Stereoselective Construction of 1,3-Diol Derivatives via Nucleophilic Reaction to *β*-Methoxyacylsilanes

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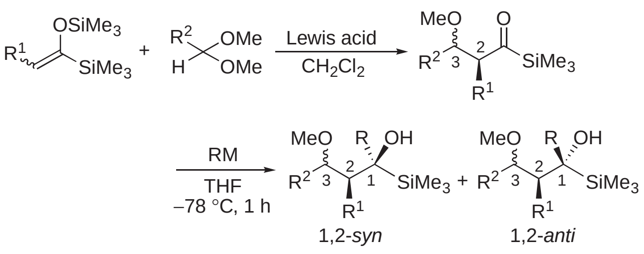
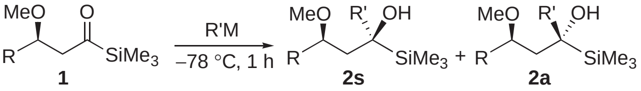
The stereoselectivity of 1,3-asymmetric induction in the nucleophilic addition to β-methoxyacylsilanes having no substituent at the α-position is largely dependent on the kind of nucleophiles. In a similar reaction employed α-substituted β-methoxyacylsilanes, three diastereoisomers of 1,3-diol derivatives having the three contiguous stereogenic centers among four possible diastereomeric products are yielded with high stereoselectivity. The protiodesilylation of the resulting α-silylalcohols proceeds with complete retention of the configuration.

Acylsilanes have received considerable attention due to their unusual spectroscopic properties, novel chemical reactivity, and their utility as useful synthons in organic synthesis.[1,2] Several procedures using acylsilanes have been developed for the asymmetric synthesis.[2] In particular, we were interested in the stereoselective syntheses of 1,3-diol derivatives from acylsilanes.[3] A few years ago, we presented that the Lewis acid mediated aldol reaction using silyl enol ethers derived from simple acylsilanes gave the corresponding β-methoxyacylsilanes having the contiguous stereogenic centers,[4] and the subsequent nucleophilic addition reaction to the acylsilanes obtained by the above aldol reaction led to the construction of 1,3-diol derivatives having three contiguous stereogenic centers (Scheme 1).[3a,5] However, the stereoselectivity in these nucleophilic addition reaction was strongly influenced by the bulkiness of the α-substituent of acylsilanes, and a mixture of 1,2-syn and 1,2-anti isomers was produced with preference of the former (syn and anti refer to the relationship between R^1 and OH). Thus, in order to obtain both isomers with high diastereoselectivity, we decided to investigate the effect of counter cation of nucleophile and solvent in nucleophilic addition reaction. We considered that a bulky silyl group acts as a directing group for selectivity in this reaction.[6] In addition, it is known that the protiodesilylation of α-silylalcohols easily proceeds with complete retention of the configuration.[7] Consequently, this method would be useful for the stereoselective construction of 1,3-diol derivatives. Here, we wish to describe an efficient, convenient, and stereoselective synthesis of 1,3-diol derivatives having three contiguous stereogenic centers using the reaction of β-methoxyacylsilanes with simple nucleophilic reagents and the subsequent protiodesilylation.



Scheme 1.

Table 1. Reaction of β-methoxyacylsilanes with various organometallic reagents



Entry	R	$R'M$[a]	Solvent	Yield[b]/%	**2s**:**2a**[c]
1	Ph	MeLi	THF	87	53:47
2	Ph	MeLi	Et_2O	99	4:96
3	Me	MeLi	Et_2O	84	6:94
4	n-C_7H_{15}	MeLi	Et_2O	81	10:90
5	i-C_3H_7	MeLi	Et_2O	86	10:90
6	Ph	PhLi	Et_2O	97	17:83
7	Ph	MeLi	CH_2Cl_2	92	4:96
8	Ph	MeMgBr	THF	99	40:60
9	Ph	$MeCeCl_2$[d]	THF	94	86:14
10	Ph	Me_3Al	Toluene	89	95:5
11	Me	Me_3Al	Toluene	83	95:5
12	n-C_7H_{15}	Me_3Al	Toluene	70	90:10
13	i-C_3H_7	Me_3Al	Toluene	75	90:10
14	Ph	Et_3Al	Toluene	58	93:7

[a] Molar ratio; **1**/R′Li = 1:2, **1**/MeMgBr = 1:2, **1**/$MeCeCl_2$ = 1:4, **1**/R'_3Al = 1:4. [b] Isolated yield. [c] Determined by ^1H NMR analysis (270 MHz). [d] Generated from MeLi and $CeCl_3$.

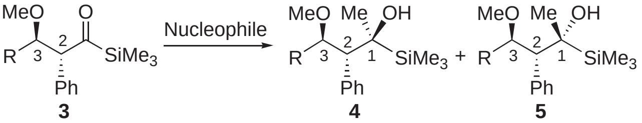
The reaction of β-methoxyacylsilanes **1** having no substituent at the α-position with several nucleophiles was carried out.[8] The results are shown in Table 1. The reaction with methyllithium in THF proceeded smoothly to afford the corresponding diastereomeric mixture of 1,3-syn isomer **2s** and 1,3-anti isomer **2a** with low diastereoselectivity (Entry 1), whereas high 1,3-anti selectivity was observed in the reaction with organolithium reagents using diethyl ether or dichloromethane as a solvent (Entries 2–7). On the other hand, alkylcerium reagent reacted to afford **2s** predominantly (Entry 9). It should be noted that high 1,3-syn selectivity was observed in the reaction with trialkylaluminum in toluene (Entries 10–14).

Next, the stereoselectivity of the nucleophilic addition reaction to α-phenyl-β-methoxyacylsilanes under the above optimized conditions was investigated. The treatment of 2,3-*anti*-methoxyacylsilanes **3** with methyllithium in diethyl ether or trimethylaluminum in toluene was examined. The reaction proceeded smoothly to afford the corresponding 3-methoxysilylalcohols **4** and **5** in high yields. These results are summarized in Table 2. The reaction with methyllithium gave 1,2-syn isomers **5** (syn refers to the relationship between OH and Ph group at the β-position) with excellent diastereoselectivity (Entries 1 and 2), whereas 1,2-anti isomers **4** were formed with modest to high diastereoselectivity by the reaction with trimethylaluminum (Entries 3 and 4). On the other hand, both reactions with methyllithium and trimethylaluminum proceeded to give the corresponding 1,2-syn adducts **8** exclusively from 2,3-*syn*-methoxyacylsilanes **6**. The results are shown in Table 3. Consequently, three diastereoisomers (**4**, **5**, and **8**) of 1,3-diol derivatives having the three contiguous stereogenic centers among four possible diastereomeric products were respectively yielded with high stereoselectivity.

Although a detailed mechanism has not yet been clarified, it seems that the diastereoselectivity of the reaction with methyllithium is strongly influenced by the α-substituent of acylsilanes, and 1,2-*syn*-silylalcohols **5** and **8** are produced via β-chelate transition state.[3a,8] Especially, silylalcohol **5** has also a 1,3-anti relationship observed preferentially in Table 1, and hence **5** is obtained with excellent diastereoselectivity (>99%). On the other hand, the reaction with trimethylaluminum also proceeds with 1,2-syn selectivity. However, 1,3-syn selectivity observed in the reaction of acylsilanes having no substituent at the α-position would be preferable to 1,2-syn selectivity, thus silylalcohol **4** is yielded with modest to high diastereoselectivity, whereas silylalcohol **8** is obtained with excellent diastereoselectivity because of both relationships of 1,3-syn and 1,2-syn.

The protiodesilylation of α-silylalcohols proceeds with complete retention of the configuration.[7] Thus, protiodesilylation of silyl-substituted 1,3-diol derivatives **4** and **5** derived from 2,3-*anti*-3-methoxy-2-phenyl-1-silylbutanone was examined respectively (Scheme 2). Treatment of α-silylalcohol **4** with tetrabutylammonium fluoride (TBAF) followed by etherification of the resulting alcohol gave the corresponding *dl*-2,3-dimethoxypentane derivative quantitatively. Similarly, α-silylalcohol **5** was transformed to *meso*-2,3-dimethoxypentane derivative.

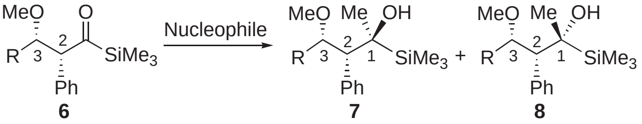
Table 2. Nucleophilic addition to 2,3-*anti*-3-methoxyacylsilanes



Entry	R	Nucleophile	Yield[a]/%	**4**:**5**[b]
1	Ph	MeLi	99	1:>99
2	Me	MeLi	95	1:>99
3	Ph	Me_3Al	90	96:4
4	Me	Me_3Al	92	79:21

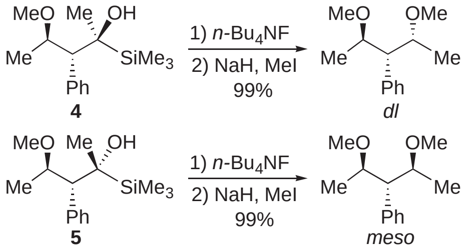
[a]Isolated yield. [b]Determined by ^1H NMR analysis (270 MHz).

Table 3. Nucleophilic addition to 2,3-*syn*-3-methoxyacylsilanes



Entry	R	Nucleophile	Yield[a]/%	**7**:**8**[b]
1	Ph	MeLi	60	3:97
2	Me	MeLi	99	1:>99
3	Ph	Me_3Al	92	1:>99
4	Me	Me_3Al	99	1:>99

[a]Isolated yield. [b]Determined by ^1H NMR analysis (270 MHz).



Scheme 2. Protiodesilylation of γ-methoxy-α-silylalcohols.

In summary, stereoselective construction of 1,3-diol derivatives via nucleophilic reaction to β-methoxyacylsilanes has been described. Further studies are aimed at expanding the scope of these reactions in our laboratory.

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