

Silicon(IV) reagents

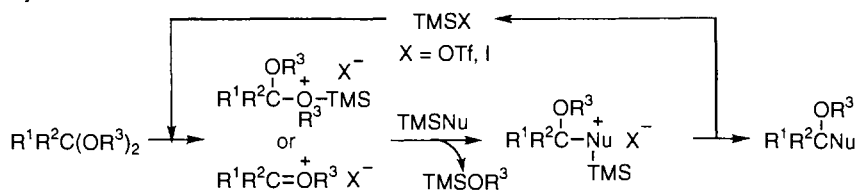
AKIRA HOSOMI and KATSUKIYO MIURA

1. Introduction

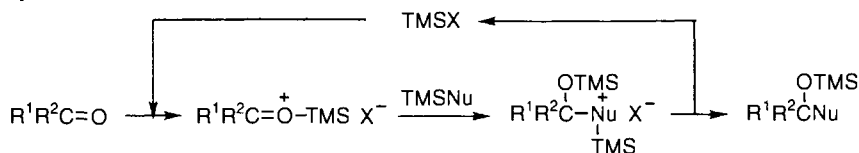
Organosilicon compounds are one of the most widely and frequently used organometallics in organic synthesis. They are easy to handle and synthesize due to their thermal and aerial stability, and exhibit a variety of reactivities derived from the electropositive nature of silicon as well as the steric and electronic effects of the silyl group.^{1,2} Silicon reagents play important roles as not only protecting agents and masked nucleophiles but also Lewis acids. The Lewis acidity of alkyl- and alkoxy-silanes is much weaker than that of the corresponding group III metal compounds. However, when one of the four ligands on silicon is changed to a soft Lewis base such as triflate (OTf) or iodide (I), the acidity becomes strong enough for synthetic use as Lewis acid catalyst.³⁻⁸ Trimethylsilyl trifluoromethanesulfonate (TMSOTf) and iodotrimethylsilane (TMSI), bearing one Lewis-acidic co-ordination site, interact strongly to various heteroatoms, particularly oxygen, to activate the carbon-heteroatom bond. Although it is also known that five co-ordinated silicates and angle strained silanes have moderate Lewis acidity, these types of Lewis acids are only utilized to intramolecularly assist the addition of silylated nucleophiles as shown in the reactions of allylsilicates^{9,10} and enoxysilacyclobutane.¹¹

The synthetic reactions mediated by TMSOTf³⁻⁵ and TMSI⁶⁻⁸ have been extensively developed in the last two decades. The silicon-centred Lewis acids are frequently employed for the reactions of trimethylsilylated nucleophiles (TMSNu) with acetals ($R^1R^2C(OR^3)_2$) and carbonyl compounds ($R^1R^2C=O$), which usually proceed with a catalytic amount of TMSX (X = OTf, I) under mild conditions, forming C-heteroatom, C-C, and C-H bonds in high efficiency (Scheme 8.1). The plausible catalytic cycles A and B consist of three parts: polarization of the substrates by TMSX, nucleophilic attack of TMSNu to the resultant oxonium or carbenium ion intermediates, and dissociation into TMSX and the products. This chapter describes the synthetic utility of the TMSOTf- and TMSI-catalysed reactions.

Cycle A.



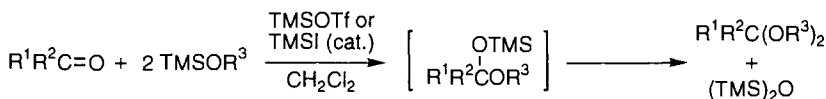
Cycle B.



Scheme 8.1

2. Carbon–oxygen and carbon–nitrogen bond formation

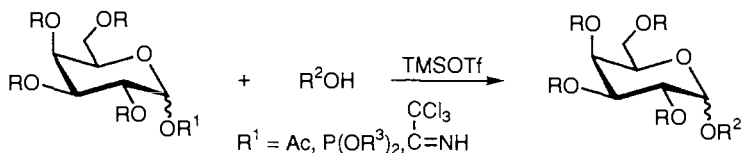
Aldehydes and ketones readily react with two equivalents of alkyl silyl ethers in the presence of TMSOTf or TMSI to afford dialkyl acetals in good yields (Scheme 8.2).^{12,13} The acid-catalysed reaction would initially form silyl alkyl acetals by nucleophilic addition of alkyl silyl ethers *via* the catalytic cycle B, and then, the acetals would turn dialkyl acetals by the successive nucleophilic substitution *via* the catalytic cycle A (Scheme 8.1). The driving force of the reaction is the great stability of hexamethyldisiloxane formed as a by-product. This method is particularly suited for the acetalization of unsaturated aldehydes and ketones without isomerization of the double bond.¹⁴



Scheme 8.2

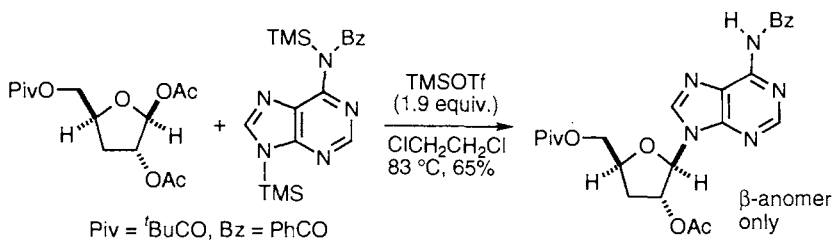
Transacetalization with alcohols or alkyl silyl ethers can also be induced by a catalytic or a stoichiometric amount of TMSOTf. The combination of TMSOTf with glycosyl acetates, trichloroacetimides, or phosphites is widely utilized as a tool of *O*-glycosylation for the synthesis of oligosaccharides (Scheme 8.3).^{15,16}

The prominent ability of TMSOTf is also exerted in nucleoside synthesis. The oxocarbenium ions generated from glycosyl acetates react with silylated heterocyclic bases to afford nucleosides (Scheme 8.4).^{17,18} In this case, an ex-



Scheme 8.3

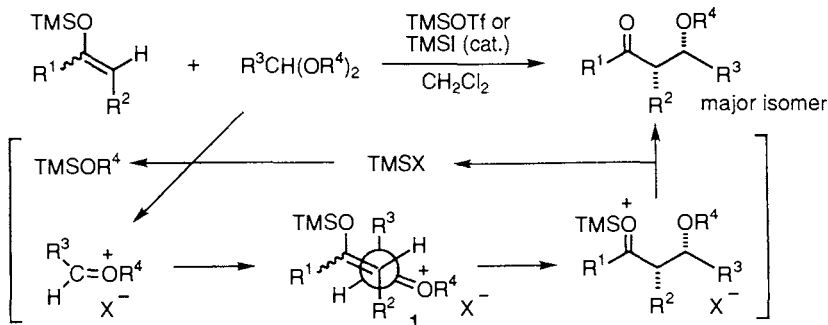
cess amount of TMSOTf is required for high efficiency. The major advantage of TMSOTf compared to SnCl₄ or other Lewis acids is to interact reversibly with the heterocycles without their deactivation.



Scheme 8.4

3. Carbon–carbon bond formation

The Mukaiyama cross-aldol reaction is one of the most powerful and selective methods for the construction of carbon–carbon bonds. This well-established transformation involves the reaction of silyl enolates with carbonyl compounds or their derivatives in the presence of an activator such as Lewis acid or fluoride ion.^{19,20} TMSOTf and TMSI can effectively promote this process with a catalytic quantity unlike TiCl₄, SnCl₄, and BF₃•Et₂O, which are required with a stoichiometric quantity. For instance, acetals and orthoesters react with silyl enolates in the presence of 1–10 mol% of TMSOTf or TMSI in CH₂Cl₂ at –78 °C to give β-alkoxy carbonyl compounds in high yield (Scheme 8.5 and



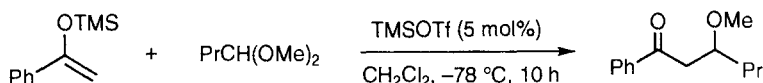
Scheme 8.5

Protocol 1).^{21–23} The aldol products do not undergo β -elimination of alcohols under the reaction conditions. In addition, this aldol reaction exhibits moderate to high erythroselectivity regardless of the geometry of silyl enolate.^{21,22} The stereochemical outcome can be rationalized by the acyclic transition state **1** in the reaction of silyl enolates with oxocarbenium ion intermediates. The aldol reaction of aldehydes and ketones with silyl enolates is also catalysed by TMSOTf,²⁴ although these electrophiles are less reactive than the corresponding acetals.

Protocol 1.

TMSOTf-catalysed reaction of 1-trimethylsiloxy-1-phenylethene with 1,1-dimethoxybutane^{21,22} (Scheme 8.6)

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.



Scheme 8.6

Equipment

- A two-necked, round-bottomed flask (100 mL) fitted with a magnetic stirring bar, rubber septum, and three-way stopcock connected to a vacuum source and a nitrogen balloon
- Dry glass syringes (volume appropriate for quantity of solution to be transferred) with stainless-steel needles
- Dry ice–methanol bath

Materials

- 1,1-Dimethoxybutane^a (FW 118.2), 1.30 g, 11 mmol **flammable, irritant**
- 1-Trimethylsiloxy-1-phenylethene^b (FW 192.3), 1.92 g, 2.05 mL, 10 mmol **moisture sensitive, irritant**
- Trimethylsilyl trifluoromethanesulfonate^c (FW 222.3), 1.11 g, 0.97 mL, 0.50 mmol **flammable, corrosive**
- Freshly distilled (CaH₂) dichloromethane, 30 + 5 mL **toxic, irritant**

1. Dry the two-necked flask with an electric heat gun under vacuum, and introduce nitrogen gas from the balloon. Repeat this operation two more times. After cooling to room temperature, add 1,1-dimethoxybutane and 30 mL of dry CH₂Cl₂ *via* syringes.
2. Stir the mixture and cool to –78 °C (dry ice–methanol bath). Add 1-trimethylsiloxy-1-phenylethene to the solution *via* a syringe.
3. After 10 min, add a solution of trimethylsilyl trifluoromethanesulfonate in 5 mL of CH₂Cl₂ dropwise over 5 min *via* a syringe.
4. After stirring for 10 h at –78 °C, remove the septum and pour the reaction mixture into 50 mL of saturated aqueous NaHCO₃ solution.
5. Transfer the bilayer to a separating funnel and remove the organic layer. Extract the aqueous layer twice with 30 mL of CH₂Cl₂.

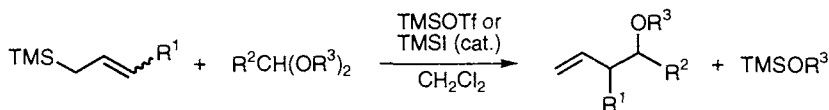
6. Pass the combined organic layer through a short K_2CO_3 column and concentrate *in vacuo*.
7. Purify the resulting oil by column chromatography on silica gel using hexane–ether (10:1). 3-Methoxy-1-phenylhexan-1-one (FW 206.3) is obtained in 75% yield (1.55 g).

^a Prepared by acid-catalysed reaction of butanal with methanol.²⁵

^b Prepared according to a published procedure.²⁶ Commercially available from Aldrich.

^c A colourless fluid liquid boiling at 45–47 °C at 17 mmHg. Commercially available from Aldrich. It can be easily prepared from trimethylsilyl chloride and trifluoromethane sulfonic acid.²⁷

The Hosomi–Sakurai reaction, the Lewis acid- or fluoride ion-mediated allylation using allylsilanes, can transfer functionalized allyl groups onto various carbon electrophiles with high regio-, stereo-, and chemoselectivity.²⁹ This synthetically valuable transformation as well as the Mukaiyama reaction is effectively induced by TMSOTf and TMSI. In the presence of a catalytic amount of TMSOTf or TMSI, acetals react with allylsilanes at the γ -position to give homoallyl ethers in good yields (Scheme 8.7).^{30–32} The use of chiral crotylsilane derivatives achieves high levels of acyclic stereocontrol.³³ Aldehydes and ketones can be directly led to homoallyl ethers by *in situ* acetalization with alkyl silyl ethers followed by allylation (Protocol 2).¹³ This consecutive reaction is applicable to asymmetric synthesis of homoallyl alcohols using homochiral alkyl silyl ethers.³⁴



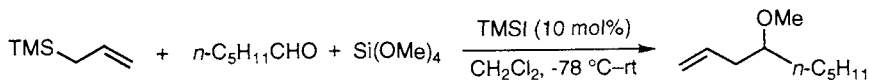
Scheme 8.7

Although TMSOTf and TMSI effect the allylation of aldehydes, their catalytic activities are considerably low. However, TMSB(OTf)₄, a supersilylating agent, is an excellent catalyst for the allylation.³⁵

Protocol 2.

TMSI-catalysed consecutive acetalization and allylation of hexanal to 4-methoxy-1-nonene¹³ (Scheme 8.8)

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.



Scheme 8.8

Protocol 2. Continued**Equipment**

- A two-necked, round-bottomed flask (100 mL) fitted with a magnetic stirring bar, rubber septum, and three-way stopcock connected to a vacuum source and a nitrogen balloon
- Dry glass syringes (volume appropriate for quantity of solution to be transferred) with stainless-steel needles
- Dry ice–methanol bath and ice–water bath

Materials

- | | |
|---|-----------------------------|
| • Freshly distilled (CaCl ₂) hexanal (FW 100.2), 1.00 g, 1.20 mL, 10 mmol | flammable, irritant |
| • Freshly distilled (CaH ₂) dichloromethane, 30 mL | toxic, irritant |
| • Tetramethoxysilane (FW 152.2), 1.67 g, 1.62 mL, 11 mmol | flammable, corrosive |
| • Allyltrimethylsilane (FW 114.3), 1.37 g, 1.91 mL, 12 mmol | flammable, irritant |
| • Iodotrimethylsilane ^a (FW 200.1), 0.20 g, 0.14 mL, 1.0 mmol | flammable, corrosive |
| • Pyridine, 0.5 mL | flammable, toxic |

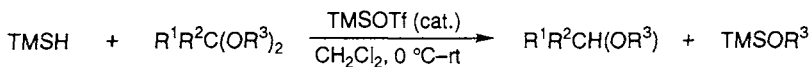
1. Dry the two-necked flask with an electric heat gun under vacuum, and introduce nitrogen gas from the balloon. Repeat this operation two more times. After cooling to room temperature, add hexanal, dry CH₂Cl₂, tetramethoxysilane, and allyltrimethylsilane *via* syringes.
2. Stir the mixture and cool to –78°C (dry ice–methanol bath).
3. Add iodotrimethylsilane to the solution *via* a syringe and stir for 15 min at –78°C.
4. Then, warm the reaction vessel to 0°C with an ice–water bath.
5. After stirring for 3 h, add pyridine *via* a syringe.
6. After stirring for 5 min, remove the septum from the flask and pour the reaction mixture into 50 mL of saturated aqueous NaHCO₃ solution.
7. Transfer the bilayer to a separating funnel and remove the organic layer. Extract the aqueous layer twice with 30 mL of Et₂O.
8. Pass the combined organic layer through a short Na₂SO₄ column and concentrate *in vacuo*.
9. Purify the resulting oil by column chromatography on silica gel using hexane–ether (20:1). 4-Methoxy-1-nonen (FW 156.3) is obtained in 94% yield (1.47 g).

^aA colourless liquid boiling at 108°C at 760 mmHg. Commercially available. It can be easily prepared from hexamethyldisilane and iodine in quantitative yield as shown in Protocol 4.³⁶

4. Carbon–hydrogen bond formation

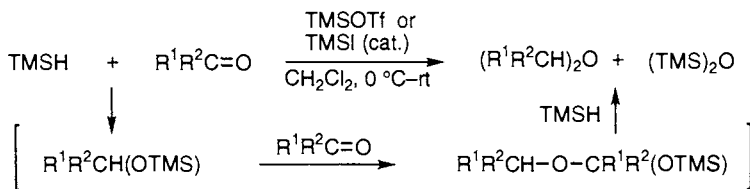
A catalytic amount of TMSOTf successfully induces the reductive cleavage of acetals with trimethylsilane (TMSH) to afford the corresponding ethers in high yields (Scheme 8.9).³⁷ However, the TMSOTf- and TMSI-catalysed reactions of aldehydes or ketones with TMSH do not give silyl ethers but

8: Silicon(IV) reagents



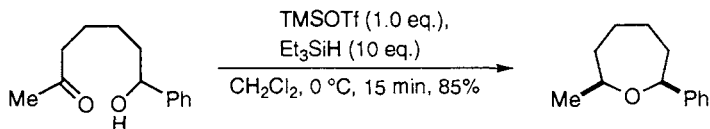
Scheme 8.9

symmetrical ethers (Scheme 8.10).³⁸ This reductive condensation can be applied for the cyclization of 1,4- and 1,5-diketones to cyclic ethers.³⁹ The formation of the symmetrical ethers is probably because the intermediary silyl ether attacks the activated C=O bond faster than TMSH. Indeed, under the similar conditions, the reaction of ketones or aldehydes with alkyl silyl ethers results in the selective formation of unsymmetrical ethers (Protocol 3).³⁸



Scheme 8.10

The combination of TMSOTf with hydrosilanes is also effective for the reductive cyclization of hydroxyketones (Scheme 8.11).⁴⁰

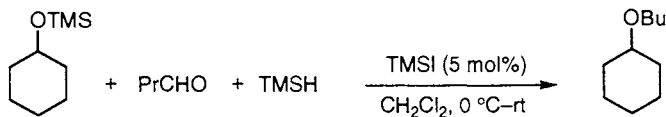


Scheme 8.11

Protocol 3.

TMSI-catalysed reductive condensation of butanal with cyclohexyloxy-trimethylsilane using trimethylsilane³⁸ (Scheme 8.12)

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.



Scheme 8.12

Protocol 3. Continued**Equipment**

- A three-necked, round-bottomed flask (100 mL) fitted with a magnetic stirring bar, a rubber septum, thermometer, and three-way stopcock connected to a vacuum source and a nitrogen balloon
- A bubbler containing liquid paraffin
- Tygon tubing attached to a stainless-steel needle
- Dry glass syringes (volume appropriate for quantity of solution to be transferred) with stainless-steel needles
- Ice-water bath

Materials

- Iodine (FW 253.8), 0.13 g, 0.50 mmol **highly toxic, corrosive**
- Hexamethyldisilane (FW 146.4), 79 mg, 0.11 mL, 0.54 mmol **flammable, irritant**
- Freshly distilled (CaH₂) dichloromethane, 14 + 10 mL **toxic, irritant**
- Freshly distilled (CaCl₂) butanal (FW 72.11), 0.72 g, 0.90 mL, 10 mmol **flammable, corrosive**
- Cyclohexyloxytrimethylsilane^a (FW 172.3), 1.72 g, 2.01 mL, 10 mmol **flammable, moisture sensitive**
- Trimethylsilane^b (FW 74.2) in a gas cylinder **flammable**

1. Dry the three-necked flask with an electric heat gun under vacuum, and introduce nitrogen gas from the balloon. Repeat this operation two more times. After cooling to room temperature, remove the septum, quickly add iodine, and attach the septum under a stream of nitrogen.
2. Add hexamethyldisilane and 14 mL of dry CH₂Cl₂ *via* syringes.
3. Stir the violet solution at room temperature for 10 min, and then, cool to 0°C with the ice-water bath.
4. Add a solution of butanal and cyclohexyloxytrimethylsilane in 10 mL of CH₂Cl₂ *via* a syringe.
5. After stirring for 10 min, replace the vacuum source with a bubbler and turn the stopcock to the bubbler from the nitrogen source.
6. Add trimethylsilane directly from a gas cylinder by means of Tygon tubing attached to a stainless-steel needle inserted through the septum. Slowly bubble the gas through the solution until the colour changes from violet to red-gold. During the bubbling, the internal temperature rises from 0°C to 15°C.
7. Stop the addition of trimethylsilane, remove the cold bath, and stir at room temperature for 2 h.
8. Remove the septum and pour the reaction mixture into 30 mL of 10% aqueous Na₂S₂O₃ solution.
9. Transfer the bilayer to a separating funnel and remove the aqueous layer. Similarly, wash the organic layer three more times with 30 mL of 10% aqueous Na₂S₂O₃ solution and four times with 30 mL of water.
10. Dry the organic layer over MgSO₄ and concentrate *in vacuo*.

11. Purify the crude product by distillation. Cyclohexyl butyl ether (FW 156.3, b.p. 68–70°C/0.08 mmHg) is obtained in 93% yield (1.45 g).

^aPrepared from cyclohexanol and chlorotrimethylsilane in the presence of triethylamine.⁴¹ Commercially available from Shin-Etsu Chemical Co. Ltd.

^bB.p. 6.7°C. Commercially available from Strem Chemicals Inc. or Chisso Co. Ltd. It can be prepared from chlorotrimethylsilane and lithium aluminum hydride.⁴²

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