Tris(2,6-diphenylbenzyl)silyl Group as a New and Highly Effective Protector for Carboxylic Acids: Unusual Behavior of Such Carboxylic Esters toward Common Nucleophiles and Bases

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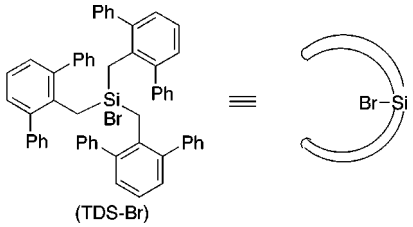
Carboxylic acids are found in almost all living organisms and are certainly indispensable compounds. They also play an important role in organic chemistry and hence are often utilized in their protective forms for two reasons: (1) The acidic proton of the carboxyl functional group (−COOH) can be masked by conversion to the corresponding esters and amides. (2) The carbonyl group of −COOH can be protected as oxazolines and ortho esters to prevent against nucleophilic attack and/or α-deprotonation.[1] However, the latter carbonyl protection has not been widely utilized due to the troublesome functional group transformation of multifunctional molecules.[2−5] Here we report that the bowl-shaped tris(2,6-diphenylbenzyl)silyl (TDS) group can be successfully utilized as a new and highly effective protector of carboxylic acids against various nucleophilic attacks and α-deprotonation.



The requisite TDS-Br can be conveniently synthesized from commercially available 2-chloro-6-phenyltoluene in a four-step sequence as shown in Scheme 1.[6]

Protection of a series of carboxylic acids **1** with TDS-Br can be effected by treatment with AgOTf in CH_2Cl_2 at room temperature for several hours to furnish TDS esters **2** in moderate to high yields. The primary structure of TDS acetate **2a** was determined by single-crystal X-ray diffraction analysis as shown in Figure 1.[7]

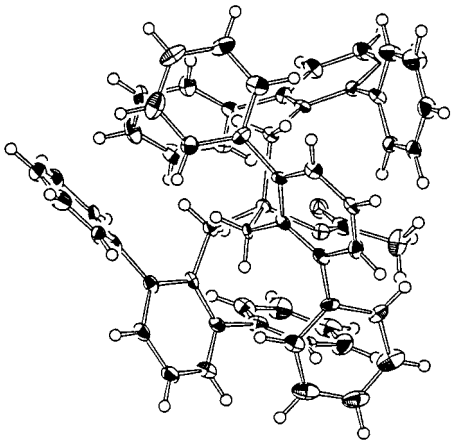
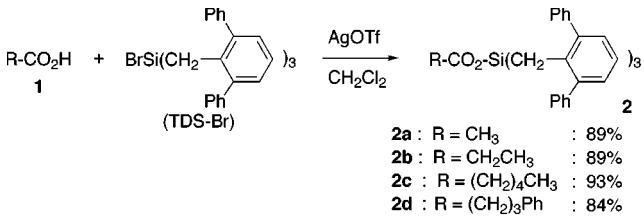


Figure 1. ORTEP diagram of the TDS acetate **2a**.



The TDS esters **2** thus prepared are found to be unusually stable toward a variety of reactive nucleophiles and bases. Indeed, reaction of TDS propionate **2b** with excess BuLi (2.5 equiv) at −78 °C for 1 h resulted, after quenching with benzaldehyde acceptor at −78 °C, in recovery of most (∼97%) of the starting TDS ester **2b**.[8] Attempted deuteration with D_2O in place of benzaldehyde also gave the TDS ester **2b** in almost quantitative yield without any deuterium incorporation. The stability of TDS propionate **2b** toward excess BuLi (2.5 equiv) under various reaction conditions is reported as follows: ∼93% recovery of **2b** at −78 °C for 5 h; 74% recovery of **2b** at −40 °C for 1.5 h;[9] 24% recovery of **2b** at −20 °C for 1 h.[10] Other alkyllithiums (MeLi and *t*-BuLi), Grignard reagents (MeMgBr),[11] and base (LDA) gave similar results at −78 °C for 5 h (95−98% recovery of the TDS ester **2b**). In marked contrast, however, treatment of the previously known bulky *tert*-butyldiphenylsilyl propionate (**3b**) and 2,6-di-*tert*-butyl-4-methylphenyl propionate (**4b**) with BuLi (1.2−2.5 equiv) in THF at −78 °C for 1 h and subsequent addition of benzaldehyde at this temperature gave rise to ester cleavage product **5** and aldol **6** (R = CH_3), respectively, as major products.[12−14] Other TDS esters, **2c** and **2d**, exhibited similar unreactivity toward RLi nucleophiles at −78 °C for several hours. However, only TDS acetate **2a** is somewhat susceptible toward

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(6) Weber, W. P. *Silicon Reagents for Organic Synthesis*; Springer-Verlag: Berlin, 1983.

(7) The single crystal of **2a** was obtained by recrystallization from dichloromethane/hexane solvents. Crystal structure data for **2a**: $C_{59}H_{48}O_2Si$, $M_w = 817.10$, triclinic, space group $P1$, $a = 13.6993$ Å, $b = 30.9205$ Å, $c = 12.2388$ Å, $V = 4691.1$ Å^3, $Z = 2$, $D_{calcd} = 1.217$ g cm^{-1}, $R_1 = 0.222$.

(8) The butylation product of benzaldehyde, 1-phenyl-1-pentanol, was obtained in 91% yield.

(9) Quenching of this solution with benzaldehyde (2.5 equiv) gave *erythro*-aldol product (16%) and TDS-OH (5%). This result indicates 16% of α-deprotonation and 5% of ester cleavage.

(10) Ester cleavage product, TDS-OH (73%) without α-deprotonation.

(11) Attempted reaction of **2b** in THF with MeMgBr (2.5 equiv) in ether at room temperature for 5 h resulted in recovery of most of the **2b** (∼98%).

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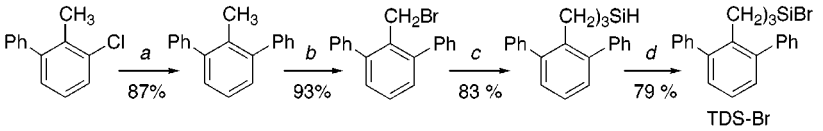
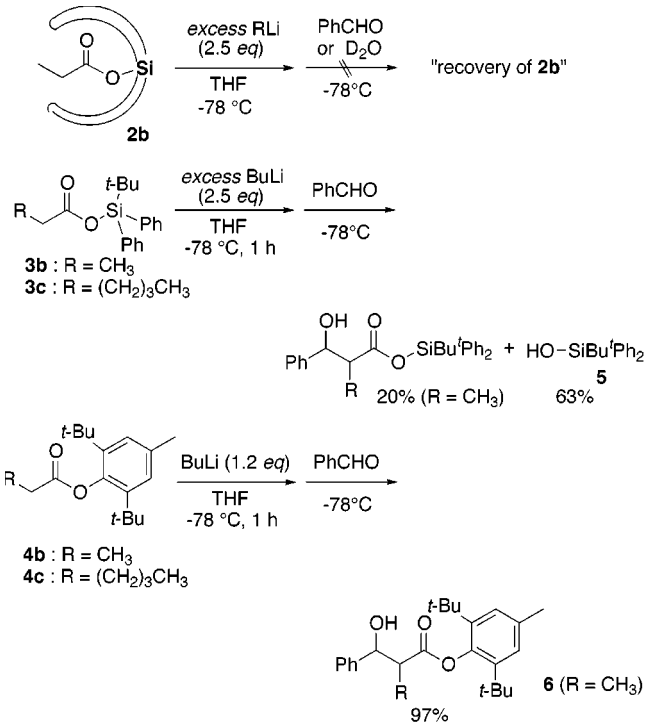
Scheme 1[a]



[a] Conditions: (a) catalytic $NiCl_2$(dppe) (5 mol %), PhMgBr; (b) catalytic $(PhCO_2)_2$ (5 mol %), NBS; (c) Mg, $HSiCl_3$; (d) Br_2.

α-deprotonation with RLi to furnish an aldol product upon reaction with benzaldehyde.[15]



The high shielding effect of the bowl-shaped TDS moiety toward carboxyl and even α-protons was also verified by carrying out a ^{1}H NMR spectral study of TDS caproate **2c** in $CDCl_3$, where the upfield shift of pentyl protons in **2c** compared to other caproyl analogues, **3c** and **4c**, is clearly observed.

$$XO_2C\text{-}\overset{\alpha}{C}H_2\text{-}\overset{\beta}{C}H_2\text{-}\overset{\gamma}{C}H_2\text{-}\overset{\delta}{C}H_2\text{-}\overset{\varepsilon}{C}H_3$$

^{1}H NMR Data	α-H	β-H	γ-H	δ-H	ε-H
2c	δ 1.60	δ 0.85	δ 0.85	δ 1.10	δ 0.75
3c	δ 2.40	δ 1.68	δ 1.35	δ 1.35	δ 0.89
4c	δ 2.60	δ 1.70	δ 1.35	δ 1.35	δ 0.92

Based on the X-ray data, a space-filling model of the TDS acetate **2a** is depicted in Figure 2, suggesting the existence of an appropriate molecular pocket around acetyl protons as well as carboxyl moiety for shielding against nucleophilic attack and α-deprotonation. This inference is in accord with the ^{1}H NMR data on the upfield shift of ester protons in TDS caproate **2c**.

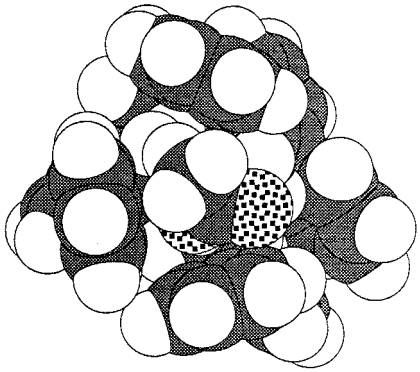
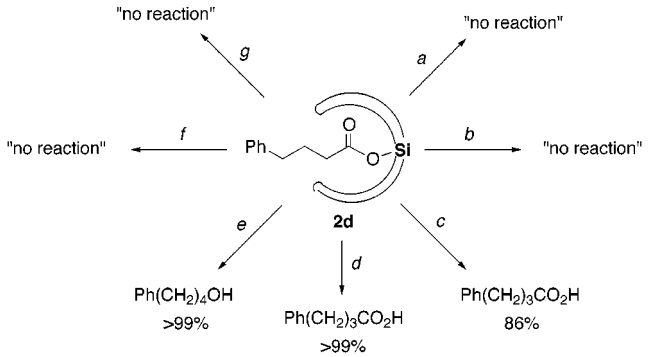


Figure 2. Space-filling model of the TDS acetate **2a**.

Scheme 2[a]



[a] Conditions: (a) AcOH/THF/H_2O (4:2:1), 40 °C, 4 h; (b) $LiAlH_4$ (3 equiv)/THF, 0 °C, 0.5 h and 25 °C, 5 h; (c) KOBu^t (10 equiv)/DMSO, 25 °C, 1 h; (d) Py·HF/THF (1:2), 50 °C, 5 h; (e) DIBAH (5 equiv), toluene, 0 °C, 0.5 h; (f) 1 N HCl/THF (1:10), 40 °C, 4 h; (g) aqueous NaOH/EtOH/THF (1:1:2), 50 °C, 5 h.

The functional group susceptibility of the TDS esters **2** for various acidic and basic conditions is summarized in Scheme 2. Under certain deprotection conditions, the TDS esters **2** can be conveniently cleaved to the corresponding carboxylic acids **1** and alcohols, as exemplified by conversion of TDS ester **2d** to acid **1** (R = $(CH_2)_3$Ph) with KOBu^t in DMSO (or Py·HF in THF)[16] and $Ph(CH_2)_4OH$ with DIBAH in CH_2Cl_2.[1]

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Supporting Information Available: Representative experimental procedure as well as spectroscopic characterization of all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Reaction of 2,6-di-*tert*-butyl-4-methylphenyl propionate (**4b**) with BuLi (1.2−2.5 equiv) in THF at −78 °C for 1 h and quenching with D_2O at this temperature gave 2,6-di-*tert*-butyl-4-methylphenyl α-deuteriopropionate in 98% yield.
(15) For example, reaction of TDS acetate **2a** in THF with BuLi (1.5 equiv) in hexane at −78 °C for 2 h and subsequent treatment with PhCHO (1.5 equiv) at −78 °C for 30 min gave aldol product in 48% yield with 46% recovery of **2a**.
(16) Tris(2,6-diphenylbenzyl)silyl fluoride (TDS-F) was also isolated in 99% yield.