Unusually Stable Silyl Ketones with Bowl-shaped Tris(2,6-diphenylbenzyl)silyl Group for Various Nucleophilic Attacks and α-Deprotonation

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Abstract: A newly designed, bowl-shaped tris(2,6-diphenylbenzyl)silyl (TDS) group can be successfully utilized as a highly effective shield of ketone carbonyls for various nucleophilic attacks and α -deprotonation. The high shielding effect of the bowl-shaped TDS moiety toward carbonyl and even α -protons is verified by the ¹H NMR study of TDS ketone **1a** in CDCl₃, and by its X-ray analysis. The TDS ketone **1b** can be cleaved with Bu₄NF/BF₃·OEt₂.

Key words: ketone, silicon, nucleophilic attack, alkyllithium, Grignard reagent

Ketone carbonyls are one of the most popular and valuable functional groups in organic synthesis, and are often masked as ketals, thioketals, enol silyl ethers, enamines, oximes, substituted hydrazones, cyanohydrins, and Schiff bases for further chemoselective transformations of multifunctional organic molecules.¹ However, the shield of ketone carbonyls without affecting carbonyl moieties has never been developed to a useful level due to the lack of appropriate methodologies. Here, we wish to report a new carbonyl shielding approach against various nucleophilic attack using the bowl-shaped tris(2,6-diphenylbenzyl)silyl (TDS) group (Scheme 1).^{2,3}



Scheme 1

We examined the blocking ability of the TDS moiety for ketone carbonyl toward a variety of reactive nucleophiles. Thus, reaction of α -TDS ketone **1b**⁴ in THF with excess BuLi (3 equiv) at -78 °C for 2 hours, at -40 °C for 1 hour, and at -20 °C for 1 hour resulted, after quenching with benzaldehyde acceptor at -78 °C, in recovery of most (~92%) of the starting α -TDS ketone **1b** without formation of **2b** or **3** via nucleophilic alkylation and α -deproto-

nation, respectively (Scheme 2).⁵ The stability of α-TDS ketone 1b toward excess BuLi (3 equiv) under various reaction conditions follows: 99% recovery at -40 °C for 6 hours; 83% recovery at -20 °C for 4 hours; 58% recovery at 0 °C for 30 minutes. Other alkyllithiums (MeLi and t-BuLi), Grignard reagent (MeMgBr), and base (LDA) exhibited similar unreactivity as shown in the Table (entries 4–8). In marked contrast, however, treatment of α -trimethylsilyl ketone 4 with BuLi (3 equiv) in THF at -78 °C for 1 hour and subsequent addition of benzaldehyde at this temperature gave rise to butylation product 5 (30%) and enone 6 (45%) via α -deprotonation, aldol intermediate 7, and its subsequent Peterson elimination. Other selected examples with different TDS ketones toward RLi and Grignard nucleophiles are also included in the Table. Another TDS ketone 1c exhibited similar unreactivity toward MeMgBr and RLi nucleophiles at low to room temperature for several hours. Sterically less hindered a-TDS ketone 1a is readily susceptible to nucleophilic attack with BuLi to furnish alcohol **2a** ($R = CH_2CH_2Ph$; n = 1) (entry 2), and α -deprotonation with bulky *t*-BuLi to furnish an aldol product 8 upon reaction with benzaldehyde in high yield (entry 3). A similar tendency is also observed in the case of β -TDS ketones **1d** and **1e** (entries 12–18).

The high shielding effect of the bowl-shaped TDS moiety toward ketone carbonyl and even α -protons was verified by ¹H NMR spectral study of α -TDS ketone **1a** in CDCl₃,



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R—C—(($CH_2)_{n}[TDS] = \frac{R^{1}-N}{T}$	1 (3 eq) PhCH0 HF -78	D (3 eq) 3°C 1 + R	$ \begin{array}{ccc} R^1 & & & H & CH_2PI \\ -C - (CH_2)_n \cdot [TDS] & + & Ph - C \cdot CH - C \cdot \\ & & & & H & H \\ OH & - & & & OH & H \end{array} $	h —CH ₂ -[TDS]			
Entry	T Ketone 1		R ¹ -M	Reaction Condition	8 % Yield	% Yield of Products		
5	R	n		(°C, h)	1	2 8		
1	CH ₂ CH ₂ Ph	1	MeMgBr	-78, 5; -40, 1	92			
2			BuLi	-78, 1		86		
3			t-BuLi	-78, 4		90		
4	CH(CH ₂ Ph) ₂	1	MeLi	-78, 4; -20, 2; 0, 0.5	99			
5			MeMgBr ^b	0, 3; 25, 1	94			
6			BuLi	-78, 2; -40, 1; -20, 1	92			
7			t-BuLi	-78, 4	93			
8			LDA	-78, 2; 0, 3	99			
9	CH(CH ₂ CH ₃) ₂	1	MeMgBr ^b	-20, 1; 0, 1; 25, 1	99			
10			BuLi	-78, 2; -40, 2; -20, 1	87			
11			t-BuLi	-78, 2; -40, 2; -20, 1	87			
12	C(CH ₃) ₃	2	MeMgBr	-20, 1; 0, 1; 25, 0.5	91			
13			BuLi	78, 1	61	33		
14			t-BuLi	78, 2; -40, 2; -20, 1	91			
15	Ph	2	MeMgBr	-20, 0.5; 0, 2	47	46		
16				-78, 4	99			
17			BuLi	-78, 0.3		99		
18			t-BuLi	-78, 0.5; -20, 3	99			

Table	Reactivity	of α - and	β-TDS	Ketones	toward	Alkyllithium	ıs, Grignard	l Reagent	or Base ^a
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^a Reaction of α - and β -TDS ketones 1 in THF with alkyllithiums, Grignard reagent or base (3 equiv) was carried out under the indicated reaction conditions, and subsequently treated with benzaldehyde (3 equiv) at -78 °C for 1 h.

^b Use of THF/ether solvents (volume ratio, 1:2).

where the upfield shift of β -phenethyl protons in **1a** compared to the corresponding α -trimethylsilyl ketone and the parent methyl β -phenethyl ketone is clearly observed (Figure 1).

$\alpha' \qquad \alpha \beta$ X-CH ₂ -(O=)C-CH ₂ -CH ₂ -Ph						
¹ H NMR Data	α'-H	α-H	β-Н	aromatic-H		
[TDS]-CH2COCH2CH2Ph	δ 0.74	δ 1.54	δ 2.05	δ 6.93 & 7.18		
Me ₃ Si-CH ₂ COCH ₂ CH ₂ Ph	δ 2.21	δ 2.67	δ 2.88	δ 7.18 & 7.27		
CH ₃ COCH ₂ CH ₂ Ph	δ 2.12	δ 2.74	δ 2.88	δ 7.18 & 7.27		

Figure 1

The primary structure of α -TDS ketone **1a** was determined by single-crystal X-ray diffraction analysis as shown in Figure 2,⁶ which suggests the existence of an ap-

propriate molecular pocket around carbonyl protons as well as α -protons for shielding against nucleophilic attack and α -deprotonation. This inference is in accord with the ¹H NMR data on the upfield shift of ketone protons in α -TDS ketone **1a**.

The TDS protecting group of the α -TDS ketone **1b** is readily cleaved to the corresponding ketones **9** by treatment with tetrabutylammonium fluoride/BF₃·OEt₂ complex in acetonitrile/dichloromethane cosolvent under the standard conditions (Scheme 3).⁷







Figure 2 ORTEP diagram of α-TDS ketone 1a

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Scheme 4 Conditions: (a) cat. $Pd(OAc)_2$ (20 mol%), 30% H_2O_2 , solvent; (b) *t*-BuLi, BnBr, THF; (c) *t*-BuLi, HMPA, BnBr, THF.

- (4) Synthesis of α-TDS ketones 1a and 1b (Scheme 4): The starting allylsilane 10 was prepared from allyltrichlorosilane in a similar manner as described in the synthesis of tris(2,6-diphenylbenzyl)silane. See ref.²
- (5) Quenching with D₂O in place of benzaldehyde acceptor resulted in 99% recovery of the starting α-TDS ketone 1b.
- (6) The single-crystal of α -TDS ketone **1a** was obtained by recrystallization from benzene/ether solvents. Crystal structure data for **1a**: C₆₇H₅₆OSi·2 C₆H₆, $M_w = 1061.47$, monoclinic, space group P-2/a (#13), a = 20.629 Å, b = 14.155 Å, c = 22.437 Å, V = 6274.8 Å³, Z = 4, $D_{calcd} = 1.111$ gcm⁻³, $R_1 = 0.121$.
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