Graphical Abstract

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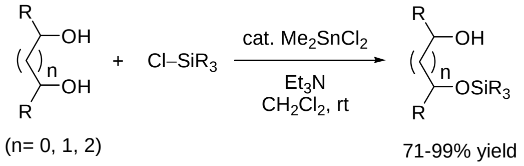

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Catalytic monosilylation of 1,2-diols

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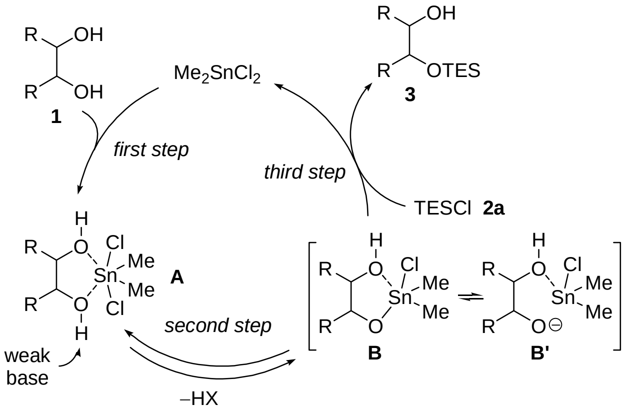
ABSTRACT

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.

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 mono-deprotection of bis-silyl ethers has been pursued to obtain silyloxy alcohols,[6] organocatalytic enantioselective methods were recently developed by Snapper[7] and Tan[8] 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 dichloride[10] or copper(II) salts[11] 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.

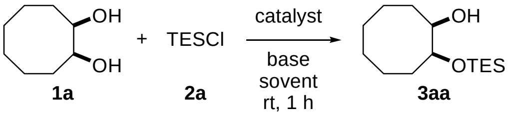
Our working hypothesis for the catalytic selective monosilylation of 1,2-diols is shown in Scheme 1. Dimethyltin dichloride (Me_2SnCl_2)[12] and triethylsilyl chloride (TESCl) **2a** represent a catalyst and a silylating reagent, respectively. The monosilylation would proceed as below. First of all, 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]

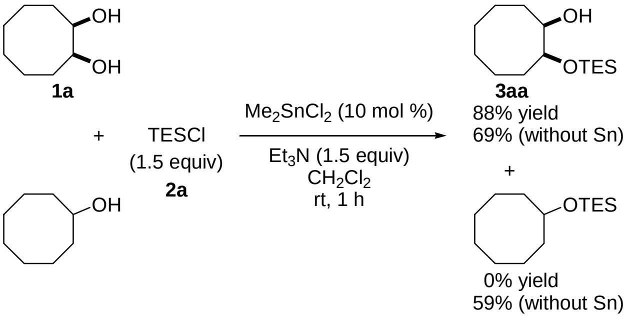


Entry	Catalyst	Base	Solvent	Yield (%)[b]
1	$Cu(OTf)_2$	Et_3N	CH_2Cl_2	82
2	$Pd(OAc)_2$	Et_3N	CH_2Cl_2	72
3	Me_2SnCl_2	Et_3N	CH_2Cl_2	99
4	Me_2SnCl_2	(*i*-Pr)$_2$NEt	CH_2Cl_2	73
5	Me_2SnCl_2	DMAP	CH_2Cl_2	60
6	Me_2SnCl_2	Pyridine	CH_2Cl_2	0
7	Me_2SnCl_2	Et_3N	toluene	81
8	Me_2SnCl_2	Et_3N	AcOEt	96
9[c]	Me_2SnCl_2	Et_3N	CH_2Cl_2	91
10	none	Et_3N	CH_2Cl_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] Me_2SnCl_2 (1 mol %) was used.



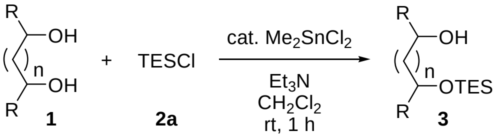
Scheme 2. Silylation using *cis*-1,2-cyclooctanediol and cyclooctanol.

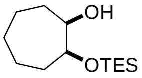
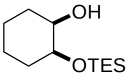
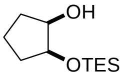
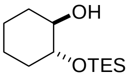
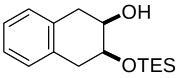
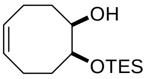
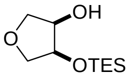
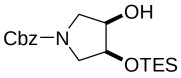
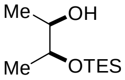
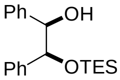
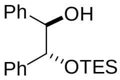
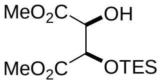
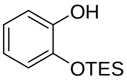
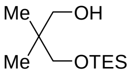
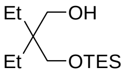
In addition, this catalytic system showed quite high chemoselectivity (Scheme 2). The catalytic silylation with 1:1 mixture of *cis*-1,2-cyclooctanediol **1a** and cyclooctanol was conducted to give only the desired monosilylated product **3aa** in 88% yield.[14] In the absence of Sn catalyst, the monosilylated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

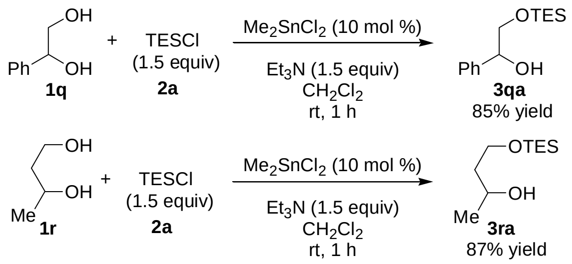


Entry	Diol **1**	Product	**3**	Yield (%)[b]
1	**1b**		**3ba**	92
2	**1c**		**3ca**	88
3	**1d**		**3da**	99
4	**1e**		**3ea**	78
5	**1f**		**3fa**	97
6	**1g**		**3ga**	99
7	**1h**		**3ha**	94
8	**1i**		**3ia**	92
9	**1j**		**3ja**	88
10	**1k**		**3ka**	97
11	**1l**		**3la**	89
12	**1m**		**3ma**	87
13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

[a] Reaction conditions: diol **1** (0.5 mmol), TESCl **2a** (1.5 equiv), Me_2SnCl_2 (10 mol %), Et_3N (1.5 equiv), CH_2Cl_2 (3 mL), rt, 1 h.

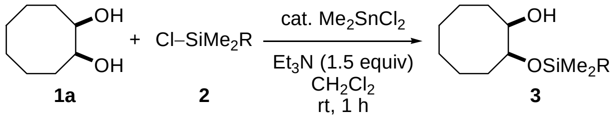
[b] Isolated yield.

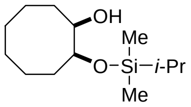
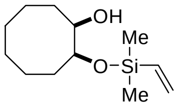
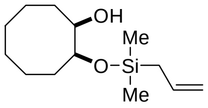
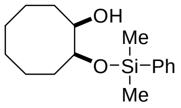
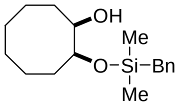
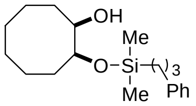
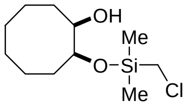
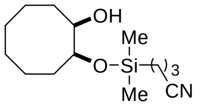
The more sterically bulky reagent **2b** led to no significant decrease in yield (entry 1).[16] The introduction of silyl groups bearing olefin moieties, which can be synthetic footholds, was also succeeded with high yields (entries 2 and 3). The monosilylation using reagents with phenyl group had no 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 chemo-selectivity. Further efforts will be focused on the development of asymmetric silylation of 1,2-diols in our research group.

Acknowledgments

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6. Review: (a) Crouch, R. D. *Tetrahedron* **2004**, *60*, 5833-5871. Recent examples: (b) Yeom, C.-E.; Kim, Y. J.; Lee, S. Y.; Shin, Y. J.; Kim, B. M. *Tetrahedron* **2005**, *61*, 12227-12237. (c) Yang, Y.-Q.; Cui, J.-R.; Zhu, L.-G.: Sun, Y.-P.; Wu, Y. *Synlett* **2006**, 1260-1262. (d) Yeom, C.-E.; Kim, H. W.; Lee, S. Y.; Kim, B. M. *Synlett* **2007**, 146-150. (e) Wang, B.; Sun, H.-X.; Sun, Z.-H. *J. Org. Chem.* **2009**, *74*, 1781-1784. (f) Fustero, S.; Sancho, A. G.; Aceña J. L.; Sanz-Cervera, J. F. *J. Org. Chem.* **2009**, *74*, 6398-6401.
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12. Organotins are known to be toxic at relatively low levels of exposure, not only to marine invertebrates but also for mammals and other animals. The most toxic organotin compounds are the trialkyltin compounds, with the ethyl derivative in each group being reported as the most toxic. See: (a) Poller, R. C. *The Chemistry of Organotin Compounds*. Logos Press: london, 1970. (b) Nath, M. *Appl. Organometal. Chem.* **2008**, *22*, 598-612.
13. 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.