

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

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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,  $\text{Cp}_2\text{Zr(H)Cl}$  (**1**), which effects the chemistry;<sup>1</sup> and (4) excellent regio- and stereochemical control of reagent addition.<sup>2</sup> Although the intermediate vinylzirconates can be employed in selected coupling reactions to form quite valuable carbon-carbon bonds,<sup>2</sup> there is no widely utilized method for directly transferring these vinylic ligands in a Michael sense to  $\alpha,\beta$ -unsaturated ketones.<sup>3</sup> 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.<sup>4</sup>

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,<sup>5</sup> thereby forming **3**. A cooled solution of  $\text{Me}_2\text{Cu(CN)Li}_2$ <sup>6</sup> (from  $2\text{MeLi} + \text{CuCN}$  in THF or  $\text{Et}_2\text{O}$  at  $-78^\circ\text{C}$ ) is subsequently added and the mixture stirred at this temperature for ca. 15 min. The transmetalation,<sup>7</sup> 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  $\beta$  side chain (**6**) characteristic of the potent antisecretory agent misoprostol, without recourse to initially preformed, isolated vinylic halide or stannane (patented) intermediates.<sup>8</sup>

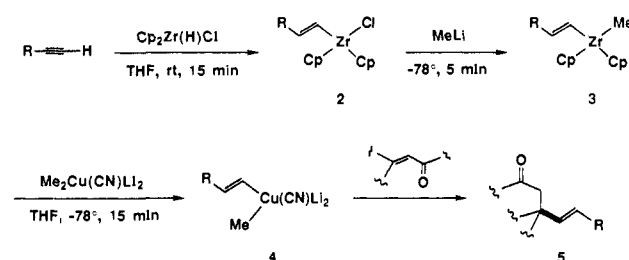
Alternative modes of addition have also been developed which effect this Zr-to-Cu transmetalation. Since the MeLi/ $\text{Me}_2\text{Cu(CN)Li}_2$  series is tantamount to adding the elements of  $3\text{RLi} +$

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

Educi	Acetylene	Conditions	Product <sup>a</sup>	Yield(%) <sup>b</sup>
		THF/DME -78°, 15 min		quant
		THF/Et <sub>2</sub> O -78°, 5 min		86
		THF, BF <sub>3</sub> ·Et <sub>2</sub> O DME <sup>c</sup> , -78°, 1h		78
		THF/Et <sub>2</sub> O -78°, 10 min		81
		THF -78°, 3.5h		82
		THF/Et <sub>2</sub> O -78°, 10 min		92

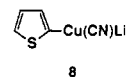
<sup>a</sup> All products were fully characterized by IR, NMR, MS, and HRMS data. <sup>b</sup> Isolated, chromatographically pure materials. <sup>c</sup> One equivalent was added to assist in the transmetalation step.

### Scheme I



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



When commercially available,<sup>9</sup> lower order cyanocuprate **8** is used in place of **7** (combination 2),<sup>10</sup> together with an initial 2 equiv of MeLi,<sup>11</sup> 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  $-78^\circ\text{C}$ ) to vinylzirconate **2**, to which is then added LiCl-solubilized CuCN<sup>12</sup> in THF (combination 3) to induce vinylic cuprate formation. Scheme III highlights a few challenging cases, including those resulting in production of protected PGE<sub>1</sub> (**9**) and its 15-methyl analogue (**10**).

In summary, a transmetalation sequence<sup>13</sup> has been developed that allows for the direct conversion of terminal acetylenes, via

(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.<sup>7b</sup>

(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.

† 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) Transmetalations between HO cyanocuprates and vinylstannanes were the first reactions of this type.<sup>4b</sup> Very recently, vinylalanes have been shown to participate in related exchanges.<sup>4c</sup> (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.

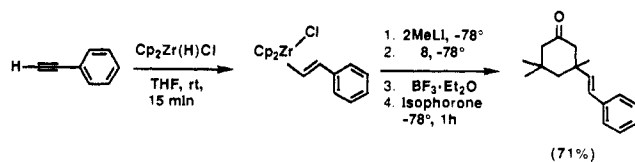
(5) See, for example: Buchwald, S. L.; Nielsen, R. B. *J. Am. Chem. Soc.* **1989**, 111, 2870.

(6) It is particularly worthy of note that this process does *not* occur when  $\text{Me}_2\text{CuLi}$  is used in place of  $\text{Me}_2\text{Cu(CN)Li}_2$ .

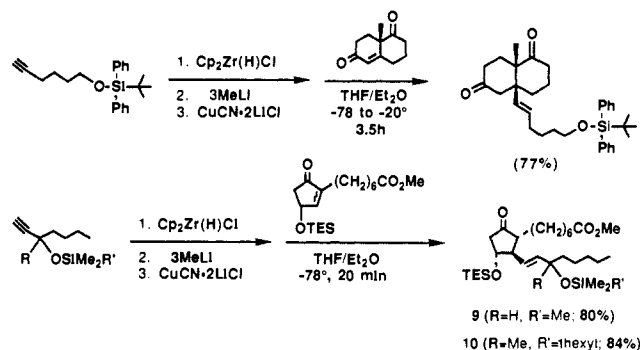
(7) (a) Note that, unlike the case of carbo(hydro)aluminum/transmetalation,<sup>4c</sup> there is no need to carry out a solvent exchange when this procedure is used. (b) There is a clear dependence of this process on the quality of the MeLi employed to form  $\text{Me}_2\text{Cu(CN)Li}_2$ . Impurities 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.

Scheme II



Scheme III



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  $-78^{\circ}\text{C}$ , and can be carried out in one flask. Thus, this new chemistry significantly extends the usefulness of the hydrozirconation process,<sup>1,2</sup> while reinforcing the prominent role played by organocopper complexes as powerful tools for carbon-carbon bond constructions.<sup>14,15</sup>

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**Registry No.** 6, 128217-18-5; 7, 41753-78-0; 8, 112426-02-5; 9, 128217-25-4; 10, 128217-26-5;  $\text{Me}_2\text{Cu}(\text{CN})\text{Li}_2$ , 80473-70-7;  $\text{Me}_2\text{C}=\text{CHCHO}$ , 107-86-8;  $\text{HC}\equiv\text{CCH}_2\text{OSiPh}_2\text{Bu-}t$ , 88159-06-2;  $\text{HC}\equiv\text{C}-n\text{-C}_6\text{H}_{13}$ , 629-05-0;  $\text{HC}\equiv\text{CPh}$ , 536-74-3;  $\text{HC}\equiv\text{C}(\text{CH}_2)_4\text{OSiPh}_2\text{Bu-}t$ , 128217-23-2;  $\text{HC}\equiv\text{CCH}(\text{OSiMe}_2)(\text{CH}_2)_3\text{H}$ , 73061-39-9;  $\text{HC}\equiv\text{C}(\text{Me})(\text{OSiMe}_2(\text{CMe}_2\text{CHMe}_2))(\text{CH}_2)_3\text{H}$ , 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*-butyldiphenylsilyloxy)-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-(trimethylsilyloxy)-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*-butyldiphenylsilyloxy)-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.

(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<sup>†</sup>

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In our continuing effort to develop more efficient syntheses of antiulcer prostaglandin analogues,<sup>1</sup> 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 vinylic cuprate to a substituted cyclopentenone.<sup>2</sup> The cuprate was prepared from a mixture of vinylstannanes<sup>3,4</sup> or a vinyl iodide.<sup>5</sup> 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.<sup>1</sup> Hydrozirconation of 4-methyl-4-[(trimethylsilyloxy)-1-octyne (**1**,  $\text{R}_1 = \text{CH}_2\text{C}(\text{CH}_3)(\text{OTMS})-n\text{-C}_4\text{H}_9$  in Scheme I) with the Schwartz reagent ( $\text{Cp}_2\text{Zr}(\text{H})\text{Cl}$ )<sup>6</sup> in THF at room temperature gave the alkenylzirconium intermediate **2** with  $>98\%$  *E* selectivity.<sup>7-9</sup> Transmetalation of the vinylzirconium intermediate **2** was accomplished by the addition of 2 equiv of *n*-butyllithium or methylolithium<sup>10</sup> at  $-30$  to  $-78^{\circ}\text{C}$ .<sup>11</sup> Sequential addition of 1 equiv each of copper cyanide and methylolithium at  $-30$  to  $-78^{\circ}\text{C}$  completed the in situ generation of the higher order cyanocuprate

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<sup>§</sup>Gastrointestinal Diseases Research Department.

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(11) The mechanism of the zirconium-lithium exchange reaction has yet to be resolved.<sup>12,13</sup>

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