



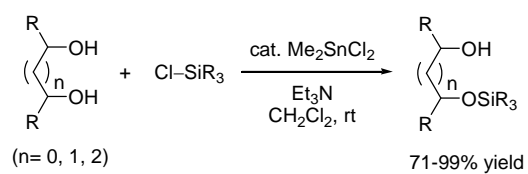
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Graphical Abstract

Catalytic monosilylation of 1,2-diols

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Catalytic monosilylation of 1,2-diols

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ABSTRACT

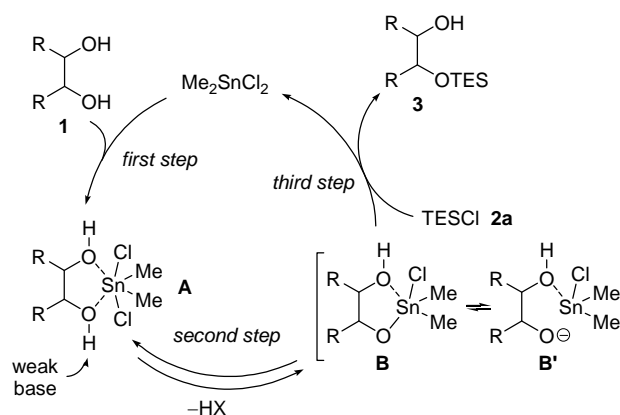
The selective monosilylation of 1,2-diols catalyzed by dimethyltin dichloride was successfully developed. This procedure was applied to various 1,2-diols, giving monosilylated products in good to excellent yields with high chemoselectivity.

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Selective protection of diols is highly important in organic synthesis.¹ In the past, a variety of methods for the catalytic monoprotection of 1,2-diols, such as acetylation,² benzoylation,³ tosylation,⁴ have been developed to achieve high selectivity.⁵ Especially, the selective monosilylation of 1,2-diols is quite significant because silyl groups are one of the most useful protective groups of hydroxyl moieties.¹ While selective monoprotection of bis-silyl ethers has been pursued to obtain silyloxy alcohols,⁶ organocatalytic enantioselective methods were recently developed by Snapper⁷ and Tan⁸ in addition to the biphasic process.⁹ However, selective monosilylation controlled by metal catalysts has not been reported.

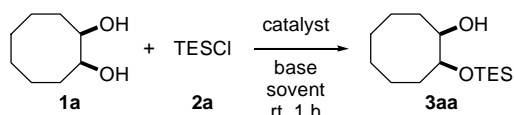
On the other hand, we have already developed the effective methods for catalytic monoprotection of 1,2-diols with Lewis acid such as dimethyltin dichloride¹⁰ or copper(II) salts¹¹ in the presence of weak bases. We envisioned this method could be applied to catalytic monosilylation of 1,2-diols. Herein, we wish to report the first example of selective monosilylation of 1,2-diols catalyzed by the metal catalyst.

Our working hypothesis for the catalytic selective monosilylation of 1,2-diols is shown in Scheme 1. Dimethyltin dichloride (Me_2SnCl_2)¹² and triethylsilyl chloride (TESCl) **2a** represent a catalyst and a silylating reagent, respectively. The monosilylation would proceed as below. First of all, 1,2-diol **1** is recognized by the Sn catalyst and the five-membered intermediate **A** is formed with the bidentate coordination of 1,2-diol **1** to the Sn catalyst. Second, the complex **A** is selectively deprotonated by weak base, in which the pK_a value of 1,2-diol **1** would be lowered due to the coordination of 1,2-diol **1** to the metal center. Finally, the activated intermediate **B** (or **B'**) with a higher reactivity than 1,2-diol **1** reacts with TESCl, affording the monosilylated product **3**. The difficulty for **3** in coordinating to the metal center would suppress the oversilylation.



Scheme 1. Working hypothesis for chemoselective monosilylation catalyzed by Me_2SnCl_2 .

Based on this concept, we began investigations with the optimization of reaction conditions using *cis*-1,2-cyclooctanediol **1a** and TESCl as model substrates (Table 1). In the examination of metal catalysts, dimethyltin dichloride gave the desired product **3aa** in quantitative yield,¹³ while Cu and Pd catalysts led to high yields (entries 1-3). Screening of bases revealed that organic bases were suitable for this transformation and triethylamine afforded the superior result (entries 3-6). Whereas the monosilylation in less polar toluene led to the reduced efficiency, the result in high polar ethyl acetate was also excellent (entries 7 and 8). The catalyst loading was successfully reduced to 1 mol % with comparable isolated yield to the reaction with 10 mol % catalyst (entries 3 and 9). On the other hand, the silylation reaction without dimethyltin dichloride led to the significant decrease in yield (entry 10).

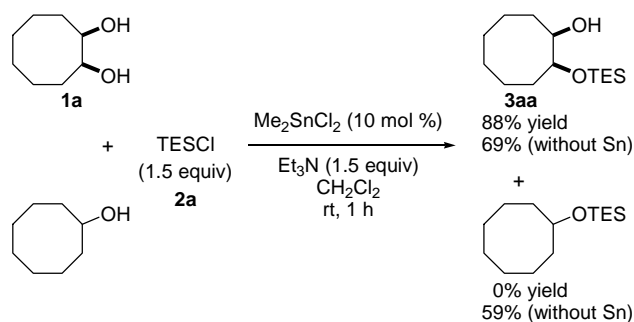
Table 1. Optimization of reaction conditions^a

Entry	Catalyst	Base	Solvent	Yield (%) ^b
1	Cu(OTf) ₂	Et ₃ N	CH ₂ Cl ₂	82
2	Pd(OAc) ₂	Et ₃ N	CH ₂ Cl ₂	72
3	Me ₂ SnCl ₂	Et ₃ N	CH ₂ Cl ₂	99
4	Me ₂ SnCl ₂	(<i>i</i> -Pr) ₂ NEt	CH ₂ Cl ₂	73
5	Me ₂ SnCl ₂	DMAP	CH ₂ Cl ₂	60
6	Me ₂ SnCl ₂	Pyridine	CH ₂ Cl ₂	0
7	Me ₂ SnCl ₂	Et ₃ N	toluene	81
8	Me ₂ SnCl ₂	Et ₃ N	AcOEt	96
9 ^c	Me ₂ SnCl ₂	Et ₃ N	CH ₂ Cl ₂	91
10	none	Et ₃ N	CH ₂ Cl ₂	65

^a Reaction conditions: diol **1a** (0.5 mmol), TESCl **2a** (1.5 equiv), catalyst (10 mol %), Base (1.5 equiv), Solvent (3 mL), rt, 1 h.

^b Isolated yield.

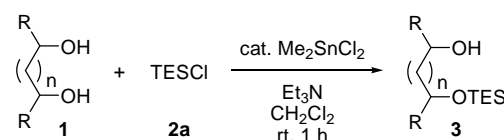
^c Me₂SnCl₂ (1 mol %) was used.

**Scheme 2.** Silylation using *cis*-1,2-cyclooctanediol and cyclooctanol.

In addition, this catalytic system showed quite high chemoselectivity (Scheme 2). The catalytic silylation with 1:1 mixture of *cis*-1,2-cyclooctanediol **1a** and cyclooctanol was conducted to give only the desired monosilylated product **3aa** in 88% yield.¹⁴ In the absence of Sn catalyst, the monosilylated product **3aa** and the silylated mono-ol were obtained in 69% and 59% yields, respectively.¹⁵

With the optimal conditions in hand, we next explored the scope of 1,2-diols (Table 2). While aliphatic cyclic *cis*-1,2-diols **1b-d** gave the desired product **3ba-da** in excellent yields (entries 1-3), the *trans*-isomer **1e** showed the lower reactivity (entry 4). High yields were observed in the reaction with cyclic *cis*-1,2-diols bearing π -bonds (entries 5 and 6). The heterocyclic *cis*-2,3-diols containing oxygen and nitrogen atoms were also converted efficiently, leading to excellent results (entries 7 and 8). In the monosilylation of linear 1,2-diols, both meso- and threo-isomers **1j-l** gave the desired products in high yields (entries 9-11). The 1,2-diol bearing ester groups **1m** showed the high reactivity and catechol **1n** was also proved to be a suitable substrate (entries 12 and 13). The 1,3-diols **1o-p** were still transformed readily, leading to high yields (entries 14 and 15). Also, the monosilylation of unsymmetrical 1,2-diol **1q** and 1,3-diol **1r** smoothly proceeded to give the regioselectively monosilylated product **3qa** and **3ra** in high yields (Scheme 3).

The investigation of various silylating reagents in the monosilylation of *cis*-1,2-cyclooctanediol **1a** was conducted (Table 3).

Table 2. Scope of diols^a

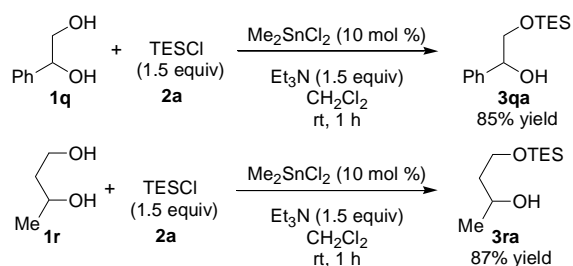
Entry	Diol 1	Product 3	Yield (%) ^b
1	1b	3ba	92
2	1c	3ca	88
3	1d	3da	99
4	1e	3ea	78
5	1f	3fa	97
6	1g	3ga	99
7	1h	3ha	94
8	1i	3ia	92
9	1j	3ja	88
10	1k	3ka	97
11	1l	3la	89
12	1m	3ma	87
13	1n	3na	71
14	1o	3oa	92
15	1p	3pa	85

^a Reaction conditions: diol **1** (0.5 mmol), TESCl **2a** (1.5 equiv), Me₂SnCl₂ (10 mol %), Et₃N (1.5 equiv), CH₂Cl₂ (3 mL), rt, 1 h.

^b Isolated yield.

The more sterically bulky reagent **2b** led to no significant decrease in yield (entry 1).¹⁶ The introduction of silyl groups bearing olefin moieties, which can be synthetic footholds, was also succeeded with high yields (entries 2 and 3). The monosilylation using reagents with phenyl group had no difficulty, leading to excellent results (entries 4-6). The silylating reagents

bearing reactive moieties, such as chlorine and cyano group, reacted efficiently with no side product (entries 7 and 8).



Scheme 3. Silylation of unsymmetrical 1,2- and 1,3-diols.

Table 3. Scope of silylating reagents^a

Entry	2	Product	3	Yield (%) ^b
1	2b		3ab	91
2	2c		3ac	83
3	2d		3ad	79
4 ^c	2e		3ae	89
5	2f		3af	87
6 ^c	2g		3ag	84
7	2h		3ah	82
8	2p		3ai	99

^a Reaction conditions: diol **1a** (0.5 mmol), silylating reagent **2** (1.2 equiv), Me_2SnCl_2 (10 mol %), Et_3N (1.5 equiv), CH_2Cl_2 (3 mL), rt, 1 h.

^b Isolated yield.

^c Silylating reagent **2** (1.5 equiv) was used.

In summary, we successfully developed the first selective monosilylation of 1,2-diols catalyzed by metal complexes. This process tolerated a variety of substrates with high chemoselectivity. Further efforts will be focused on the development of asymmetric silylation of 1,2-diols in our research group.

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- Representative procedure. To the mixture of diol **1a** (0.5 mmol), triethylamine (1.5 equiv), and dimethyltin dichloride (10 mol %) in CH_2Cl_2 (3 mL) was added TESCl **2a** (1.5 equiv). The mixture was stirred for 1 h at rt. After water was added, the resulting mixture was extracted with ethyl acetate and the combined organic layers were dried with anhydrous magnesium sulfate. After

filtration, the volatile components were removed with a rotary evaporator. Purification of the crude product through silica gel column chromatography gave **3aa** in 99% yield.

14. In this case, cyclooctanol was recovered in 99%.
15. By using imidazole (1.5 equiv) without Me_2SnCl_2 , the monosilylated product **3aa** and the silylated mono-ol were obtained in 43% and 50% yields, respectively.
16. The reaction of **1a** with *tert*-butyldimethylsilyl chloride (TBSCl) did not proceed to recover **1a** under the reaction conditions.