon of a Second, Different Electrophile E^2 to 5

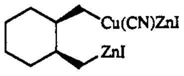
entry	heterobimetallic reagent	electrophile E^1	intermediate organometallic 5[g]	electrophile E^2	product of type 6	overall yield[a] (%)
1	4a	PhCHO[b]	$PhCH(OM)(CH_2)_4M$ 5a	I_2	$PhCH(OH)(CH_2)_4I$ 6a	59
2	4a	c-HexCHO[b]	c-$HexCH(OM)(CH_2)_4M$ 5b	ethyl α-(bromomethyl)acrylate[h]	 6b	62
3	4a	$BuC{\equiv}CI$[c]	$BuC{\equiv}C(CH_2)_4M$ 5c	PhCHO[b]	$BuC{\equiv}C(CH_2)_4CH(OH)Ph$ 6c	64
4	4a	cyclohexenone[d]	 5d	ethyl α-(bromomethyl)acrylate[h]	 6d	70
5	4a	benzylideneacetone[d]	 5e	Me_3SnCl[i]	$H_3CC(O)CH_2CH(Ph)(CH_2)_4SnMe_3$ 6e	65
6	4a	nitrostyrene[e]	$MO_2N{=}C(H)CH(Ph)(CH_2)_4M$ 5f	allyl bromide	$O_2NCH_2CH(Ph)(CH_2)_5CH{=}CH_2$ 6f	81
7	4a	$(EtO_2C)_2C{=}C(H)Ph$[f]	 5g	Me_3SnCl[i]	$(EtO_2C)_2CHCH(Ph)(CH_2)_4SnMe_3$ 6g	74
8	4a	cyclohexenone[d]	 5d		 6h	64
9	4a	$MeO_2C(CH_2)_4CHO$[b]	$MeO_2C(CH_2)_4CH(OM)(CH_2)_4M$ 5h	ethyl α-(bromomethyl)acrylate[h]	 6i	68
10	4b	PhCHO[b]	$PhCH(OM)(CH_2)_6M$ 5i	ethyl α-(bromomethyl)acrylate[h]	$PhCH(OH)(CH_2)_6C(CO_2Et){=}CH_2$ 6j	67
11	4c	cyclohexenone[d]	 5j	2-(bromomethyl)-1-hexene[h]	 6k	59
12	4c	nitrostyrene[e]	$MO_2N{=}C(H)CH(Ph)(CH_2)_6M$ 5k	allyl bromide[h]	$O_2NCH_2CH(Ph)(CH_2)_7C(H){=}CH_2$ 6l	64
13	4d	cyclohexenone[d]	 5l	allyl bromide[h]	 6m	74[k]
14	4d	nitrostyrene[e]	 5m	H_2O	 6n	74[k]
15	4e	$(EtO_2C)_2C{=}C(H)Ph$[f]	 5n	allyl bromide[h]	 6o	75[k]

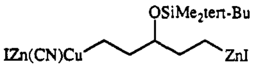
[a] Isolated yields of analytically pure products. Satisfactory spectral data (IR, ^1H, ^{13}C NMR, high-resolution mass spectra) were obtained for all compounds. [b] Aldehyde (0.7 equiv), $BF_3{\cdot}OEt_2$ (2 equiv), −78 °C to −20 °C, 15 h. [c] Hexynyl iodide (0.7 equiv), −78 °C to −35 °C, 15 h. [d] Enone (0.7 equiv), Me_3SiCl (2 equiv), −78 °C to −25 °C, 15 h. [e] Nitrostyrene (0.7 equiv), −78 °C to −10 °C, 2 h. [f] Diethyl benzylidenemalonate (0.7 equiv), −78 °C to −25 °C, 6 h. [g] M = Cu(CN)ZnI or ZnI. [h] Allylic bromide (1.5 equiv), −78 °C to 25 °C, 0.5 h. [i] Me_3SnCl (1.5 equiv), −78 °C to 25 °C, 1 h. [j] 3-Iodo-2-cyclohexen-1-one (1.5 equiv), −78 °C to +25 °C, 15 h. [k] Mixture of diastereoisomers.

equiv) is added to the reaction mixture, furnishing the desired monocoupling product with less than 5% of symmetrical dicoupling adduct ($E^1(CH_2)_nE^1$). The addition of pentane was found to be critical for this selectivity and can be rationalized by assuming that this low dielectric constant solvent favors the formation of higher aggregates of **5** having lower reactivities.[7] As shown in Table I, bimetallic reagents in which the two metals are separated by 4, 5, or 6 carbon atoms display excellent selectivities. More substituted reagents such as **4d** can be readily prepared.[8] The coupling of **4d** with electrophiles yields pure *cis*-1,2-cyclohexane derivatives (entries 13 and 14). Finally, the functionalized[9] heterobimetallic **4e** (entry 15) reacts selectively with diethyl benzylidenemalonate and allyl bromide, affording the desired coupling product **6o** in 75% yield.

$IZn(CN)Cu(CH_2)_nZnI$

4a: n = 4
4b: n = 5
4c: n = 6


4d


4e

We have observed that the zinc and the copper homobimetallics ($IZn(CH_2)_4ZnI$ (**8**) and $IZn(CN)Cu(CH_2)_4Cu(CN)ZnI$ (**9**)) did not undergo selective reactions. Thus the *dicopper reagent* **9** reacts with benzaldehyde (0.7 equiv) in the presence of $BF_3{\cdot}OEt_2$ (2 equiv) and leads to a mixture of the desired monoadduct **5a** and the diadduct $PhCH(OM)(CH_2)_4CH(OM)Ph$ (60:40 ratio by GLC analysis of an hydrolyzed reaction aliquot). The remarkable aspect of the reactivity of the *heterobimetallics* of zinc and copper **4** is the broad range of electrophiles[10] which react selectively to give functionalized organometallics of type **5** (Table I). Nevertheless, we observed that electrophiles which react with organozinc halides (RZnX) in the presence of *a catalytic amount* of $CuCN{\cdot}2LiCl$ such as acyl chlorides or allylic halides[6] did not display this selectivity and their reaction with **4** afforded a mixture of mono- and diadducts under various reaction conditions. The unique selectivity displayed by the reagents **4** can be explained by the high reactivity of the carbon-copper bond (compared to the carbon-zinc bond) toward electrophiles leading to intermediate organometallics **5** (Table I), the structures of which are best viewed as being mixed copper-zinc clusters also containing lithium salts coming from $CuCN{\cdot}2LiCl$. These reagents have a diminished reactivity,[11] which is accentuated by the presence of pentane as cosolvent and in some cases by chelating interactions (as for the compounds **5a-b,f-i,k,m,n**). This preliminary study shows that the two primary carbon-metal bonds of a 1,*n*-heterobimetallic reagent of zinc and copper (*n* = 4-6) can be differentiated by a variety of electrophiles E^1 allowing a new approach to various types of new highly functionalized intermediate zinc and copper organometallics **5** (Table I). After their coupling with a second, different electrophile E^2 a broad range of polyfunctional molecules are obtained. Extensions of this method are currently underway in our laboratories.

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Supplementary Material Available: Characterization data for all new compounds (10 pages). Ordering information is given on any current masthead page.

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(7) (a) McGarrity, J. F.; Ogle, C. A. *J. Am. Chem. Soc.* **1985**, *107*, 1805. (b) McGarrity, J. F.; Ogle, C. A.; Brich, Z.; Loosli, H.-R. *J. Am. Chem. Soc.* **1985**, *107*, 1810. (c) Kaufmann, E.; Raghavachari, K.; Reed, A. E.; Schleyer, P. v. R. *Organometallics* **1988**, *7*, 1597. (d) Bates, T. F.; Clarke, M. T.; Thomas, R. D. *J. Am. Chem. Soc.* **1988**, *110*, 5109.

(8) 1,2-Diiodomethylcyclohexane was prepared from 1,2-dihydroxymethylcyclohexane via the dimesylate: (a) Haggis, G. A.; Owen, L. N. *J. Chem. Soc.* **1953**, 389. (b) Bailey, W. F.; Gagnier, P. R.; Patricia, J. J. *J. Org. Chem.* **1984**, *44*, 2098.

(9) 1,5-Diiodo-3-[(*tert*-butyldimethylsilyl)oxy]pentane was prepared from diethyl 1,3-acetonedicarboxylate via standard procedures (see supplementary material).

(10) Symmetrical di-Grignard reagents do not react selectively with electrophiles (see: (a) Bickelhaupt, F. In *Organometallics in Organic Synthesis 2*; Springer: Berlin-Heidelberg, 1989; p 145. (b) Raston, C. L.; Salem, G. In *The Chemistry of the Metal-Carbon Bond*; Hartley, F. R., Ed.; John Wiley: New York 1987; Vol 4, Chapter 2, p 159) and only *unsymmetrical* dimetallics bearing two carbon-metal bonds having a very different reactivity undergo selective reactions (see ref 1f, 10a and Rieke, R. D.; Xiong, H. *J. Org. Chem.* **1991**, *56*, 3109).

(11) It has been observed in related studies that the reactivity of the copper reagents RCu(CN)ZnI is strongly reduced in the presence of an excess of zinc halides. Since 1 equiv of ZnX_2 is liberated in the reaction of the bimetallics **4** with E^1, the reactivity of compounds **5** is expected to be lower than the one of **4**.

A Direct Preparation of Vinylogous Acyl Anion Equivalents

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Summary: Unmasked vinylogous acyl anion equivalents **2** were prepared by the insertion of zinc to various β-halo, α,β-unsaturated ketones and esters **1**. The new reagents **2** react with various electrophiles in the presence of $CuCN{\cdot}2LiCl$ or catalytic amounts of Pd(0) complexes in excellent yields.

Acyl anion equivalents[2] form an important class of reagents that display an umpolung of the carbonyl group reactivity (d^1 reagents).[3] Many acyl anion equivalents are masked carbonyl derivatives, which, after the reaction with an electrophile, have to be converted to the free carbonyl

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[1] Permanent address: Nizam College, Osmania University, Hyderabad, India.

(2) For a comprehensive list of acyl anions, see: *Umpolung Synthons*; Hase, T. A., Ed.; John Wiley and Sons: New York, 1987.

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