It should also be noted that equatorial attack on enone 4 suffers from the initial torsional strain due to the near-eclipsing arrangement of the newly forming bond and the axial C–H bond at C-6 and the strain due to the increasing eclipsing between the C=O bond and the equatorial C–H bond at C-6 as the reaction proceeds. Therefore, these torsional effects may be partially responsible for the high axial stereoselectivities observed. In conclusion, the observation delineated above with a highly hindered, conformationally rigid 2-alkylidenecyclohexanone and sterically demanding nucleophiles provides an interesting example where the orbital overlap between the forming bond and the C=C π-system appears to be, at least partially, a significant factor in contributing to the highly selective 1,2-axial additions by a various nucleophiles.

Acknowledgment. We are grateful to the National Institutes of Health (Grant DK-30025) for financial support of this work.

Supplementary Material Available: NMR (^{1}H and ^{13}C) spectroscopic and microanalytical data of **1**, **3**, **7ax** (R = Ph, Me, and *n*-Bu), and **7eq** (R = *n*-Bu) and the LIS data of **7ax** (R = *n*-Bu, Ph, and CH_3) and **7eq** (R = *n*-Bu) (5 pages). Ordering information is given on any current masthead page.

Propargyl and Allyl Grignard and Zinc Reagents. Regioselective Alkylation and Its Application to the Synthesis of PGE_3 and $F_{3\alpha}$ Methyl Ester

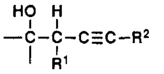
Akira Yanagisawa, Shigeki Habaue, and Hisashi Yamamoto*

Department of Applied Chemistry, Nagoya University, Chikusa, Nagoya 464-01, Japan

Received May 30, 1989

Summary: Regioselective propargylation and allylation were achieved using acylsilanes as electrophiles, and this methodology was applied to the synthesis of PGE_3 and $F_{3\alpha}$ methyl ester.

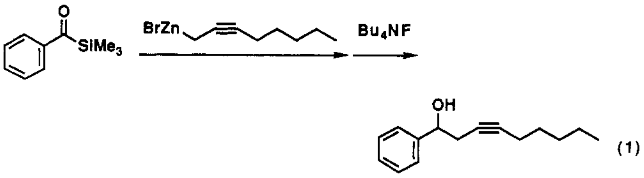
Sir: Methods which have been described previously from our laboratories[1] and others[2] permit the regiospecific synthesis of homopropargyl alcohols of type I, II, and IV from propargylorganometallics, but not of type III. Indeed, the regiocontrolled synthesis of III from the corresponding organometallics has remained an unsolved problem in organic synthesis. The structural features of III, on the other hand, are of great importance in many natural product syntheses. We shall describe a new approach to the synthesis of homopropargyl alcohol of type III which closes this methodological gap[3] using acylsilanes as the electrophiles.



$$-\overset{\text{HO}}{\underset{|}{\overset{|}{\text{C}}}}-\overset{\text{H}}{\underset{\text{R}^1}{\overset{|}{\underset{|}{\text{C}}}}}-\text{C}\equiv\text{C}-\text{R}^2$$

I: $R^1 = R^2 = H$ III: $R^1 = H$; $R^2 = $ Alkyl
II: $R^1 = $ Alkyl; $R^2 = H$ IV: $R^1 = R^2 = $ Alkyl

Treatment of the zinc reagent, derived from 2-octynyl bromide and zinc dust in THF, with benzoyltrimethylsilane[4] followed by desilylation afforded only the homopropargylic alcohol without contamination of any regioisomer (eq 1). With benzaldehyde, in contrast, a 35:65 mixture of acetylenic and allenic alcohol was obtained using the same zinc reagent.



(1)

The methodology described above was applied to the synthesis of PGs of the 3 series. The syntheses of PGE_3 and $PGF_{3\alpha}$ methyl esters were carried out by starting from the readily available aldehyde **1**.[5] Treatment of **1** in THF with the *E* enolate prepared from [(trimethylsilyl)acetyl]trimethylsilane[6] and lithium diisopropylamide, afforded the *E* α,β-unsaturated acylsilane **2** (68% yield). Acylsilane **2** was converted exclusively (α/γ = >99:1) to the desired $PGF_{3\alpha}$ derivative **3** in 92% yield by means of the zinc reagent derived from 2-pentynyl bromide and zinc dust in THF. Formylation of the C-15 hydroxyl group of **3** with acetic–formic anhydride and 4-(dimethylamino)pyridine in dichloromethane gave **4**, further transformed into **5** by reaction with tetrabutylammonium fluoride in THF in 67% overall yield.[7] $PGF_{3\alpha}$ derivative **5** was converted to the PGE_3 derivative **8** by a three-step sequence:

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(1) (a) Ishiguro, M.; Ikeda, N.; Yamamoto, H. *J. Org. Chem.* **1982**, *47*, 2225. (b) Furuta, K.; Ishiguro, M.; Haruta, R.; Ikeda, N.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2768.

(2) (a) Daniels, R. G.; Paquette, L. A. *Tetrahedron Lett.* **1981**, *22*, 1579. (b) Corey, E. J.; Rucker, C. *Tetrahedron Lett.* **1982**, *23*, 719. Review: Epsztein, R. *Comprehensive Carbanion Chemistry*; Buncel, E., Durst, T., Eds.; Elsevier: New York, 1984; Part B, Chapter 3.

(3) Danheiser described synthesis of type III homopropargylic alcohols from aldehydes and allenylsilanes: Danheiser, R. L.; Carini, D. J.; Kwasigroch, C. A. *J. Org. Chem.* **1986**, *51*, 3870.

(4) Acylsilanes can be prepared from the following. (a) 1,3-Dithians: Brook, A. G.; Duff, J. M.; Jones, P. F.; Davis, N. R. *J. Am. Chem. Soc.* **1967**, *89*, 431. Corey, E. J.; Seebach, D.; Freedman, R. *J. Am. Chem. Soc.* **1967**, *89*, 434. (b) Acyl chlorides: Yamamoto, K.; Hayashi, A.; Suzuki, S.; Tsuji, J. *Organometallics* **1987**, *6*, 974. Kang, J.; Lee, J. H.; Kim, K. S.; Jeong, J. U.; Pyun, C. *Tetrahedron Lett.* **1987**, *28*, 3261. Capperucci, A.; Degl'Innocenti, A.; Faggi, C.; Ricci, A. *J. Org. Chem.* **1988**, *53*, 3612. Furstner, A.; Weidmann, H. *J. Organomet. Chem.* **1988**, *354*, 15. (c) (α-Hydroxyalkyl)silanes: Danheiser, R. L.; Fink, D. M.; Okano, K.; Tsai, Y.-M.; Szczepanski, S. W. *J. Org. Chem.* **1985**, *50*, 5393. Linderman, R. J.; Suhr, Y. *J. Org. Chem.* **1988**, *53*, 1569. (d) Alkoxyallenes: Clinet, J.-C.; Linstrumelle, G. *Tetrahedron Lett.* **1980**, *21*, 3987. Reich, H. J.; Kelly, M. J. *J. Am. Chem. Soc.* **1982**, *104*, 1119. (e) Thiocarboxylic acid *S*-esters: Kuwajima, I.; Mori, A.; Kato, M. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 2634. (f) Alkynylsilanes.[6] For reviews of preparation of acylsilanes, see: Colvin, E. W. *Silicon Reagents in Organic Synthesis*; Academic Press: London, 1988; Chapter 12.

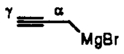
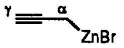
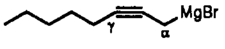
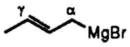
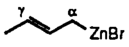
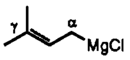
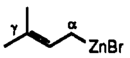
(5) The aldehyde 1 was generously supplied by Ono Pharmaceutical Co.

(6) (a) Miller, J. A.; Zweifel, G. *Synthesis* **1981**, 288. (b) Miller, J. A.; Zweifel, G. *J. Am. Chem. Soc.* **1981**, *103*, 6217.

(7) A definite but not unexpected limitation of the new method has been found to occur in cases where allylic alcohol was produced. Thus the desilylation of the unprotected 3 caused an allylic rearrangement reaction. This limitation was circumvented by a simple formylation followed by desilylation.

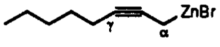
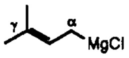
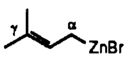
0022-3263/89/1954-5198$01.50/0

Table I. Regioselectivity of Allylation and Propargylation with Aldehydes[a]

		reactant		
entry	nucleophile[b]	PhCHO α/γ^c	$PhCOSiMe_3{}^{4b}$ α/γ^c	$PhCOSi(i\text{-}Pr)_3{}^{4a}$ α/γ^c
1		>99:1		
2		92:8	93:7	>99:1
3		30:70	41:59	>99:1
4		35:65	>99:1	
5		<1:99	<1:99	<1:99
6		<1:99	3:97	>99:1
7		<1:99	2:98	86:14
8		<1:99	90:10	>99:1

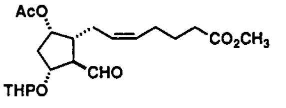
[a] The reaction was conducted as follows: To a solution of organozinc bromide (2.5–3 equiv) in THF or organomagnesium halide (2–2.5 equiv) in ether was added an aldehyde (1 equiv) at 0 °C, and the resulting mixture was stirred at this temperature for 20–60 min. Unless otherwise specified, the yield of the reaction is generally 80–95%. [b] Prepared by treatment of activated zinc powder or magnesium chips with the corresponding alkyl halide in THF or ether, respectively, at 0 °C for 30–60 min. [c] The α/γ ratios of products were determined by 200-MHz ^1H NMR analysis.

Table II. Regioselectivity of Allylation and Propargylation with Aliphatic Aldehydes[a]

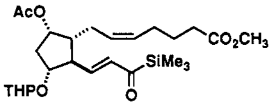
		reactant		
entry	nucleophile	$n\text{-}C_5H_{11}CHO$ α/γ^b	$n\text{-}C_5H_{11}COSiMe_3{}^{4a}$ α/γ^b	$n\text{-}C_5H_{11}COSi(i\text{-}Pr)_3{}^{4a}$ α/γ^b
1		36:64	43:57	96:4
2		21:79	>99:1	
3		<1:99	2:98	87:13
4		<1:99	89:11	>99:1[c]
5		46:54	95:5	

[a] The reaction was conducted by the similar method described in footnotes a and b of Table I. Unless otherwise specified, the yield of the reaction is generally 80–95%. [b] The α/γ ratios of products were determined by 200-MHz ^1H NMR analysis. [c] The reaction was carried out in CH_2Cl_2 at 40 °C for 1 h.

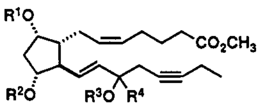
(1) tetrahydropyranyl (THP) protection of the C-15 hydroxyl group giving **6** (77%), (2) deacetylation with methanolic sodium methoxide to afford **7** (96%), and (3) Jones oxidation of the C-9 hydroxyl group to **8** (67%). Hydrolysis of the THP groups with 3:1:1 mixture of acetic acid, water, and THF led to **9** in 85% yield with $15\alpha/15\beta$ ratio of 54:46. Finally, partial hydrogenation of the triple bond in the 15α isomer of **9**, giving the *Z* double bond, was accomplished over Lindlar catalyst to afford quantitatively PGE_3 methyl ester in 99% yield, $[\alpha]^{21}_D$ −80.0° (*c* 0.64, $CHCl_3$).[8,9] $PGF_{3\alpha}$ methyl ester is also accessible from intermediate **5** in three steps. Removal of the THP group from **5** with a 3:1:1 mixture of acetic acid, water, and THF gave **10** in 89% yield with $15\alpha/15\beta$ ratio of 56:44. Partial hydrogenation of the acetylenic linkage in the 15α isomer of **10** and subsequent treatment with a methanolic sodium methoxide quantitatively formed $PGF_{3\alpha}$ methyl ester, $[\alpha]^{22}_D$ +22.0° (*c* 0.45, $CHCl_3$).[8c,9]



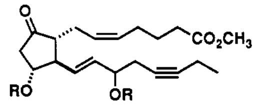
1



2



3, R^1=Ac; R^2=THP; R^3=H; R^4=$SiMe_3$
4, R^1=Ac; R^2=THP; R^3=HCO; R^4=$SiMe_3$
5, R^1=Ac; R^2=THP; R^3=R^4=H
6, R^1=Ac; R^2=R^3=THP; R^4=H
7, R^1=R^4=H; R^2=R^3=THP
10, R^1=Ac; R^2=R^3=R^4=H



8, R=THP
9, R=H

The syntheses of PGE_3 and $PGF_{3\alpha}$ described above clearly demonstrate the practical utility of the new process in selective organic synthesis. We next turned our attention to the generality of the new method and examined various combinations of propargylic and allylic metal reagents with benzoylsilanes. Some of our results are illustrated in Table I. Because of the bulk of the triisopropylsilyl group, its use resulted in a greater measure of

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(8) (a) Samuelsson, B. *J. Am. Chem. Soc.* **1963**, *85*, 1878. (b) Axen, U.; Thompson, J. L.; Pike, J. E. *J. Chem. Soc., Chem. Commun.* **1970**, 602. (c) Corey, E. J.; Shirahama, H.; Yamamoto, H.; Terashima, S.; Venkateswarlu, A.; Schaaf, T. K. *J. Am. Chem. Soc.* **1971**, *93*, 1490.

(9) Satisfactory analytical and spectral data were obtained.

stereochemical control than the more common trimethylsilyl unit. For example, the condensation of allylic zinc reagents with benzoyl triisopropylsilane produced the α-adduct exclusively.

The overall applicability of the process is quite broad.[10] Similar results were obtained using α,β-unsaturated or aliphatic aldehydes, with organozinc, magnesium, lithium,[10a,11] or potassium reagents. Some of our results are shown in Table II.

Noteworthy is the example that condensation of *cis*-2-pentenyl potassium[12,13] prepared from *cis*-2-pentene, potassium *tert*-butoxide, TMEDA, and a solution of *n*-butyllithium in hexane with hexanoyltrimethylsilane in THF at −78 °C for 20 min followed by desilylation afforded the homoallylic alcohol in 72% yield with α/γ ratio of 20:1. The desired α-adduct exhibited high *Z* selectivity (Z/E = 99:1).[14,15]

The above example provides further evidence for the power of this new process and demonstrates that its use can lead to a profound simplification of the problem of synthesis of various derivatives from fatty acid cascades, an increasingly important class of biologically active molecules. The versatility of acylsilanes as electrophiles for the ambident nucleophiles has been demonstrated.[16]

Acknowledgment. Partial financial support from the Ministry of Education, Japanese Government, is gratefully acknowledged.

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(10) Other examples of the use of acylsilane in organic synthesis: (a) Wilson, S. R.; Hague, M. S.; Misra, R. N. *J. Org. Chem.* **1982**, *47*, 747. (b) Nakada, M.; Urano, Y.; Kobayashi, S.; Ohno, M. *J. Am. Chem. Soc.* **1988**, *110*, 4826.

(11) Similar regioselectivity was observed by Noyori in reactions between allenyltin/alkyllithium and acyl silanes: Suzuki, M.; Morita, Y.; Noyori, R. 56th Annual Meeting of the Chemical Society of Japan Abstract 3XIIA33, Tokyo, 1988.

(12) (a) Schlosser, M.; Hartmann, J.; David, V. *Helv. Chim. Acta* **1974**, *57*, 1567. (b) Schlosser, M.; Hartmann, J. *J. Am. Chem. Soc.* **1976**, *98*, 4674. (c) Stähle, M.; Hartmann, J.; Schlosser, M. *Helv. Chim. Acta* **1977**, *60*, 1730.

(13) Brandsma, L.; Verkruijsse, H. D. *Preparative Polar Organometallic Chemistry*; Springer-Verlag: New York, 1986.

(14) Recent example of *Z*-selective allylation of aldehydes: Guo, B.-S.; Doubleday, W.; Cohen, T. *J. Am. Chem. Soc.* **1987**, *109*, 4710.

(15) The isomer ratio, Z/E, was determined by 500-MHz ^{1}H NMR assay.

(16) Satisfactory IR, ^{1}H NMR, and ^{13}C NMR spectra as well as microanalytical data were obtained for all new compounds.

The Addition of the Highly Functionalized Zinc, Copper Reagents RCu(CN)ZnI to Nitro Olefins

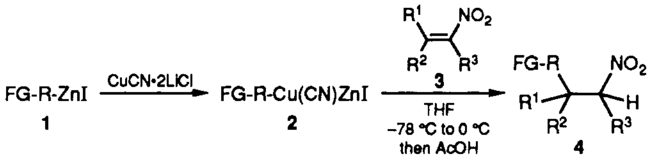
Carole Retherford, Ming Chang P. Yeh, Ioana Schipor, Huai Gu Chen, and Paul Knochel*

Department of Chemistry, The University of Michigan, Ann Arbor, Michigan 48109

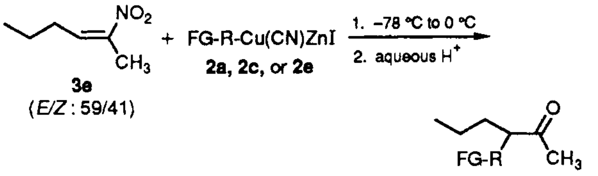
Received July 18, 1989

Summary: The addition of the highly functionalized zinc and copper organometallics FG-RCu(CN)ZnI to nitro olefins furnishes polyfunctional nitroalkanes in good to excellent yields; with α-substituted nitro olefins, the Michael adducts can be directly converted into polyfunctional ketones.

Scheme I



Scheme II



6a FG-R: $(CH_2)_3CO_2Et$ (82%)
6b FG-R: $(CH_2)_3CN$ (76%)
6c FG-R: $(CH_2)_6OAc$ (71%)

Sir: The addition of carbon nucleophiles to nitro olefins represents an easy access to a variety of nitroalkanes which are versatile intermediates in organic synthesis.[1] Several classes of stabilized lithium nucleophiles such as enolates or sulfur stabilized anions[2] as well as nonstabilized lithium,[2-4] magnesium,[4,5] cadmium[6] organometallics, zincates,[7] allylic tin[8] and silicon[9] derivatives, and recently organoaluminum[10] compounds have been shown to add to nitro olefins in satisfactory yields. Surprisingly, the reports on the addition of organocopper derivatives[7,11] to nitro olefins are rare and the reactions proceed generally in moderate yields.

We reported previously,[12] that the polyfunctionalized zinc organometallics FG-R-ZnI 1 could be readily trans-

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(1) (a) Seebach, D.; Colvin, E. W.; Lehr, F.; Weller, T. *Chimia* **1979**, *33*, 1. (b) Yoshikoshi, A.; Miyashita, M. *Acc. Chem. Res.* **1985**, *18*, 284. (c) Rosini, G.; Ballini, R. *Synthesis* **1988**, 833.

(2) (a) Seebach, D.; Leitz, H. F. *Angew. Chem.* **1971**, *83*, 542; *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 501. (b) Seebach, D.; Leitz, H. F.; Ehrig, V. *Chem. Ber.* **1975**, *108*, 1924. (c) Seebach, D.; Ehrig, V.; Leitz, H. F.; Henning, R. *Chem. Ber.* **1975**, *108*, 1946. (d) Ehrig, V.; Seebach, D. *Chem. Ber.* **1975**, *108*, 1961.

(3) (a) Bedford, C. D.; Nielsen, A. T. *J. Org. Chem.* **1978**, *43*, 2460. (b) Severin, T.; Scheel, D.; Adlikary, P. *Chem. Ber.* **1969**, *102*, 2966.

(4) (a) Seebach, D.; Knochel, P. *Helv. Chim. Acta* **1984**, *67*, 261. (b) Seebach, D.; Calderari, G.; Knochel, P. *Tetrahedron* **1985**, *41*, 4861. (c) Hayama, T.; Tomoda, S.; Takeuchi, Y.; Nomura, Y. *Tetrahedron Lett.* **1983**, *24*, 2795.

(5) (a) Buckley, D. G. *J. Chem. Soc.* **1947**, 1494. (b) Buckley, D. G.; Ellery, E. *J. Chem. Soc.* **1947**, 1497. (c) Corey, E. J.; Estreicher, H. *J. Am. Chem. Soc.* **1978**, *100*, 6294. (d) Ashwood, M. S.; Bell, L. A.; Houghton, P. G.; Wright, S. H. B. *Synthesis* **1988**, 379.

(6) Michel, J.; Henry-Basch, E. *C. R. Acad. Sci.; Ser. C* **1966**, *262*, 1274.

(7) Langer, W.; Seebach, D. *Helv. Chim. Acta* **1979**, *62*, 1710.

(8) Uno, H.; Watanabe, N.; Fujiki, S.; Suzuki, H. *Synthesis* **1987**, 471.

(9) (a) Ochiai, M.; Arimoto, M.; Fujita, E. *Tetrahedron Lett.* **1981**, *22*, 1115. (b) Uno, H.; Fujiki, S.; Suzuki, H. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 1267.

(10) (a) Pecunioso, A.; Menicagli, R. *Tetrahedron* **1987**, *43*, 5411. (b) Pecunioso, A.; Menicagli, R. *J. Org. Chem.* **1988**, *53*, 45. (c) Pecunioso, A.; Menicagli, R. *J. Org. Chem.* **1989**, *54*, 2391.

(11) (a) Bowlus, S. B. *Tetrahedron Lett.* **1975**, 3591. (b) Hansson, A.-T.; Nilsson, M. *Tetrahedron* **1982**, *38*, 389. (c) Stiver, S.; Yates, P. *J. Chem. Soc., Chem. Commun.* **1983**, 50.

(12) (a) Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390. (b) Berk, S. C.; Knochel, P.; Yeh, M. C. P. *J. Org. Chem.* **1988**, *53*, 5789.

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