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Catalytic silylation of secondary alcohols by pyridine *N*-oxide derivative

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ABSTRACT

The reaction of *t*-butyldiphenylsilyl (TBDPS) chloride with secondary alcohols was catalyzed by pyrrolidinopyridine *N*-oxide (PPYO) in the presence of diisopropylethylamine (DIPEA) at room temperature, giving the corresponding TBDPS ethers in high yields.

The silyl group is one of the most useful protecting groups in organic synthesis and various methods have been reported for the *t*-butyldimethylsilyl (TBDMS) and *t*-butyldiphenylsilyl (TBDPS) etherification of alcohols. In the most popular method, treatment of parent alcohols with silyl halide (e.g., TBDMSCl, TBDPSCl) and imidazole is available to introduce the silyl group to various alcohols in good yields.[1] For secondary or bulky alcohols, the combination of silyl triflate and 2,6-lutidine is a powerful method that is often chosen.[2] Moreover, a number of catalytic conditions for the silylation have been explored using various combinations of bases and solvents.[3] In particular, it is well known that conditions using *N*,*N*-dimethylaminopyridine (DMAP) catalyst, silyl chloride, and triethylamine can selectively introduce the silyl group to primary alcohols in the presence of secondary alcohols.[4] However, TBDPS etherification of secondary alcohols under catalytic conditions has proved difficult because of steric hindrance. Verkade and coworkers reported that amino-phosphine $P(MeNCH_2CH_2)_3N$ effectively and strongly catalyzes the silylation of various alcohols, but a high temperature is needed to complete the reaction in the case of TBDPS etherification of secondary alcohols.[5] In their paper, DMAP was noted to be an inefficient catalyst for TBDPS etherification of secondary alcohol (36% yield after 24 h using 20 mol % DMAP catalyst at 50 °C). To our knowledge, catalysts that have strong activity for TBDPS etherification of secondary alcohols at low temperatures are very rare. Herein, we report the development of mild catalytic conditions for TBDPS etherification of secondary alcohols using pyridine *N*-oxide derivatives. *N*,*N*-Dimethylaminopyridine *N*-oxide (DMAPO) and pyrrolidinopyridine *N*-oxide (PPYO) can be prepared easily from commercially available DMAP and pyrrolidinopyridine.[6] Shiina et al., reported that the combination of DMAPO and 2-methyl-6-nitrobenzoic anhydride promotes efficient peptide coupling and macrolactonization.[7] In another study, chiral pyridine *N*-oxide derivatives were used as organocatalysts for asymmetric allylation of aldehyde.[8] Recently, the combination of DMAPO and a chiral hydrogen-bonding catalyst was found to exhibit acylation activity for the kinetic resolution of allylic amine.[9] Against this background, the present study is the first Letter of catalytic silylation of secondary alcohols using pyridine *N*-oxide derivatives.

To begin, we chose (−)-menthol (**1**) as a standard substrate for investigating the reaction conditions (Table 1). Treatment of **1** with TBDPSCl and a bulky base such as 2,4,6-collidine or diisopropylethylamine (DIPEA) in CH_2Cl_2 at room temperature resulted in no formation of the silylated product **2** (entries 1 and 2). These results show that the conditions using amine base alone are ineffective in this case. When 20 mol % of DMAP was used as catalyst, only a trace amount of TBDPS ether **2** was obtained (entry 3). In contrast, the use of DMAPO instead of DMAP accelerated the silylation to provide **2** in 71% yield (entry 4).

We next investigated the optimal base for this reaction. As shown in entry 5, the conditions using 2 equiv of PPYO in the absence of amine base resulted in no reaction. By using 1.5 equiv of NEt_3, 2,6-lutidine, or 2,4,6-collidine in the presence of 20 mol % of PPYO, the silylated product **2** was obtained in moderate yield

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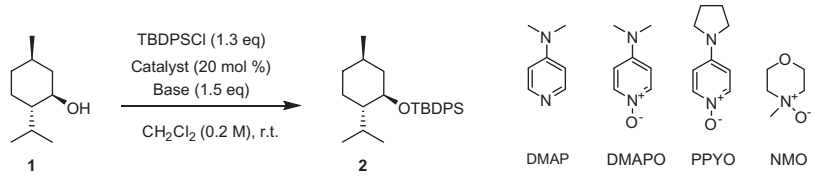
Table 1
Catalyst and base screening for TBDPS etherification of (−)-menthol (**1**)

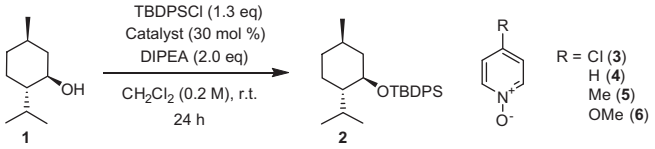


Entry	Catalyst	Base	Yield of **2**[a] (%)	Recovery of **1** (%)
1[b]	None	2,4,6-Collidine	0	~100
2[b]	None	DIPEA	0	~100
3[b]	DMAP	DIPEA	8	88
4[b]	DMAPO	DIPEA	71	25
5[c]	PPYO[d]	None	0	~100
6[c]	PPYO	2,4,6-Collidine	63	34
7[c]	PPYO	NEt_3	75	21
8[c]	PPYO	2,6-Lutidine	51	47
9[c]	PPYO	DIPEA	93	0
10[c]	NMO	DIPEA	0	~100

[a] Isolated yield.
[b] Reaction time: 14 h.
[c] Reaction time: 24 h.
[d] 2.0 equiv of PPYO was used.

(entries 6–8, respectively). Finally, DIPEA was found to be the optimal base (entry 9). The combination of PPYO catalyst and DIPEA base gave **2** in excellent yield. In contrast, the use of *N*-methylmorpholine *N*-oxide (NMO) as catalyst gave no reaction (entry 10). These results demonstrate that both the pyridine *N*-oxide catalyst and the amine base are crucial for this reaction.

To investigate substituent effects at the 4-position of pyridine, we next examined silylation using various pyridine *N*-oxide derivatives with different substituents at the 4-position



(Fig. 1).[10] In this examination, we used 1.3 equiv of TBDPSCl and 2.0 equiv of DIPEA as base, and 30 mol % of a pyridine *N*-oxide derivative as catalyst. For comparison, DMAP-catalyzed TBDPS etherification was also run under the same reaction conditions, providing **2** in 18% yield with 80% recovery of **1**. Among the other catalysts tested (**3**–**6**, DMAPO, and PPYO), only the *N*-oxide derivatives bearing an electron donating group at the 4-position of the pyridine ring were found to be effective for the silylation. In particular, PPYO showed the strongest activity of the *N*-oxide derivatives. The increase in the activity of the catalyst corresponded to an increase in the basicity of the pyridine nitrogen. A similar trend has been observed for the acylation activity of DMAP and pyrrolidinopyridine.[11]

A possible reaction mechanism for the catalytic TBDPS etherification of secondary alcohol by PPYO is shown in Figure 2. First, an intermediate (**A**) is formed from TBDPSCl and PPYO. The formation of **A** was supported by an NMR analysis of a mixture of TBDPSCl and PPYO (see the Supplementary data).[12] Then, the secondary alcohol can receive the TBDPS group from **A** to give the silylated product (**B**) and PPYO is regenerated to return the catalytic cycle. DIPEA may be necessary to capture HCl.

To expand the scope of this reaction, we explored the use of various secondary alcohols (Table 2). Substrates **1**, *trans*-2-phenyl-1-cyclohexanol, 2-methyl-2,4-pentanediol, and *meso*-cyclohexanediol were treated under the optimized conditions to afford TBDPS ethers in 98%, 97%, 93%, and 94% yields, respectively, (entries 1–4).[13] Moreover, the hindered *ortho*-disubstituted phenol derivative was silylated in 96% yield (entry 5). This reaction reached completion in just 15 min. The silylation of (−)-borneol (entry 6), which contains a quaternary carbon atom adjacent to

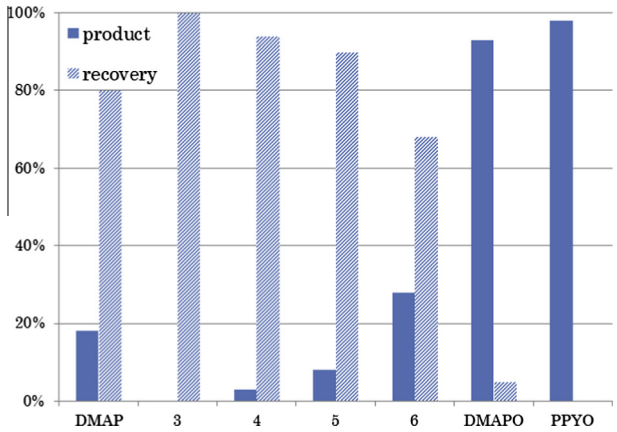


Figure 1. Substituent effects at the 4-position of the pyridine ring.

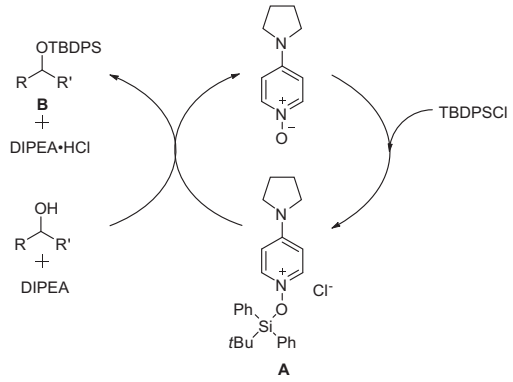
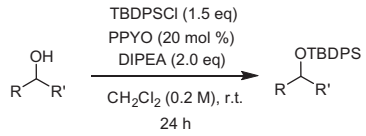
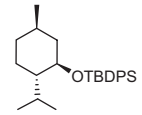


Figure 2. A possible mechanism of TBDPS etherification by PPYO.

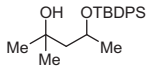
Table 2
Formation of TBDPS ethers from various secondary alcohols



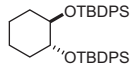


1. 98%

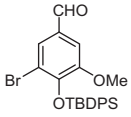
2. 97%



3. 93%



4. 94%



5.[a] 96%

6. 95%

[a] Reaction time: 15 min.

the hydroxyl group, also proceeded smoothly. These results show that PPYO can be used to catalyze the formation of TBDPS ethers from a wide range of secondary alcohols.

In conclusion, we have developed a novel method for catalytic TBDPS etherification of various secondary alcohols using DMAPO and PPYO. The reaction proceeds under mild conditions to provide the TBDPS ethers in high yields. Our group is currently working on an asymmetric version of this reaction using chiral pyridine *N*-oxide catalysts.

Acknowledgments

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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.2014.10.087.

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10. For the data in Figure 1, see the Table in the Supplementary data.
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12. PPYO disappeared and the new signals were observed in the ^{1}H NMR spectrum of a mixture of TBDPSCl and PPYO (ca. 1:0.3).
13. *Typical procedure for the silylation of* ***1*** *in* Table 2: To a stirred solution of (−)-menthol (**1**) (20.0 mg, 0.128 mmol, 1.0 equiv), PPYO (4.2 mg, 20 mol %), and DIPEA (44.6 μL, 0.256 mmol, 2.0 equiv) in CH_2Cl_2 (0.6 mL) was added TBDPSCl (49.9 μL, 0.192 mmol, 1.5 equiv). The mixture was stirred at room temperature for 24 h, quenched with 1 M aqueous HCl (10 mL), and extracted with EtOAc (10 mL × 3). The combined extracts were washed with water (10 mL) and saturated brine (10 mL), dried, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 20:1) to give 49.4 mg (98% yield) of **2**.