

Efficient Protidesilylation of Unactivated C(sp³)–SiMe₂Ph Bonds Using Tetrabutylammonium Fluoride

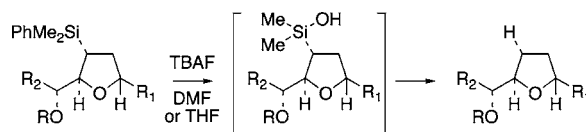
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ABSTRACT



The protidesilylation of unactivated C(sp³)–SiMe₂Ph bonds proceeds efficiently by treatment with tetrabutylammonium fluoride in wet DMF or THF via isolable dimethylsilanol intermediates.

An important strategy for the stereoselective synthesis of highly substituted tetrahydrofurans involves the [3+2]-annulation of chiral crotyl- and allylsilanes with aldehydes.¹ Our laboratory has contributed to this area by demonstrating the predictable stereochemical outcome of [3+2]-annulation reactions of chiral allylsilanes via a formal three-component coupling of two aldehydes and the chiral γ -silyl-substituted allylborane **1** (Figure 1).^{2,3} Initial coupling of chiral allylborane **1** with an aldehyde (R₁CHO) followed by exposure of the protected α -hydroxy allylsilane **2** to a Lewis acid and a second aldehyde (R₂CHO), selectively affords either cis- or trans-substituted tetrahydrofurans **3** or **4** in good yields. Importantly, the stereochemistry of the [3+2]-annulation reaction is determined by the nature of the Lewis acid employed (Figure 1).^{2a} The 2,5-cis tetrahydrofuran **3** is obtained typically with $\geq 20:1$ selectivity when BF₃·OEt₂ is employed, while the diastereomeric 2,5-trans disubstituted

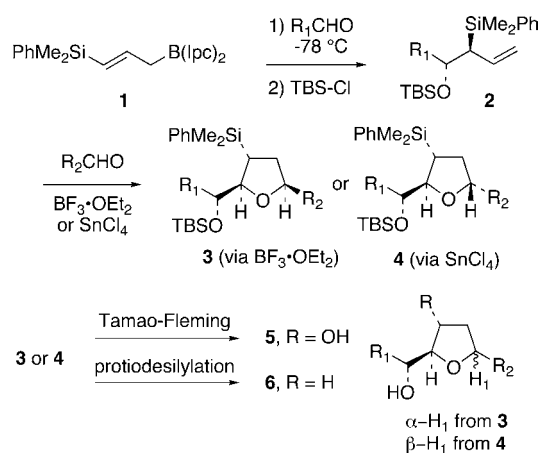


Figure 1. Three-component coupling strategy for the stereocontrolled synthesis of tetrahydrofurans.

tetrahydrofuran **4** is obtained, also typically with $\geq 20:1$ d.s., by using SnCl₄ (via a chelate-controlled transition state, requiring that R₂CHO be capable of chelate formation). In principle, manipulation of the –SiMe₂Ph substituent in **3** or **4** via Tamao–Fleming oxidation⁴ or protidesilylation⁵

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(1) (a) Panek, J.; Yang, M. *J. Am. Chem. Soc.* **1991**, *113*, 9868. (b) Panek, J.; Beresis, R. *J. Org. Chem.* **1993**, *58*, 809. (c) Masse, C. E.; Panek, J. S. *Chem. Rev.* **1995**, *95*, 1293. (d) Peng, Z. H.; Woerpel, K. A. *Org. Lett.* **2002**, *4*, 2945. (e) Peng, Z. H.; Woerpel, K. A. *J. Am. Chem. Soc.* **2003**, *125*, 6018.

(2) (a) Micalizio, G. C.; Roush, W. R. *Org. Lett.* **2000**, *2*, 461. (b) Micalizio, G. C.; Roush, W. R. *Org. Lett.* **2001**, *3*, 1949. (c) Shotwell, J. B.; Roush, W. R. *Org. Lett.* **2004**, *6*, 3865.

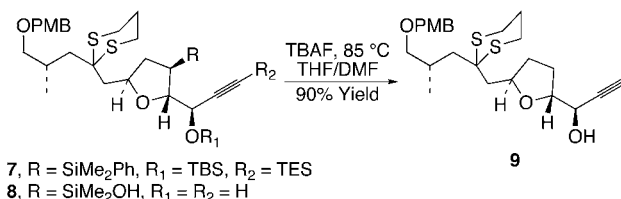
(3) Roush, W.; Pinchuk, A.; Micalizio, G. *Tetrahedron Lett.* **2000**, *41*, 9413.

should allow for general access to tetrahydrofurans **5** and **6**, respectively.

The established literature procedure for protidesilylation of unactivated C(sp³)–SiMe₂R bonds (i.e., RCH₂SiMe₃ or RCH₂SiMe₂Ph → RCH₃) involves extended basic hydrolysis (DMSO/H₂O, 5–10% KOtBu, 18-crown-6, 95 °C, 2–7 days).^{2,5} Although tetrahydrofurans **6** can be obtained from **3** or **4** using this procedure,² the extended reaction times and extremely harsh conditions severely limit the potential applications of this method, with protidesilylation generally failing for substrates with any reasonably complex R₁ or R₂ (vide infra).^{2c}

During the course of several ongoing studies in natural product synthesis, it became paramount that a mild method for accomplishing this protidesilylation (e.g., **3** or **4** → **6**) reaction be developed. In particular, in connection with studies on the synthesis of amphidinolide F,⁶ we demonstrated that protidesilylation of highly functionalized tetrahydrofurans of general structure **4** could be effected by treatment with tetrabutylammonium fluoride (TBAF) in DMF (Scheme 1).^{2c} We report herein a much wider range of

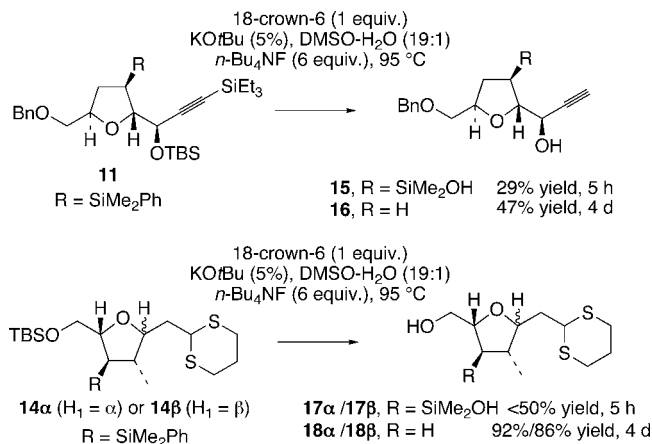
Scheme 1. Key TBAF-Mediated Protidesilylation of an Amphidinolide F Precursor (**7**)^{3c}



examples of this process, which serve to define the scope of this mild and efficient protidesilylation reaction.

We began with a careful exploration of the original Hudrlik-type conditions^{5a–c} by using tetrahydrofurans **11** and **14α/β** (Scheme 2).⁷ Initially, we anticipated that a neighboring hydroxyl group was required to activate the –SiMe₂Ph group toward protidesilylation by analogy to the trimethylsilyl substrates investigated by Hudrlik,^{5a–c} the diphen-

Scheme 2. Protidesilylations of Tetrahydrofurans **11** and **14α/β** by Using TBAF-Modified Literature Conditions

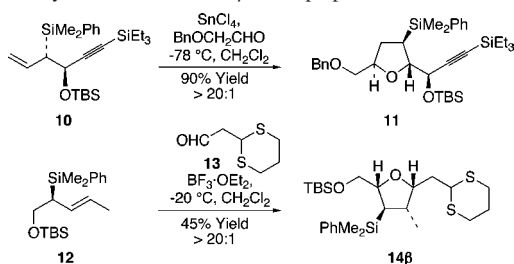


ylsilyl analogues explored by Landais,^{5d} and the isolated siloxanes investigated by Hoveyda and Stork.^{5e,8} Accordingly, TBAF was added to the standard Hudrlik reaction conditions (DMSO/H₂O, 5–10% KOtBu, 18-crown-6, 95 °C) to effect in situ desilylation of the TBS ethers present in both substrates. Unfortunately, these reactions were highly irreproducible, requiring reaction times from 1 day to 1 week for complete conversion. The long reaction times necessitated that these experiments be performed in sealed pressure tubes (to prevent evaporation of solvent), which proved highly inconvenient for reaction monitoring. In addition, significant decomposition of even the relatively simple tetrahydrofuran **11** was observed.

Interestingly, brief treatment of both **11** and **14α** or **14β** under the TBAF-modified Hudrlik conditions led to the generation of the sensitive but isolable silanols **15**, **17α**, and **17β** after aqueous workup (Scheme 2).⁹ Both **15** and **17α/β** were competent in the further conversion to **16** and **18α/β** upon exposure to the reaction conditions. These silanol intermediates are likely not accessible from the corresponding trimethylsilyl derivatives explored by Hudrlik.⁵ This suggested to us that the protidesilylation of –SiMe₂Ph groups might occur via a different mechanistic pathway compared to the –SiMe₃ derivatives and that a cyclic silicate or siloxane may not be a required intermediate.

Significant differences in substrate scope for the present process compared to the –SiMe₃ substrates studied by Hudrlik quickly became evident. Tetrahydrofurans **19–21**¹⁰ undergo smooth carbon–silicon bond cleavage to afford protidesilylated adducts **22–24** in good yields (entries 1–3, conditions A, Table 1). Interestingly, the protidesilylation of **20** and **21** proceeds smoothly even though they lack a

- (4) Jones, G. R.; Landais, Y. *Tetrahedron* **1996**, 52, 7599.
(5) (a) Hudrlik, P.; Hudrlik, A.; Kulkarni, A. *J. Am. Chem. Soc.* **1982**, 104, 6809. (b) Hudrlik, P.; Holmes, P.; Hudrlik, A. *Tetrahedron Lett.* **1988**, 29, 6395. (c) Hudrlik, P.; Gebreselassie, P.; Tafesse, L.; Hudrlik, A. *Tetrahedron Lett.* **2003**, 44, 3409. (d) Landais, Y.; Mahieux, C. *Tetrahedron Lett.* **2005**, 46, 675. (e) Stork, G.; Sofia, M. J. *J. Am. Chem. Soc.* **1986**, 108, 6826.
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(7) Tetrahydrofurans **11** and **14β** were prepared as summarized below.

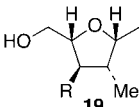
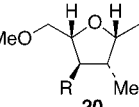
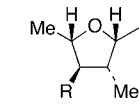


- (8) Hale, M.; Hoveyda, A. *J. Org. Chem.* **1992**, 57, 1643.

- (9) See: Murakami, M.; Sugimoto, M.; Fujimoto, K.; Nakamura, H.; Andersson, P.; Ito, Y. *J. Am. Chem. Soc.* **1995**, 115, 6487. In our hands, silanols **17α/β** show a marked propensity toward oligomerization upon attempted isolation (see Supporting Information). These oligomeric mixtures are competent intermediates toward further protidesilylation.

- (10) Available from the [3+2]-annulation of **12** with α-benzyloxyacetaldehyde under noncholate conditions and subsequent standard transformations (see Supporting Information).

Table 1. Probing the Role of Neighboring Hydroxyl Assistance in the Protidesilylation of **19–21**

entry	substrate R = SiMe ₂ Ph	product R = H	cond. A	cond. B
1		22	85%	83%
2		23	92%	82%
3		24	91%	83%
4	11	16	47%	86%
5	14α	18α	92%	99%

A: 18-crown-6 (1 equiv.), KO^tBu (5%), DMSO/H₂O (19:1), 95 °C, TBAF (6 equiv.), 1–7 d

B: TBAF (3 equiv.), DMF/THF, 75 °C, 4–16 hr

proximal hydroxyl group—clearly indicating that a neighboring hydroxyl group is not required for the protidesilylation of –SiMe₂Ph groups.¹¹

A systematic study of the reagents employed for the conversion of **21** to **24** indicated that TBAF played a role beyond simple in situ desilylation of the silicon protecting groups. In fact, commercial (wet) TBAF alone¹² (added as a solution in tetrahydrofuran) to **19–21** in either wet DMF or THF led to rapid and clean conversion to the corresponding protidesilylated products **22–24**, again via the intermediacy of the corresponding silanols (entries 1–3, conditions B, Table 1).¹³ Importantly, a substantial improvement in the isolated yield of **16** from the protidesilylation of **11** was realized under these new conditions (entry 4, Table 1).

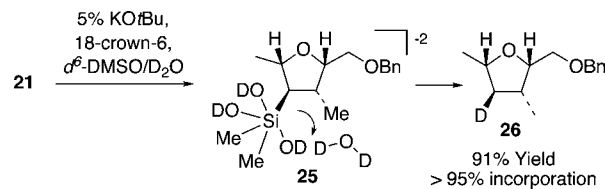
The reproducible isolation of silanol intermediates in all the systems studied, as well as the competence of these silanols toward further protidesilylation, suggests that the Ph–SiMe₂R bond undergoes rapid protidesilylation as an

(11) Silanols corresponding to **20** and **21** (R = SiMe₂OH) have been isolated and fully characterized. These silanols are easily handled, suggesting that the oligomerization of **17α/β** proceeds via condensation of the C(7) hydroxyl and silanol (see Supporting Information).

(12) For protidesilylations of stabilized or C(sp²) systems via silanol intermediates, see: (a) Anderson, J.; Flaherty, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3025. (b) Anderson, J. C.; Munday, R. H. *J. Org. Chem.* **2004**, 69, 8971. (c) Anderson, J. C.; Anguille, S.; Bailey, R. *Chem. Commun.* **2002**, 2018. Where silanols have not been implicated: (d) Hulme, A. N.; Henry, S. S.; Meyers, A. I. *J. Org. Chem.* **1995**, 60, 1265. (e) Ni, Y.; Montgomery, J. *J. Am. Chem. Soc.* **2004**, 126, 11162.

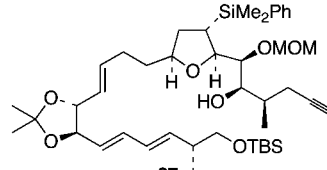
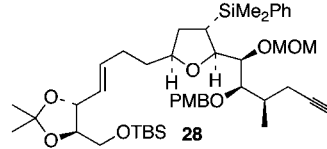
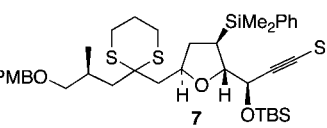
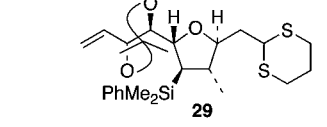
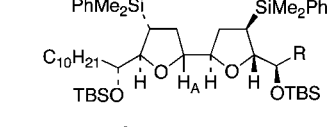
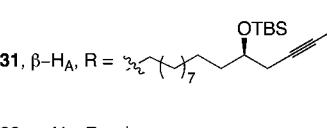
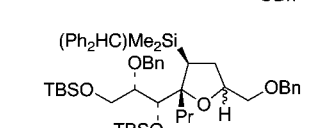
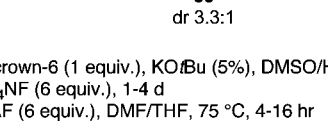
(13) TBAF is apparently unique in promoting this reaction, as screening of several other fluoride sources for protidesilylation of **21** (CsF, KF, TAS–F) in various solvent/temperature combinations (MeCN, DMF, DMSO, 23 °C → 90 °C, pressure tube) led only to recovered starting materials. Additionally, tetrabutylammonium hydroxide does not promote this transformation (see ref 2c).

Scheme 3. Protonation of Intermediate Silanols Proceeds with Retention of Stereochemistry



initial step.^{12a–c} The deuterium-labeling study illustrated in Scheme 3 indicates that the Si–substrate bond in a subse-

Table 2. Key Protidesilylation Reactions Directed toward Natural Product Syntheses

entry	substrate	product (all Si→H)	cond. A	cond. B
1		34	<10%	91%
2		35	<10%	97%
3		9	0–48%	90%
4		36	41%	87%
5		37	<20%	60%
6		38	0–40%	55%
7		39	0–50%	72%
8		40	76%	77%

A: 18-crown-6 (1 equiv.), KO^tBu (5%), DMSO/H₂O (19:1), 95 °C, *n*Bu₄NF (6 equiv.), 1–4 d

B: TBAF (6 equiv.), DMF/THF, 75 °C, 4–16 hr

quently formed silicate intermediate (e.g., **25**)¹⁴ is sufficiently nucleophilic to undergo efficient and stereoselective protonolysis with complete retention of stereochemistry in the one case studied (i.e., **25** → **26**, Scheme 3). The significant enhancement of reaction rate (5 d → 4 h) of the TBAF-mediated protidesilylation reaction (new conditions) compared to the original hydroxide-mediated reaction conditions⁵ indicates that a fluorosilicate intermediate analogous to **25** with –F replacing one or more –OD groups in **25** may be a key intermediate in the TBAF-mediated process.

This TBAF-mediated procedure for protidesilylation of unactivated C(sp³)–SiMe₂Ph bonds has proven to be crucial in our efforts to apply the [3+2]-annulation reaction strategy in a variety of ongoing total synthetic endeavors. Specifically, amphidinolide E precursors **27** and **28**, which could only be coaxed into slow decomposition using the original Hudrlik-type protocol,⁵ now undergo efficient protidesilylation in >90% yield (entries 1–2, Table 2). Furthermore, global desilylation of **7** and **29** afford versatile C(15)–C(26)^{2c} and C(1)–C(9) fragments of amphidinolide F (entries 3–4, Table 2). Bis-tetrahydrofurans **30**–**32**, assembled using sequential [3+2] annulations,¹⁵ can be efficiently protidesilylated using this modified protocol (entries 5–7, Table 2) and represent important steps in our ongoing efforts toward asimicin and a variety of other Annonaceous acetogenins. The protidesilylation of the benzhydryldimethylsilane **33** (entry 8, Table 2) is noteworthy in that the reaction proceeded with comparable efficiency using either method A or B. Interestingly, the conversion of **33** to **40** was found to proceed through a stable cyclic siloxane intermediate, the only such example uncovered during the course of these studies.¹⁶

In conclusion, a systematic investigation of the protidesilylation reactions of Me₂PhSi-substituted tetrahydrofurans

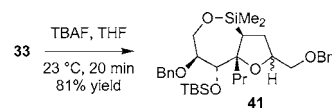
has revealed that (i) free hydroxyl groups adjacent to the silicon substituent are not required for activation of the C(sp³)–SiMe₂Ph bond (**20** → **23**, **21** → **24**, **28** → **35**, and **29** → **36**), (ii) silanols (i.e., RSiMe₂OH) are isolable intermediates and are competent for conversion to protidesilylated products when resubjected to the reaction conditions, and (iii) use of TBAF (wet) rather than KO^tBu and 18-crown-6 leads to a substantial increase in reaction rate, functional group tolerance, and overall efficiency in the protidesilylation of –SiMe₂Ph groups. Applications of this method in the total synthesis of natural products will be reported in due course.

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Supporting Information Available: Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(16) Siloxane **41** was formed cleanly upon brief exposure of **33** to excess TBAF at room temperature:



Siloxane **41** was efficiently protidesilylated to give **40** upon exposure to the reagent combination of method B (89% yield).

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