Cyanocuprate-*Catalyzed* 1,4-Additions of Vinylic Zirconocenes Using a Zincate as an Organolithium "Shuttle". A New and Potentially Practical Approach to 3-Component Couplings

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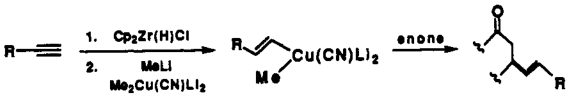
The combination of hydrozirconation/transmetalation from zirconium to copper has recently resulted in an efficient, direct method for vinyl ligand transfer in a 1,4-sense to enones starting with terminal acetylenes (Scheme I).[1] To further enhance the attractiveness of this chemistry, the next hurdle in its evolutionary development is the nontrivial objective of making the sequence catalytic in copper.[2] We now report a novel solution to this goal, as well as the potential for this protocol to be utilized in highly valued three-component couplings (3-CCs).[1]

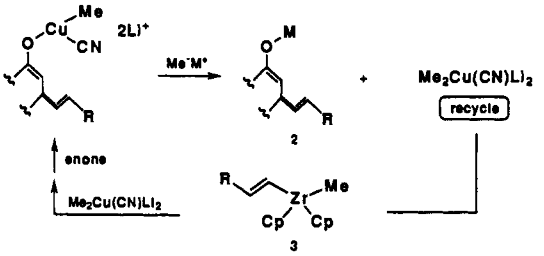
Given the 1:1 substrate:cuprate stoichiometry associated with our original procedure,[1] the initial adduct is formally a copper/lithium enolate, **1** (Scheme II).[3] In order to regenerate the higher order cuprate ($Me_2Cu(CN)Li_2$) for recycling into the vinyl zirconocene-to-1,4-vinyl adduct conversion (*i.e.*, **3** to **1**), a source of methyl anion (Me^-M^+) is required. Methyllithium itself, or any hard carbanionic equivalent, is unacceptable, since it cannot be tolerated by the educt. What does effect the desired transmetalation at −78 °C and yet does not compete with the cuprate as a Michael donor is the zincate, Me_3ZnLi.[4] This species, in effect, acts as a "shuttle", transporting the elements of MeLi to copper in enolate **1**. The overall procedure itself is summarized in Scheme III, and several representative examples can be found in Table I. Of special note is the observation that quantities as low as 5 mol % cuprate are sufficient.

Attempts to use the zincate itself (*i.e.*, without cuprate) to effect both the transmetalation and the subsequent Michael addition were not, in general, successful, although it is clear that transmetalation does occur to varying extents.[5] Since 1,4-additions of *mixed* zincates to enones are not known to be high yielding[6] (with the exception of those involving cyclopentenones),[7] it is difficult to pinpoint just where the problems lie. Nonetheless, once the cuprate is present, the zincate is subordinated to its primary role as a soft source of MeLi, which it performs very efficiently at low temperatures. It is the cuprate, therefore, which is responsible for getting the vinyl ligand from zirconium to the enolate stage.[8]

Scheme I



Scheme II



Scheme III

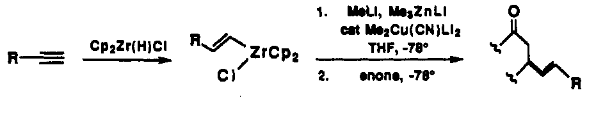
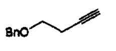
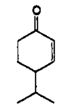
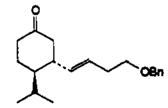
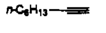
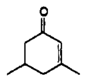
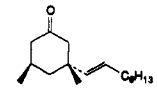
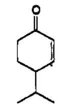
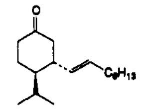
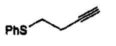
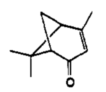
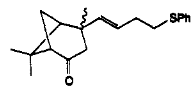
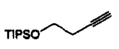
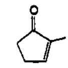
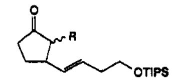
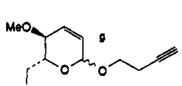
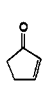
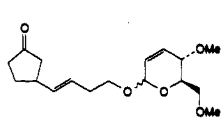
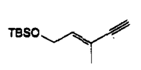
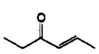
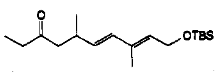


Table I. Cyanocuprate-Catalyzed Transmetalation–1,4-Additions to Enones

1-alkyne	enone	product[a]	yield (%)[b]
			81[c]
			84[c]
			81[d]
			71[c]
			81[c,e] 88[c,f]
			87[h]
			86[c]

[a] Fully characterized by IR, NMR, MS, and HRMS data. [b] Isolated. [c] Using 20 mol % cuprate. [d] Using 5 mol % cuprate. [e] R = Me; a 9:1 mix of isomers. [f] R = H. [g] An 8:1 mix of α:β isomers. [h] Using 10 mol % cuprate.

Finally, it has not gone unnoticed that the transmetalation between enolate **1** and Me_3ZnLi is likely to give rise to a zinc enolate **2**, M = $ZnMe_2Li$,[9] precisely the type of species found by Noyori *et al.*, in their much heralded 3-CC route to prostaglandin skeleta.[7,10] In principle, therefore, intermediate **2** (rather than the corresponding copper/lithium enolate, **1**)[11] should be capable

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[1] Lipshutz, B. H.; Keil, R. *J. Am. Chem. Soc.* **1992**, *114*, 7919.

[2] For a related process using copper *salts* and *alkyl* zirconocenes, see: Wipf, P.; Smitrovich, J. H. *J. Org. Chem.* **1991**, *56*, 6494.

[3] Christenson, B.; Olsson, T.; Ullenius, C. *Tetrahedron* **1989**, *45*, 523 and references therein.

[4] Isobe, M.; Kondo, S.; Nagasawa, N.; Goto, T. *Chem. Lett.* **1977**, 679.

[5] Lipshutz, B. H.; Arai, M.; Keil, R.; Wood, M. R., unpublished results.

[6] Tuckmantel, W.; Oshima, K.; Nozaki, H. *Chem. Ber.* **1986**, *119*, 104. Kjonaas, R. A.; Vawter, E. J. *J. Org. Chem.* **1986**, *51*, 3993.

[7] Morita, Y.; Suzuki, M.; Noyori, R. *J. Org. Chem.* **1989**, *54*, 1785.

[8] Control experiments using mixed zincates on β,β-disubstituted enones clearly indicate that the cuprate is by far the more reactive species.

[9] Given the presence of Cp_2ZrMe_2, a zirconium enolate (or mix of both) cannot be ruled out. Nonetheless, these are equally reactive species, *cf.*: Evans, D. A.; McGee, L. R. *Tetrahedron Lett.* **1980**, *20*, 3975.

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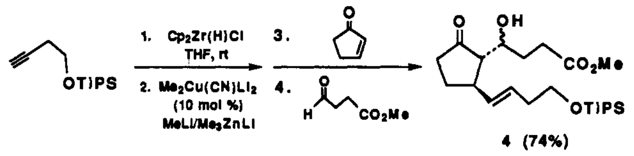
Scheme IV



of trapping electrophiles, suggesting the possibility of a *catalytic cuprate-based approach to 3-CC starting with a 1-alkyne*. In a preliminary experiment, the conjugate addition–aldol reaction scenario does in fact lead to the desired α,β-disubstituted ketone (Scheme IV). Remarkably, the yield of adduct **4** represents the culmination of six sequential events (hydrozirconation, MeLi addition to Zr, transmetalation by Cu, 1,4-addition, transmetalation by Zn, and an aldol reaction) in one flask mediated by four different but mutually compatible organometallics, each operating in a chemospecific fashion.

In summary, a new[12] one-pot method for carrying out cuprate 1,4-additions of vinylic ligands to conjugated enones has been developed which *originates from 1-alkynes and relies on catalytic amounts of copper*.[13] The method is highlighted by the unprecedented use of a zincate as a carrier of MeLi which converts a copper/lithium enolate to a reactive zinc enolate, thereby not only recycling the cuprate but providing an opportunity for additional C–C bond construction.[13-15] Further details on the scope of this technology will be reported shortly.

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Supplementary Material Available: NMR spectral data for all products (4 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(10) Noyori, R.; Suzuki, M. *Chem. Tracts: Org. Chem.* **1990**, *3*, 173. Suzuki, M.; Morita, Y.; Koyano, H.; Koga, M.; Noyori, R. *Tetrahedron* **1990**, *46*, 4809. Suzuki, M.; Koyano, H.; Noyori, R. *Synlett* **1989**, 22.

(11) Copper/lithium enolates are notoriously unreactive, *cf.*: Chapdelaine, M. J.; Hulce, M. *Org. React.* (*New York*) **1990**, *38*, 225.

(12) A patent application has been filed on behalf of the University of California.

(13) A representative procedure for the preparation of cyclopentanone **4** can be found in the supplementary material provided.

(14) For a related process using Me$_3$Al, see: Westermann, J.; Nickisch, K. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1368.

(15) A typical procedure, given for the preparation of product **4**, is as follows: To a 10-mL round-bottom flask equipped with a stir bar and septum and having been cooled under a stream of argon was added 260 mg of Cp$_2$Zr(H)Cl (1 mmol), followed by 3 mL of THF and 267 μL of TIPS-protected homopropargyl alcohol (1 mmol). The reaction was shielded from light by aluminum foil and allowed to stir for 30 min after which it was complete as evidenced by a homogeneous solution. After the mixture was cooled to –78 °C, 0.50 mL of MeLi in ether (1 mmol) were added dropwise over 1 min. At the same time, to another 10-mL round-bottom flask equipped with a stir bar and septum and cooled under argon was added 4.9 mg of CuCN (0.05 mmol) followed by 0.5 mL of THF. After the mixture was cooled to –78 °C, 0.61 mL of ZnMe$_2$ in heptane (0.52 mmol) were added dropwise to the stirred slurry. After addition, 0.32 mL of MeLi in ether (0.63 mmol) was added slowly. This two-phase slurry was then placed in an ice bath for 10 min during which time both phases became homogeneous. This solution was then cooled back to –78 °C and the solution containing the vinyl zirconocene was then transferred *via* canula into the flask containing the cuprate/zincate, both at –78 °C. After 5 min of stirring, 43 μL of cyclopentenone (0.5 mmol) was added in 4-μL aliquots over 55 min, followed by 10 min of additional reaction time. The aldehyde (215 μL, 2.0 mmol) in 1 mL of ether at –78 °C was then added *via* canula. After 10 min at –78 °C, the reaction was quenched in the hood with 1 mL of 5% HCl at –78 °C. The reaction mixture was transferred to a separatory funnel containing an additional 14 mL of 5% HCl and 25 mL of ether. The aqueous layer was extracted twice with 25 mL of ether. The combined organic layers were washed 3 times with 20 mL of brine and then dried over Na$_2$SO$_4$. After concentration *in vacuo*, flash chromatography on silica gel using 6:1 (petroleum ether–ethyl acetate) afforded 158 mg consisting of two isomeric products, 74% (12:1 ratio of isomers). Major isomers: TLC [petroleum ether–ethyl acetate, 80/20], R_f 0.30; ^{1}H NMR (500 MHz CDCl$_3$) δ 1.02 (d, J = 5 Hz, 18H, CH$_3$), 1.04 (hept, J = 5 Hz, 3H, CH), 2.25 (dt, J = 7, 7 Hz, 2H, CH$_2$), 2.43 (t, J = 7 Hz, 2H, CH$_2$), 3.68 (t, J = 7 Hz, 2H, CH$_2$), 3.63 (s, 3H, CH$_3$), 3.37 (bd, J = 4 Hz, 1H, OH), 5.54 (dd, J = 16, 9 Hz, 1H, vinylic), 5.60 (dt, J = 16, 7 Hz, 1H, vinylic), 1.6–2.7 (m, 9H, aliphatic); ^{13}C NMR (50 MHz, CDCl$_3$) δ 221.29, 174.22, 134.10, 128.96, 70.71, 63.03, 58.90, 51.57, 43.54, 38.35, 36.24, 30.16, 28.40, 28.25, 17.99, 11.93; IR (neat) cm^{-1} 3525 (b, m), 2942 (s), 2866 (s), 1739 (s), 1461 (m), 1437 (m), 1165 (s), 1014 (s), 1250 (s), 681 (m), 970 (m); EIMS, *m/e* (rel intensity) 383 (2.1, (M$^+$ – *i*-Pr)), 365 (13.6), 351 (14.6), 268 (22.3), 267 (100), 239 (15.7), 231 (12.6), 157 (14.6), 145 (25.6), 131 (39.4), 119 (35.7), 105 (16.7), 103 (43.7), 91 (22.5), 88 (27.6), 87 (186), 85 (33.9), 79 (16.5), 77 (18.3), 75 (66.4), 73 (16.1), 67 (72.0), 61 (43.0), 59 (46.4), 57 (19.1), 55 (24.6), 45 (19.9); HREIMS calcd (M$^+$ – *i*-Pr) 383.2218, found 383.2254. Minor isomer: TLC [petroleum ether–ethyl acetate, 80/20] R_f 0.24; ^{1}H NMR (500 MHz, CDCl$_3$) δ 1.03 (d, J = 5 Hz, 18H, CH$_3$), 1.05 (hept, J = 5 Hz, 3H, CH), 2.25 (dt, J = 7, 7 Hz, 2H, CH$_2$), 3.68 (t, J = 7 Hz, 2H, CH$_2$), 3.92 (m, 1H, OH), 5.46 (dd, J = 15, 8 Hz, 1H, vinylic), 5.61 (dt, J = 15, 7 Hz, 1H, vinylic), 1.6–2.8 (m, 11H, aliphatic); ^{13}C NMR (50 MHz, CDCl$_3$) δ 220.74, 174.20, 134.06, 128.53, 70.05, 63.07, 59.46, 51.66, 41.68, 38.68, 36.26, 30.94, 28.99, 28.33, 18.00, 11.94; IR (neat) cm^{-1} 3525 (b, m), 2942 (s), 2866 (s), 1739 (s), 1461 (m), 1437 (m), 1250 (s), 1165 (s), 1014 (s), 970 (m), 681 (m); EIMS, *m/e* (rel intensity) 383 (M$^+$ – *i*-Pr, 1.7), 365 (28.8), 351 (45.7), 268 (21.8), 267 (100), 203 (24.2), 175 (17.8), 157 (21.3), 145 (36.0), 131 (58.6), 119 (51.3), 117 (18.7), 115 (16.6), 105 (23.4), 103 (56.9), 91 (31.5), 88 (25.9), 87 (21.2), 85 (41.0), 81 (19.0), 79 (25.1), 77 (22.5), 75 (85.6), 73 (210), 67 (753), 61 (55.2), 59 (52.4), 57 (18.9), 55 (24.2), 45 (16.3), 43 (15.5); HREIMS calcd (M$^+$ – *i*-Pr) 383.2238, found 383.2254.