Michael Additions of Functionalized Organozinc Reagents Mediated by Catalytic Quantities of Copper(I)

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One of the most impressive advances in organocopper chemistry over the past decade has been the development of methodology for preparing cuprates bearing ligands which contain various electrophilic centers. Existing protocols to these valuable reagents include (1) oxidative addition of extremely reactive Rieke copper to alkyl halides,[1] (2) insertion of Zn(0) into alkyl halides followed by transmetalation with CuCN•2LiCl,[2] and (3) low-temperature transmetalations between functionalized vinylzirconocenes and higher order (HO) cyanocuprates (Figure 1).[3] While each has its virtues, they share the common feature of being stoichiometric in copper. Isolated reports exist suggesting that catalytic copper salts can be used, although requirements such as higher temperatures and/or longer reaction times, and especially excesses of HMPA, detract from these methods.[4] We now describe a simple, general procedure for effecting Michael additions of functionalized organozinc reagents through the intermediacy of a cyanocuprate which is *catalytic* in Cu(I).

A functionalized organozinc halide, FG–R–Zn–X (**1**), is readily formed from zinc metal and an alkyl iodide.[2,5] Addition of MeLi (1 equiv) at −78 °C leads predominantly to a mixed dialkylzinc FG–R–Zn–Me (**2**). Exposure of this species to as little as 5 mol % of the HO cyanocuprate $Me_2Cu(CN)Li_2$ (from CuCN + 2MeLi)[6] in THF at −78 °C in the presence of Me_3SiCl (2–3 equiv)[7] effects transmetalation to **3**.[8] Introduction of an enone leads to 1,4-delivery of the functionalized group FG–R– (Scheme 1).

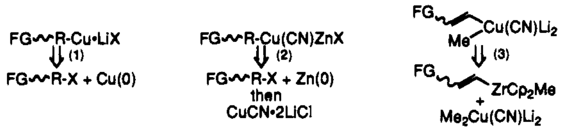


Figure 1.

Scheme 1.

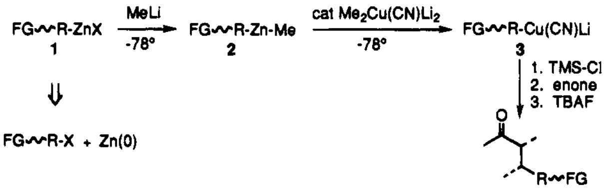
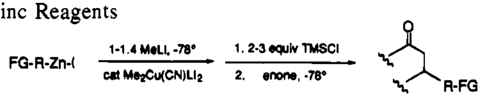
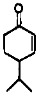
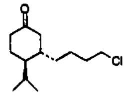
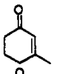
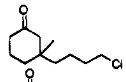
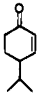
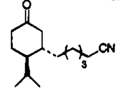
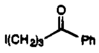
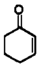
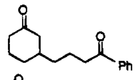
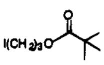
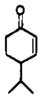
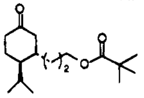
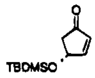
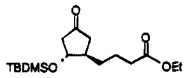
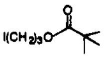
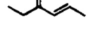
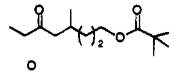
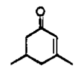
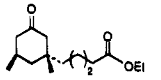
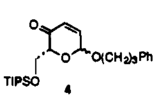
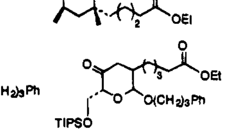
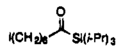
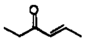
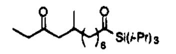


Table 1. Cuprate-Catalyzed 1,4-Additions of Functionalized Organozinc Reagents



Entry	Iodide	Enone	Product[a]	Yield(%)[b]
1	$I(CH_2)_4Cl$			89[c]
2	$I(CH_2)_4Cl$			83[d]
3	$I(CH_2)_5CN$			85[e]
4				85[f]
5				74[d,g,h]
6	$I(CH_2)_3CO_2Et$			81[j]
7				85
8	$I(CH_2)_4CO_2Et$			72[d,i,j]
9	$I(CH_2)_4CO_2Et$	 4		83[i,k,l]
10				74[l]

[a] Fully characterized by IR, NMR, MS, and HRMS data. [b] Isolated, chromatographically purified material. [c] A 9:1 mixture of diastereomers (^{1}H NMR). [d] 10 equiv of TMSCl was used. [e] A 10:1 mixture of diastereomers (by ^{1}H NMR). [f] Using 5 equiv of Zn(0) to prepare the zinc reagent. [g] Using FG-R-Zn-Me + 20 mol % MeCu(CN)Li. [h] Using 5% cuprate; yield with 10 mol % cuprate was 75%; with 20 mol % cuprate, yield was 77%. [i] A 7:1 mixture of diastereomers (by GC). [j] Only one diastereomer detected and/or isolated (by ^{1}H NMR or GC). [k] 10% starting material recovered. [l] Using 15 % cuprate and 4 equiv zinc reagent. [m] Only one diastereomer of the enone was used.

Results from a number of representative examples are summarized in Table 1. Chloride (entries 1, 2), nitrile (entry 3), ketone (entry 4), and ester (entries 5–9) moieties are all tolerated in these catalytic couplings, which (unlike most reactions of, *e.g.*, $FG-RCu(CN)ZnX)^2$ occur at −78 °C. Cyclic as well as acyclic substrates are amenable, and β,β-disubstituted cyclic enones react nicely (entries 2, 8),[9] as do highly oxygenated systems (*e.g.*, glycal **4**, entry 9). Transfer, apparently for the first time via organozinc chemistry, of a (TIPS) acylsilane (entry 10)[10] has also been effected, allowing for subsequent

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[1] Rieke, R. D.; Stack, D. E.; Dawson, B. T.; Wu, T.-C. *J. Org. Chem.* **1993**, *58*, 2483. Ebert, G. W.; Klein, W. R. *J. Org. Chem.* **1991**, *56*, 4744. Rieke, R. D.; Klein, W. R.; Wu, T.-C. *J. Org. Chem.* **1993**, *58*, 2492. Rieke, R. D.; Wehmeyer, R. M.; Wu, T.-C.; Ebert, G. W. *Tetrahedron* **1989**, *45*, 443. Rieke, R. D.; Wu, T.-C.; Stinn, D. E.; Wehmeyer, R. M. *Synth. Commun.* **1989**, *19*, 1833. Stack, D. E.; Dawson, B. T.; Rieke, R. D. *J. Am. Chem. Soc.* **1991**, *113*, 4672; **1992**, *114*, 5110. Stack, D. E.; Klein, W. R.; Rieke, R. D. *Tetrahedron Lett.* **1993**, *34*, 3063. Hanson, M. V.; Brown, J. D.; Rieke, R. D.; Niu, Q. J. *Tetrahedron Lett.* **1994**, *35*, 7205.

[2] Rozema, M. J.; AchyuthaRao, S.; Knochel, P. *J. Org. Chem.* **1992**, *57*, 1956. Rozema, M. J.; Eisenberg, C.; Lutjens, H.; Ostwald, R.; Belyk, K.; Knochel, P. *Tetrahedron Lett.* **1993**, *34*, 3115. Klement, I.; Knochel, P.; Chau, K.; Cahiez, G. *Tetrahedron Lett.* **1994**, *35*, 1177. Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117. Knochel, P. *Comprehensive Organometallic Chemistry II*; Pergamon Press: New York, in press.

[3] Lipshutz, B. H.; Keil, R. *J. Am. Chem. Soc.* **1992**, *114*, 7919. See also: Hojo, M.; Harada, H.; Hosomi, A. *Chem. Lett.* **1994**, 437.

[4] Nakamura, E.; Aoki, S.; Sekiya, K.; Oshino, H.; Kuwajima, I. *J. Am. Chem. Soc.* **1987**, *109*, 8056. Nakamura, E.; Kuwajima, I. *Org. Synth.* **1988**, *66*, 43. Kuwajima, I.; Nakamura, E. *Top. Curr. Chem.* **1990**, *155*, 1. Nakamura, E. *Synlett* **1991**, 539. Tamaru, Y.; Tanigawa, H.; Yamamoto, T.; Yoshida, Z. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 351.

[5] Jubert, C.; Knochel, P. *J. Org. Chem.* **1992**, *57*, 5425.

[6] Lipshutz, B. H. In *Organometallics in Synthesis. A Manual*; Schlosser, M., Ed., Wiley: New York, 1994; pp 283–382. Lipshutz, B. H.; Sengupta, S. *Org. React.* (New York), **1992**, *41*, 135.

[7] Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6015; 6019. Alexakis, A.; Berlan, J.; Besace, Y. *Tetrahedron Lett.* **1986**, *27*, 1047. Nakamura, E.; Matsuzawa, S.; Horiguchi, Y.; Kuwajima, I. *Tetrahedron Lett.* **1986**, *27*, 4029.

[8] Catalytic amounts of cuprate less than 5 mol % were not examined.

[9] For reasons which we do not understand, an acyclic β,β-disubstituted enone (*e.g.*, mesityl oxide) repeatedly gave none of the expected 1,4-adduct; mainly the 1,2-product was isolated.

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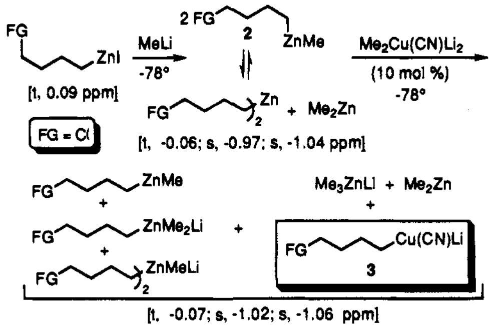
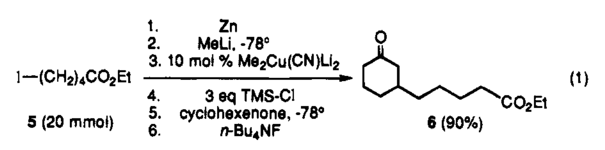
Scheme 2. ^{1}H NMR Data for a Mixture of Reagent **2** (FG = Cl) and Catalytic Higher Order Dimethyl Cyanocuprate



conversion to numerous functional groups, including an aldehyde. Most educts were fully consumed under the influence of 3 equiv of TMS-Cl, although more hindered enones required 10 equiv of this inexpensive additive (*e.g.*, entry 2). In all cases, the initial adduct is the TMS enol ether, which is readily cleaved with fluoride ion in THF to the corresponding ketone upon workup. The process is amenable to scale-up, as ester iodide **5** could be converted to keto ester **6** in a 20 mmol reaction in 90% isolated yield (eq 1).



The key to this Zn-to-Cu ligand exchange is the use of a dialkyl zinc FG−R−Zn−R′ (rather than FG-R-Zn-X),[2] as well as an anionic Cu(I) species (*i.e.*, a cuprate, as opposed to a salt such as CuCN•2LiCl alone).[11] This combination allows for rapid exchange of ligands between metals, including enolates attached initially to copper once 1,4-addition has taken place.[12] A low-temperature ^{1}H NMR study on the reagent mix itself revealed the *complete disappearance of the methyl singlet due to (catalytic)* $Me_2Cu(CN)Li_2$ *(*δ *−1.58)*. The mixed zinc species FG−R−Zn−Me (**2**), in equilibrium with a mixture of homozinc reagents,[13] has its three signals shifted slightly to higher field (*i.e.*, in the direction of a methyl zinc*ate*; Scheme 2). In return for methyl donation by the cuprate, the desired, transferrable group FG−R− must reside on copper. Unfortunately, the methylene protons next to copper in **3** (a triplet at δ −0.28; *cf.* data for an authentic sample, Scheme 2)[14] are not observed, nor are those adjacent to zinc in mixed zincate **7** (δ −0.31).[15] This is expected not only from an equilibrium strongly favoring a lower order (LO) cuprate,[16] but also due to the low percentages of both species present relative to neutral **2**. Hence, that the mixed cyanocuprate FG−R−Cu(CN)Li is generated *in situ* cannot be unequivocally established. Nonetheless, these data do suggest that rapid ligand exchanges produce a non-methyl-containing LO cuprate which, together with TMS-Cl, is likely to be the active species.[17] Addition of excess TMS-Cl to this solution at −78 °C had no effect on these ^{1}H chemical shifts, as anticipated.[7,18]

In summary, a new transmetalation process has been disclosed for converting functionalized organozinc halides to reactive *lithio*cuprates. The methodology takes advantage of the facility with which ligands can be exchanged between zinc and copper, ultimately providing a means of effecting rapid and efficient Michael additions. While somewhat akin to existing procedures,[1,2,4] these valued conjugate additions can now be conducted utilizing *catalytic* amounts of the transition metal involved, which translates into a far more economical and "environmentally friendly" approach.[19]

Acknowledgment. We warmly thank the NSF (CHE 93-03883) and the NIH (GM 40287) for their financial support of our programs, Prof. P. Knochel (Marburg) for details on the preparation of ω-oxozinc halides, and V. Chang and C. Lindsley (UCSB) for technical support.

Supplementary Material Available: Spectral data for all new compounds and ^{1}H and ^{13}C NMR data for products listed in Table 1 (26 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

JA943505W

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[10] Lipshutz, B. H.; Lindsley, C.; Susfalk, R.; Gross, T. *Tetrahedron Lett.* **1994**, *35*, 8999 and references therein.

[11] Use of 10 mol % CuCN (with or without LiCl) in place of $Me_2Cu(CN)Li_2$, together with FG-RZnMe, did lead to the 1,4-adduct in 67% yield *upon warming to room temperature*. Repeating this experiment, but adding additional MeLi (20 mol %) prior to quenching, increased the yield to 78%, further demonstrating the importance of added methyl ligands to the exchange process. For a related report based on a HO *magnesio* cuprate used *stoichiometrically*, see: Tucker, C. E.; Knochel, P. *J. Org. Chem.* **1993**, *58*, 4781.

[12] Lipshutz, B. H.; Wood, M. R. *J. Am. Chem. Soc.* **1993**, *115*, 12625.

[13] Srebnik, M.; Laloe, E. *Tetrahedron Lett.* **1994**, *35*, 5587. Nehl, H.; Scheidt, W. R. *J. Organomet. Chem.* **1985**, *289*, 1.

[14] An authentic sample was prepared from the chloro iodide *via* lithiation followed by treatment with CuCN•2LiCl, in THF.

[15] Prepared by combining Me_2Zn with 1-lithio-4-chlorobutane in THF at −78 °C.

[16] Lipshutz, B. H.; Wood, M. R. *Tetrahedron Lett.* **1994**, *35*, 6433.

[17] Control experiments using our standard reaction conditions (*i.e.*, *cf.* Table 1) but *without copper* present led to none of the 1,4-adduct. Subsequent introduction of a catalytic amount of copper to this unreactive mixture restored activity, and the 1,4 product was formed in good yield.

[18] Lipshutz, B. H.; Dimock, S. H.; James, B. *J. Am. Chem. Soc.* **1993**, *115*, 9283.

[19] The preparation of ethyl 5-(3′-oxocyclohexyl)pentanoate (**6**, eq 1) is representative, on a larger scale, of all products listed in Table 1. To a 50 mL round bottom flask equipped with a stir bar and septum and having been cooled under a stream of argon was added zinc powder (3.0 g, 46 mmol), followed by 16 mL of THF and 1,2-dibromoethane (155 μL, 1.78 mmol). This stirred slurry was heated to *ca.* 65 °C for 1 min using a heat gun. After this time, the flask was placed in a tap water bath (*ca.* 23 °C). TMS-Cl (155 μL, 1.20 mmol) was then added, and the slurry was stirred for 15 min. Neat ethyl 5-iodovalerate (6.7 mL, 40.0 mmol) was then added dropwise over 10 min. The flask was then placed in a 35 °C oil bath for overnight stirring. The reaction was initially exothermic, and THF was seen slowly refluxing around the neck of the round bottom flask. Dry ice was used to cool the neck of the flask so that the septum was not extracted by the THF. Twelve hours later, when the reaction was judged complete by TLC, the oil bath was removed. As usual, the presence of a white "dust", that never quite settles out, was noted. The reaction was allowed to cool to room temperature, at which time 20 mL of THF was added to the stirred slurry. Stirring was then halted, and the solids were allowed to settle, such that the THF solution of the alkylzinc iodide could be transferred *via* cannula to a clean, dry 250 mL round bottom flask equipped with a stir bar and septum. Two additional washes of THF (29 mL each) were then carried out to ensure complete transfer and proper dilution of alkylzinc iodide. This solution was then cooled to −78 °C, and MeLi in ether (23 mL, 36 mmol, 1.56 M) was added dropwise over 15 min. During the same time that the alkylmethylzinc was being formed, to a 25 mL round bottom flask, equipped with a stir bar and septum and having been cooled under argon, was added CuCN (178.9 mg, 2.0 mmol), followed by 10 mL of THF. The mixture was cooled to −78 °C, and MeLi in ether (2.6 mL, 4.0 mmol, 1.56 M) was added slowly. Once the addition of MeLi was complete, the slurry was gently warmed until the reaction mixture became homogeneous, and then it was recooled to −78 °C. With both solutions at −78 °C, the higher order dimethyl cyanocuprate was transferred *via* cannula to the alkylmethylzinc reagent. After 5 min at −78 °C, neat TMS-Cl (7.77 mL, 60.0 mmol) was added dropwise over 10 min, followed by 10 more minutes of stirring. Finally, neat 2-cyclohexenone (2.02 mL, 20.0 mmol) was added dropwise over 15 min *via* syringe. After 4.5 h, the reaction was complete as determined by TLC and was quenched by pouring the reaction mixture into 200 mL of pH 7 buffer and 200 mL of Et_2O in a 1 L separatory funnel. An additional 25 mL of ether was used to complete the transfer. The aqueous layer was further extracted with an additional 50 mL of ether. The combined organic layers were shaken for 5 min with 50 mL of 1 M TBAF in THF (Aldrich), followed by three washes with 100 mL of brine. The organics were then dried over anhydrous $MgSO_4$. After concentration *in vacuo*, flash chromatography on silica gel using 10:1 petroleum ether/ethyl acetate afforded 4.09 g (90%) of the product as a clear, pale-yellow oil: TLC (petroleum ether/ethyl ether 10:1) R_f 0.11; IR (neat) 2933(s), 2861(s), 1734(s), 1188(m) cm^{-1}; ^{1}H NMR δ 4.07 (q, J = 7.1 Hz, 2 H), 2.4−2.2 (m, 6 H), 2.0−1.5 (m, 6 H), 1.3 (m, 5 H), 1.2 (t, J = 7.2 Hz, 3 H); ^{13}C NMR δ 211.6, 173.4, 60.1, 47.9, 41.3, 38.3, 36.1, 34.1, 31.1, 26.0, 26.1, 24.8, 14.1; EIMS, *m/e* (relative intensity) 226 (M$^+$, 2), 181 (7), 135 (5), 101 (7), 98 (8), 97 (100), 82 (6), 81 (7), 67 (7), 55 (16); HREIMS calcd for [M$^+$, $C_{13}H_{22}O_3$] 226.1563, found 226.1569.