Hydrozirconation–Transmetalation. A Mild, Direct Route to Higher Order Vinylic Cuprates from Monosubstituted Acetylenes

Bruce H. Lipshutz* and Edmund L. Ellsworth†

Department of Chemistry, University of California
Santa Barbara, California 93106

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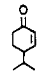
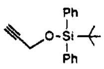
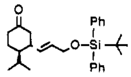
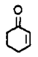
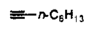
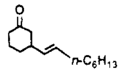
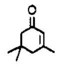
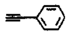
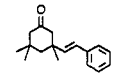
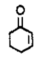
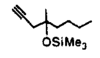
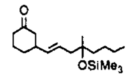
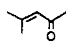
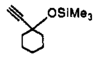
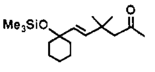
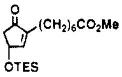
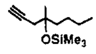
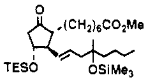
Hydrozirconation of acetylenes, especially 1-alkynes, is an important reaction in synthetic chemistry for several reasons: (1) the mild nature of the conditions involved; (2) efficiency; (3) commercial availability of Schwartz's reagent, $Cp_2Zr(H)Cl$ (**1**), which effects the chemistry;[1] and (4) excellent regio- and stereochemical control of reagent addition.[2] Although the intermediate vinylzirconates can be employed in selected coupling reactions to form quite valuable carbon–carbon bonds,[2] there is no widely utilized method for directly transferring these vinylic ligands in a Michael sense to α,β-unsaturated ketones.[3] We now describe a new, efficient solution to this problem based on a ligand-exchange phenomenon which occurs between a simple higher order (HO) cyanocuprate and a vinylzirconate leading directly to reactive vinylic cuprates.[4]

Treatment of a 1-alkyne with **1** is best carried out, for subsequent transmetalation purposes, in THF at room temperature. The resulting intermediate **2** is then exposed to 1 equiv of MeLi,[5] thereby forming **3**. A cooled solution of $Me_2Cu(CN)Li_2$[6] (from 2MeLi + CuCN in THF or Et_2O at −78 °C) is subsequently added and the mixture stirred at this temperature for ca. 15 min. The transmetalation,[7] presumably forming mixed HO cuprate **4**, is then followed by addition of an enone to afford adduct **5** (Scheme I).

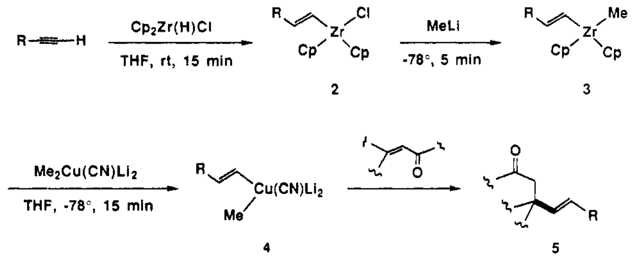
The examples in Table I illustrate the power of this new coupling sequence. Noteworthy is the introduction of a β side chain (**6**) characteristic of the potent antisecretory agent misoprostol, without recourse to initially preformed, isolated vinylic halide or stannane (patented) intermediates.[8]

Table I. 1,4-Addition Reactions of Mixed Vinylic Cyanocuprates Formed via Transmetalations of Vinylzirconates Derived from 1-Alkynes

Educt	Acetylene	Conditions	Product[a]	Yield(%)[b]
		THF/DME -78°, 15 min		quant
		THF/Et_2O -78°, 5 min		86
		THF, $BF_3 \cdot Et_2O$ DME[c], -78°, 1h		78
		THF/Et_2O -78°, 10 min		81
		THF -78°, 3.5h		82
	 **6**	THF/Et_2O -78°, 10 min		92

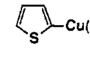
[a] All products were fully characterized by IR, NMR, MS, and HRMS data. [b] Isolated, chromatographically pure materials. [c] One equivalent was added to assist in the transmetalation step.

Scheme I



Alternative modes of addition have also been developed which effect this Zr-to-Cu transmetalation. Since the $MeLi/Me_2Cu(CN)Li_2$ series is tantamount to adding the elements of 3RLi + CuCN (combination 1, eq 1), there are two other combinations that should afford the same net ligand transfer from vinylzirconate **2** to cuprate **4**.

Combination 1		Combination 2		Combination 3	
$MeLi + Me_2Cu(CN)Li_2$	$\equiv$	$2MeLi + MeCu(CN)Li$	$\equiv$	$3MeLi + CuCN$	(Eq. 1)
		7			


8

When commercially available,[9] lower order cyanocuprate **8** is used in place of **7** (combination 2),[10] together with an initial 2 equiv of MeLi,[11] the transmetalation can likewise be carried out as illustrated in Scheme II.

Perhaps the simplest scenario involves introduction of 3 equiv of MeLi (precooled to −78 °C) to vinylzirconate **2**, to which is then added LiCl-solubilized CuCN[12] in THF (combination 3) to induce vinylic cuprate formation. Scheme III highlights a few challenging cases, including those resulting in production of protected PGE_1 (**9**) and its 15-methyl analogue (**10**).

In summary, a transmetalation sequence[13] has been developed that allows for the direct conversion of terminal acetylenes, via

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† Proctor & Gamble Predoctoral Fellow, 1989–1990.

(1) Hart, D. W.; Blackburn, T. F.; Schwartz, J. *J. Am. Chem. Soc.* **1975**, *97*, 679.

(2) Reviews: Negishi, E.; Takahashi, T. *Synthesis* **1988**, 1. Negishi, E.; Takahashi, T. *Aldrichimica Acta* **1985**, *18*, 31. Negishi, E. *Pure Appl. Chem.* **1981**, *53*, 2333. Schwartz, J.; Labinger, J. A. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 333.

(3) An early observation by Schwartz using a vinylzirconate and CuOTf resulted in the successful 1,4-addition to methyl vinyl ketone; cf.: Yoshifuji, M.; Loots, M.; Schwartz, J. *Tetrahedron Lett.* **1977**, 1303. Reduced nickel salts also allow for conjugate delivery of vinylic ligands via vinylzirconates; cf.: Loots, M.; Schwartz, J. *J. Am. Chem. Soc.* **1977**, *99*, 8045.

(4) (a) Transmetallations between HO cyanocuprates and vinylstannanes were the first reactions of this type.[4b] Very recently, vinylalanes have been shown to participate in related exchanges.[4c] (b) Behling, J. R.; Babiak, K. A.; Ng, J. S.; Campbell, A. L.; Moretti, R.; Koerner, M.; Lipshutz, B. H. *J. Am. Chem. Soc.* **1988**, *110*, 2641. (c) Ireland, R. E.; Wipf, P. *J. Org. Chem.* **1990**, *55*, 1425.

(5) See, for example: Buchwald, S. L.; Nielsen, R. B. *J. Am. Chem. Soc.* **1989**, *111*, 2870.

(6) It is particularly worthy of note that this process does *not* occur when Me_2CuLi is used in place of $Me_2Cu(CN)Li_2$.

(7) (a) Note that, unlike the case of carbo(hydro)alumination/transmetalation,[4c] there is no need to carry out a solvent exchange when this procedure is used. (b) There is a clear dependence of this process on the quality of the MeLi employed to form $Me_2Cu(CN)Li_2$. Impurities such as hydroxide and alkoxides can severely compromise the extent of transmetalation. It has been found, however, that for most cases, inclusion of only 1 equiv of DME (see Table I) can negate this as yet unexplained phenomenon.

(8) For representative examples, see: Suzuki, M.; Kawagishi, T.; Yanagisawa, A.; Suzuki, T.; Okamura, N.; Noyori, R. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 1299. Nicolau, G.; Cosulich, D. B.; Tonelli, A.; Chen, S. M.; Purzinsky, M. S.; Blum, D. *Prostaglandins* **1986**, *31*, 811. Newton, R. F.; Reynolds, D. P. *J. Chem. Soc., Perkin Trans. 1* **1983**, 683.

(9) Available from Aldrich, catalog no. 32,417-5.

(10) Lipshutz, B. H.; Koerner, M.; Parker, D. A. *Tetrahedron Lett.* **1987**, *28*, 945.

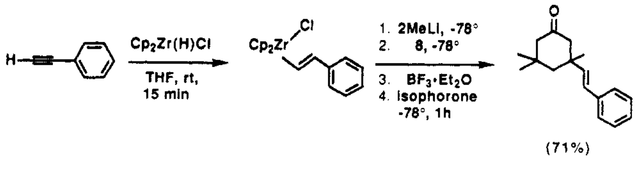
(11) These alternative transmetalation schemes do not seem to be sensitive to impurities in the MeLi.[7b]

(12) Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390.

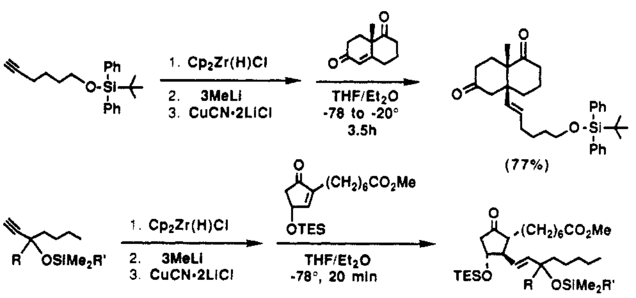
(13) A patent application on behalf of the authors has been filed by the University of California.

0002-7863/90/1512-7440$02.50/0

Scheme II



Scheme III



9 (R=H, R'=Me; 80%)
10 (R=Me, R'=thexyl; 84%)

zirconium intermediates, to vinylic cuprates, which readily participate in conjugate addition schemes. All of the events leading up to the cuprate from the initial vinylzirconate occur rapidly, even at −78 °C, and can be carried out in one flask. Thus, this new chemistry significantly extends the usefulness of the hydrozirconation process,[1,2] while reinforcing the prominent role played by organocopper complexes as powerful tools for carbon–carbon bond constructions.[14,15]

Acknowledgment. We are grateful to the NSF for financial support. The $Cp_2Zr(H)Cl$ used in these and related studies was generously supplied by L. Kelly and J. Sullivan (Boulder Scientific Company), to whom we are indebted. The MeLi in THF/cumene was graciously provided by Dr. T. L. Rathman (Lithco).

Registry No. 6, 128217-18-5; **7**, 41753-78-0; **8**, 112426-02-5; **9**, 128217-25-4; **10**, 128217-26-5; $Me_2Cu(CN)Li_2$, 80473-70-7; $Me_2C{=}CHCHO$, 107-86-8; $HC{\equiv}CCH_2OSiPh_2Bu$-*t*, 88159-06-2; $HC{\equiv}C$-*n*-C_6H_{13}, 629-05-0; $HC{\equiv}CPh$, 536-74-3; $HC{\equiv}C(CH_2)_4OSiPh_2Bu$-*t*, 128217-23-2; $HC{\equiv}CCH(OSiMe_3)(CH_2)_5H$, 73061-39-9; $HC{\equiv}CC(Me)(OSiMe_2(CMe_2CHMe_2))(CH_2)_5H$, 128217-24-3; isophorone, 78-59-1; 3-(1-phenylethen-2-yl)-3,5,5-trimethylcyclohexanone, 128242-24-0; methyl 7-(5-oxo-3-[(triethylacetyl)oxy]-1-cyclopenten-1-yl)heptanoate, 112713-92-5; 4-isopropyl-3-[(1-(*tert*-butyldiphenylsiloxy)-2-propen-3-yl]cyclohexanone, 128217-19-6; 3-(1-octen-1-yl)cyclohexanone, 128217-20-9; trimethyl[(1-methyl-(3-(oxocyclohex-3-yl)-2-propenyl)pentyl)oxy]silane, 128217-21-0; 1-ethynyl-1-(trimethylsilyloxy)cyclohexane, 62785-90-4; 4,4-dimethyl-6-(cyclohex-1-(trimethylsiloxy)-1-yl)-5-hexen-2-one, 128217-22-1; protected misoprostol, 84024-39-5; 4-isopropyl-2-cyclohexenone, 500-02-7; 2-cyclohexenone, 930-68-7; 8a-methyl-1,2,3,4,6,7,8,8a-octahydronaphthalene-1,6-dione, 100348-93-4; 4a-[6-(*tert*-butyldiphenylsiloxy)-1-hexen-1-yl]-8a-methyldecahydronaphthalene-1,6-dione, 128242-25-1.

Supplementary Material Available: Detailed experimental procedures for each of the three transmetalation schemes and characterization data for all new compounds (7 pages). Ordering information is given on any current masthead page.

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(14) For reviews on HO cyanocuprate chemistry, see: Lipshutz, B. H. *Synlett* **1990**, 119; *Synthesis* **1987**, 325. Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A. *Tetrahedron* **1984**, *40*, 5005. For an updated review on the entire area of organocopper chemistry, see: Lipshutz, B. H., Sengupta, S. *Org. React.* (N.Y.), in press.

(15) Substitution reactions of mixed vinylic HO cyanocuprates formed by using this new technology will be described in due course: Lipshutz, B. H., Kato, K., unpublished observations.

One-Pot Synthesis of Protected Prostaglandins from Alkynes and Cyclopentenones. In Situ Generation of Higher Order Cyanocuprates Derived from Alkenylzirconium Intermediates[†]

Kevin A. Babiak,*[,‡] James R. Behling,[‡] John H. Dygos,[‡]
Kathleen T. McLaughlin,[‡] John S. Ng,*[,‡] Vincent J. Kalish,[§]
Steven W. Kramer,[§] and Robert L. Shone[§]

Chemical Development Department and
Gastrointestinal Diseases Research Department
Searle Research and Development, Skokie, Illinois 60077

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In our continuing effort to develop more efficient syntheses of antiulcer prostaglandin analogues,[1] we sought a convergent process that could easily be carried out on a kilogram scale. The approach used in these laboratories involved the conjugate addition of a functionalized vinylcuprate to a substituted cyclopentenone.[2] The cuprate was prepared from a mixture of vinylstannanes[3,4] or a vinyl iodide.[5] Major disadvantages of these methods included the nonstereoselectivity of hydrostannation and the instability of the vinyl iodide intermediates.

Here we report the development of a one-pot prostaglandin synthesis based on a new method for generating higher order cyanocuprates directly from vinylzirconium intermediates. Our synthesis employs the chemoselective and stereoselective hydrozirconation of an alkyne and the in situ transmetalation to generate a higher order cyanocuprate. The subsequent conjugate addition of the resultant reagent to a substituted cyclopentenone provides a route to protected prostaglandins in one operation (Scheme I).

Our synthesis is illustrated by the preparation of misoprostol, a commercially available prostaglandin antiulcer drug.[1] Hydrozirconation of 4-methyl-4-[(trimethylsilyl)oxy]-1-octyne (**1**, $R_1 = CH_2C(CH_3)(OTMS)$-*n*-C_4H_9 in Scheme I) with the Schwartz reagent ($Cp_2Zr(H)Cl$)[6] in THF at room temperature gave the alkenylzirconium intermediate **2** with >98% *E* selectivity.[7-9] Transmetalation of the vinylzirconium intermediate **2** was accomplished by the addition of 2 equiv of *n*-butyllithium or methyllithium[10] at −30 to −78 °C.[11] Sequential addition of 1 equiv each of copper cyanide and methyllithium at −30 to −78 °C completed the in situ generation of the higher order cyanocuprate

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[†] We are indebted to Professor Bruce Lipshutz for holding up his manuscript to allow for simultaneous publication.

[‡] Chemical Development Department.

[§] Gastrointestinal Diseases Research Department.

(1) (a) Collins, P. W. *Med. Res. Rev.* **1990**, *10*, 149. (b) Collins, P. W. *J. Med. Chem.* **1986**, *29*, 437.

(2) Collins, P. W.; Dajani, E. Z.; Bruhn, M.; Brown, C. H.; Palmer, J. R.; Pappo, R. *Tetrahedron Lett.* **1975**, 4217.

(3) Collins, P. W.; Jung, C. J.; Gasiecki, A.; Pappo, R. *Tetrahedron Lett.* **1978**, 3187.

(4) Collins, P. W.; Gasiecki, A.; Perkins, W. E.; Gullikson, G. W.; Bianchi, R. G.; Kramer, S. W.; Ng, J. S.; Yonan, E. E.; Swenton, L.; Jones, P. H.; Bauer, R. F. *J. Med. Chem.*, in press.

(5) (a) Pappo, R.; Collins, P. W. U.S. Patent 3965143. (b) Sih, C. U.S. Patents 3962351, 3962352, and 3962353. (c) Collins, P. W.; Dajani, E. Z.; Driskill, D. R.; Bruhn, M. S.; Jung, C. J.; Pappo, R. *J. Med. Chem.* **1977**, *20*, 1152. (d) Negishi, E. *Organometallics in Organic Synthesis*; John Wiley and Sons: New York, 1980; Vol. 1, Chapter 5.

(6) Buchwald, S. L.; LaMaire, S. J.; Nielsen, R. B.; Watson, B. T.; King, S. M. *Tetrahedron Lett.* **1987**, *28*, 3895 and references cited therein.

(7) Hart, D. W.; Blackburn, T. F.; Schwartz, J. *J. Am. Chem. Soc.* **1975**, *97*, 679.

(8) Grieco, P. A.; Ohfune, Y.; Owens, W. *J. Am. Chem. Soc.* **1979**, *101*, 4749.

(9) Larock, R. C.; Kondo, F.; Narayanan, K.; Hsu, M.-F. H. *Tetrahedron Lett.* **1989**, *30*, 5737.

(10) For large-scale synthesis, it was convenient to use the stable, nonpyrophoric methyllithium in THF/cumene from FMC Corporation, Lithium Division.

(11) The mechanism of the zirconium–lithium exchange reaction has yet to be resolved.[12,13]

(12) Schwartz, J. *J. Organomet. Chem. Libr.* **1976**, *1*, 480.

(13) Negishi, E.; Takahashi, T. *Aldrichimica Acta* **1985**, *18*, 36.