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Amine-free silylation of alcohols under 4-methylpyridine *N*-oxide-catalyzed conditions

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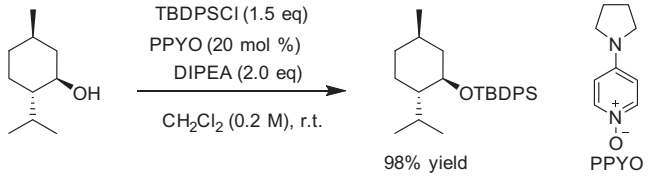
ABSTRACT

Amine-free silylation of various alcohols catalyzed by 4-methylpyridine *N*-oxide in the presence of MS4A at room temperature was developed. This simple method gave various silyl ethers in a high yield.

The silyl group is one of the most useful protecting groups in organic synthesis and various methods have been reported for the triethylsilyl (TES), *t*-butyldimethylsilyl (TBS), *t*-butyldiphenylsilyl (TBDPS), and triisopropylsilyl (TIPS) etherification of alcohols. Generally, silyl groups can be introduced to various alcohols in good yield by treating the parent alcohols with a silyl halide and an amine (imidazole or tertiary amine such as NEt_3, DIPEA) to trap the strong acid that is generated.[1] The combination of silyl triflate and 2,6-lutidine is often chosen for secondary or bulky alcohols.[2] Moreover, a number of conditions for various purposes, such as regio- or chemoselective silylation, have been explored with various combinations of reagents, catalysts, bases, and solvents.[3] These are simple, effective methods for silyl etherification. However, silyl etherification often requires the addition of more than equivalent of the amine with respect to the silyl reagent and substrate. Low molecular weight amines, such as triethylamine, are toxic and irritating to the eyes, nose, and skin, although the amines play a significant role for silyl etherification. Therefore, safer conditions for alcohol silylation are required. Recently, we reported that the combination of TBDPSCl, DIPEA, and pyrrolidinopyridine *N*-oxide (PPYO) catalyst silylates various secondary alcohols (Scheme 1),[4] and that pyridine *N*-oxide has excellent catalytic activity. Herein, we focused on molecular sieves (MS) as an alternative to amines in combination with the pyridine *N*-oxide catalyst. Molecular sieves have a three-dimensional interconnecting network of silica and alumina tetrahedra and absorb molecules of a specific size after water is removed from this network.[5] Thus, MS are widely used as water scavengers to dry organic solvents and reagents in organic synthesis. Some reactions using MS as an acidic or basic reagent have been reported. For instance, acetylation,[6] deacetylation,[7] and polycyclization[8] using MS3A or 4A have been developed, and MS5A-mediated acetal protection also has been reported.[9] However, to our knowledge, catalytic silylation using MS4A as an alternative to amines has not yet been reported. Herein, we describe the amine-free silylation of primary and secondary alcohols using 4-methylpyridine *N*-oxide and MS4A.



Scheme 1. Catalytic silylation of secondary alcohol by PPYO.

We chose 2-(3,4-dimethoxyphenyl)ethanol (**1**) as a standard substrate for catalyst screening (Table 1). Treatment of **1** with 2 equiv TBDPSCl and 500 wt % activated MS4A powder[10] in CH_2Cl_2 at room temperature for 1 h did not produce silylated product **2** (entry 1). These results show that the conditions using MS4A alone are ineffective. When 30 mol % imidazole was used as the catalyst, only a small amount of TBDPS ether **2** was obtained (entry 2). Dimethylaminopyridine (DMAP)-catalyzed conditions gave **2** in moderate yield (entry 3). In contrast, using pyridine *N*-oxide

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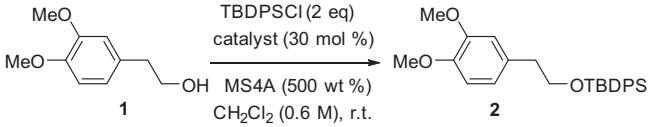
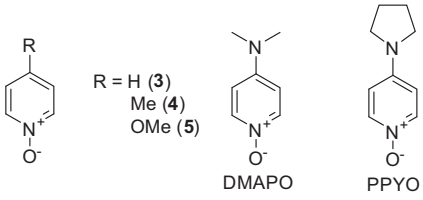
Table 1
Catalyst screening for TBDPS etherification



Entry	Catalyst	Yield of **2** (%)	Recovery of **1** (%)
1	None	0	~100
2	Imidazole	15	82
3	DMAP	40	53
4	Pyr-*N*-oxide (**3**)	85	13
5	4-Me-Pyr-*N*-oxide (**4**)	98	0
6	4-OMe-Pyr-*N*-oxide (**5**)	95	3
7	DMAPO	70	24
8	PPYO	73	25



derivatives instead of imidazole or DMAP provided **2**. The *N*-oxide derivatives **3**, **4**, and **5** bearing H, Me, and OMe at the 4-position of the pyridine ring, respectively, were more effective for the TBDPS

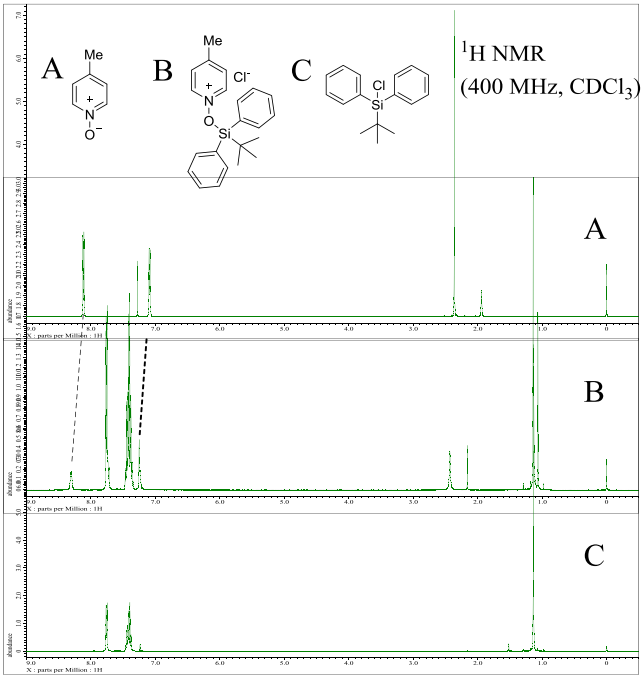
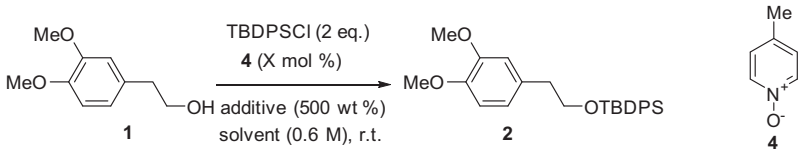


Figure 1. NMR study of 4-methylpyridine *N*-oxide and TBDPSCl.

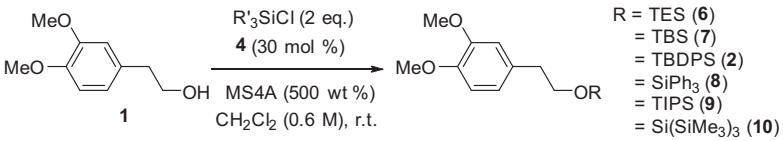
Table 2
Optimization of TBDPS etherification



Entry	Additive	Solvent	X (mol %)	Time	Yield of **2** (%)	Recovery of **1** (%)
1	MS4A	Toluene	30	3 h	55	43
2	MS4A	THF	30	3 h	43	54
3	MS4A	CH_2Cl_2	30	25 min	98	0
4	MS4A	DMF	30	1 h	97	0
5	None	CH_2Cl_2	30	24 h	22	75
6	MS4A	CH_2Cl_2	20	55 min	98	0
7	MS4A	CH_2Cl_2	10	80 min	98	0
8	MS4A	CH_2Cl_2	5	120 min	97	0
9[a]	MS4A	CH_2Cl_2	10	80 min	98	0
10	MS3A	CH_2Cl_2	10	80 min	98	0
11	MS5A	CH_2Cl_2	10	60 h	96	0

[a] 1.4 equiv of TBDPSCl was used.

Table 3
Scope of silyl reagents for catalyst **4** with MS4A



Entry	R'_3SiCl	Time	Yield of silyl ether (%)	Recovery of **1** (%)
1	TESCl	3 h	86	10
2	TBSCl	1 h	96	0
3	TBDPSCl	25 min	98	0
4	Ph_3SiCl	15 h	96	0
5[a]	TIPSCl	5 h	85	10
6[a]	$(Me_3Si)_3SiCl$	5 h	90	6

[a] Run at 50 °C.

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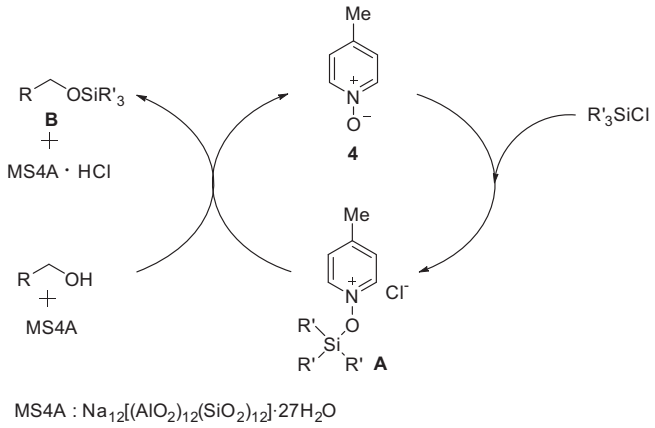


Figure 2. A possible mechanism of amine-free silyl etherification by 4-methylpyridine *N*-oxide and MS4A.

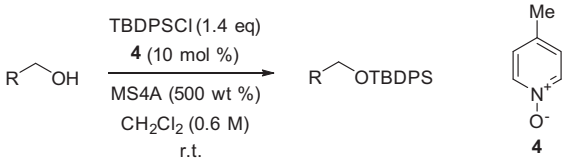
etherification of **1** than DMAP *N*-oxide (DMAPO) or PPYO[11] bearing an amino group (entries 4–8). In particular, 4-methylpyridine *N*-oxide (**4**), which is a weaker base than DMAPO or PPYO, showed the highest activity among these pyridine *N*-oxide derivatives (entry 5).

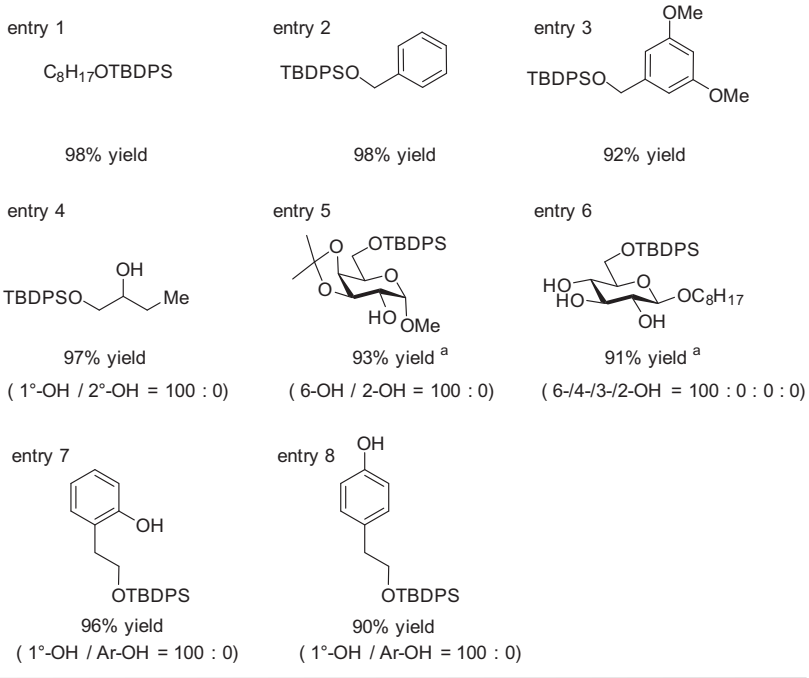
Next, we investigated the optimal reaction conditions (Table 2). Treatment of **1** with 30 mol % of **4**, 2 equiv TBDPSCl and 500 wt % activated MS4A in toluene or THF at room temperature resulted in a moderate yield (entries 1 and 2). When CH_2Cl_2 was used as the solvent, the reaction proceeded quickly and gave product **2** in 98% yield (entry 3). DMF showed similar reactivity to CH_2Cl_2 (entry 4). In contrast, the conditions without MS4A for 24 h resulted in a low yield (entry 5). These results demonstrated that both 4-pyridine *N*-oxide and MS4A are crucial for this reaction. We found that the minimum amount of the catalyst required to complete the silylation (entries 6–8) was only 5 mol % of **4**, although the reaction time was extended slightly (entry 8). The amount of silyl reagent was decreased to 1.4 equiv and similar activity was observed (entry 9).[12] To investigate the pore size of MS, MS3A and MS5A were also tested. As a result, MS3A showed similar results to those obtained by MS4A. On the other hand, the reaction time was extended when MS5A was used.

We examined the versatility of the catalyst system for various silyl reagents (Table 3). The reactions proceeded smoothly at room temperature when less hindered silyl reagents, such as TESCl, TBSCl, and TBDPSCl, were used (entries 1–3). The combination of **4** with triphenylsilyl chloride also gave desired product **8** in an excellent yield, although the reaction time was long owing to the bulkiness of the reagent (entry 4). We examined more bulky silyl reagents (entries 5 and 6), and the silylation of **1** by TIPSCl or tris(trimethylsilyl)silyl chloride was very slow at room temperature. However, at 50 °C, a high yield was obtained. Thus, the combination of **4** and MS4A can be used to catalyze the formation of various silyl ethers.

To investigate the reaction mechanism for this amine-free silylation, we conducted an NMR study (Fig. 1). A mixture of TBDPSCl and 20 mol % of **4** in $CDCl_3$ at room temperature gave ^1H NMR spectrum **B**. Comparing **B** with the spectra of only **4** (**A**) and only TBDPSCl (**C**) shows that both the aromatic protons and 4-methyl group of **4** shifted downfield and a new *t*Bu group peak appeared at 1.08 ppm.

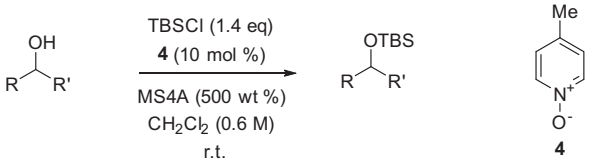
Table 4
Formation of TBDPS ethers from various alcohols

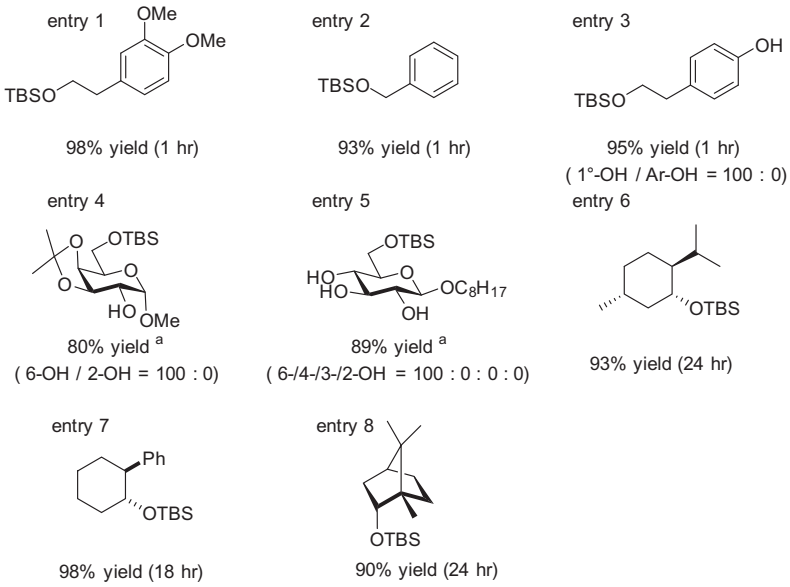




[a]30 mol % of **4** was used.

Table 5
Formation of TBS ethers from various alcohols





[a]30 mol % of **4** was used.

Based on this NMR experiment, we propose a reaction mechanism for the catalytic silylation of alcohols by 4-methylpyridine *N*-oxide (Fig. 2). First, R'_3SiCl and **4** form intermediate **A**. The formation of **A** is supported by NMR analysis of a mixture of R'_3SiCl and **4** (Fig. 1). Then, the alcohol receives the R'_3Si group from **A** to give silylated product **B**, and **4** is regenerated to complete the catalytic cycle. MS4A captures the HCl generated.

To expand the scope of this reaction, we explored the use of various alcohols (Table 4). General primary alcohols, such as octanol, benzyl alcohol, and 3,5-dimethoxybenzyl alcohol, were treated under the optimized conditions to afford TBDPS ethers in 98%, 98%, and 92% yields, respectively (entries 1–3). Next, we examined selective TBDPS etherification of substrates bearing both primary and secondary alcohols. The primary alcohols, 1,2-butanediol, a D-galactose derivative, and octyl β-D-glucopyranoside, were converted to TBDPS ethers in high yield with perfect regioselectivity (entries 4–6). In addition, selective silylation of primary alcohols in the presence of a phenol group was examined. The two hydroxy groups were distinguished under these conditions, and the primary alcohol was preferentially silylated because of the weak nucleophilicity of phenol and the weak basicity of MS4A (entries 7 and 8). However, these conditions were ineffective for TBDPS etherification of the secondary alcohol.

Finally, we investigated TBS etherification of various alcohols (Table 5). This catalyst system exhibited similar activity and regioselectivity to TBDPS etherification (entries 1–5). A major difference is that the TBS etherification of secondary alcohol proceeded in high yield, although a prolonged reaction time was required. (−)-Menthol and *trans*-2-phenyl-1-cyclohexanol were treated under optimized conditions to afford TBS ethers in 93% and 98% yields (entries 6 and 7). Moreover, the silylation of (−)-borneol containing hindered secondary alcohol proceeded smoothly (entry 8). These results show that this catalyst system can be applied to a wide range of alcohols.

In conclusion, we have developed a method for amine-free silyl etherification of various primary and secondary alcohols using 4-methylpyridine *N*-oxide and MS4A powder. The reaction proceeds under mild conditions to provide various silyl ethers in high yield. We are currently developing other new methods using pyridine *N*-oxide catalysts.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.12.114.

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10. MS4A powder was activated by flame-drying for 30 min under high vacuum before use.
11. PPYO was prepared by the described procedure: Katritzky, A. R.; Rasala, D.; Brito-Palma, F. J. *Chem. Res. (S)* **1988**, 42–43.
12. Optimized procedure for the silylation of **1** in Table 2 (entry 9): To a stirred solution of 2-(3,4-dimethoxyphenyl)ethanol (**1**) (100 mg, 0.550 mmol, 1.0 equiv), **4** (6 mg, 10 mol %) and MS4A (500 mg, 500 wt % of **1**) in CH_2Cl_2 (1.0 mL) was added TBDPSCl (200 μL, 0.77 mmol, 1.4 equiv). The mixture was stirred at room temperature for 80 min, quenched with 1 M aqueous HCl (30 mL), and extracted with EtOAc (30 mL × 3). The combined extracts were washed with water (30 mL) and saturated brine (30 mL), dried and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:20) to provide 226 mg (98% yield) of **2** as a colorless oil.