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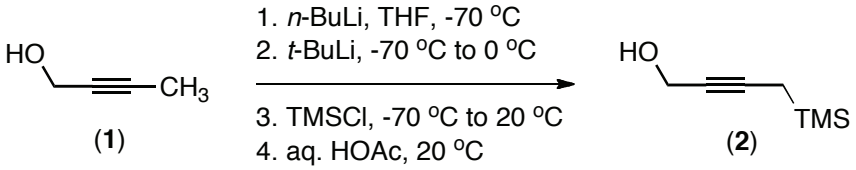
September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

AN ECONOMICAL SYNTHESIS OF 4-TRIMETHYLSILYL-2-BUTYN-1-OL



Submitted by Alexander N. Wein, Rongbiao Tong, and Frank E. McDonald.[1]
Checked by Florian Bächle and Andreas Pfaltz.[2]

1. Procedure

Caution! tert-Butyllithium is extremely pyrophoric and must not be allowed to come into contact with the atmosphere. This reagent should only be handled by individuals trained in its proper and safe use. It is recommended that transfers be carried out by using a 20-mL or smaller glass syringe filled to no more than 2/3 capacity, or by cannula. For a discussion of procedures for handling air-sensitive reagents, see Aldrich Technical Bulletin AL-134.

*4-Trimethylsilyl-2-butyn-1-ol (**2**).* A 500-mL three-necked, round-bottomed flask equipped with a two-tap Schlenk adapter connected to a bubbler and an argon/vacuum manifold (Note 1) in the left neck, a scaled 50-mL dropping funnel closed with a rubber septum on top in the middle neck, a rubber septum on the right neck and a magnetic stir bar (3 cm) is flame-dried, vented with argon and then allowed to cool to room temperature under argon atmosphere (Note 2). The rubber septum on the right is replaced by a low temperature thermometer. The flask is charged with anhydrous THF (150 mL) (Note 3), and 2-butyn-1-ol (**1**, 5.38 mL, 5.00 g, 69.9 mmol) (Note 4) is added. This solution is cooled to −70 °C (internal temperature) with a dry ice-acetone bath. Once cooled, *n*-butyllithium (2.5 M in hexanes, 28.0 mL, 69.9 mmol, 1.0 equiv) (Note 5) is added dropwise over the course of 80 min (Note 6), and afterwards the solution is stirred for an additional 10 min. Next, *tert*-butyllithium (1.7 M in pentane, 45.2 mL, 76.9 mmol, 1.1 equiv) (Note 7) is added dropwise over the course of 60 min (Note 8). The solution develops a yellow color during the addition of the alkyllithium reagents. After the addition of *tert*-butyllithium is completed,

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the reaction mixture is slowly warmed to 0 °C during two hours by keeping the flask directly over the dry ice-acetone bath. Formation of a precipitate is first observed between −45 °C and −30 °C and the mixture becomes cloudier as the temperature warms towards 0 °C. After two hours, the reaction vessel is maintained at 0 °C for 20 min with an ice-water bath.

The dropping funnel is replaced by a rubber septum, and the reaction vessel is recooled to −70 °C with a dry ice-acetone bath. Trimethylsilyl chloride (17.7 mL, 15.2 g, 140 mmol, 2.0 equiv, Note 9) is added *via* syringe pump at 45 mL / h to the suspension of the dianionic intermediate. During this addition the color changes from dark yellow to light brown and the precipitate dissolves again (Note 10). The reaction mixture is allowed to warm to room temperature and stirred overnight (16-17 h). The solution becomes orange, and a cream colored precipitate is formed during this period.

The reaction is then quenched by adding saturated aqueous ammonium chloride (100 mL) to the reaction mixture at room temperature, and the biphasic mixture is stirred vigorously for 5 min. Water (100 mL) is added to dissolve the precipitated salts, and the mixture is stirred for additional 25 min. Diethyl ether (100 mL) is added to dilute the organic layer, and the layers are separated in a 1-L separatory funnel. The aqueous layer is extracted with diethyl ether (2 x 25 mL), and the combined organic layers are transferred to a round-bottomed flask and concentrated to ~75 mL by rotary evaporation (35 °C, 210 mmHg) (Note 11). To this solution, a magnetic stir bar (3 cm) is added and 8.73 M acetic acid (15 mL, 130 mmol) (Note 12) is added to cleave the trimethylsilyl ether. The reaction mixture is stirred for one hour until full conversion is achieved according to TLC analysis (Note 13). The reaction mixture is then neutralized by portionwise addition of saturated aqueous sodium bicarbonate until the aqueous layer is slightly basic to pH paper (Note 14). The biphasic solution is transferred to a 1-L separatory funnel and the organic layer is collected. The aqueous layer is extracted with diethyl ether (2 x 50 mL), the combined organic layers are washed with brine (1 x 100 mL) and then dried over magnesium sulfate. After vacuum filtration through a medium porosity fritted funnel packed with Celite and washing with diethyl ether (2 x 25 mL), the crude mixture is concentrated under reduced pressure by rotary evaporation (35° C, 150 mmHg) to give a yellow oil (Note 15).

This crude product is purified by vacuum distillation over the course of five to six hours at 75 mmHg. A vacuum distillation setup consisting of a

oil bath, a flask charged with compound, a 40 cm silvered and vacuum-jacketed Vigreux column, a distillation head with condenser and an udder connected to four 25-mL round-bottomed flasks immersed in a ice-water bath is used (Note 16). At 45 °C and 75 mmHg the first fraction is collected, which consists of trimethylsilanol. Subsequently the oil bath temperature is slowly increased to 140 °C, and the distillate obtained during this period is combined with the first fraction. The boiling point reaches 115 °C before it then drops. Then the oil bath temperature is increased to 145 °C. At this temperature a mixture of side product and desired product with a boiling point of 121 °C is collected in the second fraction (~ 2 g). After 1.5 hours the oil bath temperature is increased to 150 °C. The desired product is collected in fraction three with a boiling point of 124 °C. A slow increase of the oil bath temperature to 165 °C, followed by a slow decrease of the pressure to 23 mmHg provides additional product in high purity, which is collected in fraction four (Note 17). The combined fractions three and four give the product, 4-trimethylsilyl-2-butyn-1-ol (**2**) in 35-37% yield (3.5-3.7 g) as colorless oil that is stored in the freezer at –20 °C (Notes 18 and 19). The identity of the product is confirmed by ^{1}H NMR, ^{13}C NMR, IR and elemental analysis (Note 20).

2. Notes

1. A two-tap Schlenk adapter connected to a bubbler and an argon/vacuum manifold is illustrated in Yu, J.; Truc, V.; Riebel, P.; Hierl, E.; Mudryk, B. *Org. Synth.* **2008**, *85*, 64-71.

2. All steps prior to the aqueous ammonium chloride quench were conducted with careful exclusion of air and moisture, using argon as an inert atmosphere.

3. Anhydrous tetrahydrofuran was purchased from Sigma-Aldrich and was stored over oven-dried 3Å molecular sieves under argon. Before each reaction, the water content of the THF was determined with a Denver Instruments Model 275KF Colorimetric Karl-Fischer Titrator to ensure less than 10 ppm water.

4. 2-Butyn-1-ol (**1**) was purchased from Sigma-Aldrich (98%) and used without further purification.

5. *n*-Butyllithium (2.5 M in hexanes) was purchased from Sigma-Aldrich and used as received.

6. *n*-Butyllithium was added discontinuously in order to keep the internal temperature between −70 °C and −65 °C. Slow addition was necessary since the reaction is highly exothermic. The submitters used a syringe pump with a flow rate of 60 mL / h for the addition of *n*-butyllithium.

7. *tert*-Butyllithium (1.7 M in pentane) was purchased from Sigma-Aldrich and used as received. *tert*-Butyllithium is highly pyrophoric, and extra care should be taken in handling. *tert*-Butyllithum was transferred *via* cannula transfer to the dropping funnel under argon pressure using a stainless steel cannula.

8. The internal temperature was kept between −70 °C and −65 °C during addition of *tert*-butyllithium. The submitters used a syringe pump with a flow rate of 60 mL / h for the addition of *tert*-butyllithium. However, *Organic Syntheses* recommends that addition of *tert*-butyllithium by syringe pump be avoided.

9. Trimethylsilyl chloride was purchased from Sigma-Aldrich (≥98%) and used without further purification. This reagent is corrosive and evolves hydrochloric acid gas in the presence of moisture.

10. The submitters observed a colorless solution after addition of the first equivalent of trimethylsilyl chloride. After addition of the second equivalent the submitters observed a light green solution.

11. Pressure was set at 450 mmHg. When most of the diethyl ether was evaporated the pressure was reduced to 210 mmHg. The checkers observed formation of a light grey precipitate during evaporation of the solvent which dissolved again upon addition of aqueous acetic acid.

12. This corresponds to a 50% aqueous solution of acetic acid. This reagent is corrosive.

13. Thin layer chromatographic analysis was conducted with silica gel-coated polyester sheets (Macherey-Nagel), using cyclohexane : ethyl acetate (4 : 1) as eluent, and were developed with *p*-anisaldehyde / aqueous sulfuric acid. Under these conditions, the intermediate trimethylsilyl ether exhibited an R_f of 0.9 (and stained red) and the product alcohol (**2**) exhibited an R_f of 0.4 (and stained red). The submitters used hexanes : ethyl acetate (4 : 1) as eluent and observed the same R_f values.

14. A volume of 150-160 mL of saturated aqueous sodium bicarbonate was added.

15. The diethyl ether was removed at 450 mmHg. Afterwards the pressure was stepwise reduced to 150 mmHg.

16. The submitters used a 20 cm vacuum-jacketed Vigreux column and a pressure of 150 mmHg for the distillation. However in the checkers' hand a complete separation of the major side product and the product was not possible with this procedure. The removed side product was always obtained as a mixed fraction with the product. Due to the high temperatures during the six-hour distillation, formation of a decomposition product was observed which was difficult to separate. The checkers identified the major side product by ^{1}H NMR, ^{13}C NMR and IR being most likely the isomerized allene (2-(trimethylsilyl)buta-2,3-dien-1-ol).

17. The submitters described an impurity at 119 °C (150 mmHg), followed by the product at 123 °C (150 mmHg).

18. The submitters described the product as a stable, pale yellow oil. However the checkers observed the development of a yellow color and new peaks in ^{1}H NMR upon storage of the product at room temperature.

19. The checkers could isolate another 0.8–1.1 g of product by subjecting the mixed fraction two to flash column chromatography. Flash column chromatography was performed using a 5.5 cm wide and 22 cm high column packed with Fluka silica gel 60 (powder, 0.040–0.063 mm, 250 g) and 20 mL fractions. The eluent used was cyclohexane : ethyl acetate (6 : 1), with $KMnO_4$ as TLC stain ($R_f$allene = 0.24, $R_f$product = 0.18, $R_f$impurity = 0.13). After a 250 mL forerun and five mixed fractions with the allene, pure product appeared in fractions 29-50.

20. For (**2**): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.08 (s, 9 H), 1.47 (t, J = 2.6 Hz, 2 H), 1.93 (br s, 1 H), 4.21 (td, J = 2.6 Hz, 0.5 Hz, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: –2.0, 7.2, 51.6, 77.3, 84.4; IR (neat film, NaCl): 3548, 3110, 2848, 2216, 1249, 1011, 851 cm^{-1}; Anal. calcd. for $C_7H_{14}OSi$: C: 59.09, H: 9.92; found: C: 58.84, H: 9.88.

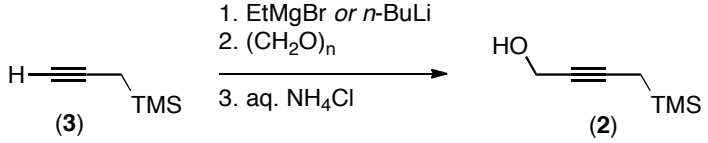
Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press: Washington, DC, 1995. Specifically, aqueous and organic phase wastes (residual solvents) were separated before disposal, and solid wastes ($MgSO_4$, Celite) were also separated before disposal. As standard operating procedure, personnel should wear safety glasses, a laboratory jacket, and latex gloves for each step.

3. Discussion

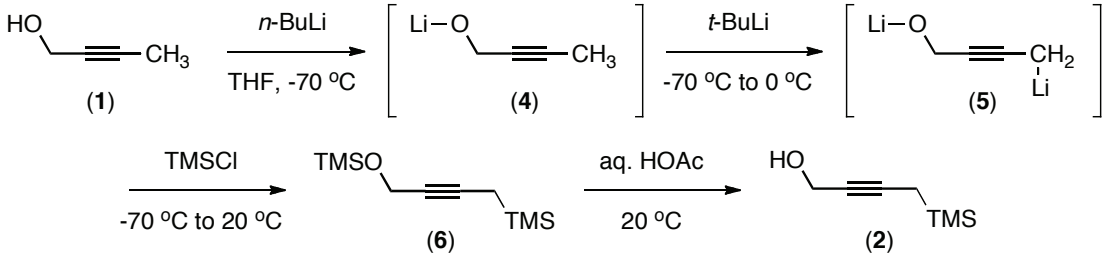
The title compound, 4-trimethylsilyl-2-butyn-1-ol (**2**), was originally prepared by formylation of the metal acetylide arising from 3-trimethylsilyl-1-propyne (**3**, **Figure 1**).[3]

Figure 1. Original synthesis of 4-trimethylsilyl-2-butyn-1-ol (**2**)



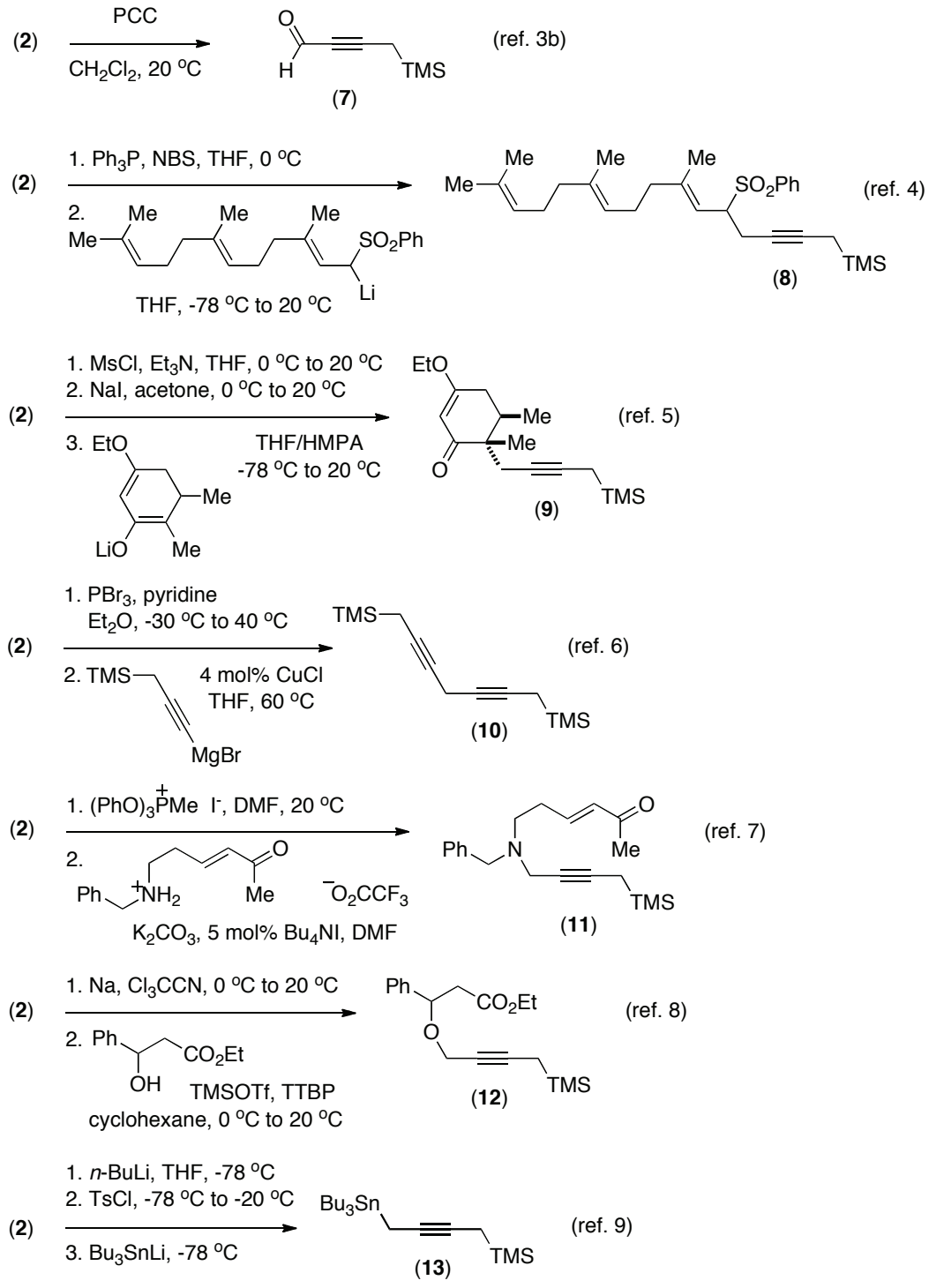
In our hands, we have found that yields are variable in the original procedure, as the formaldehyde (generated by heating paraformaldehyde) condenses and repolymerizes upon addition to the cold (-78 °C) alkynyllithium solution, thus blocking the inlet. Furthermore, 3-trimethylsilyl-1-propyne (**3**) is relatively expensive. The alternative preparation described here begins with commercially available 2-butyn-1-ol (**1**), beginning with sequential *O*- and *C*-deprotonation followed by double silylation of (**5**), and concluding with chemoselective hydrolysis of the silyl ether (**6**, **Figure 2**).[4]

Figure 2. This synthesis of 4-trimethylsilyl-2-butyn-1-ol (**2**), depicting key intermediates



The alcohol of the title compound (**2**) can be converted into several other functional groups, such as the aldehyde (**7**, **Figure 3**),[3b] as well as conversion into electrophilic derivatives for formation of carbon-carbon,[4-6] carbon-nitrogen,[7] carbon-oxygen,[8] and carbon-tin bonds.[9] The internal

Figure 3. Functionalization of the alcohol of (**2**)



alkyne can also be converted into the *trans*- or *cis*-alkenes (**14**, **15**, **Figure 4**), as functionalized allylic silane reagents.[3c,10] Lewis acid-promoted protonation of (**2**) affords 2,3-butadien-1-ol (**16**).[11] The hydroxyl group directs hydrostannylation to the proximal carbon of the alkyne, to afford the

Z-vinylstannane (**17**) under kinetic conditions.[12] The propargylic silane serves as a nucleophile upon Lewis acid-promoted reactions with aldehydes to provide functionalized allenes (**18**), (**20**), and (**21**, **Figure 5**).[3a,8,13] The corresponding transformations with acetals and *N*-acylaminals have also been reported.[14,15]

Figure 4. Functionalization of the alkyne of (**2**)

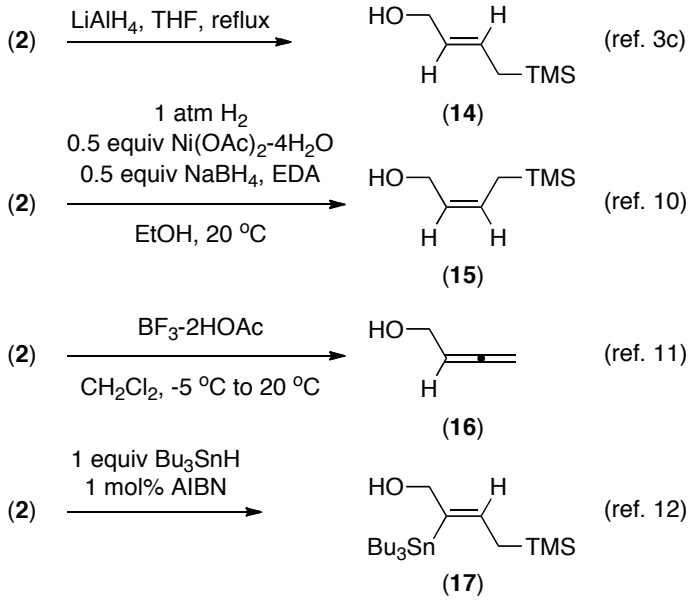
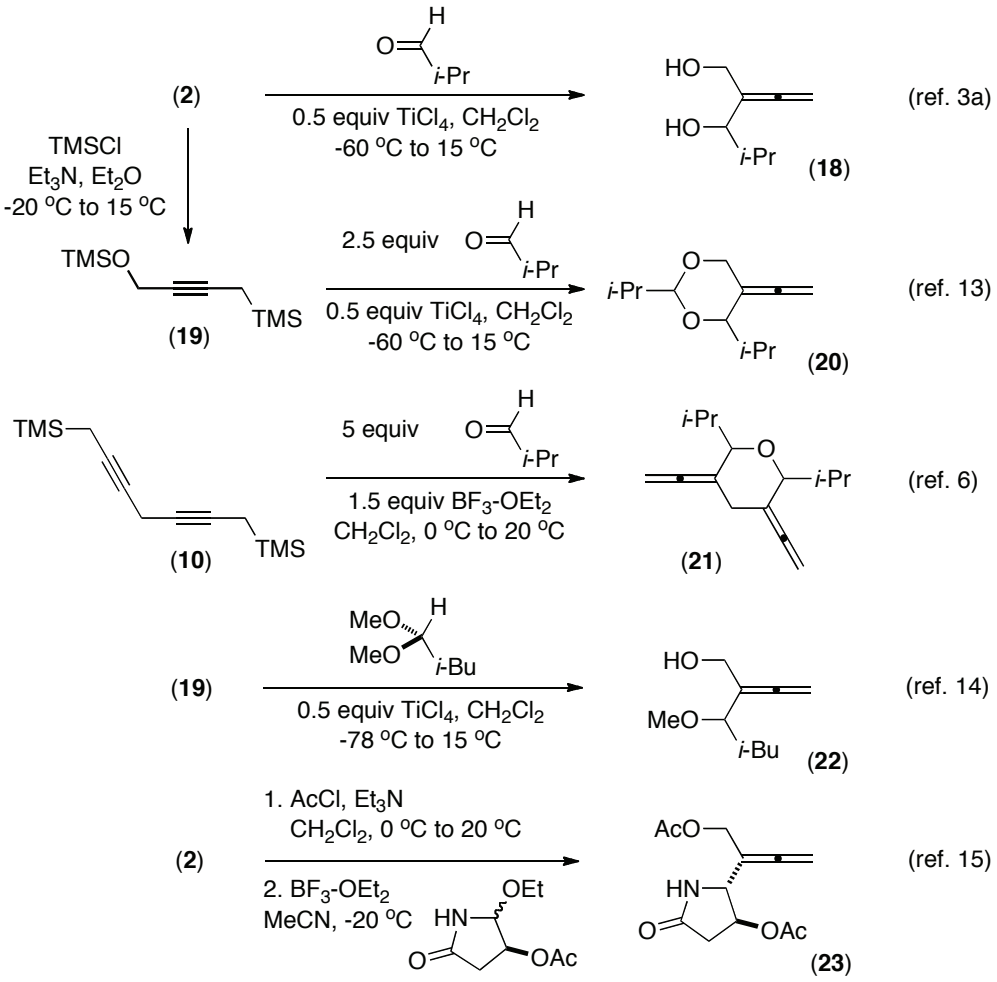
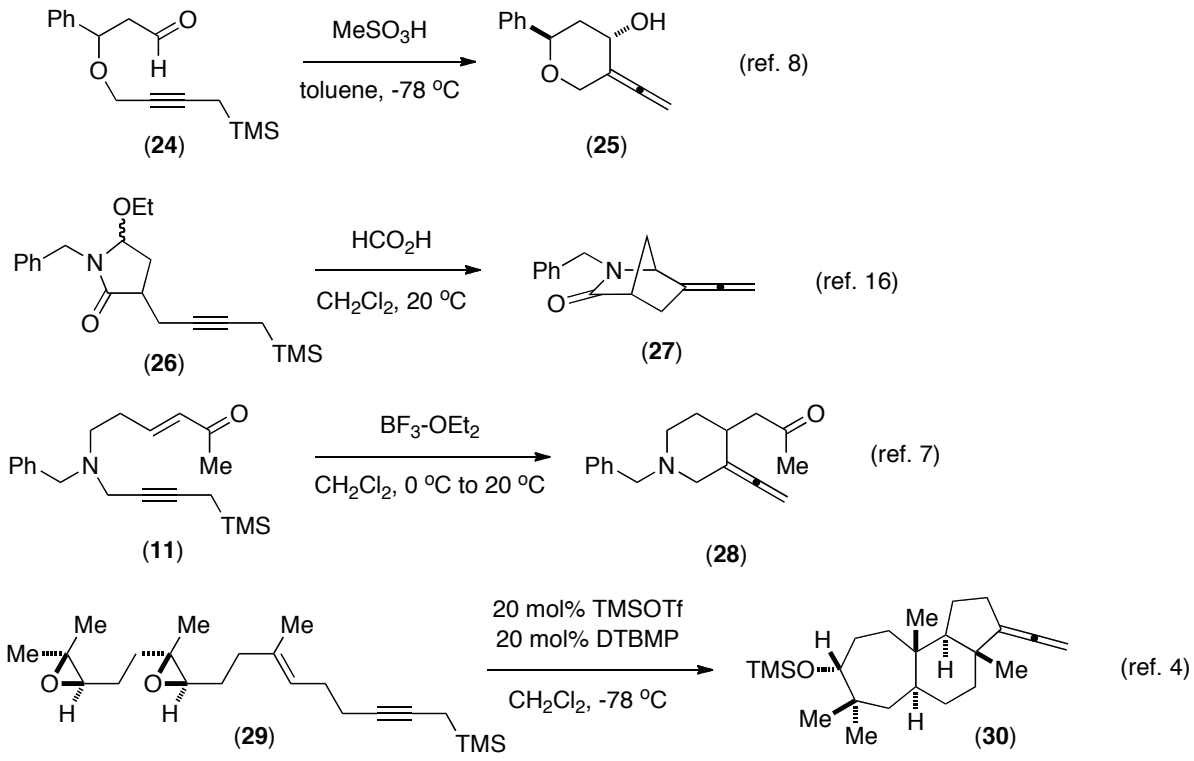


Figure 5. Intermolecular additions of propargylic silanes arising from (**2**)



Several Brønsted acid-promoted intramolecular cyclizations have also been accomplished with propargylic silanes arising from (**2**), tethered to aldehydes (**24**) or *N*-acylaminals (**26**), forming the corresponding cyclic structures bearing exocyclic allenes (**25**, **27**, **Figure 6**).[8,16] Moreover, Lewis acid-promoted cyclizations have also been reported in conjugate additions with (**11**) as well as polyepoxide-alkene cyclizations from (**29**), to provide the corresponding exocyclic allenes (**28**, **30**).[4,7]

Figure 6. Intramolecular cyclizations of propargylic silanes arising from (**2**)



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Appendix
Chemical Abstracts Nomenclature (Registry Number)

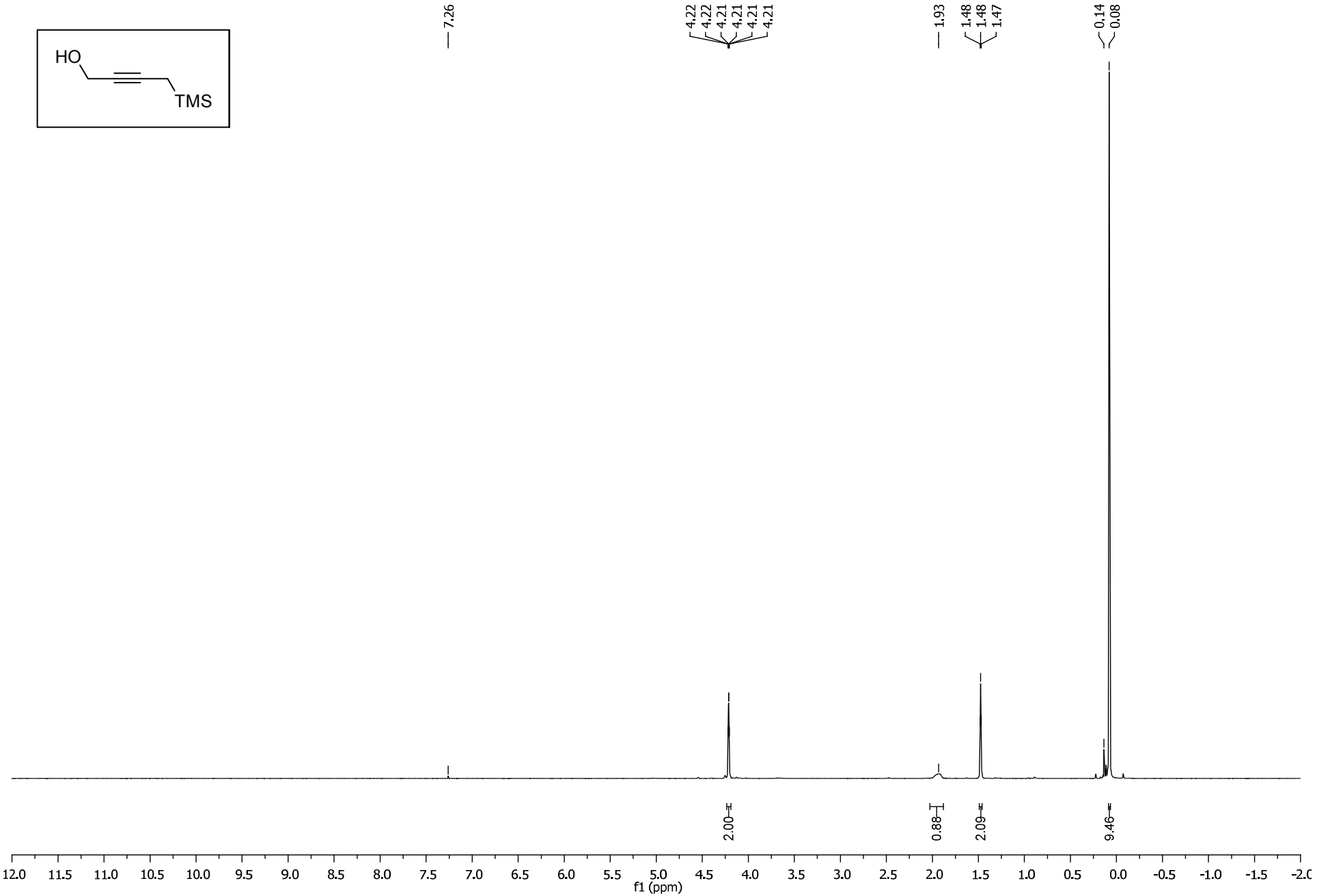
2-Butyn-1-ol; (764-01-2)
n-Butyllithium; (109-72-8)
tert-Butyllithium; (594-19-4)
Chlorotrimethylsilane; (75-77-4)

Frank McDonald received his B.S. degree in chemistry from Texas A&M University in 1984, and completed his Ph.D. degree at Stanford University under the direction of Paul Wender in 1990. After an American Cancer Society postdoctoral fellowship at Yale University with Samuel Danishefsky, he began his independent career as Assistant Professor of Chemistry at Northwestern University, rising to Associate Professor in 1997. In 1998 he moved to Emory University where he is currently Professor of Chemistry. His research interests include the invention of new chemical transformations, explorations in biomimetic synthetic pathways, and applications to the total synthesis of natural products.

Alexander Wein was born in Dalton, Georgia in 1987. He graduated from Emory University *summa cum laude* with B.S. degree in chemistry in 2010, and engaged in research in both inorganic and organic chemistry with Profs. Jack Eichler and Frank McDonald, respectively. He is currently an IRTA fellow at the National Institute of Allergy and Infectious Diseases at the National Institutes of Health in Bethesda, Maryland.

Rongbiao Tong was born in 1976 in Guangdong, China. He obtained his B.S. in chemistry in 2000 at Hunan University, China and then M.S. in organic chemistry in 2003. He subsequently moved to Emory University to continue his research as a doctoral student under the supervision of Professor Frank E. McDonald, working on biomimetic cascade cyclization and total synthesis. After receiving his Ph.D. in 2008, he began his postdoctoral research in the laboratory of Professor Amos B. Smith at the University of Pennsylvania, focusing on anion relay chemistry.

Florian Bächle was born in Bad Säckingen (Germany) in 1983. He studied chemistry at the University of Heidelberg where he obtained his diploma in February 2010 under the supervision of Prof. Günter Helmchen. He joined the group of Prof. Andreas Pfaltz at the University of Basel as a Ph.D. student in April 2010. Currently he is working on the ESI-MS screening of organocatalyzed reactions.



^{1}H NMR of 4-TRIMETHYLSILYL-2-BUTYN-1-OL