Communications to the Editor

In Situ Cuprate Formation via Transmetalation between Vinylstannanes and Higher Order Cyanocuprates

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In spite of the continuing popularity of stoichiometric dilithiocuprates in synthetic chemistry,[2] one aspect of their chemistry that has been time invariant is their mode of preparation.[2] Whether a lower order (LO), R_1R_2CuLi, or higher order (HO), $R_1R_2Cu(CN)Li_2$, cuprate is desired, a Cu(I) salt is routinely treated with n equivalents (n = 1,2) of an organolithium (RLi) to effect either initial metathesis followed by *ate* formation (n = 2 with copper(I) halides) or direct *ate* formation with CuCN (n = 1 or 2).[2] And yet, outside of the organocopper arena, preformed organotransition-metal complexes, arrived at via *ligand* exchange processes between metal centers, are now commonplace.[3] The facility with which this phenomenon occurs with copper between LO[4a] and HO[4b] organocuprate complexes has only recently been demonstrated. On the basis of these observations, we now describe a novel route to HO mixed vinyl cyanocuprates which takes advantage of ligand migration between HO cuprates and vinylstannanes,[5] thereby bypassing the normally required[2] generation of a vinyllithium(s) for the preparation of highly utilized vinyl cuprates.

Exposure of a vinylstannane[6] to 1 equiv of $Me_2Cu(CN)Li_2$ in THF at ambient temperature for ca. 1 h leads to the quantitative in situ generated mixed HO reagent **1** and a tetraalkyltin. These

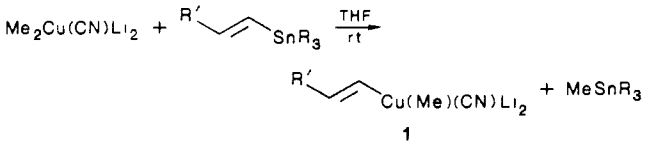

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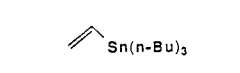
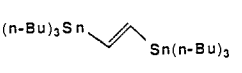
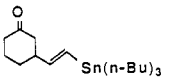
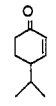
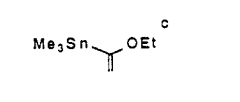
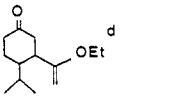
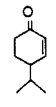
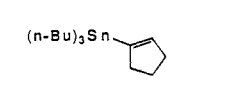
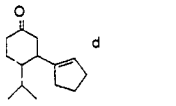
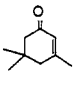
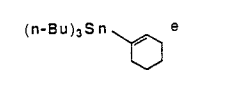
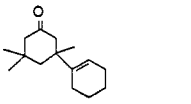
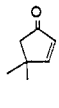
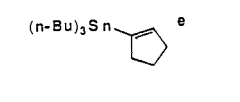
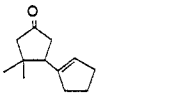
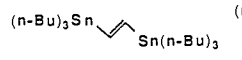
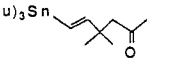
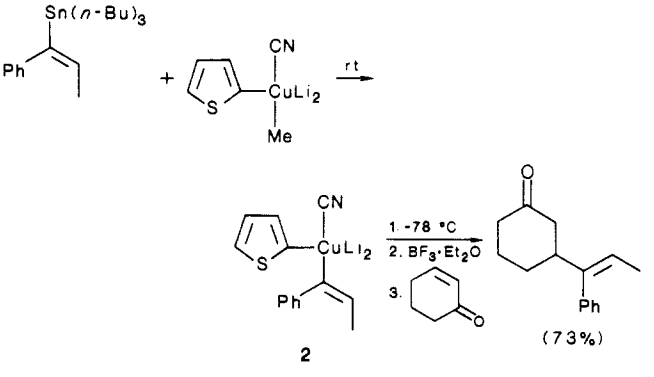
Table I. In Situ Cuprate Formation/Conjugate Addition Reactions Using $Me_2Cu(CN)Li_2$

Enone	Stannane	Product[a]	Yield (%)[b]
			95
			93
			76
			94
			quant.
			92
			92

[a] All products were fully characterized by spectroscopic analyses (IR, NMR, MS) and gave satisfactory high resolution MS and/or combustion data. [b] Isolated yields of chromatographically pure material. [c] Stannane (2 equiv) was needed to form the divinyl cuprate to prevent competitive methyl transfer in this case. [d] A single diastereomer was formed. [e] Stannane (1.5 equiv) was used.

Scheme I



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ligand exchange reactions appear to be quantitative, presumably driven by both the preferential release of a vinyl group from tin[7] as well as the presumed $d\pi^*$ backbonding gained by attachment to copper.[8] Once generation of the new cuprate reagent is

(1) A. P. Sloan Foundation Fellow, 1984-1988. Camile and Henry Dreyfus Teacher-Scholar, 1984-1989.

(2) For recent reviews, see: (a) Lipshutz, B. H. *Synthesis* **1987**, 325. (b) Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A. *Tetrahedron* **1984**, *40*, 5005. (c) Posner, G. H. *An Introduction to Synthesis Using Organocopper Reagents*; Wiley: NY, 1980. (d) Normant, J. F. Pure Appl. Chem. **1978**, *50*, 709. (e) *J. Organomet. Chem. Lib.* **1976**, *1*, 219. (f) Marino, J. P. *Ann. Rep. Med. Chem.* **1975**, *10*, 327. (g) Posner, G. H. *Org. React.* **1975**, *22*, 253. (h) Posner, G. H. *Org. React.* **1972**, *19*, 1. (i) Jukes, A. E. *Adv. Organomet. Chem.* **1974**, *12*, 215.

(3) Negishi, E. In *Organometallics in Organic Synthesis*; Wiley: NY, 1980; Vol. 1. Collman, J.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. In *Organotransition Metal Chemistry*; University Science Books: Mill Valley, CA, 1987.

(4) (a) Lipshutz, B. H.; Kozlowski, J. A.; Breneman, C. M. *Tetrahedron Lett.* **1985**, *26*, 5911. (b) Lipshutz, B. H.; Kozlowski, J. A.; Wilhelm, R. S. *J. Org. Chem.* **1984**, *49*, 3943.

(5) A patent application covering the technology described herein has been filed by the G. D. Searle & Co authors of this communication.

(6) Vinylstannanes used in this work were prepared via (a) hydrostannylation of the corresponding acetylenes or (b) from quenching of vinyl anions (with R_3SnCl) formed from trisylhydrazones: cf. (a) Pereyre, M.; Quintard, J. P.; Rahm, A. In *Tin in Organic Synthesis*; Butterworths: London, 1987. (b) Chamberlin, A. R.; Stenke, J. E.; Bond, F. T. *J. Org. Chem.* **1978**, *43*, 147.

(7) Labadie, J. W.; Stille, J. K. *J. Am. Chem. Soc.* **1983**, *105*, 6129.

(8) This phenomenon presumably accounts for the limited transferability of acetylene and cyano ligands from copper(I) *ate* complexes: cf. Corey, E. J.; Beames, D. J. *J. Am. Chem. Soc.* **1972**, *94*, 7210. House, H. O.; Umen, M. *J. Org. Chem.* **1973**, *38*, 3893. Corey, E. J.; Floyd, D.; Lipshutz, B. H. *J. Org. Chem.* **1978**, *43*, 3418. Acker, R. D. *Tetrahedron Lett.* **1978**, 2399. Hamon, L.; Levisalles, J. *J. Organomet. Chem.* **1983**, *251*, 133.

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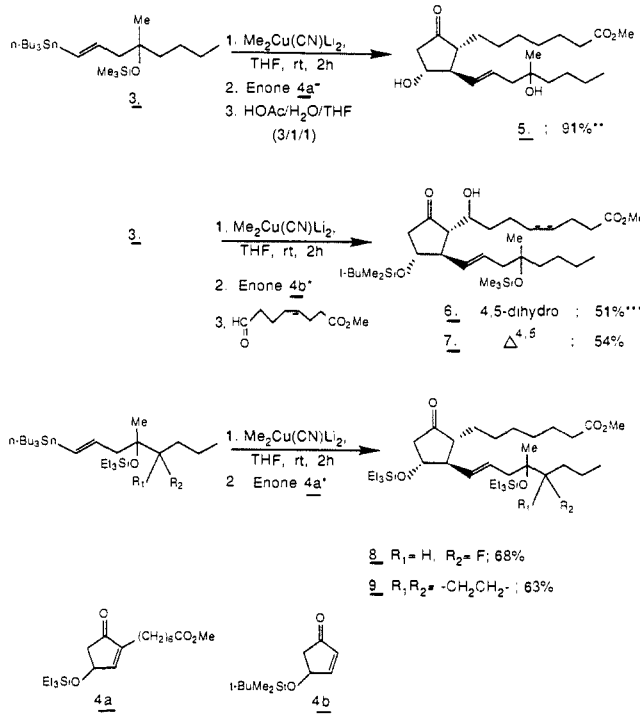
Scheme II[a]



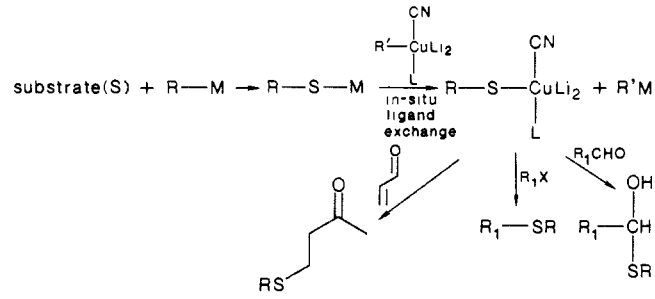
[a] (**) Optimized yield of isolated material devoid of the 8-epi isomer; (***) unoptimized isolated yields of isomerically pure material (except where indicated).

complete,[9] its handling is identical with that for **1** generated from the corresponding vinyllithium and lower order cyanocuprate MeCu(CN)Li. Hence, cooling **1** to −78 °C and subsequent addition of an enone smoothly effects 1,4-addition of the vinyl residue with retention of olefin geometry and virtually complete selectivity of vinyl over methyl transfer.[10] Representative examples are listed in Table I and attest to the generality of this method.[11]

In anticipation of performing substitution employing this chemistry, it was necessary to examine in situ cuprate formation from Me(2-Th)Cu(CN)Li_2, formed from commercially available 2-ThCu(CN)Li[12] and MeLi, so as to generate **2** rather than **1**.[11b] Albeit a slower process, transmetalation does take place, as illustrated in Scheme I.

The ease and simplicity associated with this new protocol for cuprate formation[13] has been successfully applied to prostaglandin synthesis. Misoprostol, **5**, a PGE_1 analogue with pharmacologically important antisecretory activity,[14] can be rapidly assembled via this technology, as shown in Scheme II. Analogues are also readily formed (e.g., **8** and **9**). Alternatively, both the α- and β-side chains may be sequentially added in a Noyori-type three-component coupling sequence[15] to a simpler enone with use of the in situ technique (see Scheme II: **6** and **7**).[16]

In summary, the concept of ligand exchange between an organometallic species and a preformed HO cuprate has been demonstrated in this initia. report by using vinylstannanes as examples. Several other preformed organometallics prone to transmetalation are being actively investigated as precursors to cuprates (i.e., as shown below with RM, M = e.g., B, Zr, Al, Zn, etc.).



Acknowledgment. Financial support (to B.H.L.) provided by the Petroleum Research Fund, administered by the American Chemical Society, and the Sloan and Dreyfus Foundations, is gratefully acknowledged. We thank the F.N.R.S. for a postdoctoral fellowship (to R.M.). The assistance of L. Swenton, P. Finnegan, and J. Hribar in the Physical Methodology Department (G. D. Searle) and T. Kosobud and H. Bush in the Chemical Development Chromatography group (G. D. Searle) is greatly appreciated. Also, the technical assistance of S. Regan in Synthesis Chemical Development (G. D. Searle) is acknowledged.

Registry No. **1** (R′ = CH_2=CH), 91328-63-1; **1** (R′ = (*E*)-Bu_3SnCH=CH), 112713-99-2; **1** (R′ = H_2C=C(OEt)), 112714-00-8; **1** (R′ = 1-cyclopentenyl), 112714-01-9; **1** (R′ = 1-cyclohexenyl), 112714-02-0; **2**, 112714-04-2; **3**, 69442-81-5; **4a**, 112713-92-5; **4b**, 56745-67-6; **5**, 59122-46-2; **6**, 112713-93-6; **7**, 112713-94-7; **8**, 112713-97-0; **9**, 112713-98-1; $Me_2Cu(CN)Li_2$, 80473-70-7; Me(2-Th)Cu(CN)-Li_2, 112714-03-1; 2-Th-Cu(CN)Li, 112426-02-5; 2-cyclohexenone, 930-68-7; 4-(1-methylethyl)-2-cyclohexenone, 500-02-7; 3,5,5-trimethyl-2-cyclohexenone, 78-59-1; 4,4-dimethyl-2-cyclopentenone, 22748-16-9; 4-methyl-3-penten-2-one, 141-79-7; tributylvinylstannane, 7486-35-3; (*E*)-1,2-bis(tributylstannyl)ethane, 14275-61-7; (1-ethoxyethenyl)trimethylstannane, 112713-84-5; (1-cyclopentenyl)tributylstannane, 91897-90-4; (1-cyclohexenyl)tributylstannane, 100073-20-9; 3-vinylcyclohexanone, 1740-63-2; 3-((*E*)-2-tributylstannylethenyl)cyclohexanone, 54125-16-5; 3-(1-ethoxyethenyl)-4-(1-methylethyl)cyclohexanone, 112713-85-6; 3-(1-cyclopentenyl)-4-(1-methylethyl)cyclohexanone, 112713-86-7; 3-(1-cyclohexenyl)-3,5,5-trimethylcyclohexanone, 112713-87-8; 3,3-dimethyl-4-(1-cyclopentenyl)cyclopentanone, 112713-88-9; (3,3-dimethyl-5-oxo-1-hexen-1-yl)tributylstannane,

(9) HO cuprate reagents generated via the in situ technique demonstrate good thermal stability similar to those formed in the standard[2a,b] manner. See, also: Lipshutz, B. H.; Koerner, M.; Parker, D. A. *Tetrahedron Lett.* **1987**, *28*, 945.

(10) Lipshutz, B. H.; Wilhelm, R. S.; Koslowski, J. A. *J. Org. Chem.* **1984**, *49*, 3938. The same selectivity has been noted with lower order reagents: cf. Posner, G. H.; Sterling, J. J.; Whitten, C. E.; Lentz, C. M.; Brunelle, D. J. *J. Am. Chem. Soc.* **1975**, *97*, 107.

(11) (a) The choice of $Me_2Cu(CN)Li_2$ for the in situ generation of vinyl cuprates was based upon the optimization of results obtained for misoprostol (**5**). However, the following cuprates have also been shown to undergo in situ ligand exchange with vinylstannanes: Me(Bu)Cu(CN)Li_2,[4b] Bu_2Cu(CN)Li_2,[4b] Me(2-Th)Cu(CN)Li_2,[11b] Bu(2-Th)Cu(CN)Li_2,[11b] Me_2Cu(SCN)Li_2,[11c] and Me(2-Th)Cu(SCN)Li_2.[11c] Me(Ph)Cu(CN)Li_2 and Ph_2Cu(CN)Li_2 did not transmetalate by using the standard conditions involving $Me_2Cu(CN)Li_2$. No attempts were made to identify alternate conditions for transmetalations with phenyl-containing cuprates. The reasons for their reduced reactivity toward in situ ligand exchange are unclear at this time but may simply reflect the opportunity for aromatic ring dπ* backbonding with copper(I). (b) Lipshutz, B. H.; Kozlowski, J. A.; Parker, D. A.; Nguyen, S. L.; McCarthy, K. E. *J. Organomet. Chem.* **1985**, *285*, 437. (c) Lipshutz, B. H.; Kozlowski, J. A.; Wilhelm, R. S. *J. Org. Chem.* **1983**, *48*, 546.

(12) Available from the Aldrich Chemical Company, as lithium 2-thienylcyanocuprate (catalog no. 32,417-5).

(13) A typical procedure for the preparation of misoprostol is as follows: Copper cyanide (1.21 g, 13.5 mmol, flame dried under Argon) in THF (15 mL) was treated with methyllithium (20.6 mL, 1.44 M in diethyl ether, 29.7 mmol) at 0 °C. The cooling bath was removed, and vinylstannane (7.65 g, 15.2 mmol) in THF (15 mL) was added. After 1.5 h at ambient temperature the mixture was cooled to −64 °C (dry ice–isopropyl alcohol), and the enone (3.2 g, 9.63 mmol) in THF (15 mL) was added rapidly via cannula. The temperature rose to −35 °C. After 3 min, the mixture was quenched into a 9:1 saturated ammonium chloride/ammonium hydroxide solution. Ether extraction followed by solvent removal provided 11 g of residue which was solvolyzed (3:1:1, acetic acid, THF, water, 100 mL) and chromatographed (silica gel, EtOAc/hexane eluent) to provide 3.15 g of product (8.2 mmol, 91%) which was identical in all respects with an authentic standard of misoprostol; cf. Collins, P. W., et al. *J. Med. Chem.* **1977**, *20*, 1152. This reaction has been successfully carried out on a mole scale in pilot plant equipment.

(14) Collins, P. *J. Med. Chem.* **1986**, *29*, 437 and references therein.

(15) Suzuski, M.; Yanagisawa, A.; Noyori, R. *J. Am. Chem. Soc.* **1985**, *107*, 3348.

(16) All new compounds were fully characterized by IR, NMR, MS, and HRMS, or combustion analyses.

112713-89-0; 3-((*E*)-1-phenylpropen-1-yl)cyclohexanone, 112713-90-3; ((*E*)-1-phenylpropen-1-yl)tributylstannane, 112713-91-4; methyl 7-formylheptanoate, 3884-92-2; methyl 7-formyl-4-(*Z*)-heptenoate, 82302-70-3; 5-fluoro-1-(tributylstannyl)-4-(triethylsilyloxy)-4-methyl-1-octene, 112713-95-8; 1-propyl-1-[5-(tributylstannyl)-2-(triethylsilyloxy)-(*E*)-4-penten-2-yl]cyclobutane, 112713-96-9.

Supplementary Material Available: Experimental and spectral data for entries 2–7 in Table I, the product with 73% yield in Scheme I, and compounds **5–9** in Scheme II (5 pages). Ordering information is given on any current masthead page.

Semibullvalenes IV: 2,6- and 2,8-Trapping of the Bicyclo[3.3.0]octadienyl Diradical with Oxygen†

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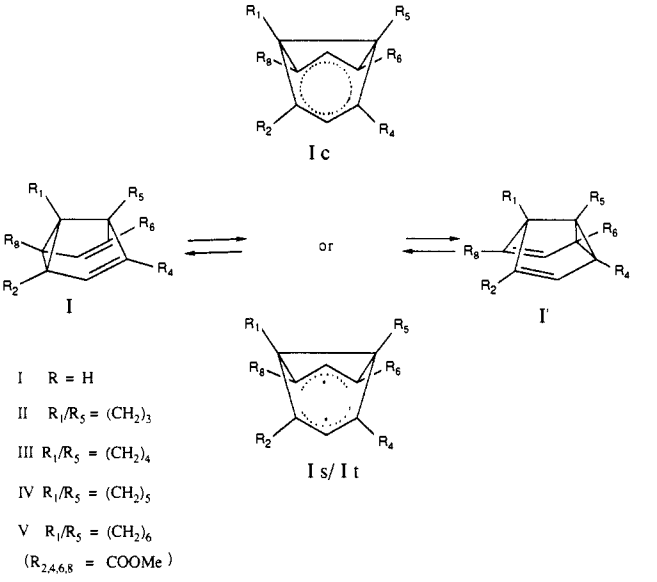
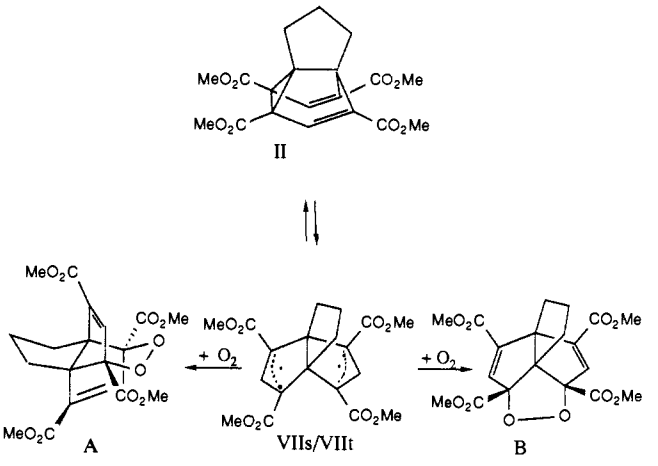
Semibullvalenes undergo a facile degenerate Cope rearrangement I to I′ whose activation energy barrier is the lowest known to date.[1,2] They are also, together with cyclooctatetraenes, members of the C_8H_8 hydrocarbon family interrelated through a multitude of thermal and photochemical rearrangements.[3,4] Among the transition states considered for the Cope rearrangement, Is (singlet) and It (triplet), the two states of the bicyclooctadienyl diradical involving bond breaking before significant bond forming, and Ic (concerted), the bishomoaromatic state with synchronous bond breaking and bond forming, have been the focus of many investigations.[5] In our continuing study of substituted semibullvalenes aimed toward crossing the bridge between valence tautomerism and resonance, we investigated the 1,5-annulated

Scheme I. The Cope Rearrangement in Semibullvalenes

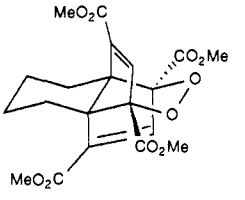


Scheme II



2,4,6,8-tetrcarbomethoxysemibullvalenes II through V[6,7] (see Scheme I).

The behavior of these closely related molecules showed some rather striking differences among each other and in comparison to 1,5-dimethyl-2,4,6,8-tetracarbomethoxysemibullvalene.[6] 1,5-Cyclohexano-2,4,6,8-tetracarbomethoxysemibullvalene (III), a yellow crystalline compound mp 128–129 °C, converted readily in the dark, in solution, and as a solid into a colorless compound VI mp 151.5–153 °C.[7] The mass spectrum and the microanalysis indicated the presence of two oxygen atoms in the molecule.[8] The X-ray determination[9] proved the structure of VI to be an adduct of one oxygen molecule to positions 2 and 6 of semibullvalene III yielding a doubly bridged *trans*-dioxadecalin structure VI.



1,5-Cyclopentano-2,4,6,8-tetracarbomethoxysemibullvalene (II)

† A preliminary account of these results has been reported at the 192nd National Meeting of the American Chemical Society, Anaheim, CA; 1986; Paper no. 255, Organic Section and at the 193rd National Meeting of the American Chemical Society, Denver, CO; 1987; Organic Poster Session, Poster No. 2.

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