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Diastereoselective aldol condensation of acylsilane silyl enol ethers with acetals

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Abstract—Treatment of *E*- or *Z*-acylsilane silyl enol ethers derived from acylsilanes having an enolizable methylene proton with a mixture of aromatic aldehyde dimethyl acetals and $TiCl_4$ in dichloromethane gives the corresponding 2,3-*anti*-3-methoxyacylsilanes in high d.e., independent of the geometry of double bond in acylsilane silyl enol ethers. On the other hand, *E*-acylsilane silyl enol ethers react with acetals of aliphatic aldehydes to afford the corresponding aldol adducts with *syn*-selectivity, while the reaction of *Z*-isomers provides the products with *anti*-selectivity.

1. Introduction

Acylsilanes have received considerable attention due to their unusual spectroscopic properties, novel chemical reactivity, and their utility as useful synthons in organic synthesis.[1] While a number of methods for the preparation of simple acylsilanes have been developed, more highly functionalized acylsilanes are much less well known, especially, it is relatively difficult to introduce substituents at the α and β positions of the carbonyl group of acylsilanes diastereoselectively.[2,3]

We thought that the α,β-disubstituted acylsilanes can be synthesized by Mukaiyama aldol reaction.[4] Since the Mukaiyama aldol reaction is one of the most useful method for the stereoselective construction of carbon–carbon bond,[5] the reaction using enol ethers of simple acylsilanes[1c,6] with acetals is expected to give the functionalized acylsilanes. In this reaction, the regeneration of silylcarbonyl group and the formation of carbon–carbon bond would take place at the same time. The resulting α,β-disubstituted acylsilanes would be useful synthetic intermediates as valuable building blocks. However, only a few reports have been published for the Mukaiyama aldol reaction with enol ethers of acylsilanes.[7] Kuwajima et al. have reported that boron trifluoride diethyl etherate catalyzed coupling of enol ethers of acylsilanes with acetals provided β-alkoxyacylsilanes,[7a] without description of diastereoselectivity of resulting aldol adducts.

Here, we wish to report a convenient method of diastereoselective construction of acylsilanes having the contiguous stereogenic centers using the Lewis acid mediated aldol reaction of acylsilane silyl enol ethers **1** with acetals and the details of diastereoselectivity of this aldol reaction.

2. Results and discussion

2.1. Preparation of acylsilane silyl enol ethers

The *E*-isomers of acylsilane silyl enol ethers **1** were prepared by the treatment of enolizable acylsilanes[8] with LDA at 25°C in THF/HMPA, followed by reaction of the resulting enolates with trimethylsilyl chloride (*E*-**1**/*Z*-**1**=99–82:1–18). On the other hand, the corresponding isomeric silyl enol ethers *Z*-**1** were obtained by the treatment of acylsilanes with LDA at −78°C in THF, followed by the addition of trimethylsilyl chloride (*E*-**1**/*Z*-**1**=10–11:90–89). The pure *E*- or *Z*-isomer as a starting silyl enol ether is required to study the stereoselectivity of aldol reaction, but the products **1** obtained under the above conditions were a mixture of *E*- and *Z*-isomers in most cases as shown in Scheme 1. The complete separation of these isomers by column chromatography on silica-gel was difficult. In this study, *E*- or *Z*-isomer containing a small quantity of the other one was used as a starting material in most cases.

Additionally, when phosphonium diylide[9] generated by the treatment of dibenzyldiphenylphosphonium bromide with *n*-butyllithium was employed as a base in THF, geometrically pure *E*-isomers were obtained. However, this method was unsuitable for a large scale synthesis of **1**.

Keywords: acetals; aldol reactions; diastereoselection; enol ethers; silicon and compounds.

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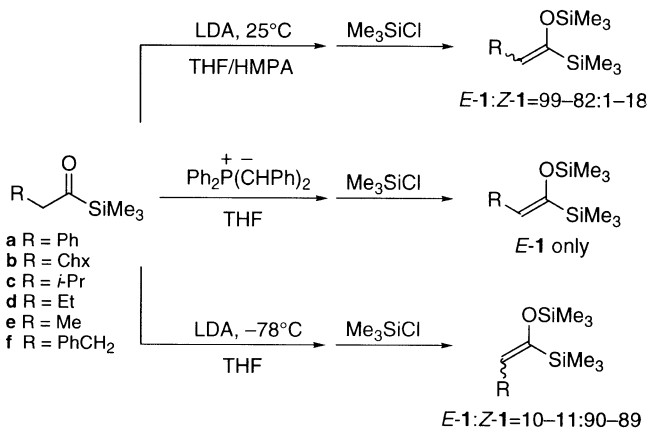


Scheme 1. Synthesis of acylsilane silyl enol ethers.

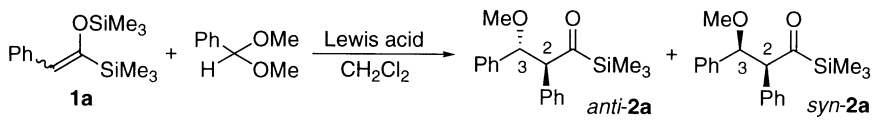
2.2. Aldol reaction of acylsilane silyl enol ethers with acetals

First, the reaction of *E*- or *Z*-**1a** with benzaldehyde dimethyl acetal was examined in the presence of various Lewis acids. The results are summarized in Table 1. As Lewis acids we employed titanium tetrachloride,[10] tin tetrachloride,[11] boron trifluoride diethyl etherate[7a] and trimethylsilyl triflate.[12] All reactions were carried out in dichloromethane. Using titanium tetrachloride as an activating agent, the reaction proceeded smoothly at −78°C to afford the corresponding 2,3-*anti*-3-methoxyacylsilane **2a** in good yields with a high *anti*-selectivity, irrespective of the geometry of double bond in **1a** (entries 1 and 2). Higher yields were observed in the reaction of *E*-**1a** using tin tetrachloride or boron trifluoride diethyl etherate (entries 3 and 5), however, the stereoselectivity in these reactions was lower than that in the reaction using titanium tetrachloride (entry 1). On the other hand, the similar reaction of *Z*-**1a** using these Lewis acids resulted in the lower yields (entries 2, 4, 6 and 8). The reaction using trimethylsilyl triflate as a Lewis acid gave the aldol adducts with the moderate yield and diastereoselectivity (entries 7 and 8). Among several Lewis acids tested, titanium chloride was suitable for this reaction, and hence all of the following aldol reactions with acetals were carried out using titanium tetrachloride in dichloromethane at −78°C for 1 h. In addition, the use of catalytic amounts of Lewis acid led to the decrease in product yield, and the reaction using benzaldehyde instead of the corresponding dimethyl acetal as a starting substrate did not proceed at all.

The aldol reaction of **1** having an aliphatic group with benzaldehyde dimethyl acetal in the presence of titanium chloride was carried out in dichloromethane at −78°C under argon. The results are shown in Table 2. In all cases, the corresponding 2,3-*anti*-products **2** were preferentially obtained in good yields. Both reactions of *E*- and *Z*-**1b** (R=cyclohexyl) gave 2,3-*anti*-**2b** in good yields with an *anti*-selectivity (entries 1 and 2). The reaction of *E*-**1b** gave 2,3-*anti*-**2b** in high yield relative to that of *Z*-**1b**, whereas the reaction of *Z*-**1b** provided the corresponding **2b** with high diastereoselectivity relative to that of *E*-**1b**. The reaction using **1d** (R=ethyl), **1e** (R=methyl) or **1f** (R=benzyl) showed high diastereoselectivity (entries 4–6), whereas **1b** (R=cyclohexyl) or **1c** (R=isopropyl) showed little diastereoselectivity (entries 1 and 3). The ratio of *anti*/*syn* in **2** was influenced by the bulkiness of the aliphatic substituent and the geometry of **1**.

In order to examine the structural effect of acetal on the stereochemistry of this aldol reaction, the reaction using cyclic acetal[13] was carried out under similar conditions as above. The reaction of **1** with 2-phenyl-1,3-dioxane **3** gave the corresponding aldol adducts **4** in good yields. The results are shown in Table 3. In the reaction of *E*-**1a** with **3**, *anti* and *syn* aldols were produced in a ratio of 95:5 (entry 1), which showed higher diastereoselectivity than the reaction of *E*-**1a** with benzaldehyde dimethyl acetal (Table 1, entry 1). Similarly, the reaction of *Z*-**1a** gave a mixture of aldols in a ratio of 96:4 (entry 2). The reaction of **1d** with **3** also showed higher diastereoselectivity (entry 4) than the reaction with dimethyl acetal (Table 2, entry 4). On the other hand, the moderate diastereoselectivity was observed in the reaction of **1c** with **3** (entry 3), whereas little selectivity was showed in the reaction with dimethyl acetal as mentioned above (Table 2, entry 3). The

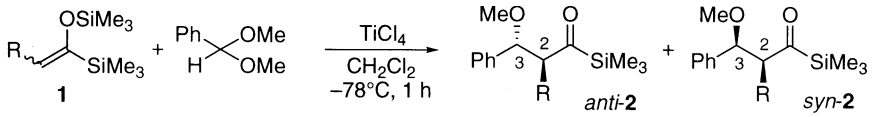
Table 1. Effect of Lewis acids in aldol reaction



Entry	**1a** *E*/*Z*	Lewis acid	Temperature (°C)	Time (h)	**2a**	
					Yield (%)[a]	*anti*/*syn*[b]
1	96/4	$TiCl_4$	−78	1	86	87/13
2	1/99				76	96/4
3	96/4	$SnCl_4$	−78	1	96	81/19
4	13/87				50	94/6
5	92/8	$BF_3{\cdot}OEt_2$	−30	2	92	80/20
6	12/88				45	89/11
7	92/8	$CF_3SO_3SiMe_3$	−30	1	76	76/24
8	24/76				77	84/16

Molar ratio: **1a**/acetal/Lewis acid=1:1:1.
[a] Isolated yield.
[b] Determined by ^{1}H NMR analysis.

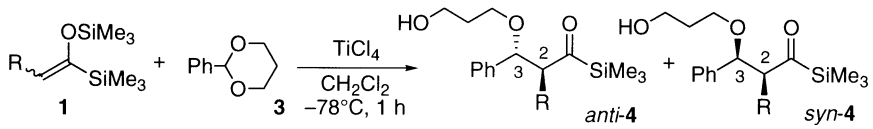
Table 2. Aldol reaction of acylsilane silyl enol ethers **1** with benzaldehyde dimethyl acetal using $TiCl_4$



Entry	Substrate	R	*E*/*Z*	Product	Yield (%)[a]	*anti*/*syn*[b]
1	**1b**	Chx[c]	99/1	**2b**	93	62/38
2	**1b**	Chx[c]	1/99	**2b**	85	73/27
3	**1c**	*i*-Pr	83/17	**2c**	98	56/44
4	**1d**	Et	80/20	**2d**	85	92/8
5	**1e**	Me	99/1	**2e**	71	96/4
6	**1f**	$PhCH_2$	96/4	**2f**	84	86/14

Molar ratio: **1**/acetal/$TiCl_4$=1:1:1.
[a] Isolated yield.
[b] Determined by ^1H NMR analysis.
[c] Chx=Cyclohexyl.

Table 3. Aldol reaction using 2-phenyl-1,3-dioxane



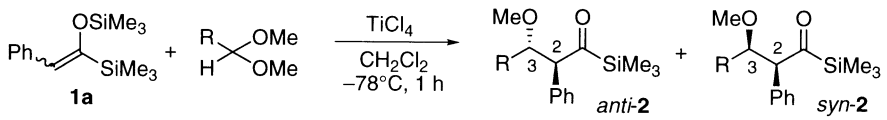
Entry	Substrate	R	*E*/*Z*	Product	Yield (%)[a]	*anti*/*syn*[b]
1	**1a**	Ph	95/5	**4a**	91	95/5
2	**1a**	Ph	15/85	**4a**	76	96/4
3	**1c**	*i*-Pr	99/1	**4c**	70	73/27
4	**1d**	Et	99/1	**4d**	51	97/3
5	**1e**	Me	99/1	**4e**	84	95/5

Molar ratio: **1/3**/$TiCl_4$=1:1:1.
[a] Isolated yield.
[b] Determined by ^1H NMR analysis.

diastereoselectivity of the reaction with **3** was, therefore, higher than that of the similar reaction with dimethyl acetal, irrespective of the geometry in **1**.

Next, several dimethyl acetals derived from aromatic and aliphatic aldehydes were examined in the aldol reaction with **1a**, and the results are shown in Table 4. The reaction of *E*- or *Z*-**1a** with dimethyl acetals of aromatic aldehydes afforded the *anti* aldol adducts preferentially, irrespective of the geometry in **1a** (entries 1–4). On the other hand, acetals of aliphatic aldehydes reacted with *E*-**1a** to yield the corresponding adducts with low stereoselectivity (entries 5, 7 and 9), while high *anti*-selectivity was observed in the reaction of acetals of aliphatic aldehydes with *Z*-**1a** (entries 6, 8 and 10).

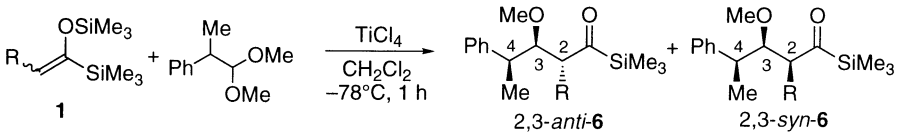
Table 4. Substituent effect of acetal in aldol reaction of acylsilane silyl enol ether **1a**



Entry	**1a** *E*/*Z*	Acetal R	Product	Yield (%)[a]	*anti*/*syn*[b]
1	95/5	Ph	**2a**	86	87/13
2	15/85	Ph	**2a**	76	96/4
3	95/5	*o*-CH_3–C_6H_4	**2g**	73	89/11
4	15/85	*o*-CH_3–C_6H_4	**2g**	15	86/14
5	95/5	Me	**2h**	52	49/51
6	15/85	Me	**2h**	64	89/11
7	95/5	*n*-C_7H_{15}	**2i**	69	46/54
8	15/85	*n*-C_7H_{15}	**2i**	69	87/13
9	95/5	$PhCH_2$	**2j**	80	37/63
10	15/85	$PhCH_2$	**2j**	76	88/12

Molar ratio: **1a**/acetal/$TiCl_4$=1:1:1.
[a] Isolated yield.
[b] Determined by ^1H NMR analysis.

Table 5. Aldol reaction using 2-phenylpropionaldehyde dimethyl acetal



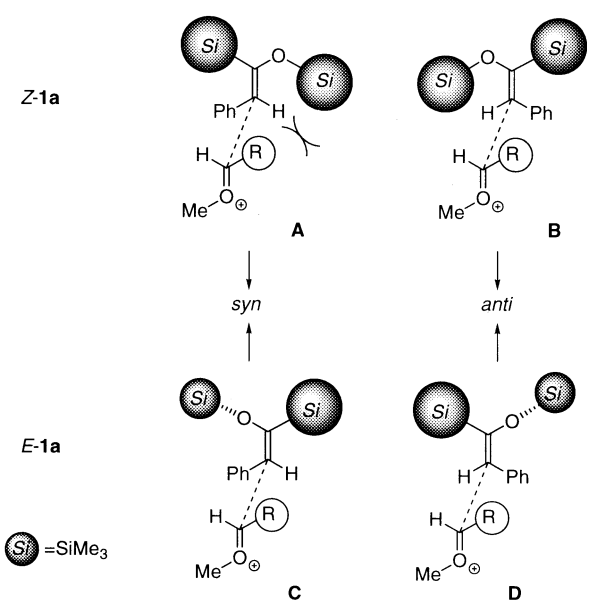
Entry	Substrate	R	*E*/*Z*	Product	Yield (%)[a]	2,3-*anti*/2,3-*syn*[b]
1	**1a**	Ph	95/5	**6a**	84	25/75
2	**1a**	Ph	15/85	**6a**	29	82/18
3	**1b**	Chx[c]	99/1	**6b**	79	9/91
4	**1c**	*i*-Pr	83/17	**6c**	60	10/90
5	**1d**	Et	80/20	**6d**	76	37/63
6	**1f**	$PhCH_2$	75/25	**6f**	97	38/62

Molar ratio: **1**/acetal/$TiCl_4$=1:1:1.
[a] Isolated yield.
[b] Determined by ^1H NMR analysis.
[c] Chx=Cyclohexyl.

The aldol reaction using the chiral acetals as the substrate provides the corresponding aldols containing the contiguous chiral centers.[14] Then we turned out attention to the aldol reaction of **1** with 2-phenylpropionaldehyde dimethyl acetal as an acetal having a stereogenic center. The reaction was carried out in a similar manner as above, and the results are summarized in Table 5. In all cases, only two isomers (2,3-*anti*-3,4-*syn*-**6** and 2,3-*syn*-3,4-*syn*-**6**) among the four possible diastereomeric products were formed with complete Cram-type (3,4-*syn*) selectivity. Similar to the results of the reaction of **1** with aliphatic acetals (Table 4, entries 5–10), the reaction of *E*-**1** gave 2,3-*syn*-**6**, whereas that of *Z*-**1** gave 2,3-*anti*-**6**, respectively. For the reaction of **1** having aliphatic substituent, the stereoselectivity of the reaction increased with increasing the bulkiness of the substituent R (entries 3–6).

2.3. Mechanistic considerations

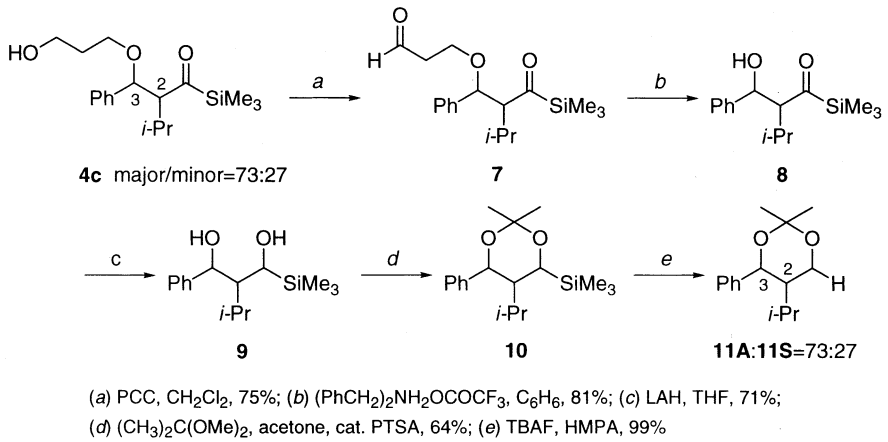
In general, the stereoselection of Lewis acid mediated aldol reactions of silyl enol ether with aldehyde is understood by assuming acyclic extended transition structures.[15] Thus, the following mechanism for the reaction of **1a** derived from benzyl silyl ketone with acetal is proposed (Scheme 2). The proposed open model assumes that two oxygen atoms are as remote as possible in order to minimize their electrostatic repulsion. For the *Z* isomers, Si group attached to oxygen atom is on the sp^2 plane of the carbon–carbon double bond apart from Si group because of the steric repulsion between Si(O) and Si group, so transition structure **A** is disfavored compared to **B** by the large nonbonded steric repulsion between Si(O) and R. Thus, the reaction of *Z*-**1** leads to *anti* products with high stereoselectivity by way of transition structure **B**. In contrast, *E*-**1** adopts conformations in which Si group attached to oxygen atom is below the sp^2 plane of the carbon–carbon double bond because of the steric repulsion between Si(O) and the phenyl group that is coplanar to the sp^2 plane of the carbon–carbon double bond.[16] In the case of the reaction using acetals of aromatic aldehydes, transition structure **C** is disfavored compared to **D** by the nonbonded steric repulsion between Si and R. In addition, transition structure **D** may be favored by a π–π stacking between the phenyl group of **1a** and the aromatic group of acetal. As a result, the reaction of *E* isomers with acetals of aromatic aldehydes is *anti* selective. On the other hand, transition structure **D** is disfavored due to the *gauche* repulsion between the phenyl group of **1a** and R where acetals of aliphatic aldehydes are used. In addition, the nonbonded steric repulsion between Si and aliphatic group in **C** would be smaller than that between Si and aromatic group. Thus, the reaction of *E* isomers with acetals of aliphatic aldehydes proceeded with low diastereoselectivity. Similarly, the results in Table 2 can also be explained as mentioned above using the models exchanged between Ph and R. On the whole, approach of acetal moiety to **1** in transition structure **C** or **D** would be easier than that in transition structure **A** or **B**, so higher yields were observed in the reaction of *E*-**1** with acetals of aromatic aldehydes.



Scheme 2.

2.4. Stereochemical assignment

Stereochemical assignment of the resulting aldol adduct **4c** was performed by conversion into the corresponding acetone ketal (Scheme 3). Treatment of a diastereomeric mixture **4c** (73:27), obtained by the reaction of 2-phenyl-1,3-dioxane with silyl enol ether **1c** (Table 3, entry 3), with PCC in dichloromethane followed by ether cleavage



Scheme 3. Conversion of aldol adduct **4c** into cyclic ketal.

(β-elimination) with dibenzylammonium trifluoroacetate gave 3-hydroxyacylsilane **8**.[13c,17] Reduction of the carbonyl group of the resulting acylsilane **8** with LAH yielded the 1,3-dihydroxypropylsilane derivative **9**, which was then subjected to treatment with acetone dimethyl acetal,[18] affording the 2-silyl-1,3-dioxane derivative **10**. Protiodesilylation of the resulting cyclic acetal **10** by tetrabutylammonium fluoride gave a mixture of two diastereomers (**11A/11S**=73:27).[19]

The vicinal coupling constant of 10.6 Hz observed between the protons on C-2 and C-3 in the ^{1}H NMR spectrum of major product **11A** indicates an axial–axial arrangement of these two protons, which is correlated to 2,3-*anti* configuration in major isomer of aldol **4c**. On the other hand, the corresponding vicinal coupling constant of 3.4 Hz for **11S** indicates an axial–equatorial arrangement of these two protons, so the minor isomer of aldol **4c** is assigned to 2,3-*syn* configuration (Scheme 4). Thus, the stereoconfiguration of other aldol adducts **2** and **4** was predicted by comparing with the $^3J(H^2,H^3)$ coupling constants of **4c**.

3. Conclusion

In summary, $TiCl_4$-catalyzed aldol reaction of acylsilane silyl enol ethers and acetals has been described. Silyl enol ethers derived from enolizable acylsilanes reacted with acetals of aromatic aldehydes to afford the corresponding aldol adducts in high yields with good *anti*-selectivity, irrespective of the double bond stereochemistry in acylsilane silyl enol ethers. On the other hand, *E*-isomers of silyl enol ethers reacted with acetals of aliphatic aldehydes to afford the corresponding adducts with *syn*-selectivity, while the reaction of *Z*-isomers with acetals of aliphatic aldehydes gave the corresponding adducts with *anti*-selectivity. In particular, when 2-phenylpropionaldehyde dimethyl acetal with a stereogenic center was used, complete β,γ-diastereoselectivity of aldol adducts was observed. Further applications of the resulting acylsilanes are now in progress in our laboratory. The results will be reported in due course.

4. Experimental

4.1. General

IR spectra were recorded on a JASCO A-202 or SHIMADZU FTIR-8300 infrared spectrometer.^{1}H and ^{13}C NMR spectra were recorded on a JEOL JNM FX-100s, LA-400 spectrometer, and tetramethylsilane (TMS) served as the internal standard. Mass spectra were recorded on a JEOL JMS-SX102A, JMS-AM50 or Hitachi M-80 mass spectrometer.

Thin layer chromatography and flash-column chromatography were performed by the use of Merck's silica-gel 60F 254 and silica-gel BW-127ZH (Fuji Silysia), respectively.

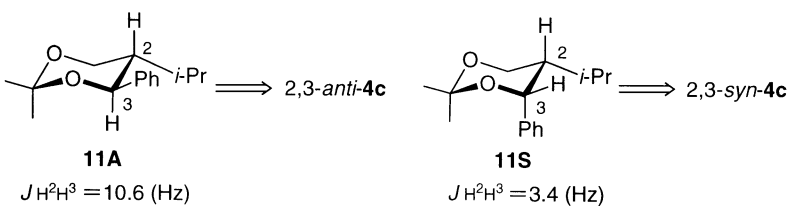
All the solvents were distilled and stored over a drying agent. *n*-Butyllithium (1.6 M solution in hexane) was purchased from Aldrich Chemical Co., Inc.

All reactions were carried out under argon atmosphere in dried glassware.

Acylsilanes were prepared according to the literature procedures.

4.2. A typical procedure for the preparation of *E*-1-trimethylsiloxy-1-trimethylsilyl-2-phenylethylene

A 300 ml, four-necked, round-bottomed flask equipped with an argon inlet adapter, rubber septum, thermometer, drop-



Scheme 4.

funnel, and magnetic stirring bar was charged with 150 ml of dry THF and diisopropylamine (2.8 ml, 20 mmol), cooled to −78°C and *n*-butyllithium (1.6 M solution in hexane, 12.5 ml, 20 mmol) was added slowly over several minutes. After 30 min, 20 ml of hexamethylphosphoric triamide and a solution of 20 ml of acylsilane in THF were added. After 5 min, the reaction mixture was warmed to room temperature. After stirring for 1.5 h, a solution of Me_3SiCl (2.6 g, 24 mmol) was added, and then stirred further 30 min. Saturated NaCl solution was then added, and aqueous layer was extracted with diethyl ether. The combined organic phase were washed with saturated NaCl solution, and dried over Na_2SO_4, filtered, concentrated. Column chromatography on a silica-gel afforded *E*-1-trimethyloxy-1-trimethylsilyl-2-phenylethylene as pale yellow oils.

4.3. A typical procedure for the preparation of *Z*-1-trimethylsiloxy-1-trimethylsilyl-2-phenylethylene

A 300 ml, four-necked, round-bottomed flask equipped with an argon inlet adapter, rubber septum, thermometer, dropfunnel, and magnetic stirring bar was charged with 150 ml of dry THF and diisopropylamine (2.8 ml, 20 mmol), cooled to −78°C and *n*-butyllithium (1.6 M solution in hexane, 12.5 ml, 20 mmol) was added slowly over several minutes. After 30 min, a solution of 20 ml of acylsilane in THF was added. After 30 min, a solution of Me_3SiCl (2.6 g, 24 mmol) was added, The reaction mixture was stirred 30 min and then allowed to warm to room temperature. Saturated NaCl solution was then added, and aqueous layer was extracted with diethyl ether. The combined organic phase were washed with saturated NaCl solution, and dried over Na_2SO_4, filtered, concentrated. Column chromatography on a silica-gel afforded *Z*-1-trimethyloxy-1-trimethylsilyl-2-phenylethylene as pale yellow oils.

4.4. Aldol reaction of acylsilane silyl enol ether with acetal

A 30 ml of, three-necked, round-bottomed flask equipped with argon adapter, rubber septum, thermometer and magnetic stirring bar was charged with 5 ml of dichloromethane and 0.5 mmol of Lewis acid. This solution was cooled to −78°C and acetal solution (0.5 mmol in 1 ml of dichloromethane) was added rapidly via syringe. After 5 min, a solution of acylsilane silyl enol ether (0.5 mmol) was added. After completion of the reaction evidenced by GC (usually after being stirred for 1 h at −78°C), saturated NaCl solution was then added, and the resulting mixture was separated. The aqueous layer was extracted with diethyl ether. The combined organic phase was washed with saturated NaCl solution, and dried over Na_2SO_4, filtered, concentrated. Column chromatography on a silica-gel afforded 3-alkoxyacylsilanes as pale yellow oils.

4.4.1. 3-Methoxy-2,3-diphenyl-1-trimethylsilyl-1-propanone (2a). IR (neat) 3100, 3090, 3060, 2990, 2960, 2930, 2850, 1655, 1595, 1500, 1460, 1260, 1110, 840 cm^{-1}. HRMS calcd for $C_{18}H_{20}OSi$ ($[M-CH_3OH]^+$) 280.1283, found 280.1275. *anti*-**2a**: ^1H NMR ($CDCl_3$) δ 7.23–6.79 (m, 10H), 4.79 (d, J=10.0 Hz, 1H), 4.45 (d, J=10.0 Hz, 1H), 3.16 (s, 3H), 0.08 (s, 9H). *syn*-**2a**: ^1H NMR ($CDCl_3$) δ 7.44–7.19 (m, 10H), 4.79 (d, J=9.0 Hz, 1H), 4.53 (d, J=9.0 Hz, 1H), 3.04 (s, 3H), −0.19 (s, 9H).

4.4.2. 2-Cyclohexyl-3-methoxy-3-phenyl-1-trimethylsilyl-1-propanone (2b). IR (neat) 3080, 3050, 3020, 2920, 2840, 2810, 1705, 1635, 1450, 1245, 1200, 1090, 840 cm^{-1}. HRMS calcd for $C_{18}H_{26}OSi$ ($[M-CH_3OH]^+$) 286.1753, found 286.1760. *anti*-**2b**: ^1H NMR ($CDCl_3$) δ 7.38–6.98 (m, 5H), 4.33 (d, J=10.3 Hz, 1H), 3.68 (dd, J=10.3, 3.9 Hz, 1H), 3.10 (s, 3H), 1.97–0.72 (m, 11H), −0.23 (s, 9H). *syn*-**2b**: ^1H NMR ($CDCl_3$) δ 7.95–7.10 (m, 5H), 4.44 (d, J=9.5 Hz, 1H), 3.37 (dd, J=9.5, 4.6 Hz, 1H), 2.98 (s, 3H), 1.95–0.50 (m, 11H), 0.18 (s, 9H).

4.4.3. 2-Isopropyl-3-methoxy-3-phenyl-1-trimethylsilyl-1-propanone (2c). IR (neat) 3090, 3070, 3040, 2970, 2905, 2890, 2820, 1635, 1495, 1465, 1455, 1385, 1365, 1255, 1135, 1105, 1085, 845 cm^{-1}. HRMS calcd for $C_{16}H_{26}O_2Si$ (M^+) 278.1702, found 278.1710. *anti*-**2c**: ^1H NMR ($CDCl_3$) δ 7.32–7.01 (m, 5H), 4.32 (d, J=10.3 Hz, 1H), 3.69 (dd, J=10.3, 4.2 Hz, 1H), 3.11 (s, 3H), 2.27–2.01 (m, 1H), 1.03 (d, J=6.8 Hz, 3H), 1.00 (d, J=7.1 Hz, 3H), −0.22 (s, 9H). *syn*-**2c**: ^1H NMR ($CDCl_3$) δ 7.33 (br, 5H), 4.40 (d, J=9.5 Hz, 1H), 3.39 (dd, J=9.5 Hz, 5.5 Hz, 1H), 2.99 (s, 3H), 1.65–1.40 (m, 1H), 0.78 (d, J=6.8 Hz, 6H), 0.19 (s, 9H).

4.4.4. 2-Ethyl-3-methoxy-3-phenyl-1-trimethylsilyl-1-propanone (2d). IR (neat) 3120, 3100, 3065, 3005, 2970, 2945, 2920, 2850, 1655, 1510, 1465, 1260, 1215, 1140, 1105, 965, 849 cm^{-1}. HRMS calcd for $C_{13}H_{19}O_2Si$ ($[M-C_2H_5]^+$) 235.1154, found 235.1171. *anti*-**2d**: ^1H NMR ($CDCl_3$) δ 7.36–7.23 (m, 5H), 4.13 (d, J=10.0 Hz, 1H), 3.31 (dt, J=10.0, 3.4 Hz, 1H), 2.99 (s, 3H), 1.67–1.34 (m, 2H), 0.58 (t, J=7.1 Hz, 3H), 0.24 (s, 9H). *syn*-**2d**: ^1H NMR ($CDCl_3$) δ 3.14 (s, 3H), −0.14 (s, 9H).

4.4.5. 2,3-*anti*-2-Methyl-3-methoxy-3-phenyl-1-trimethylsilyl-1-propanone (*anti*-2e). IR (neat) 3086, 3063, 3030, 2963, 2932, 2903, 1643, 1454, 1248, 1096 cm^{-1}. HRMS calcd for $C_{14}H_{22}O_2Si$ (M^+) 250.1389, found 250.1381. ^1H NMR ($CDCl_3$) δ 7.90–7.23 (m, 5H), 4.18 (d, J=9.9 Hz, 1H), 3.35 (dq, J=9.9, 7.1 Hz, 1H), 3.03 (s, 3H), 0.59 (d, J=7.1 Hz, 3H), 0.25 (s, 9H).

4.4.6. 2-Benzyl-3-methoxy-3-phenyl-1-trimethylsilyl-1-propanone (2f). IR (neat) 3095, 3075, 3045, 2970, 2945, 2920, 2830, 1645, 1605, 1498, 1455, 1255, 1205, 1105, 1090, 845 cm^{-1}. HRMS calcd for $C_{19}H_{22}OSi$ ($[M-CH_3OH]^+$) 294.1440, found 294.1441. *anti*-**2f**: ^1H NMR ($CDCl_3$) δ 7.78–6.82 (m, 10H), 4.17 (d, J=10.0 Hz, 1H), 3.96–3.71 (m, 1H), 3.00 (s, 3H), 2.74 (dd, J=12.9, 11.5 Hz, 1H), 2.06 (dd, J=12.9, 3.4 Hz, 1H), −0.09 (s, 9H). *syn*-**2f**: ^1H NMR ($CDCl_3$) δ 3.19 (s, 3H), −0.58 (s, 9H).

4.4.7. 3-Methoxy-2-phenyl-3-(2-tolyl)-1-trimethylsilyl-1-propanone (2g). IR (neat) 2920, 1661, 1249, 1100 cm^{-1}. HRMS calcd for $C_{20}H_{26}O_2Si$ (M^+) 326.1702, found 326.1722. *anti*-**2g**: ^1H NMR ($CDCl_3$) δ 7.40–6.82 (m, 9H), 5.12 (d, J=10.0 Hz, 1H), 4.57 (d, J=10.0 Hz, 1H), 3.11 (s, 3H), 1.94 (s, 3H), 0.09 (s, 9H). *syn*-**2g**: ^1H NMR ($CDCl_3$) δ 7.40–6.82 (m, 9H), 5.03 (d, J=8.3 Hz, 1H), 4.60 (d, J=8.3 Hz, 1H), 3.00 (s, 3H), 2.44 (s, 3H), −0.17 (s, 9H).

4.4.8. 3-Methoxy-2-phenyl-1-trimethylsilyl-1-butanone (2h). IR (neat) 2900, 1653, 1250, 1100 cm^{-1}. HRMS calcd for $C_{13}H_{18}OSi$ ($[M-CH_3OH]^+$) 218.1127, found 218.1131. *anti*-**2h**: ^1H NMR ($CDCl_3$) δ 7.25–7.15 (m, 5H), 4.10 (d, J=9.5 Hz, 1H), 3.96 (dq, J=9.5, 9.3 Hz, 1H), 3.20 (s, 3H), 0.82 (d, 3H), 0.00 (s, 9H). *syn*-**2h**: ^1H NMR ($CDCl_3$) δ 7.35–7.10 (m, 5H), 4.05 (d, J=8.5 Hz, 1H), 3.96 (dq, J=8.5, 6.1 Hz, 1H), 3.01 (s, 3H), 1.08 (d, 3H), −0.06 (s, 9H).

4.4.9. 3-Methoxy-2-phenyl-1-trimethylsilyl-1-decanone (2i). IR (neat) 3063, 3028, 2928, 2856, 1643, 1454, 1250, 1099 cm^{-1}. HRMS calcd for $C_{20}H_{34}O_2Si$ (M^+) 334.2328, found 334.2333. *anti*-**2i**: ^1H NMR ($CDCl_3$) δ 7.31–7.13 (m, 5H), 4.34 (d, J=9.6 Hz, 1H), 3.98–3.93 (m, 1H), 3.32 (s, 3H), 1.30–1.03 (m, 12H), 0.84 (t, J=6.9 Hz, 3H), 0.06 (s, 9H). *syn*-**2i**: ^1H NMR ($CDCl_3$) δ 7.38–7.19 (m, 5H), 4.16 (d, J=8.2 Hz, 1H), 3.82–3.75 (m, 1H), 3.00 (s, 3H), 1.48–1.16 (m, 12H), 0.88 (t, J=6.9 Hz, 3H), 0.00 (s, 9H).

4.4.10. 3-Methoxy-2,4-diphenyl-1-trimethylsilyl-1-butanone (2j). IR (neat) 2920, 1640, 1250, 1100 cm^{-1}. HRMS calcd for $C_{19}H_{22}OSi$ ($[M-CH_3OH]^+$) 294.1440, found 294.1439. *anti*-**2j**: ^1H NMR ($CDCl_3$) δ 7.32–7.01 (m, 10H), 4.30 (d, J=9.5 Hz, 1H), 4.16 (ddd, J=9.5, 8.0, 2.9 Hz, 1H), 3.10 (s, 3H), 2.64 (dd, J=14.0, 2.9 Hz, 1H), 2.36 (dd, J=14.0, 8.0 Hz, 1H), 0.03 (s, 9H). *syn*-**2j**: ^1H NMR ($CDCl_3$) δ 7.44–7.12 (m, 10H), 4.03 (d, J=6.9 Hz, 1H), 4.03 (ddd, J=6.9, 6.3, 3.3 Hz, 1H), 2.90 (s, 3H), 2.87 (dd, J=14.0, 3.3 Hz, 1H), 2.71 (dd, J=14.0, 6.3 Hz, 1H), 0.03 (s, 9H).

4.4.11. 2,3-*anti*-3-(3′-Hydroxypropyloxy)-2,3-diphenyl-1-trimethylsilyl-1-propanone (*anti*-4a). IR (neat) 3555, 2890, 1640, 1250, 1110 cm^{-1}. HRMS calcd for $C_{18}H_{20}OSi$ ($[M-CH_3OH]^+$) 280.1283, found 280.1283. ^1H NMR ($CDCl_3$) δ 7.34–6.83 (m, 10H), 4.88 (d, J=9.9 Hz, 1H), 4.45 (d, J=9.9 Hz, 1H), 3.70 (t, 2H), 3.47 (m, 2H), 2.73 (br, 1H), 1.72 (m, 2H), 0.09 (s, 9H).

4.4.12. 3-(3′-Hydroxypropyloxy)-2-isopropyl-3-phenyl-1-trimethylsilyl-1-propanone (4c). IR (neat) 3461, 1633, 1250, 1100 cm^{-1}. HRMS calcd for $C_{18}H_{30}O_2Si$ (M^+) 322.1964, found 322.1963. *anti*-**4c**: ^1H NMR ($CDCl_3$) δ 7.35–7.16 (m, 5H), 4.42 (d, J=10.2 Hz, 1H), 3.70 (m, 2H), 3.47 (m, 2H), 3.36 (t, 1H), 1.80 (br, 1H), 1.55 (m, 3H), 1.05 (d, 3H), 1.00 (d, 3H), −0.23 (s, 9H). *syn*-**4c**: ^1H NMR ($CDCl_3$) δ 7.37–7.20 (m, 5H), 4.52 (d, J=9.0 Hz, 1H), 3.61 (m, 2H), 3.49 (dd, 2H), 3.28 (t, 1H), 2.17 (br, 1H), 1.57 (m, 2H), 1.71 (m, 1H), 0.81 (d, 3H), 0.76 (d, 3H), 0.15 (s, 9H).

4.4.13. 2,3-*anti*-2-Ethyl-3-(3′-hydroxypropyloxy)-3-phenyl-1-trimethylsilyl-1-propanone (*anti*-4d). IR (neat) 3440, 1645, 1252, 1100 cm^{-1}. HRMS calcd for $C_{14}H_{20}OSi$ ($[M-C_3H_8O_2]^+$) 232.1283, found 232.1270. ^1H NMR ($CDCl_3$) δ 7.38–7.26 (m, 5H), 4.32 (d, J=9.8 Hz, 1H), 3.61 (ddd, 2H), 3.38 (dt, J=9.8 Hz, 1H), 3.26 (t, 2H), 1.87 (br, 1H), 1.66 (m, 2H), 1.41 (m, 2H), 0.60 (t, 3H), 0.24 (s, 9H).

4.4.14. 2,3-*anti*-3-(3′-Hydroxypropyloxy)-2-methyl-3-phenyl-1-trimethylsilyl-1-propanone (*anti*-4e). IR (neat) 3483, 3094, 3065, 3030, 2959, 2930, 2874, 1643, 1454, 1250, 1090 cm^{-1}. HRMS calcd for $C_{13}H_{18}OSi$ ($[M-C_3H_8O_2]^+$) 218.1127, found 218.1131. ^1H NMR ($CDCl_3$) δ 7.47–7.24 (m, 5H), 4.38 (d, J=9.9 Hz, 1H), 3.63 (t, J=5.3 Hz, 2H), 3.38 (dq, J=9.9, 7.1 Hz, 1H), 3.32 (t, J=5.8 Hz, 2H), 2.02 (br, 1H), 1.75–1.57 (m, 2H), 0.59 (d, J=7.1 Hz, 3H), 0.26 (s, 9H).

4.4.15. 3-Methoxy-2,4-diphenyl-1-trimethylsilyl-1-pentanone (6a). IR (neat) 2900, 1655, 1255, 1100 cm^{-1}. HRMS calcd for $C_{20}H_{24}OSi$ ($[M-CH_3OH]^+$) 308.1596, found 308.1609. 2,3-*anti*-**6a**: ^1H NMR ($CDCl_3$) δ 7.54–7.16 (m, 10H), 4.49 (d, J=10.0 Hz, 1H), 4.09 (dd, J=10.0, 2.2 Hz, 1H), 2.86 (s, 3H), 2.50 (m, 1H), 1.25 (d, 3H), 0.07 (s, 9H). 2,3-*syn*-**6a**: ^1H NMR ($CDCl_3$) δ 7.31–7.12 (m, 10H), 4.14 (d, J=6.8 Hz, 1H), 3.96 (dd, J=6.8, 5.6 Hz, 1H), 2.88 (s, 3H), 1.45 (m, 1H), 1.28 (d, 3H), −0.09 (s, 9H).

4.4.16. 2-Cyclohexyl-3-methoxy-4-phenyl-1-trimethylsilyl-1-pentanone (6b). IR (neat) 3060, 3035, 2980, 2940, 2850, 1632, 1498, 1450, 1248, 1094, 842 cm^{-1}. HRMS calcd for $C_{21}H_{34}O_2Si$ (M^+) 346.2328, found 346.2321. 2,3-*anti*-**6b**: ^1H NMR ($CDCl_3$) δ 7.46–6.98 (m, 5H), 3.62 (dd, J=8.1, 3.4 Hz, 1H), 3.43 (dd, J=8.1, 4.4 Hz, 1H), 3.08 (s, 3H), 2.66 (dq, J=7.0, 3.4 Hz, 1H), 1.88–0.63 (m, 11H), 1.27 (d, J=7.0 Hz, 3H), 0.14 (s, 9H). 2,3-*syn*-**6b**: ^1H NMR ($CDCl_3$) δ 2.96 (s, 3H), 0.16 (s, 9H).

4.4.17. 2-Isopropyl-3-methoxy-4-phenyl-1-trimethylsilyl-1-pentanone (6c). IR (neat) 3080, 3060, 3035, 2970, 2940, 2905, 2880, 2830, 1642, 1498, 1452, 1250, 1090, 845 cm^{-1}. HRMS calcd for $C_{18}H_{30}O_2Si$ (M^+) 306.2015, found 306.2025. 2,3-*anti*-**6c**: ^1H NMR ($CDCl_3$) δ 7.41–7.02 (m, 5H), 3.63 (dd, J=8.2, 3.7 Hz, 1H), 3.42 (dd, J=8.2, 4.9 Hz, 1H), 3.07 (s, 3H), 2.67 (dq, J=7.1, 3.7 Hz, 1H), 2.13–1.92 (m, 1H), 1.24 (d, J=7.1 Hz, 3H), 0.93 (t, J=7.1 Hz, 3H), 0.15 (s, 9H). 2,3-*syn*-**6c**: ^1H NMR ($CDCl_3$) δ 2.65 (s, 3H), 1.31 (d, J=7.0 Hz, 3H), 0.17 (s, 9H).

4.4.18. 2-Ethyl-3-methoxy-4-phenyl-1-trimethylsilyl-1-pentanone (6d). IR (neat) 3080, 3060, 3040, 2970, 2970, 2945, 2880, 2840, 1640, 1499, 1455, 1380, 1255, 1097, 845 cm^{-1}. HRMS calcd for $C_{17}H_{28}O_2Si$ (M^+) 292.1859, found 292.1843. 2,3-*anti*-**6d**: ^1H NMR ($CDCl_3$) δ 7.31–7.19 (m, 5H), 3.43 (dd, J=9.2, 3.4 Hz, 1H), 3.29 (ddd, J=10.1, 9.2, 3.7 Hz, 1H), 2.89 (dq, J=7.0, 3.4 Hz, 1H), 2.74 (s, 3H), 1.73–1.65 (m, 1H), 1.38–1.32 (m, 1H), 1.34 (d, J=7.0 Hz, 3H), 0.77 (t, J=7.0 Hz, 3H), 0.17 (s, 9H). 2,3-*syn*-**6d**: ^1H NMR ($CDCl_3$) δ 7.33–7.21 (m, 5H), 3.52 (dd, J=6.1, 5.8 Hz, 1H), 3.15 (s, 3H), 3.00 (ddd, J=9.2, 5.8, 4.0 Hz, 1H), 2.76 (dq, J=7.0, 6.7 Hz, 1H), 1.85–1.74 (m, 1H), 1.57–1.45 (m, 1H), 1.31 (d, J=7.0 Hz, 3H), 0.76 (t, J=7.5 Hz, 3H), 0.12 (s, 9H).

4.4.19. 2-Benzyl-3-methoxy-4-phenyl-1-trimethylsilyl-1-pentanone (6f). IR (neat) 3075, 3055, 3020, 2970, 2960, 2895, 2820, 1638, 1602, 1497, 1449, 1245, 1083, 835 cm^{-1}. HRMS calcd for $C_{22}H_{30}O_2Si$ (M^+) 354.2015, found 354.2015. 2,3-*anti*-**6f**: ^1H NMR ($CDCl_3$) δ 7.31–7.01 (m, 10H), 3.78 (ddd, J=11.3, 9.5, 4.0 Hz, 1H), 3.46 (dd, J=9.5, 3.4 Hz, 1H), 3.04 (dq, J=7.0, 3.4 Hz, 1H), 2.93–2.72 (m, 1H), 2.70 (s, 3H), 2.56 (dd, J=13.1, 4.0 Hz, 1H), 1.44 (d, J=7.0 Hz, 3H), −0.16 (s, 9H). 2,3-*syn*-**6f**: ^1H NMR ($CDCl_3$) δ 7.35–7.02 (m, 10H), 3.52 (ddd, J=10.4, 4.9,

4.0 Hz, 1H), 3.47 (dd, *J*=6.3, 4.9 Hz, 1H), 3.22 (s, 3H), 2.98 (dq, *J*=13.4, 10.4 Hz, 1H), 2.83 (dd, *J*=13.4, 3.7 Hz, 1H), 2.76 (qu, *J*=6.7 Hz, 1H), 1.37 (d, *J*=7.0 Hz, 3H), −0.16 (s, 9H).

4.5. Conversion of aldol adducts into cyclic ketals (11)

4.5.1. 2-Isopropyl-3-(3′-oxopropyloxy)-3-phenyl-1-trimethylsilylpropanone (7).[13c] A 30 ml of, three-necked, round-bottomed flask equipped with argon adapter, rubber septum, thermometer and magnetic stirring bar was charged with dichloromethane (5 ml) and 1.05 mmol of the diastereomeric mixture of aldol adducts (73:27) and pyridinium chlorochromate (3.2 mmol) added. This mixture was stirred at room temperature in a flask protected from light. 10 ml of ether was then added and the product filtered through Florisil. The residue was washed with 100 ml of ether and the triturant was then passed through the column. The solvent was evaporated to give diastereomeric mixture of keto aldehyde **7** (73:27) in 75% yield. This material was used directly without purification.

4.5.2. 3-Hydroxy-2-isopropyl-3-phenyl-1-trimethylsilylpropanone (8).[13c] The diastereomeric mixture of keto aldehyde (0.93 mmol) was dissolved in benzene (12 ml). To this stirred solution at 50°C was added dibenzylammonium trifluoroacetate (3.86 mmol). After 10 min the solution was applied to a silica-gel column and eluted successively with hexane (100 ml), ether (200 ml). The corresponding 3-hydroxy acylsilane **8** (73:27) was thus obtained in 81% yield. This material was used directly without purification.

4.5.3. 1,3-Dihydroxy-2-isopropyl-3-phenyl-1-trimethylsilylpropane (9). The diastereomeric mixture of 3-hydroxy acylsilane (1 mmol) was dissolved THF (5 ml). This solution was cooled to −78°C and lithium aluminum hydride solution (2 mmol in THF) was added slowly. After 30 min, 5 ml of methanol was added to quench, and the resulting mixture was partitioned between H_2O and diethyl ether. The aqueous layer was extracted with diethyl ether. The combined organic phase were washed with saturated NaCl solution, and dried over Na_2SO_4, filtered, concentrated. Column chromatography on a silica-gel afforded dihydroxytrimethylsilylpropane **9** (73:27) in 71% yield. IR (neat) 3381, 3313, 3302, 1493, 1452, 1251, 1035, 1025, 1002, 996 cm^{-1}. HRMS calcd for $C_{15}H_{26}O_2Si$ (M^+) 266.1702, found 266.1686. Major isomer: ^1H NMR ($CDCl_3$) δ 7.23–7.18 (m, 5H), 5.09 (d, *J*=7.2 Hz, 1H), 3.39 (s, 1H), 3.14 (s, 1H), 2.20 (m, 1H), 1.53 (ddd, 1H), 1.17 (d, 3H), 1.08 (d, 3H), 0.04 (s, 9H). Minor isomer: ^1H NMR ($CDCl_3$) δ 7.26–7.21 (m, 5H), 5.25 (d, *J*=2.0 Hz, 1H), 3.85 (s, 1H), 2.67 (s, 1H), 2.06 (m, 1H), 1.83 (ddd, 1H), 1.27 (d, 3H), 1.11 (d, 3H), −0.04 (s, 9H).

4.5.4. 5-Isopropyl-2,2-dimethyl-6-phenyl-4-trimethylsilyl-1,3-dioxane (10).[18] The diastereomeric mixture of dihydroxytrimethylsilylpropane (0.2 mmol) was dissolved in dry acetone (1.5 ml) and reacted at 23°C for 2 h with acetone dimethyl acetal (0.62 mmol) and *p*-toluene sulfonic acid (3 mg). It was poured on 3 ml of an ice-cold $NaCO_3$ solution, the acetone was evaporated, and the aqueous residue extracted with ether. Evaporation of the solvent and column chromatography on a silica-gel gave dioxane derivative (**10**) in 64% yield. IR (neat) 3033, 2956, 2930, 2915, 2901, 2818, 2341, 1952, 1361, 1100, 1030 cm^{-1}. HRMS calcd for $C_{15}H_{21}O_2$ ($[M-SiMe_3]^+$) 233.1542, found 233.1537. Major isomer: ^1H NMR ($CDCl_3$) δ 7.42–7.23 (m, 5H), 4.66 (d, *J*=8.1 Hz, 1H), 3.92 (d, *J*=5.4 Hz, 1H), 2.23 (m, 1H), 1.99 (m, 1H), 1.43 (s, 3H), 1.26 (s, 3H), 1.19 (d, 3H), 0.59 (d, 3H), 0.11 (s, 9H). Minor isomer: ^1H NMR ($CDCl_3$) δ 7.41–7.18 (m, 5H), 5.23 (d, *J*=3.1 Hz, 1H), 3.98 (d, *J*=2.9 Hz, 1H), 1.83 (m, 1H), 1.66 (m, 1H), 1.49 (m, 1H), 1.43 (s, 3H), 1.11 (d, 3H), 0.44 (d, 3H), 0.10 (s, 9H).

4.5.5. 5-Isopropyl-2,2-dimethyl-4-phenyl-1,3-dioxane (11). The diastereomeric mixture of dioxane derivative **10** (0.1 mmol) was dissolved in hexamethylphosphoric triamide (1 ml) and tetrabutylammonium fluoride solution (0.5 mmol in THF) was added and reacted at 40°C for 8 h. It was poured on NaCl solution, and the resulting mixture was partitioned between H_2O and diethyl ether. The aqueous layer was extracted with diethyl ether. The combined organic phase were washed with saturated NaCl solution, and dried over Na_2SO_4, filtered, concentrated. Column chromatography on a silica-gel afforded the corresponding dioxane derivative **11A/S** in 99% yield (73:27). IR (neat) 2960, 1380, 1369, 1230, 1196, 1165, 1107, 1021 cm^{-1}. HRMS calcd for $C_{15}H_{22}O_2$ (M^+) 234.1620, found 234.1624. Major isomer **11A**: ^1H NMR ($CDCl_3$) δ 7.40–7.25 (m, 5H), 4.75 (d, *J*=0.6 Hz, 1H), 3.94 (dd, 1H), 3.88 (dd, 1H), 1.90 (m, 1H), 1.55 (s, 3H), 1.45 (s, 3H), 1.41 (m, 1H), 1.19 (d, 3H), 0.59 (d, 3H). Minor isomer **11S**: ^1H NMR ($CDCl_3$) δ 7.40–7.21 (m, 5H), 5.27 (d, *J*=3.5 Hz, 1H), 4.18 (dd, *J*=12.0, 3.5 Hz, 1H), 4.05 (dd, *J*=12.0, 1.5 Hz, 1H), 1.59 (m, 1H), 1.53 (s, 3H), 1.49 (s, 3H), 1.47 (m, 1H), 1.04 (d, 3H), 0.67 (d, 3H).

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