

COMMUNICATION

Practical Method for Hydroxyl-Group Protection Using Strontium Metal and Readily Available Silyl Chlorides

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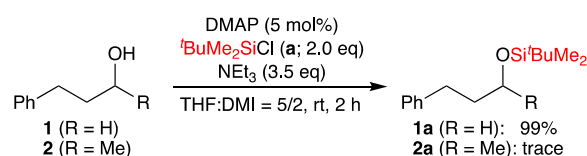
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We have found that the etherification of silyl-protected secondary alcohols proceeds smoothly in the presence of strontium metal using silyl chloride instead of the expensive, yet more reactive, and commonly used silyl triflate. The reaction occurred almost completely with various alcohols.

In organic synthesis, if a chemical reaction is targeted toward a specific functional group in a compound bearing multiple functional groups, the synthesis of the target compound is difficult if a more active functional group is present. In this case, a molecular transformation reaction, known as "protection," is often used to temporarily render the highly reactive functional group inactive.¹ If the protecting groups are not present in the final product, a deprotection step is necessary at a certain point in the synthesis, thus resulting in a multi-step reaction. Despite this disadvantage, protecting groups are still widely used.

Among the different functional groups, protection of the hydroxyl group of alcohols is extremely important, and several protecting groups have been developed. Among these groups, silyl ethers, with a general structure of OSiR₃, are widely used because variations in the R group lead to significant differences in the stability of the protecting group.² The most common method for alcohol protection with silyl ethers is via substitution reactions in the presence of a base.^{1a-c,2f} However, since the reaction mechanism involves a reactive five-coordinate intermediate, the alcohol bulkiness and the type of silyl ether significantly influence the reactivity.

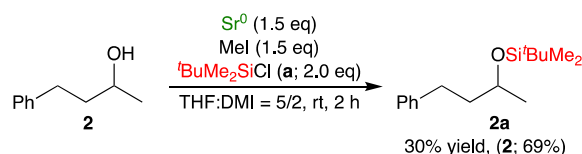
In fact, when *tert*-butyldimethylsilyl chloride³ (TBSCl) **a** was used as a silylating agent to protect the primary alcohol 3-phenylpropanol **1** in the presence of the commonly used triethylamine with DMAP as a catalyst,⁴ the reaction proceeded with 99% yield within 2 h. However, the protection of the



Scheme 1 Limitations of the reaction with silyl chloride under general conditions.

secondary alcohol 4-phenyl-2-butanol **2** under the same conditions resulted in trace amounts of the product (Scheme 1). Owing to the low reactivity of TBSCl, *tert*-butyldimethylsilyl triflate is commonly used for the protection of secondary alcohols,⁵ because it has a higher leaving ability as compared to TBSCl. However, silyl triflates are considerably more expensive than silyl chlorides. In addition, if a small amount of water is present in the reaction system, it may react with silyl triflate, resulting in triflic acid, a strong acid, which may adversely affect the compound. There is a reported case of alcohol protection using TBSCl with DMSO as an activator, however, only five out of 13 cases of mainly primary alcohols achieved yields of over 90%, which is not considered sufficient from the point of view of 'protection'.⁶

Our group has been investigating synthetic reactions using organostrontium compounds⁷ as organometallic compounds of alkaline-earth elements. Only a few studies have reported the preparation and reactivity of organostrontium compounds.⁸⁻¹¹ Our group has already reported the smooth alkylation of aldehydes¹² or imines¹³ and the dialkylation of an ester¹⁴ using metallic Sr and alkyl iodide under mild conditions.¹⁵ The electronegativity of Sr is close to that of Li and Mg (Li = 0.98, Mg = 1.31, Sr = 0.95 on the Pauling scale, respectively),¹⁶ but Sr has a larger ionic radius (Li⁺ = 76, Mg²⁺ = 72, Sr²⁺ = 118 in pm,



Scheme 2 Initial attempt for silylation of alcohol in the presence of strontium metal.

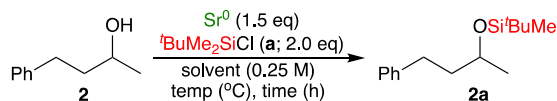
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Table 1 Optimization of reaction conditions



| Entry | solvent | Temp (°C) | Time (h) | 2a (%) | Recovered 2 (%) |
|-----------------|---------|-----------|----------|--------|-----------------|
| 1 ^a | THF | 30 | 2 | 4 | 96 |
| 2 ^a | DMI | 30 | 2 | 21 | 79 |
| 3 ^a | DMF | 30 | 2 | 80 | 20 |
| 4 ^a | DMA | 30 | 2 | 84 | 15 |
| 5 | DMF | 30 | 2 | 72 | 26 |
| 6 | DMA | 30 | 2 | 86 | 12 |
| 7 ^b | DMA | 30 | 2 | 84 | 16 |
| 8 ^b | DMA | 30 | 6 | 86 | 13 |
| 9 ^b | DMA | 30 | 12 | 90 | 10 |
| 10 ^b | DMA | 30 | 24 | quant | - |
| 11 ^b | DMA | 50 | 8 | quant | - |
| 12 ^b | DMA | 70 | 5 | quant | - |
| 13 ^b | DMA | 90 | 2 | quant | - |

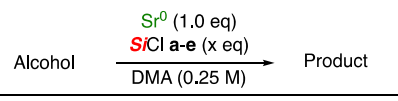
^a with 1.5 eq of MeI. ^b 1.0 eq of Sr⁰ was used. DMI: 1,3-dimethyl-2-imidazolidinone, DMF: *N,N*-dimethylformamide, DMA: *N,N*-dimethylacetamide.

respectively).¹⁷ The reaction of Sr metal with alcohols results in strontium alkoxide, where the bond distance between Sr and O is large, with an increase in the partial negative charge of oxygen. This renders oxygen atoms more electronegative, which can easily react with electrophiles with low leaving ability. When TBSCl was applied in the presence of Sr, the reaction proceeded even within 2 h (Scheme 2). Therefore, an additional experiment was conducted to develop a protective group for alcohols using inexpensive chlorosilanes.

First, the choice of solvent was investigated at a temperature of 30 °C and a reaction time of 2 h (Table 1). The results showed that the more polar solvents resulted in better yields (entries 1-4). Surprisingly, when DMF or DMA was chosen as a solvent, methyl iodide did not necessarily generate methyl strontium iodide (entries 3-6).¹⁵ A slight decrease in the yield was observed when DMF was used as the solvent (entry 5); however, a decrease in the yield was not observed with DMA (entry 6). Furthermore, the reduction in the amount of Sr metal from 1.5 equivalents to 1.0 equivalents did not decrease the yield (entry 7). Thin-layer chromatography (TLC) results showed that the reaction was almost complete even within 2 h, with 16% of the starting material being recovered after quenching the reaction system; therefore, the reaction time was investigated (entries 7-10). As the reaction time was extended, the target product was obtained in a higher yield. After 24 h, a quantitative yield was obtained (entry 10). When the reaction temperature was increased to 90 °C, the reaction time could be shortened to a minimum of 2 h to complete the target silyl etherification reaction without any side reactions (entries 11-13). Therefore, depending on the thermal stability of the starting material itself, silyl etherification can be carried out efficiently.

Based on the results obtained for the silyl etherification of alcohol **2**, various types of alcohols were studied (Table 2). The desired silyl etherification proceeded smoothly with both a primary alcohol **1** and secondary alcohols, such as cyclohexanol,

Table 2 Substrate scope



| Entry | Product ^a | Conditions: x (eq), Temp (°C), Time | Yield (%) |
|-------|----------------------|--|---|
| 1 | | 1a 2.0, 30, 24 h | quant |
| 2 | | 2a 2.0, 30, 24 h (Table 1, entry 10) | quant |
| 3 | | 3a 2.0, 30, 24 h | 99 |
| 4 | | 4a 2.0, 30, 24 h | 99 |
| 5 | | 5a 2.0, 30, 24 h | 98 (2) ^b |
| 6 | | 6a 2.0, 30, 24 h | 75 (21) ^b |
| 7 | | 6a 2.0, 30, 48 h | 94 (5) ^b |
| 8 | | 6a 2.0, 50, 24 h | 97 (3) ^b |
| 9 | | 7a 2.0, 30, 24 h | quant |
| 10 | | 2b 2.0, 30, 24 h | 75 (21) ^b |
| 11 | | 2b 2.0, 50, 24 h | quant |
| 12 | | 2b 2.0, 90, 6 h | 99 |
| 13 | | 2c 2.0, 30, 24 h | 56 (43) ^b |
| 14 | | 2c 2.0, 90, 24 h | 96 (4) ^b |
| 15 | | 2c 4.0, 30, 72 h | 94 (5) ^b |
| 16 | | 2c 4.0, 50, 24 h | quant |
| 17 | | 2d 2.0, 30, 24 h | 14 (86) ^b |
| 18 | | 2d 4.0, 30, 72 h | 49 (51) ^b |
| 19 | | 2d 4.0, 50, 96 h | 94 (6) ^b |
| 20 | | 2d 4.0, 90, 48 h | 99 |
| 21 | | 2e 2.0, 30, 24 h | 19 (77) ^b |
| 22 | | 2e 5.0, 50, 96 h | 93 |
| 23 | | 2e 5.0, 90, 48 h | 97 |
| 24 | | 8a 4.0 ^c , 30, 24 h | 98 |
| 25 | | 9a 12.0 ^d , 30, 24 h | 81 |
| 26 | | 9a 8.0 ^e , 30, 72 h | 95 |
| 27 | | 9a 8.0 ^e , 50, 48 h | 97 |
| 28 | | 10a 8.0 ^e , 30, 24 h | 64 (10a) + 28(12a+13a) ^f |
| 29 | | 10a 8.0 ^e , 50, 48 h | 65 (10a) + 7 (11a) + 25(12a+13a) ^g |
| 30 | | 10a 8.0 ^e + 4.0, 50, 48 h + 24 h | 78 (10a) + 7 (11a) + 11(12a+13a) ^h |

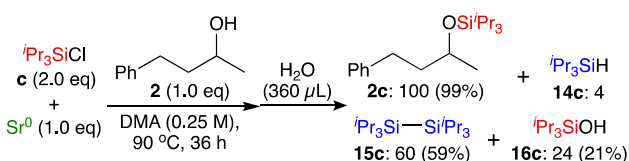
^aTBS: *tert*-Butyldimethylsilyl ^bIn the parentheses, the isolated yield of the recovered alcohols ^c Sr (2.0 eq) ^d Sr (6.0 eq) ^e Sr (4.0 eq) ^f12a/13a=42:58 ^g12a/13a=81:19 ^h12a/13a=55:45

2-cyclohexenol, and 2-indanol (entries 1-5). A slight decrease in reactivity was observed when 2,4,6-trimethyl phenol was used as the starting material (entry 6), although it was found that the yield could be improved by increasing either the reaction time

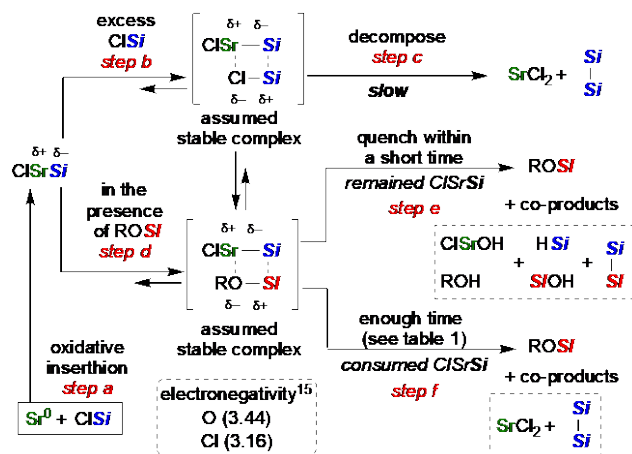
(entry 7) or the reaction temperature (entry 8). Phenethyl alcohol, a secondary benzyl alcohol, also resulted in silyl ethers under moderate conditions (entry 9). On the other hand, the reactivity decreased drastically with bulkier silyl chlorides. However, the desired silyl ethers were obtained in good yields by extending the reaction time, increasing the reaction temperature as described above, and using an excess of silyl chloride (entries 10–24). A characteristic feature of the method developed in this study is that side reactions did not occur, although relatively long reaction times were required. Therefore, even if the desired silyl ether was not obtained in good yield, the unreacted alcohol could be recovered. On the other hand, when 1,2:5,6-Di-*O*-cylcohexylidene-*D*-mannitol was used as a substrate, only one alcohol was silyl-protected, even with excess silyl chloride (entry 24). This result may be due to the sharp sensitivity to the steric environment of the alcohols. Therefore, using unprotected *D*-mannitol as a substrate, only the 1,2,5,6-protected form was successfully synthesised in high yield, as expected (entries 25–27). For methyl α -*D*-glucopyranoside, mixtures of several products were observed at 30 °C; however, only the 2,3,6- form was obtained as a tri-protected compound (entry 28). When the reaction temperature is increased to 50 °C, the disilyl compound is still present and the 2,4,6-form is also appeared as a by-product, although further reactions with additional **a** can bring the disilyl compound to the trisilyl compound (entries 29–30).

The reaction mechanism according to previous studies is that strontium alkoxide is formed from Sr metal and alcohol reaction with silyl chloride. However, this reaction mechanism alone cannot explain the two unusual phenomena observed in entries 7–10 of Table 1: i) the reaction was complete on the TLC; however, when the reaction was quenched, the starting material was recovered, and ii) the ratio of the recovered material gradually decreased upon increasing the reaction time. We therefore carried out further investigations into the reaction mechanism.¹⁸

The reaction was not complete under the conditions listed in Table 2, entry 14 (2.0 eq **2c**, 90 °C, 24 h); however, the reaction proceeded completely when the reaction time was extended to 36 h, and **2c** was obtained quantitatively. Based on the above conditions, upon stirring Sr metal with **c** in DMA at 90 °C, gradual salt formation was observed. After 36 h of stirring, alcohol **2** was added to the mixture and reacted for another 36 h; however, the silyl etherification reaction hardly proceeded, and the starting material was recovered quantitatively. Moreover, the addition of 2 eq (200 mol%) of **c** to 1 eq of Sr metal in the absence of alcohol **2** resulted in their conversion mostly to disilane **15c** (180 mol%) and the rest to silanol **16c** (10 mol%).¹⁸ Hence, the reaction proceeded only when Sr metal was

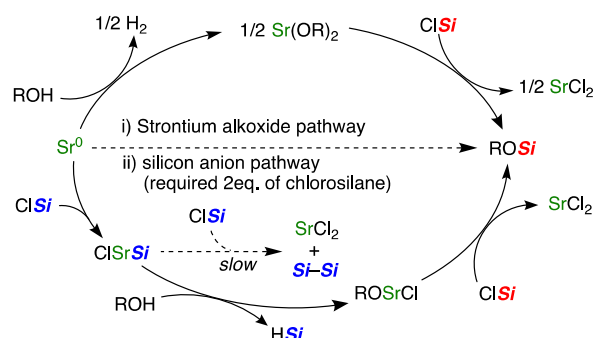


Scheme 3 The ratio of the reaction mixture after quench analyzed by $^1\text{H-NMR}$ (isolated yield, in the parentheses)



present with **c**, which became an inactive compound without silyl etherification ability. On the other hand, the reaction of alcohol **2**, **c**, and Sr metal was carried out at 90 °C for 36 h. Water was then added until the salt was dissolved, the reaction system was directly analyzed by $^1\text{H-NMR}$, showing the production of **2c** (100), **14c** (4), **15c** (60), and **16c** (24). Then, **2c** (99%), **15c** (59%), and **16c** (21%) were isolated by careful purification of therecovered crude compounds (Scheme 3).

It is widely known that when chlorosilane is mixed with alkali metals, such as Li¹⁹ or Na,²⁰ these metals act as reducing agents, thus producing disilane. Disilane can be also synthesized using metallic Sm,²¹ a low-valent Ti reagent prepared from TiCl_4 with metallic Zn,²² and metallic Mg.²³ Furthermore, an example of a metal exchange reaction between chlorosilane and Grignard reagent to generate silyl magnesium species has been reported.²⁴ Therefore, it is strongly expected that the corresponding silyl strontium chloride can be generated by the oxidative insertion of Sr metal into chlorosilane (Scheme 4; step a). Based on the electronegativity of each element, the charge distribution in the Si-Sr bonds suggests that the Si atom is more electronegative. In this situation, if chlorosilane is present in excess, it can form a relatively stable oligomeric complex with silyl strontium chloride at a ratio of 1:1 to electrostatic interactions (step b). The complex can also undergo an irreversible disilane formation reaction to resolve charge separation (step c). Similarly, silyl strontium chloride can form a one-to-one oligomeric complex in the presence of silyl ether, the target of this reaction (step d). The fact that the silyl ether



compound was obtained quantitatively suggests that the intermolecular bonds in this complex are not easily broken. However, the silicon-oxygen bond of the silyl ether is weakened by the coordination of silyl strontium chloride, and some of them may be broken by the quenching step (step e). With an increase in reaction time, silyl strontium chloride, which formed a strong complex with the target material, gradually reacted with the excess chlorosilane present in the reaction system to form disilane, which is finally consumed into an amount that does not affect the quench operation (step f). The lack of rapid formation of disilanes in the presence of excess chlorosilane and the scale of electronegativity suggest that strontium is more strongly coordinated to the oxygen atom in equilibrium between the two oligomers.

Two possible competing reaction mechanisms are shown in Scheme 5: i) is the initially assumed reaction mechanism, and ii) is the reaction mechanism suggested by the results of disilane formation. Because there is almost no generation of silane **8**, reaction mechanism i) appears to be the main route according to the experimental conditions of this study.

In conclusion, we have found that the etherification of silyl-protected secondary alcohols, which is difficult with silyl chlorides, proceeds smoothly with Sr metal. The reaction is extremely clean and proceeds without by-products on various alcohols. Although the duration of the reaction is long, the results suggest that this is due to the involvement of silyl strontium chloride in the reaction pathway. The reaction time could be also reduced by increasing the reaction temperature.

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Conflicts of interest

There are no conflicts to declare.

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