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(Triisopropylsilyl)acetaldehyde acetal as a novel protective group for 1,2-diols

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Abstract—(Triisopropylsilyl)acetaldehyde dimethyl acetal (TIPS-ADMA) was synthesized from chlorotriisopropylsilane in three steps. Cyclic and acyclic 1,2-diols can be transformed to (triisopropylsilyl)ethylidene acetals (TIPS-AA). Removal of the acetal by $LiBF_4$ regenerates the starting diol in excellent yield even in the presence of an acetonide of 1,2-diol. The TIPS-AA group can survive under the deprotection conditions of the acetonide in acetic acid at 80 °C. Selective protection of 2,3- and 4,6-diols for *O*-methyl D-mannoside with TIPS-ADMA and selective deprotection of the acetals have been achieved.

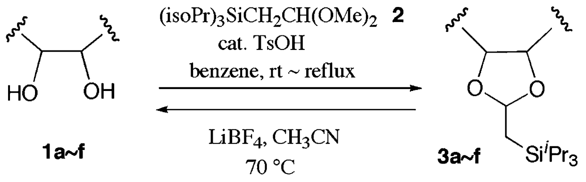
Selective protection and deprotection of poly-functional groups are important issues in synthetic organic chemistry. Acetals have been used as a common masking group of 1,2- and 1,3-diols and widely employed in organic synthesis.[1] Generally, acetals are stable under basic conditions or against with nucleophiles and can be removed under acidic conditions, although other deprotection conditions are also available for specific acetals, for example, hydrogenolysis for arylidene acetals,[2] oxidative hydrolysis of *p*-methoxybenzylidene acetals,[3] reductive cleavage of diphenylidene acetals[4] or fluoride-promoted deprotection for silylene and siloxanylidene acetals.[5] Nonetheless, an alternative method for formation–removal of acetal is necessary in certain cases.

Recently, Fukuyama reported the *p*-silyloxyarylidene acetal of 1,2-diol.[6] This protective group is effective for acid-fragile molecules. In fact, it was removed elegantly under non-acidic conditions by a combination of fluoride and base. On the other hand, in our on-going project, an acetal that can survive under weak to medium acidic conditions and can be removed under a specific condition other than acidic conditions is highly desirable.

Herein, we report a (triisopropylsilyl)acetaldehyde acetal (TIPS-AA) **3** as a new protective group for 1,2-diols, which can be formed by the reaction of **1** with (triisopropylsilyl)acetaldehyde dimethyl acetal (TIPS-ADMA) **2**, and cleaved with $LiBF_4$ in acetonitrile specifically (see Scheme 1).

The synthesis of (triisopropylsilyl)acetaldehyde **5** was reported previously by Lipshutz et al.[7] in four steps from chlorotriisopropylsilane with vinyl lithium. We have now improved the synthesis of **5** in two steps. Allylation of chlorotriisopropylsilane followed by oxidative cleavage of the alkenyl bond with ozone to give **5** in 80% yield.[8] An acetal formation of **5** with trimethyl orthoformate was carried out in methanol in the presence of TsOH or CSA to give **2** in 85% yield (see Scheme 2).

Acetalization of 1,2-diols was carried out with **2** in the presence of TsOH catalyst in benzene.[9] The results are listed in Table 1. The acetal formation of *cis*-cyclopentane-1,2-diol **1a** and **1b** proceeded very well at room temperature to give the corresponding acetal **3a** and **3b** in 86% and 85% yields, respectively. The reactions of *cis*-cyclohexane-1,2-diol **1c** and acyclic 1,2-diols **1d**–**f** required refluxing conditions to give **3c**, **3d**–**f** in excellent yields.



Scheme 1.

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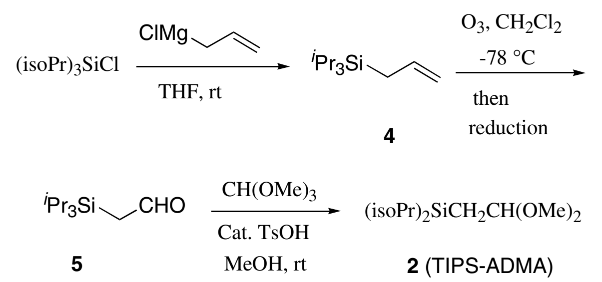
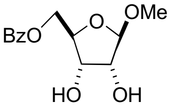
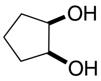
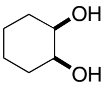
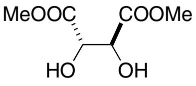
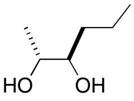
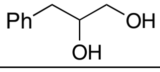


Scheme 2.

Initially, we considered that fluoride anion might promote desilylation of **3** and that successive cleavage of the O–C bond of acetal could give vinyl ether, which would be hydrolyzed easily by a very weak acid to regenerate the original diol **1**. However, a number of fluoride ion sources such as TBAF, KF, and CsF under various reaction conditions, including reactions at high temperature and under microwave assistance were all fruitless. These results indicate that a selective deprotection of silyl ether is possible in the presence of TIPS-AA. The deprotection proceeded by treatment with mineral and organosulfonic acids such as HCl or TsOH. In fact, compound **3a** is hydrolyzed quickly below pH 2 but slowly at pH 3. Interestingly, it is stable above pH 4, and survives in acetic acid even at 80 °C for several hours. Subsequently we have examined $LiBF_4$[10] and found to be effective for removal of TIPS-AA.[11] Although the reaction required heating in acetonitrile at 70 °C, a clean deprotection took place for 2-tri-isopropylsilylmethy-1,3-dioxolanes **3a–f**.[12] The results are listed in Table 2.

Table 1. The reaction of 1,2-diols with TIPS-ADMA

Entry	Diol **1**		Conditions[a] (temp)	Product **3**	Yield[b] (%)
1		**1a**	rt	**3a**[c]	86
2		**1b**	rt 60 °C[e]	**3b**[c]	69[d] 85
3		**1c**	Reflux	**3c**[c]	84
4		**1d**	Reflux	**3d**[c]	89
5		**1e**	Reflux[f]	**3e**[c]	81[d]
6		**1f**	Reflux	**3f**[c]	98

[a] In benzene for 1 h.

[b] Isolated yields.

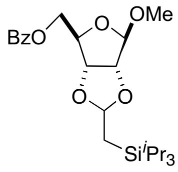
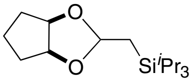
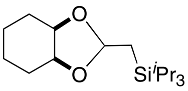
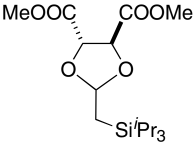
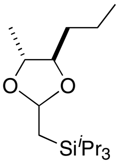
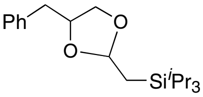
[c] Diastereomeric ratios; **3a** (1:3), **3b** (1:5), **3c** (2:5), **3e** (1:1), **3f** (3:5).

[d] Some recovery of the starting diol.

[e] 3 h.

[f] 2 h.

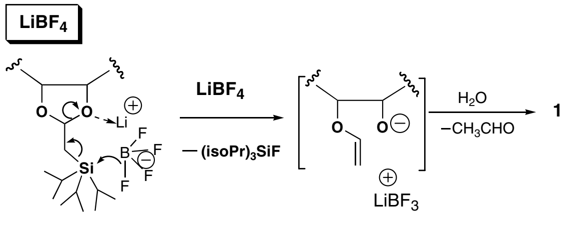
Table 2. Deprotection of TIPS-AA by $LiBF_4$

Entry	Acetal **3**		Conditions[a] Time (h)	Yield[b] (%)
1		**3a**	15	89
2		**3b**	19	85
3		**3c**	8	92
4		**3d**	3	84
5		**3e**	5	90
6		**3f**	11	85

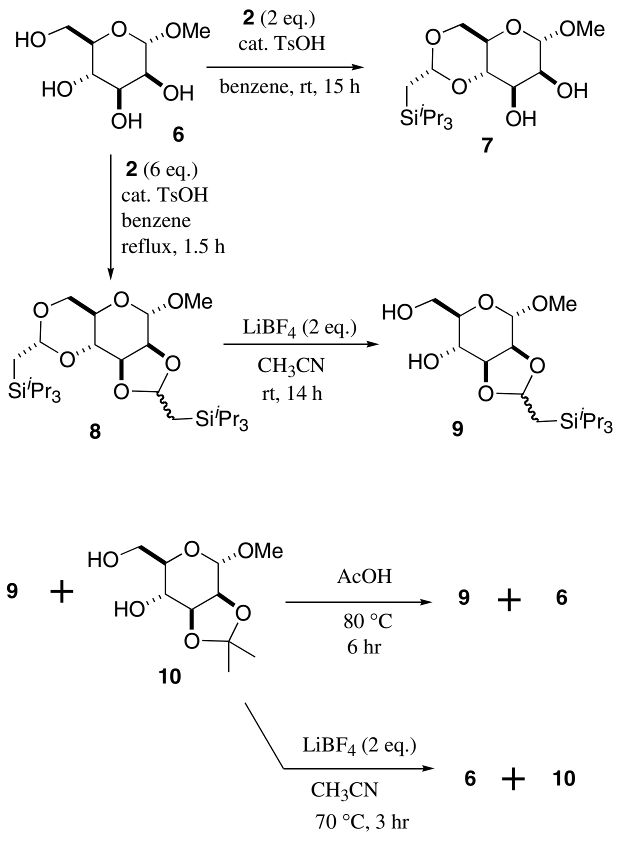
[a] In CH_3CN at 70 °C.

[b] Isolated yields.

The failure in deprotection with simple fluoride anion clearly indicates that fluoride anion itself cannot initiate cleavage of the C–Si bond. In order to cleave this bond, an activation of the C–O bond is required. Lithium cation of $LiBF_4$ may play an important role in the activation of the acetal bond to assist nucleophilic cleavage of the C–Si bond with fluoride anion. After this process, vinyl ether and lithium alkoxytrifluoroborate could be produced, and this intermediate may be hydrolyzed during an aqueous work-up to give acetaldehyde and **1** (see Scheme 3).



Scheme 3.



Scheme 4.

Since the rates of cyclic acetal formation of 1,2-diol and 1,3-diol, and the rates of deprotection of five-membered and six-membered cyclic acetals were different, selective protection and deprotection for polyols could be possible[1b] and be useful for carbohydrate synthesis. Selective protections of 2,3- and 4,6-diols of *O*-methyl D-mannoside have been accomplished, as shown in Scheme 4. When **6** was treated with **2** in the presence of TsOH in benzene at room temperature, mono acetal **7** was obtained in 68% yield. While, the reaction with an excess of **2** at refluxing temperature in benzene gave diacetal **8** in 85% yield. Six-membered acetal was removed selectively with $LiBF_4$ in acetonitrile at room temperature to give mono acetal **9** in 74% yield.

Studies of chemo-selective deprotection in TIPS-AA **9** and acetonide **10** were examined. When a mixture of compounds **9** and **10** was exposed to acetic acid at 80 °C for 6 h, acetonide **10** was hydrolyzed to give **6** but **9** was recovered quantitatively. On the other hand, the same mixture was heated with $LiBF_4$ in acetonitrile at 70 °C for 3 h, only the TIPS-AA of **9** was hydrolyzed to give **6** selectively.

In summary, we have prepared TIPS-ADMA **2** in three steps from chlorotriisopropylsilane. TIPS-ADMA serves as an excellent acetalization reagent for 1,2-diols.

The resulting TIPS-AA **3** is stable in hot acetic acid and can be removed by $LiBF_4$ selectively.[13] TIPS-AA is a unique protecting group and will be useful in organic synthesis.[12] The specific use for the synthesis of complex natural products are in progress.

Acknowledgements

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7. Lipshutz, B. H.; Lindsley, C.; Susfalk, R.; Gross, T. *Tetrahedron Lett.* **1994**, *35*, 8999.
8. Alternatively, OsO_4 catalyzed dihydroxylation and $NaIO_4$ promoted cleavage of the diol gave **5**.
9. General procedure: A mixture of diol **1** (1 mmol), **2** (252 mg, 2 mmol), and anhydrous *p*-TsOH (17 mg) was stirred in benzene (2 mL) at the temperature indicated in Table 1. After the reaction was completed, the mixture was quenched with saturated $NaHCO_3$ solution and extracted with EtOAc. Compound **3** was obtained after a purification by column chromatography on silica gel.
10. Hydrolysis of 2-substituted 1,3-dioxolane was known at a slow rate in wet acetonitrile with $LiBF_4$. Lipshutz, B. H.; Harvey, P. F. *Syn. Commun.* **1982**, *12*, 267.
11. A mixture of **3** (1 mmol) and $LiBF_4$ (184 mg, 2 mmol) in acetonitrile (8 mL) was heated at 70 °C. After cooling, the mixture was diluted with EtOAc (50 mL) and washed with water and brine. The organic extract was dried over $MgSO_4$ and condensed. The residue was purified by flush column chromatography on silica gel to give diol **1**.
12. Similar deprotection of 4-trimethysilylmethyl-1,3-dioxolanes lead to ketone or aldehyde was reported. See, Lillie, B. M.; Avery, M. A. *Tetrahedron Lett.* **1994**, *35*, 969.
13. More details of protection and deprotection for TIPS-AA of 1,2- and 1,3-diols including scope and limitation will be described in a full article.