Di-\(\text{t}\)-butylsilyl Bis(trifluoromethane-sulfonate)

\[
\text{t-Bu}_2\text{Si(OSO}_2\text{CF}_3)_2
\]

[85272-31-7] \(\text{C}_{10}\text{H}_{18}\text{F}_6\text{O}_6\text{S}_2\text{Si}\) (MW 440.44)

InChI = 1S/\text{C}_{10}\text{H}_{18}\text{F}_6\text{O}_6\text{S}_2\text{Si}/c1-7(2,3)25(8(4,5)6,21-23(17,18)9(11,12)13)22-24(19,20)10(14,15)16/h1-6H3

IndChKey = HUHKPYLEVGCITG-UHFFFAOYSA-N

(reagent for the protection of diols)

**Physical Data:** bp 73–75 °C/0.35 mmHg; \(d\) 1.208 g cm\(^{-3}\).

**Solubility:** sol most common organic solvents.

**Form Supplied in:** liquid.

**Preparative Method:** by the treatment of di-\(\text{t}\)-butylchlorosilane with Trifluoromethanesulfonic Acid, followed by distillation (71% yield).\(^1\)

**Purification:** distillation.

**Handling, Storage, and Precautions:** moisture sensitive; reacts with hydroxyllic solvents; corrosive.

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**Original Commentary**

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**Protection of Alcohols.** Di-\(\text{t}\)-butylsilyl bis(trifluoromethanesulfonate) is a reagent for the selective protection of polyhydroxy compounds. This reagent reacts with 1,2-, 1,3-, and 1,4-diols under mild conditions to give the corresponding dialkylsilylene derivatives. Even pinacol reacts to give the silylene derivative. Deprotection is conveniently achieved by using aqueous Hydrofluoric Acid in acetonitrile (eq 1).

\[
\begin{align*}
\text{H}_2\text{O} + & \quad \text{t-Bu}_2\text{Si(O)}_2(\text{OTf})_2 \\
\text{HF (aq), MeCN, 25 °C} & \quad \rightarrow \quad \text{t-Bu}_2\text{Si(O)}_2(\text{OTf})_2 \\
\text{96%} & \quad \rightarrow \quad \text{t-Bu}_2\text{Si(O)}_2(\text{OTf})_2
\end{align*}
\]

Unlike Di-\(\text{t}\)-butylchlorosilane, this reagent reacts with hindered alcohols. Even pinacol reacts to give the silylene derivative (100 °C, 24 h, 70%). Di-\(\text{t}\)-butylsilylene derivatives of 1,2-diols are more reactive than those of 1,3- and 1,4-diols and undergo rapid hydrolysis (5 min) in THF/H\(_2\)O at pH 10, while the 1,3- and 1,4-derivatives are unaffected at pH 4–10 (22 °C) for several hours. This protecting group is stable under the conditions of PDC oxidation of alcohols (CH\(_2\)Cl\(_2\), 25 °C, 27 h) and tosylation of alcohols (pyridine, 25 °C, 27 h).

The reagent has a limited use for the protection of alcohols but has been used to protect nucleosides (eq 2).\(^5\) The procedure consists of sequential addition of the ditriflate and Triethylamine to the nucleoside in DMF. The choice of solvent is critical.

**Derivatization of Alcohols.** Di-\(\text{t}\)-butylsilyl bis(trifluoromethanesulfonate) has been used to derivatize hindered diols, to give derivatives such as (1), for analysis by gas chromatography–electron impact mass spectrometry.\(^6\) The major fragmentation is that of the Si–C bonds.

**Reagent in Enantioselective Additions.** In a study of enantioselective conjugate addition to cyclohexanone it was found that the presence of HMPA and various silyl reagents markedly increases the enantioselectivity (eq 4). Di-\(\text{t}\)-butylsilyl bis(trifluoromethanesulfonate) gives a 67% yield and 40% ee but \(\text{t-Butyldiphenylchlorosilane}\) gives a 97% yield and 78% ee.
Other Substitution Reactions. An extremely hindered silyl reagent, tri-tert-butylsilyl trifluoromethanesulfonate, was prepared from di-tert-butylsilyl bis(trifluoromethanesulfonate) and tert-Butyllithium (eq 5). This reagent might find use in the protection of alcohols.

In conjunction with the study of alkyl-substituted silyl triflates, (2) and (3) have been prepared from the corresponding alkyllithium reagents and di-tert-butylylsil bis(trifluoromethanesulfonate).

The preparation of other derivatives of di-tert-butylylsil bis(trifluoromethanesulfonate) using germanium and phosphorus nucleophiles has been reported and provides bifunctional silanes such as (4) and (5).

A compound closely related to di-tert-butylylsil bis(trifluoromethanesulfonate) is di-tert-butylchlorosilyl trifluoromethanesulfonate, which has been used to tether two structurally different alcohol derivatives in order to effect an intramolecular Diels–Alder reaction (eq 6).

First Update

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In the past 10 years, there has been a dramatic increase in use of di-tert-butylylsil bis(trifluoromethanesulfonate) as a protecting group for diols to provide the required orthogonality or to impart selectivity in various reactions both in synthesis of natural products and in carbohydrate and oligonucleotide syntheses.

Applications in Total Synthesis of Natural Products and Development of New Methods. Paterson et al. strategically used di-tert-butylylsil bis(trifluoromethanesulfonate) to avoid differential protection of C21 and C23 hydroxyl groups in their efforts to synthesize the C19–C32 fragment of swinholide A (eq 7). The elaboration of the fragment to the natural product was reported in the subsequent communications and the authors were able to remove the silylene protecting group using HF-pyridine. The authors have also reported similar application of di-tert-butylylsil bis(trifluoromethanesulfonate) to protect 1,3-diols in total synthesis of concanamycin A.

The first total synthesis of concanamycin F by Toshima et al. also utilized di-tert-butylylsil bis(trifluoromethanesulfonate) for protection of 1,3-diols. The key aldol reaction between (11) and (12) was best achieved using PhBCl2 and i-Pr2NEt in CH2Cl2 at −78 °C to provide the desired aldol as the sole isomer in 84% yield. The selective deprotection of di-tert-butylylsilene was then achieved using HF-pyridine, which resulted in concomitant formation of the hemiacetal. Removal of the diethylisopropylsilyl group using TBAF provided concanamycin F.

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1. NaOMe, MeOH, rt 4 h, 91%
2. Dess–Martin periodinane Py, CH₂Cl₂, rt, 2.5 h, 93%

**ODEIPS**

DEIPS = SiEt₂-i-Pr

(11)

(16), concanamycin F
In another report, Panek and Jain used chiral allylsilane methodology for construction of C1–C17 polypropionate fragment of ru- tamycin B and oligomycin C. The aldehyde partner used for the sequence consisted of a diol protected as a di-tert-butylsilylene. The reaction proceeded in the presence of TiCl4 in excellent diastereoselectivity and yield (eq 9).

\[
\text{OOSi} \quad \text{t-Bu} \quad \text{t-Bu} \quad \text{CH}_3 \quad \text{CH}_3 \\
\text{OH} \\
\text{CH}_3 \quad \text{CO}_2 \text{Me} \\
\text{TiCl}_4, \text{CH}_2\text{Cl}_2 \\
-78 \text{ to } -35 ^\circ \text{C} \quad \text{CH}_3\text{C} \quad \text{CO}_2\text{Me} \\
90\% \quad \text{diastereoselection: } >30:1 \text{ syn:anti}
\]

Di Fabio et al. reported synthesis of 3-alkoxy-substituted trinems from commercially available 4-acetoxy-3-[((R)-l-tert-butyldimethylsilyloxyethyl]-2-azetidinone. Epoxide was treated with ceric ammonium nitrate in acetonitrile to provide the intermediate nitrate ester in 55% yield. Simultaneous protection of the secondary alcohol and the amide was accomplished using di-tert-butylsilyl bis(trifluoromethanesulfonate) to provide the tricyclic β-lactam. Removal of the nitro group by catalytic hydrogenation provided the desired secondary alcohol that was alkylated with allyl bromide to provide in quantitative yield (eq 10).

\[
\text{NH} \\
\text{ONO}_2 \\
\text{Si} \quad \text{t-Bu}_2\text{Si(OTf)}_2, \text{CH}_2\text{Cl}_2, 0 ^\circ \text{C} \text{, 12 h} \\
55\% \\
80\%
\]

Hillaert and Van Calenbergh have reported synthesis of (S)-3-(hydroxymethyl)butane-1,2,4-triol, a versatile, chiral building block that can be transformed into useful compounds such as (S,S)-4-(hydroxymethyl)pyrrolidine-3-ol and oxetanocin A. The authors reported a short synthesis of the protected triol from the epoxide in six steps. The use of di-tert-butylsilylene as the protecting group provided the desired differentiation of the hydroxyl groups, which was necessary for their successful investigation into the stereoselective synthesis of \(N\)-homoceramides (eq 13).

A successful approach to construction of the tricyclic core common to hamigeran terpenes was demonstrated using an intramolecular Pauson–Khand reaction. For an effective cyclization, the authors report that it was necessary to tether the olefin-containing moiety to the aromatic framework to reduce its conformational mobility using the di-tert-butylsilylene protecting group (eq 11).

Stoltz and coworkers reported a highly selective catalytic reductive isomerization reaction using 10% Pd/C and hydrogen in MeOH. During their explorations of the total synthesis of (+)-dragmacidin F, olefin isomerization using the carbonate was developed. The authors provided evidence that the method does not proceed via a stepwise reduction/elimination sequence or a π-allylpalladium intermediate. Replacement of the carbonate by a dioxasilyl linkage, however, did not result in isomerization, only diastereoselective reduction of the exo-olefin was observed (eq 12).

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Synthesis of polypropionate marine natural product (+)-membrenone C and its 7-epi-isomer has been reported using a key desymmetrization technique to create five contiguous chiral centers from bicyclic precursor. The diol was protected using di-tert-butylsilyl bis(trifluoromethanesulfonate) and further elaborated into the natural product and its epimer (eq 14). In a separate communication, Perkins et al. utilized di-tert-butylsilyl bis(trifluoromethanesulfonate) for synthesis of a model system en route to the polypropionate natural products auripyrones A and B.

Danishefsky and coworkers reported studies toward the total synthesis of tetrahydroisoquinoline alkaloid, ecteinascidin. The synthesis required a pentasubstituted E-ring system where they utilized the di-tert-butylsilylene protecting group in the sequence to prepare the di-tert-butylsilylene acids. In addition to above examples, protection of 1,3-diol using di-tert-butylsilyl bis(trifluoromethanesulfonate) has been reported in the synthesis of Brasilinolides, polyol fragments of ansamycin antibiotics, (±)-epi-stegobinone, 24-demethylbafilomycin C1, peloruside A, bafilomycin A1, premisakinolide A, (+)-papulacandin D, and other polyether natural products such as maitotoxin, yessotoxin, and gambieric acids.

A mixed di-tert-butylsilylene has been prepared from (S)-5-hexen-2-ol and prochiral 1,4-pentadiene-3-ol for synthesis of (2S,7S)-dibutyroxynonane, the sex pheromone of Sitodiplosis mосellana. The intermediate was then subjected to ring closing metathesis to provide the diene in 70% yield over two steps (eq 16). Deprotection of the nine-membered silylene was achieved using TBAF under refluxing condition in the presence of molecular sieves. Reduction with H2/PtO2 and diacetylation yielded the desired (2S,7S)-dibutyroxynonane in 22% overall yield.
In a separate communication, Kita and coworkers also reported an enantiodivergent synthesis of an ABCDE ring analog of the antitumor antibiotic fredericamycin A via an intramolecular [4 + 2] cycloaddition. Late-stage oxidations were performed on the di-tert-butylsilylene for protection of phenolic hydroxyl groups. Syntheses of both (R)- and (S)-enantiomers were reported (eq 18).37

Craig and coworkers have reported stereocontrolled polyol synthesis via C–H insertion reactions of silicon-tethered diazooacetates.39 Menthol was treated with di-tert-butylsilyl bis(trifluoromethanesulfonate) and the product was condensed with ethyl diazoacetate to provide the precursor 57a to the C–H insertion reaction (eq 20). The rhodium(II) octanoate-catalyzed decomposition of the diazooacetate 57a, however, did not provide the desired C–H insertion product, although the reaction was successful with disopropylsilyl bis(trifluoromethanesulfonate) (eq 20).
Applications in Carbohydrate and Oligonucleotide Syntheses. In efforts to synthesize aza-C-disaccharides, Bau- 
dat and Vogel used a key cross-aldolization of aldehyde 62 and (-)(15R,4R,5R,6R)-6-chloro-5-(phenylseleno)-7-oxabicyc-
ol[2.2.1]heptan-2-one ((-)-63) to provide the product alcohol 64 stereoselectively in 70% yield. The stereochemistry of the aldol 
product was confirmed by reduction of the ketone followed by pro-
tection of the diol using di-tert-butylsilyl bis(trifluoromethanesul-
fonate) providing a mixture of rotamers 65 resulting from benzyl 
carbamate. Treatment of this mixture with m-CPBA provided the 
vinylic chloride 66 that displayed typical ¹H NMR vicinal coupling 
constants, thus confirming the stereochemistry of exo-anti aldol 
(+)-66 (eq 22). A NOE experiment further confirmed the structure 
of (+)-66.41

In a study about stereoselective alkylation of chiral monoperox-
ides, Ahmed and Dussault focused on induction from 2-, 3-, and 
4-substituted monoperoxyacetals. It was observed that neigh-
boring iodo-, alkoxy-, acetoxy-, and silyl, groups imparted useful 
levels of diastereoselection in the Lewis acid-mediated alkylation 
of monoperoxyacetals. While investigating 1,3-stereoinduction, 
the homoallylic alcohol 59 was ozonized and the resultant hy-
droperoxy alcohol was silylated using di-tert-butylsilyl bis(trifu-
oromethanesulfonate) to provide 3-sila-1,2,4-trioxepane 60. 
Unfortunately, the substrate provided only 5% of allylated sila-
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While investigating glycosyl phosphates for selective synthesis of α and β-glycosidic linkages using conformationally restrained mannosyl phosphate 69, Seebeger and coworkers observed only the desired α-isomer 71 by virtue of the participating pivaloyl group as expected (eq 23). These reactions were high yielding, fast, and completely selective.

In a study of synthesis and conformational analysis of arabino-furanosyl oligosaccharide analogs in which one ring is locked into either the E3 or "E" conformation, Houseknecht and Lowary used di-tert-butylsilylene 73 to protect the 1, 4-diol. The di-tert-butylsilylene 73 is stable under a variety of reaction conditions and can be easily removed under mild HF–pyridine conditions (eq 24).
Electrophilic glycosidation of 3,5-O-(di-tert butylsilylene)-4-thioglycal 80 has been reported to exclusively provide the β-anomer of 4′-thionucleosides irrespective of the nucleobase employed. The face selectivity of the approach to 1′,2′-double bond by the incoming electrophile can be controlled by changing the protecting group of the 3′- and 5′-hydroxyl groups. Hence, approach to the α-face using NIS or PhSeCl increased in the order of 3′,5′-O-(di-tert butylsilylene):DTBS > 3′,5′-O(1,1,3,3-tetraisopropylsiloxane-1,3-diyi):TIPDS > 3′,5′-bis-O-(tert-butyldimethylsilyl):TBDMS (eq 25).44

Ohnishiy and Ichikawa reported a stereoselective synthesis of a C-glycoside analog of N-Fmoc-serine β-N-acetylgulosaminide (85) using a key Ramberg–Bäcklund rearrangement.45 The di-tert-butylsilylene protecting group provided the desired stability under the strongly basic conditions of the rearrangement (eq 26).

In a report on synthesis of 5′-O-DMT-N-acetyl-2′-O-TBDMS-protected nucleoside precursors for phosphoramidite RNA synthesis, Serebryany and Beigelman used di-tert-butylsilyl bis(trifluoromethanesulfonate) to protect 3′- and 5′-hydroxyl functions of a nucleoside.46 The silylated derivatives were obtained in high yields and were crystalline and easy to purify. Acylation of the N2-position of the guanosine derivative provided crystalline compound 89 in quantitative yield. Deprotection of the silylene 89 using mild HF–pyridine followed by protection of the primary alcohol with dimethoxytrityl chloride in pyridine gave the desired compound 90 in about 60% yield over five steps (eq 27).46

Synthesis of 2′-C-difluoromethylinaronucleosides has been separately reported where simultaneous protection of the 3′- and 5′-hydroxyl groups of the methyl D-ribose with di-tert-butylsilyl bis(trifluoromethanesulfonate) afforded the silylene 91.47 Dess–Martin periodinane oxidation of the C-2 hydroxyl group followed by nucleophilic addition of difluoromethyl phenyl sulfone in the presence of lithium hexamethyldisilazane converted 91 exclusively to sulfone 92 in 57% yield. Reduction of the sulfone using SmI2, coupling with persilylated bases, and a sequence of deprotection steps provided the desired 2′-C-difluoromethylinaronucleosides (eq 28).47
Van der Marel and coworkers reported a novel method to prepare pyrophosphates by coupling of a sugar phosphate and a nucleoside phosphoramidite. Benzyl-2-acetamido-2-deoxy-α-D-glucoside 95 was first protected using di-tert-butylsilyl bis-(trifluoromethanesulfonate) to improve solubility of GlcNAc derivative. In four additional steps, the silyl ketal was converted into the tetrabutylammonium salt of GlcNAc-α-1-phosphate 97. Uridine phosphoramidite 98 was then coupled with GlcNAc-α-1-phosphate 97 in the presence of dicyanoimidazole. The reaction was monitored using ³¹P NMR spectroscopy. Upon complete disappearance of amidite 99, the mixture was treated with t-butylperoxide to provide diastereomeric cyanoethyl-protected pyrophosphate 100. The cyanoethyl group was then removed by treatment with anhydrous DBU, followed by treatment with HF/NEt₃ to deprotect the di-tert-butylsilylene group, and finally ammonium hydroxide was used to hydrolyze the acetate protecting groups to provide UDP-N-acetylglucosamine 101 in 76% yield (eq 29).
Kishi and coworkers reported a protocol to improve the overall stereoselectivity of the Ireland–Claisen rearrangement for pyranoid and furanoid glucals. To prepare building blocks for marine natural product halichondrins, the authors reported synthesis of silylene in two steps from d-galactal. Under the conditions reported by Ireland (LHMDS, TBSCI, HMPA, THF, −78 °C), was converted to the corresponding O-silyl ketene acetal , which was estimated as a 7.3:1 mixture of Z- and E- as monitored using 1H NMR analysis. Upon heating at 80 °C in benzene for 1 day, this mixture furnished the carboxylate as a single diastereomer in >85% yield, along with and E- in ca. 12% combined yield. The authors further provided experimental evidence that Claisen rearrangement took place through Z- and that the Me stereochemistry of indicated that the Claisen rearrangement proceeded exclusively via the boatlike transition state (eq 30).

A practical approach for the stereoselective introduction of β-arabinofuranosides has been developed by locking an arabinosyl donor in a conformation in which nucleophilic attack from the β-face is favored. This was achieved by using di-tert-butyldisilyl bis(trifluoromethanesulfonate) to protect the C-5 and C-3 hydroxyl groups. This resulted in C-5 and O-3 in a pseudoequatorial orientation, resulting in a perfect chair conformation of the protecting group. The nucleophilic attack from the α-face is disfavored due to unfavorable steric interactions with H-2. The glycosyl donor was prepared in two convenient steps from commercially available thioglycoside . The coupling of the conformationally constrained glycosyl donor with the glycosyl acceptor in the presence of the powerful thiophilic promoter system N-iodosuccinimide/silver triflate (NIS/AgOTf) in DCM at −30 °C gave disaccharide with excellent β-selectivity (β:α = 15:1) in 91% yield (eq 31).

Another β-selective glycosylation was reported by Lowary and coworkers who intended to study ligand specificity of CS-35, a monoclonal antibody that recognizes mycobacterial lipoarabinomannan. Selective glycosylation followed by two-step deprotection of the hydroxyl groups provided the desired pentasaccharide in 51% overall yield (eq 32). Subsequently, Crich et al. studied the importance of the activation method for the observed selectivity in glycosylation using 3,5-O-(di-tert-butyldisilylene)-2-O-benzylarabinofuranosides as glycosyl donors for the synthesis of β-arabinofuranosides.

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**Diagram:**

1. t-BuSi(OTf)₂, 2,6-lutidine DMF/DCM, 0 °C, 81%
2. BnBr, NaH, THF, 79%

102 → 103 → 104

107

NIS/AgOTf, DCM, −30 °C

β:α = 15:1 91%

108

109

106

107

108

109

106

107

108

109
A novel six-step synthesis of $N_2$-dimethylamino-2'-O-methylguanosine has been reported.\(^{53}\) The synthesis utilizes di-tert-butyldisilene protection for 3'- and 5'-hydroxyl groups. The arenesulfonylation at the O6 position of 3'- and 5'-O-protected guanosine without 2'-O-protection was found to be completely selective. Compound 117 is a useful intermediate for oligonucleotide construction (eq 33). A similar application of di-tert-butyldisilene protecting group was originally reported for the synthesis of $N_2$-isobutyryl-2'-O-methyl guanosine.\(^{54}\)

Sabatino and Damha recently reported synthesis, characterization, and properties of oxepane nucleic acids.\(^{55}\) These sugar phosphate oligomers have the pentofuranose ring of DNA and RNA replaced with a seven-membered sugar ring. The oxepane nucleoside monomers were prepared from the ring expansion reaction of a cyclopropanated glycal, 118, and their conversion into phosphoramidite derivatives. Properties of these oxepane nucleic acids were then compared to naturally occurring DNA (eq 34).
Regioselective Monodeprotection. The monodeprotection of di-tert-butylsilylene ethers prepared from substituted 1,3-pentanediols and 2,4-hexanediols has been achieved with BF₃·SMe₂. The reaction is highly selective and provides access to 1,3-diols silylated at the sterically more hindered position. This is consistent with coordination of boron to the sterically more accessible oxygen prior to intramolecular delivery of fluoride. The reaction conditions for deprotection are compatible with esters, allyl ethers, and TIPS ethers. The resulting secondary di-tert-butylfluorosilyl ethers are stable to various conditions including low pH aqueous solutions and silica gel chromatography; the di-tert-butylfluorosilyl ethers are readily cleaved with HF–pyridine. An example is provided below (eq 35).

Reagents and conditions: (a) t-Bu₂Si(OtBu)₂, DMF, pyr. (b) (1) Ac₂O/Py; (2) TMS-allyl, TMSOTf; (c) Bu₄NF, THF.

In another report, Gabrielli utilized the same reaction, as published by Hoberg, to protect diols (O-4 and O-6) of d-glucal and d-galactal. The reaction was performed under very mild conditions (−40 °C, 30 min) using di-tert-butylfluorosilyl ether in DMF to produce the 4,6-O-protected D-glucals from d-glucal and the 4,6-O-protected d-galactal from d-glucal in 96 and 83% yield, respectively.

Silylidene glycals 128 and 129 are stable synthons that can subsequently undergo a series of reactions that ultimately affords the expected disaccharide 138 and 140 (eq 37).
Reagents and conditions: (a) (1) NIS, H₂O, CH₃CN, rt, 25–45 min; (2) NaHCO₃, Na₂S₂O₄, THF, rt, 3–4 h. (b) Fetizon reagent, benzene, reflux, 3–20 h. (c) DMSO, trifluoroacetic anhydride, CH₂Cl₂, −60 to −30 °C, 1.5 h. (d) IBX, EtOAc, 80 °C, 2.5–3.5 h. (e) Ph₄NCl, CHCl₃, pyr., rt, 15 min. (f) 3,4,6-Tri-O-benzyl-d-glucal, 60 °C, 22 h–3 days. (g) TBAF, DMF, rt, 1.5 h, 71%.

Recently, di-i-butylsilyl bis(trifluoromethanesulfonate) was used by Lewis and coworkers for the preparation of silane derivatives by selective protection of diols in polyhydroxy compounds (eq 38).

Pieters and coworkers used di-i-butylsilyl bis(trifluoromethanesulfonate) for the protection of diols in the synthesis of derivatives for an antifungal agent named papulacandin D. Synthesis of a β-glucose moiety present in the core structure of the compound initiated with glycal, which was treated with di-i-butylsilyl bis(trifluoromethanesulfonate) in the presence of pyridine and DMF at −40 °C to afford O-4- and O-6-protected β-glucal. Following four additional steps, the synthesized silanol building block and compound were subjected to a palladium-catalyzed cross-coupling reaction using Pd₂(db)₃ to furnish compound. After several reaction transformations, compound was obtained having the silane moiety intact, ultimately being treated with TBAHF in THF for removal. Deprotection of the TIPS group was achieved with TBAF and only thereafter the cyclic silyl protecting group was reinstalled to obtain compound. A variety of compounds were obtained from compound, all of which were treated with TBAHF in THF resulting in deprotection of the silane group to form compounds (eq 39).
Reagents and conditions: (a) $^1$Bu$_2$Si(OTf)$_2$, DMF, pyr. (b) Pd$_2$(dba)$_3$·CHCl$_3$, NaO'Bu, toluene, 50°C, 6–20 h. (c) Pd/C, NaHCO$_3$, H$_2$, THF, rt, 1.5 h. (d) MOMCl, DIPEA, DMAP, CH$_2$Cl$_2$, rt, 4 d. (e) TBAHF, THF, rt, 2 d. (f) TBAF·3H$_2$O, THF, rt, 3 d. (g) $^1$Bu$_2$Si(OTf)$_2$, pyr., DMF, $-40$°C to rt, 2 h. (h) (1) RCOOH, NEt$_3$, 2,4,6-trichlorobenzoyl chloride, toluene, rt, 1 h, DMAP, toluene, rt, 3 h; (2) TBAHF, THF, rt, 2–3 days; (3) Dowex 50 x 8, MeOH, 50°C, 20 h.

As a component of the synthesis of acid-sensitive biomaterials useful for drug delivery and degradable devices, Parrott et al. utilized a bifunctional silyl ether linker for the construction of relevant medical devices. Di-$t$-butylsilyl ditriflate was used for the introduction of silyl ether linker in alkaline conditions (eq 40).

With a strategy to synthesize a safe, effective, and acid-labile prodrug, Parrott et al. (eq 41) introduced bifunctional silyl ether linkers by treating di-$t$-butylsilyl ditriflate or dichlorodialkyl silane with the pendant alcohol on chemotherapeutics such as Camptothecin (CPT), Dasatinib (DAS), and Gemcitabine (GEM). The asymmetric bifunctional silyl ether prodrugs were incorporated into nanoparticles and the combination as a whole ascertained the release of therapeutics in active form under biological acidic conditions with no trace of the silyl ether modification on the drug.
Maas and coworkers reported a reaction of dialkylsilyl-bis(trifluoromethanesulfonates) with equimolar amounts of diazoacetates in the presence of a tertiary amine resulting in [(trifluoromethylsulfonyloxy)-dialkylsilyl] diazoacetates, where nucleophilic substitution of the trifloxy group could take place with alcohol to form alkoxy- (or alkenyloxy-, alkinyloxy-) dialkylsilyldiazoacetates. However, the same reagent when reacted with 2 equiv of diazoacetates formed dialkylsilyl-bisdiazoacetates, and with diazomethyl ketones formed the corresponding dialkylsilyle-bis(diazomethyl ketones), which was reported as being stable when the alkyl group was bulky such as the tert-butyl group. Therefore, the reagent di-t-butylsilyl-bis(trifluoromethanesulfonates) could be useful when in a 2:1 ratio (with respect to 2 equiv diazoacetates and 1 equiv di-t-butylsilyl-bis(trifluoromethanesulfonates)) for generating the desired product (eq 42).

\[
\begin{align*}
R^1\text{Si(OTf)}_2 + n\text{HC}^\text{C}^\text{COOR}^2 + n\text{NEt(Pr)}_2 \\
R^1 = \text{Me, iPr, tBu} & \quad R^2 = \text{Me, Et}
\end{align*}
\]

Massaro et al. utilized di-t-butylsilyle-bis(trifluoromethanesulfonate) as a promoter for a Boekelheide-type reaction to synthesize pyrrolidines and piperidines from (amino-alkyl)pyridine N-oxides (eq 43). Generally, the Boekelheide reaction requires activation of pyridine N-oxides by electrophilic agents such as Ac_2O, P_2O_5, TsCl, or TFAA that make this reaction one of limited use due to the need for protection of other functional groups in the molecule that cannot tolerate the use of such reactive promoters. This reaction proceeds through the activation of the pyridine ring followed by a nucleophilic attack to form the Boekelheide intermediate. This group introduced nucleophiles bonded to the pyridine ring that undergo intramolecular cyclization to form N-heterocycles.

\[
\begin{align*}
\text{DCM, 2 h, rt} & \quad 52\% \text{ (MW: 78\%)}
\end{align*}
\]

Treatment of amino pyridine N-oxide 157 with di-t-butylsilyle-bis(trifluoromethanesulfonate) and triethylamine in dichloromethane resulted in intramolecular cyclization to form pyrrolidine 158 in 52\% yield along with the compound 139 derived from a Boekelheide rearrangement in 30\% yield. Microwave irradiation (50°C, 250 W, 20 min) increased the product yield up to 78\%. The oxophilic nature of the promoter featuring a nonnucleophilic counterion was considered to be compatible in the presence of unprotected basic amines that lead to the participation of an amine in the intramolecular cyclization with activated pyridine N-oxide.

The analogous quinoline N-oxide, under the same reaction conditions, resulted in the desired cyclized product in 51\% yield under normal conditions and 75\% yield when microwave irradiation was used (eq 44).

\[
\begin{align*}
\text{DCM, 2 h, rt} & \quad \text{MW: 75\%}
\end{align*}
\]

2-(N-Benzylpiperidine-2-yl)pyridine was synthesized in 38\% yield under normal reaction conditions and in 60\% yield when microwave irradiation was used from a compound having one carbon more in the alkyl chain carrying the amino group (eq 45).
To extend the scope of this reaction, the group investigated intramolecular cyclization reactions at position 4 of the pyridine ring. When (4-aminoalkyl)pyridine N-oxides were subjected to the same reaction conditions, corresponding pyrrolidine and piperidine were obtained in 45 and 35% yield, respectively, under normal reaction conditions and 62 and 48%, respectively, under microwave irradiation (eq 46).

\[
\begin{align*}
\text{N} & \quad \text{O} \\
\text{Bn} & \quad \text{N}
\end{align*}
\]

Again they investigated the effect of substituents on the lateral chain, for both the chemical and the stereochemical behavior (eq 47).

Mori and Hayashi reported an enantioselective synthetic approach to 1,3-O-di-tert-butylsilylene-protected d- and l-erythritols 160 and 161 (eq 48) from d-glucose that are chiral building blocks for highly symmetrical transfused polytetrahydropyran 162 (eq 49). Di-tert-butylsilyl bis(trifluoromethanesulfonate) was used for the protection of the diols that was regarded as a better protecting group due to the reduced acid lability of silylene relative to an acetal.

Reagents and conditions: (a) (1) NaIO₄, NaHCO₃; (2) NaBH₄. (b) tBu₂Si(OTf)₂, 2,6-lutidine, DMF. (c) H₂, Pd(OH)₂/C, EtOAc. (d) (1) NaIO₄, OsO₄, MeOH, H₂O; (2) NaBH₄, MeOH.
In a report aiming to examine the mechanism of T-cell help for the production of B-cell antibodies, Besra and coworkers synthesized a novel haptenated derivative of α-d-galactosyl ceramide. To synthesize the sugar moiety present in the hapten, di-t-butylsilyl-bis(trifluoromethanesulfonate) was used for the protection of O-4 and O-6 of the sugar as a cyclic silylene, which after glycosylation was deprotected by treating with TBAF in THF (eq 50).

Reagents and conditions: (a) n-BuLi, THF, −100 °C. (b) (1) TsOH, MeOH; (2) MgBr₂·OEt₂; (3) DBU. (c) NaBH₄. (d) H₂, Pd(OH)₂/C.

Painter and coworkers also reported the synthesis of α-d-galactosyl ceramide with the use of di-t-butylsilyl-bis(trifluoromethanesulfonate) (eq 51).
For synthesizing microcrystalline solids in which organic molecules are bonded to each other through O–Si–O linkages, phenylacetylene nitrile molecules with an attached terminal hydroxyl group bearing an alkoxy methyl side chain was treated with di-t-butyldimethylsilane bis(trifluoromethanesulfonate) to afford covalent O–Si–O bonds between adjacent phenylacetylene molecules (eq 52).\(^{70}\)

Nierengarten and coworkers\(^ {71}\) explored a regioselective synthesis of fullerene bis-adducts by a double or multiple Bingel\(^ {72}\) reaction between C\(_{60}\) and linear or macrocyclic di-t-butyldimethylsilylene-tethered bis-malonates. The di-t-butyldimethylsilylene played a role as a protecting group as well as a directing group. The deprotection of silylene was achieved by treatment with HF-pyridine in THF or 20 equiv of BF\(_3\)-Et\(_2\)O in CH\(_2\)Cl\(_2\)/CH\(_3\)CN and the product was obtained in excellent yield (eqs 53 and 54).
Reagents and conditions: (a) $t$Bu$_2$Si(OTf)$_2$, DMF, pyr., rt, 12 h.
(b) C$_{60}$, DBU, I$_2$, PhMe, $-15^\circ$C, 1 h. (c) BF$_3$·Et$_2$O, CH$_2$Cl$_2$, CH$_3$CN, rt, 12 h.

Nierengarten and coworkers$^{73}$ also illustrated the application of di-$t$-butyldimethylsilyl bis(trifluoromethanesulfonate) in C$_{60}$ chemistry (eq 55).
Reagents and conditions: (a) n-BuLi, THF, 0 °C, 1 h, then \( \text{t-Bu}_2\text{Si(OTf)}_2 \), 0 °C, 1 h (81%). (b) \( \text{pTsOH} \), EtOH, rt, 12 h (78%). (c) Malonyl chloride, DMAP, \( \text{CH}_2\text{Cl}_2 \), rt, 12 h (9%). (d) \( \text{C}_6\text{H}_{60} \), DBU, I\(_2\), PhMe, \(-15^\circ\text{C}, 1\text{ h} \) (5: 8%, 6: 18%).

Piccirilli and coworkers\(^\text{74}\) reported (eq 56) efficient methods for the synthesis of five C-nucleoside phosphoramidite derivatives (186a–186e). Starting from commercially available 2-amino-5-bromopyrimidine or 2-amino-5-bromopyridine 178, they synthesized intermediate 179a or 179b, which reacted with \( \text{t-Bu}_2\text{Si(OTf)}_2 \) in DMF to form the corresponding cyclic silylene derivatives in good yield, thus affording regioselective protection of the 2'-hydroxyl group as a 2'-O-TBS ether. After installing all the suitable protecting groups, silyl ether was removed with the aid of pyridinium poly-(HF) in THF.
Reagents and conditions: (a) 'Bu₂Si(OTf)₂, DMF, 0°C. (b) TBSCI, pyr., 1H-imidazole. (c) (NH₄)₂Ce(NO₃)₆, CH₃CN:H₂O (98:2), 50°C. (d) DMF-DMA, MeOH. (e) HF-pyr., THF. (f) DMTCl, pyr. (g) i-Pr₂NP(OCH₂CH₂CN)Cl, 1-methylimidazole, i-Pr₂NEt, DCM.

The other synthesized nucleosides (186c-186e) used 'Bu₂Si(OTf)₂ to protect O-3' and O-5' of sugar moiety.

In an attempt to develop 5-hmC phosphoramidite building blocks using readily removable protecting groups, that is, TBDMS for 5-hydroxymethyl group, Dai et al. utilized 'Bu₂Si(OTf)₂ group for the protection of O-3' and O-5'. The initial strategy started with the conversion of commercially available 2'-deoxyuridine to compound 189 followed by the regioisomer 190. Owing to the difficulty in separation of compound 189 and 190 by column chromatography, the mixture was treated with di-tert-butyldimethylsilyl bistri fluoride in DMF that resulted in the protection of diol 189 to afford compound 191 leading to the separation from compound 190 (eq 57).
Reagents and conditions: (a) (HCHO), Et$_3$N, CH$_3$CN/H$_2$O. (b) AgNO$_3$, TBDMS-Cl, THF/pyr. (c) 'Bu$_2$Si(OTf)$_2$, DMF.

To increase the product yield, another strategy was followed by initiating the reaction with 6-iodo-3', 5'-di-O-TBDMS-2'-deoxyuridine 192 and after conducting multiple steps, the desired phosphoramidite 201 was obtained. Within the synthetic strategy, the diol was protected as a silylene, the removal of which was accomplished with HF-pyridine in DMF (eq 58).
In an effort to synthesize two xRNA (size-expanded RNA) monomer phosphoramidite derivatives (compounds 208 and 214) for their successful incorporation into synthetic oligoribonucleotides to examine their use as probes of positional steric sensitivity in RNAi, Kool and coworkers\textsuperscript{76} exploited di-\textit{i}-butylsilyl bistriflate for the protection of diol of rxA (size-expanded versions of adenosine) triol 202 as well as rxU (size-expanded versions of uridine) triol 209.\textsuperscript{77} The silylene protection ascertained the required regiospecific protection of xRNA monomer for automated oligonucleotide synthesis (eqs 59 and 60).

Reagents and conditions: (a) \textit{i}Bu$_2$Si(OTf)$_2$, DMF, 0°C to rt, 1 h, 85%. (b) TBDMSI, imidazole, pyr., rt, overnight, 88%. (c) N,N-Dimethylacetamide dimethyl acetal, MeOH, rt, 90%. (d) HF-pyr., THF, 0°C to rt, 15 min, 87%. (e) DMTCI, DMAP, pyr., 12 h, 86%. (f) 2-Cyanoethyl\textit{N},\textit{N}-diisopropylchlorophosphoramidite, 1-methylimidazole, i-Pr$_2$NEt, CH$_2$Cl$_2$, rt, 6 h, 87%.
Reagents and conditions: (a) $t$Bu$_2$Si(OTf)$_2$, DMF, 0°C to rt, 1 h, 71%. (b) TBDMSCI, imidazole, pyr., rt, overnight, 89%. (c) HF-pyr., THF, 0°C to rt, 15 min, 86%. (d) DMTCI, AgNO$_3$, 2,6-di-$t$-butylpyridine, CH$_3$CN, rt, 20 min, 82%. (e) 2-Cyanoethyl $N,N,N'$-$N'$-tetraisopropylphosphordiamidite, pyridinium trifluoroacetate, CH$_3$CN, rt, 18 h, 92%.

In the mechanistic studies of spore photoproduct lyase, via single cysteine mutation, Li’s research group synthesized TpTOH from thymine residue. After installation of the hydroxyl group on the methyl moiety of the thymine, the diol was protected using di-$t$-butyrsilyl bistriflate (eq 61).

Reagents and conditions: (a) (HCHO)$_x$, Et$_3$N, H$_2$O. (b) (1) $t$Bu$_2$Si(OTf)$_2$, DMF; (2) AgNO$_3$, TBSCI, THF/pyr. (c) (1) HF-pyr., THF; (2) DMTCl, pyr.; (3) Ac$_2$O/pyr. (d) $p$-TsOH, MeOH. Richichi et al. reported the use of di-$t$-butyrsilyl bis(trifluoromethanesulfonate) for the synthesis of $\alpha$-$O$-fucosyl derivative (eq 62).
Reagents and conditions: (a) Bu₂Si(OTf), pyr., 0 °C, 1 h, 62%. (b) CHCl₃, 0 °C, 48 h, 76%.