Aluminium Triflate [Al(OTf)₃] as a Recyclable Catalyst for the Conversion of α-Hydroxyphosphonates, Alcohols and Phenols to Their Corresponding O-Silylated Products with Hexamethyldisilazane (HMDS)

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Abstract: Al(OTf)₃, as a recyclable catalyst conducts the efficient conversion of various types of α-hydroxyphosphonates to their corresponding α-trimethylsilyloxyphosphonates with HMDS catalyzed by iodine, Cu(OTf)₂ and Mg(OTf)₂. α-Trimethylsilyloxyphosphonates are attractive compounds from different views. They are potential synthons of masked acyl anions which react with various ketones to produce the corresponding α-hydroxyketones. Unsymmetrical ketones can be also produced by the reaction of α-lithiated α-trimethylsilyloxyphosphonates with alkylating agents. α-Lithiated α-trimethylsilyloxyphosphonates can undergo acylation with a variety of acylating agents to produce the corresponding α-acylated products. These compounds in turn, can be easily transformed to α-hydroxyketones by the cleavage of Si-O bond and elimination of dialkyl phosphate in alkaline media.

The common methods for the preparation of α-trimethylsilyloxyphosphonates include reaction of aldehydes with either diethyl trimethylsilyloxyphosphate or the mixture of triethylphosphite and trimethylsilyl chloride. These protocols need harsh reaction conditions and long reaction times. The other method includes the reaction of trialkyl phosphate with silyl phenyl ketone, which requires a long reaction time (12 h) and also proceeds at a rather high temperature (80 °C). Procedures for the preparation of α-trimethylsilyloxyphosphonates by direct silylation of α-hydroxyphosphonates are limited to only a few reports.

Except in our reported methods in which HMDS has been used as a silylating agent at room temperature, in the only other available method, hexamethylsilathiane has been used as a silylating agent at 50–70 °C.9 We now report Al(OTf)₃ as a reusable, efficient and easy to handle catalyst for the high yielding preparation of diethyl α-trimethylsilyloxyphosphonates 2a–o by direct reaction of diethyl α-hydroxyphosphonates 1a–o with HMDS at room temperature using neat conditions (Scheme 1, Table 1).

In conjunction with our interest in the development of synthetic methods for the preparation of phosphonate derivatives from α-hydroxyphosphonates, we have focused our attention to the preparation of α-trimethylsilyloxyphosphonates with HMDS catalyzed by Al(OTf)₃. In order to show the advantage and limitation of Al(OTf)₃, we have compared the catalytic activity of this catalyst with LiOTf, Ce(OTf)₄, Hg(OTf)₂ and Cu(OTf)₂.
Mg(OTf)₂,¹⁹ and Lewis acids such as AlCl₃, ZnCl₂,²⁰a Zn(bipy)_₃Cl₂,²⁰b FeCl₃, Fe(bipy)Cl₃,²⁰b CuCl₂, MgCl₂, and ZrOCl₂·8H₂O for the silylation of 1a as a model compound, with HMDS in the absence of solvent at room temperature in our laboratory. We found that Al(OTf)₃ was the most effective catalyst and is comparable with Mg(OTf)₂ among the other catalysts we have studied for this purpose (Table 2).

In the reactions we have studied, fast evolution of NH₃ was observed. We were also able to recover Al(OTf)₃ and reuse it without loss of its catalytic activity. Therefore, we have proposed a mechanism in which the generation of NH₃ and the catalytic role of Al(OTf)₃ in a catalytic cycle are clarified (Scheme 2).

In this mechanism, we have suggested that a Lewis acid-base interaction between metal triflate and nitrogen in HMDS polarizes N–Si bond of HMDS to produce a reactive silylating agent, 3. Both Mg²⁺ and Al³⁺ that are harder Lewis acids in comparison with Li⁺, Cu²⁺, Ce⁴⁺, and Hg²⁺ interact more strongly with the nitrogen atom as a hard Lewis base in HMDS. Therefore, N–Si bond polarization effected by Mg(OTf)₂ and Al(OTf)₃ is more pronounced (Table 2) than those generated by LiOTf, Cu(OTf)₂, Ce(OTf)₃, and Hg(OTf)₂. This qualitative explanation justifies the higher activity of Mg(OTf)₂ and Al(OTf)₃ than the other triflates we have studied.

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Treatment of several of alcohols with HMDS and the catalyst in the absence of solvent at room temperature produces the corresponding trimethylsilyl ethers in excellent yields (Table 3). Substituted benzylic alcohols containing electron-donating and electron-withdrawing groups, primary and allylic alcohols are also protected efficiently in short reaction times in high yields (Table 3, entries 1–14). Silylation of secondary and tertiary aliphatic alcohols requires longer reaction times under similar reaction conditions (Table 3, entries 16–23). We have also tried silylation of cholesterol under solvent-free conditions in the presence of this catalyst with HMDS. Our observation shows that this compound does not undergo silylation under such conditions and the starting material was isolated intact after 24 hours. However, we tried this reaction at room temperature in solution using CH2Cl2. The reaction proceeded well and the desired compound was isolated in 97% yield after 80 minutes (Table 3, entry 15). Silylation of phenolic hydroxyl group also proceeded smoothly by this method. Our studies show that p-cresol is silylated faster and in a higher yield than phenol and p-chlorophenol (Table 3, entries 24–26). Silylation of thiols and amines by this protocol failed; the starting materials were isolated from the mixture after 48 hours (Table 3, entries 27–29).

In conclusion, Al(OTf)3 is a mild and efficient catalyst for the preparation of varieties of diethyl α-trimethylsilyloxyphosphonates by direct silylation of diethyl α-hydroxyphosphonates with HMDS. Cleavages of C–P or Si–O bonds are not observed in the process of the reactions. High yields, solvent-free, mild reaction conditions, short reaction times, reusability of the catalyst and easy work-up are the strong points of the protocol for the preparation of α-trimethylsilyloxyphosphonate compounds. The protocol is applicable to the efficient silylation of alcohols and phenols in high yields.

Chemicals were purchased from Merck and Fluka. The products were characterized by comparison of their physical data with those of known samples or by their spectral data. IR spectra were run on a Shimadzu model 8300 FT-IR spectrophotometer. NMR spectra were recorded on a Bruker Avance DPX-250 spectrometer at 250 MHz for 1H NMR and at 62.5 MHz for 13C NMR. Mass spectra were recorded on a Shimadzu GCMS-QP 1000 EX spectrometer. The purity of the products and the progress of the reactions were accomplished by TLC on silica gel polygram SILG/UV254 plates.

**Preparation of Diethyl α-Trimethylsilyloxyphosphonates (2); General Procedure**

Al(OTf)3 (0.05 mmol, 0.024 g) was added to a stirring mixture of 1 (1 mmol, 0.218–0.342 g) and HMDS (0.7 mmol, 0.113 g) at r.t. The reaction progress was monitored by TLC. After completion of the reaction, Et2O (10 mL) was added to the reaction mixture, which

### Table 3  Silylation of Alcohols and Phenols with HMDS in the Presence of Al(OTf)3 at Room Temperature

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Time (min)</th>
<th>Yielda (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C6H5CH2OH</td>
<td>–e</td>
<td>95b</td>
</tr>
<tr>
<td>2</td>
<td>4-CH3C6H5CH2OH</td>
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<td>93b</td>
</tr>
<tr>
<td>3</td>
<td>4-CH2OC6H5CH2OH</td>
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<tr>
<td>4</td>
<td>4-CIC6H5CH2OH</td>
<td>–e</td>
<td>90b</td>
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<tr>
<td>5</td>
<td>2-O2NC6H5CH2OH</td>
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<td>90b</td>
</tr>
<tr>
<td>6</td>
<td>PhCH(CH3)OH</td>
<td>–e</td>
<td>92b</td>
</tr>
<tr>
<td>7</td>
<td>Anthracene-9-methanol</td>
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<td>95b</td>
</tr>
<tr>
<td>8</td>
<td>(Ph)2CHOH</td>
<td>–e</td>
<td>95b</td>
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<tr>
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<td>CH2=CHCH2OH</td>
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<td>95b</td>
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<tr>
<td>10</td>
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<td>90b</td>
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<tr>
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<td>C6H5NH2</td>
<td>48 h</td>
<td>–f</td>
</tr>
<tr>
<td>29</td>
<td>Cyclohexyl amine</td>
<td>48 h</td>
<td>–f</td>
</tr>
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</table>

a Yields of isolated products.
b The molar ratio of substrate–HMDS–Al(OTf)3 was 1:0.5:0.01.
c The molar ratio of substrate–HMDS–Al(OTf)3 was 1:0.7:0.01.
d CH2Cl2 was used as solvent.
e Immediate reaction occurred.
f Reaction did not occur.
was then washed with H₂O (3 × 10 mL). The aqueous layer was separated and evaporated under reduced pressure to afford the catalyst. The organic layer was dried over anhyd Na₂SO₄. After evaporation of the solvent, the pure product (2) was isolated without requiring further purification in 90–97% yields (Table 1).

**Trimethylsilylation of Alcohols and Phenols with HMDS Using Al(OTf)₃ in Neat Conditions; General Procedure**

Al(OTf)₃ (0.01 mmol, 0.005 g) was added to a stirring mixture of alcohol or phenol (1 mmol) and HMDS (0.5–0.7 mmol, 0.08–0.113 g) at rt. The reaction progress was monitored by TLC or GC. After completion of the reaction, Et₂O (10 mL) was added to this reaction mixture, which was then washed with H₂O (3 × 10 mL). The aqueous layer was separated and evaporated under reduced pressure to afford the catalyst. The organic layer was dried over anhyd Na₂SO₄. After evaporation of the solvent, almost pure trimethylsilyl ether was obtained. Pure product was obtained by column chromatography in 70–97% yields (Table 2).

### Spectral Data and the Elemental Analysis of Unknown Diethyl α-Trimethylsilyloxyphosphonates

#### Diethyl α-Trimethylsilyloxy-2,4,6-trimethylbenzylphosphonate (2d)

**IR (neat):** OH Peak was absent.

**¹H NMR (CDCl₃):** δ = 0.04 [s, 9 H, Si(CH₃)₃], 1.02 (t, JₜHM = 7 Hz, 3 H, 2-CH₃(CH₂)₃), 1.22 (t, JₜHM = 7 Hz, 3 H, 2-CH₂(CH₂)₃), 2.12 (s, 3 H, CH₃), 2.25 (s, 3 H, CH₂), 2.51 (s, 3 H, CH₃), 3.58–3.68 (m, 1 H, 2-CH₂(OH)), 3.81–3.90 (m, 1 H, 2-OC₃H₃), 3.91–3.99 (m, 4 H, 2-OC₂H₃), 4.83 (d, JₜPH = 18.3 Hz, 1 H, CH), 6.66 (s, 1 H, C₆H₃), 6.72 (s, 1 H, C₆H₃).

**¹³C NMR (CDCl₃):** δ = 15.90 (C₆H₃), 21.16, 21.67, 21.69 (CH₃), 26.70 (JₚC = 7 Hz, 1 H, 2-CH₂(OH)), 62.70 (JₚC = 5.9 Hz, 2-CH₂(CH₂)₃), 62.92 (JₚC = 7.1 Hz, 2-CH₂(CH₂)₃), 69.06 (JₚC = 177 Hz, C₂H₄), 129.05 (JₚC = 2 Hz, C₆H₃), 130.25 (C₂H₄), 131.57 (JₚC = 3.3 Hz, C₆H₃), 136.08 (JₚC = 8.1 Hz, C₆H₃), 137.41 (JₚC = 3.4 Hz, C₆H₃), 139.88 (JₚC = 4.2 Hz, C₆H₃).

**MS (70 eV):** m/z (%) = 439 (2.4) [247 + Si(CH₃)₃], 389 (93.5) [Si(CH₃)₃], 173 (2.4) [247 – Si(CH₃)₃], 73 (93.5) [Si(CH₃)₃].

**Anal. Calcd for C₁₇H₃₁O₄PSi: C, 56.98; H, 8.66. Found: C, 56.90; H, 8.70.**

#### Diethyl α-Trimethylsilyloxy-2,6-dichlorobenzylphosphonate (2h)

**IR (neat):** OH Peak was absent.

**¹H NMR (CDCl₃):** δ = 0.00 [s, 9 H, Si(CH₃)₃], 1.07–1.24 (m, 6 H, 2-OCH₂(CH₂)₃), 3.89–4.15 (m, 4 H, 2-OCH₂CH₂), 5.81 (d, JₜPH = 19.3 Hz, 1 H, CH), 7.03–7.10 (m, 1 H, C₆H₃), 7.26–7.25 (m, 1 H, C₆H₃).

**¹³C NMR (CDCl₃):** δ = 0.00 [Si(CH₃)₃], 16.86 (d, JₚC = 6.8 Hz, 2-OCH₂CH₂), 16.96 (d, JₚC = 6.8 Hz, 2-OCH₂CH₂), 63.35 (d, JₚC = 7.1 Hz, 2-OCH₂CH₂), 63.60 (d, JₚC = 7.1 Hz, 2-OCH₂CH₂), 70.02 (d, JₚC = 179.8 Hz, CH), 128.60 (JₚC = 2.0 Hz, C₂H₄), 129.99 (d, JₚC = 2.9 Hz, C₆H₃), 131.31 (d, JₚC = 2.8 Hz, C₆H₃), 135.73 (d, JₚC = 8.2 Hz, C₆H₃), 136.87 (d, JₚC = 4.9 Hz, C₂H₄).

**MS (70 eV):** m/z (%) = 457 (100) [M + Si(CH₃)₃], 389 (2.3) [M + 4], 387 (10.8) [M + 2], 385 (14.9) [M⁺], 247 (52.2) [M – P(O)(OEt)₂], 173 (2.4) [247 – Si(CH₃)₃], 73 (93.5) [Si(CH₃)₃].

**Anal. Calcd for C₁₄H₂₃Cl₂O₃PSi: C, 43.64; H, 5.97. Found: C, 43.60; H, 5.91.**

#### Diethyl α-Trimethylsilyloxy-2-naphthylphosphonate (2l)

**IR (neat):** OH Peak was absent.

**¹H NMR (CDCl₃):** δ = 0.00 [s, 9 H, Si(CH₃)₃], 1.09–1.17 (m, 6 H, 2-OCH₂CH₂), 3.90–4.01 (m, 4 H, 2-OCH₂CH₂), 4.83 (d, JₜPH = 14.5 Hz, 1 H, CH), 7.14–7.41 (m, 4 H, C₂H₄).
13C NMR (CDCl3): δ = 0.47 [Si(CH3)3], 16.44–16.59 (2-OCH2CH3), 62.94–63.50 (2-CH2CH3), 71.43 (d, JCH = 171.16 Hz, CH), 124.47–139.73 (C6H4).

Diethyl α-Trimethylsilylxylo-2-nitrobenzylphosphonate (2i)
IR (neat): OH Peak was absent.

1H NMR (CDCl3): δ = 0.00 [s, 9 H, Si(CH3)3], 1.01–1.11 (m, 6 H, 2-OCH2CH3), 3.83–3.97 (m, 4 H, 2-OCH2CH3), 6.02 (d, JHH = 15.9 Hz, 1 H, CH), 7.28 (t, JHH = 7.3 Hz, 1 H, C6H4), 7.41 (t, JHH = 7.4 Hz, 1 H, C6H4), 8.01 (d, JHH = 7.9 Hz, 1 H, C6H4), 7.72–7.80 (m, 2 H, CH).

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References