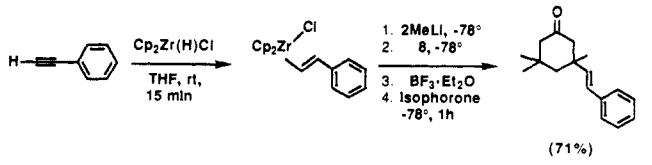
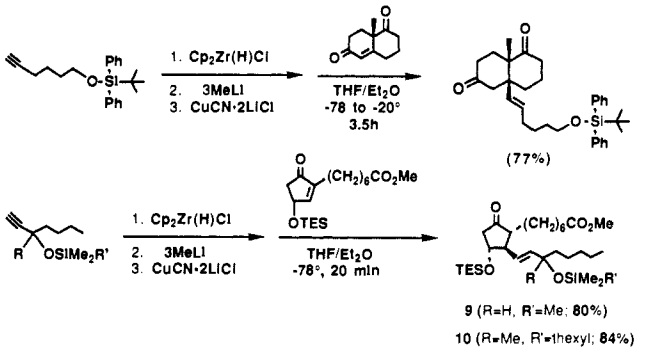
Scheme II



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 °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; $HC{\equiv}CCH_2OSiPh_2Bu\text{-}t$, 88159-06-2; $HC{\equiv}C\text{-}n\text{-}C_6H_{13}$, 629-05-0; $HC{\equiv}CPh$, 536-74-3; $HC{\equiv}C(CH_2)_4OSiPh_2Bu\text{-}t$, 128217-23-2; $HC{\equiv}CCH(OSiMe_3)(CH_2)_5H$, 73061-39-9; $HC{=}CC(Me)(OSiMe_2(CMe_2CHMe_2))(CH_2)_5H$, 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.

(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†

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Received May 29, 1990

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**, $R_1 = CH_2C(CH_3)(OTMS)\text{-}n\text{-}C_4H_9$ 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

† 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.

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(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.

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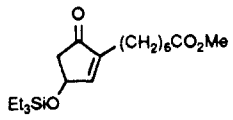
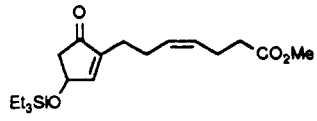
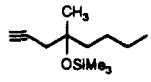
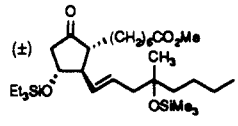
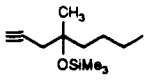
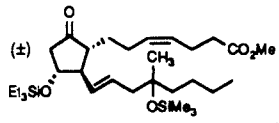
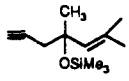
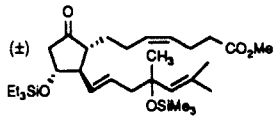
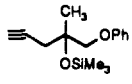
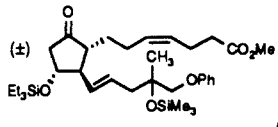
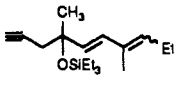
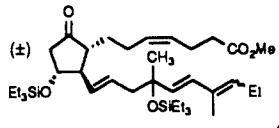
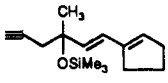
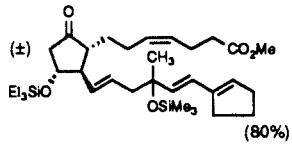
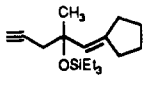
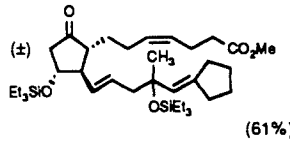
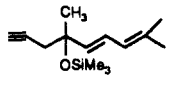
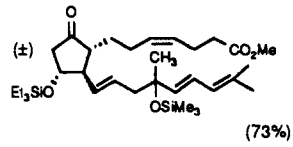
Table I. In Situ Cuprate Formation/Conjugate Addition Reaction from Alkynes



4a



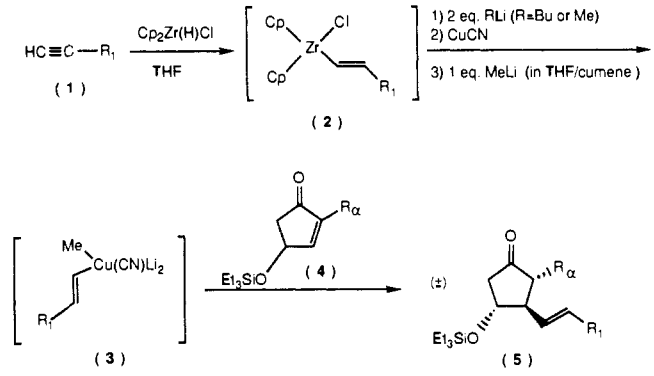
4b

entry	enone	alkyne	product (yields[a])
1	4a		 (73%[b])
2	4b		 (71%[b])
3	4b		 (66%[b])
4	4b		 (55%[b])
5	4b		 (80%[c])
6	4b		 (80%)
7	4b		 (61%)
8	4b		 (73%)

[a] Isolated yields of products after purification by silica gel chromatography. [b] Isolated yields of the purified deprotected prostaglandins after desilylation in aqueous acetone with a catalytic amount of PPTS. [c] This compound was not available via the vinylstannane or the vinyl iodide methods.

3.[14] Treatment of 3 with (±)-methyl 7-[5-oxo-3-[(triethylsilyl)oxy]-1-cyclopenten-1-yl]heptanoate **4a** at a low temperature (−30 to −78 °C) resulted in a 73% yield of protected misoprostol **5**.[15]

Scheme I[a]



[a] For misoprostol synthesis: $R_1 = CH_2C(CH_3)(OTMS)$-*n*-Bu and $R_\alpha = (CH_2)_6CO_2Me$.

The hydrozirconation of dienynes proceeded chemoselectively to afford the product of alkyne hydrometalation with only 1–3% attack on the diene function. The resulting vinylzirconium intermediates also underwent transmetalation to form the corresponding higher order cyanocuprates which are suitable for conjugate addition (entries 5, 6, and 8, Table I). The generality of this methodology is demonstrated by the successful syntheses of a variety of pharmacologically important prostaglandins (Table I).

This new one-pot procedure for the transformation of alkynes into higher order cyanocuprates and their subsequent conjugate addition to cyclopentenones has the following advantages: (a) it eliminates the need to handle toxic alkyltin compounds; (b) it eliminates the need to isolate and purify sensitive ω side chain intermediates (vinylstannanes or vinyl iodides); and (c) it allows for the preparation of a prostaglandin analogue (entry 5, Table I) that was not obtainable via vinylstannanes or vinyl iodides.

In summary, this process offers a short and efficient synthesis of prostaglandins directly from alkyne precursors and functionalized cyclopentenones. Additionally it provides a viable method for practical large-scale prostaglandin syntheses.

Acknowledgment. We are grateful to Dr. Arthur Campbell, Dr. Paul Collins, Prof. Bruce Lipshutz, and Prof. Paul Grieco for helpful discussions. We are also indebted to Ms. Cara Weyker of the Chemical Development Chromatography Group and Ms. Lydia Swenton of the Physical Methodology Group for their analytical support.

Supplementary Material Available: Complete analytical characterizations for the products listed in Table I as well as full experimental details for the preparation of misoprostol employing the typical procedures described in Scheme I (5 pages). Ordering information is given on any current masthead page.

(14) (a) Lipschutz, B. H. *Synthesis* **1987**, 325. (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.

(15) The crude protected misoprostol could be purified by chromatography on silica gel or deprotected directly under acidic conditions [aqueous acetone and a catalytic amount of pyridinium *p*-toluenesulfonate (PPTS) or acetic acid–THF–water (3:1:1 mixture)] to give misoprostol.