Lithiated 5,6-Dihydro-4*H*-1,2-oxazines: Synthesis, Highly Diastereoselective Reactions with Electrophiles, and Subsequent Transformations

Hans-Ulrich Reißig*, Claudia Hippeli[1)]

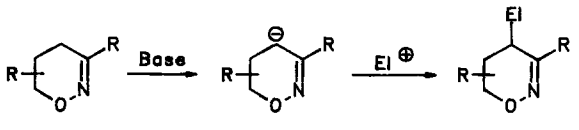
Institut für Organische Chemie der Technischen Hochschule Darmstadt,
Petersenstraße 22, D-6100 Darmstadt

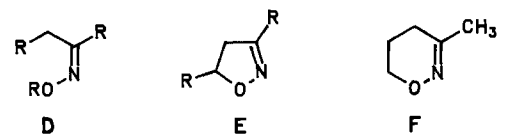
Received May 14, 1990

Key Words: 1,2-Oxazines / Deprotonation, stereoselective / Substitution with retention of configuration / Ring opening, reductive / Amino alcohols

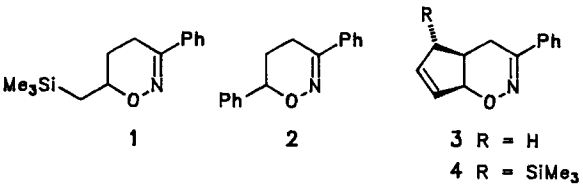
The 6-(trimethylsilyl)methyl-substituted 1,2-oxazine **1** can smoothly be deprotonated with *n*-butyllithium at C-4 to give a lithiated species which reacts with a variety of electrophiles to provide the new 1,2-oxazines **5**–**16** in good yields. Besides the preparative aspect of these transformations, the high stereoselectivity of many reactions is also interesting from a mechanistic point of view. By deprotonation of the 4-deuterated compound **5a** it has been proven that *n*-butyllithium removes exclusively the proton (or deuteron) *cis* to the 6-CH_2SiMe_3 group. Also, in most cases the reaction of lithiated **1** with electrophiles occurs with *overall retention of configuration* to afford preferentially *cis*-1,2-oxazines (series **a**). A mechanistic proposal for this highly stereoselective deprotonation process, which seems to be governed by the 1,2-oxazine oxygen, is discussed including a comparison with a recently reported ab initio calculation dealing with oxime ethers. Similar deprotonation/substitution reactions are described for 1,2-oxazines **14**, **2**, **3**, and **4**. Possibly due to a differing carbanion structure a deviating behavior is observed in some cases. Several acid-induced and reductive ring-opening reactions of **1**, **6a**, **8a**, and **14a** demonstrate the potential of 4-substituted 1,2-oxazines for the stereoselective synthesis of polyfunctionalized compounds.

5,6-Dihydro-4*H*-1,2-oxazines **A** (herein abbreviated as 1,2-oxazines) are heterocycles with a promising potential for the synthesis of polyfunctional compounds[2)]. They can easily be prepared by the hetero-Diels-Alder reaction of electron-rich olefins with nitroso alkenes as developed by Gilchrist and coworkers[3)]. By use of silylated dienophiles we were able to extend the scope of this [4 + 2] cycloaddition considerably[4)]. In this contribution we will include our results on the substitution of 1,2-oxazines **A** proceeding via the carbanion **B** to give heterocycles **C** which incorporate an electrophile El at C-4 and are not easily available otherwise.





The analogous sequence is well-known for oxime ethers **D**[5)] or the related isoxazolines **E**[6)]. However, for the six-membered heterocyclic system **A** we are only aware of Shatzmiller's reports dealing with compound **F** and the *regioselectivity* of its deprotonation[7)]. We have examined the feasibility of the sequence **A** → **B** → **C** using the monocyclic 1,2-oxazines **1** and **2**, and after having discovered the surprisingly high stereoselectivity[8)] we have extended our investigation to the bicyclic compounds **3** and **4**.



Results Obtained with the 6-(Trimethylsilyl)methyl-Substituted 1,2-Oxazine 1

The addition of *n*-butyllithium (1.5 equivalents) to 1,2-oxazine **1** in tetrahydrofuran smoothly produces the corresponding carbanion (−78°C, 15 min). The red solution, when treated with the corresponding electrophile (3 equivalents), provides the new 4-substituted 1,2-oxazines **5**–**11** (equation 1, Table 1) after aqueous workup.

For the alkylation with methyl iodide or allyl bromide the addition of tetramethylethylenediamine (TMEDA) is required (entries 2 and 3). Otherwise, either no reaction occurs at low temperature or the carbanion decomposes during warming-up. Ethyl iodide does not react at all with lithiated **1**, even in the presence of hexamethylphosphorus triamide (HMPT) as more powerful complexing agent[1)].

To our surprise, only one diastereomer is formed in most cases (entries 1–5) as unambiguously established by the ^{1}H-

  0009–2940/91/0101–0115 $ 3.50+.25/0

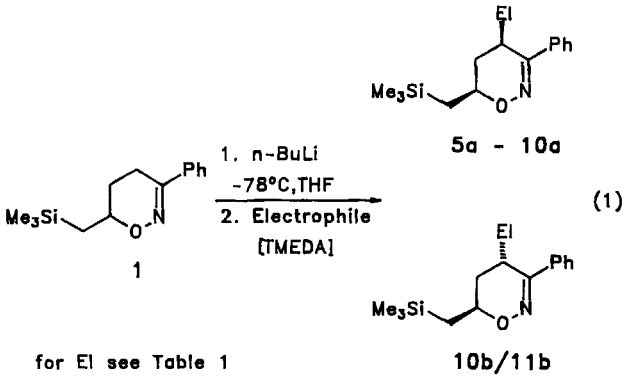


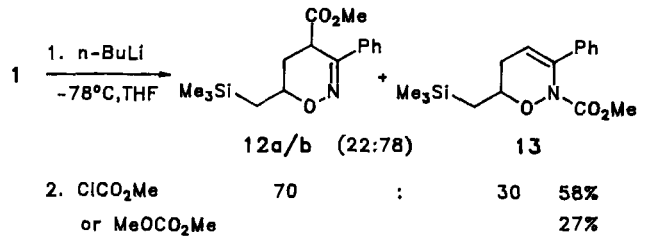
Table 1. Reactions of deprotonated 1,2-oxazine **1** with D_2O and carbon electrophiles (according to equation 1)

Entry	Electrophile	El	Product	**a** : **b** *cis* : *trans* [a]	Yield (%)[b]
1	D_2O	D	**5a**	> 97 : 3	99
2	MeI (+ TMEDA)	Me	**6a**	> 97 : 3	56
3	Allylbromide (+ TMEDA)	Allyl	**7a**	> 97 : 3	83
4	Acetone	Me_2COH	**8a**	> 97 : 3	70
5	Benzophenone	Ph_2COH	**9a**	> 97 : 3	53
6	Acetaldehyde	MeHCOH	**10 a/b**	50 : 50[c]	83
7	Methyl Chloroacetate	$ClCH_2CO$	**11b**	< 3 : 97[d]	42

[a] According to high-field ^{1}H-NMR spectra of the *crude* products. — [b] Yield of purified product. — [c] Four diastereomers in a ratio of approximately 1:1:1:1. — [d] Ratio determined after purification.

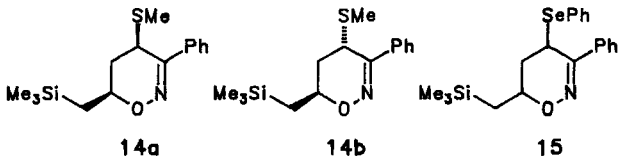
NMR data of the *crude* products. These data also prove the *cis* stereochemistry of 1,2-oxazines **5a**–**9a** and the *trans* substitution in compound **11b**. The addition of acetaldehyde to the carbanion is virtually unselective (entry 6). All four diastereomers have been found in approximately equal amounts. This is also observed when benzaldehyde is used, however, the products could not be purified in this case[1].

The addition of methyl α-chloroacetate furnishing the α-chloro ketone **11b** (entry 7) proceeds with moderate yield.

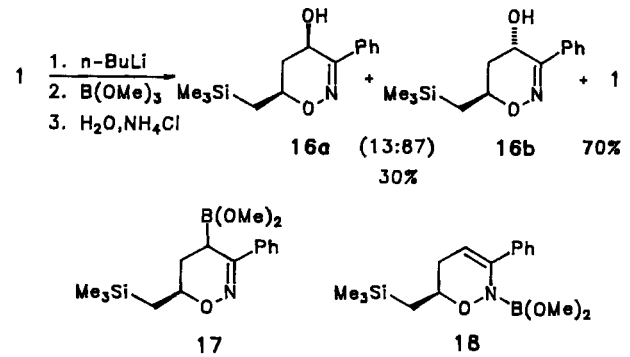


Certainly, the stereochemistry of this compound is not a matter of kinetic control, but results from the equilibration by deprotonation and protonation of **11**. This may also be true for the reaction of lithiated **1** with methyl chloroformate. In addition to the expected 4-substituted 1,2-oxazine **12**, found as a 22:78 *cis/trans* mixture, about 30% of the isolated material consists of the *N*-acylated compound **13**. This enamide derivative is exclusively obtained, although in low yield, when dimethyl carbonate is employed as electrophile.

Attempts to introduce formyl or acetyl groups into **1** by use of dimethylformamide or ethyl acetate, respectively, have failed[1]. On the other hand, the reaction of lithiated **1** with dimethyl disulfide gives **14a/b** in excellent yield (85%) as a 70:30 *cis/trans* mixture. Using PhSeCl as electrophile, we have been able to prepare the 4-selenenylated compound **15**, but the *cis/trans* ratio (15:85) is not very revealing due to the low yield of 37%. Since 1,2-oxazine **15** decomposes rather rapidly, it cannot be converted into a 4,5-unsaturated 1,2-oxazine by oxidation/elimination[1].



An attempt to introduce a 4-hydroxy function by the method developed by Jäger and coworkers[9] (for hydroxylation of isoxazolines) has led to an unexpected result. Aqueous workup directly furnishes compound **16** (**a**:**b** = 13:87) in 30% yield together with 70% of the starting compound **1**. The amount of **16** cannot be increased by oxidative workup employing H_2O_2 (70%) which should convert the boron intermediate **17** into the hydroxy compound **16**. Possibly, **16** is formed via an *N*-borylated species **18**. During workup this rather electron-rich olefin is presumed to react with atmospheric oxygen to give **16**. The starting compound **1** is regenerated from **18** by simple protonation.



Experiments using chlorotrimethylsilane or *tert*-butylchlorodimethylsilane as electrophiles have not been suc-

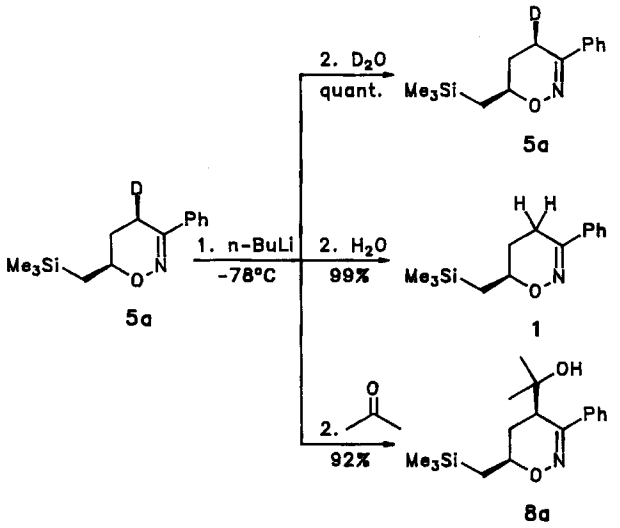
cessful. Although a fast reaction of lithiated **1** with these silylating agents is indicated by the change of color, no defined products can be isolated, even not under conditions of "dry workup"[1].

Control Experiments

The transformations described so far demonstrate that smooth generation of lithiated **1** is possible *without addition* of *n*-butyllithium to the C=N bond[10]. More surprisingly, high diastereoselectivities have been attained by reaction with certain electrophiles (Table 1: entries 1–5). To confirm the stereochemical assignments in **6a** and **14a/b** we performed equilibration experiments employing sodium methoxide in methanol (24 h, 20°C). While pure *cis*-substituted compound **6a** was reisolated unchanged (77% recovery), a shift from **a**:**b** = 70:30 to **a**:**b** = 20:80 was observed with the corresponding 4-methylthio-substituted 1,2-oxazine **14** (97% recovery). We assume that **14b** (*trans*) is thermodynamically more stable because of the steric interference of the pseudoequatorial 4-SMe group with the phenyl group in the *cis* compound **14a**, which is avoided in **14b**. A *stereoelectronic effect* might further favor the pseudoaxial location of the methylthio group due to a stabilizing interaction of the C–S σ*-orbital with the π orbital of the C=N–O moiety[11]. These equilibration experiments also reveal that **14** is more acidic than the 4-methylated 1,2-oxazine **6a**.

To understand the stereochemical outcome observed with lithiated **1**, a few control experiments have been performed. First, we have repeated the deprotonation and deuteration (see entry 1) in the presence of TMEDA. The decolorization of the solution containing lithiated **1** occurs much faster, but again exclusively **5a** (*cis*) is isolated. We thus conclude that the complexing agent increases only the rate, but does not alter the stereochemistry of the reaction. Apparently, the structure of the intermediate anion is not fundamentally changed by the presence of TMEDA.

To distinguish whether the high diastereoselectivities are caused by selective reactions of the anion with the electrophiles or by a stereoselective deprotonation of **1**, the lithiation of the deuterated compound **5a** has been studied.

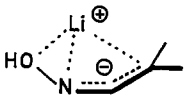


Treatment of **5a** with *n*-butyllithium and workup with D_2O furnish the apparently unchanged starting compound. Double deuterated 1,2-oxazine has not been detected. On the other hand, metalation of **5a** and workup with H_2O provide exclusively **1**, whereas the addition of acetone gives **8a**. Both products do not contain more than 3% (analytical limit of NMR spectroscopy) of deuterium at C-4.

Discussion

The experiments described prove that the base *n*-butyllithium highly discriminates between the deuteron (*cis*) and the proton (*trans*) in **5a**, removing exclusively the deuteron and thus counteracting the expected kinetic isotope effect! Only protons (or deuterons) located *cis* to the 6-substituent in **1** (or **5a**) are acidic. In addition, *the overall substitution occurs with retention of configuration* in entries 1–5. Although there are related highly stereoselective metalation/substitution processes reported in the literature, none of these are directly related to our system[12].

In order to understand these results knowledge of the exact structure of the lithiated species involved would be helpful. So far, no experimental data are available[13], but recent ab initio calculations on metalated oxime ethers indicate that the metal cation strongly interacts with the carbon, the nitrogen and the oxygen of the anion moiety (see ion pair **G**)[14].

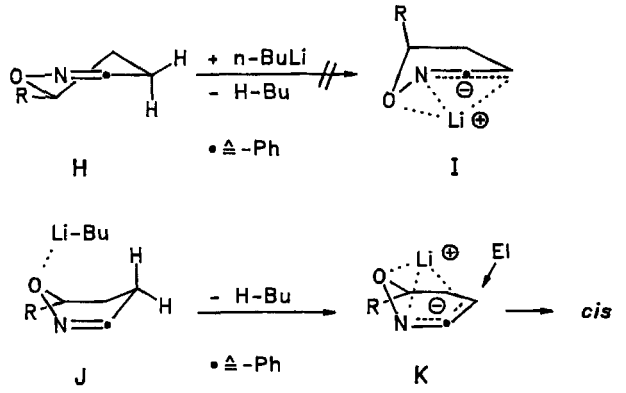


G

For 1,2-oxazine **1** the expected half-chair conformation **H** predominates with the bulky (trimethylsilyl)methyl group in a pseudo-equatorial position as is demonstrated by the ^{1}H-NMR data[4] and force-field calculations[1]. In this conformation the axial proton at C-4 is properly aligned with respect to the p-orbitals of the C=N bond. However, an interaction of the lithium cation with the oxygen would require a flip, bringing the 6-substituent into a pseudoaxial position (see **H**→**I**). On the other hand, a conformational modification of **H** before deprotonation to the (twist) boat **J** should not require much energy since the CH_2SiMe_3 group can retain a pseudoequatorial position. Now all prerequisites for the proton abstraction are favorable: complexation of oxygen with lithium and coplanarity of the axial C–H bond with respect to the C=N system's p-orbitals. Therefore, the ion pair **K** can directly result from **J** without severe conformational changes. This – admittedly speculative – model explains why it is the proton *cis* to the CH_2SiMe_3 group exclusively which is acidic.

An interpretation of the reaction of the lithiated **1** with electrophiles must also be speculative. To explain the majority of results we assume that the ion pair **K** is configurationally stable[15] and the lithium cation directs the attacking electrophile to give finally the *cis*-substituted products (entries 1–5). Thus, the S_E2 process occurs with retention of configuration as is known for the reaction of many or-

ganolithium species[16], although cases with interesting dependence of the substitution on the nature of the electrophile employed have been reported[17].

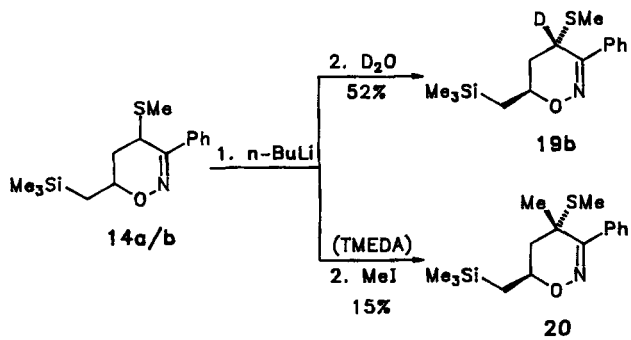


Concerning **K** the most reactive electrophiles such as aldehydes are unselective. Possibly, they do not require the steering effect of the cation. However, as long as no experimental information is available on these details our mechanistic picture must neglect effects such as nature of the ion pair (tight or loose) and aggregation, which could also strongly influence the reaction's course.

For dimethyl disulfide and other hetero electrophiles a SET mechanism could also be responsible for the deviating diastereoselectivity. Due to the higher acidity of the products (e.g. **14**, see below) some equilibration might be possible under the reaction conditions. This is apparent for transformations leading to the carbonyl compounds (**11** and **12**). *N* acylation of the ambident system **K** has only been observed with reagents of the type $X-CO_2Me$. It is questionable whether the HSAB principle can be applied to explain the regioselectivity in these reactions (X = OMe, hard reagent: *N* acylation; X = Cl, softer reagent: *C* and *N* acylation)[18].

Results with Other Monocyclic 1,2-Oxazines

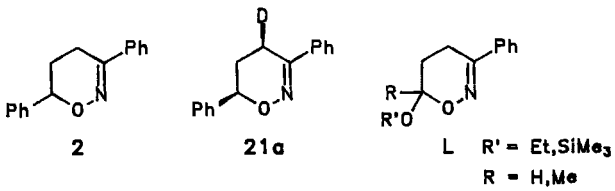
Starting from 4-substituted 1,2-oxazines **6a** and **14** we have examined the possibility to introduce a second group to C-4. In accordance with the equilibration studies (see chapter Control Experiments) we have not been able to deprotonate the 4-methyl-substituted compound **6a**, while the methylthio derivative **14** is converted into the corresponding carbanion. The reaction with D_2O affords *trans*-1,2-oxazine **19b**. By activation with TMEDA and addition of methyl iodide, **14** is converted into the expected 4-disubstituted compound **20** in low yield. The stereochemical assignment for **20** is tentative and made in analogy to that of **19b**[19].



The experiments with **6a** confirm that this 1,2-oxazine is not acidic at all. This can be attributed to the steric and inductive effect of the 4-methyl group, but we believe that **6a** does not fulfill the stereoelectronic prerequisite for the deprotonation. A conformation similar to **J** is not possible for *cis*-substituted 1,2-oxazines like **6a** without placing the CH_2SiMe_3 in an axial position.

This argument is not valid for the methylthio-substituted 1,2-oxazine **14**, since the hetero group enhances the acidity, and therefore the stereoelectronic requirements for deprotonation as well as the structure of the resulting carbanion could be rather different from those of **1**. For this reason, we will not further discuss the stereochemistry of products **19** and **20**.

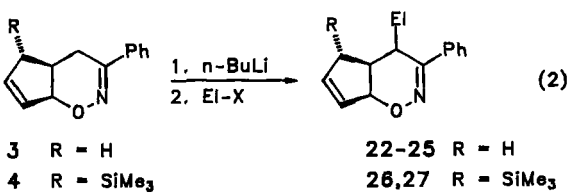
The diphenyl-substituted 1,2-oxazine **2** can also be deprotonated and stereoselectively deuterated to give exclusively **21a**. In this respect **2** behaves similar to **1**. However, we have not yet been able to trap this carbanion with alkyl halides or aldehydes[1] which may be attributed to the rather low solubility of **2** and its lithium salt in tetrahydrofuran at low temperature.



Attempts to generate and trap anions derived from 6-alkoxy- or 6-siloxy-substituted 1,2-oxazines **L** have also failed[1]. The various reaction conditions applied resulted either in the isolation of unconsumed starting compound or complete decomposition of 1,2-oxazines (β elimination?). It might be the exocyclic oxygen at C-6 which misleads the attacking base (*n*-butyllithium or others[1]) and prevents the required arrangement of type **J** for smooth deprotonation at C-4.

Results with Bicyclic 1,2-Oxazines 3 and 4

The two bicyclic 1,2-oxazines **3** and **4** undergo the desired deprotonation/substitution sequence very smoothly to furnish the products **22**–**27** (equation 2, Table 2). With respect to the *cis*/*trans* ratio there seems to be a consistent trend, with small electrophiles (D_2O) favoring the formation of *cis*-substituted 1,2-oxazines, whereas the use of the more bulky acetone leads exclusively to the *trans* isomers.



(2)

Table 2. Reactions of deprotonated bicyclic 1,2-oxazines **3** or **4** with electrophiles (according to equation 2)

1,2-Oxazine	Electrophile	El	Product	**a** : **b** *cis* : *trans* [a]	Yield (%)[b]
3	D_2O	D	**22**	91 : 9	96
3	MeI	Me	**23**	77 : 23	74
3	Me_2S_2	MeS	**24**	31 : 69	94
3	Acetone	Me_2COH	**25**	< 3 : 97	86
4	D_2O	D	**26**	83 : 17	90
4	Acetone	Me_2COH	**27**	< 3 : 97	78

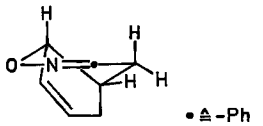
[a] According to high-field ^{1}H-NMR spectra of the *crude* products. — [b] Yield of purified product.

The experiments performed do not allow us to distinguish whether the different selectivity patterns of **3** and **4** compared to **1** are caused by a nonstereoselective deprotonation or by the different reactivity of the lithiated intermediates toward the electrophiles. It is apparent that the geometric restrictions in bicyclic 1,2-oxazines **3** and **4** can strongly influence both crucial steps. The structure of deprotonated **3** (orange solution) should be different from that of lithiated **1** (red solution) because it is more reactive. Despite its higher degree of substitution this carbanion smoothly reacts with methyl iodide to give **23a/b** without the requirement of activation by TMEDA.

Configurational Assignments

The stereochemical assignment of monocyclic 4-substituted 1,2-oxazines is relatively straightforward and follows the rules reported for other heterocycles of this type[4]. Most indicative are the coupling constants as determined by ^{1}H-NMR spectroscopy. The half-chair conformation is preferred in most examples. Thus, 6-H always has coupling constants of 2 and 11 Hz demonstrating the pseudoequatorial location of 6-CH_2SiMe_3. In *cis* isomers (series **a**) 4-H shows 9–10 Hz for the axial/axial and 5–8 Hz for the axial/equatorial coupling with 5-H. Therefore, the 4-substituent must be in a pseudoequatorial position. On the other hand, for *trans*-1,2-oxazines (series **b**) we have found J_{ee} = 1–1.5 Hz and J_{ae} = 4–6 Hz between protons 4-H and 5-H. This proves that the group at C-4 has a pseudoaxial orientation in these compounds. The half-chair is no more perfect when this substituent becomes rather bulky as indicated by the deviating coupling constants in **8a**, **9a**, and **14a** (see Table 5). The repulsion of the pseudoequatorial 4-substituent and the 3-phenyl group should be responsible for this effect, which is in accordance with force-field calculations[1].

For the assignment of bicyclic 1,2-oxazines **22**–**27** it is important to identify equatorial and axial 4-H in the starting compounds **3** and **4** by NOE experiments[4b]. Thus, it has been demonstrated that the signal of the axial 4-H (*trans* to the annulated cyclopentene ring) appears at lower field than that of the equatorial 4-H (*cis* to the second ring). This effect and the coupling constants observed for **3** and **4** are evidence that a somewhat deformed half-chair similar to **M** is the preferred conformation of these 1,2-oxazines.

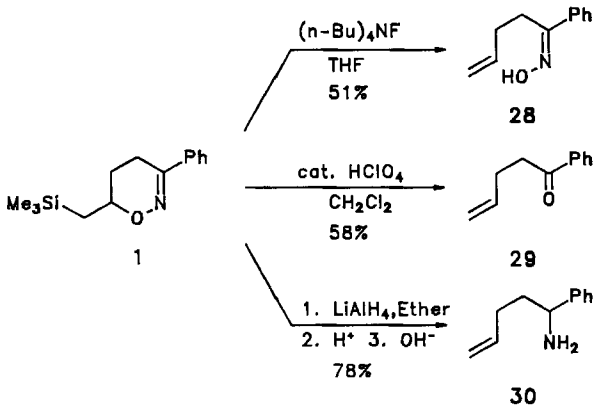


M

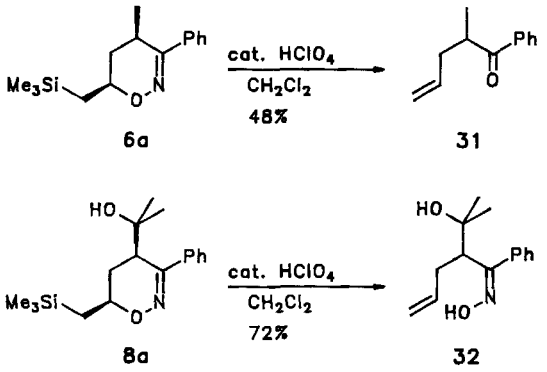
Thus, the stereochemical assignment of compounds **22**–**27** (as indicated in Table 2) obtained after deprotonation/substitution from **3** and **4** is facilitated by making use of the chemical shifts. The coupling constants of the compounds with bulky C-4 substituents (**24**, **25**, and **27**) indicate again a more severe perturbation of the half-chair conformation **M**. However, it has to be stressed that there is some ambiguity in the examples where only one isomer is formed. For this reason, we are reticent concerning the mechanistic interpretation of these experiments.

Ring-Opening Reactions

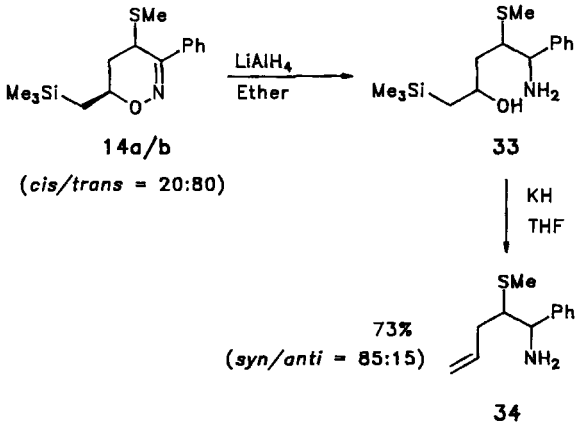
When treated with tetrabutylammonium fluoride, the 1,2-oxazine **1** is converted into the γ,δ-unsaturated oxime **28** in 51% yield. Fluoride-induced desilylation of the 6-CH_2SiMe_3 moiety accompanied by elimination of the oxygen function creates the double bond. Attempts to trap an intermediate carbanion by performing this reaction in the presence of benzaldehyde have been unsuccessful. Earlier we have demonstrated[4a] that **1** is transformed into the ketone **29** by catalysis with strong acids[20], while the reduction with $LiAlH_4$ followed by acid-induced Peterson-type elimination gives the unsaturated amine **30**.



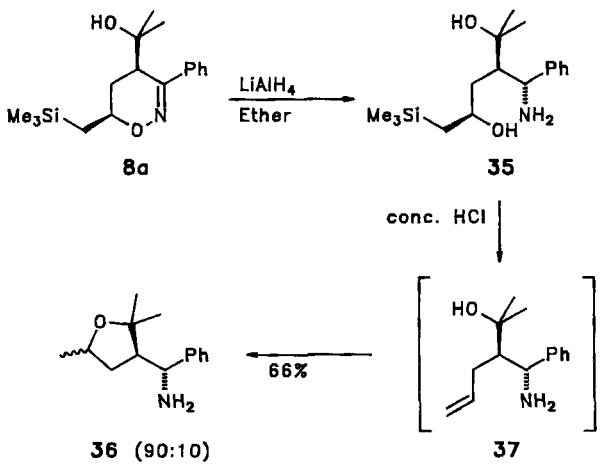
Similar experiments have been executed with the corresponding 4-substituted 1,2-oxazines. Thus, by cleavage with acid, **6a** is converted into the expected ketone **31**, whereas the acetone adduct **8a** is transformed into the oxime **32**. Even with equimolar amounts of acid, **32** is not deoximated to the ketone. The sulfur compound **14a/b** does not react with $HClO_4$ or H_2SO_4 at 20 °C, and at higher temperature complete decomposition is observed[1].



The reduction of **14a/b** with $LiAlH_4$ in ether affords a mixture of amino alcohols **33** after workup under neutral conditions. The diastereomeric distribution of the products cannot be determined at this stage. However, treatment of **33** with potassium hydride in tetrahydrofuran provides a 85:15 mixture of γ,δ-unsaturated amines **34** in 73% overall yield. The relative stereochemistry at C-1 and C-2 of **34** is



determined by the reduction and it should not be altered under the conditions of an anionic Peterson elimination in the second step. The *syn/anti* assignment is based on the ^{1}H-NMR data and on mechanistic probability. The hydride reagent should attack the C=N bond of **14** *anti* to the 4-methylthio group to provide preferentially the compound with *syn* stereochemistry[21].



The reduction of the stereochemically homogeneous acetone adduct **8a** with $LiAlH_4$ furnishes *one diastereomer* of the amino diol **35**. Unfortunately, this compound cannot be transformed into the desired olefin **37** under basic conditions (KH or NaH in THF). The treatment of **35** with concentrated HCl gives the tetrahydrofuran derivative **36** as a 90:10 mixture of stereoisomers, which are very likely formed by acid-catalyzed cyclization of the intermediate **37**. Although the NMR data are not conclusive, we assume that **36** is a mixture of *cis/trans* isomers. The stereochemistry of the tetrahydrofuran ring is determined by the cyclization step **37** → **36**, and not during the reduction process **8a** → **35**, which is very selective. The attack of the hydride reagent at

Table 3. Reaction of deprotonated 1,2-oxazine **1** with electrophiles (according to the general procedure)

1,2-Oxazine g (mmol)	Electrophile g (mmol)	Time (h) (Temp.°C)	Product (*cis:trans*)[a]	Yield g
1 0.247 (1.00)	D_2O 10 ml	0.2 (-78)	**5a** (> 97:3)	99% 0.245[b]
1 0.742 (3.00)	Methyliodide[c] 1.28 (9.00)	16 (-78→20)	**6a** (> 97:3)	56% 0.441[e]
1 0.495 (2.00)	Allylbromide[c] 0.726 (6.00)	16 (-78→20)[d]	**7a** (> 97:3)	83% 0.479[e]
1 2.47 (10.0)	Acetone 1.74 (30.0)	0.5 (-78)	**8a** (> 97:3)	70% 2.15[f]
1 0.247 (1.00)	Benzophenone 0.547 (3.00)	1.5 (-78)	**9a** (> 97:3)	53% 0.226[f]
1 0.247 (1.00)	Acetaldehyde 0.132 (3.00)	0.5 (-78)	**10a/b** (50:50)[g]	83% 0.231
1 0.247 (1.00)	Methyl Chloroacetate 0.284 (2.62)	0.5 (-78)	**11b** (< 3:97)	42% 0.135[f]
1 0.247 (1.00)	Methyl Chloroformate 0.284 (3.00)	2 (-78)	**12a/b**[h] (22:78)	58% 0.177
1 0.247 (1.00)	Dimethyl Carbonate 0.270 (3.00)	1 (-78)	**13**	27% 0.082[f]
1 0.247 (1.00)	Dimethyldisulfide 0.220 (2.34)	0.5 (-78)	**14a/b** (70:30)	85% 0.250[f]
1 0.247 (1.00)	Phenylselenenylchloride 0.192 (1.00)	4 (-78)	**15a/b** (15:85)	37% 0.148[f,i]
1 0.247 (1.00)	Trimethyl Borate 0.327 (3.00)	2 (-78)	**16a/b**[j] (13:87)	30% 0.078[f]

[a] This ratio was determined for the crude product. – [b] M.p. 42°C. – [c] Addition of 1 equivalent of TMEDA before reaction with *n*-butyllithium. – [d] Very slow warming-up to room temp. – [e] Colorless oil after chromatography (Al_2O_3, pentane/ethyl acetate, 4:1). – [f] Colorless crystals after recrystallization from pentane/diethyl ether. – [g] Four diastereomers (approximately 1:1:1:1); colorless oil after chromatography (Al_2O_3); one isomer was separated by chromatography (SiO_2, pentane/ethyl acetate, 4:1). – [h] Contains 30% of **13** separated by chromatography (Al_2O_3). – [i] Compound not obtained analytically pure. – [j] Separation from **1** (70%) by chromatography (Al_2O_3, ethyl acetate).

8a should occur *syn* to the C-4 substituent providing **35** with the relative stereochemistry as drawn. $LiAlH_4$ should first react with the free hydroxy group in **8a** and therefore it will deliver the hydride to the more hindered face of the 1,2-oxazine. Similar effects have been demonstrated by Jäger et al. in the isoxazoline series[21].

These preliminary studies show that the 4-substituted 1,2-oxazines derived from the easily available heterocycle **1** should have some potential for stereoselective synthesis of polyfunctionalized acyclic compounds. A systematic investigation of these transformations has still to be undertaken.

We are very grateful to the *Deutsche Forschungsgemeinschaft*, the *Fonds der Chemischen Industrie*, and the *Vereinigung von Freunden der Technischen Hochschule zu Darmstadt* for the generous financial support. Large parts of this paper were written during a visiting professorship at the University of Rennes I. H.-U. R. thanks Prof. *R. Carrié* and Dr. *M. Vaultier* for their warm hospitality.

Experimental

For general informations see ref.[4b]. – Starting compounds: **1**[4a], **2**[3b], **3**[3a], and **4**[4b]. All reactions were executed in flame-dried flasks under a slight pressure of dry nitrogen. Solvents and liquid reagents were added by syringe. Tetrahydrofuran was distilled from K/benzophenone just before use. The electrophiles employed were purified by distillation and/or filtration through a pad of Al_2O_3. Tetramethylethylenediamine (TMEDA) was distilled from CaH_2 and stored over molecular sieves. The concentration of *n*-butyllithium (approximately 2.0 M solution in hexane, Aldrich) was determined by the diphenylacetic acid method[22]. All chiral products were obtained as racemates.

General Procedure for the Deprotonation of 1,2-Oxazines and Reactions with Electrophiles: The corresponding 1,2-oxazine was dissolved in dry tetrahydrofuran (10 ml/1 mmol of 1,2-oxazine) and at −78°C 1.5 equivalents of *n*-butyllithium were added. After stirring for 15 min at this temperature the resulting deeply colored solution of the carbanion was treated with 3 equivalents of the

Table 4. Analytical data of ...-5,6-dihydro-3-phenyl-6-[(trimethylsilyl)methyl]-4*H*-1,2-oxazines **6a–20a/b**

Compound		IR ν [cm⁻¹]	M.P. [°C]	Elemental Analysis	C	H	N
4-Methyl...	**6a**	(KBr) 3120-3020, 2980-2840 (C-H), 1595 (C=N)	118	$C_{15}H_{23}NOSi$ (261.4)			
				Calcd.	68.91	8.87	5.36
				Found	68.41	8.97	5.27
4-Allyl...	**7a**	(KBr) 3100-3050, 3000-2830 (C-H), 1630 (C=C), 1595 (C=N)	52-56	$C_{17}H_{25}NOSi$ (287.5)			
				Calcd.	71.03	8.77	4.87
				Found	71.26	8.87	4.77
4-[(1-Hydroxy-1-methyl)ethyl]...	**8a**	($CHCl_3$) 3600-3560 (OH), 3080-2800 (C-H), 1590 (C=N)	123-124	$C_{17}H_{27}NO_2Si$ (305.5)			
				Calcd.	66.86	8.91	4.58
				Found	66.82	8.92	4.50
4-[(1-Hydroxy-1,1-diphenyl)-methyl]...	**9a**	($CHCl_3$) 3600-3500 (OH), 3100-2750 (C-H), 1590 (C=N)	145-149	$C_{27}H_{31}NO_2Si$ (429.6)			
				Calcd.	75.48	7.27	3.26
				Found	75.20	7.25	3.26
4-(1-Hydroxyethyl)...	**10a/b**	($CHCl_3$) 3600-3200 (OH), 3100-2850 (C-H), 1595 (C=N)	110-113[a]	$C_{16}H_{25}NO_2Si$ (291.5)			
				Calcd.	65.93	8.65	4.81
				Found	65.96	8.79	4.77
4-(Chloracetyl)...	**11b**	(KBr) 3100-3000, 2980-2850 (C-H), 1730 (C=O), 1585 (C=N)	80-82	$C_{16}H_{22}ClNO_2Si$ (323.9)			
				Calcd.	59.33	6.85	4.32
				Found	59.59	6.74	4.27
4-Methoxycarbonyl...	**12a/b**	(KBr) 3100-3000, 3000-2830 (C-H), 1735 (C=O), 1590 (C=N)	78-84	$C_{16}H_{23}NO_3Si$ (305.5)			
				Calcd.	62.92	7.59	4.59
				Found	62.67	7.64	4.43
[b]	**13**	(KBr) 3100-3000, 3000-2800 (C-H), 1720 (C=O), 1650 (C=C)	94	$C_{16}H_{23}NO_3Si$ (305.5)			
				Calcd.	62.92	7.59	4.59
				Found	63.00	7.37	4.48
4-Methylthio...	**14a/b**	(KBr) 3100-3000, 3000-2800 (C-H), 1590 (C=N)	90-92	$C_{15}H_{23}NOSSi$ (293.6)			
				Calcd.	61.37	7.90	4.77
				Found	61.50	7.82	4.73
4-Phenylselenenyl ...	**15a/b**	(film) 3100-3000, 3000-2850 (C-H), 1580 (C=N)	146-148	$C_{20}H_{25}NOSeSi$ (402.5) [c]			
4-Hydroxy...	**16a/b**	(KBr) 3600-3100 (OH), 3100-2890 (C-H), 1600 (C=N)	158-159	$C_{14}H_{21}NO_2Si$ (263.4)			
				Calcd.	63.84	8.04	5.32
				Found	63.60	7.60	5.60
4-Methyl-4-methylthio...	**20**	(KBr) 3100-3000, 3000-2800 (C-H), 1580 (C=N)	105-106	$C_{16}H_{25}NOSSi$ (307.5)			
				Calcd.	62.49	8.19	4.55
				Found	62.09	8.11	4.50

[a] One isomer of four. – [b] 5,6-Dihydro-2-(methoxycarbonyl)-6-[(trimethylsilyl)methyl]-2*H*-1,2-oxazine. – [c] Due to fast decomposition no correct elemental analysis available.

Table 5. ^{1}H-NMR data (300 MHz, $CDCl_3$) of 1,2-oxazines **5a–21a** [a]

Compound	6-H_a (1 H) dtd[b]	4-H (1 H) dd[b]	5-H_e (1 H) ddd[b]	5-H_a (1 H) ddd[b]	Other Signals	$SiMe_3$ (9 H) s
1[c]	3.76 (2, 7, 11)	2.21 ddd (2, 7, 18) 2.01 ddd (7, 10, 18)	1.69 tdd (2, 7, 14)	1.59 dddd (7, 10, 11, 14)	1.16, 0.95 (2 dd, J = 7, 14 Hz, 2 H, 6-CH_2)	0.18
5a (*cis*)	3.79 (2, 7, 11)	2.60 (8, 11) ($J_{H/D}$ = 2.5)	2.10 (2.5, 8, 13.5)	1.78 td (11, 13.5)	1.15, 0.93 (2 dd, J = 7, 15 Hz, 2 H, 6-CH_2)	0.10
6a (*cis*)	3.90 (2, 7, 11)	2.99 dqd (7, 8, 11)	2.22 (2, 7, 14)	1.56 td (11, 14)	1.11, 0.89 (2 dd, J = 7, 15 Hz, 2 H, 6-CH_2), 1.02 (d, J = 8 Hz, 3 H, Me)	0.10
7a (*cis*)	3.95 (2, 7, 11)	3.10 dtd (3.5, 8, 11)	2.19 (2, 8, 13.5)	1.70 td (11, 13.5)	5.67 (m_c, 1 H, -CH=), 5.08, 5.01 (AB of ABX-system, J_{AB} = 2, J_{AX} = 10, J_{BX} = 17 Hz, 2 H, =CH_2), 2.36 (m_c, 1 H, 4-CH_2), 2.08 (td, J = 8, 14 Hz, 1 H, 4-CH_2), 1.16, 0.93 (2 dd, J = 7, 15 Hz, 2 H, 6-CH_2)	0.10
8a (*cis*)	3.73 (4, 7.5, 11.5)	3.20 (7.5, 9)	2.20 (4, 9, 13.5)	1.97 (7.5,11.5,13.5)	1.90 (s, 1 H, OH), 1.14, 1.11 (2 s, 6 H, 2 Me), 1.13, 0.94 (2 dd, J = 7.5, 14.5 Hz, 2 H, 6-CH_2)	0.09
9a (*cis*)	3.78 (5, 7, 10)	4.19 (5, 10)	2.21 m_c		7.2, 6.9 (2 m_c, 8 H, 2 H, 2 Ph) 4.27 (s, 1 H, OH), 1.16, 0.92 (2 dd, J = 7.5, 16 Hz, 2 H, 6-CH_2)	0.10
10[d]	3.86 (2.5, 7, 11.5)	3.39 dt (5.5, 9)	2.15 (2.5, 9, 13.5)	1.87 (9, 12, 13.5)	4.09 (dq, J = 5.5, 6 Hz, 1 H, CHOH), 1.77 (s, 1 H, OH), 1.17, 0.94 (2 dd, J = 7, 14 Hz, 2 H, 6-CH_2), 0.98 (d, J = 6 Hz, 3 H, Me)	0.03
11b (*trans*)	3.96 (2, 7, 11)	4.29 (1, 6)	2.24 (1, 2, 14)	1.87 (6, 11, 14)	4.05 (s, 2 H, $COCH_2$), 1.11, 0.91 (2 dd, J = 7, 14 Hz, 2 H, 6-CH_2)	0.11
12a (*cis*)	e)	3.85 (8, 10)	e)	e)	3.50 (s, 3 H, CO_2Me), 1.22, 0.98 (2 dd, J = 7, 14 Hz, 2 H, 6-CH_2)	0.10
12b (*trans*)	4.09 (2, 7, 11)	3.82 (1, 6)	2.28 (1, 2, 14)	1.88 (6, 11, 14)	3.62 (s, 3 H, CO_2Me), 1.22, 0.98 (2 dd, J = 7, 14 Hz, 2 H, 6-CH_2)	0.14
13[f]	4.10 (m_c)	5.51 t (4)	2.34 m_c		3.68 (s, 3 H, CO_2Me), 1.23, 0.94 (2 dd, J = 6.5, 15 Hz, 2 H, 6-CH_2)	0.12
14a (*cis*)	3.88 (2, 7, 11)	3.93 t (10)	2.49 (2, 10, 14)	2.22 (10, 11, 14)	1.86 (s, 3 H, SMe), 1.15, 0.96 (2 dd, J = 7, 15 Hz, 2 H, 6-CH_2)	0.10
14b (*trans*)	4.28 (2, 7, 11)	3.73 d[g] (4)	2.23 d[g] (14)	1.94 (4, 11, 14)	2.11 (s, 3 H, SMe), 1.20, 0.96 (2 dd, J = 7, 15 Hz, 2 H, 6-CH_2)	0.13
15a (*cis*)	4.11 (2, 7, 11)	4.85 (7.5, 10)	2.44 (2, 7.5, 14)	e)	7.64, 7.51, 7.28 (3 m_c, 10 H, Ph) 1.20, 0.96 (2 dd, J = 7, 13.5 Hz, 2 H, 6-CH_2)	0.11
15b (*trans*)	4.01 (2, 7, 11)	4.62 (1.5, 4)	2.14 (1.5, 2, 14)	1.79 (4, 11, 14)	7.64,7.51, 7.28 (3 m_c, 10 H, Ph) 1.20, 0.96 (2 dd, J = 7, 13.5 Hz, 2 H, 6-CH_2)	0.12
16a (*cis*)	4.13 (2, 7, 11)	4.87 (7.5, 10)	e)	e)	4.42 (s, 1 H, OH), 1.22, 0.98 (2 dd, J = 7, 14 Hz, 2 H, 6-CH_2)	0.16
16b (*trans*)	4.07 (2, 7, 11)	4.62 (1.5, 4)	2.14 (1.5, 2, 14)	1.62 (4, 11, 14)	4.80 (s, 1 H, OH), 1.22, 0.98 (2 dd, J = 7, 14 Hz, 2 H, 6-CH_2)	0.18
19b (*trans*)	4.27 (2, 7, 11)	-	2.22 dd (2, 14)	1.93 dd (11, 14)	2.10 (s, 3 H, SMe), 1.20, 0.96 (2 dd, J = 7, 15 Hz, 2 H, 6-CH_2)	0.12
20	4.49 (2, 7, 11)	-	2.25 dd (2, 14)	1.78 dd (11, 14)	2.10 (s, 3 H, SMe), 1.19, 0.92 (2 dd, J = 7, 15 Hz, 2 H, 6-CH_2) 1.32 (s, 3 H, Me)	0.14
21a (*cis*)	4.80 dd (2.5, 10.5)	2.72 (8, 11) ($J_{H/D}$ = 2.5 Hz)	2.30 (2.5, 8, 13)	2.20 (10.5, 11, 13)	7.6, 7.4 (2 m_c, 2 H, 8 H, Ph)	-

[a] All compounds: δ = 7.7, 7.4 (2m_c, 2 H, 3 H, Ph). – [b] Multiplicity of the signal if not indicated; values in parentheses: coupling constants in Hz. – [c] Solvent: C_6D_6. – [d] One isomer of four; Me signals of other isomers: δ = 1.05, 0.86, 0.83. – [e] Signal hidden. – [f] δ = 7.25 (m_c, 5 H, Ph). – [g] Broad signal.

corresponding electrophile. The reaction time and the temperature at which the workup was performed are indicated in Tables 3, 6, and 8. The workup procedure involved addition of saturated aqueous ammonium chloride solution (10 ml/1 mmol of 1,2-oxazine), extraction with CH_2Cl_2, drying with $MgSO_4$, and purification by chromatography and/or recrystallization from pentane/diethyl ether. For spectroscopic and analytical data see Tables 4, 5, 7, 9, 10, and 11.

Table 6. Control experiments with **1** or **5a** and deprotonation of 1,2-oxazines **14a/b** and **2** (according to the general procedure)

1,2-Oxazine g (mmol)	Electrophile	Time (h) (Temp.°C)	Product (*cis:trans*)[a]	Yield g
1 0.247 (1.00)[b]	D_2O 1 ml	0.5 (-78)	**5a** (> 97:3)	91% 0.225
5a 0.124 (0.50)	D_2O 1 ml	2 (-78)	**5a** (> 97:3)	100%[c] 0.124
5a 0.163 (0.66)	H_2O 10 ml	2 (-78)	**1**	99%[c] 0.160
5a 0.124 (0.50)	Acetone 0.116 g (2.00 mmol)	2 (-78)	**8a** (> 97:3)	92% 0.140
14a/b[d] 0.293 (1.00)	D_2O 2 ml	1 (-78)	**19b** (< 3:97)[e]	52% 0.152[f]
14a/b[d] 0.293 (1.00)[b]	Methyliodide 0.426 g (3.00 mmol)	16 (-78→20)	**20** (> 90:10)	15% 0.046[g]
2[h] 0.426 (2.00)	D_2O 4 ml	1 (-78→20)	**21a** (> 97:3)	100% 0.427[i]

[a] This ratio was determined for the crude product. – [b] Addition of 0.116 g (1.00 mmol) of TMEDA before reaction with *n*-butyllithium. – [c] Yield of the crude product (pure according to NMR spectroscopy). – [d] *cis/trans* = 70:30. – [e] Contains approximately 13% of **14**. – [f] Colorless oil after chromatography (Al_2O_3, pentane/ethyl acetate, 4:1). – [g] Colorless crystals (m.p. 105–106°C)[19]. – [h] 1,2-Oxazine **2** and lithiated **2** (reddish brown suspension) were not completely dissolved. – [i] After treatment with diethyl ether colorless crystals (m.p. 153–154°C).

Equilibration Experiments: 1,2-Oxazine **6a** (0.104 g, 0.400 mmol) was stirred for 24 h in 10 ml of dry methanol containing NaOMe (5.00 mmol). Extractive workup with dichloromethane/water provided 0.080 g (77%) of **6a**. The NMR spectra prove that no configurational change has occurred (*cis:trans* > 97:3).

1,2-Oxazine **14a/b** (*cis:trans* = 70:30; 0.294 g, 1.00 mmol) was treated as above to afford 0.285 g (97%) of **14a/b** (*cis:trans* = 20:80) as determined by NMR spectroscopy.

1-Phenyl-4-penten-1-one Oxime (**28**): 1,2-Oxazine **1** (0.248 g, 1.00 mmol) was stirred in a solution of 0.632 g (2.00 mmol) of $(n\text{-}Bu)_4NF \cdot 3\,H_2O$ in 10 ml of dry tetrahydrofuran (containing 2.00 g of molecular sieves, 4 Å). After 4 h at room temp., 5 ml of water was added and the mixture was extracted with dichloromethane. Drying ($MgSO_4$), evaporation of the solvents, filtration through a pad of Al_2O_3 (ethyl acetate), and distillation (100–150°C/0.02 Torr) provided 0.089 g (51%) of **28** as colorless crystals (m.p. 49–51°C). – ^1H NMR ($CDCl_3$): δ = 9.8–8.3 (m, 1H, OH), 7.6–7.2 (m, 5H, Ph), 6.1–5.3 (m, 1H, 4-H), 5.1–4.8 (m, 2H, 5-H), 3.0–2.6 (m, 2H, 2-H), 2.4–1.9 (m, 2H, 3-H). – IR (KBr): $\tilde{\nu}$ = 3600–3100 cm^{-1} (O–H), 3100–3000 (=C–H), 3000–2750 (C–H), 1640 (C=C), 1585 (C=N).

$C_{11}H_{13}NO$ (175.2) Calcd. C 75.40 H 7.48 N 7.99
Found C 74.98 H 7.42 N 7.56

Table 7. ^{13}C-NMR data of 1,2-oxazines **5a–21a** (δ, multiplicity)[a]

Compound	C-3 s	C-6 d	C-4 d	C-5 t	Other Signals	$SiMe_3$ q
5a (*cis*)	154.1	76.6	22.4[b]	27.4	22.9 (t, CH_2SiMe_3)	-0.80
6a (*cis*)	161.2	74.5	28.4	38.2	23.1 (t, CH_2SiMe_3) 19.3 (q, Me)	-0.50
7a (*cis*)	160.2	74.1	32.4	37.0[c]	134.0 (d, =CH), 117.5 (t, $=CH_2$), 34.6[c] (t, 4-CH_2) 22.5 (t, CH_2SiMe_3)	-0.80
8a (*cis*)	165.8	75.7	45.0	35.2	76.6 (s, HOC), 28.9, 28.5 (2 q, Me), 24.1 (t, CH_2SiMe_3)	-0.20
9a[d] (*cis*)	169.5	76.0	43.8	35.4	81.2 (s, COH) 23.4 (t, CH_2SiMe_3)	-0.90
11b (*trans*)	149.9	70.7	42.3	29.3	199.2 (s, C=O) 47.5 (t, CH_2Cl) 22.3 (t, CH_2SiMe_3)	-0.90
12a (*cis*)	152.8	73.1	40.7	32.3	171.4 (s, C=O) 52.2 (q, Me) 22.6 (t, CH_2SiMe_3)	-0.95
12b (*trans*)	149.6	71.0	37.9	30.3	171.4 (s, C=O) 52.4 (q, Me) 22.6 (t, CH_2SiMe_3)	-0.95
13	140.1	78.8	111.8	33.6	155.1 (s, C=O) 53.2 (q, Me) 22.9 (t, CH_2SiMe_3)	-1.30
14a (*cis*)	157.1	75.0	36.1	37.0	22.9 (t, CH_2SiMe_3) 11.4 (q, SMe)	-0.89
14b (*trans*)	157.0	71.0	37.2	33.3	22.5 (t, CH_2SiMe_3) 15.3 (q, SMe)	-0.80
15b (*trans*)	154.5	70.4	57.9	36.8	22.9 (t, CH_2SiMe_3)[e]	-0.93
16a (*cis*)	[f]	75.1	61.5	38.7	23.2 (t, CH_2SiMe_3)	-0.70
16b (*trans*)	155.2	70.7	58.2	38.2	22.9 (t, CH_2SiMe_3)	-0.80
19b (*trans*)	152.3	71.2	34.6[b]	33.4	22.6 (t, CH_2SiMe_3) 15.5 (q, SMe)	-0.90
20	157.3	72.3	42.3[g]	42.8	23.2 (t, CH_2SiMe_3) 25.6, 12.7 (2 q, SMe, Me)	-0.60
21a (*cis*)	154.3	77.0	22.0[b]	26.0	- [h]	-

[a] Signals of the phenyl group: δ = 136.9–135.8, 1 s, 129.6–125.3, 3 d. – [b] Multiplet. – [c] Assignment ambiguous; the marked values are exchangeable. – [d] Signals of the phenyl groups: δ = 145.1–135.6, 3 s, 129.0–126.1, 9 d. – [e] Further signals in the C_6H_5 region for SeC_6H_5. – [f] Signal not identified. – [g] Singlet. – [h] Signals of the phenyl groups: δ = 139.8, 135.8, 2 s, 129.4–125.4, 6 d.

Table 8. Deprotonation of bicyclic 1,2-oxazines **3** and **4** (according to the general procedure)

1,2-Oxazine g (mmol)	Electrophile g (mmol)	Time (h) (Temp.°C)	Product (*cis:trans*)[a]	Yield g
3 0.199 (1.00)	D_2O 2 ml	0.5 (-78)	**22a/b** (91:9)	96% 0.192
3 0.398 (2.00)	Methyliodide 0.852 (6.00)	16 (-78→20)	**23a/b** (77:23)	74% 0.317
3 0.199 (1.00)	Dimethyl-disulfide 0.141 (1.50)	2 (-78)	**24a/b** (31:69)	94% 0.231
3 0.199 (1.00)	Acetone 0.087 (1.50)	2 (-78)	**25b** (< 3:97)	86% 0.220[b]
4 0.135 (0.50)	D_2O 2 ml	1 (-78)	**26a/b** (83:17)	90% 0.122[c]
4 0.271 (1.00)	Acetone 0.174 (3.00)	2 (-78)	**27b** (< 3:97)	78% 0.258[b]

[a] This ratio was determined for the crude product; **22** and **24**–**27** gave colorless crystals after recrystallization from pentane/diethyl ether. – [b] A few percent of starting material recovered. – [c] M.p. 83–85°C.

2-Methyl-1-phenyl-4-penten-1-one (**31**): A solution of 1,2-oxazine **6a** (0.255 g, 0.98 mmol) in 10 ml of dichloromethane was stirred with three drops of $HClO_4$ (70%) at room temp. for 48 h. Addition of K_2CO_3, filtration, concentration, and distillation (125°C/0.02 Torr) afforded 0.082 g (48%) of **31** as colorless oil. – ^{1}H NMR ($CDCl_3$): δ = 7.5 (m_c, 5H, Ph), 6.3–5.8 (m, 1H, =CH), 5.10 (m_c, 2H, $=CH_2$), 3.2 (m_c, 1H, C*H*Me), 2.6–2.3 (m, 2H, CH_2), 1.30 (d, *J* = 7 Hz, 3H, Me). – IR (film): $\tilde{\nu}$ = 3100–3000 cm^{-1} (=C–H), 2980–2800 (O–H), 1680 (C=O), 1640 (C=C). – These spectral data agree with those in ref.[23].

2-[(1-Hydroxy-1-methyl)ethyl]-1-phenyl-4-penten-1-one Oxime (**32**): A solution of 1,2-oxazine **8a** (0.293 g, 0.96 mmol) in 5 ml of dichloromethane was stirred with three drops of $HClO_4$ (70%) at room temp. for 24 h. Addition of K_2CO_3, filtration, evaporation, and distillation (100°C/0.02 Torr) afforded 0.161 g (72%) of **32** as colorless oil. – ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.65, 7.04 (2 m_c, 2H, 3H, Ph), 5.72 (m_c, 1H, =CH), 5.02, 4.92 (2 m_c, 2H, $=CH_2$), 4.0 (s, 1H, OH), 3.26 (t, *J* = 6 Hz, 1H, 2-H), 2.39 (t with fine coupling, *J* = 6 Hz, 2H, 3-H), 1.50, 1.32 (2 s, 6H, 2Me), NOH not identified. – ^{13}C NMR ($CDCl_3$): δ = 160.5 (s, C=N), 137.5 (d, C-4), 130.0, 129.1, 128.5, 128.1 (s, 3 d, Ph), 117.1 (t, C-5), 86.9 (s, CMe_2), 53.6 (d, C-2), 31.9 (t, C-3), 29.4, 19.7 (2 q, 2Me). – IR (film): $\tilde{\nu}$ = 3400–3100 cm^{-1} (O–H), 3100–3000 (=C–H), 3000–2750 (C–H), 1640 (C=C), 1590 (C=N).

$C_{14}H_{19}NO_2$ (233.3) Calcd. C 72.07 H 8.21 N 6.00
Found C 72.10 H 7.95 N 6.26

2-Methylthio-1-phenyl-4-pentenyl-1-amine (**34**): A solution of 1,2-oxazine **14a/b** (0.294 g, 1.00 mmol, *cis:trans* = 20:80) in 10 ml of dry diethyl ether was stirred with $LiAlH_4$ (59 mg, 1.5 mmol) at room temp. for 48 h. The mixture was slowly treated with 10 ml of water and extracted with dichloromethane. Drying of the organic extracts ($MgSO_4$) and concentration gave a yellow oil, which was dissolved in 10 ml of dry tetrahydrofuran and treated with potassium hydride (0.120 g, 3.00 mmol). After stirring at room temp. for 1 h, 10 ml of aqueous NH_4Cl solution was added. Extraction with dichloromethane, drying ($MgSO_4$), evaporation, and distillation (120°C/0.02 Torr) provided 0.151 g (73%) of **34** as colorless oil (*syn:anti* = 85:15). – ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.3 (m_c, 5H, Ph), 5.88 (m_c, 1H, 4-H), 5.1–4.95 (m, 2H, 5-H), 4.22 (d, *J* = 4.5 Hz, 0.15H, 1-H, minor isomer), 4.02 (s, 2H, NH_2), 3.93 (d, *J* = 7.5 Hz, 0.85H, 1-H, major isomer), 2.9–2.7 (m, 1H, 2-H), 2.3–2.0 (m, 2H, 3-H), 2.10 (s, 2.55H, SMe, major isomer), 1.92 (s, 0.45H, SMe, minor isomer). – ^{13}C NMR ($CDCl_3$, signals of the minor isomer in parentheses): δ = 143.7 (s, *i*-Ph), 135.8 (136.2) (d, C-4), 128.6, 127.4, 127.2 (128.2, 127.0, 126.3) (3 d, Ph), 116.6 (114.8) (t, C-5), 58.3, 55.6 (57.2, 55.1) (2 d, C-1, C-2), 36.3 (34.4) (t, C-3), 13.6 (14.1) (q, SMe). – IR (film): $\tilde{\nu}$ = 3600–3100 cm^{-1} (NH_2), 3100–3000 (=C–H), 3000–2800 (C–H), 1630 (C=C).

$C_{12}H_{17}NS$ (207.3) Calcd. C 69.52 H 8.26 N 6.76
Found C 69.45 H 8.40 N 6.30

3-(α-Aminobenzyl)-2,2,5-trimethyltetrahydrofuran (**36**): A solution of 1,2-oxazine **8a** (0.293 g, 1.00 mmol, >97% *cis*) in 10 ml of

Table 9. Analytical data of ...-4,4a,5,7a-tetrahydro-3-phenylcyclopent[*e*]-1,2-oxazines **23**–**27**

Compound		IR ν [cm^{-1}]	M.P. [°C]	Elemental Analysis	C	H	N
4-Methyl...	**23a/b**	(KBr) 3100-2800 (C-H), 1590 (C=N)	[a]	$C_{14}H_{15}NO$ (213.3)			
				Calcd.	78.84	7.09	6.58
				Found	78.35	7.11	6.37
4-Methylthio...	**24a/b**	(KBr) 3100-2850 (C-H), 1610 (C=N)	72-79	$C_{14}H_{15}NOS$ (245.2)			
				Calcd.	68.52	6.17	5.71
				Found	68.59	6.14	5.69
4-[(1-Hydroxy-1-methyl)-ethyl]...	**25b**	(KBr) 3700-3100 (OH), 3080-2800 (C-H), 1590 (C=N)	140-144	$C_{16}H_{19}NO_2$ (257.3)			
				Calcd.	74.68	7.44	5.44
				Found	74.42	7.58	5.39
4-[(1-Hydroxy-1-methyl)ethyl]-5-trimethylsilyl...	**27b**	(KBr) 3600-3100 (OH), 3100-2890 (C-H), 1610 (C=N)	90-95	$C_{19}H_{27}NO_2Si$ (329.5)			
				Calcd.	69.27	8.26	4.25
				Found	69.20	8.43	4.21

[a] Pale yellow oil.

Table 10. ^{1}H-NMR data (300 MHz, $CDCl_3$) of bicyclic 1,2-oxazines **3** and **22a**–**27b**[a]

Compound	6-H (1 H) ddd[b]	7-H (1 H) td[b]	7a-H (1 H) d[b,c]	4-H (1 H) d[b]	4a-H (1 H) m_c[b]	Other Signals
3	6.01 (1, 2, 5)	5.69 (2, 5)	4.99 (7)	2.72 dd (7, 14) 2.42 dd (7, 14)	2.92	2.67 (tdd[c]), J = 2, 8, 17 Hz, 1 H, 5-H), 2.20 (ddd[c]), J = 2, 5, 17 Hz, 1 H, 5-H)
22a (*cis*)	6.00 m_c	5.79 m_c	4.95 (7)	2.73 (7) ($J_{H/D}$ = 2)	2.88	2.63 (dd[c]), J = 8, 17 Hz, 1 H, 5-H) 2.16 (dd[c]), J = 5, 17 Hz, 1 H, 5-H)
22b (*trans*)	d]	d]	d]	2.44 (7) ($J_{H/D}$ = 2)	d]	d]
23a (*cis*)	6.10 (1, 2, 5)	5.89 (2, 5)	4.95 (8)	3.08 quin. (7)	2.85	2.7-2.0 (m, 2 H, 5-H), 1.18 (d, J = 7 Hz, 3 H, Me)
23b (*trans*)	6.01 m_c	5.79 m_c	5.29[e] (9)	f]	d]	1.39 (d, J = 7 Hz, 3 H, Me)[d]
24a (*cis*)	6.19 m_c	5.82 m_c	4.83 (8)	3.92 (7.5)	d]	2.01 (s, 3 H, SMe)[d]
24b (*trans*)	5.91 m_c	5.82 m_c	5.39 (9)	3.77 (2)	3.39 ddt (2, 5, 9)	3.05, 2.65 (2 mc, 2 H, 5-H) 2.17 (s, 3 H, SMe)
25b (*trans*)	5.92 m_c	5.79 m_c	5.42 (10)	2.99 s[e]	3.59 ddt (1, 4, 10)	3.0-2.5 (m, 1 H, 5-H), 2.4-2.0 (m, 1 H, 5-H), 1.38, 1.13 (2 s, 6 H, 2 Me), 3.49 (s, 1 H, OH)
26a (*cis*)	5.99 m_c	5.69 (2, 6)	4.99 m_c	2.71[e] (7)	2.81	1.81 (m_c, 1 H, 5-H) 0.00 (s, 9 H, $SiMe_3$)
26b (*trans*)	d]	d]	d]	2.40[e] (7)	d]	d]
27b (*trans*)	5.83 m_c	5.60 m_c	5.35[e] (9)	2.85 s[e]	3.41 dd (4, 9)	3.50 (s, 1 H, OH), 1.80 (m_c, 1 H, 5-H), 1.33, 1.06 (2 s, 6 H, 2 Me), 0.05 (s, 9 H, $SiMe_3$)

[a] All compounds: δ = 7.7, 7.4 (2 m_c, 2 H, 3 H, Ph). – [b] Multiplicity of the signal if not indicated; values in parentheses: coupling constants in Hz. – [c] With further fine coupling. – [d] Not identified. – [e] Broadened signal. – [f] Signal hidden, but >0.2 ppm at higher field compared to 4-H of **23a**.

Table 11. ^{13}C-NMR data (δ, multiplicity) of bicyclic 1,2-oxazines **3** and **22a**–**27b**[a]

Compound	C-3 s	C-7 d	C-6 d	C-7a d	C-5 t	C-4a d	C-4 d	Other Signals
3	169.8	137.0[b]	128.0[b]	84.7	36.6	39.6	26.7 t	-
22a (*cis*)	169.6	136.7[b]	128.4[b]	84.5	39.3	36.3	26.3 m	-
23a (*cis*)	173.7	136.8[b]	128.9[b]	85.0	34.5	40.4	29.9	13.2 (q, Me)
23b (*trans*)	170.6	136.2[b]	129.2[b]	83.3	39.6	42.2	32.8	17.7 (q, Me)
24a (*cis*)	169.3	137.7[b]	130.3[b]	84.4	35.9	40.2	39.4	16.6 (q, SMe)
24b (*trans*)	165.4	135.4[b]	130.4[b]	83.1	40.0	41.7	40.0	15.7 (q, SMe)
25b (*trans*)	171.5	136.2[b]	128.7[b]	85.7	49.5	36.1	30.0	73.5 (s, COH), 29.3, 26.3 (2 q, Me)
26a (*cis*)	170.0	138.7[b]	130.0[b]	85.1	43.1 d	39.4	27.0 m	-3.3 (q, $SiMe_3$)
27b (*trans*)	172.3	138.9[b]	130.3[b]	86.6	50.4 d	44.0	39.4	73.5 (s, COH), 30.1, 27.6 (2 q, 2 Me) -3.3 (q, $SiMe_3$)

[a] Signals of the phenyl group: δ = 136.4–135.8, 1 s, 129.6–125.4, 3 d. – [b] Assignment ambiguous; signals are exchangeable.

dry diethyl ether was stirred with $LiAlH_4$ (59 mg, 1.50 mmol) at room temp. for 16 h. After slow addition of water (10 ml) the mixture was extracted with dichloromethane. Drying ($MgSO_4$) and concentration of the organic extracts provided the amino diol **35** (0.243 g, 79%) as yellow oil (diastereomeric ratio >90:10), which could not be purified without decomposition. – ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.6, 7.3 (2 m_c, 2H, 3H, Ph), 4.66 (broad s, 1H, CH–N), 3.52 (m_c, 1H, CH–O), 1.91 (broad s, 3H, OH, NH_2), 1.58, 1.28 (2 s, 6H, 2 Me), 1.38–1.20 (m, 3H, CH, CH_2), 0.68 (d, J = 6.5 Hz, 2H, CH_2Si), 0.05 (s, 9H, $SiMe_3$). – ^{13}C NMR ($CDCl_3$): δ = 145.2, 128.8, 127.4, 126.0 (s, 3 d, Ph), 72.3 (s, $HOCMe_2$), 70.1 (d, HOCH), 55.5, 49.8 (2 d, $CHNH_2$, CH), 35.3, 28.4 (2 t, 2 CH_2), 29.9, 29.0 (2 q, 2 Me), –1.3 (q, $SiMc_3$).

For the synthesis of **36**, a solution of **8a** (0.293 g, 1.00 mmol) was treated with $LiAlH_4$ as described, but concentrated HCl (10 ml) was slowly added for the workup. The mixture was stirred at room temp. for 2 h, diluted with water, and extracted with *tert*-butyl methyl ether. The organic phase was stirred with sodium hydroxide pellets (2 g), filtered, and concentrated. Distillation (100°C/0.02 Torr) provided 0.145 g (66%) of **36** as colorless oil (ratio of diastereomers 90:10). – ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.20 (m_c, 5H, Ph), 4.10 (m_c, 1H, 5-H), 3.78 (d, J = 9 Hz, 0.9H, 3-CH, major isomer), 3.68 (d, J = 9 Hz, 0.1H, 3-CH, minor isomer), 2.3 (m_c, 1H, 3-H), 2.2–1.0 (m, 4H, 4-H, NH_2), 1.25 (d, J = 6 Hz, 2.7H, 5-Me, major isomer), 1.20 (d, J = 7 Hz, 0.3H, 5-Me, minor isomer), 1.08, 0.71 (2 s, 2.7H each, 2-Me, major isomer), 1.04, 0.62 (2 s, 0.3H each, 2-Me, minor isomer). – ^{13}C NMR ($CDCl_3$, values of the minor isomer in parentheses): δ = 144.3, 128.5, 127.5, 126.5 (s, 3 d, Ph), 79.6 (81.0) (s, C-2), 71.5 (69.8) (d, C-5), 56.5, 56.0 (57.2, 54.2) (2 d, C-3, 3-C), 38.3 (37.2) (t, C-4), 29.2, 24.8, 23.1 (3 q, 2-Me, 5-Me). – IR (film): $\tilde{\nu}$ = 3600–3200 cm^{-1} (NH_2), 3100–3000 (=C–H), 3000–2800 (C–H).

$C_{14}H_{21}NO$ (219.3) Calcd. C 76.67 H 9.65 N 6.39
Found C 76.65 H 9.83 N 5.78

CAS Registry Numbers

1: 109925-98-6 / **3**: 79894-87-4 / **4**: 124462-62-0 / **5a**: 115117-93-6 / **6a**: 115117-95-8 / **7a**: 115117-97-0 / **8a**: 115117-99-2 / **9a**: 115118-01-9 / **10a** (isomer 1): 115183-53-4 / **10a** (isomer 2): 115118-05-3 / **10b** (isomer 1): 115183-55-6 / **10b** (isomer 2): 115183-54-5 / **11b**: 128710-02-1 / **12a**: 128710-09-8 / **12b**: 128710-10-1 / **13**: 128710-11-2 / **14a**: 115118-03-1 / **14b**: 115118-04-2 / **15a**: 128710-12-3 / **15b**: 128710-13-4 / **16a**: 128710-14-5 / **16b**: 128710-15-6 / **19b**: 128710-16-7 / **20**: 128710-17-8 / **21a**: 128710-18-9 / **22a**: 128710-03-2 / **22b**: 128779-02-2 / **23a**: 128710-04-3 / **23b**: 128779-03-3 / **24a**: 128710-05-4 / **24b**: 128779-04-4 / **25b**: 128710-06-5 / **26a**: 128710-07-6 / **26b**: 128779-05-5 / **27b**: 128710-08-7 / **28**: 59239-04-2 / **31**: 17180-49-3 / **32**: 128710-19-0 / *syn*-**34**: 128731-84-0 / *anti*-**34**: 128710-22-5 / **35** (isomer 1): 128779-06-6 / **35** (isomer 2): 128710-21-4 / **36** (isomer 1): 128710-20-3 / **36** (isomer 2): 128710-23-6

[1] C. Hippeli, *Dissertation*, Technische Hochschule Darmstadt, 1989.

[2] T. L. Gilchrist, D. A. Lingham, T. G. Roberts, *J. Chem. Soc., Chem. Commun.* **1979**, 1089. – T. L. Gilchrist, T. G. Roberts, *J. Chem. Soc., Chem. Commun.* **1979**, 1090. – T. L. Gilchrist, G. M. Iskander, A. K. Yagoub, *J. Chem. Soc., Perkin Trans. 1*, **1985**, 2769. – E. J. T. Chrystal, T. L. Gilchrist, W. Stretch, *J. Chem. Res (S)* **1987**, 180; *J. Chem. Res. (M)* **1987**, 1563. – W. Oppolzer, M. Petrzilka, K. Bättig, *Helv. Chim. Acta* **60** (1977) 2964. – W. Oppolzer, K. Bättig, T. Hudlicky, *Tetrahedron* **36** (1981) 4359. – H. C. J. Ottenheijm, *Chimia* **39** (1985) 89. – R. Plate, P. H. H. Hermkens, H. Behm, H. C. J. Ottenheijm, *J. Org. Chem.* **52** (1987) 560. – R. Henning, U. Lerch, H. Urbach, *Synthesis* **1989**, 265. – C. Hippeli, R. Zimmer, H.-U. Reißig, *Liebigs Ann. Chem.* **1990**, 469. – C. Hippeli, H.-U. Reißig, *Liebigs Ann. Chem.* **1990**, 475.

[3] [3a] R. Faragher, T. L. Gilchrist, *J. Chem. Soc., Perkin Trans. 1*, **1979**, 249. – [3b] D. E. Davies, T. L. Gilchrist, T. G. Roberts, *J. Chem. Soc., Perkin Trans. 1*, **1983**, 1275. – [3c] T. L. Gilchrist, T. G. Roberts, *J. Chem. Soc., Perkin Trans. 1*, **1983**, 1283. – [3d] Review: T. L. Gilchrist, *Chem. Soc. Rev.* **12** (1983) 53.

[4] [4a] C. Hippeli, H.-U. Reißig, *Synthesis* **1987**, 77. – [4b] C. Hippeli, H.-U. Reißig, *Liebigs Ann. Chem.* **1990**, 217. – [4c] H.-U. Reißig, C. Hippeli, T. Arnold, *Chem. Ber.* **123** (1990) 2403.

[5] [5a] T. A. Spencer, C. W. Leong, *Tetrahedron Lett.* **1975**, 3889. – [5b] R. R. Fraser, K. L. Dhawan, *J. Chem. Soc., Chem. Commun.* **1976**, 674. – [5c] H. E. Ensley, R. Lohr, *Tetrahedron Lett.* **1978**, 1415. – [5d] R. E. Gawley, E. J. Termine, J. Aube, *Tetrahedron Lett.* **21** (1980) 3115. – [5e] S. Shatzmiller, R. Lidor, *Synthesis* **1983**, 590.

[6] [6a] V. Jäger, W. Schwab, *Tetrahedron Lett.* **1978**, 3129. – [6b] H. Grund, V. Jäger, *Liebigs Ann. Chem.* **1980**, 80. – [6c] Review: V. Jäger, I. Müller, R. Schohe, M. Frey, R. Ehrler, B. Häfele, D. Schröder, *Lect. Heterocycl. Chem.* **8** (1985) 79. – [6d] For a careful discussion of the reactions of isoxazoline anions and their possible structures, see: R. Ehrler, *Dissertation*, University of Würzburg, 1985. – [6e] S. Shatzmiller, E. Shalom, R. Lidor, E. Tartovski, *Liebigs Ann. Chem.* **1983**, 906. – [6f] A. P. Kozikowski, A. K. Gosh, *J. Org. Chem.* **49** (1984) 2762. – [6g] R. Annunziata, M. Cinquini, F. Cozzi, L. Raimondi, *Tetrahedron* **42** (1986) 2129. – [6h] D. P. Curran, J.-C. Chao, *J. Am. Chem. Soc.* **109** (1987) 3036.

[7] R. Lidor, S. Shatzmiller, *J. Am. Chem. Soc.* **103** (1981) 5916. – S. Shatzmiller, R. Lidor, E. Shalom, *Isr. J. Chem.* **27** (1986) 33.

[8] For a preliminary communication see: C. Hippeli, H.-U. Reißig, *J. Org. Chem.* **53** (1988) 3884.

[9] W. Schwab, V. Jäger, *Angew. Chem.* **93** (1981) 578; *Angew. Chem. Int. Ed. Engl.* **20** (1981) 603.

[10] T. Kolasa, S. Sharma, M. J. Miller, *Tetrahedron Lett.* **28** (1987) 4973. – K. E. Rodriques, A. Basha, J. B. Summers, D. W. Brooks, *Tetrahedron Lett.* **29** (1988) 3455, and ref. cited therein.

[11] For the allylic effect in sugar derivatives see: R. Angerbauer, R. R. Schmidt, *Carbohydr. Res.* **89** (1981) 193.

[12] [12a] The most related systems are deprotonated isoxazolines frequently reacting with electrophiles with high stereoselectivity. However, the deprotonation step does not seem to be stereoselective as is the case of 1,2-oxazine **1**. Two diastereomeric isoxazolines are reported to provide the same intermediate (W. Schwab, *Dissertation*, University of Gießen, 1981; also see ref.[6c]; we are grateful to Prof. V. Jäger, University of Würzburg, for generous exchange of information). – [12b] For oxime ethers (ref.[5b]) and oximes [R. E. Lyle, J. E. Saavedra, G. G. Lyle, H. M. Fribush, J. L. Marshall, W. Lijinsky, G. M. Singer, *Tetrahedron Lett.* **1976**, 4431] of 4-*tert*-butylcyclohexanone regio- and stereoselective deprotonation and deuteration/alkylation have been demonstrated. Due to the conformational fixation of these compounds only axial protons *syn* to the exocyclic oxygen function are replaced with retention of configuration. – [12c] For stereoselective metalations and substitutions α to the nitrogen functions which are not capable to stabilize a carbanion by conjugation see: A. I. Meyers, D. A. Dickman, *J. Am. Chem. Soc.* **109** (1987) 1263 and earlier work of this group; J. Blagg, S. G. Davies, *Tetrahedron* **43** (1987) 4463; R. E. Gawley, G. C. Hart, L. J. Bartolotti, *J. Org. Chem.* **54** (1989) 175; R. E. Gawley, K. Rein, S. Chemburkar, *J. Org. Chem.* **54** (1989) 3003.

[13] Even at low temperature the NMR spectra of solutions of lithiated **1** gave only very diffuse signals.

[14] R. Glaser, A. Streitwieser, Jr., *J. Am. Chem. Soc.* **109** (1987) 1258. – R. Glaser, A. Streitwieser, Jr., *Pure Appl. Chem.* **60** (1988) 195. – R. Glaser, A. Streitwieser, Jr., *J. Am. Chem. Soc.* **111**, (1989) 7340 and 8799.

[15] We cannot exclude the possibility of **K** being in very fast equilibrium with other species. To explain our results, **K** must then be by far the most reactive intermediate.

[16] J. March, *Advanced Organic Chemistry*, p. 512, John Wiley & Sons, New York, 1985. – For more recent examples involving organolithium compounds see: ref.[12b], ref.[12c] and P. G. McDougal, B. D. Condon, M. D. Laffosse, Jr., A. M. Lauro, D. Van Derveer, *Tetrahedron Lett.* **29** (1988) 2547; R. W. Hoffmann, M. Bewersdorf, K. Dittrich, M. Krüger, R. Stürmer, *Angew. Chem.* **100** (1988) 1232; *Angew. Chem. Int. Ed. Engl.* **27** (1988) 1176; D. Enders, G. Bachstädter, K. A. M. Kremer, M. Marsch, K. Harms, G. Boche, *Angew. Chem.* **100** (1988) 1580; *Angew. Chem. Int. Ed. Engl.* **27** (1988) 1522; S. D. Rychnovsky, D. E. Mickus, *Tetrahedron Lett.* **30** (1989) 3011.

[17] For examples demonstrating a dependence of the stereochemical course of the S_E2 process on the nature of the electrophile employed (and the reaction conditions) see: A. I. Meyers, D. A. Dickman, *J. Am. Chem. Soc.* **109** (1987) 1263. – K. Rein, M. Goicoechea-Pappas, T. V. Anklekar, G. C. Hart, G. A. Smith, R. E. Gawley, *J. Am. Chem. Soc.* **111** (1989) 2211.

[18] We are not aware of reports on related acylation reactions comparing $ClCO_2Me$ and $MeOCO_2Me$. For a discussion of the regiochemistry of reactions of ambident anions see: R. Gompper, H.-U. Wagner, *Angew. Chem.* **88** (1976) 389; *Angew. Chem. Int. Ed. Engl.* **15** (1976) 321.

[19] The crude product of this reaction was a 1:1 mixture of **20** and **6a**! Apparently, a sulfur – lithium exchange occurred at the stage of **20** to give the anion of **6a**. This process was not observed in the corresponding deuteration experiment giving exclusively **19b**. Further experiments are required to clarify these results.

[20] S. Nakanishi, M. Higuchi, T. C. Flood, *J. Chem. Soc., Chem. Commun.* **1986**, 30.

[21] For related reductions of isoxazolines see: V. Jäger, V. Buß, W. Schwab, *Liebigs Ann. Chem.* **1980**, 122; ref.[6c] and ref. cited therein; R. Ehrler, *Dissertation*, University of Würzburg 1985.

[22] W. G. Kofron, L. M. Baclawski, *J. Org. Chem.* **41** (1976) 1879.

[23] E. N. Marvell, T. H.-C. Li, *J. Am. Chem. Soc.* **100** (1978) 883.

[162/90]