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# Stereoselective Transformations Starting with Chiral (Alkoxy)methyl-Substituted Organosilicon Compounds

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**Abstract.** The following short review summarizes the results we achieved with the investigation of chiral silicon groups as auxiliaries for the enantioselective synthesis. (Alkoxy)methyl-substituted silicon compounds with 'Si-centered chirality', which were prepared in optically active form by application of a bioreduction, have been efficiently used as starting materials for a number of stereoselective reactions. Acylsilanes of this type upon treatment with organometallic reagents gave rise to 1,2-addition products with high degrees of stereoselectivities. The respective  $\alpha$ -hydroxysilanes could be stereospecifically desilylated to chiral secondary alcohols, or, depending on the substitution pattern, further used as starting compounds for stereocontrolled oxidation, Cope- or Claisen-type rearrangement reactions. Chiral  $\alpha$ -metallated vinylsilanes were converted to  $\alpha$ -silyl-substituted allylic alcohols and to  $\alpha$ -silyl-substituted  $\alpha,\beta$ -unsaturated ketones. The prior led to chiral allenes in a Peterson-type reaction – however, without stereoselectivity – the latter delivered stereoselectively  $\beta$ -chiral silicon-free ketones upon stereocontrolled conjugate cuprate addition followed by removal of the silicon auxiliary.

## 1. Introduction

Organosilicon chemistry has undergone a tremendous development over the last two or three decades. It is fair to state that nowadays, the majority of multistep organic syntheses makes use of organosilicon compounds in one way or another: as reagents for C,C-bond formations, for functional-group transformations, or for functional-group protections. With the advancing interest in the preparation of enantiomerically pure compounds, it is not surprising that also attention has been increasingly directed towards stereoselective processes involving chiral silicon compounds [1–6]. Some rather impressive results were obtained, e.g., with chiral allyl-

silanes **1** that gave in highly enantioselective allylation reactions rise to a variety of compounds [5][6]. The chiral allylsilanes **1**, however, do not possess a 'chiral silicon moiety' which delivers stereochemical information onto a carbon framework; the stereochemical information is already stored on the reactive group, which itself is attached to an 'achiral silicon group' (silanes of the type **A** with 'proximate C-centered chirality' [4]). Transfer of chirality from a chiral silicon auxiliary to a neighboring prostereogenic group, however, has been realized with silanes of the type **B** and **C**. These compounds have located the chirality either on an inert side chain (compounds of the type **B** with 'remote C-centered chirality') or – in form of a stereogenic center – on silicon itself (compounds of the type **C** with 'Si-centered chirality' [4]). It is just astonishing, though, how little work has been performed with such substrates. Some remarkable stereoselectivities were lately

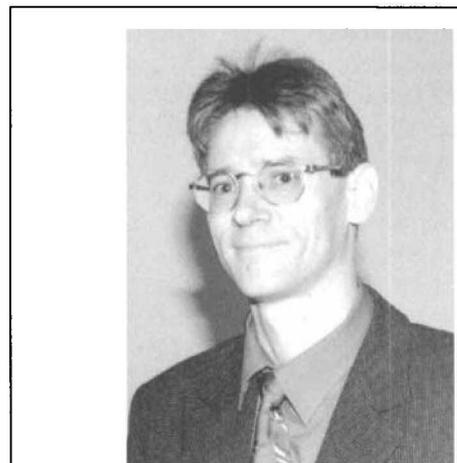


Foto: R. Hanck, Basel

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attained in several transformations with proline-derived chiral silanes **2** (that are of the type **B**) [2]. The scope of reactions with this type of substrates, however, is limited, since no common chiral silicon precursor (like, e.g., a chlorosilane) is employed. So far, only little use of chiral silicon compounds of the type **C** has been made for the enantioselective synthesis [1–5]. This is probably due to the low stereoselectivities that were obtained in several reactions where almost exclusively derivatives of **3** have been used as the chiral starting compounds.

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Enhanced stereoselectivities were expected to be attained, if (alkoxy)methyl-substituted chiral silanes **4** were used instead of derivatives of **3**. These compounds should be enabled to form cyclic chelate intermediates or transition states with cationic additives (metals, M). As a consequence of the rigid intermediary structure, they should effect an improved discrimination of the different spatial approaches of the reacting species. This is in fact observed, as will be shown in this short review: below, we describe the preparation of chiral (benzyloxy)methyl-substituted silanes and some subsequent stereoselective transformations. Focus will be directed on the primary and subsequent reactions of two types of chiral organosilicon compounds, namely acylsilanes **5** and  $\alpha$ -metallated vinylsilanes **6**. These substrates should stereoselectively react either as electrophiles at the prostereogenic carbonyl group or as nucleophiles with

external prostereogenic electrophiles, respectively, leading to novel chiral compounds amenable to further transformations.

## 2. Preparation of Chiral (Alkoxy)methyl-Substituted Silanes

Racemic chiral (alkoxy)methyl-substituted silanes were prepared straightforwardly from commercial (chloromethyl)dichloro(methyl)silane (**7**) [7]: Stepwise substitution of the Cl-atoms (*via* bis(benzyloxy)silane intermediates) – first at the chloromethyl group with the benzyloxy residue, then at the silicon center with the *tert*-butyl group – provided the racemic chlorosilane **8** (Scheme 1), which could be used as the common precursor for the synthesis of a variety of silanes. Compound **8** was thus converted into acylsilanes **5** by reaction with acyl-anion equiv-

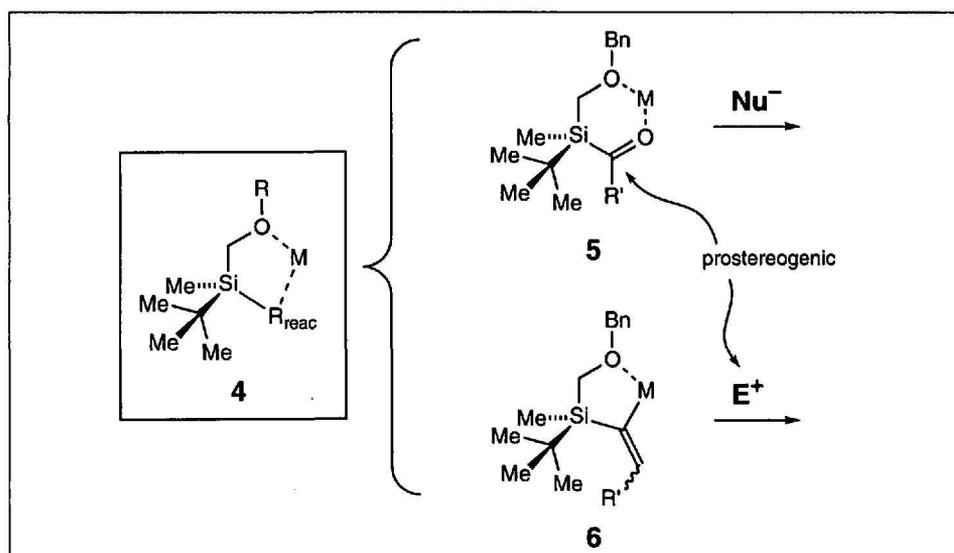
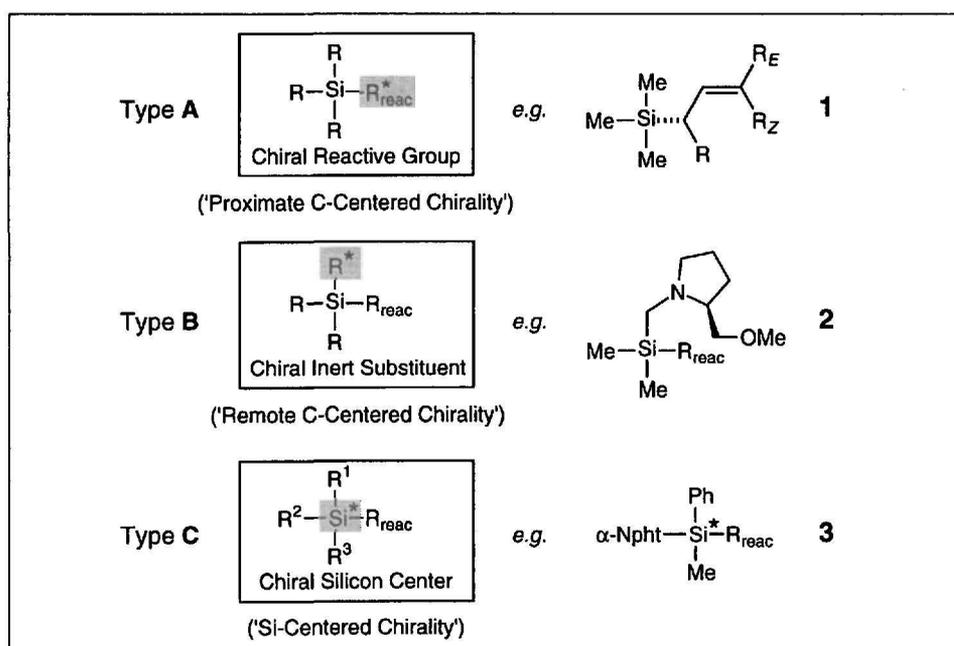
alents, followed by the respective functional-group interconversion. They were alternatively transferred into ( $\alpha$ -iodovinyl)silanes **10** (the ultimate precursors of  $\alpha$ -metallated vinylsilanes **6**) by treatment with a suitable lithium acetylide, reduction of the obtained alkynylsilanes **9** with diisobutylaluminum hydride (DIBALH), and quenching of the resultant vinylalane with iodine [8]. The stereochemistry around the C=C bond of **10** can be controlled by the proper choice of the reduction conditions; for (*E*)-configured silanes **10**, the C=C bond geometry can also be inverted in the course of the subsequent metallation step.

Optically active acylsilanes **5** are accessible by using a biotransformation step: *e.g.*, ( $\pm$ )-**5a** is recognized by several microorganisms as a substrate and is reduced stereospecifically to the corresponding  $\alpha$ -hydroxysilanes (+)-(*SiR,R*)-**11a** and (+)-(*SiS,R*)-**11a'** (Scheme 2) [9][10]. These diastereomeric alcohols were separated by chromatography and reoxidized to (–)-(*R*)-**5a** and (+)-(*S*)-**5a**, respectively. Alternatively, the two alcohols can be converted to the hydrosilanes (+)-(*S*)-**12a** and (–)-(*R*)-**12a** by treatment with KH (*Brook* rearrangement [11][12]) and reduction of the thus obtained silyl ethers with LiAlH<sub>4</sub> [13]. Best results in the biotransformation step were obtained with immobilized resting cells of *Trigonopsis variabilis* (DSM 70714), which provided the desired products not only in high chemical yields and with enantiomeric excesses > 96%, but also allowed to develop a handy workup procedure.

## 3. Stereoselective Reactions Starting with Chiral Acylsilanes

### 3.1. 1,2-Addition to the Carbonyl Group

The 1,2-addition of organometallic reagents to the carbonyl group of acylsilanes **5** afforded the respective addition products **13** with varying degrees of diastereoselectivity [7][14] (Scheme 3, shown exemplary for the conversion of (–)-(*R*)-**5a** to (+)-(*SiR,R*)-**13a**). Particularly high selectivities were attained, when the reactions were carried out in nonbasic solvents, like, *e.g.*, hexane (up to 99% de). For instance, the treatment of (–)-(*R*)-**5a** with PhLi in hexane provided predominantly (*SiR,R*)-**13a** ((*SiR,R*)-**13a**/(*SiR,S*)-**13a** = 10:1). The selectivity dropped drastically with increasing basicity of the solvent, and it was even reversed when the transformations were performed in THF (ratio 1:3) or in Et<sub>2</sub>O/DMPU (= 3,4,5,6-

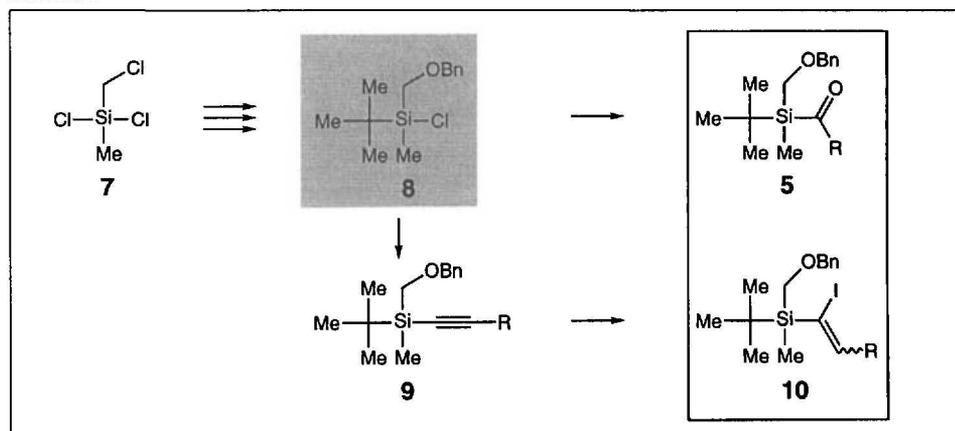


tetrahydro-1,3-dimethylpyrimidin-2(1H)-one mixtures (ratio 1:4). No solvent dependence of the stereochemistry of 1,2-additions to chiral acylsilanes derived from **3** were observed. These results – together with others – indicate that the 1,2-additions proceed in nonpolar solvents, as expected, *via* intermediary chelate structures. These structures are, however, not chair-like six-membered chelates, as initially proposed [14]: the stereochemical outcome of the transformations is just reversed to that anticipated on the basis of such intermediates. As mentioned above, (+)-(*SiR,R*)-**13a** was primarily formed from (–)-(*R*)-**5a** (92% ee, for absolute configuration see [15]) by reaction with PhLi under ‘chelate-controlled’ conditions. This was proven by the conversion of (*SiR,R*)-**13a** to (+)-(*R*)-1-phenylethanol ((+)-(*R*)-**15**, 88% ee), applying the stereochemically well-established *Brook* rearrangement [16] (formation of (*SiR,R*)-**14** by treatment of (*SiR,R*)-**13a** with KH), followed by removal of the silicon group.

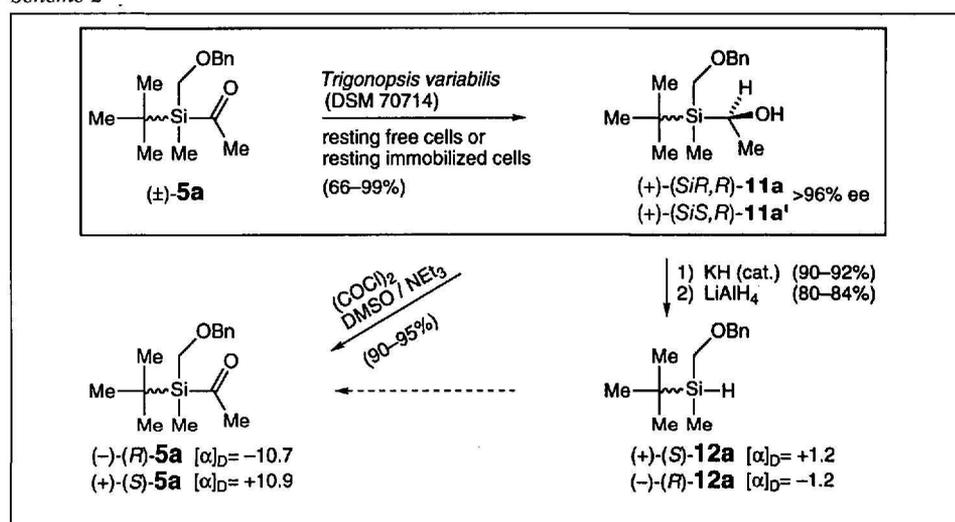
### 3.2. Cope and Ireland Ester-Enolate Rearrangements

It cannot be the ultimate goal of the research with chiral silicon compounds to prepare enantiomerically enriched secondary alcohols like, *e.g.*, (+)-(*R*)-**15**. In fact, we were rather interested to use the above-discussed 1,2-addition of organometallic reagents to chiral acylsilanes for the stereoselective preparation of substrates amenable to subsequent stereoselective transformations, making use of the newly introduced chirality of the molecules or of the chirality still residing on silicon. Thus, silicon-substituted compounds that are suitable for *Cope* and *Ireland* ester-enolate rearrangements were synthesized with this method. Reaction of either  $\alpha,\beta$ -unsaturated acylsilane **5b** with allyl *Grignard* reagents or of  $\beta,\gamma$ -unsaturated carbonyl compounds **5c, d** with vinyl-lithium species afforded 1,5-dienes **16a–d** requested for the *Cope* rearrangement (Scheme 4) [19]. The first pathway to access these compounds is unsatisfactory, though, because it provides the desired products with low stereoselectivities only. Excellent selectivities were exhibited by the second procedure, but that entry to compounds of the type **16** is still problematic due to the difficult preparation of the  $\beta,\gamma$ -unsaturated acylsilane precursors **5c, d**: these substrates isomerize readily – under mild basic or acidic conditions, *e.g.*, upon chromatography – to the thermodynamically more stable  $\alpha,\beta$ -unsaturated isomers. Nevertheless, the compounds **16a–d** were heated for a prolonged time to 200°, and they

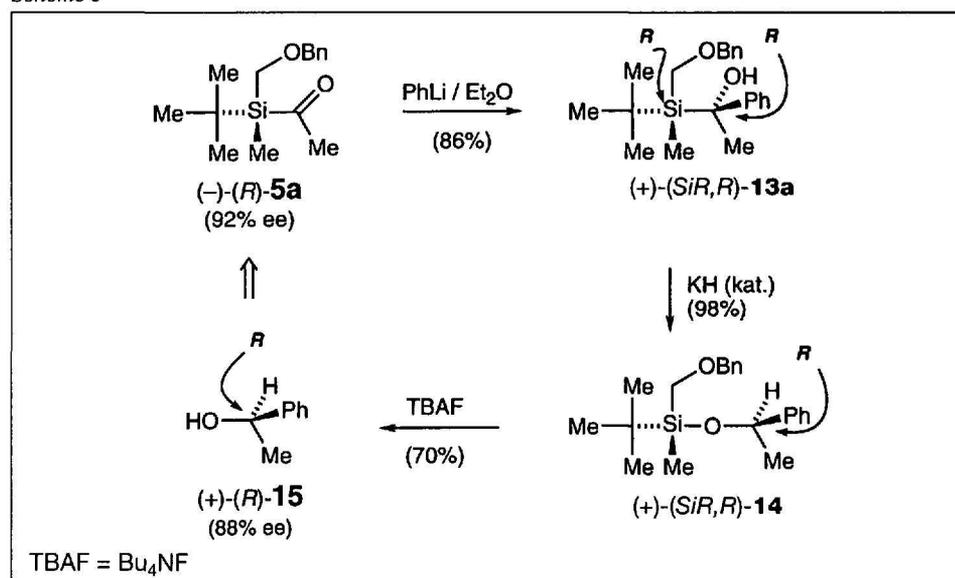
Scheme 1



Scheme 2



Scheme 3



provided the respective acylsilanes **17a–d** in high chemical and stereochemical yields. The rearrangement conditions are rather drastic, but milder versions of the oxy-*Cope* rearrangement, *i.e.*, base- or acid-catalyzed variations, were not applicable due to undesired *Brook* rearrangements or H<sub>2</sub>O eliminations. The *Cope* reactions,

though not proven yet, are thought to proceed *via* six-membered chair-like transition states locating the silyl group in equatorial position. These transition states were calculated to be lowest in energy.

*Ireland* ester-enolate rearrangement precursors were obtained from an acylsilane, too (Scheme 5) [20]. The major prod-

ucts arising from the highly stereoselective addition of vinyl organometallic species to ( $\pm$ )-**5a**,  $\alpha$ -silylated allylic alcohols **18a** and **18b**, and compound **18c** that was formed stereospecifically from **18a** by the action of lithium cyclohexyl(isopropyl)amide (LICA) were acylated *via* their magnesium alkoxide to **19a–c** and **20a–c**. Treat-

ment of these esters with LICA and trimethylchlorosilane (TMSCl), the *Ireland* ester-enolate rearrangement conditions [21][22], afforded the  $\alpha$ -TMS-substituted  $\gamma,\delta$ -unsaturated carboxylic acids of the types **21** and **22** (Scheme 6). The reaction is stereospecific, proceeding most probably *via* a chair-like six-membered transi-

tion state with the ketene acetal (*Z*)-configured. The creation of  $\alpha$ -silylated carboxylic acids in the *Ireland* ester-enolate rearrangement was rather astonishing, but is not without precedence: these types of products were often obtained as minor side products. Their formation was suppressed by the use of (*tert*-butyl)chlorodimethylsilane (TBDMSCl) instead of TMSCl [23][24]. In our case, however, attempts to perform the *Claisen*-type rearrangement in presence of TBDMSCl led solely to compounds **23a–c/24a–c**, the starting esters silylated in  $\alpha$ -position to the ester group.

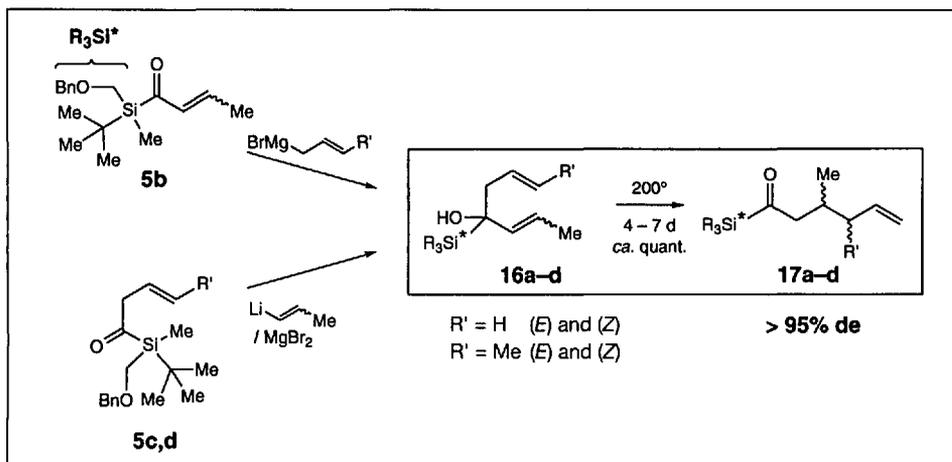
The removal of the TMS group of **21a–c** and **22a–c** can be performed chemoselectively by treatment of the compounds with  $\text{Et}_3\text{N} \cdot 3 \text{HF}$ . Under these conditions, the chiral silicon moiety is not affected. The reaction, however, is not stereoselective, giving rise to approximately equimolar amounts of the epimeric products **26a, b** and **26c, d** starting from **22a** or **22b, c**, respectively. The configuration of the chiral center at C(2), however, could possibly be adjusted as required in a later stage of a synthesis. At the moment, the  $\alpha$ -desilylated vinylsilanes of the type **25** and **26** are under investigation as starting materials for substitution reactions with electrophiles.

### 3.3. Reaction Cascade Leading to Aldol-Type Products

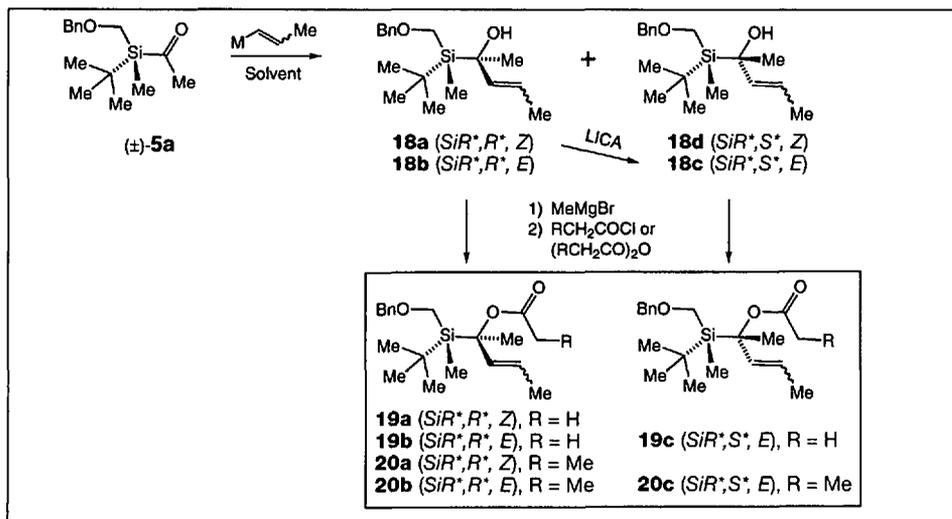
Allylic alcohols are prime candidates for stereoselective *Lewis*-acid-catalyzed epoxidations with peroxides, and we anticipated  $\alpha$ -silylated allylic alcohols of the type **18** as particularly attractive substrates (Scheme 7): they do not only possess the potential for an intramolecular chirality transfer during the oxidation process, but also embody the possibility of a subsequent transformation leading to aldol-type products.  $\alpha$ -Hydroxy- $\beta,\gamma$ -epoxysilanes **27**, deriving from silanes **18**, should be amenable to *Brook* rearrangement, which would lead, after eliminative opening of the oxirane, to silyl enol ethers **28** of aldols. Preparation of aldols on this pathway would allow a stereoselective entry also to compounds that are not readily accessed by the aldol reaction itself; the acylsilane would have acted as a synthetic equivalent of an acyl cation, and a vinyl bromide as a  $\beta$ -hydroxy anion equivalent.

The reaction of allylic alcohols of the type **18** with *tert*-butyl hydroperoxide (TBHP) in presence of  $\text{V}(\text{O})\text{acac}_2$  (acac = acetylacetonate) gave in fact rise to aldol-type products (Scheme 8) [25]. However, not silyl enol ethers of the type **28** but  $\alpha$ -silylated  $\beta$ -hydroxyketones of the type **29**

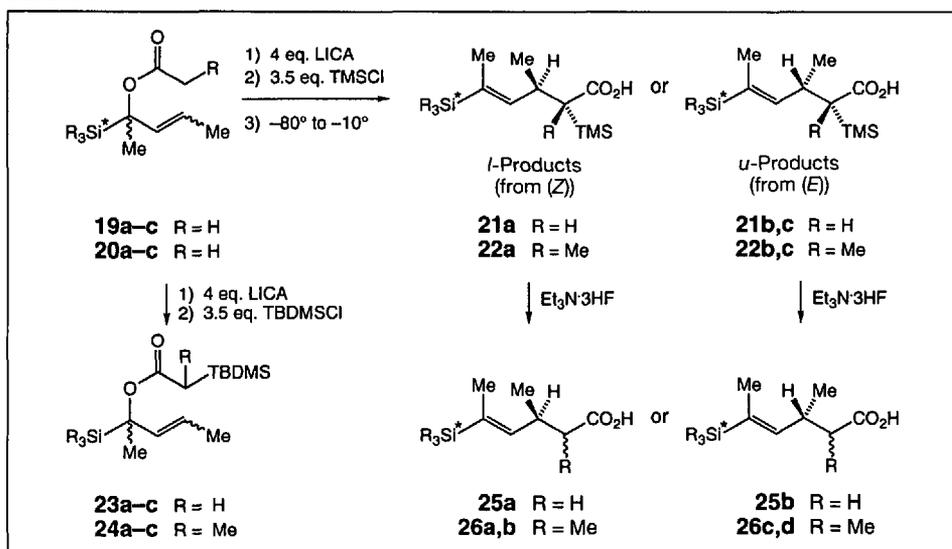
Scheme 4



Scheme 5



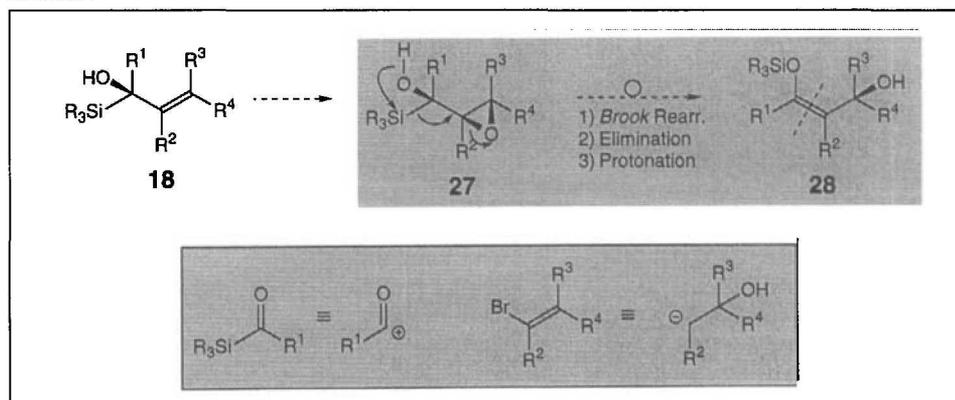
Scheme 6



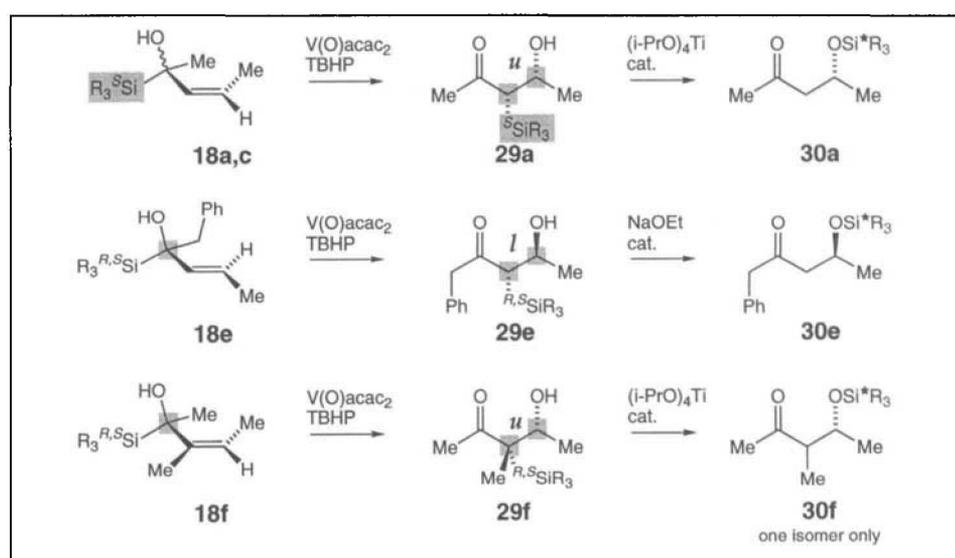
were formed. Evidently, the intermediary epoxides did not rearrange in a *Brook*- but rather in a pinacol-type fashion (see *Scheme 9*). The stereoselectivities of the reactions involved in the cascade were virtually quantitative. The  $\pi$ -face selectivity of the epoxidation step, however, was not consistent throughout the investigation of all compounds. It was strongly dependent on the substitution pattern of the starting materials. Whereas the attack of oxygen to **18a, c** was stereochemically controlled by the chiral center at silicon, the carbinol chiral center was substantial for the  $\pi$ -face differentiation in compounds with spatially increased groups at C(1) (e.g., **18e**) or at C(2) (e.g., **18f**) of the allyl system. For **18a, c**, the chelate transition structures shown in *Scheme 9* were proposed to explain the stereochemical outcome. It is assumed that such chelate structures are no more accessible for more encumbered starting materials, and consequently, a different reaction course must be followed.

The removal of the silicon auxiliary in compounds **29** presents at the moment a forward problem. Silicon shift from carbon to the hydroxy O-atom by a 1,3-*Brook* rearrangement can be brought about by Lewis acid as well as by base catalysis, but the yields of the respective products **30** are rather low. Elimination to  $\alpha,\beta$ -unsaturated ketones is the major side reaction, which we have not been able to suppress so far.

Scheme 7



Scheme 8

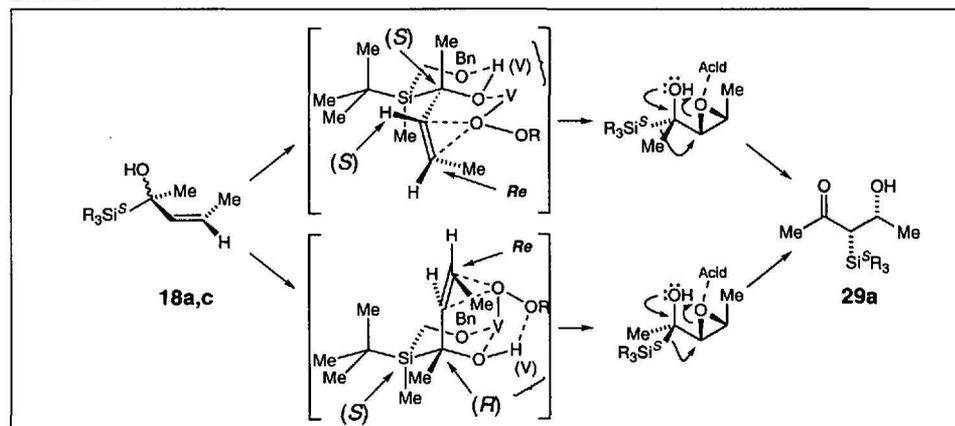


#### 4. Stereoselective Reactions Starting with $\alpha$ -Metallated Vinylsilanes

##### 4.1. Addition to Aldehydes and Formation of Chiral Allenes

The addition of the chiral lithiated vinylsilanes **31**, prepared from the respective vinyl iodides **10** (preparation see *Scheme 1*) either under preservation or inversion of the C=C bond geometry, reacted with aldehydes to afford the corresponding  $\beta$ -silylated allylic alcohols **32/32'** in good chemical yields (*Scheme 10*) [8]. The stereoselectivities of the reactions, however, were fairly poor (67% diastereoselectivity at its best) and could not be improved with reasonable effort. This result was somewhat disappointing but was in fact not too surprising, since by considerations of structure models, no evidently favored approach of the chiral nucleophile to one of the  $\pi$ -faces of the prochiral electrophile could be recognized. Highly diastereomerically enriched samples of alcohols **32** were finally still obtained in a roundabout way: oxidation of epimeric mixtures of **32/32'** to their common  $\alpha,\beta$ -unsaturated ketones **33** and re-

Scheme 9



reduction with  $\text{LiAlH}_4$  afforded the respective alcohols in ratios of ca. 10:1 [26].

With the allylic alcohols **32** at hand, we tested their potential as starting materials for the preparation of chiral allenes by means of a *Peterson*-type olefination. The allene formation was optimized with several *O*-acyl-substituted compounds of the type **34**. It was found that the treatment of the *O*-acetyl derivatives with  $\text{CsF}$  in DMSO at 100–120° gives the best results: yields of up to 95% of the parent allenes **35**

were gained. This is a remarkable improvement as compared to earlier attempts of other groups that delivered allenes with 60% yield at their best [27][28]. Though the reaction rates were higher with starting compounds possessing better leaving groups (e.g., chloro- or dichloroacetates), such substrates gave still lower yields of the desired allenes due to more side reactions.

Much to our disappointment, the fluoride treatment of optically active silane (–)

(*SiR,E*)-**34a** – obtained from (–)-(*R*)-**5a** by  $\alpha$ -methylation, Shapiro reaction, reaction with benzaldehyde, and acetylation (Scheme 11) – gave the corresponding allene **35a** in low yields and as a racemate only. The earlier results from Torres *et al.* [29], who obtained the same product through a similar pathway in 18% ee (assumingly by an *anti*-elimination), could not be verified with our compound. Supposedly, the formation of the allenes proceeds mainly by an  $E_1$  rather than an  $E_2$  mechanism. The  $E_1$  mechanism is probably particularly favored for the (*E*)-configured starting materials, where the transition states for concerted  $E_2$  elimination processes are strongly disfavored due to large  $A_{1,3}$ -strain. The  $E_2$  mechanism could, however, still be preferred for the (*Z*)-configured silylated elimination precursors. Since optically active (*Z*)-configured acetates of the type **34** are not accessible to date, this cannot be tested momentarily.

#### 4.2. Conjugate Cuprate Additions

The  $\alpha,\beta$ -unsaturated  $\alpha$ -silylated ketones **33a–c**, obtained by oxidation of the alcohols **32a–c/32a–c'**, were assumed to be suitable substrates for the stereoselective 1,4-addition of organocuprate reagents. Since  $\text{LiAlH}_4$  reductions already led with high stereoselectivity to the respective allylic alcohols **32**, the conjugate cuprate addition, which would also be stereochemically controlled by 1,3-chiral

induction, was anticipated to be highly stereoselective, too. In fact, the reaction of several organocuprates with compounds **33a–c** delivered the corresponding addition products **37**, trapped as silyl enol ethers **36**, with high chemical and stereochemical yields (Scheme 12) [30]. Particularly good results were obtained with the (*Z*)-configured starting material **33a**; but the stereoselectivities were also satisfactory with the (*E*)-configured ketone **33b**. Only with **33c**, where the group  $R^1$  is rather bulky, the stereoselectivities dropped to almost zero. This is probably due to unfavorable steric interactions between the groups  $R^1$  and  $R^2$ , which prevent the formation of chelate intermediates such as that shown in Scheme 13 with (+)-(*R*)-**33a**. Chelates of that type are thought to be responsible for the high  $\pi$ -face differentiation in the addition reactions to the compounds **33**. The stereochemical result of the reaction of optically active (+)-(*R*)-**33a** with  $\text{Ph}_2\text{CuLi}$  is consistent with an attack of the cuprate at the least hindered face – opposite to the *tert*-butyl group – of the C=C bond of such a lithium chelate. This attack of the reagent leads to (–)-(*SiR,3S*)-**37a/37a'** and finally to (–)-(*R*)-**38**, which was compared with an authentic sample. The formation of an acyclic  $\beta$ -chiral ketone by means of an auxiliary-assisted stereoselective cuprate addition in an enantiomeric excess of 93% represents to our knowledge the best example of such a reaction.

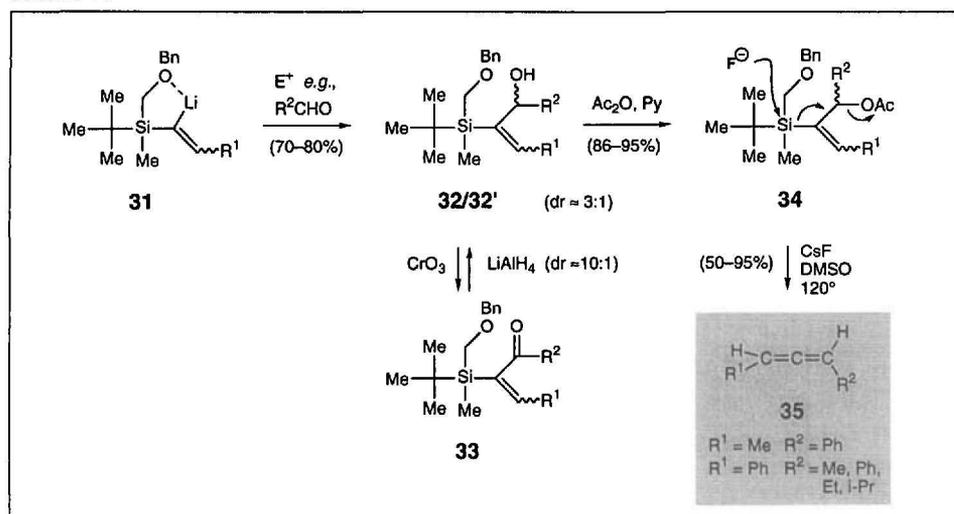
#### 5. The Fate of the Chiral Silicon Group

Using a chiral auxiliary in stoichiometric amounts, as we do it with our transformation, one must argue that it is necessary to recover this group in optically active form for recycling. We were in fact confident that this might be possible, since most transformations involving substitution at silicon proceed with high degrees of stereoselectivity [31]. Since we performed our reactions only in a few cases with optically active material, we simply did not have had the opportunity to test this matter too closely yet. In the preparation of (+)-(*R*)-1-phenylethanol (Scheme 3), we were able to isolate the respective silicon component as the respective fluoro- and hydroxysilanes or, when the silicon group was removed reductively by treatment of (+)-(*SiR,R*)-**14** with  $\text{LiAlH}_4$ , as the hydrosilane. All three compounds showed low optical rotations only. Similar results were obtained with the recovered silane components from the preparation of allene ( $\pm$ )-**35a** (Scheme 11) or  $\beta$ -chiral ketone (–)-(*R*)-**38** (Scheme 13). We have not been able to determine the enantiomeric excesses of the respective silane substrates yet. We expect, however, considerable loss of chiral information in the formation of the fluoro- and hydroxysilanes, since fluorosilanes racemize readily under the influence of fluoride ions, and because the hydroxysilane was possibly formed by hydrolysis *via* the respective fluorosilane. To establish the chiral silicon auxiliary as a synthetically useful group, it remains still ample research to be done in respect to enable the recovery of the auxiliary in a chirally integer form.

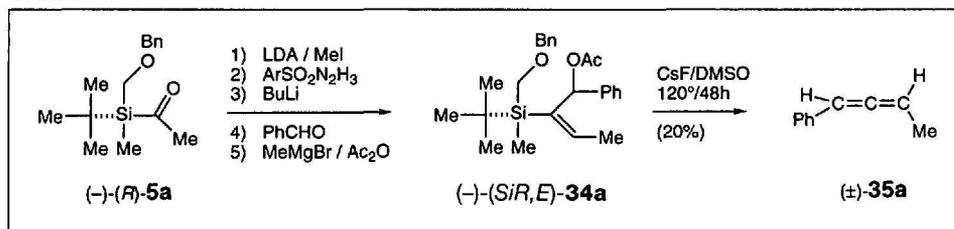
#### 6. Conclusion

We have shown with a number of rather simple reactions that 'Si-centered' chiral silicon auxiliaries can efficiently be used as stereochemical directors in enantioselective syntheses of silicon-free organic molecules. The scope of transformations that might be aided by chiral silicon is far from exhaustively explored yet, and we will further invest our full enthusiasm in the exploration of more applications of 'our' auxiliary. A drawback in the field of the chemistry with chiral (alkoxy)methyl-substituted silicon compounds, however, is still the rather troublesome and laborious access to optically active chiral silanes and, as discussed above, the unsolved problem of recovery of the chiral auxiliary. Even though the biotransformation leading to

Scheme 10



Scheme 11



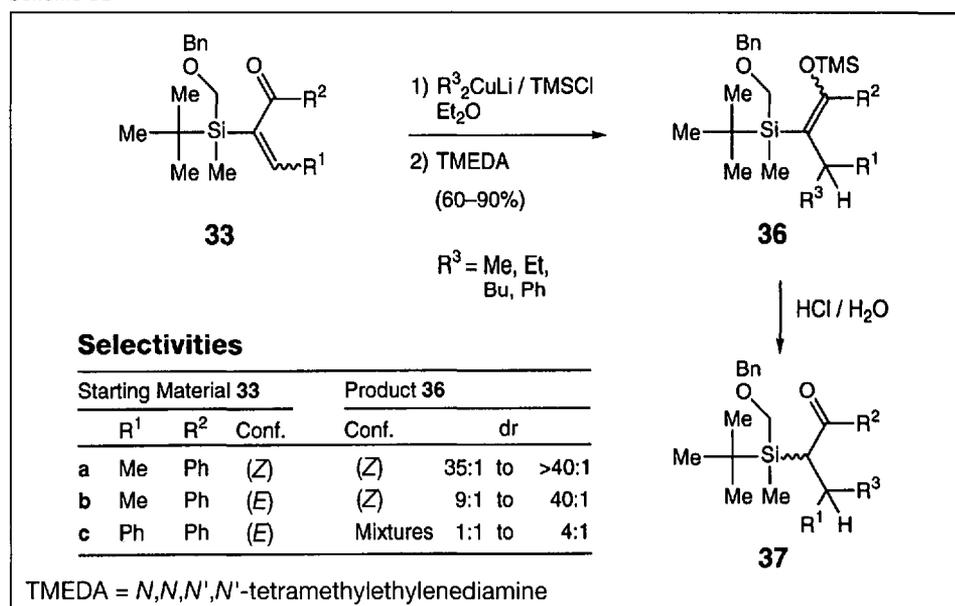
the 'enantiomerically pure' acetylsilanes **5a** can probably be scaled-up to our liking, it still requires the respective large-scale instrumentation. A possible alternative might be to shift our attention more to chiral compounds of the type **B** that possess chiral bidentate substituents. The access to a silicon compound that could be used as a common substrate for the preparation of a variety of silane derivatives would then be required.

I would like to express my undivided gratitude to my coworkers who all have contributed and some of them still contribute with their indefatigable and enthusiastic work to the results presented above (and to other results not shown here). These are: S. Bratovanov, Dr. A. Chapeaurouge, Dr. V. Enev, J. Fässler, S. Gassmann, P. Koch-Huber, Z. Molnar, J. Schröder, R. Smith, and Dr. D. Stojanova. I would like to thank also to the people in Stuttgart and Braunschweig, to Prof. C. Sydta, Dr. M. Pietzsch, and Dr. L. Fischer, for the fruitful collaboration in the biotransformations, to Prof. M. Hesse and his group for providing us with laboratory space and regular occasions for discussions, and to the members of the Institute of Organic Chemistry at the University of Zürich, particularly L. Bigler, N. Bild, A. Guggisberg, Dr. R. Kunz, Dr. A. Linden, and Dr. D. Nanz for supporting our activities with their expertise. The Swiss National Science Foundation is gratefully acknowledged for the financial support.

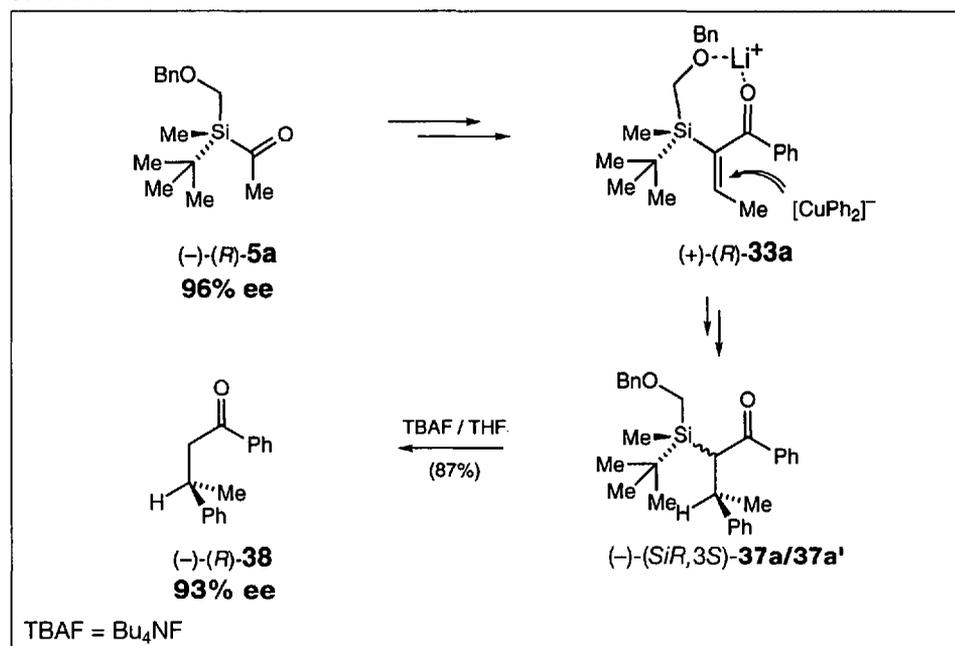
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Scheme 12



Scheme 13



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