# Organic Syntheses

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

GENERATION OF AN ACETYLENE-TITANIUM ALKOXIDE COMPLEX: PREPARATION OF (*Z*)-1,2-DIDEUTERIO-1-(TRIMETHYLSILYL)-1-HEXENE
[(Silane, (1,2-dideuterio-1-hexenyl)trimethyl-, (*Z*)-)]
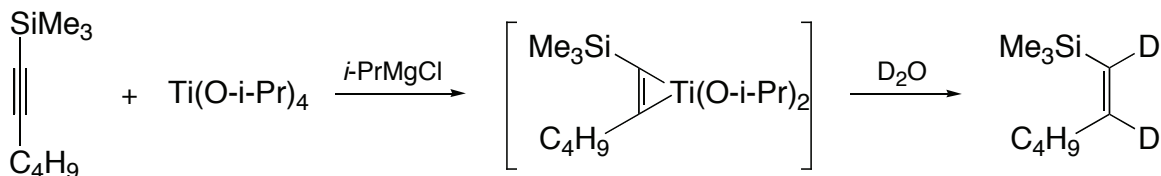
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Checked by Katherine Hervert and Louis Hegedus.

1. Procedure

An oven-dried, 1-L, two-necked, round-bottomed flask is equipped with a stirring bar and 100-mL, pressure-equalizing addition funnel, the top of which is fitted with a rubber septum. The other neck of the flask is fitted with a three-way stopcock, one outlet of which is capped with a rubber septum and the other is connected alternately to a vacuum/argon gas system. The flask is evacuated, then flushed with argon; this operation is repeated twice. After 400 mL of anhydrous diethyl ether (Note 1), 1-(trimethylsilyl)-1-hexyne (Note 2) (5.00 g, 32.40 mmol) and freshly distilled titanium tetraisopropoxide (Note 3) (11.95 mL, 40.50 mmol) are added in this order through the septum of the three-way stopcock via syringe. The resulting solution is stirred and cooled in a dry ice-hexane bath to ca. −78 °C. The addition funnel is charged via syringe through the rubber septum with a solution of isopropylmagnesium chloride in diethyl ether (Note 4) (50.62 mL of a 2.0M solution in ether, 101.24 mmol), which then is added dropwise to the cold mixture over 30 min. The mixture is warmed to −50 °C over 30 min (and turns black) and is aged for 3 h at −50 °C to insure completion of reaction (Note 5). Deuterium oxide (12 mL) (Note 6) is rapidly added via the addition funnel to the cooled reaction mixture with stirring. The cooling bath is then removed and the reaction mixture is allowed to warm to room temperature. At this point, the addition funnel and three-way stopcock are removed. After anhydrous sodium sulfate (100 g) is added to the

heterogeneous mixture, the suspension is stirred at room temperature for 10 min and filtered under vacuum through a short pad of Celite, which is washed with small portions of ether. The combined filtrate and washings are concentrated with a rotary evaporator (Note 7) to approximately 30 mL, which is transferred to a 50-mL distillation flask with the aid of small portions of ether. The crude product is purified by distillation under partial vacuum to furnish 3.56-4.47 g (69-87%) of the olefin, bp 128-129 °C (350 mm), as a colorless liquid (Notes 8, 9).

2. Notes

1. Anhydrous diethyl ether was purchased from Kanto Chemical Co., Ltd. (Japan).

2. 1-(Trimethylsilyl)-1-hexyne was purchased from Aldrich Chemical Co., Inc. and used as received. Alternatively, this can be prepared according to a method described in Organic Syntheses.[2]

3. Titanium isopropoxide was purchased from Tokyo Kasei Kogyo Co., Ltd. (Japan), distilled before use, and stored under an argon atmosphere.

4. A 2.0M solution of isopropylmagnesium chloride in diethyl ether was purchased from Aldrich Chemical Co., Inc. and used as received.

5. Reduction of the amount of the ethyl ether (initially 400 mL) increases the formation of the 2:1 acetylene-titanium alkoxide complex, i.e., a titanacyclopentadiene. However, under these conditions, hydrolysis of the reaction mixture reveals that the formation of 2,3-dibutyl-1,4-bis(trimethylsilyl)-1,3-butadiene arising from the titanacyclopentadiene is less than 3%. In any event, after distillation, this diene does not contaminate the desired product.

6. Deuterium oxide (100.0 atom% D) was purchased from Aldrich Chemical Co., Inc.

7. The product is moderately volatile so that extensive concentration under reduced pressure decreases the yield. When most of the solvent is removed under atmospheric pressure with a standard distillation apparatus (rather than with a rotary evaporator), the product is obtained in 87% yield.

8. The spectra are as follows: IR (neat) cm^{-1}: 2957, 2927, 2862, 1585 (C=C), 1459, 1248 (Si-Me), 839, 756. ^{1}H NMR (300 MHz, CDCl$_3$): δ 0.14

(s, 9 H, Me$_3$Si), 0.91 (t, J = 7.2, 3 H, Me), 1.35-1.55 (m, 4 H, (CH$_2$)$_2$), 2.22 (t, J = 7.2, 2 H, allylic CH$_2$). ^{13}C NMR (75 MHz, CDCl$_3$): δ 0.08 (SiMe$_3$), 13.91, 22.34, 31.90, 33.04, 128.23 (t, J ^{13}C-^{2}H = 20.5), 148.96 (t, J ^{13}C-^{2}H = 22.8). Anal. Calcd for C$_9$H$_{18}$D$_2$Si: C, 68.26. Found: C, 68.11. Deuterium incorporation α and β to the silyl group is determined by ^{1}H NMR analysis to be >99.5%.

9. Structural identification, except for the deuterium incorporation, is secured through (Z)-1-(trimethylsilyl)-1-hexene, a known compound obtained by hydrolysis of the acetylene-titanium complex with H$_2$O instead of D$_2$O using the same procedure. Spectra for the unlabeled product follow: IR (neat) cm^{-1}: 2958, 2925, 2859, 1607 (C=C), 1458, 1249 (Si-Me), 837, 763; ^{1}H NMR (300 MHz, CDCl$_3$): δ 0.11 (s, 9 H, Me$_3$Si), 0.90 (t, J = 7.2, 3 H, Me), 1.25-1.45 (m, 4 H, (CH$_2$)$_2$), 2.12 (symmetrical m, 2 H, allylic CH$_2$), 5.47 (d/t, J = 13.8, 1.2, 1 H, Me$_3$SiCH=C), 6.30 (d/t, J = 13.8, 7.2, 1 H, CH=CHSiMe$_3$). ^{13}C NMR (75 MHz, CDCl$_3$): δ 0.09 (SiMe$_3$), 13.90, 22.31, 31.99, 33.18, 128.80, 149.41. These data are in good agreement with reported values.[3] The ratio of Z and E isomers is determined to be >99.5:0.5 by ^{1}H NMR analysis of this sample. No contamination by the saturated silane is also confirmed by NMR analysis.
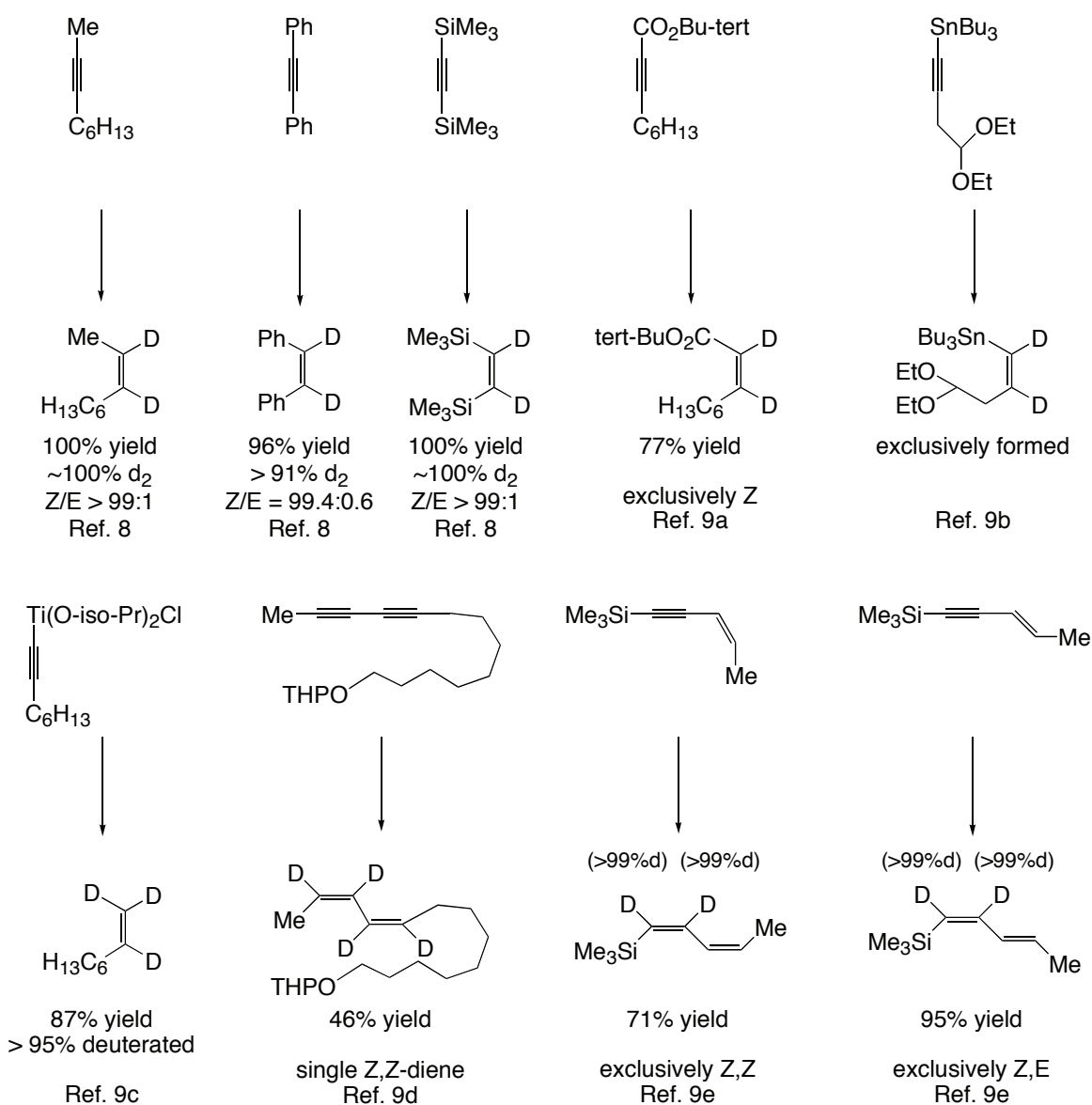

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC 1995.

3. Discussion

Isomerically pure 1-alkenylsilanes are useful intermediates in organic synthesis.[4] Thus, their deuterium-labeled counterparts are versatile precursors for the preparation of labeled organic molecules. Catalytic reduction of acetylenes using deuterium gas (D$_2$) is a convenient method to prepare D-labeled olefins.[5] However, some drawbacks have been observed, including scrambling between hydrogen atoms in the substrate and D$_2$ (which decreases the degree of deuterium uptake as well as the positional

selectivity[6]), the variable E/Z ratio of the resulting olefinic bond,[7] and over-reduction of the acetylenic bond.[5] In addition, handling (and indeed availability) of the required amount of D_2 may be often problematic in some laboratories. The method described herein[8] is a convenient alternative to reduction with D_2 because (1) high deuterium incorporation of the vinylic positions and (2) formation of the Z-olefin is insured, and finally (3) inexpensive reagents (including D_2O as the source of deuterium) are utilized. The labeled olefins shown in the Table have been prepared by this method.[8,9]
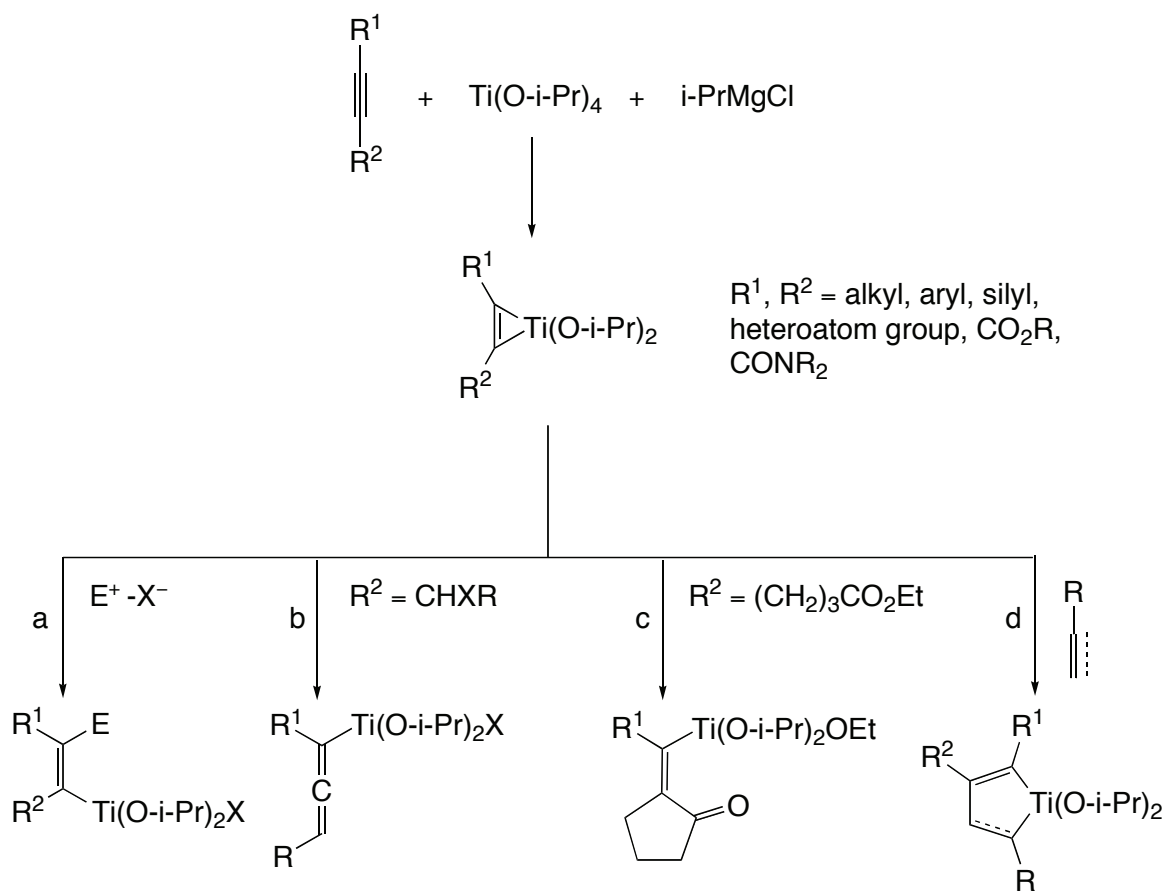
Table. Preparation of (Z)-Dideuterio Alkenes

100% yield	96% yield	100% yield	77% yield	exclusively formed
~100% d_2	> 91% d_2	~100% d_2		
Z/E > 99:1	Z/E = 99.4:0.6	Z/E > 99:1	exclusively Z	
Ref. 8	Ref. 8	Ref. 8	Ref. 9a	Ref. 9b

87% yield	46% yield	71% yield	95% yield
> 95% deuterated			
	single Z,Z-diene	exclusively Z,Z	exclusively Z,E
Ref. 9c	Ref. 9d	Ref. 9e	Ref. 9e

More importantly, the procedure represents a novel method for the generation of a new type of acetylene-Group 4 transition metal complex (**1** in the Scheme[10]). Acetylene-metal complexes often have been utilized as useful intermediates in organic synthesis, even though their structures may not be known.[11] The Scheme summarizes the four types of transformations available to the titanium complex **1**[10]: i) **1** can serve as a cis-1,2-bis-carbanionic species, which are otherwise difficult to generate, and affords adducts upon reaction with a variety of electrophiles (route a); ii) allenyl- or propargyltitanium reagents are generated from acetylenes having an appropriate leaving group at the propargylic position (route b); iii) the carbon-titanium bond of the complex reacts intramolecularly with an ester carbonyl group to give unsaturated carbonyl compounds (route c); iv) complex **1** participates in coupling reactions with other olefins or acetylenes to give the corresponding titanacycles, enabling a variety of subsequent synthetic applications (route d).

The synthetic advantages of the titanium alkoxide complex **1** over other Group 4 metal complexes such as titanocene or zirconocene-based ones are: i) the titanium alkoxide is very inexpensive compared with metallocene reagents; ii) the reaction work up is very simple, since titanium is completely hydrolyzed to give water-soluble inorganic salts, readily separable from the desired organic product(s); iii) various functionalized acetylene complexes have been generated for the first time; and finally, iv) several reactions, some of which cannot be accomplished by conventional Group 4 metal complexes, are now feasible through these new acetylene complexes.[10]

Scheme. Generation of and Synthetically Useful Reactions of Acetylene-Titanium Complexes 1

R^1 —‖— R^2 + $Ti(O\text{-}i\text{-}Pr)_4$ + $i\text{-}PrMgCl$

$\downarrow$

R^1, R^2 = alkyl, aryl, silyl, heteroatom group, CO_2R, $CONR_2$

a $E^+\text{-}X^-$

b $R^2 = CHXR$

c $R^2 = (CH_2)_3CO_2Et$

d R

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2. Stang, P. J.; Kitamura, T. *Org. Synth., Coll. Vol. IX*, **1998**, 477.

3. (a) Soderquist, J. A. ; Santiago, B. *Tetrahedron Lett.* **1990**, *31*, 5113. (b) Doyle, M. M.; Jackson, W R.; Perlmutter, P. *Aust. J. Chem.* **1989**, *42*, 1907. See also: (c) Sato, F.; Ishikawa, H.; Sato, M. *Tetrahedron Lett.* **1981**, *22*, 85. (d) Miller R. B.; McGarvey, G. *J. Org. Chem.* **1978**, *43*, 4424. (e) Miller, R. B.; Reichenbach, T. *Tetrahedron Lett.* **1974**, *15*, 543.

4. (a) Weber, W. P. In *Silicon Reagents for Organic Synthesis*; Springer-Verlag: Berlin, **1983**; p. 79. (b) Colvin, E. W. In *Silicon in Organic Synthesis*; Butterworth, Sevenoaks, **1981**; p. 44. (c) Fleming, I.; Dunogués, J.; Smithers, R. In *Organic Reactions*; Kende, A. S., Ed.; Wiley: New York, **1989**; Vol. *37*, p. 57. (d) Fleming, I.; Barbero, A.; Walter, D. *Chem. Rev.* **1997**, *97*, 2063.

5. Freifelder, M. *Catalytic Hydrogenation in Organic Synthesis. Procedures and Commentary*; Wiley: New York, 1978; p. 10. Rylander, P. N. In *Selections from the Aldrichimica Acta*; Aldrich: Milwaukee, 1984; p. 195; *Aldrichimica Acta*, **1979**, *12*, 53.

6. March J. *Advanced Organic Chemistry*; 4th ed., Wiley: New York **1992**; p. 776.

7. Ref. 4b, p. 48. Ref. 3d. Overman, L. E.; Brown, M. J.; McCann, S. F. *Org. Synth. Coll. Vol. VIII*, **1993**, 609.

8. Harada, K.; Urabe, H.; Sato, F. *Tetrahedron Lett.* **1995**, *36*, 3203.

9. (a) Hamada, T.; Suzuki, D.; Urabe, H.; Sato F. *J. Am. Chem. Soc.* **1999**, *121*, 7342. (b) Launay, V.; Beaudet, I.; Quintard, J.-P. *Synlett* **1997**, 821. (c) Averbuj, C.; Kaftanov, J.; Marek, I. *Synlett* **1999**, 1939. (d) Hungerford, N. L.; Kitching, W. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1839. (e) Hamada, T.; Mizojiri, R.; Urabe, H.; Sato F. *J. Am. Chem. Soc.* **2000**, *122*, 7138. See also: (f) Sawada, D.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 10521.

10. (a) Sato, F.; Urabe, H.; Okamoto, S. *Pure Appl. Chem.* **1999**, 71, 1511. (b) Sato, F.; Urabe, H.; Okamoto, S. *Chem. Rev.* **2000**, *100*, 2835. (c) Sato, F.; Urabe, H.; Okamoto, S. *Synlett* **2000**, 753. (d) Sato, F.; Okamoto, S. *Adv. Synth. Catal.* **2001**, *343*, 759-784. (e) Sato, F.; Urabe, H. In *Titanium and Zirconium in Organic Synthesis*; Marek, I., Ed.; Wiley-VCH: Weinheim, 2002, 319-354. (f) See also: Kulinkovich, O. G.; de Meijere, *A. Chem. Rev.* **2000**, *100,* 2789. (g) Eisch, J. J. *J. Organomet. Chem.* **2001**, *617-618*, 148.

11. (a) Buchwald, S. L.; Nielsen, R. B. *Chem. Rev.* **1988**, *88*, 1047. (b) Negishi, E.; Takahashi, T. *Acc. Chem. Res.* **1994**, *27*, 124. (c) Ohff, A.; Pulst, S.; Lefeber, C.; Peulecke, N.; Arndt, P.; Burlakov, V. V.; Rosenthal, U. *Synlett* **1996**, *111*. (d) Negishi, E.; Takahashi, T. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 755. (e) Kataoka, Y.; Miyai, J.; Oshima, K.; Takai, K.; Utimoto, K. *J. Org. Chem.* **1992**, *57*, 1973. (f) Hartung, J. B., Jr.; Pedersen, S. F. *J. Am. Chem. Soc.* **1989**, *111*, 5468. (g) Strickler, J. R.; Bruck, M. A.; Wexler, P. A.; Wigley, D. E. *Organometallics* **1990**, *9*, 266.

Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

1-(Trimethylsilyl)-1-hexyne: Silane, 1-hexynyltrimethyl- (13); (3844-94-8)

Titanium tetraisopropoxide: Titanium, tetrakis(2-propanolato)-, 2-Propanol, titanium (4+) (9); (546-68-9)

Isopropylmagnesium chloride: Magnesium, chloro(1-methylethyl)- (13); (1068-55-9)

(*Z*)-1-(Trimethylsilyl)-1-hexene: Silane, 1-hexenyltrimethyl-, (*Z*)- (12); (52835-06-0)