New Silicon Groups as Potential Chiral Auxiliaries. Synthesis and Highly Selective Chiral 1,6-Induction in 1,2-Additions to Acylsilanes

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Chiral silicon groups possessing an asymmetric and chelating alkoxymethyl substituent at silicon have been prepared, and it was shown that these groups may have substantial utility as stereodirecting auxiliaries. For the 1,2-addition of organometallic species to chiral acylsilanes, auxiliaries with a single stereogenic center at position 6 with respect to the reactive carbonyl C atom proved particularly valuable. Compounds with such auxiliaries are easily accessible in enantiomerically pure form, and the chiral groups induce π-facial selectivities of as high as 98:2. In an example it is shown that chiral 1,6-induction may dominate over 1,5-induction.

Introduction

We have demonstrated previously, particularly with acylsilanes of type **1** (R_{reac} = acyl), that silyl groups **A** (Figure 1) with "silicon-centered" chirality and a silicon-bound alkoxymethyl substituent can act as powerful stereochemical directors in chelate-controlled diastereoselective transformations.[1] A number of chiral carbon frameworks have been stereoselectively prepared with precursors possessing such groups, such as secondary alcohols,[2] α,β-substituted δ-silylated γ,δ-unsaturated carboxylic acids,[3] β,γ-substituted δ,ϵ-unsaturated acyl silanes,[4] aldol type products and derivatives thereof,[5] and β-chiral ketones.[6] Of particular interest to us are chiral α-hydroxyallylsilanes of type **3** that are accessible in high enantiomeric purity by stereoselective addition of vinyl organometallic reagents to chiral acylsilanes of type **1**[1], combining the structural and chemical features of α-hydroxysilanes, allylsilanes, and allylic alcohols. We are presently exploring the unique chemical behavior of these polyfunctional compounds in more detail with the plan to apply them to the synthesis of stereochemically more complex structures.

The use of chiral groups of type **A** for the enantioselective preparation of compounds **3**, however, suffers a drawback. Enantiomerically enriched compounds with such groups—though accessible through resolution of a racemate[2]—are rather laborious to prepare. In addition, the chiral auxiliaries, due to possible racemization under nucleophilic conditions, are not easily recovered with stereochemical integrity after they have done their duty. We thus searched for alternative chiral silicon auxiliaries and envisioned groups of type **B** as suitable candidates. Such groups should be readily available by coupling of a chiral C framework with a symmetric silane portion through an O atom. Despite the remote location of the asymmetric unit from a potential reactive group attached to silicon, high stereodirecting effects can still be expected on the basis of "chelate-controlled" reactions.[7,8]

In this paper we present the synthesis of acylsilanes of type **2** (R_{reac} = acyl) with groups **B** and the results of the first investigation of stereoselective 1,2-additions to their carbonyl groups. We focus here primarily on structure/selectivity relationships and the influence of the reaction conditions on the stereoselective outcome of the transformations to lay a basis for subsequent investigations.

Results and Discussion

Synthesis of the New Chiral Auxiliaries. Enantiomerically enriched compounds of type **2** have been prepared by following two strategies (Scheme 1): (A) by regioselective opening of an epoxide **4** with the alcohol function of hydroxymethyl-substituted silane **5** and (B) by substitution of a leaving group X in a compound of type **7** with an enantiomerically enriched alkoxy equivalent of type **6**. For both strategies, Ph-substituted silanes were used as the silicon-containing starting materials. The Ph groups attached to silicon play the role of protective groups for hetero substituents or for hydrogen, which would be displaced in the course of the coupling reactions. The chiral frameworks to be connected to the silicon moieties either were prepared from enantiomerically enriched material deriving from the chiral pool or were synthesized analogous to published protocols.

When strategy A was followed, the first optically active hydrosilane, **10**, was prepared, a universal pre-

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(1) Bienz, S. *Chimia* **1997**, *51*, 133.
(2) Huber, P.; Bratovanov, S.; Bienz, S.; Syldatk, C.; Pietzsch, M. *Tetrahedron: Asymmetry* **1996**, *7*, 69.
(3) Enev, V.; Stojanova, D.; Bienz, S. *Helv. Chim. Acta* **1996**, *79*, 391.
(4) Koch, P.; Kunz, R. W.; Bienz, S. *Mol. Online* **1999**, *3*, 9.
(5) Fässler, J.; Linden, A.; Bienz, S. *Tetrahedron* **1999**, *55*, 1717.
(6) Bratovanov, S.; Bienz, S. *Tetrahedron: Asymmetry* **1997**, *8*, 1587.
(7) Lodge, E. P.; Heathcock, C. H. *J. Am. Chem. Soc.* **1987**, *109*, 3353.
(8) Bienz, S.; Chapeaurouge, A. *Helv. Chim. Acta* **1991**, *74*, 1477.

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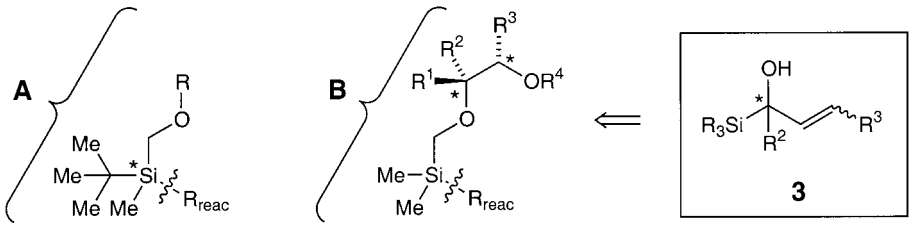
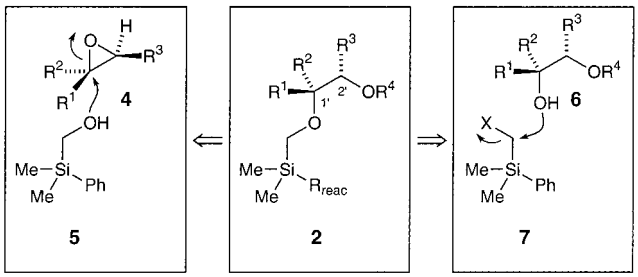


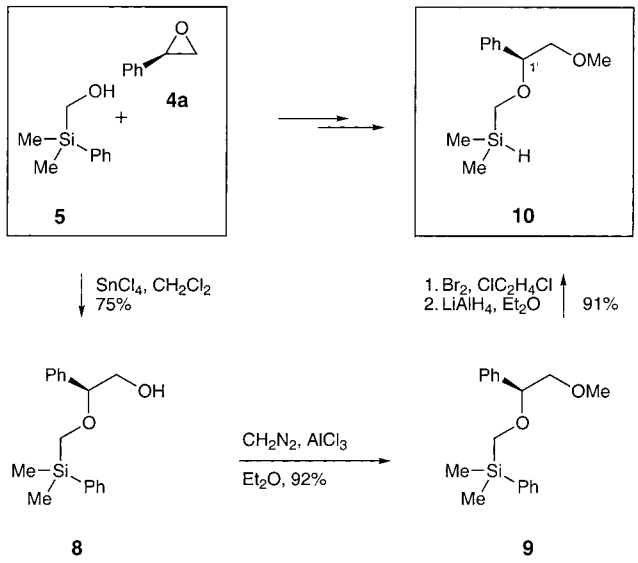
1 2

Figure 1. Chiral silicon auxiliaries.

Scheme 1

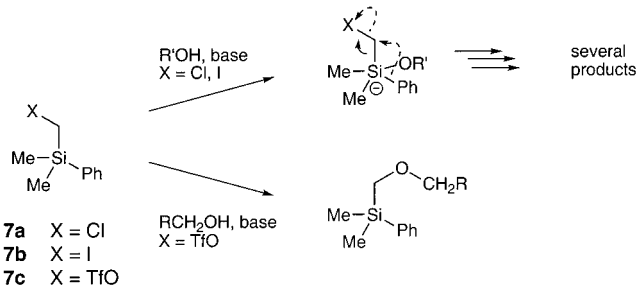


Scheme 2



cursor for silanes possessing a single stereogenic center at C(1′) of the side chain. The sequence is outlined in Scheme 2. Regioselective opening of enantiomerically enriched (*R*)-styrene oxide (**4a**, ≥98% ee) by reaction with hydroxymethyl-substituted silane **5** in the presence of $SnCl_4$ afforded alcohol **8** in 75% yield and 66% ee. The stereoselectivity of this reaction was not optimized, and the loss of chiral information was not altogether unexpected.[9,10] The stereochemical result, however, was sufficient for the initial stage of our investigation, where only diastereomeric excesses had to be determined to quantify the stereoselectivities. However, enantiomerically enriched material was still necessary for the investigation, because it was needed for the assignment of relative configurations and thus for the determination

Scheme 3



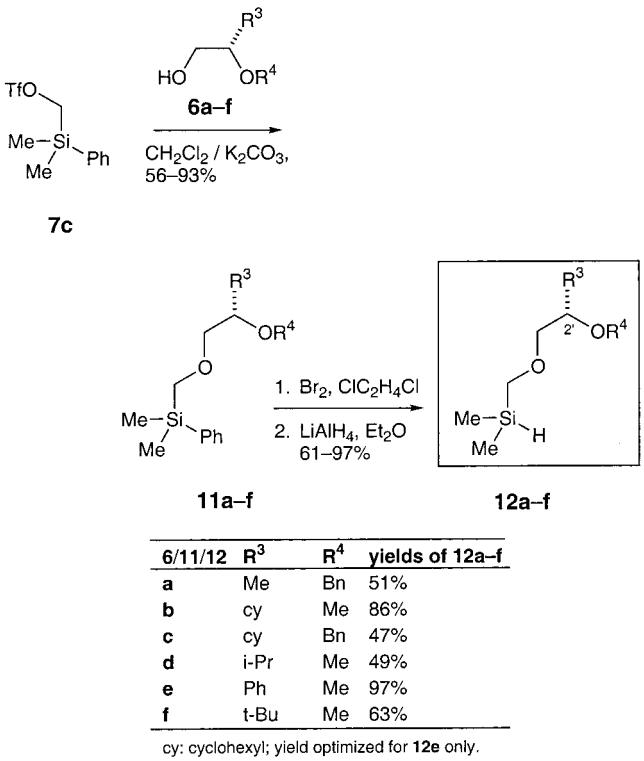
of the relative π-sites of the nucleophilic attacks to the carbonyl groups.

Compound **8** was methylated at the hydroxy O atom by treatment with CH_2N_2 in the presence of $AlCl_3$[11] to afford silane **9** in 92% yield. Replacement of the Ph group at silicon was effected by electrophilic aromatic substitution. This reaction, however, was more problematic than expected. Several methods described in the literature to replace an aryl group at silicon (actually designed for the opposite purpose, namely to replace a silicon group at an aromatic system)[12−14] proved not applicable for our substrate. A modification of the bromination protocol of Ponomarenko[15] was finally successful: treatment of **9** in the presence of a catalytic amount of Fe with 1.2 equiv of Br_2 in 1,2-dichloroethane at −30 °C, instead of using Br_2 at 50 °C as the solvent, delivered a highly reactive and moisture-sensitive bromosilane that was immediately reduced with $LiAlH_4$ to form hydrosilane **10** (91% yield over the two steps). This compound was readily purified by chromatography and can be kept on stock at 4 °C for a prolonged period of time without change.

Strategy B was followed for the preparation of hydrosilanes possessing a stereogenic center at C(2′) alone or in combination with a stereogenic center at C(1′). Preliminary experiments with silanes **7a**,**b** showed that substitution of the halogen atom is not readily accomplished with alcohols as nucleophiles (Scheme 3). The reactions of compound **7a**,**b** with several alcohols in the presence of base gave at best only small amounts of the desired products. Decomposition was the major path of the reactions. Most possibly, the hard and silicophilic alkoxides attacked the Si center rather than

(9) Bittman, R.; Guivisdalsky, P. N. *J. Am. Chem. Soc.* **1989**, *111*, 3077.
(10) Moberg, C.; Ràkos, L.; Tottie, L. *Tetrahedron Lett.* **1992**, *33*, 2191.
(11) Müller, E.; Heischkeil, R.; Bauer, M. *Z. Naturforsch.* **1964**, *677*, 55.
(12) Jacob, L. A.; Chen, B.-L.; Stec, D. *Synthesis* **1993**, *6*, 611.
(13) Wilbur, D. S.; Stone, W. E.; Anderson, K. W. *J. Org. Chem.* **1983**, *48*, 1542.
(14) Wilson, S. R.; Jacob, L. A. *J. Org. Chem.* **1986**, *51*, 4833.
(15) Ponomarenko, V. A.; Snegora, A. D.; Egorov, Y. P. *Bull. Acad. Sci. USSR* **1960**, 222.

Scheme 4



6/11/12	R^3	R^4	yields of 12a–f
a	Me	Bn	51%
b	cy	Me	86%
c	cy	Bn	47%
d	i-Pr	Me	49%
e	Ph	Me	97%
f	t-Bu	Me	63%

cy: cyclohexyl; yield optimized for **12e** only.

the α-C atom, initiating a substitutive 1,2-Ph shift to the electrophilic α-position[16,17] or launching replacement of the halogenomethyl group *in toto*.[18,19] Treatment of the analogous triflate **7c** (triflate = TfO = trifluoromethanesulfonate), on the other hand, with primary—but not with secondary—alcohols and with base[20] afforded reliable amounts of the desired substitution products.

Hence, for the preparation of hydrosilanes **12a**–**f**, each possessing a single stereogenic center at C(2′) of the side chain, the direct coupling method was appropriate (Scheme 4). Triflate **7c** was coupled with primary alcohols **6a**–**f** to afford ethers **11a**–**f** in 56–93% yield. The reaction was best performed in CH_2Cl_2 and in the presence of K_2CO_3 as the base. The alternative use of other bases such as, for example, pyridine or NaH or of other solvents proved disadvantageous. The syntheses of hydrosilanes **12a**–**f** were finally completed in 61–97% yield from **11a**–**f** by bromination and subsequent reduction with $LiAlH_4$ as described above.

The enantiomerically enriched alcohols **6a**–**f** utilized for the coupling reaction with **7c** were obtained along a multistep procedure by methylation[21,22] or benzylation[23] of the hydroxy group of the respective α-hydroxyacids (≥98% ee) followed by reduction of the carboxylic function to the primary alcohol as described by Lewis and Mislow.[24] The enantiomeric purities of the samples obtained this way were virtually complete (≥98% ee, determined, for example, for **6e** by ^{1}H NMR with its Mosher ester), and the configurational purity of the stereogenic unit in alcohols **6a**–**f** was retained throughout the subsequent transformations: the final hydrosilanes **12a**–**f** exhibited the same enantiomeric purities as the alcohols **6a**–**f**, which was determined for **12e** by ^{1}H NMR spectroscopy in the presence of the Pirkle additive.[25]

Since the direct coupling of silanes **7** with secondary alcohols is not feasible, the alternative route via ester **14** was developed for the preparation of the hydrosilanes **17a**,**b**, possessing stereogenic centers on both C(1′) and C(2′) of the side chain (Scheme 5). In contrast to the reaction with alcoholates, the coupling of potassium carboxylates with chloromethyl-substituted or, preferentially as we found, with iodomethyl-substituted silanes in dipolar solvents is usually not problematic.[26] Treatment of iodomethyl-substituted compound **7b** with potassium carboxylate **13** in DMSO at 50 °C thus afforded the desired ester **14** in 93% yield. Subsequent reaction with Tebbe reagent[27] in the presence of pyridine,[28,29] under carefully optimized reaction conditions, gave rise to the acid-sensitive vinyl ether **15** (83%). The double bond of **15** was immediately hydrogenated at ambient pressure with Pd/C as the catalyst and in the presence of NaOH to provide the two isomeric silanes **16a**,**b** in 83% yield (ratio 60:40). These compounds were separated by chromatography and individually converted into the corresponding hydrosilanes **17a**,**b** (97–98% yields) by bromination and subsequent reduction as described before.

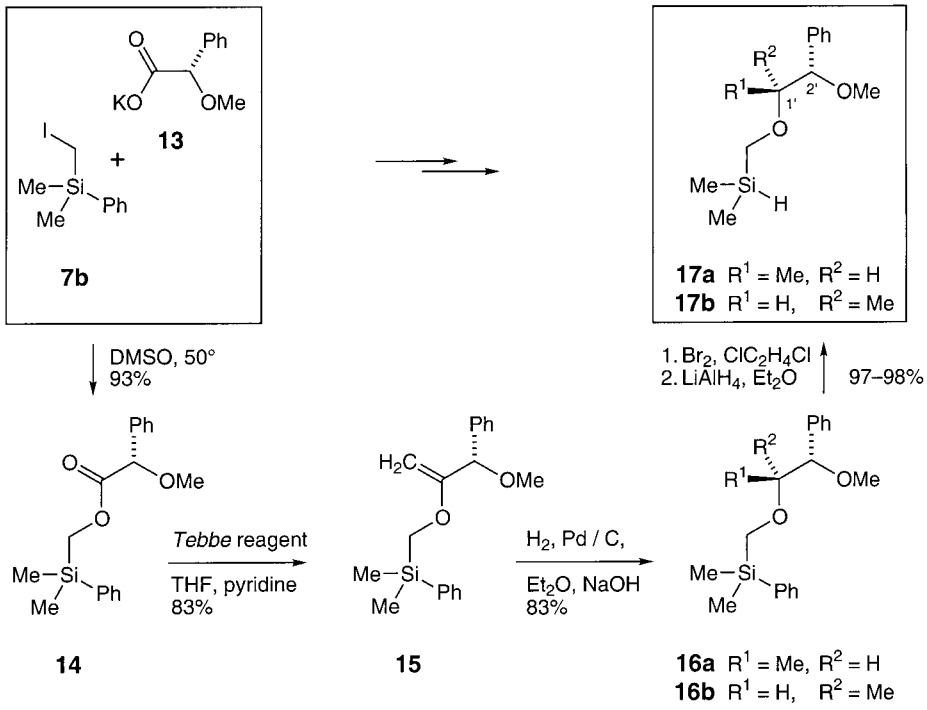
In the course of the Tebbe reaction/hydrogenation step some racemization took place. Whereas ester **14** was obtained in virtually enantiomerically pure form from carboxylate **13** (≥98% ee, from L-(+)-mandelic acid), the products **16a**,**b** arose with approximately 60% and 84% ee only. We assume that the chiral information was partially lost in the course of the hydrogenation reaction. Since, as discussed before, the enantiomeric purity of the test substrates was of lesser importance at this stage of the investigation, optimization of the transformation has not been performed yet.

To obtain the acylsilanes **18**, **19a**–**f**, and **20a**,**b** needed for the following investigation, hydrosilanes **10**, **12a**–**f**, and **17a**,**b** were treated subsequently with elemental Cl_2 in CCl_4 and (1-ethoxyvinyl)lithium in THF (Scheme 6).[30] Direct hydrolysis of the silylated enol ethers by treatment with aqueous HCl rendered the desired products in overall 41–92% yields.

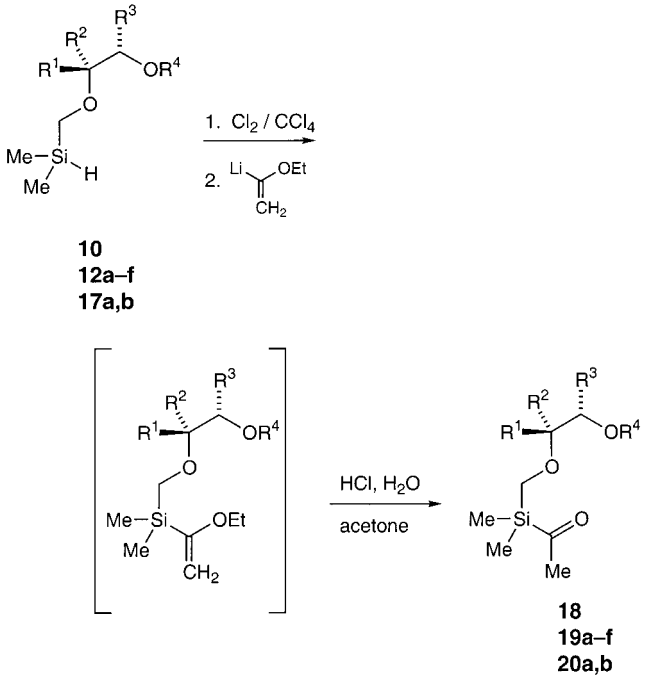
Thus, all three types of chiral acylsilanes **18**–**20** can

(16) Hudrlik, P. F.; Abdallah, Y. M.; Kulkarni, A. K.; Hudrlik, A. M. *J. Org. Chem.* **1992**, *57*, 6552.
(17) Sato, Y.; Toyo'oka, T.; Aoyama, T.; Shirai, H. *J. Org. Chem.* **1976**, *41*, 3559.
(18) Kreeger, R. L.; Menard, P. R.; Sans, E. A.; Shechter, H. *Tetrahedron Lett.* **1985**, *26*, 1115.
(19) Sans, E. A.; Shechter, H. *Tetrahedron Lett.* **1985**, *26*, 1119.
(20) Baum, K.; Lerdal, D. A.; Horn, J. S. *J. Org. Chem.* **1978**, *43*, 203.
(21) Izquierdo, I.; Plaza, M. T. *J. Carbohydr. Chem.* **1996**, 303.
(22) Carballeira, N. M.; Nestor, M.; Colon, R.; Emiliano, A. *J. Nat. Prod.* **1998**, *61*, 675.
(23) Iversen, T.; Bundle, D. R. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2251.
(24) Lewis, R. A.; Mislow, K. *J. Am. Chem. Soc.* **1969**, *91*, 7009.
(25) Pirkle, W. H.; Sikkenaga, D. L.; Pavlin, M. S. *J. Org. Chem.* **1977**, *42*, 384.
(26) Petrov, A. D.; Mironov, V. F.; Pogonkina, N. A. *Dokl. Akad. Nauk SSSR* **1955**, *100*, 81.
(27) Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 3611.
(28) Brown-Wensley, K. A.; Buckwald, S. L.; Cannizzo, L.; Clawson, L.; Ho, S.; Meinhardt, D.; Stille, J. R.; Straus, D.; Grubbs, R. H. *Pure Appl. Chem.* **1983**, *55*, 1733.
(29) Pine, S. H.; Pettit, R. J.; Geib, G. D.; Cruz, S. G.; Gallego, C. H.; Tijerina, T.; Pine, R. D. *J. Org. Chem.* **1985**, *50*, 1212.
(30) Chapeaurouge, A.; Bienz, S. *Helv. Chim. Acta* **1993**, *76*, 1876.

Scheme 5



Scheme 6



Comp.	R^1	R^2	R^3	R^4	yields of 18–20
10/18	Ph	H	H	Me	75%
12a/19a	H	H	Me	Bn	65%
12b/19b	H	H	cy	Me	69%
12c/19c	H	H	cy	Bn	41%
12d/19d	H	H	i-Pr	Me	47%
12e/19e	H	H	Ph	Me	92%
12f/19f	H	H	t-Bu	Me	62%
17a/20a	Me	H	Ph	Me	83%
17b/20b	H	Me	Ph	Me	90%

cy: cyclohexyl; yield optimized for **19e** only.

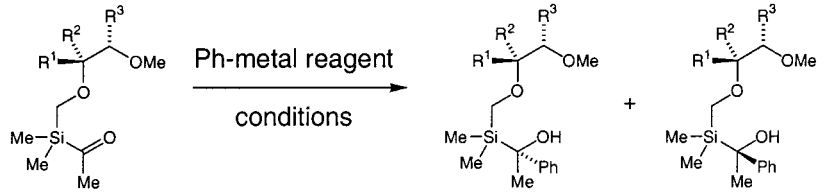
be readily prepared in enantiomerically enriched form from easily accessible chiral frameworks over only a few steps. The synthesis of compounds of type **19** with a single center of chirality at C(2′) of the side chain is particularly commendable because it is straightforward, generally applicable, not problematic with respect to stereoselectivity, and high-yielding.

Diastereoselective 1,2-Addition of Organometallic Reagents to the Carbonyl Group of Chiral Acylsilanes. The 1,2-addition of Ph-metallic reagents to the carbonyl group of the chiral acylsilanes **18**, **19a**−**f**, and **20a**,**b** was chosen as the initial test reaction to study the influence of different reaction conditions and of the location and configuration of the stereogenic centers located at C(1′) and/or C(2′) of the side chain on the stereoselectivity. The particular test reaction with Ph-metallic reagents was chosen because it allows a direct comparison of the stereochemical results with earlier results obtained with chiral auxiliaries of type **A**.[30]

Thus, acylsilanes **18**, **19a**−**f**, and **20a**,**b** were treated with Ph-metallic reagents under several conditions to afford, as expected, mixtures of diastereomeric alcohols **21/21′**, **22a**−**f**/**22a′**−**f′**, and **23a**,**b**/**23a′**,**b′** (Tables 1 and 2). It is readily recognized from the compilations in Tables 1 and 2 that high stereoselectivities of up to 98:2 have been attained with the new auxiliaries (the best result was obtained with **19e**: entry 12, Table 1) and that the degree of π-facial selectivity is strongly dependent on the reaction conditions as well as the exact structure of the substrate. The dependencies of the stereoselectivities upon structural and particularly experimental conditions is not unexpected and parallels earlier observations done with "silicon-centered" chiral acylsilanes of type **1**.[3,8,30]

Role of Complexation and Influence of the Metal. With respect to the reaction conditions, highest stereoselectivities were obtained when the substrates **18**, **19a**−**f**, and **20a**,**b** were complexed to a Lewis acid prior to their treatment with nucleophiles, when poorly

Table 1. Addition of Phenylorganometallic Reagents to the Carbonyl Group of Chiral Acylsilanes: Influence of the Reaction Conditions and the Position of the Stereogenic Center on the Silyl Group[a]



18, 19e, 20a,b **21, 22e, 23a,b** **21', 22e', 23a',b'**

	starting materials				conditions			products		
entry	no.	R^1	R^2	R^3	Ph-metal	additive	solvent	no.	ratio	yield (%)
1	**18**	Ph	H	H	PhMgBr	$MgBr_2$	CH_2Cl_2	**21/21′**	93:7	90
2	**18**	Ph	H	H	PhMgBr	$MgBr_2$	Et_2O	**21/21′**	89:11	83
3	**18**	Ph	H	H	PhMgBr		Et_2O	**21/21′**	76:24	82
4	**18**	Ph	H	H	PhMgBr		THF	**21/21′**	55:45	96
5	**18**	Ph	H	H	PhMgBr	$ZnBr_2$	Et_2O	**21/21′**	83:17	50
6	**18**	Ph	H	H	PhLi	$MgBr_2$	Et_2O	**21/21′**	85:15	55
7	**18**	Ph	H	H	PhLi		Et_2O	**21/21′**	44:56	90
8	**18**	Ph	H	H	PhLi		THF	**21/21′**	54:46	72
9	**18**	Ph	H	H	Ph_2CuLi		Et_2O	**21/21′**	68:32	66
10	**18**	Ph	H	H	$Ph_3TiOiPr$		Et_2O	**21/21′**	60:40	76
11	**18**	Ph	H	H	Ph_4Ti		Et_2O	**21/21′**	58:42	58
12	**19e**	H	H	Ph	PhMgBr	$MgBr_2$	CH_2Cl_2	**22e/22e′**	98:2	99
13	**19e**	H	H	Ph	PhMgBr	$MgBr_2$	Et_2O	**22e/22e′**	91:9	93
14	**19e**	H	H	Ph	PhMgBr		Et_2O	**22e/22e′**	63:37	76
15	**19e**	H	H	Ph	PhMgBr		THF	**22e/22e′**	40:60	84
16	**19e**	H	H	Ph	PhLi	$MgBr_2$	Et_2O	**22e/22e′**	80:20	53
17	**19e**	H	H	Ph	PhLi	$ZnBr_2$	Et_2O	**22e/22e′**	23:77	51
18	**19e**	H	H	Ph	PhLi	$CeCl_3$	Et_2O	**22e/22e′**	21:79	55
19	**19e**	H	H	Ph	PhLi		Et_2O	**22e/22e′**	20:80	83
20	**19e**	H	H	Ph	PhLi		THF	**22e/22e′**	49:51	92
21	**20a**	Me	H	Ph	PhMgBr	$MgBr_2$	CH_2Cl_2	**23a/23a′**	93:7	79
22	**20a**	Me	H	Ph	PhMgBr	$MgBr_2$	Et_2O	**23a/23a′**	91:9	99
23	**20a**	Me	H	Ph	PhMgBr		Et_2O	**23a/23a′**	68:32	73
24	**20a**	Me	H	Ph	PhMgBr		THF	**23a/23a′**	38:62	60
25	**20a**	Me	H	Ph	PhLi	$MgBr_2$	Et_2O	**23a/23a′**	77:23	81
26	**20a**	Me	H	Ph	PhLi		Et_2O	**23a/23a′**	32:68	82
27	**20a**	Me	H	Ph	PhLi		THF	**23a/23a′**	51:49	83
28	**20b**	H	Me	Ph	PhMgBr	$MgBr_2$	CH_2Cl_2	**23b/23b′**	55:45	83
29	**20b**	H	Me	Ph	PhMgBr	$MgBr_2$	Et_2O	**23b/23b′**	73:27	99
30	**20b**	H	Me	Ph	PhMgBr		Et_2O	**23b/23b′**	69:31	85
31	**20b**	H	Me	Ph	PhMgBr		THF	**23b/23b′**	43:57	99
32	**20b**	H	Me	Ph	PhLi	$MgBr_2$	Et_2O	**23b/23b′**	53:47	99
31	**20b**	H	Me	Ph	PhLi		Et_2O	**23b/23b′**	47:53	89
32	**20b**	H	Me	Ph	PhLi		THF	**23b/23b′**	48:52	88

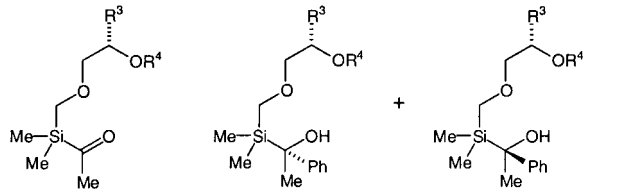
[a] Reactions were performed with 3.5 equiv of the organometallic reagent at −80 °C with precomplexation of the ketones with 2 equiv of the respective Lewis acid where mentioned.

donating solvents such as CH_2Cl_2 or Et_2O were used, and when the reactions were performed with Mg rather than with Li organometallic reagents (entries 1, 2, 5, 12, 13, 21, and 22, Table 1). Precomplexation of the acylsilanes seemed to be particularly important to ensure high stereoselectivities. If the initial addition of $MgBr_2$ or $ZnBr_2$ to the substrate was omitted, a considerable loss of selectivity was noticed in most cases (compare, for example, entries 2 and 5 with entry 3 in Table 1, for compound **18**, and related pairs of experiments for the other substrates). The same effect—even more pronounced—was observed when complexation of the substrate with metal cations was altogether suppressed. This can be effected by the use of a strongly donating solvent that competes successfully with the substrate for complexation. For instance, the reactions performed in THF showed only negligible or no stereoselectivity (see, for example, entries 4 and 8 in Table 1, for compound **18**, and related experiments for the other substrates). The almost complete loss of stereoselectivity obtained under "nonchelate-controlled" reaction conditions is in fact not too surprising.[8,31,32] The alternative π-facial directions of attack to the carbonyl groups of compounds **18**, **19a**−**f**, and **20a**,**b** are not expected to be much differentiated by the remote chiral units of the compounds if there is no chelation.

It is interesting to compare the different stereochemical outcomes of the Ph additions to compounds **18**, **19e**, and **20a**,**b** depending on the metal—Mg or Li—in the organometallic reagent and the Lewis acid additive. In contrast to the results obtained earlier with acylsilanes of type **1**,[30] it was found that the reactions of acylsilanes **18**, **19e**, and **20a**,**b** with PhLi proceeded not only with lower but, in certain cases, also with reversed π-facial selectivity as compared to the transformations with the Grignard reagent. The same reversed selectivity was found with **19e**, PhLi as the organometal, and $ZnBr_2$

(31) Ko, K.-Y.; Eliel, E. L. *J. Org. Chem.* **1986**, *51*, 5353.
(32) Keck, G. E.; Andrus, M. B.; Romer, D. R. *J. Org. Chem.* **1991**, *56*, 417.

Table 2. Addition of PhMgBr to the Carbonyl Group of Precomplexed Chiral Acylsilanes of the Type 19: Influence of the Size of the R^3 Group on the Stereoselectivity[a]



19a–f **22a–f** **22a'–f'**

	starting materials			products				
entry	no.	R^3	R^4	no.	ratio in Et_2O	ratio in CH_2Cl_2	yield (%)	*A* (kJ mol^{-1})
1	**19a**	Me	Bn	**22a**/**22a′**	62:38	65:35	80	7.28
2	**19b**	cy	Me	**22b**/**22b′**	77:23	86:14	85	9.20
3	**19c**	cy	Bn	**22c**/**22c′**	79:21	78:22	83	9.20
4	**19d**	i-Pr	Me	**22d**/**22d′**	83:17	90:10	82	9.25
5	**19e**	Ph	Me	**22e**/**22e′**	91:9	98:2	93	11.7
6	**19f**	t-Bu	Me	**22f**/**22f′**	53:47	82:18	90	19.7

[a] cy = cyclohexyl. Reactions were performed with 3.5 equiv of PhMgBr in CH_2Cl_2 at −80 °C with precomplexation of the ketone with 2 equiv of $MgBr_2$.

as well as $CeCl_3$ as the additives. The combination PhLi and $MgBr_2$ afforded the same type of stereoselection as the Grignard reagent (compare entries 1 and 2 with entries 16−19 of Table 1). The treatment of compounds **19** with organotitanium or preformed organozinc reagents gave decomposition or no reaction at all. A reversal of stereoselection depending on the type of organometallic reagent is not without precedence, and it is mostly explained by considering models of transition structures.[33]

Since the "nonchelate-controlled" transformation does not result in a pronounced reversal of π-facial selectivity, we have to conclude that two topologically different chelate transition states have to be important for the reactions with the different reagents. To obtain more information on chelate structures formed with organic Mg and Li compounds and compounds of type **19**, we have performed ab initio RHF-SCF (restricted Hartree−Fock, self-consistent field) calculations with GAUSSIAN 94[34] using the 3-21G basis set to optimize the geometries of two pairs of topologically different model complexes **24a**,**b** and **25a**,**b**. The optimized structures are shown in Figure 2 as ball-and-stick representations. The calculations suggest the structures **24a** and **25a**, with the organic residue of the organometal (in the model complex a Me group) pointing to the *si*-face of the carbonyl group, to be thermodynamically favored by 2.6−2.7 kJ mol^{-1} over the structures **24b** and **25b**, respectively. Thus, on the basis of these relative stabilities it would be anticipated that qualitatively the same stereochemical results with both the Mg and the Li organometallic reagents should be obtained. However, the thermodynamically favored ground-state structures might not be the kinetically relevant structures for the two metals. This can in fact be reasoned when the calculated chelate structures are scrutinized in more detail.

The two Mg-containing complexes **24a** and **24b** are—with respect to the environment of the reactive portions—almost identical in structure. The distances between the Me C atoms of the organometals and the electrophilic carbonyl C atoms (4.46 Å for **24a** and 4.45 Å for **24b**) as well as the angles α between the connections of these two atoms and the C,O double bonds (36.3° for both **24a** and **24b**, see Figure 2) are equal or almost equal for both structures. This is not the case for the Li complexes **25a** and **25b**. The spatial arrangements of the Me groups with respect to the carbonyl functions are fairly different for the two structures. In complex **25a**, the distance between the Me C atom of the organometal and the carbonyl C atom is larger by 0.16 Å (3.73 Å for **25a** and 3.57 Å for **25b**) and the angle α is smaller by 6.0° (62.9° for **25a** and 68.9° for **25b**).

With their almost identical "local structure around the reactive site", the two Mg complexes **24a** and **24b** would be expected to be energetically almost equidistant to the related transition states for the respective *si* or *re* attacks. Consequently, the stereoselectivity of the addition reaction to the parent acylsilane should roughly correlate to the relative stabilities of the ground-state complexes **24a**,**b**. This correlation should hold independently of the exact mechanism of the reaction, for example, for cases that would involve bimetallic complexes or intermolecular attacks, as long as the local structure around the reactive site would not become more differentiated by the involvement of the additional species.

The situation is different for the Li-containing complexes **25a**,**b**. The local structures around the reactive sites are distinctly different for the two complexes, and hence, the two complexes are certainly not equidistant from the related transition states that would lead to the two diastereomeric addition products. Thus, kinetic discrimination is possible. According to the Curtin−Hammet principle, the overall reaction could proceed predominantly via a transition state related to complex **25b** when the difference in free energy of the two topologically different transition states is sufficiently large and the interconversion of the two complexes **25a**,**b** is rapid. The observed stereochemical result suggests that these two conditions are fulfilled.

Influence of the Structure of the Substrate. The stereochemical outcome of the PhMgBr additions to a number of acylsilanes differing in the location of the chiral unit (compounds of type **18**−**20**, Table 1) and, for compounds of type **19**, the size of the R^3 group (Table 2) was studied. The investigation shows that high stereoselectivities are obtained with compounds possessing a center of chirality either at C(1′) or C(2′) of the silicon side chain (entries 1 and 2 (89−93% selectivity for compound **18**) and entries 12 and 13 (91−98% selectivity for compound **19e**) of Table 1; R^1, R^3 = Ph, respectively). With compounds **20a**,**b** the individual effects of two stereogenic centers at C(1′) and C(2′) is

(33) *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, Germany, 2000.

(34) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A. *Gaussian 94*, revision D.3; Gaussian, Inc.: Pittsburgh, PA, 1995.

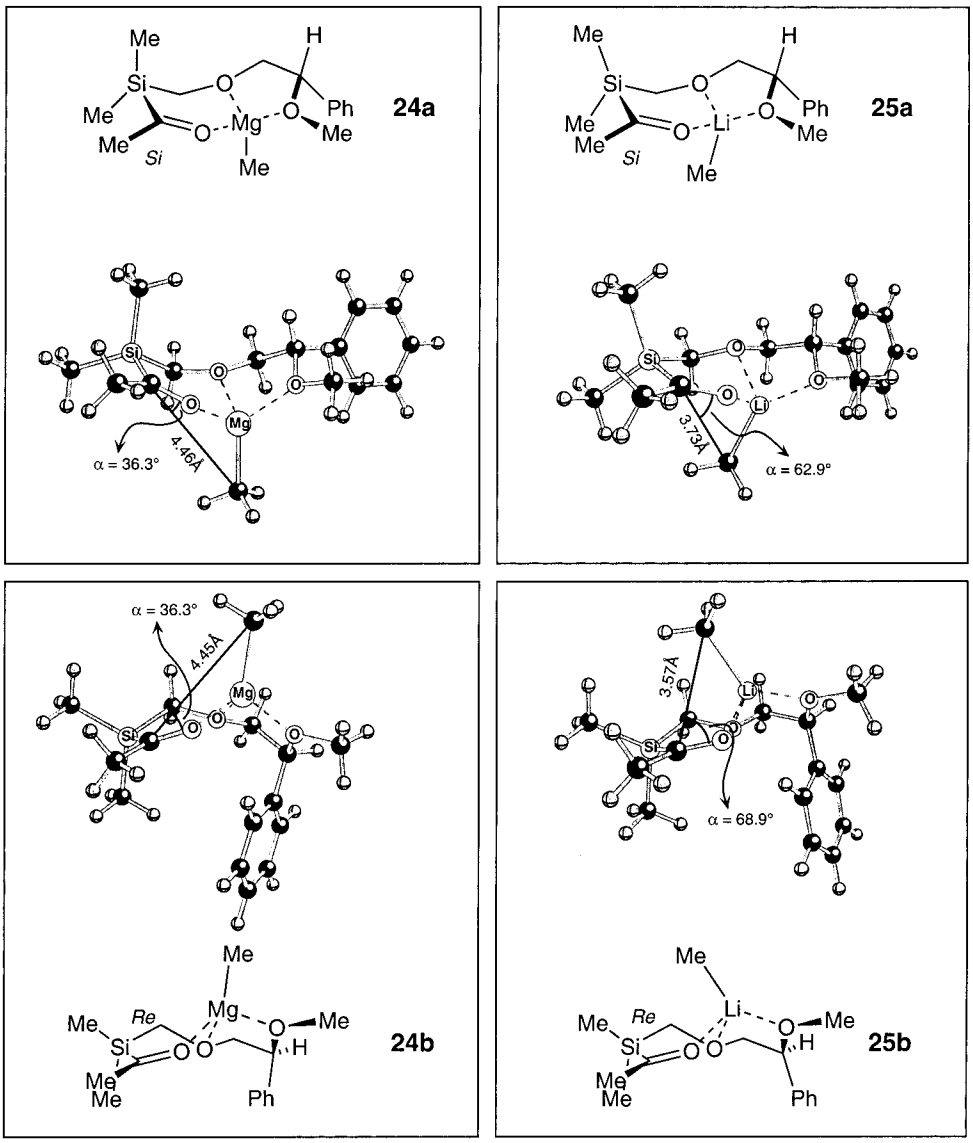


Figure 2. Calculated complex structures of a model acetylsilane with $MeMg^+$ and MeLi.

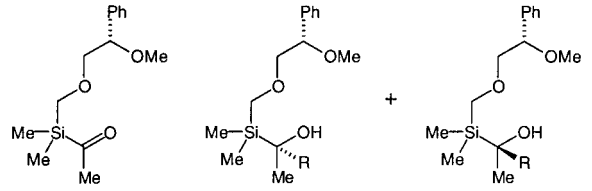
recognized. Whereas no cooperative effect of the two stereogenic elements is manifested—the selectivity of the reaction of **20a** under optimized conditions was not higher than the selectivity of the reaction with **19e** (entries 12 and 19, Table 1)—the opposing effect of the chiral elements is revealed in the reactions of **20b** (compare, for example, entries 21 and 22 for **20a** with entries 28 and 29 for **20b**, Table 1). Interestingly, in the mismatched case of compound **20b**, with the sterically more demanding Ph group at C(2′) and the smaller Me group at C(1′), the stereodirecting effect of the center of chirality at C(2′) is dominant for the reaction.

The comparison of the results obtained with compounds **19a**–**f** reveals that stereoselectivity increases with increasing size of the R^3 group (Table 2). The stereoselectivities roughly correlate with the *A* values[35] of the R^3 groups. With a very large group, such as the *t*-Bu group, however, the selectivity of the reaction performed in CH_2Cl_2 decreased markedly or, when the reaction was performed in Et_2O, almost disappeared (entry 6, Table 2). The behavior of the stereoselectivity as a function of the size of R^3 can directly be explained with the structures of the complexes **24a**,**b** depicted in Figure 2. It must be expected that complexes of type **24b** are progressively obtained over complexes of type **24a** when the R^3 group grows in size. Increasing the size of R^3 would create more steric strain in complexes of type **24b** because of larger repulsive interactions of the R^3 group with the pseudo-axial Me group at silicon. No such effect would be expected in complexes of type **24a**. The loss of selectivity accompanied by the introduction of the bulky *t*-Bu group at C(2′) is probably due to incomplete formation of the desired Mg complex in either of the two types of complexes. If complexation with the remote O-atom is not realized because of steric reasons, no or only negligible chiral induction will result.

Influence of the Nature of the Nucleophile on the Stereoselectivity. Table 3 summarizes the result of the addition of several organometals to the carbonyl group of acylsilane **19e**. It is readily recognized that the stereoselectivities of the reactions are strongly dependent on the nucleophiles. As already experienced with Si-centered chiral compounds, the stereoselectivities obtained with alkyl[30] and especially allyl[36] organometals

(35) Eliel, E. E.; Wilen, S. H. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994.

Table 3. Addition of Different Nucleophiles to the Carbonyl Group of Precomplexed Chiral Acylsilane 19e[a]



19e **22e,g–n** **22e',g'–n'**

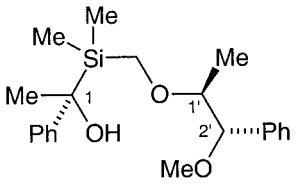
	starting materials		products		
entry	no.	nucleophile R-metal	no.	ratio	yield (%)
1	**19e**	PhMgBr	**22e/22e′**	92:8	93
2	**19e**	vinylMgBr	**22g/22g′**	96:4	93
3	**19e**	(*E*)-propenyl-Li	**22h/22h′**	98:2	79
3	**19e**	(*Z*)-propenyl-Li	**22i/22i′**	98:2	79
4	**19e**	propynyl-Li	**22j/22j′**	85:15	81
5	**19e**	EtMgBr	**22k/22k′**	58:42	97
6	**19e**	*i*-PrMgBr	**22l/22l′**	89:11	17[b]
7	**19e**	BnMgBr	**22m/22m′**	71:29	80
8	**19e**	allyl-MgBr	**22n/22n′**	55:45	91

[a] Reactions were performed with 3.5 equiv of the organometal in Et_2O at −80 °C with precomplexation of the ketone with 2 equiv of $MgBr_2$. [b] A considerable amount of Grignard reduction product (57%) was formed.

is rather low, and in the case of the larger *i*-PrMgBr, a considerable amount of Grignard reduction (57%) was observed. The selectivities are high, however, with the acetylide and with vinyl and aryl organometallics. The reaction thus allows the highly stereoselective preparation of α-hydroxyaryl and—which is of particular importance to us for our planned subsequent investigations—of α-hydroxyallylic silanes.

Removal of the Silicon Group and Assignment of the Relative Configurations. It is not trivial to assign the relative configurations of the several stereogenic centers of the addition products **21/21′**, **22a**−**f**/**22a′**−**f′**, and **23a**,**b**/**23a′**,**b′** as well as of the two starting acylsilanes **20a**,**b**. Conclusive arguments are available neither from NMR experiments nor from chiroptical methods. We succeeded, however, in assigning the several relative configurations by a combination of single-crystal X-ray analysis and chemical correlation.

The relative configurations of the two stereogenic centers of compounds **20a**,**b** have been deduced from the single-crystal X-ray analysis of *rac*-**23a**, which was obtained by partial crystallization of the major product of the PhMgBr addition to **20a**. The analysis revealed the 1*S**,1′*S**,2′*S** configurations of the three stereogenic centers (Figure 3). Since the absolute configuration at C(2′) is known to be *S* for both compounds **20a** and **20b**, compound **20a** must possess the 1*S*,2*S* and **20b** the 1*R*,2*S* configuration. Brook rearrangement of a sample of **23a/23a′** (dr 68:32, entry 23, Table 1) by the action of KH (Scheme 7) followed by cleavage of the silyl ethers **26/26′** by treatment with Bu_4NF gave finally 1-phenylethanols (*S*)-(−)-**27**/(*R*)-(+)-**27** in an enantiomeric ratio of 60:40 (determined by HPLC (Chiral-OD column) and by NMR with the Mosher ester derivative). Hence, the Brook rearrangement proceeded—as described in the literature for phenyl-substituted α-hydroxysilanes[37−39]—



rac.-**23a**

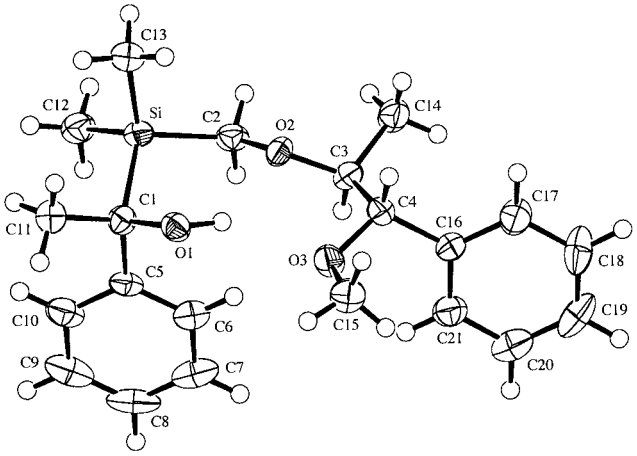
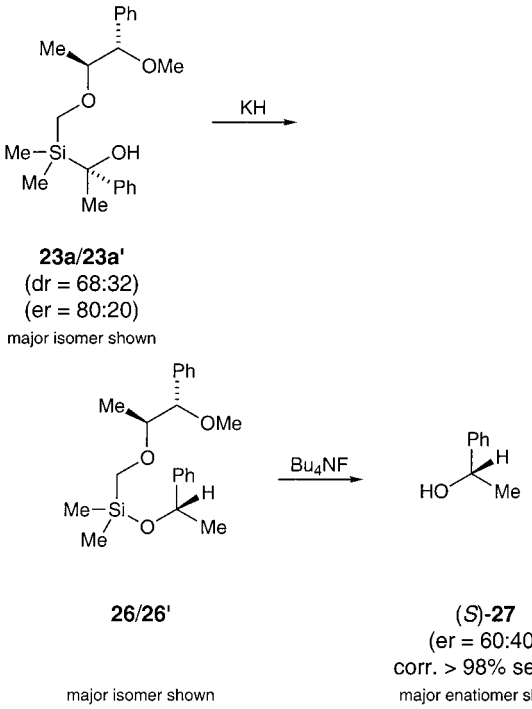


Figure 3. ORTEP plot[45] of the molecular structure of *rac*-**23a**. Ellipsoids with 50% probability are shown; H atoms are given arbitrary displacement parameters for clarity.

Scheme 7



with virtually complete stereoselectivity and with inversion of configuration at the carbon center. By chemical correlation of all pairs of diastereomers of type **21/21′**, **22/22′**, and **23/23′** with 1-phenylethanol, the configurations of the several isomers were secured as given in Tables 1 and 2.

Conclusion. Our investigation shows that chiral auxiliaries of type **B** are suited to effect high stereo-

(36) Chapeaurouge, A. University of Zurich, unpublished results.
(37) Brook, A. G.; Pascoe, J. D. *J. Am. Chem. Soc.* **1971**, *93*, 6224.
(38) Boche, G.; Opel, A.; Marsch, M.; Harms, K.; Haller, F.; Lohrenz, J. C. W.; Thümmler, C.; Koch, W. *Chem. Ber.* **1992**, *125*, 2265.
(39) Wang, Y.; Dolg, M. *Tetrahedron* **1999**, *55*, 12751.

selectivities in chelate-controlled reactions. Of particular interest was the asymmetric silicon moiety in compound **12e** and its derivatives—possessing a single stereogenic center at C(2′) of the side chain—because it is readily constructed in enantiomerically pure form and proved to be highly selective. Compound **12e** opens a new entry into the synthesis of enantiomerically enriched α-hydroxyallylsilanes and other compounds and lays the basis for a number of subsequent investigations that are planned in our laboratories.

Experimental Section

General Methods. Unless otherwise stated, manipulations were carried out under Ar in oven-dried glass equipment. For reactions, Et_2O and THF were freshly distilled from Na with benzophenone ketyl as indicator; benzene (analytical grade) was stored over Na. All organic solvents were distilled prior to use. Anhydrous $MgBr_2$ was prepared from 1,2-dibromoethane and Mg in Et_2O. Extracts were washed with saturated aqueous NH_4Cl solution and brine and were dried over $MgSO_4$. Solutions for workup procedures were prepared in deionized H_2O. Chromatography: Merck silica gel 60 (40−63 μm). IR spectra: neat liquid films between NaCl plates; in cm^{-1}. ^1H NMR spectra: in $CDCl_3$ at 300 MHz; δ in ppm relative to $CHCl_3$ (δ 7.26), with J in Hz. ^{13}C NMR spectra: in $CDCl_3$ at 75.5 MHz; δ in ppm relative to $CDCl_3$ (δ 77.0); multiplicities from DEPT-135 and DEPT-90 experiments. MS: Finnigan MAT 90 or Finnigan SSQ 700. Chemical ionization mass spectrometry (CI-MS): NH_3 as the reactant gas; quasi-molecular ions and characteristic fragments; in *m*/*z* (relative percent). Diastereomeric ratios were determined by integration of ^1H NMR spectra; enantiomeric excesses (ee) were determined by ^1H NMR via the Mosher ester derivative[40] or in the presence of the Pirkle reagent[25] or they were established by HPLC on a chiral stationary phase (Chiral-OD column). The ee values were not determined for all chiral compounds but related to the respective starting materials or to deriving products. Except for the transformations particularly mentioned in the text, it was shown that the ee values of the samples are not affected by the transformations used.

1. Preparation of Phenylsilane 9. 1.1. (*S*)-2-[(Dimethylphenylsilyl)methoxy]-2-phenylethanol (8). (*R*)-Phenyloxirane (**4a**; 310 μL, 2.71 mmol, ≥98% ee) was added over a period of 5 h at 0 °C to a solution of (hydroxymethyl)dimethylphenylsilane (**5**; 402 mg, 2.42 mmol)[41] in dry CH_2Cl_2 (8 mL) containing $SnCl_4$ (1 drop). After complete addition, it was stirred for an additional 3 h, quenched with saturated aqueous NH_4Cl solution, and extracted with Et_2O. Chromatography (hexane/Et_2O 8:2) gave **8** (516 mg, 1.8 mmol, 75%, ≥66% ee) as a colorless oil. The enantiomeric purity of **8** was determined with its *S* Mosher ester by ^1H NMR according to ref 40 (see below). $[\alpha]_D = 53.9 \pm 0.2°$ (c = 1.65, EtOH). IR: 1115, 1095, 840, 730, 700, 630, 605. ^1H NMR: 7.42−7.80 (m, 10 H); 4.15 (dd, J = 8.4, 4.2, 1 H); 3.50−3.38 (m, 2 H); 3.22, 3.04 (AB, J = 12.8, 2 H); 0.23, 0.20 (2s, 2 × 3 H). ^1H NMR of *S* Mosher ester of **8**, selected signals: 3.40 (s, MeO of (*S*,*S*)-derivative); 3.37 (*s*, MeO of *S*,*R* derivative). ^{13}C NMR: 138.5, 137.1 (2s); 133.7 (d, 2 C); 129.3 (d); 128.4 (d, 2 C); 128.0 (d); 127.8, 126.9 (2d, 2 × 2 C); 86.7 (d); 67.5 (t); 61.9 (t); −4.5, −4.6 (2*q*). CI-MS: 304 (44); 209 (100).

1.2. (*S*)-[(2-Methoxy-1-phenylethoxy)methyl]dimethylphenylsilane (9). A solution of CH_2N_2 in Et_2O[42] was added at 0 °C to a solution of **8** (300 mg, 1.05 mmol, ≥66% ee) and $AlCl_3$ (13.3 mg, 0.1 mmol) in Et_2O (2 mL) until the yellow color persisted. It was quenched by the addition of saturated aqueous NH_4Cl solution, and the mixture was extracted with Et_2O. Chromatography (hexane/Et_2O 13:1) gave **9** (291 mg, 0.97 mmol, 92%, ≥66% ee) as a colorless oil. $[\alpha]_D = 63.9 \pm 0.2°$ (c = 1.19, $CHCl_3$). IR: 1125, 1090, 840, 700, 605. ^1H NMR: 7.70−7.36 (m, 10 H); 4.50 (dd, J = 7.4, 4.2, 1 H); 3.69, 3.59 (AB of ABX, J_{AB} = 10.8, J_{AX} = 7.4, J_{BX} = 4.2, 2 H); 3.51 (*s*, 3 H); 3.41, 3.36 (AB, J = 12.8, 2 H); 0.48, 0.47 (2s, 2 × 3 H). ^{13}C NMR: 139.7, 137.6 (2s); 133.8 (d, 2 C); 129.1 (d); 128.3 (d, 3 C); 127.6, 127.0 (2d, 2 × 2 C); 85.5 (d); 77.3, 62.0 (2t); 59.4, −4.3, −4.5 (3q). CI-MS: 318 (89); 223 (100). Anal. Calcd for $C_{18}H_{24}O_2Si$ (300.47): C, 71.95; H, 8.05. Found: C, 71.70; H, 8.11.

2. Preparation of Phenylsilanes 11a−f. Representative Procedure for the Preparation of 11e. For complete procedures for all compounds, see the Supporting Information.

2.1. (*S*)-2-Methoxy-2-phenylethanol (6e). A solution of (*S*)-methoxyphenylacetate (1.322 g, 7.34 mmol, ≥98% ee)[21] in Et_2O (5 mL) was added at 0 °C to a suspension of $LiAlH_4$ (342 mg, 9.01 mmol) in Et_2O (10 mL). It was quenched after 1 h with aqueous HCl solution (10%) and extracted with Et_2O to afford, after chromatography (hexane/Et_2O 1:1), **6e** (927 mg, 6.09 mmol, 83%, ≥98% ee) as a colorless oil. The enantiomeric purity was determined by HPLC (Chiral-OD column; hexane/2-propanol 200:1; t_r((*R*)-**6e**) = 22.6 min; t_r((*S*)-**6e**) = 25.3 min). $[\alpha]_D = 140.3 \pm 0.2°$ (c = 1.08, $CHCl_3$). IR: 1115, 1065, 700. ^1H NMR: 7.44−7.30 (m, 5 H); 4.35 (dd, J = 8.2, 4.0, 1 H); 3.72, 3.66 (AB of ABX, J_{AB} = 11.7, J_{AX} = 8.2, J_{BX} = 4.0, 2 H); 3.36 (s, 3 H); 2.42 (s, 1 H). ^{13}C NMR: 138.3 (s); 128.5 (d, 2 C); 128.1 (d); 126.8 (d, 2 C); 84.6 (d); 67.3 (t); 56.9 (q). CI-MS: 170 (100); 121 (87).

2.2. (*S*)-[(2-Methoxy-2-phenylethoxy)methyl]dimethylphenylsilane (11e). Trifluoromethane sulfonic anhydride (1.05 mL, 6.45 mmol) was added dropwise at 23 °C to a solution of (hydroxymethyl)dimethylphenylsilane (**5**; 1.02 g, 6.15 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (1.40 g, 6.75 mmol) in CH_2Cl_2 (20 mL). The reaction was quenched after 2 h with saturated aqueous NH_4Cl solution and extracted with Et_2O to deliver the crude triflate **7c**. A solution of **6e** (693 mg, 4.55 mmol, ≥98% ee) in CH_2Cl_2 (5 mL) and K_2CO_3 (4.7 g, 34 mmol) were added to the triflate **7c**; the mixture was stirred for 48 h and then poured on H_2O. Extraction with CH_2Cl_2 and chromatography (hexane/Et_2O 17:1) afforded **11e** (1.250 g, 4.16 mmol, 91%, ≥98% ee) as a colorless oil. $[\alpha]_D = 41.9 \pm 0.2°$ (c = 1.13, $CHCl_3$). IR: 1115, 1110, 840, 800, 700, 630, 605. ^1H NMR: 7.44−7.15 (m, 10 H); 4.25 (dd, J = 7.3, 4.3, 1 H); 3.57, 3.37 (AB of ABX, J_{AB} = 10.5, J_{AX} = 7.3, J_{BX} = 4.3, 2 H); 3.22, 3.26 (AB, J = 12.9, 2 H); 3.20 (*s*, 3 H); 0.20 (*s*, 6 H). ^{13}C NMR: 139.6, 137.7 (2s); 133.8 (d, 2 C); 129.1 (d); 128.3 (d, 3 C); 127.7, 127.0 (2d, 2 × 2 C); 82.8 (d); 79.7, 64.8 (2t); 57.1, −4.39, −4.42 (3q). CI-MS: 318 (100); 268 (88); 223 (55). Anal. Calcd for $C_{18}H_{24}O_2Si$ (300.469): C, 71.95; H, 8.05. Found: C, 71.37; H, 8.01.

3. Preparation of Phenylsilanes 16a,b. 3.1. Potassium (*S*)-Methoxyphenylacetate (13). A mixture of $KHCO_3$ (130 mg, 1.29 mmol) and (*S*)-methoxyphenylacetic acid (212 mg, 1.27 mmol, ≥98% ee)[43] in H_2O (5 mL) was stirred at 23 °C for 4 h. The H_2O was removed by lyophilization for 15 h to leave **13** (260 mg, 1.27 mmol, 100%, ≥98% ee) as a colorless solid. Mp: 170.8−171.2 °C. IR: 2215, 1950, 1245, 1155, 1030. ^1H NMR: 7.58−7.36 (m, 5 H); 4.60 (s, 1 H); 3.24 (*s*, 3 H). ^{13}C NMR: 171.4, 138.2 (2s); 128.2 (d, 2 C); 127.2 (d); 127.1 (d, 2 C); 85.8 (d); 55.9 (q).

3.2. (Dimethylphenylsilyl)methyl (*S*)-Methoxyphenylacetate (14). Neat (iodomethyl)dimethylphenylsilane (**7b**; 5.0 mL, 23.53 mmol)[44] was added to a solution of **13** (4.432 g, 21.70 mmol, ≥98% ee) in dry DMSO (30 mL), and the resultant

(40) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.
(41) Ambasht, S.; Chiu, S. K.; Peterson, P. E.; Queen, J. *Synthesis* **1980**, 318.
(42) Hudlicky, M. *J. Org. Chem.* **1980**, *45*, 5377.
(43) Corey, E. J.; Hopkins, P. B.; Yoo, S. K. S.; Nambiar, K. P.; Falck, J. R. *J. Am. Chem. Soc.* **1979**, *101*, 7131.
(44) Huang, C. T.; Wang, P. J. *Hua Hsueh Hsueh Pao* **1959**, *25*, 341.
(45) Johnson, C. K., ORTEPII; Report ORNL-5138; Oak Ridge National Laboratory, Oak Ridge, TN, 1976.

mixture was heated to 50 °C for 15 h. It was quenched with saturated aqueous NH_4Cl solution and extracted with Et_2O. Chromatography (hexane/Et_2O 8:2) gave **14** (6.373 g, 20.27 mmol, 93%, ≥98% ee) as a colorless oil. The enantiomeric purity of **14** was determined by ^{1}H NMR (see below). $[\alpha]_D$ = 50.5 ± 0.2° (*c* = 1.00, $CHCl_3$). IR: 1745, 1250, 1170, 1115, 840, 730, 700, 600. ^{1}H NMR: 7.43−7.28 (m, 10 H); 4.74 (s, 1 H); 4.07, 3.95 (AB, *J* = 14.2, 2 H); 3.38 (s, 3 H); 0.22, 0.21 (2s, 2 × 3 H). ^{1}H NMR (5 mg (±)-**14**, 50 mg of Pirkle reagent,[25] 0.6 mL of $CDCl_3$; selected signals): 3.26 (*s*, MeO of (*S*)-**14**); 3.24 (s, MeO of (*R*)-**14**). ^{13}C NMR: 171.3, 136.5, 135.9 (3s); 133.7 (d, 2 C); 129.5, 128.6 (2d); 128.5, 127.9, 127.1 (3d, 3 × 2 C); 82.7 (d); 57.7 (t); 57.3, −4.6, −4.7 (3q). CI-MS: 332 (23), 237 (100). Anal. Calcd for $C_{18}H_{22}O_3Si$ (314.453): C, 68.75; H, 7.05. Found: C, 68.30; H, 6.82.

3.3. 2-[(Dimethylphenylsilyl)methoxy]-3-methoxy-3-phenylpropene (15). A solution of **14** (2.507 g, 7.97 mmol, ≥98% ee) in THF (10 mL) was added dropwise at −40 °C to a solution of Tebbe reagent (10 mmol)[27] in THF (10 mL). After addition of pyridine (0.1 mL), it was stirred at −40 °C for 1 h, warmed to 0 °C, and stirred for an additional 4 h. It was quenched with aqueous NaOH solution (2 M, 10 mL), extracted with Et_2O, and chromatographed (hexane/CH_2Cl_2 8:2) to give **15** (2.066 g, 6.61 mmol, 83%) as a colorless oil. The compound was immediately used for the next step. ^{1}H NMR: 7.39−7.10 (m, 10 H); 4.51 (s, 1 H); 4.29, 4.12 (2s, 2 H); 3.42, 3.37 (AB, *J* = 12.9, 2 H); 3.30 (s, 3 H); 0.20 (s, 6 H). ^{13}C NMR: 164.0, 140.2, 136.8 (3s); 133.7 (d, 2 C); 129.2 (d); 127.9, 127.7 (2d, 2 × 2 C); 127.5 (d); 127.0 (d, 2 C); 83.9 (d); 81.4, 59.6 (2t); 56.8, −4.6, −4.7 (3q). CI-MS: 313 (100), 281 (27).

3.4. (1*S*,2*S*)- and (1*R*,2*S*)-[(2-Methoxy-1-methyl-2-phenylethoxy)methyl]dimethylphenylsilane (16a,b). Enol ether **15** (1.277 g, 4.09 mmol) was dissolved in Et_2O (70 mL) and hydrogenated at 0 °C (1 atm of H_2) over Pd/C (10%, 386 mg) and in the presence of NaOH (210 mg, 5.21 mmol) until the starting material was completely consumed. Evaporation of the solvent and chromatography (hexane/CH_2Cl_2 8:2) gave a mixture of **16a** and **16b** (1.068 g, 3.40 mmol, 83%) in a ratio of 60:40. The two diastereomers were separated by preparative HPLC (Kromasil KP 100−10C18; 2 in. × 25 cm; MeOH/H_2O 75:25; flow 49 mL min^{-1}; batches of 200 mg; detection at 254 nm; t_r(**16a**) = 166.0 min; t_r(**16b**) = 182.7 min).

Data for **16a** (60% ee, determined with the deriving acylsilane **20a**) are as follows. $[\alpha]_D$ = 25.5 ± 0.2° (*c* = 1.07, $CHCl_3$). IR: 1115, 1095, 840, 730, 700. ^{1}H NMR: 7.47−7.13 (m, 10 H); 4.05 (d, *J* = 5.8, 1 H); 3.42 (quint-like m, *J* = 5.8, 1 H); 3.37, 3.27 (AB, *J* = 12.8, 2 H); 3.18 (s, 3 H); 0.79 (d, *J* = 6.4, 3 H); 0.21, 0.20 (2s, 2 × 3 H). ^{13}C NMR: 139.2, 138.0 (2s); 133.9 (d, 2 C); 129.0 (d); 127.9 (d, 2 C); 127.7 (d, 4 C); 127.4, 86.7, 82.0 (3d); 62.2 (t); 57.3, 15.2, −4.3, −4.4 (4q). CI-MS: 283 (48), 237 (100). Anal. Calcd for $C_{19}H_{26}O_2Si$ (314.50): C, 72.56; H, 8.33. Found: C, 72.48; H, 8.41.

Data for **16b** (still containing ca. 5% of **16a**, 84% ee, determined with the deriving acylsilane **20b**) are as follows. $[\alpha]_D$ = 25.6 ± 0.2° (*c* = 1.20, in $CHCl_3$). IR: 1115, 1095, 840, 730, 700. ^{1}H NMR: 7.49−7.28 (m, 10 H); 4.08 (d, *J* = 5.9, 1 H); 3.41, 3.06 (AB, *J* = 12.7, 2 H); 3.39 (quint, *J* = 6.1, 1 H); 3.29 (s, 3 H); 1.21 (d, *J* = 6.2, 3 H); 0.23, 0.20 (2s, 2 × 3 H). ^{13}C NMR: 140.1, 137.9 (2s); 133.8 (d, 2 C); 129.0 (d); 127.9 (d, 2 C); 127.6 (d, 4 C); 127.3, 86.5, 83.0 (3*d*); 62.0 (t); 57.2, 15.2, −4.5, −4.6 (4q). CI-MS: 332 (18), 283 (100), 237 (63). Anal. Calcd for $C_{19}H_{26}O_2Si$ (314.50): C, 72.56; H, 8.33. Found: C, 72.37; H, 8.07.

4. Conversion of Phenylsilanes 9, 11a−f, and 16a,b into Acetylsilanes 18, 19a−f, and 20a,b. Representative Procedure for the Conversion of 11e into 19e. For complete procedures for all compounds, see the Supporting Information.

4.1. (*S*)-[(2-Methoxy-2-phenylethoxy)methyl]dimethylsilane (12e). Fe (4 mg, 0.07 mmol) and Br_2 (40 μL, 0.78 mmol) were added at −30 °C to a solution of **11e** (196 mg, 0.65 mmol, ≥98% ee) in dry $ClCH_2CH_2Cl$ (20 mL). After 1 h, Et_2O (20 mL) and an excess of $LiAlH_4$ (ca. 2 mol equiv) were added. The mixture was stirred for 2 h at 23 °C, quenched with aqueous HCl solution (10%), extracted with Et_2O, and chromatographed (hexane/Et_2O 19:1) to give **12e** (142 mg, 0.63 mmol, 97%, ≥98% ee, determined with the deriving acylsilane **19e**) as a colorless oil. $[\alpha]_D$ = 47.7 ± 2° (*c* = 0.99, $CHCl_3$). IR: 2120, 1250, 1120, 1100, 900, 890, 700, 600. ^{1}H NMR: 7.27−7.15 (m, 5 H); 4.27 (dd, *J* = 7.6, 3.9, 1 H); 3.86−3.82 (m, 1 H); 3.55, 3.36 (AB of ABX, J_{AB} = 10.6, J_{AX} = 7.6, J_{BX} = 3.9, 2 H); 3.22, 3.16 (AB of ABX, J_{AB} = 13, J_{AX} = J_{BX} = 2.6, 2 H); 3.20 (s, 3 H); 0.01, 0.00 (2s, 2 × 3 H). ^{13}C NMR: 139.4 (s); 128.3 (d, 2 C); 127.7 (d); 126.9 (d, 2 C); 82.9 (d); 79.6, 63.6 (2t); 57.1 (q); −6.0 (q, 2 C). CI-MS: 242 (10); 223 (11); 192 (33); 121 (100). Anal. Calcd for $C_{12}H_{20}O_2Si$ (224.37): C, 64.24; H, 8.98. Found: C, 63.93; H, 8.98.

4.2. (*S*)-[(2-Methoxy-2-phenylethoxy)methyl]dimethylsilyl Methyl Ketone (19e). Cl_2 gas was passed at −25 °C through a solution of **12e** (380 mg, 1.69 mmol, ≥98% ee) in CCl_4 (10 mL) until a yellow color persisted. Excess Cl_2 was removed with a stream of N_2, CCl_4 was distilled off, and THF (10 mL) was added. The resulting solution was added to a freshly prepared solution of 1-lithio-1-ethoxyethene (6.76 mmol)[8] in THF (20 mL) at −80 °C. The mixture was warmed slowly to 23 °C, quenched with saturated aqueous NH_4Cl solution, and extracted with Et_2O. The crude product was dissolved in acetone (5 mL), aqueous HCl solution (10%, 2 mL) was added, and this mixture was stirred for 1 h at 23 °C. Extraction with Et_2O and chromatography (hexane/Et_2O 8:2) gave **19e** (415 mg, 1.56 mmol, 92%, ≥98% ee) as a colorless oil. The enantiomeric purity of **19e** was determined by ^{1}H NMR (see below). $[\alpha]_D$ = 57.8 ± 0.2 (*c* = 1.02, $CHCl_3$). IR: 1645, 1120, 1100, 845, 700, 605. ^{1}H NMR: 7.32−7.21 (m, 5 H); 4.29 (dd, *J* = 7.3, 4.3, 1 H); 3.60, 3.43 (AB of ABX, J_{AB} = 10.4, J_{AX} = 7.3, J_{BX} = 4.3, 2 H); 3.34, 3.29 (AB, *J* = 13.1, 2 H); 3.24 (s, 3 H); 2.20 (s, 3 H); 0.17, 0.15 (2s, 2 × 3 H).^{1}H NMR (5 mg of (±)-**19e**, 30 mg of Pirkle reagent,[25] 0.6 mL of $CDCl_3$; selected signals): 0.19 (s, MeSi of (*S*)-**19e**); 0.18 (s, MeSi of (*R*)-**19e**). ^{13}C NMR: 245.7, 139.3 (2s); 128.3 (d, 2 C); 127.8 (d); 126.9 (d, 2 C); 82.8 (d); 79.7, 62.7 (2t); 57.0, 36.5 (2q); −6.4 (q, 2 C). CI-MS: 284 (100); 267 (45); 235 (31); 223 (27); 121 (77).

6. Addition of Organometallic Reagents to Acylsilanes 18, 19a−f, and 20a,b. Procedure A (without Lewis Acid Additives). A solution of RMgBr (0.9 M, 3.5 equiv) or RLi (1.8 M, 3.5 equiv in Et_2O) was added at −80 °C to a solution of the respective ketone (0.05−0.1 M) in the given solvent. This mixture was stirred for 1 h at −80 °C, slowly warmed to −60 °C, and quenched by addition of HCl (2 equiv, 1 M solution in Et_2O). Extraction with Et_2O and chromatography (hexane/Et_2O 8:2) afforded the products as colorless oils.

Procedure B (with Lewis Acid Additives), A solution of $MgBr_2$ (2 equiv, 1 M solution in benzene/Et_2O (1:1)) or $ZnBr_2$ (2 equiv, 1 M solution in Et_2O) was added at −80 °C to a solution of the respective ketone in Et_2O (0.05−0.1 M) in the given solvent, and it was stirred for 30 min. After addition of RMgBr (3.5 equiv, 0.9 M solution in Et_2O) or RLi (3.5 equiv, 1.8 M, solution in Et_2O), the mixture was stirred for 1 h at −80 °C, slowly warmed to −60 °C, and quenched by the addition of HCl (2 equiv, 1 M solution in Et_2O). Workup as above afforded the products as colorless oils.

The reactions were performed with 0.1−0.3 mmol of the ketones, and the results of the transformations (yields and ratios of the diastereomers) are summarized in Tables 1−3; spectral data are given in the Supporting Information.

7. Removal of the Silicon Group. (*S*)-1-Phenylethanol ((*S*)-27). A mixture of **23a** and **23a′** (dr 68:32, 47 mg, 0.13 mmol, er 80:20, each) and KH (20% in mineral oil, 15 mg, ca. 0.07 mmol) in THF (4 mL) was stirred at −20 °C. After 90 min, $Bu_4NF{\cdot}3H_2O$ (2 mL, 1 M solution in THF, 2.00 mmol) was added, and the mixture was stirred for an additional 2 h at 23 °C. It was quenched with saturated aqueous NH_4Cl solution, extracted with Et_2O, and chromatographed (hexane/

Et_2O 8:2) to give (*S*)-**27** (13 mg, 0.11 mmol, 82%, er 60:40; corresponds to >98% stereoselectivity of the rearrangement) as a colorless oil. The spectral data were identical with those of an authentic sample. The enantiomeric purity of the sample was determined by HPLC (Chiral-OD column; hexane/*i*-PrOH 100:1; t_r((*R*)-**27**) = 23.9 min; t_r((*S*)-**27**) = 34.2 min) and by ^{1}H NMR of its *S* Mosher ester. Selected ^{1}H NMR signals: 3.71 (*s*, MeO of *R*,*S* derivative); 3.62 (*s*, MeO of *S*,*S* derivative); 1.79 (d, *J* = 6.6, *Me*CH of *R*,*S* derivative); 1.73 (d, *J* = 6.6, *Me*CH of *S*,*S* derivative).

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Supporting Information Available: Text giving a detailed description of the syntheses of all new compounds, together with the spectral data, figures giving reproductions of the ^{1}H NMR spectra of **8**, **6e**, **10**, **12c**,**d**,**f**, **15**, **17a**,**b**, **18**, **19a**−**f**, **20a**,**b**, **21**/**21′**, **22a**−**n**/**22a′**−**n′**, **23a**,**b**/**23a′**,**b′** as proof of purities, and tables giving X-ray structural data for *rac*-**23a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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