1
General Methods to Direct Selectivity

In the first chapter, we shall focus on the different modes of selectivity dealt with in organic synthesis and we shall describe the most important general methods to direct selectivity in these fields.

1.1
Chemoselectivity

The most obvious area that has already been intensely treated over many years is chemoselectivity [1].

The majority of the problems here have been solved to date, mainly with the help of protecting groups.

This is a broad field, but since it has been expertly and comprehensively covered in books [2] and review articles [3], we shall not engage in the same here.

In addition, there is a tendency in the last years to leave protecting groups altogether [4], since their removal may sometimes create problems at a later stage and since they mean additional steps, it translates into additional time and efforts.

Consequently, we nowadays aim at chemoselectivity without protecting groups.

A very simple solution is to hide the functional group in a reversible manner as, for instance, with the enolate of a carbonyl group [5].
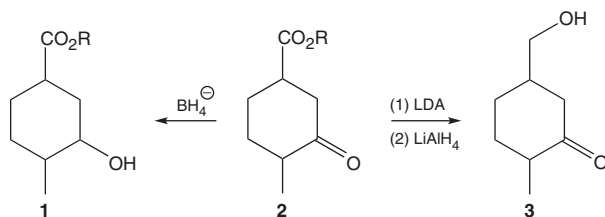
While the higher $\delta \oplus$ – character of the keto group in ketoester **2** allows for mild borohydride reduction to yield hydroxyester **1**, this may lead to preferential enolate formation followed by selective hydride reduction of the ester group to generate hydroxyketone **3**.

As polarization and enolization of carbonyl groups are the crucial steps in these efforts, one is not surprised that oxophilic countercations such as aluminum and magnesium are particularly helpful and that they manage to trigger the *in situ* enolate formation.

This is nicely demonstrated with the selective diisobutylaluminum hydride (DIBAL)-reduction of β-dicarbonyl compound **4** [6].
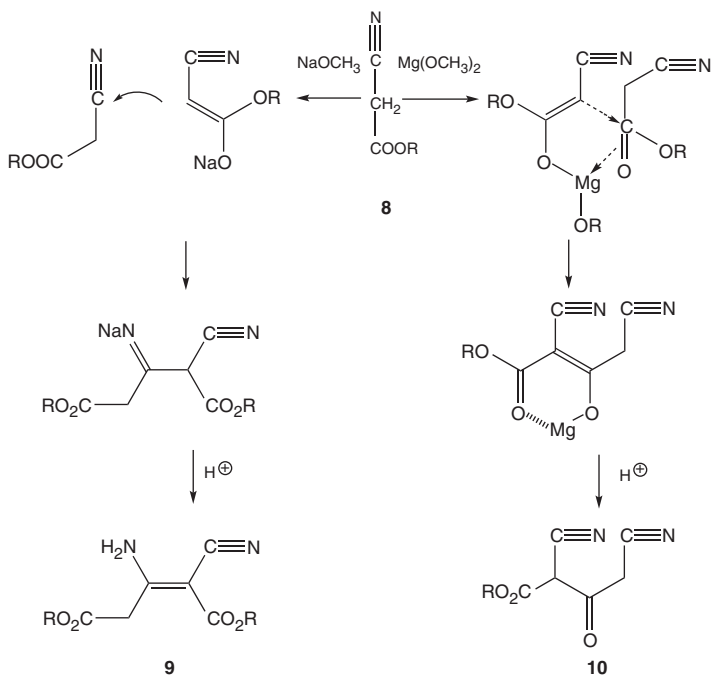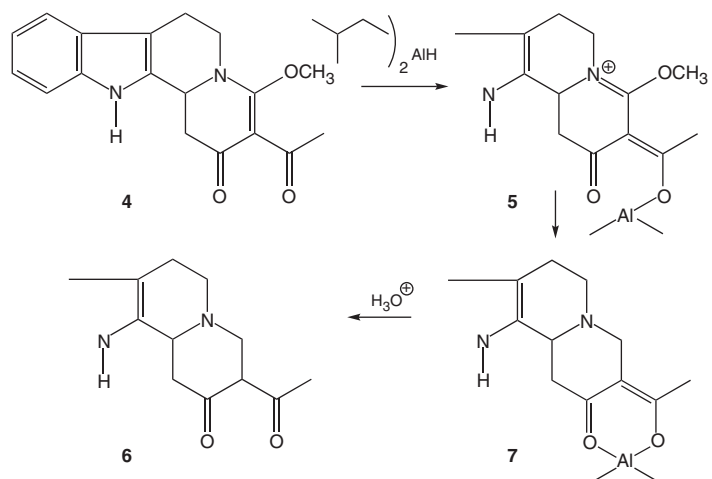
Probably the oxophilic aluminum compound attacks the carbonyl groups to form **5**, which is then reduced to enolate **7**. As long as this enolate is not quenched by protonation, one could continue with other transformations in a molecule of this type without touching the 1,3-dicarbonyl moiety. As predicted, this type of enolate formation can also be exercised with magnesium as the countercation, and as an example one notices the dimerization of cyanoacetate to form the β-dicarbonyl system **10** [7].

While deprotonation with sodium methoxide leads to nitrile attack forming enamine **9**, the employment of magnesium methoxide favors chelation of the Claisen intermediate, giving rise to the 1,3-dicarbonyl compound **10**.

In situ manipulation also plays a vital role in the selective reduction of ketoaldehyde **11** in the presence of cerium trichloride [8]
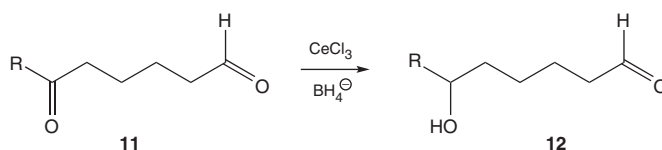

as well as in the allene formation from the butynediol derivatives **13** [9].
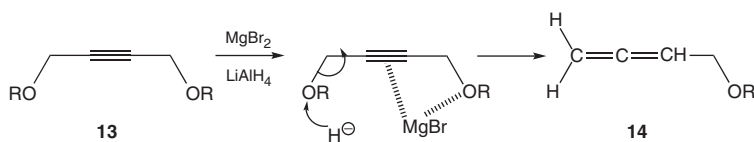
While in all these cases we dealt with complexation of the substrate to modify the electronic behavior, one may also use complexation to enhance or to reduce the reactivity of reagents [10].

Typical and very well-established borohydride complexes range from cyanoborohydride **15** via the various alkoxy compounds **16** to tris-acetoxyborohydride **17** and tris-alkylborohydride **19**.
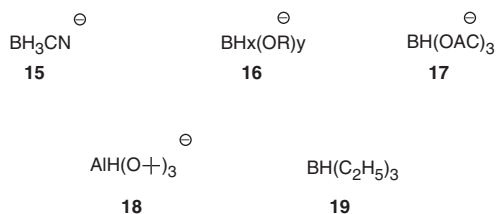
Very similar to the trisacetoxy compound **17**, which is simply obtained by dissolving sodium borohydride in acetic acid, the tris-*tert*-butoxy-alanate complex **18** is formed also on treatment of lithium alanate with *tert*-butyl alcohol.

In both cases, only three hydride anions are displaced, leading in the case of complex **18** to not only a very mild but also a space-demanding reducing agent.

Of particular importance is the *in situ* complexation of the strong and highly oxophilic dialkyl aluminum hydrides, for example, DIBAL [6, 11].

On treatment of the multifunctional indolo-quinolizidine **20** with a plain toluene solution of this reagent, one observes a very unselective and also unreliable reduction, leading to an unattractive mixture of compounds.

If, however, the toluene solution is pretreated with glycol dimethyl ether, the very selective and highly reproducible formation of hydroxyester **21** is noted [12].

The warming up of the hydride solution on addition of the diether indicates complex formation, to slow down the reactivity of the reducing reagent.
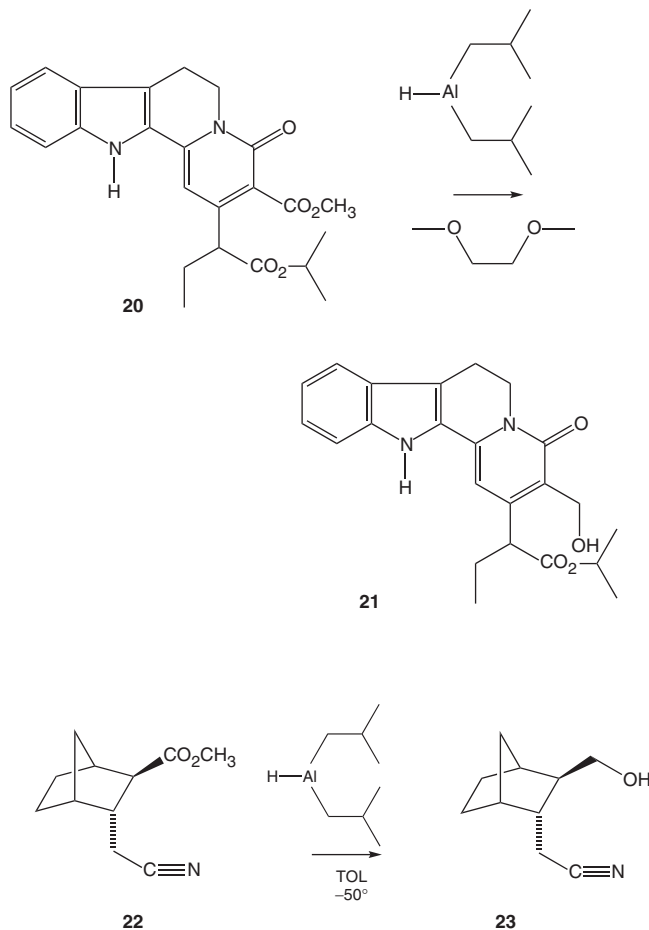
The high tendency for aluminum—oxygen interaction may also be responsible for the highly selective reduction of nitrile ester **22** with DIBAL in the absence of the diether at low temperature [13].

While the polarization of carbonyl groups and the Lewis base capacity of hydroxy groups offer a number of options for complexation, the situation is quite different with carbon–carbon double bonds.

Nevertheless, there are various possibilities to influence their reactivity along these lines too.

Neighboring hydroxy groups play a vital role in attracting and anchoring metal catalysts, which then deliver, for instance, hydrogen, into properly located double bounds.

This principle also operates very satisfactorily in oxidation reactions as the well-known and widely used Sharpless reaction clearly demonstrates.

For high chemo- and diastereoselectivity, the choice of the catalyst is of course essential and for hydrogenations very good results have been achieved with rhodium and iridium complexes [14].


24   **25**
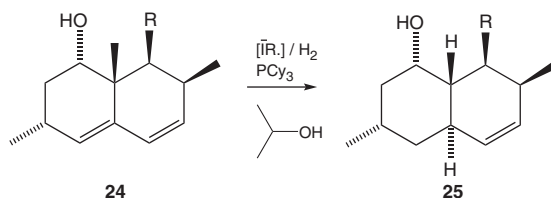
With example **24**, one should not overlook that the higher substituted double bond is hydrogenated and that the chemoselectivity of this process is accompanied by excellent diastereoselectivity. In addition, it turned out that the presence of isopropyl alcohol is mandatory for high chemoselectivity. In the absence of any complex-forming directing groups, there can be different chances for charge stabilization as an important prerequisite for selective attack at a carbon–carbon double bond.

The most simple approach could be the use of any type of Michael addition, employing strong acceptor groups such as esters, nitriles, or nitro groups.

Selective additions to these double bonds will certainly take place, but if the directing acceptor group is of no use in further operations, or maybe even absolutely unwanted, the subsequent removal of this moiety will be troublesome.

In contrast to this, trialkylsilyl groups can easily be removed and therefore offer themselves as charge stabilizer.

While alkyl substituted double bonds under normal conditions do not intervene in Grignard reactions, the trialkylsilane-substituted olefin **26** nicely forms a five-membered ring (**27**), generating a silicon–magnesium intermediate, which, representing an equivalent of a bis-anion, shows very high nucleophilicity.

26   **27**
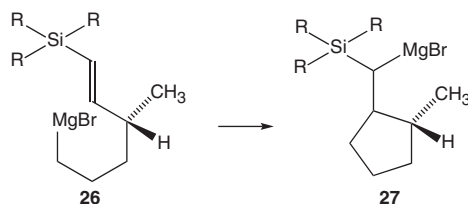
The role of silyl groups as directing centers is gaining growing importance as this moiety serves as an excellent example to illustrate the general strategies for transition state manipulation [15].

On the one hand, these groups can take the role of an active volume, influencing the course of a reaction by charge stabilization (see **28**), while on the other, space-demanding alkyl substituents, as in the TIPS-group (*tris*-isopropyl-silyl) (see **29**), render them into passive volume, which means that they influence just by their sheer size.
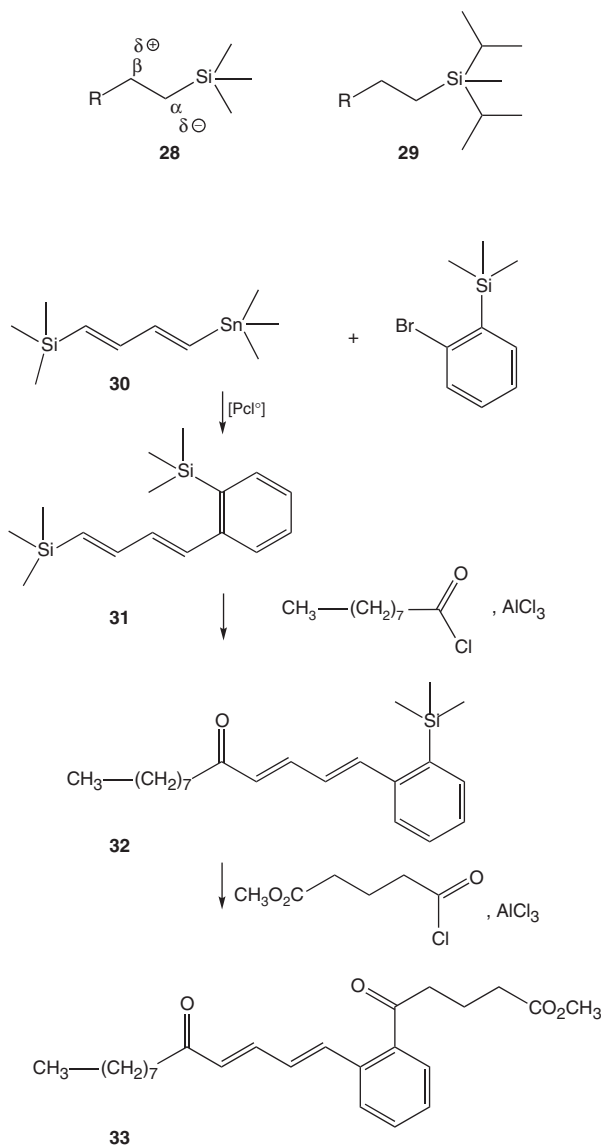
The wide range of options to use silane groups of different reactivity for chemoselective transformations is nicely demonstrated by an example from the benzleukodienes (**33**) [16].

Having seen these impressive examples, we shall not be surprised by the silyl groups in the following chapters on regioselectivity and stereoselectivity.

Chemoselectivity poses particularly demanding problems if the same functional group is present at different positions of a molecule as in sugars or glycosides.

In this case, there may be options to rely on the sterical situation, especially if one can reversibly retreat to cyclic or bicyclic structures.

Very often, however, the assistance of protecting groups will have to be considered, at least as long as purely chemical transformations are employed.

There are quite encouraging signals, however, from various types of enzymatic reactions.

It is, unfortunately, absolutely impossible to discuss the progress and the future possibilities in this field in this chapter but we include at least one example to demonstrate the capacity of these tools [17].
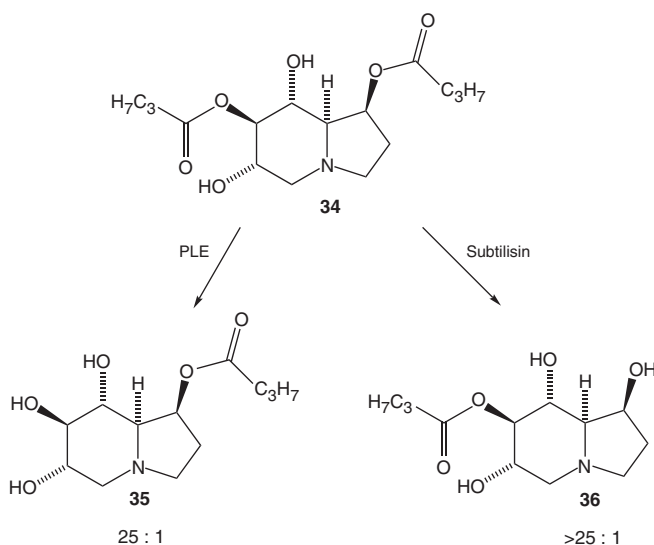
It is hard to see that any type of conventional hydrolysis could compete with these results.

1.2
Regioselectivity

Regioselectivity is of particular importance with fundamental starting materials carrying functional groups that offer two reactive positions, such as olefins, acetylenes, epoxides, anhydrides, and imides. There are additionally the two enolate

structures of ketones, as well as unsaturated carbonyl groups (1,2- vs 1,4-addition). In addition, there are a number of aromatic and heteroaromatic compounds posing various problems with regard to regioselective substitution.

With olefins, regioselectivity is governed by the Markownikov rule, but there are examples of anti-Markownikov additions, with hydroboration [18] being the most prominent one.

In case all these regulations leave deficits, one can still retreat to a few modifications of the double bond to solve the problem, as for instance, the epoxide, or the corresponding allylic or vinylic systems.

It has to be mentioned at this stage that triple bonds are posing very similar problems that are treated along the same lines.

It should be noted, however, that, in this case, hydroboration and analogous metal hydride additions generate the very useful vinyl anion equivalents **38**, which nicely contribute to the synthetic methods for allylic systems [19].
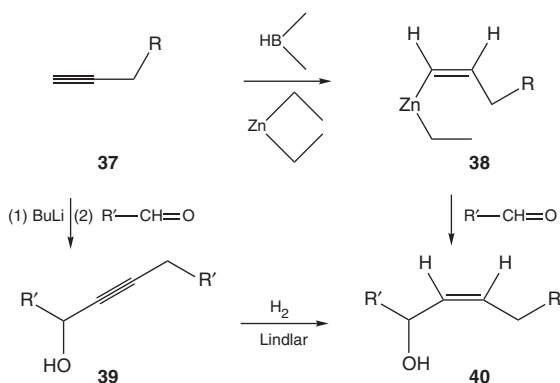

While acetylenes add directly to aldehydes and ketones to give rise to the propargylic systems **39**, which lend themselves for hydrogenation, the vinyl anions of type **38** lead directly to the corresponding allylic alcohols **40**.

Up to this point, the regioselectivity can be taken for granted. This changes, however, when we turn to the palladium-catalyzed substitutions, which have been broadly investigated in this field, with particular emphasis on the corresponding carbonates [20].

Out of the many useful transformations published, we selected just two, to demonstrate that one has two options here, leading either to direct substitution **42** [21] or to the S_N'-type products **41** [22].

While the S_N'-process introduces a functional group at the olefinic 1,3-position (**42**), direct substitution can lead to a wide choice of allylic substituents. Both can influence the reactions of the remaining double bond in various ways.

In all these metal-catalyzed substitutions, the carbon framework operates as an allylic cation equivalent. Moreover, to steer the regioselectivity one relies mainly on leaving group properties and reaction conditions.
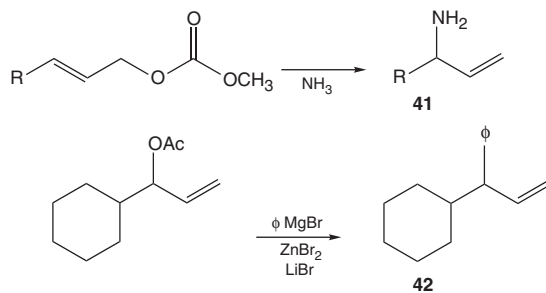
Very similar problems arise with allylic anions of type **43**.

Regioselectivity will be particularly hard to achieve if there are only small differences in space demand and electronic properties between R′ and R″.

Under these circumstances, the electrophiles may not properly differentiate between α- and γ-positions.

Again, silicon comes to the rescue [23].

Owing to charge stabilization at the α-position anion **44** gives rise to the α-substituted homoallylic alcohol **46** while the bulky TIPS group directs the electrophile into the γ-position, generating the vinyl silicon compound **47**.

The double bond in this product is again well prepared for highly regioselective transformations.

The corresponding epoxide **49**, for instance, opens regioselectively at the β-position (β-effect of silicon!) and gives rise to aldehyde **48** via silicon migration [24].
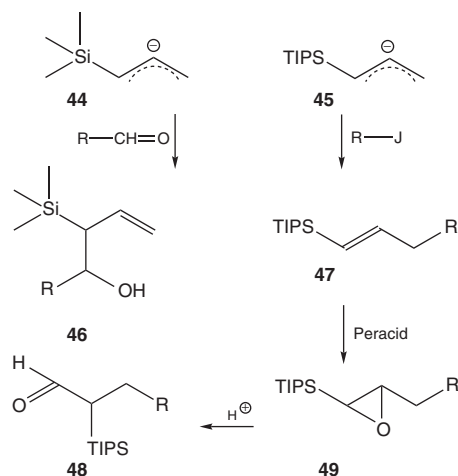
It is noteworthy that in the course of this sequence both carbon atoms of the double bond become substituted in a highly selective and predictable manner.

In this case, we deal with the electronic effect of a neighboring silicon substituent, but simply properly chosen reaction conditions can efficiently determine the outcome of epoxide ring openings too.

As one would expect, the employment of an oxophilic Lewis acid leads to cation formation at the higher substituted carbon atom of the epoxide, while attack with a strong nucleophile takes place at the less substituted one.

Aluminum hydrides serve as perfect examples for this outcome. In the case of epoxide **50**, the nucleophilic tetrahydrido anion attacks the α-carbon atom, leading to the *tert*-alcohol **52**. In contrast to this, the Lewis acid DIBAL gives rise to the primary one (**53**) under reductive shift of the double bond (see **51**) [6].
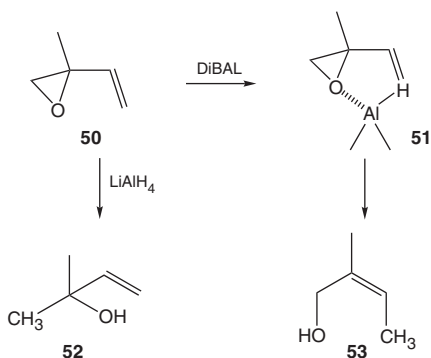
These observations lead to the general rule: Lewis acid reactions are governed by cation stability and pure nucleophilicity by steric effects.
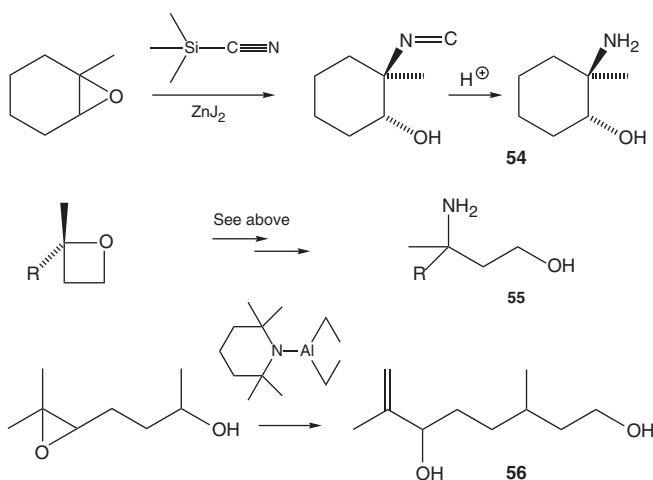
The first case is demonstrated by the regioselective formation of the highly substituted amines **54** and **55** [25].

In this connection, one may consider the regioselective formation of the elimination product **56** in the presence of a Lewis acid lacking any nucleophile, proof of the mechanistic interpretation of Lewis acid–catalyzed epoxide splitting [26].

As far as purely nucleophilic ring opening is concerned, it is very rewarding to notice that all the well-described orbital overlap requirements that are very typical for the Walden inversion process are mandatory for the epoxide reactions too.

With rigid epoxide structures, this is nicely reflected in the well-established Fürst–Plattner rule, which demands diaxial orientation for the transition state (see **57**) [27].
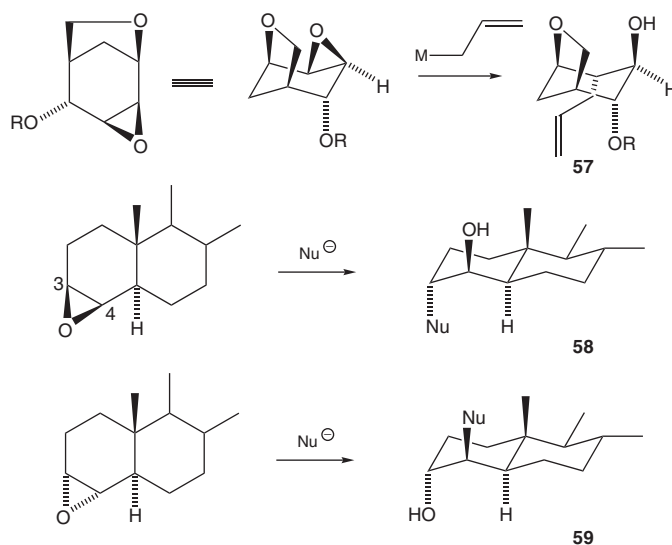

In accordance with the rule, the 3,4-epoxides of steroids or terpenes determine the regioselectivity of nucleophilic attack. Nucleophiles show up in the 3-position (**58**) with β-epoxides while the corresponding α-epoxides undergo nucleophilic ring opening at the 4-position (**59**).

This rule is extremely important for directing regioselectivity in rigid systems, and the high potential of this statement can be judged from regioselective opening to provide alcohol **57**. This is obviously also governed by the Fürst–Plattner rule [28], in spite of the handicap of having to accommodate all substituents in axial orientation.

These results indicate that to exercise very reliable and predictive regioselective epoxide transformations one has to be well aware of the mechanistic details of the process.

This can nicely be demonstrated with the intramolecular ring opening reaction of epoxide **60** [29].
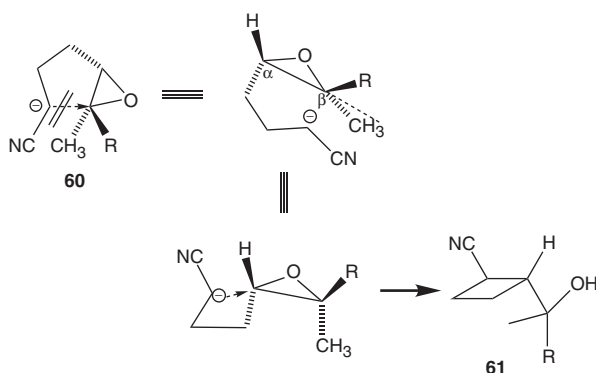
At first glance and ignoring stereochemistry, one is tempted to predict cyclopentane formation, but in this event the cyclobutane **61** is mainly formed.

Looking at the transition states, one is convinced that the carbon chain is simply too short to reach the trajectory for the first process (see dotted line), while the four-membered ring can easily be formed.

One has to realize that the stereochemical effect (axial substituents) as well as ring strain considerations are completely overruled by overlap necessities.

The final example in this series of epoxide reactions serves as a proof that the outcome of these reactions is independent of the nature of the anion involved and that an sp$_2$-centered nucleophile follows exactly the same rules.
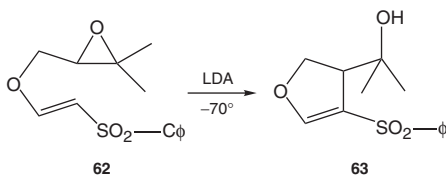
At very low temperature, the anion generated from vinyl sulfone **62** operates again in a highly regioselective manner, leading to dihydrofuran **63** [30].

Summarizing these results, we end up with two requirements: With Lewis acid catalysis it is the substitution pattern that counts, whereas orbital overlap is crucial for S$_N$2-type reactions aiming at directed regioselectivity in epoxide ring fission. Compared to just these two parameters in the epoxide case, there is quite an arsenal of tools to manipulate enolate formation in ketones. Considering the high value of this functional group for bond-forming chemistry, one is not surprised to notice that a wide variety of options to manipulate enolate formation has been investigated.

64
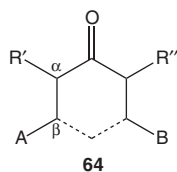
They range from number, size, and electronic properties of α- or β-substituents (see **64**) via ring size and rigidity to various derivatives of the carbonyl group such as oximes, alkylated oximes, and all types of hydrazone derivatives.

In addition, there is a multitude of variations from the side of the reagent. It starts with solvent, catalyst, and reaction temperature to continue with the size of the deprotonating species, the addition of countercations, and selected crown ethers.

Since these conditions may also control the transprotonation steps, we could also employ kinetic versus thermodynamic control.

Considering all this, very impressive results have been achieved already.

Deprotonation of ketones **65** and **67** with the bulky ''Loba''-base, for instance, proceeds with very high regioselectivity (97%) to generate the less substituted enolates **66** and **68**, quenched as silylethers [31].
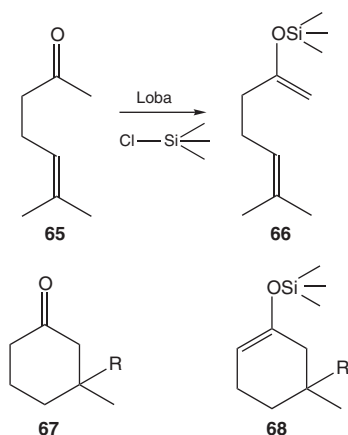
Although this certainly meets our expectations – if not to a large extent – the deprotonation of hydroazulene-ketone **69** with lithiumtriphenylmethyl leading to mainly one enolsilylether is really remarkable [32].

After palladium oxidation, cyclopentenone **70** is obtained with at least 90% selectivity. The structural difference here amounts to just one methyl group in the γ-position. However, since the seven-membered ring shows quite some conformational mobility, simply counting heads could be misleading.

69 → **70** > 90 : 10
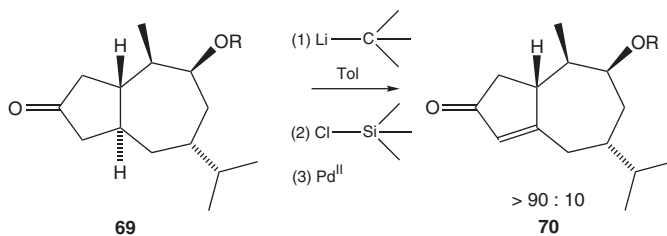
It is of course very tempting to combine sheer size of the proton acceptor with conditions of kinetic or thermodynamic control, as has been shown for α-methylcyclohexanone **71** [31b,c]
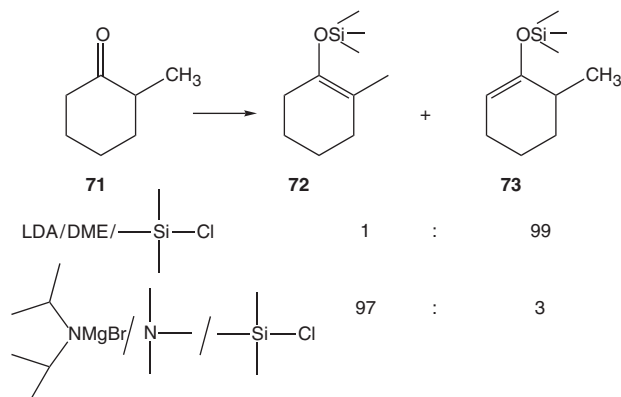
As these results show, proceeding in this manner is clearly of practical value, and Shea proved in a very detailed investigation that this strategy can be used quite efficiently for bridgehead substitution in the important bicyclic ketone **74** [33].
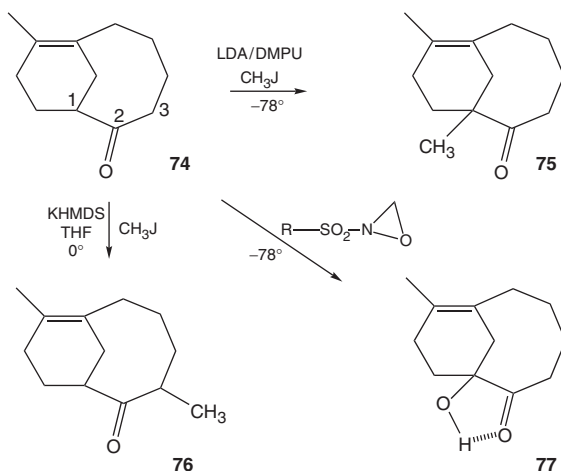
The anti-Bredt position of the 1,2-enolate, together with molecular mechanics calculations, indicates this to be the thermodynamically disfavored position.

Under kinetic control, however, it is formed with high selectivity. On methylation the bridgehead-substituted ketone **75** is obtained and on oxidation it gives rise to the bridgehead carbinol **77**.

If the deprotonation is done under thermodynamic conditions, the 3-methyl derivative **76** results from the methylation process.

It is noteworthy that these results constitute a complete reversal of the regioselectivity in enolate formation and the 99° angle of the C_1-H bond with the carbonyl group is a clearly convincing explanation of the high acidity.

As noticed with the epoxides, the intramolecular capture of enolates can be very helpful to solve regioselectivity problems too.

In the case of the bicyclic ketone **78**, the plain thermal cyclization generates synthetically unattractive mixtures of the five- as well as the six-membered ring compounds **80** and **79**.

If one starts with the separately prepared enolsilylether **81**, mercury-catalyzed cyclization gives a high yield of **79**, while the easy-to-make aldol **82** leads to **80** after a thermal retro-aldol process [34].
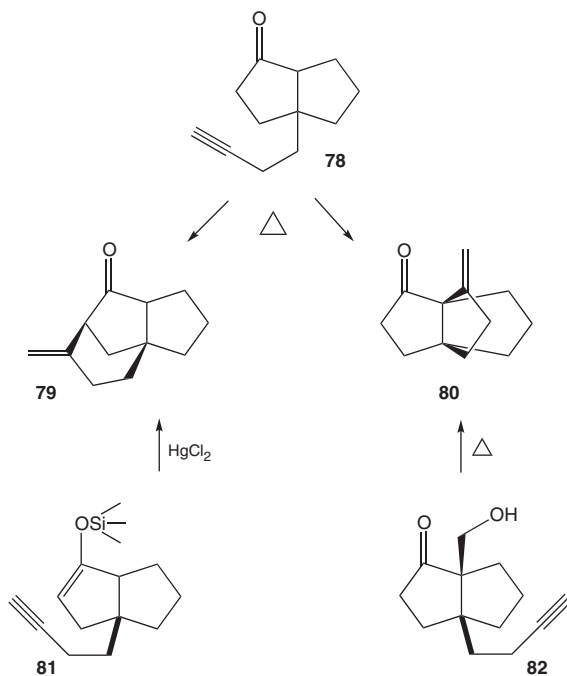
This example teaches that minor changes in the procedure can result in regioselective routes to both possible enols.

This means that to reach a special target one simply has to select the appropriate approach to the enolate needed.

Finally, this subtopic provides another generally very useful application of the active volume–passive volume principle.
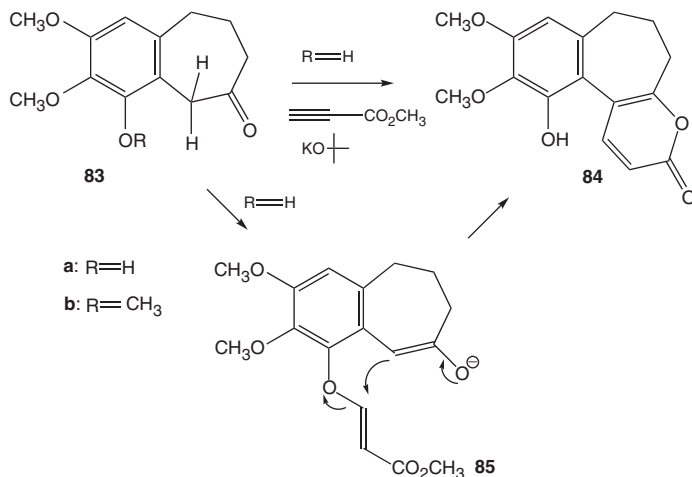

a: R=H

b: R= CH₃

Although ketone **83** at first glance appears to be a good candidate for selective alkylations or Michael additions, first experiments using the tris-methoxy compound **83b** met with complete failure.

With methyl propiolate as the electrophile a very disappointing mixture of products was obtained. The picture fortunately changed completely with the monohydroxy compound **83a**.

Michael addition with methyl propiolate led in this case directly to the tricyclic α-pyrone **84**, which is a central intermediate in Eschenmoser's colchicine synthesis [35].

Obviously, the methyl group in **83b** is not bulky enough to completely divert the electrophile from the benzylic position, thus giving rise to mixtures. To achieve complete shielding of this center, highly space-demanding groups such as pivalate, TIPS-ether, or maybe even the triphenylmethyl group will probably be necessary to create the appropriate passive volume.

In contrast to this, the free phenolic group in **83a** presents itself as active volume, probably picking up the propiolate to form an enolether, which is then transferred to the benzylic position exclusively (see **85**).

Under these circumstances, the generation of the ''wrong'' enolate will be of no consequence as long as enolate equilibration is guaranteed. The capture of the electrophile, in this case, represents a Michael addition to an acceptor-substituted acetylene, and this brings us to another subtopic in the carbonyl field that is bound to pose regioselectivity problems.

Conjugated triple bonds as well as double bonds can give rise to 1,2- or 1,4-addition products, and the picture will be even more disturbing if we should be confronted with the inverse Michael addition too.

In general, and as long as we deal with ionic additions, this process is governed by the hard–soft principle and in the case at hand, having potassium as the countercation together with a soft nucleophile, 1,4-addition can be taken for granted. An inspection of the general picture, however, reveals various possibilities to manipulate the outcome of these reactions (see **86**).
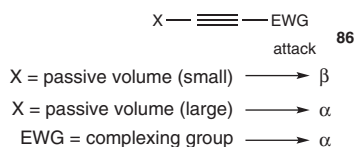
The acetylenic amides of type **87** proved to be an excellent testing ground for this behavior [36].
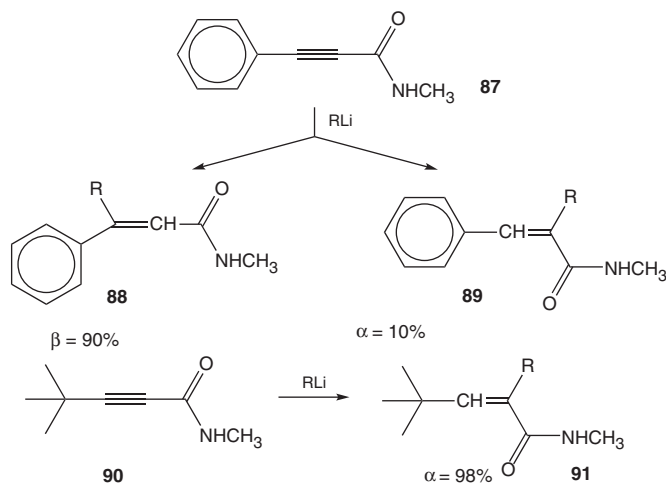
Although the complexing amide is of assistance for the α-addition, the phenyl group diverts the nucleophile only to an extent of 10% to the α-position (see **89**).

If, however, the *tert*-butyl group directs the approach, the α-addition product **91** is formed to the extent of 98%.

As different studies on the directing power of various passive volume groups have shown (see chapters 1 and 3 on stereochemistry), branched saturated substituents proved to be more space demanding than a phenyl group.

Things get a little more complicated with ambident nucleophiles and unsaturated ketones, as demonstrated with cyclopentenone **92** [37].

We notice here a quite strong solvent dependence, but although **93** formally appears a violation of the hard–soft principle, a zinc chelate such as **95** could easily explain this outcome.
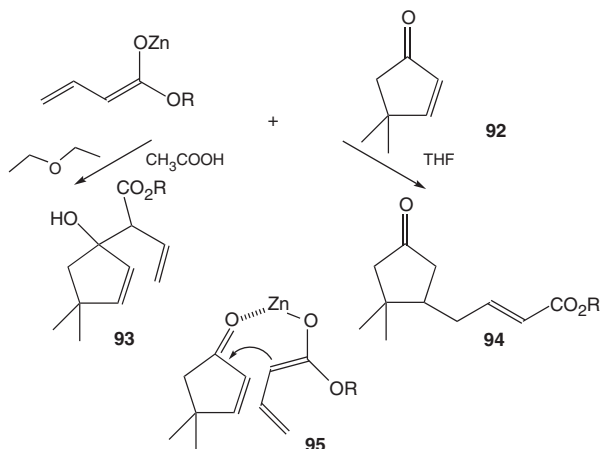
The regioselectivity with ambident anions also shows strong dependence on Lewis acid catalysis, as was nicely demonstrated with enthiolat **96** [38].
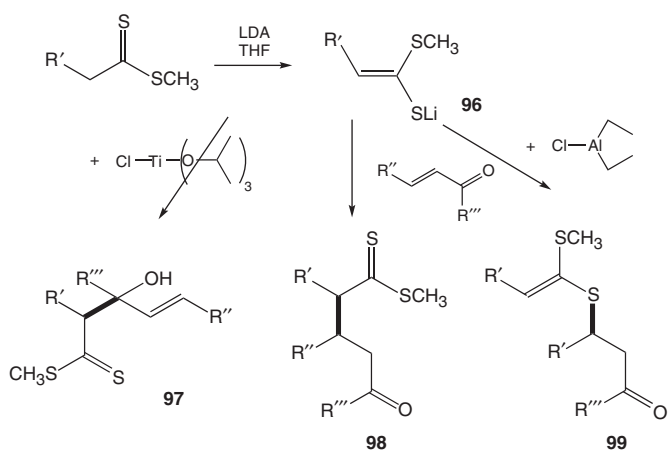
Since all the reactions were run in tetrahydrofuran, the fact that three out of four possible products can be generated selectively is solely due to the Lewis acid present. While lithium as the countercation leads to the "normal" Michael adduct **98**, titanium gives rise to the corresponding 1,2-adduct **97**. Aluminum favors 1,4-addition again but employing the sulfur atom as the nucleophile (**99**).
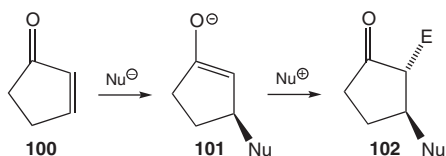
The high reliability of 1,4-addition offers an excellent chance to capture the intermediate enolate anion in a completely regioselective and diastereoselective tandem process.

This highly flexible sequence opens an easy path to 2,3-disubstituted cyclopentanones (see **102**), as has been impressively demonstrated in the total syntheses of the prostaglandins [39].

If a leaving group is placed properly in the cyclopentenone (see **103**), the trans-protonation equilibrium **104a** ⇌ **104b** will regenerate a cyclopentenone (**107**) via β-elimination.

This can then be followed by a second 1,4-addition−enolate capture sequence to provide the trisubstituted cylopentanones **105** with complete regio- and stereoselectivity. As far as the reagents involved and their sequence 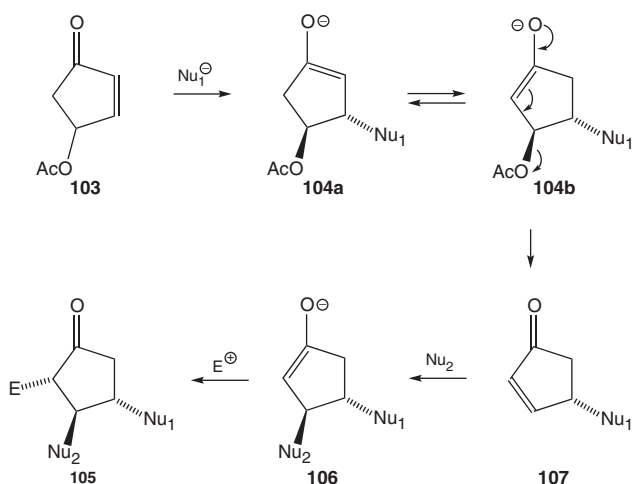of addition are concerned, one notices very high flexibility. Consequently, these reaction cascades offer easy-to-direct routes to a great number of differently substituted cyclopentanones, and if one additionally runs these cascades in an intramolecular manner, they grant access to numerous anellation products [40].

All efforts to preserve a charge or a radical in a molecule to show it around and use it for directed cascade-like reaction sequences at well-selected positions will be of great importance for the future development of an automatized and sustainable synthetic chemistry. One is therefore well advised to look for substituents or functional groups that can provide assistance in these endeavors. As far as charge stabilization is concerned, the trialkylsilyl group once again is very promising and has indeed been very helpful in Michael additions already.

The trimethylsilyl-substituted methylacrylate **108**, for instance, first presents itself as a highly reactive Michael-acceptor, which can in the next step trigger a very efficient Peterson olefination to provide the acrylates **109** and **110** [41].
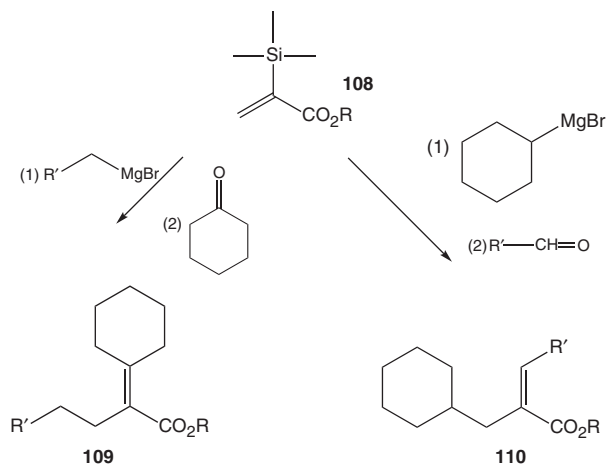
As the reaction scheme demonstrates, the nature of the donor and the electrophile can be exchanged, leading to a wide choice of substituents for substituted acrylates with predictable regioselectivity.

In a recent report on directed regiodivergent additions to a triple bond (see **111**) the change of reagents is combined with an interesting change from ionic to radical initiated additions [42].
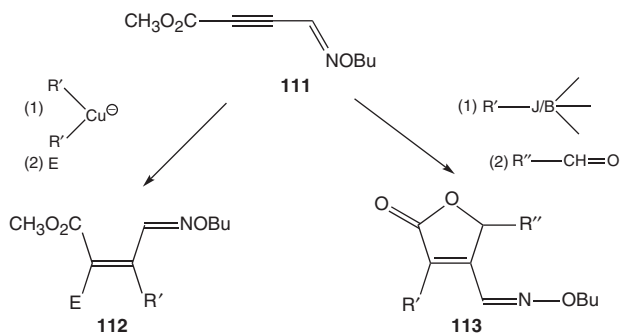
As can be expected, cuprate addition leads to β-attack, which is followed by the normal α-capture of the negative charge (see **112**). Radical attack, on the contrary, takes place at the α-position to generate a resonance-stabilized intermediate, which is terminated at the β-position.

If at this last stage an aldehyde is employed, the lactone **113** is formed.

Discussing conjugated systems, we have until now dealt with unsaturated carbonyl groups exclusively. Actually, this is just one species in the large group of unsaturated acceptors, but the observations made here and the conclusions drawn will, by and large, be valid for the whole field.

So, we add just one example from the sulfur field, and the vinyl sulfoxide **114** presented was chosen for two reasons.

First, it may operate as a very normal Michael-acceptor. However, due to the deprotonation conditions it could also lead us into the area of vinyl anions, rendering the molecule into a nucleophile. This means that with a change of the reaction conditions, we should be able to switch into a completely different line of products [43].

114

115   **116**
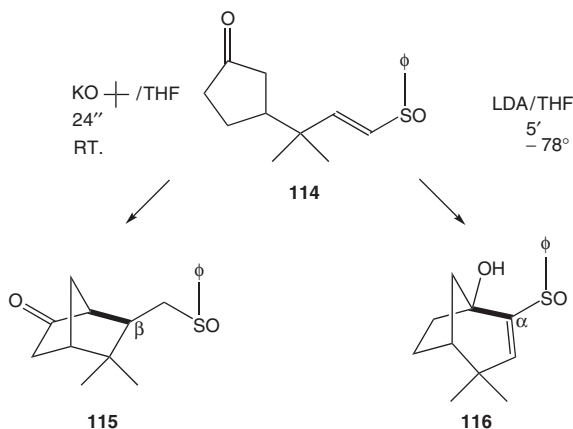
Both processes, however, take place with perfect regioselectivity (see bonds printed in bold). The kinetically controlled formation of the heteroatom-stabilized α-vinyllithium intermediate is followed by a very quick nucleophilic attack at the carbonyl group, while thermodynamic control to generate the enolate gives rise to the normal conjugate addition to the acceptor-substituted double bond. Stabilized vinyl anions such as **117**, **118**, and **119** are, owing to their constitutional and configurational stability, quite interesting homoenolate intermediates useful for regioselective double bond transformations [44].

117   **118**   **119**
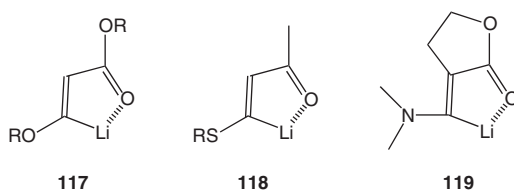
With the vinyl anion of butadiene the regioselectivity in the addition to carbonyl groups is strongly dictated by the countercation [45].
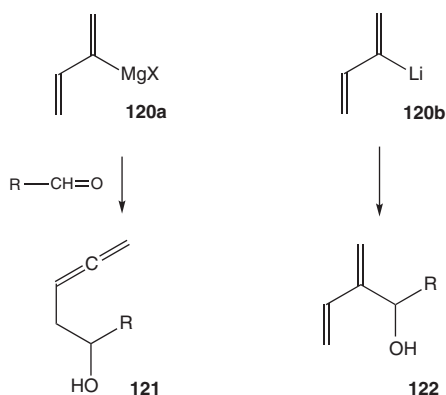
While the Grignard reagent **120a** provides a roughly 80 : 20 mixture of **121** and **122**, the corresponding lithium compound **120b** leads to the α-adduct **122** with high selectivity.

As far as polyanions of type **123** are concerned, one can generally rely on the sequence of acidities of the corresponding protons, with the position of the lowest acidity exercising the highest nucleophilicity.
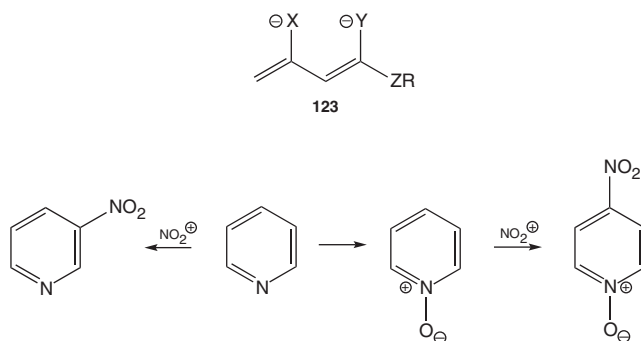
Regioselectivity in aromatic compounds is in principle dictated by substitution rules. With heteroaromatic rings, however, there is a strong influence of the involved heteroatom and its hybridization.

While pyrroles and analogous donor aromats provide substitution products easily and selectively, the acceptor aromats, for example, pyridine or quinoline, suffer from bad yields and low selectivity in standard electrophilic substitutions.

One way out of this dilemma is to bring along the substituents in question in a properly planned synthesis of the heteroaromat, but in some cases minor changes such as quarternization or *N*-oxide formation are of considerable help already.

With quarternized compounds, we switch from electrophilic to nucleophilic attack and with *N*-oxides we improve the donor capacity of the aromatic ring.

While pyridine itself leads to 3-nitropyridine under quite drastic conditions only, the 4-nitropyridine *N*-oxide is formed smoothly and in high yield.

With benzene and its derivatives, the various types of coupling reactions developed in the last decades open highly reliable routes to a wealth of substitution patterns [46–49]. In most cases, however, the corresponding halogen compounds are needed as starting materials, which does not change the substitution problem. Still, the scope is so wide that it cannot be treated in detail here.

One particular and synthetically demanding problem that requires intelligent solutions represents the generation of ensembles of ortho substituents.

This task unfolds again as a very typical case of passive volume–active volume principle.

In classical substitution reactions, ortho substitution suffers from steric hindrance. The sheer bulkiness of the substituents present blocks the substitution process.

Should the substituent present itself as active volume, however, assisting in the interaction with the approaching reagent will of course completely change the situation.

A large number of ortho-directing substituents have been developed for metalation reactions and **124–126** represent a few typical examples [50].

124   125   126
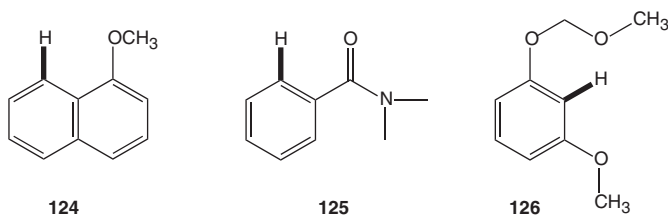
Since aromatic fluoro compounds are gaining rising importance in the field of biologically active structures, we are adding at least a few reactions to demonstrate the directing capacity of the fluoro substituent. Preferential deprotonation with *sec*-butyllithium can be achieved in both *o*-positions of aromatic fluoro compounds.

In the case of the protected *p*-fluorphenol **127**, this leads to **128** and the subsequent quenching with alkylborate gives rise to **130**, which can be used for coupling reactions as well as for substituent exchange.

The standard oxidation procedure, for instance, provides phenol **129**.

After protection, **129** undergoes a second deprotonation and capture of the corresponding *o*-lithium intermediate with dimethylformamide, and finally generates *o*-fluoraldehyde **131**. Exercising exactly the same sequence twice with the protected *p*-fluorbenzylic alcohol **132** takes us to the tris-silyl compound **134**, which, after deprotection, oxidation, and treatment with benzylic bromide provides the *p*-fluoraldehyde **133** [51].
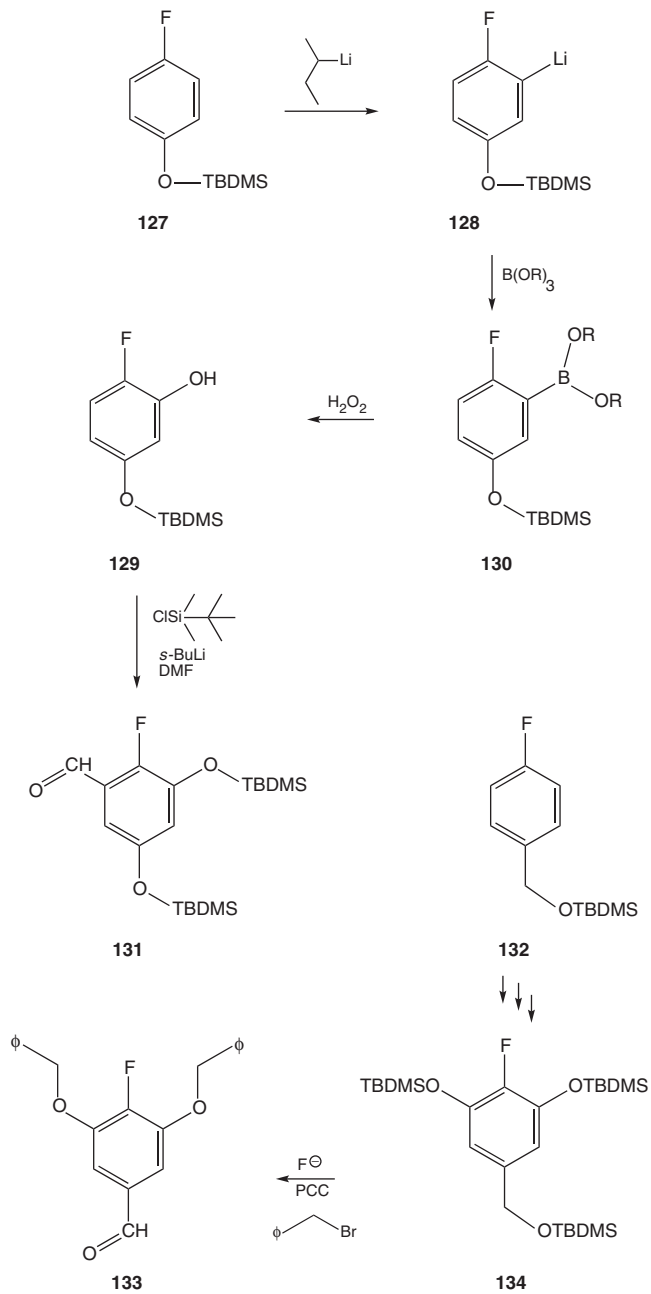
From the examples offered, one could draw the conclusion that regioselectivity is in the sole responsibility of neighboring substituents.

That this picture is too simple emerges clearly from the Grignard reactions of anhydride **135**.
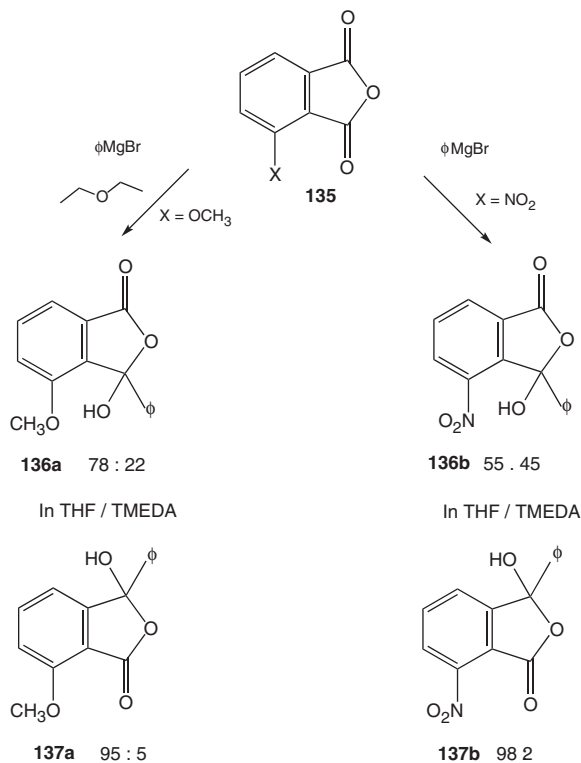
The results demonstrate very clearly the decisive role of the solvent.

In diethyl ether, the complexed reagent attacks quite slowly and leads via a late, product-orientated transition state to **136** with low selectivity, while the bulky and highly reactive TMEDA (tetramethylethylenediamine) reagent proceeds via an early transition state at the less hindered *m*-carbonyl, giving rise to **137** [52].

With anhydride **135**, we demonstrated the influence of the solvent on the reactivity of a metallo-organic reagent, resulting in the attack at special positions of the aromatic ring. With quinole acetate **138**, the correct choice of the solvent even opens an opportunity to direct an alkyl substituent either into a ring position or into a benzylic carbon atom [53].

It is probable that in dichloromethane the quinole acetate is attacked in the allylic position, similar to the well-established Sakurai process, while in the more polar acetonitrile the acetate proceeds to the elimination product **142**, which is then attacked by the nucleophile at the least hindered carbon atom.
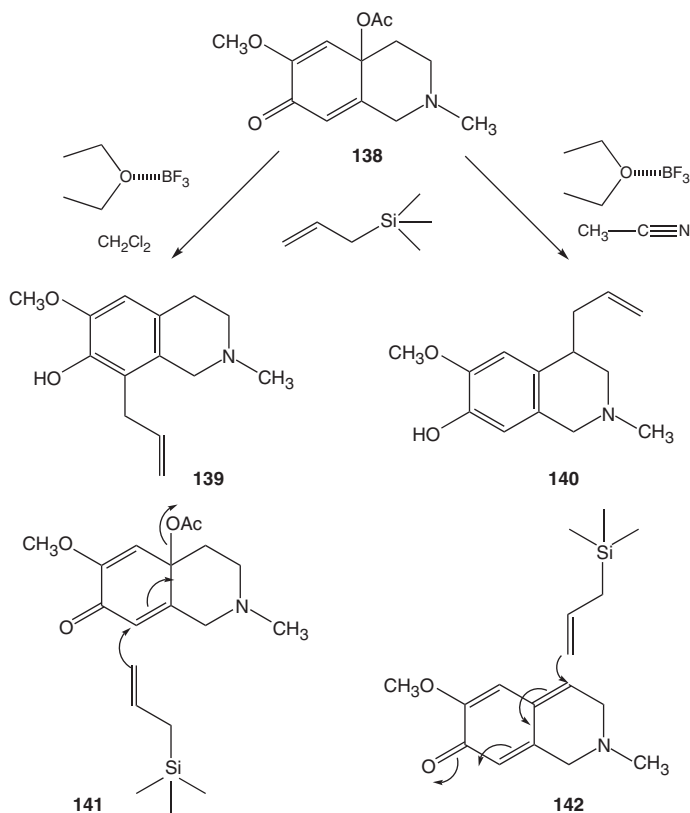
In this section, we have described some important strategies to influence and direct the chemical transformations at ambident positions in order to arrive at either one or the other possible reaction product regioselectively.

In the following sections, this will be extended to stereoselectivity and enantioselectivity.

1.3
Stereoselectivity

The reliability and the fundamental nature of the stereoelectronic principle contribute heavily to the importance of this rule as the backbone of diastereoselectivity.

Since it provides the bridge between sp$_2$- and sp$_3$-centers and since very useful and quite flexible routes lead from acetylenes (sp) to even polysubstituted olefins (sp$_2$) in a stereoselective manner, the sp $\rightarrow$ sp$_2$ $\rightarrow$ sp$_3$ sequence is of utmost importance for the whole field of stereochemistry.

Together with this sequence, the stereoelectronic principle represents the key for devising and understanding stereoselective transformations.

Depending on the electronic nature of the double bond, it paves the path to a very broad range of sp$_3$-centers in a highly selective manner. The high synthetic flexibility observed is due to the nature and the properties of the electrophile as well as of the nucleophile. Its intervention via an early **143** or late **145** transition state will determine the stereochemical outcome of the process.
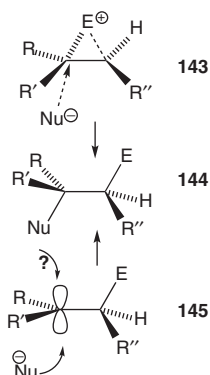
This calls for stereoselective, flexible, very reliable, and if possible simple techniques to prepare di-, tri-, and tetrasubstituted double bonds.

Although the Wittig reaction may, at first glance, appear a good choice for the preparation of olefins, one runs into difficulties very quickly when it comes to the synthesis of higher substituted olefins.

The outlook is much better with the Peterson reaction; here, at least trisubstituted double bonds with *E*- as well as with *Z*-configuration will result if the syn-elimination mode **147** or the corresponding anti version **148** is employed.
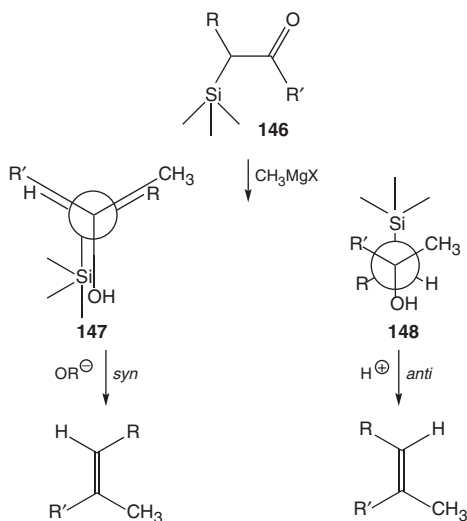
Very high chemical as well as configurational flexibility was secured from addition reactions to triple bonds, particularly when intramolecular steps promised regioselectivity.

An early, groundbreaking and easy to direct process was found in connection with aluminum hydride reductions of acetylenic esters **149** [54]
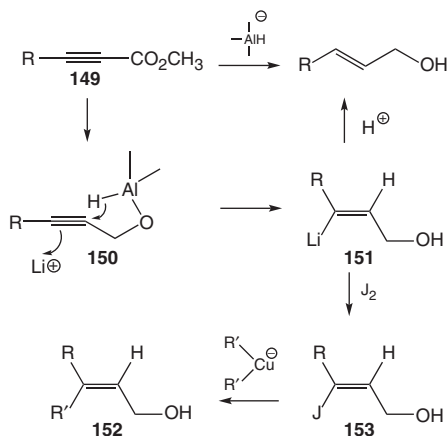
Since **151** appears a convincing intermediate in the addition process, the reaction was quenched with iodine to generate vinyl iodide **153**, which, on treatment with a cuprate, gave rise to the well-defined trisubstituted olefin **152**.

To obtain the alternate configuration **155** one simply has to exchange the substituents at the triple bond and the cuprate complex (see **154**).
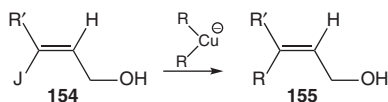
In the presence of a Lewis acid catalyst (AlCl$_3$) the regioselectivity of iodine addition is inverted, leading to the substitution pattern **157**.
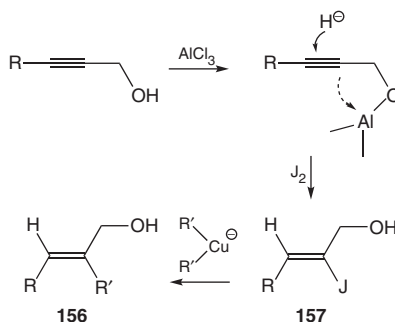
Exchange of substituents as described above widens the scope of the structures that can be addressed with this method.

The high degree of flexibility observed in triple bond additions is certainly the reason for the numerous contributions to this field.

The investigations were extended from acetylenic esters to silyl compounds, sulfones, borates, as well as alkyl- and arylacetylenes [55].

The story would still be incomplete, however, if one would not add the many options that additionally arise from general metal hydride additions as indicated in **158**.

158
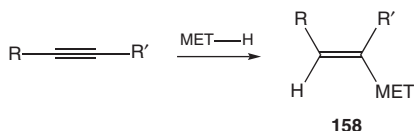
Although all this could lead to the conclusion that acetylenes are great performers and the starting material of choice for directed selectivity in olefin synthesis, one should not forget the enol derivatives of ketones and also their hydrazones as useful starting materials [56].
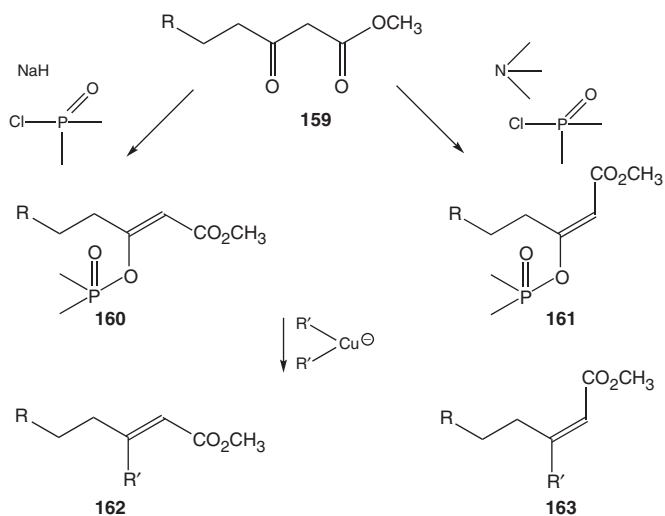
With a β-ketoester such as **159** there are very good chances to easily secure the desired double bond configuration, and the cuprate nucleophile offers additionally a very broad choice of possible substituents in **162** and **163**.

Comparable results have been reported for enol tosylates [57], such as **164**, and the hydrazone **166** served very well for the preparation of the aryl-substituted cyclic olefin **167** [58].
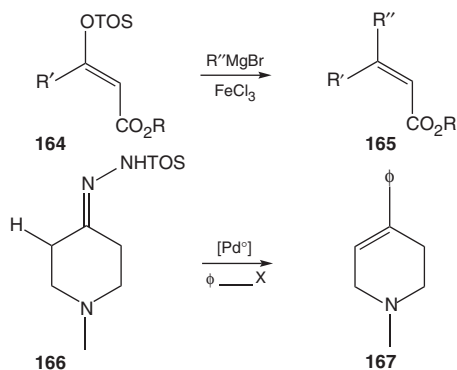
It is not the intention here to cover this field comprehensively but rather to show that there is a number of quite different and easy to direct stereoselective routes into that area.

For much more detailed information, we recommend Negishi's very broad and well-organized review article [54a].

With the properly substituted olefins at hand, we now have to address the numerous stereospecific reactions that can be employed in $sp_2 \rightarrow sp_3$ transformations.

Next to the standard electrophilic additions, the formation of haloethers and halolactones is of particular synthetic value since epoxidations and diol formation can also be run with high face selectivity; these reactions offer very short and predictable routes from simple olefins to well-defined diastereomers and enantiomers.

Generally, the directed selectivity in epoxidations is easily accomplished with the assistance of a neighboring hydroxyl group. Accepting hydrogen bonding as one important phenomenon in this behavior, one is not surprised that other groups showing hydrogen bonding capacities too can also fulfill this job, as demonstrated with olefin **168** [59].
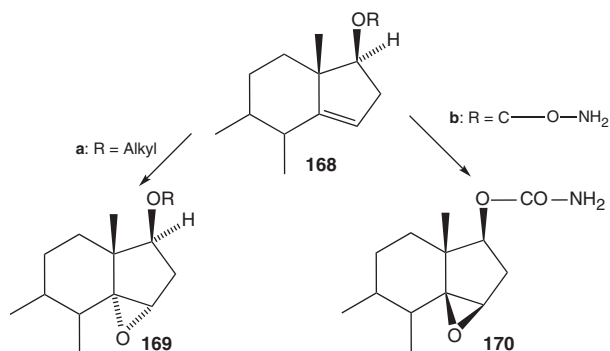
The ether group in **168a** represents a passive volume and directs the oxidant to the α-side (see **169**), while the amide group in **168b** operates as active volume that picks up and delivers the reagent from the β-side.

If in intramolecular versions, comparable to iodolactonization, the nucleophile is represented by a carbon–carbon double bond or triple bond, the stereospecific and stereoselective generation of carbon bonds is at reach (see **171** and **172**).

These π-cyclizations are, on the one hand, impressive examples of directed selectivity, since the configurations of the double bonds involved dictate the configuration of reaction products, but they can, on the other hand, also be run like a zipper though a polyolefin chain to generate pure stereoisomers of polycyclic compounds, as for instance, in the squalene monoepoxide cyclization that represents the backbone of the biogenetic pathway to steroids [60].
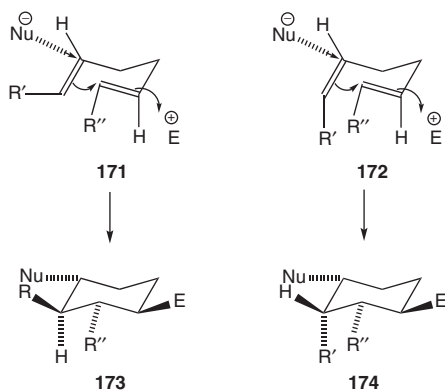
Manipulations of constitutions and configurations can again be accomplished by exchanging double bond substituents and configurations (see **173/174**).

Although we have so far seen quite a number of transformations that lead to synthetically useful compounds, we, as far as the mechanism goes, have not yet left the subject of electrophilic attack at π-systems.

Of course, there are many alternatives to transfer sp_2 configurations into well-defined sp_3-centers and certainly hydrogenation is a very simple and obvious one [14b, 61].

Keeping in mind that the substrate will have to interact with the surface of the catalyst that transfers the hydrogen atoms, one may safely predict that the configuration and conformation of the starting material will have a strong influence on the steric course of the hydrogenation.

177   **178**
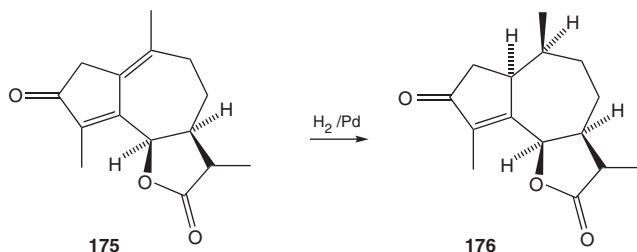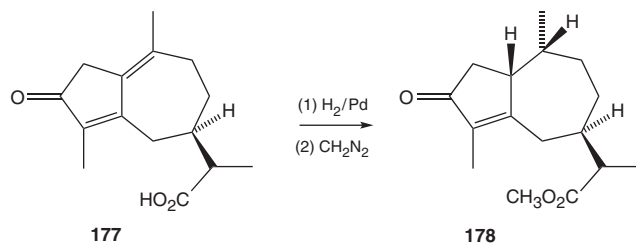
Owing to the conformational flexibility of the seven-membered ring, the hydroazu-lenes **175** and **176** serve as convincing examples for this behavior [62].

The β-orientated γ-lactone in **175** clearly shields the upper side of the hydroazu-lene, directing the hydrogen into the α-orientation (see **176**). If this particular ring is opened, one gains free access to the β-side, leading to **178**.

Needless to say that hydrogenations in general and also other processes employ-ing heterogeneous catalysis show a high dependence on substrate configuration and conformation too.

Again, we have to recommend review articles here for further information [14b, 61].

Out of the many additions possible, the wide field of cycloadditions certainly merits special scrutiny.

As in 2π-4π cycloadditions, two new bonds are formed in a highly stereoselective manner, the transition state demands are very high.

They are even more strict in intramolecular cycloadditions that they not only nicely solve regioselectivity problems but are also highly recommended for the introduction of quaternary carbon atoms [63, 64].

This works even when these centers are in close neighborhood as is demonstrated with ketone **182** [65].

179   **180**

181   **182**
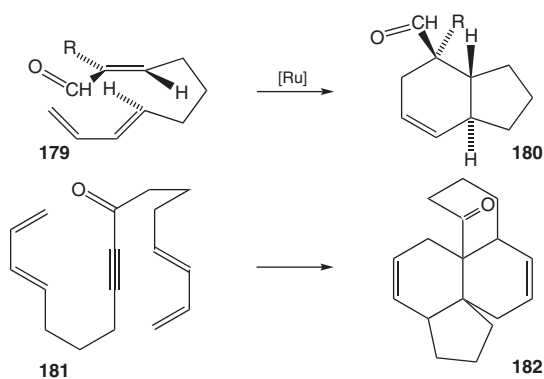
The generation of two neighboring quarternary centers is, however, only one important aspect of intramolecularization; one should additionally realize

that there is an impressive potential to manipulate the outcome of the process.

By changing the length of the carbon chain and the configuration of double bonds, this reaction can be directed into a manifold of various constitutions and configurations in the realm of polycyclic compounds.

It has to be remembered again that owing to their highly organized transition states these cycloadditions are completely stereospecific, which means that the configuration of the reaction products is determined by the configuration of the double bonds involved.

As both double bond configurations are easily available, one can switch from one diastereomer to the other just by employing the corresponding starting material, as was nicely shown with maleic and fumaric acid [66].
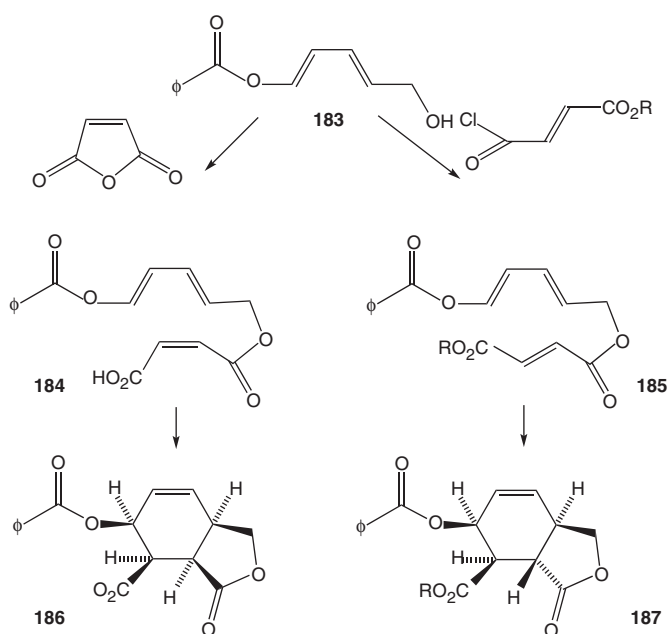
The trans-configuration of lactone **187** proves that in this case this particular carbonyl group occupies the exo-position in the transition state. This kind of violation of the endo-rule is, however, not unusual in intramolecular cycloadditions.

This observation indicates very clearly that if strain is imposed on the transition state conformation, the molecule may deviate into another arrangement, thus opening the path to an alternate configuration for the cycloaddition product.

This grants options for directed selectivity by manipulating transition state conformations with the help of space-demanding control groups. These will enlarge the rotation barriers favoring just one reaction path.

Again the trialkylsilyl group served very well in this endeavor.

While diester **188a** on heating gives rise to a mixture of stereoisomers, the corresponding vinylsilane **188b** provided the single product **189** in 85% yield [67].
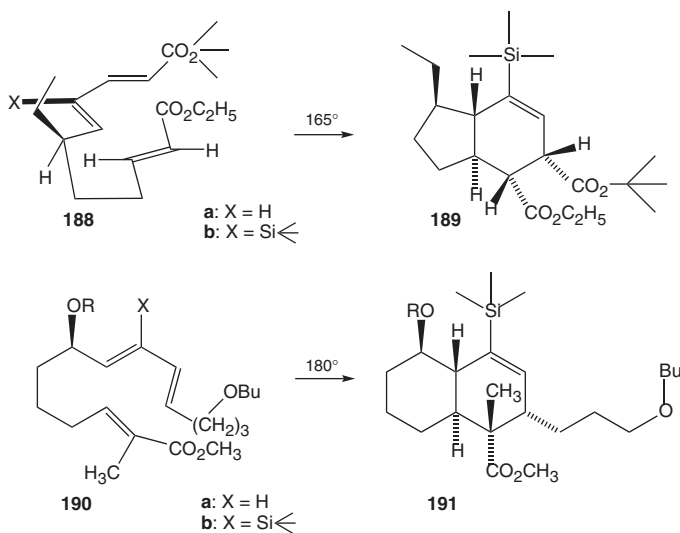
Models indicate very clearly that other transition state conformations but **188** are destabilized by steric interactions with substituent X. **188** only does not suffer from steric hindrance.

For the same reason, decalin **191** was the sole (89%) cycloaddition product from trimethylsilane diene **190b**.

It is very important for the application of this principle that the control element can be easily introduced into the carbon framework and that smooth removal would be guaranteed.

As even these very few examples show, intermolecular and intramolecular $2\pi\text{-}4\pi$ cycloadditions are the reactions of choice for stereoselective preparation of cyclic and polycyclic compounds.

It should, however, not be forgotten that next to the construction of carbon–carbon bonds these cyloadditions can also be used for the directed functionalization of selected carbon atoms.

With the nitroso group operating as a dienophile for instance, a wide range of precursors for α-amino alcohols becomes easily available.

With simple dienes there is a regioselectivity problem, but electronic orientation or intramolecularization is again very helpful as examples **192** and **193** indicate respectively [68].
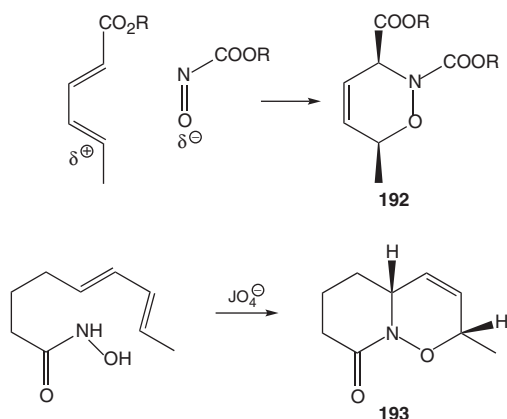
Since the N−O bond can easily be broken by reduction, **192** presents itself as a precursor for substituted α-amino acids, while **193** can lead to substituted δ-lactams [69].

A very similar development took place with 1,3-dipolar cycloadditions.

As with Diels−Alder reaction, the early phase of this cycloaddition was completely dominated by the intermolecular construction of heterocycles (see **194** and **195**).
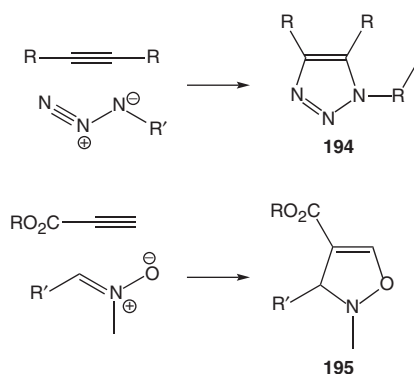
It took quite a few years for the first examples of the intramolecular version to be published and it right away proved also to be an excellent tool for the directed introduction of functionality into alicyclic as well as heterocyclic frameworks [70].

Ring formation accompanied by stereoselective functionalization takes place in a very simple way with pyrrole aldehyde **196** [71], while in the case of the

homoallylic alcohol **198** a straight carbon chain is stereoselectively transformed into the trisubstituted pyrrolidine derivative **199** [72].
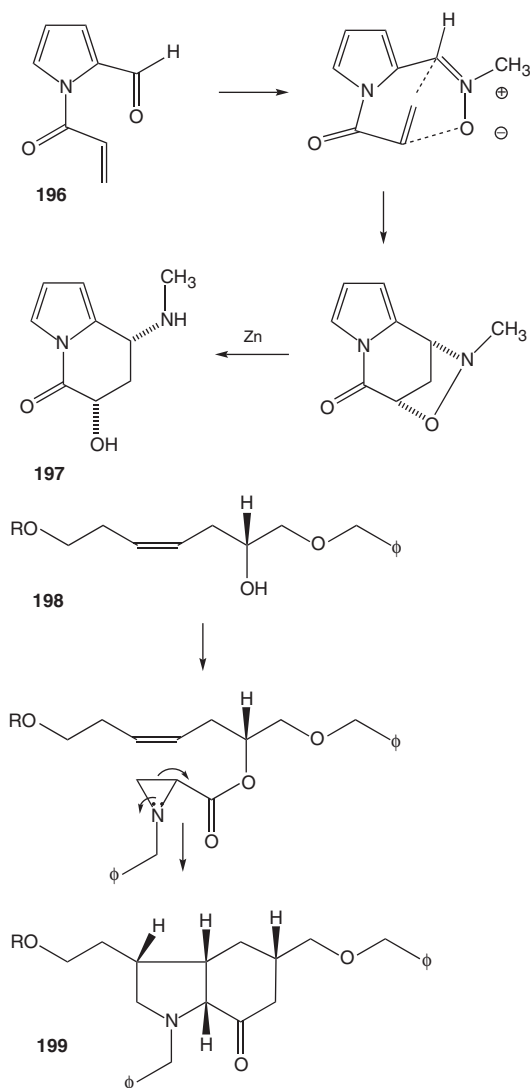
The vinyl-nitro compound **200** serves as an excellent example to demonstrate the remarkable flexibility and the very high synthetic potential for forming heterocyclic compounds in a highly predictable manner [73].

It needs only a little bit of imagination to see how the carbon chains as well as the double bond determine the structure of the heterocyclic compound.

One should not overlook the great advantage of generating the 1,3-dipole en route to the cycloaddition step.
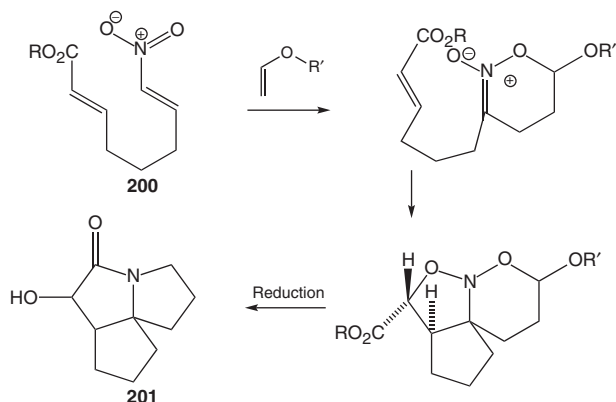
Another quite unique way of this *in situ* formation of the dipole was described in connection with the total synthesis of the spiro-piperidine system of histrionicotoxin [74].
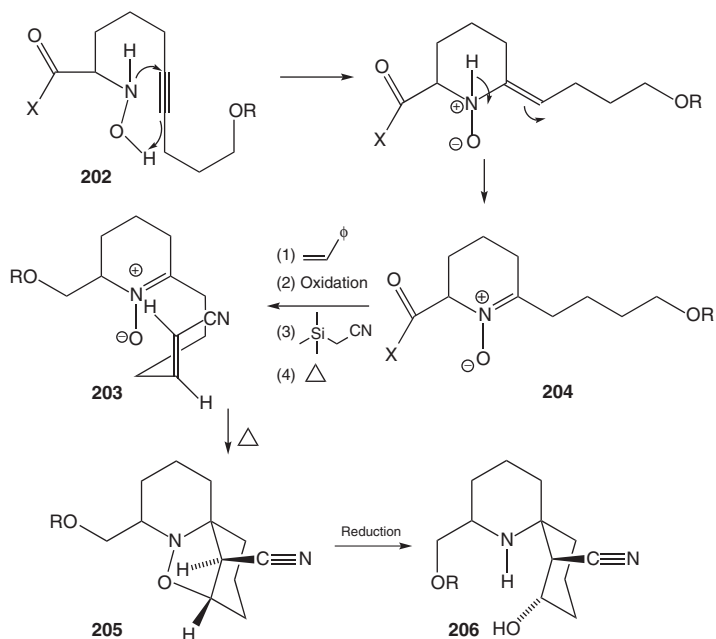
Again, the synthesis starts with a straight carbon chain, and the triple bond that had served very well for the construction of this entity combines next with

the hydroxylamine group to give rise to the desired 1,3-dipole. After protection with styrene the molecule is prepared for intramolecular 1,3-cycloaddition, which finally places the substituents into the correct configuration as mentioned before; reduction can easily split the N−O bond, leading to the desired spiro-piperidine **206**.

In all the examples given in the field of cycloadditions, we have seen the stereospecific transformation of sp$_2$-centers into well-defined sp$_3$-carbon atoms.

Things become even more exciting with 3,3-sigmatropic rearrangements in which hybridization change of four carbon atoms [75] is observed (see **207**).

207
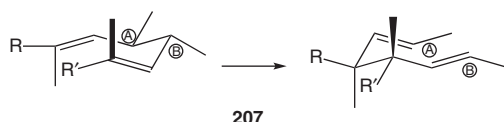
Typical examples are the Cope- and the hetero-Cope rearrangements. In the second group, the well-known Claisen rearrangement is probably the most popular version of these 3,3-sigmatropic reactions.

While in the early days of these reactions chemists were mainly interested in the constitutions that could be reached this way (aromatic substitution), it was later the directed and predictable formation of sp$_2$- as well as sp$_3$-centers that stimulated interest in this chemistry.

For the synthetic chemist, it means that along with the making and the breaking of one bond, four centers of the starting material change their hybridization status.

Bearing in mind that the formation of the new carbon−carbon bond is an intramolecular reaction, one is not surprised to notice again that even severe steric hindrance can be overcome here, leading to the highly selective generation of quarternary carbon atoms.

No wonder that nature uses a catalyzed version of this rearrangement in the biosynthesis of prephenic acid, which also documents the very important aspect of charge acceleration for 3,3-sigmatropic reactions [76].

208   **a**: X = O   **b**: X = N   **209**
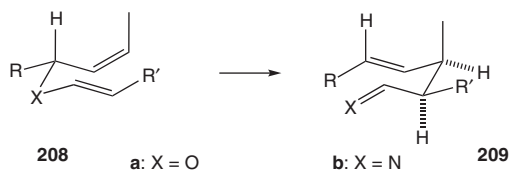
As far as directed selectivity is concerned, the Claisen (**208a**) and the aza-Claisen rearrangement (**208b**) are of particular importance, since in a very straightforward manner easily accessible C−O or C−N bond configurations are translated into the configuration of two sp$_3$-carbon atoms (see **209**).

A very useful and broadly applicable rearrangement leads to optically active, unsaturated cyclic compounds such as **211**, or the corresponding cyclohexenes, from enantiomerically pure allylic alcohols (e.g., **210**) [77].
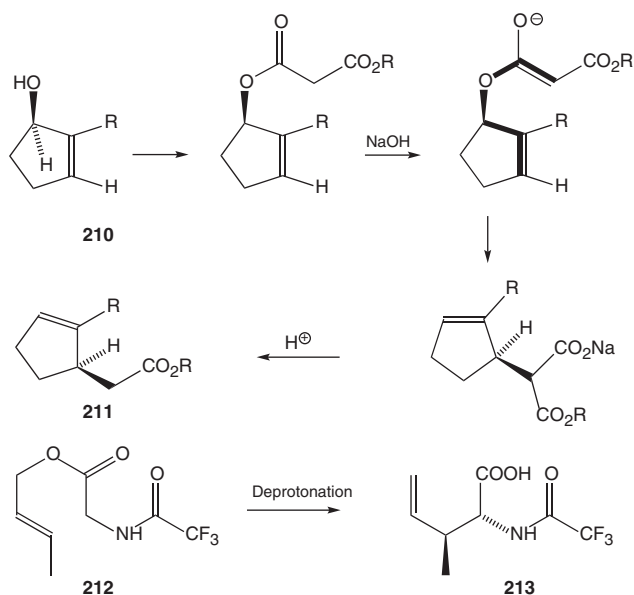
If instead of malonic acid the ester with a lysine derivative is employed in the rearrangement (see **212**), a series of unusual α-amino acids can be prepared stereoselectively (**213**) [78].
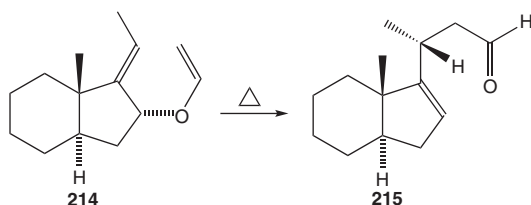
In the same manner, the configuration of the side chain of hydrindane **215** is established in a 3,3-sigmatropic rearrangement [79].

One great advantage of all the reactions cited above is certainly the fact that most of the allylic alcohols needed here as starting materials are easily available in optically pure form with chemical as well as enzymatic methods.

The steric course of the rearrangement can also be directed by an optically active ketene acetal, such as the borate **216**, leading to the enantiomerically enriched acids **217** [80].
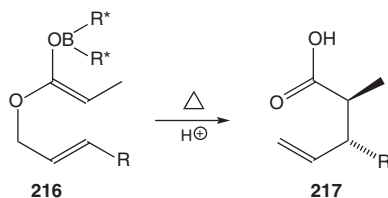
To cite at least one example of an aza-Claisen process we choose the ketene adduct **218**, which combines important mechanistic aspects with remarkable preparative value.
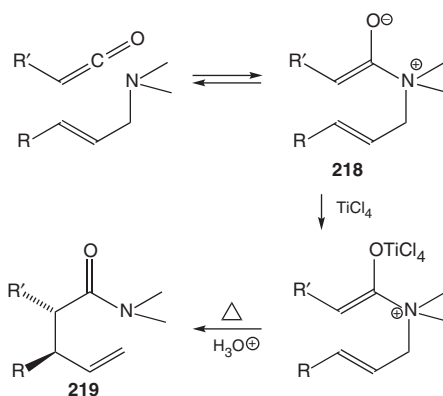
The assumption of complex **218** goes back to the very early years of enantioselective chemistry, with the aim of interpreting the catalytic action of tertiary amines in ketene additions [81].

It was quite clear at that time that a very fast equilibrium must be involved. To shift this in the desired direction an oxophilic Lewis acid (e.g., TiCl$_4$), as expected, served very well and additionally stabilized the amide group obtained in the process (see **219**) [82].

With these Claisen-type rearrangements we again have to restrict ourselves to just a few hopefully simple examples just to demonstrate the options to manipulate the steric outcome of the reaction.

Those readers who want a broad overview on the Claisen 3,3-sigmatropic rearrangements should consult the corresponding review articles or books on sigmatropic chemistry [75, 83].

The same holds for the Cope rearrangement that represents the all-carbon case of **207**.

As dienes **220** and **222** demonstrate, the configurations of the two double bonds again determine the configuration at the sp$_3$-centers. However, it has to be emphasized here that for the Cope rearrangement the phenomenon of charge acceleration turns out to be of particular importance [84].

220 **221**

222 **223**

Examples **224** [85] and **227** [86] prove that by applying this process quite complicated and configurationally demanding compounds can be prepared from easy-to-make starting materials.

224

225 **226**

227 **228**

However, there are two additional lessons to be learned from these rearrangements. First, the sigmatropic reaction starting from **224** leads regioselectively to enolate **226**, which *in situ* triggers a Dieckmann reaction to form the 1,3-diketone **225**.

This means that the charge accelerated rearrangement does not only stereoselectively give rise to two sp_3-centers, but additionally amounts to regioselective enolate formation. In other words, there is no need to take any precautions as far as selectivity is concerned; the process directs itself.

From the second example, we take the message that the educt–product relationship is for the inexperienced by no means easy to recognize at first glance (see **227**). Clearly, the recommendation here is to work backward, starting with the reaction product. Only this way can one safely make all the decisions on how to direct the molecule to the desired configuration.

For the final option to translate double bonds into sp$_3$-centers we decided on the Michael addition, since here the problem of equilibration is particularly vexing.

Obviously, the problem will always be to counteract the retro-process, which will blur the separation line between kinetic and thermodynamic control.

The way the countercation and its ability to fix the negative charge direct this process was nicely demonstrated with β-ketoester **229** [87].
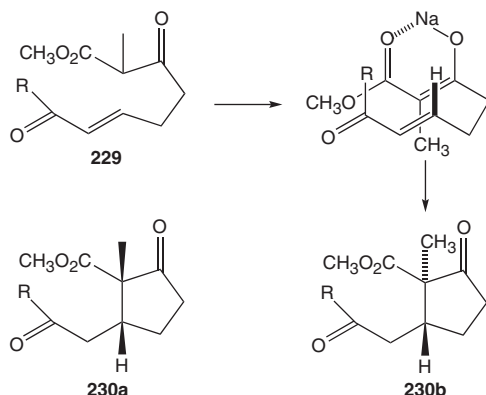
In contrast to potassium *tert*-butylate, which, owing to dissociation, gives rise to trans–cis mixtures of **230**, the highly chelating sodium cation leads to the trans-product **230b** exclusively.
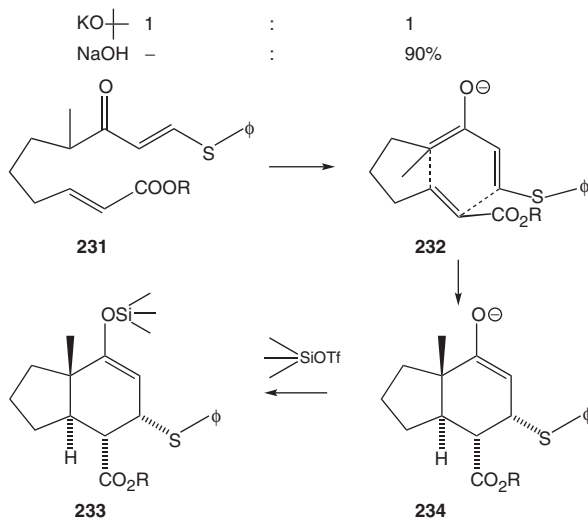
A very obvious way to quench the negative charge is treatment with an oxophilic electrophile, such as by silylation.

This was shown with ketoester **231**. The reaction sequence starting with enolate **232** can be interpreted either as a double Michael addition or as an intramolecular Diels–Alder cycloaddition (see **232**).

Whatever one decides on, the final enolate **234** can be captured by silyltriflate, to arrive at the stable enolether **233** [88].

The most simple way to get rid of the negative charge is to eliminate it as a leaving group. The fast elimination blocks any possible retro-processes, thus establishing, the anti−syn configuration for **236** [89].
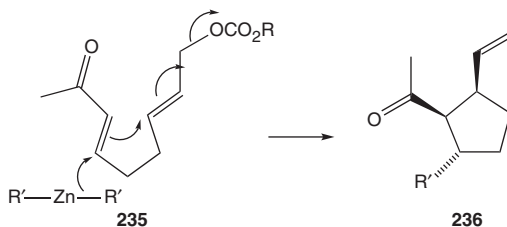
One should not overlook here that the double bond generated this way additionally holds a number of options to introduce functionality, and also for chain elongation in the metathesis or hydroformylation reaction.

In the final part of this chapter, we shift to the synthetically very important carbonyl group, which, owing to the polarization of the π-system, can easily undergo nucleophilic additions including reduction. The steric course of these reductions depends strongly on detailed reaction conditions.
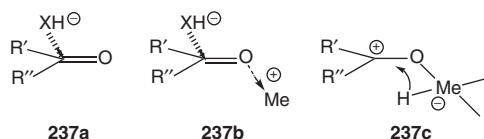
It may be sheer nucleophilicity of the hydride donor, with the corresponding countercation coming into the game at a very late stage only (**237a**).

If the countercation or any other electrophilic entity, such as hydrogen bonding, assists in the approach of the reducing agent, we would deal with **237b**, working in a highly synchronized manner in the ideal case. At the other end of the scale, the interaction would start with the electrophilic attack of an oxophilic hydride donor at the oxygen atom of the carbonyl group. This would generate positive charge at the corresponding carbon atom until internal hydride jump ends the game (**237c**).

This has very clear-cut consequences on the steric outcome of the reduction.
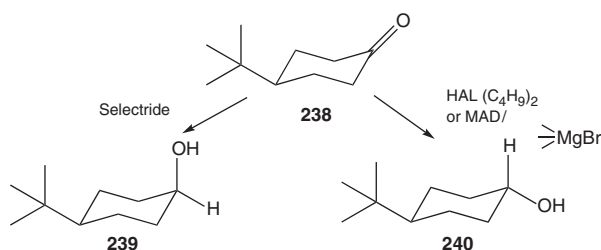
While the powerful nucleophile attacks in the equatorial trajectory, leading to the axial alcohol **239**, the interaction with a Lewis acid will orientate the bulky ate complex into the pseudoequatorial position, leading to the equatorial alcohol **240** after hydride transfer (see **237c**) [90].

This simple technique to direct the reduction with the help of solvents, reducing agents, and Lewis acids will of course quickly come to its limits, when the realm of rigid cyclic or polycyclic ketones is left.

With acyclic compounds, help from neighboring, conformation-stabilizing functional groups is needed. These certainly work particularly well, whenever rigidization [91] by complex formation is possible. Quite remarkable results are obtained with zinc borohydride.

Owing to complex formation, α-hydroxyketones give rise to the anti-diols **241** [92] while the syn-diols **242** result from the reduction of β-hydroxyketones, with good selectivity [93].
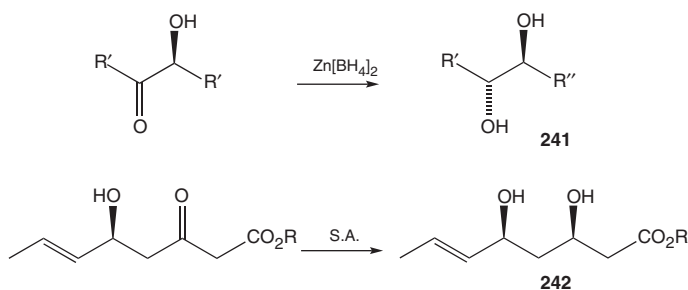
The directing power of the zinc cation becomes clearly visible in comparison to a selectride reduction, as was demonstrated with ketone **243** [94].
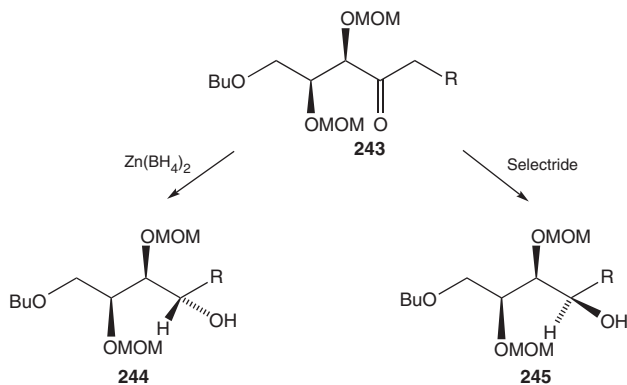
Bearing all this in mind, one is not surprised to notice that even the simple addition of zinc chloride to a hydride reduction mixture strongly influences the steric course of the process (see **246**) [95].
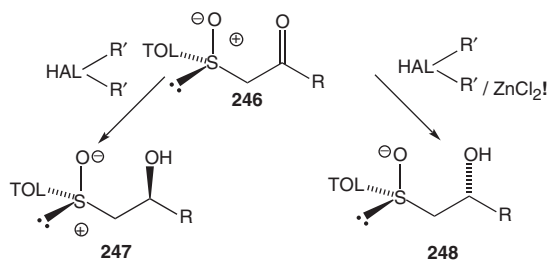
It should be noted here that the configurationally well-defined hydroxy groups in **247** and **248** together with their spatial surrounding may easily direct transformations of various functional groups in the side chain ''R.'' Since additionally the sulfoxide group may be reductively removed, ketones of type **246** present themselves as highly flexible building blocks in stereoselective synthesis. Beyond this, it should not be forgotten at this stage that the useful Pummerer reaction opens interesting pathways for the sulfoxide group too.

Very similar arguments will hold for the sulfur-containing β-ketoester **249**. In this case again, the complex-forming reducing agent calcium borohydride was used and led to the corresponding syn-product **250** [96].
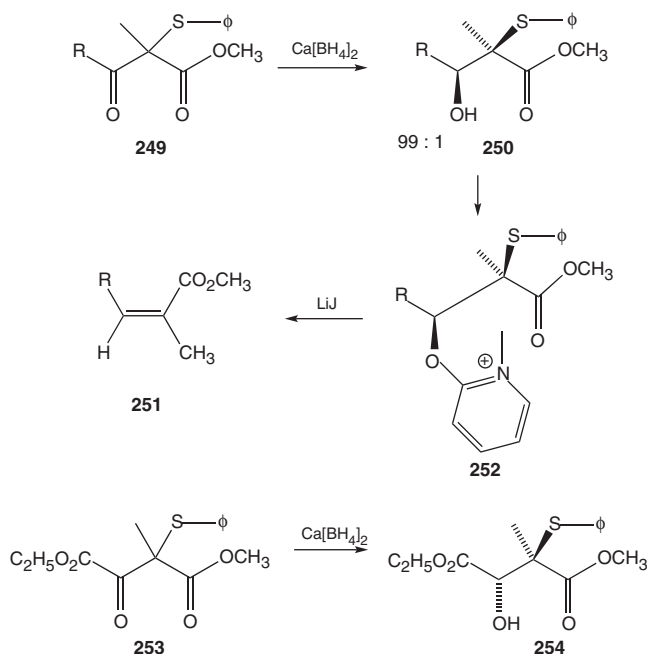
Interestingly, and not to be easily explained, complete reversal in product configuration was noticed with α-ketoester **253**.

In the syn-structure **250** the sulfur group was again not just simply reduced but was shown to be useful for the stereoselective synthesis of trisubstituted double bonds (see **251**).

The high oxophilicity of silicon was also employed in a highly selective fluoride-catalyzed reduction of ketones [97].

In a completely different strategy, a hydroxy group was either directly used as active volume to direct the reducing agent into the β-face of a carbonyl group or transformed into passive volume that shielded the β-face and forced the reducing agent into the α-orientation (see **258**) [98].
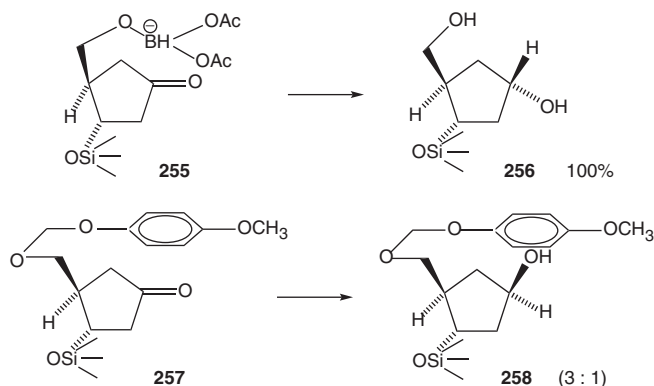
All the mechanistic considerations that have been found valid for the reductions will ''mutadis mutandis'' also hold for the nucleophilic additions of metallo-organic reagents to carbonyl groups as demonstrated with **259** and **260** [99].
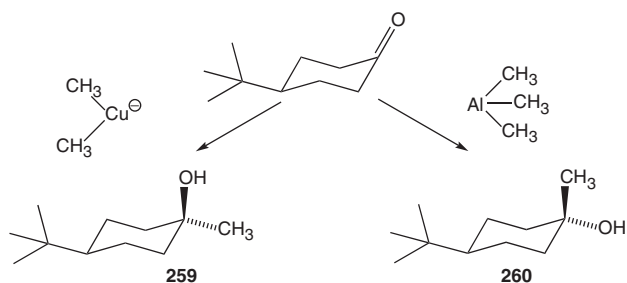
Comparable selectivities are achieved with acyclic carbonyl groups (see **261** and **262**) [100] and as it was noticed in connection with reductions, the formation of rigid complexes again has a strong influence on the steric course of nucleophilic attack.

| CH₃—Ti(O—◁)₃: | 7 | : | 93 |
| CH₃CuMgBr : | 96 | : | 4 |

Since the change of the reagent from a Lewis acid to just a strong nucleophile alters the steric course completely, we must not be surprised to notice that carbonyl additions can also be directed by the choice of the Lewis acid catalyst.

Additions with allene **263** prove this very clearly [101].

With boron trifluoride a high yield of the syn-compound **264** is obtained, while the tin-tetrachloride-catalyzed addition gives rise to the anti-product **265**.

Being aware of the fact that catalysts as well as reagents have a strong influence on the stereochemical result, it is very tempting to change the sequence of reactions to direct a stereoselective transformation.

This was exercised with ester **266**. The magnesium complex formed in the Grignard reaction was stereoselectively reduced with lithium borohydride while the aldehyde–aluminum complex formed in the low temperature DIBAL reduction is also stereoselectively attacked by the Grignard reagent [102].

This can be expected to work generally whenever an ester group has to be transformed into diols of either anti- or syn-configuration.

In the case at hand, the benzyl ether, which via complex formation directs the reaction, is however part of the molecule.

There are numerous examples, however, where such a group is deliberately introduced as a removable directing group [102]. Indeed, this technique can be applied in a great number of quite different reactions, such as the metalation and substitution of aromatic compounds, 1,4-addition and other cycloadditions, allylic substitution, and hydroformylation, just to cite a few important ones. This long list of transformations that could be manipulated with the help of removable directing groups indicates very clearly how strongly we tried to restrict ourselves to just the bare principle of influencing the steric course of reactions.

Apart from further reactions, there are additional reagents, different catalysts, and numerous other starting materials, which will respond to this kind of treatment.

1.4
Enatioselectivity

In the final part of this chapter, the focus is on the general methods to direct the configurational outcome of enantioselective reactions. This means we can leave out everything connected with auxiliaries. Here, the directing amounts just to the choice of the other enantiomer, and the same is true for large areas of homogeneous catalysis [103].

As far as heterogeneous catalysis goes, the chances to mechanistically completely understand and, as a consequence, be able to predict the configurational result are still quite limited.

This then leaves deficits for the directing of processes.

Since face selectivity is the decisive challenge in transforming prochiral centers into configurationally well-defined chiral centers, it will be worthwhile to discuss the methods to achieve face selectivity.

As probably the most important and certainly very powerful approach, one has to mention substrate-directed reactions. There are various properties of a substrate that may influence the steric course of a reaction, and the simplest and obvious one is configuration [104].

The options can be most easily demonstrated with an angular substituted *trans*-decalin (see **269**).

The ring system represents a more or less flat board with a space-demanding angular substituent in the β-position.

269
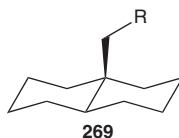
There is no doubt that any reagent approaching sp$_2$-centers in the ring system will attack in the α-orientation in a highly face-selective manner. This holds for carbonyl groups as well as double bonds and the most convincing proof for this statement is a series of stereoselective reactions of this type that have been described in the steroid field, where two angular methyl groups shield the β-side of a polycyclic molecule [105].

The situation changes completely if the substituent R in **269** represents a functional group. In that case, we deal with an active volume in this position, which could attract or even bind the reagent and thus completely reverse the steric course of the process.

The Diels–Alder adducts **270** with cyclic dienes represent another very reliable system. Since endo-adducts are generally formed, the molecule occupies a bowl-shaped conformation with a convex and a concave side.

270   **271**

272   **273**
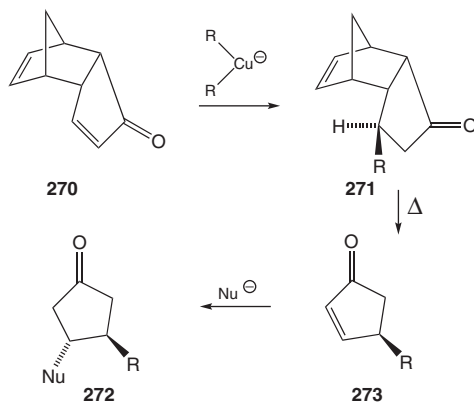
The convex side of these adducts is most easily attacked and conjugate additions therefore yield β-substituted ketones (see **271**), which can be split in a thermal retro-process to give rise to the β-substituted cyclopentenones **273** [106].

In a subsequent Michael addition, these – as described above – will certainly undergo configurational control and arrive at trans-disubstituted cyclopentanones **272**.

We operated exactly along these lines in an enantioselective synthesis of hydroazulenes starting from optically pure acetoxycylopentenone **274** [107].

A configurationally directed conjugate addition (α-attack) of butenolide **275** was followed by acetate elimination, and subsequent cuprate addition (β-attack) afforded the trans-disubstituted cyclopentanone **278**.
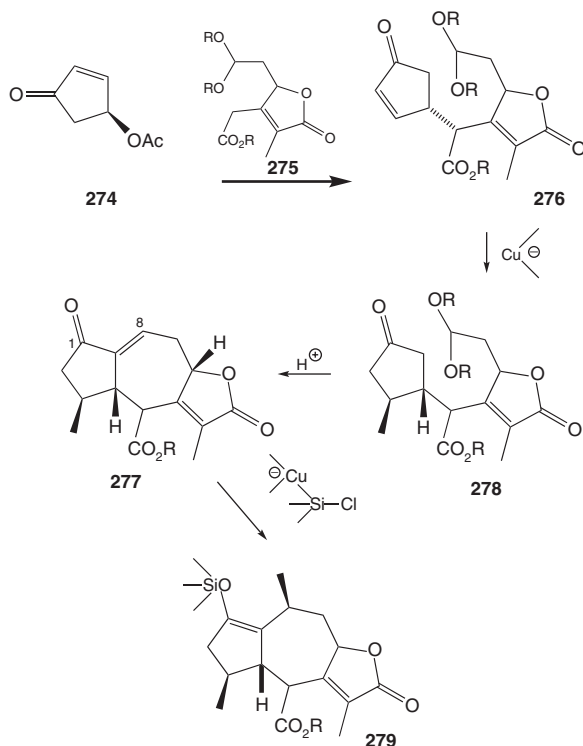
Aldolcyclization accompanied by elimination generated the unsaturated ketone **277**.

To reach the substitution pattern of the natural products in this series, the final challenge was the introduction of another β-methyl group at C_8.

At this stage, one really has to worry about the stereoselectivity of this addition; sufficient configurational assistance from any substituent neighboring the unsaturated ketone is highly improbable.

It was therefore very exciting to note that the trimethylchlorosilane-assisted cuprate addition provided a 98% yield of just one stereoisomer. Spectroscopic data proved this to be the β-isomer **279** and this assignment was confirmed by X-ray structure analysis at a later stage.

It is very hard to find convincing arguments for such clear-cut selectivity on the basis of configurational control.

If, however, the most probable conformation of the unsaturated ketone **277** is analyzed, the stereochemical result appears as an excellent example of conformational control.

While the α-face of the unsaturated ketone is shielded by the downward orientated butenolide moiety (see **280**), there is absolutely free access to the β-face of the double bond.

280
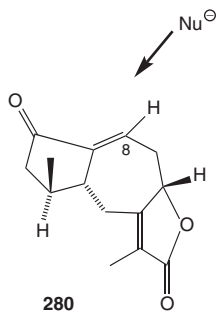
Considering this high degree of diastereoselectivity in a conformationally directed process, one is certainly well advised to take a closer look at this phenomenon.

With the aim of comparing this type of selectivity with other modes of stereo-chemical control, we shall discuss a few representative examples.

Conformational effects seem to play an important role in the prevailing β-reduction of the six-keto group in diketone **281** [108].

281   **282**
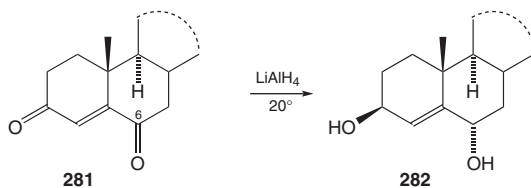
The β-hydride attack at the six-keto group is in sharp contrast to the ''normal'' β-shielding by the angular methyl group at C_9 and it indicates that configurational directing may easily be overrun by conformational control. A very similar behavior was noticed with the cyclopentadiene **283**, which is easily available as pure enantiomer [106].

283   **283′**   **284**
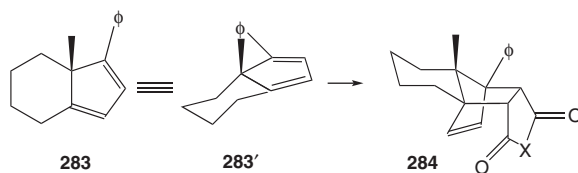
Exclusive β-addition took place in all cycloaddition reactions studied so far, clearly demonstrating that the concave–convex structure of this diene (see **283**) prohibits any approach from the α-side; again, the configurational effect of the angular methyl group is completely outrun in these reactions.

285   **286**
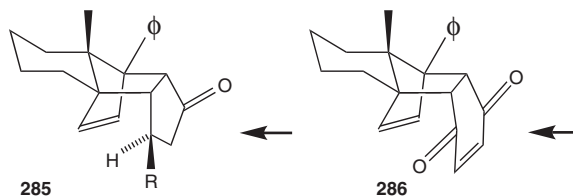
The shape of the Diels−Alder adducts **285** and **286** themselves reliably prohibits any α-addition, thus leading to very pure stereoisomers, which on heating generate enantiomerically pure retro-products [106].

The selectivities reported for these shape- or conformation-controlled reactions leave no doubt that it will often be worthwhile to consider the options on how to fix a molecule into a cleverly devised and hopefully rigid conformation, which will then guarantee the stereochemical result of subsequent reactions. It has to be underscored that to secure useful results here, the efforts to obtain conformationally fixed structures will have to be put on a very broad basis, including rigidization, by intermediate complex formation or by adsorption on selectively binding surfaces.

Under these circumstances, it could be sometimes advisable to wait with a certain critical step until the molecule reaches an advanced level in order to be able to fix the desired conformation.

As a highly interesting but unfortunately not yet very deeply exploited process, we consider electrostatic control. Whenever in a molecule a dipole generates centers of positive or negative charge one can expect interaction with the approaching charged reagents [109].

A nucleophile, for instance, will avoid electron-rich areas on its way to a prochiral carbon atom and vice versa.

288   **289**
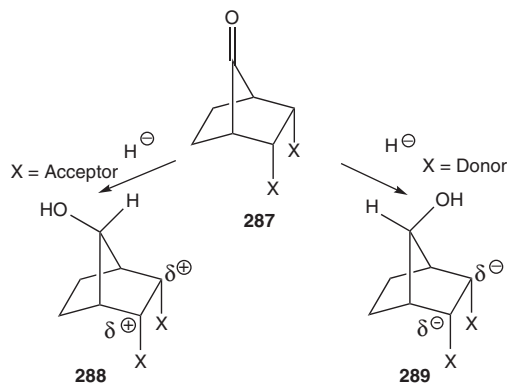
The face selectivity in hydride reductions of ketone **287** serves as an encouraging example in this field. The electronic nature of the substituents obviously influences the Dunitz-trajectory of the approaching hydride equivalent.

In the case of acceptors, the nucleophile attacks preferentially from the side of electron deficit. This and similar experiments [109] prove the existence of the effect,

but clearly this field needs a deeper analysis, demonstrating the choice of dipoles, the influence of solvents and reagents, and the importance of rigidity.

How much conformational freedom will be tolerated and what are the limits of selectivity?

Needless to say that the nature and the structure of the reagents also have to be considered. As demonstrated above, reagent control is of general importance; many nicely decorated reagents have been prepared and they could be of particular value in electrostatic control.

All the different types of approach control and of manipulating chiral centers are combined in synthetic endeavors, aiming either at one special enantiomer from a racemic mixture (enantioconvergence) or at both pure enantiomers, starting from one enantiomerically pure compound (enantiodivergence).

Both procedures have their special merits in the total synthesis of natural products or of chiral biologically active compounds. A very simple and straightforward example of enantioconvergency was reported from the cyclopentenone field.
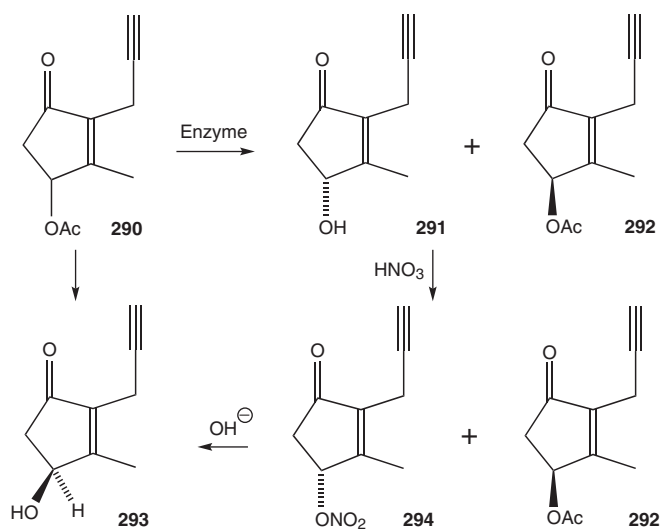
The process starts with an enantioselective enzymatic ester cleavage that converts only the α-acetate into the alcohol **291**, which without separation of the two components **291** and **292** is transformed into nitrate **294**. In the final step, treatment with alkali leads to an invertive S_N2-substitution with the nitrate and a simple ester hydrolysis with acetate **292** [110].

As a result, both components of the racemic mixture **290** converge at the enantiomerically pure alcohol **293**.

Another impressively simple and efficient procedure resulted from a very thorough investigation of the phosphine-catalyzed S_N'-substitution at the racemic mixture of allylether **293** [111].

In an enantioconvergent transformation the diphosphine **296** guided the borocuprate substitution into the anti-S_N' direction with the enantiomer **293**,
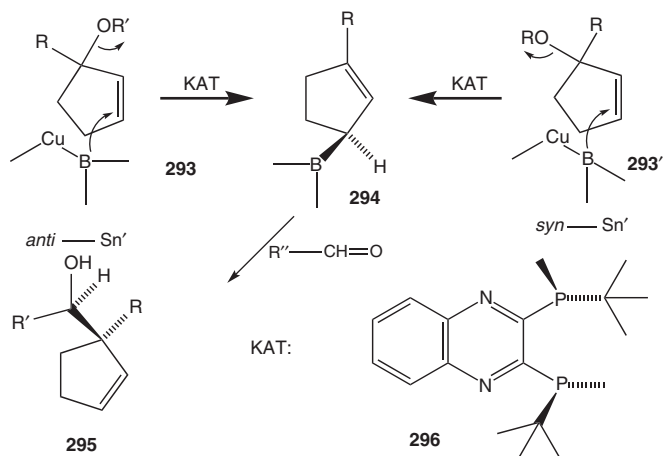
while **293′** proceeded as a syn-S_N′ substitution. The pure enantiomer **294** obtained this way finally underwent the well-established aldol-type reaction with aldehydes, leading to the cyclopentenes **295**.

The synthetic flexibility of this intermediate should not be underrated. The configurationally well-defined quarternary carbon atom is an important structural element and its applications are of course not restricted to cyclopentane derivatives. Since the double bond may be split in different ways, various ring-open polyfunctional molecules can easily be reached.
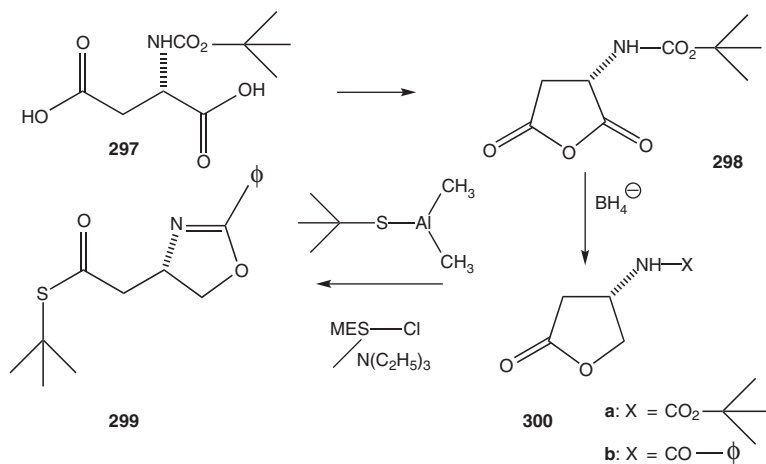
Other principal techniques for the preparation of one special enantiomer are kinetic resolution, dynamic kinetic resolution, and dynamic kinetic asymmetric transformations.

Stereocomplementary processes, which in a logical manner we will call enantiodivergent, are of particular importance if a very useful and highly flexible building

block is easily available as one enantiomer. In this case, it will be quite attractive to use any pseudosymmetric properties of this material to transform it into the other enantiomer.

A typical molecule that meets all the requirements is certainly aspartic acid **297**, which after formation of the anhydride **298** can be regioselectively reduced with borohydride to provide lactone **300**.

This reduction is the crucial step to elaborate the differential behavior of the two carboxy groups.

With the two lactones **300a** and **300b** at hand, this turns out to be a simple task as the straightforward formation of thioester **299** demonstrates.

This compound is useful in two ways: On the one hand, α-alkylation is expected to take place easily, while, on the other and selective reduction of the thioester to an aldehyde should not meet any difficulties.

For achieving high selectivity in the α-alkylation in the presence of a heteroatom, use was made of chelation control versus stereoelectronic control [112].
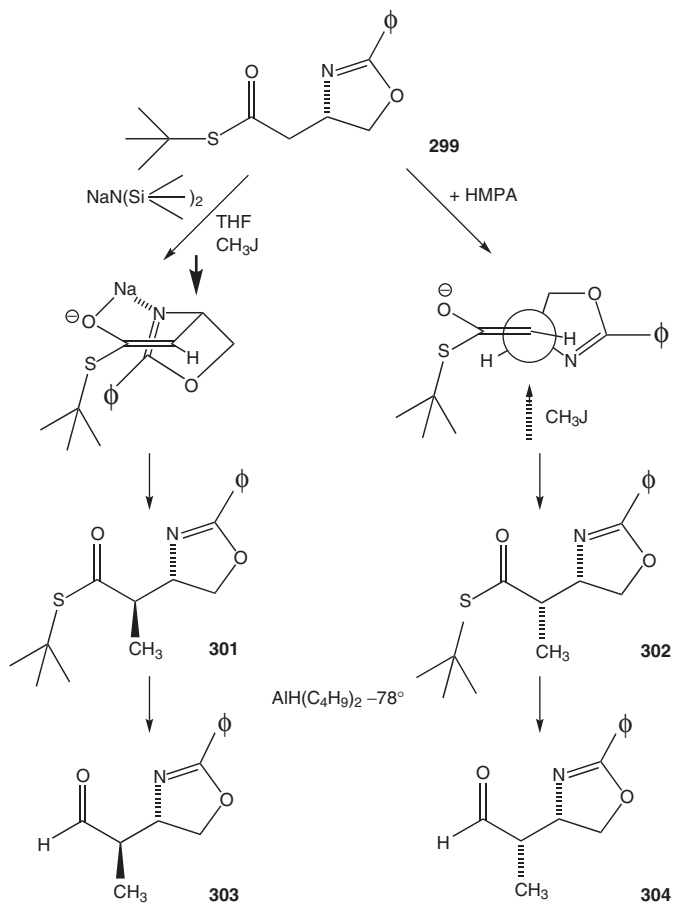
Deprotonation with sodium hexamethyldisilazane in tetrahydrofurane followed by treatment with methyliodide yielded the anti-compound **301** in a 95 : 5 ratio, while the addition of hexamethylphosphoramide (HMPA) to the above enolate broke the chelation and led to syn-compound **302** (ratio : 90 : 10) in the subsequent alkylation.

As predicted, a clean low temperature DIBAH-reduction was observed, which provided the aldehydes **303** and **304** in high yield.

These aldehydes underwent stereoselective nucleophilic additions without any configurational losses at the α-position.

The case studied in detail was the syn-selective addition of an allylic anion to aldehyde **304**.
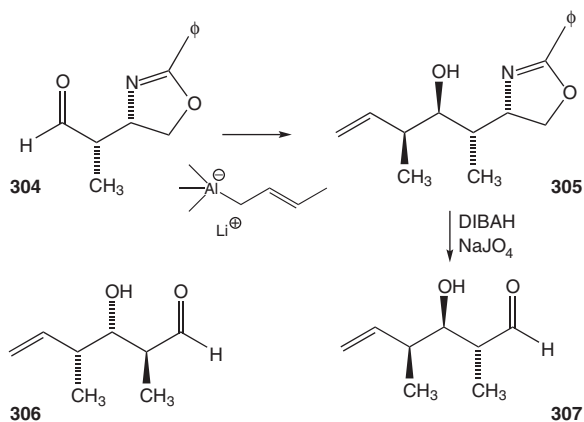
Unfortunately, there was only modest diastereoselectivity in this process, but the aldehyde **307** obtained after DIBAH-reduction and periodate cleavage did not contain any of the centers of chirality of aspartic acid any more.

As the complementary aldehyde **306** can be prepared in the same way from aldehyde **303** the whole transformation constitutes an enantiodivergent sequence.

Also in the second example was an advanced enantiomerically pure intermediate employed for conversion into antipodal compounds.

In this case, the well-established lactone **308** served as starting material for an enantiodivergent route to both enantiomers of indolizidine-diol **309** [113].

Amine opening of lactone **308** generated hydroxyamide **310**, which was chosen as the diverting point of the synthesis. The first series started with a Parikh oxidation of the primary alcohol. The resulting aldehyde ring closed to a hemi-aza-acetale, which after acetylation on treatment with boron trifluoride suffered elimination to the iminium-intermediate **311**. This cyclized stereoselectively from the convex side of the bicyclic intermediate (see **311**) to afford an unsaturated lactam. Standard operations transformed it into indolizidine diol **309**.
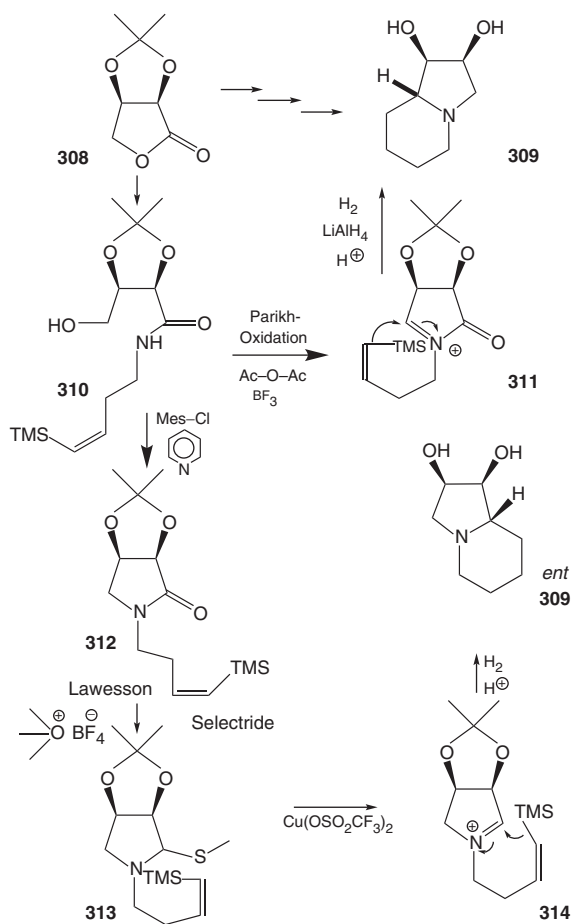
For the second enantiomer, hydroxyamide **310** was cyclized via the corresponding mesylate to lactam **312**. Lawesson's reagent afforded the corresponding thiolactam, which after alkylation and selectride-reduction led to the cyclic thia-aza-acetale **313**. Elimination followed by cyclization (see **314**) gave rise to an unsaturated indolizidine, which again with simple standard operations was transformed into the enantiomer of **309**.

The decisive aspect in this plan is to direct the regioselectivity of an iminium salt cyclization.

Such a manipulation of cyclization reactions via bond rotation was also the key operation in an enantiodivergent synthesis of vinca alkaloids.

In this case, the enantiomerically pure diverting molecule was not obtained from a natural product but was selected as a synthetically easy to prepare, optically pure advanced intermediate (see **315**).

This polycyclic lactam served as a common starting material for the enantiodivergent route to both enantiomers of eburnamonine and vincamine [114].
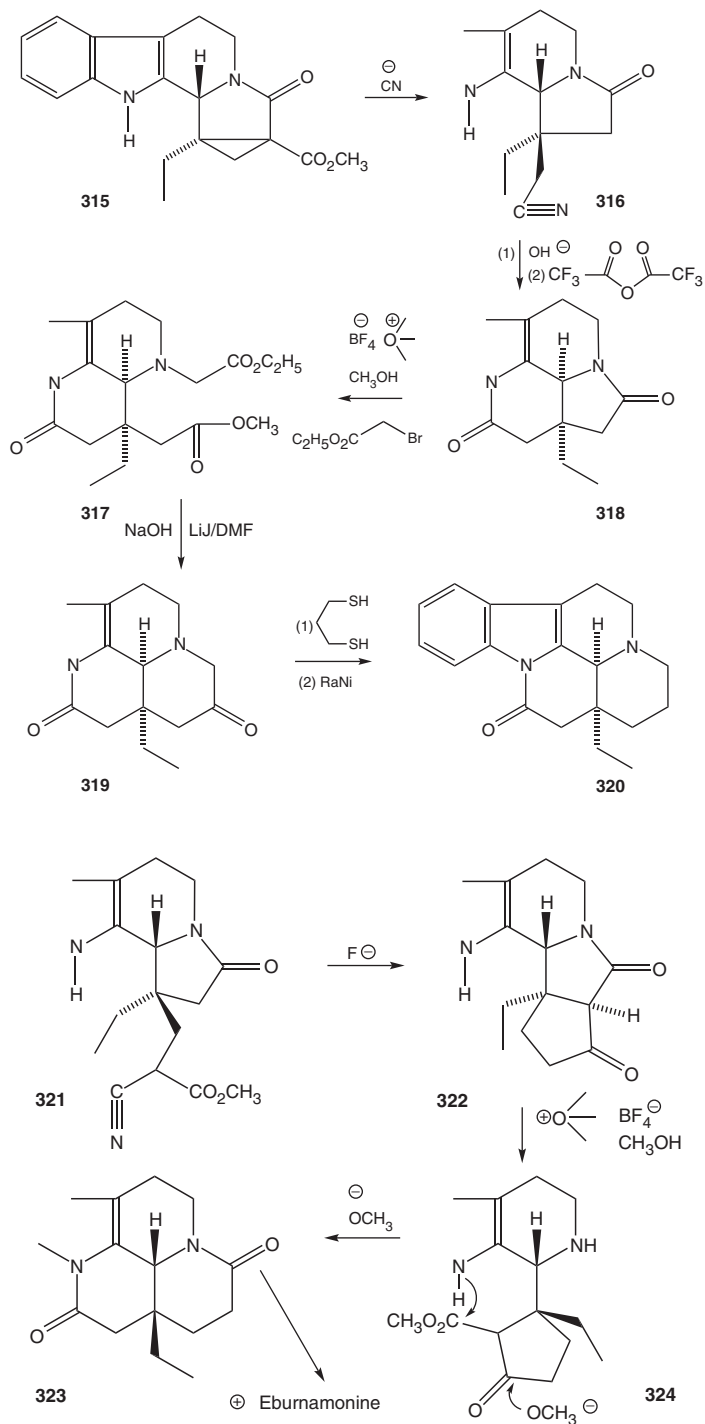
For (−)-eburnamonine **320** the cyclopropane ring of **315** was opened with potassium cyanide, the nitrile hydrolyzed, and the corresponding acid cyclized to acylindole **318**. It should not be overlooked here that the strong acid used in this process triggered the epimerization at the ring junction to the thermodynamically more stable cis-configuration. Ring opening of the γ-lactam and alkylation with bromoacetate led to diester **317**, which after Diekmann cyclization gave rise to oxo-eburnamonine **319**. Standard thioketale reduction converted this ketone into (−)-eburnamonine **320**.

For the route to (+)-eburnamonine, the cyclopropane ring was opened with cyanoacetate and the resulting lactam ester **321** was transformed into ketolactam **322** in a fluoride-catalyzed Diekmann cyclization.

The strained δ-lactam was opened smoothly to yield β-ketoester **324**, which on treatment with sodium methylate provided lactam **323**. A highly selective Borch reduction finally led to (+)-eburnamonine. Olefination of both enantiomers followed by allylic bromination and oxidation eventlessly afforded apovincamine, which had been converted into vincamine already.

While enantioconvergent as well as divergent sequences at any rate need chiral starting materials, the very useful and highly efficient differentiation of enantiotopic groups asks only for prochiral compounds, as for instance **325**. To arrive at pure enantiomers, one of the two structurally identical side chains of the starting material **325** has to be attacked enantioselectively, as is demonstrated with the Sharpless oxidation, which in this case leads to epoxide **326** as the main reaction product [115].
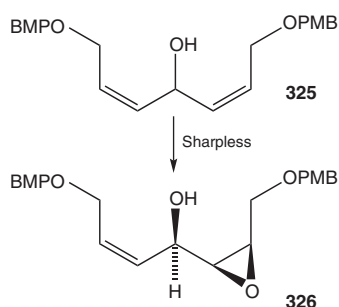
Quite a number of prochiral compounds have been investigated, and obvious advantages in this field are the good availability of most starting materials together with the fact that in some cases one can get very quickly to already quite advanced enantiopure intermediates [116].

One should also be aware of the fact that by properly choosing the reagent and the conditions, the process can be directed into one or the other absolute configuration.

This is reason enough to look very closely for every type of hidden symmetry in synthetic targets.

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