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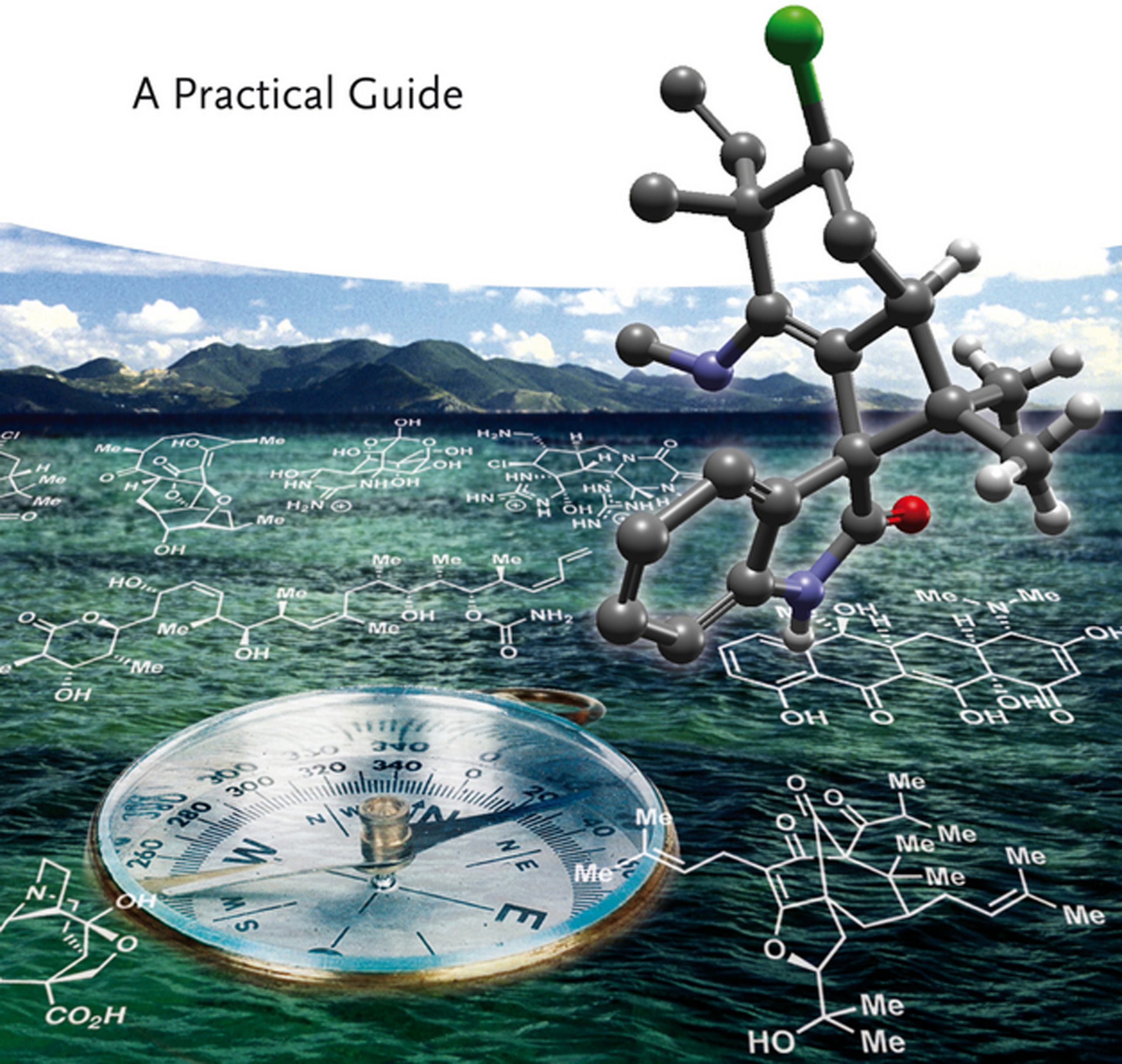
Tanja Gaich, Ekkehard Winterfeldt

Directed Selectivity in Organic Synthesis

A Practical Guide



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A Practical Guide

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Preface

Whenever the future goals of chemistry, and particularly synthetic chemistry or chemical production, are being discussed, the term sustainability will certainly play a major role in all arguments.

Although quite a bundle of aspects contribute to this important but still quite distant aim, selectivity is, doubtless, the most obvious and most important challenge in the field of synthetic chemistry.

Only with very high, reliable, and easy-to-apply and easy-to-manipulate selectivity will we ever succeed in gaining a high degree of efficiency and flexibility, which is ''Conditio Sine Qua Non'' to achieve sustainability.

In accordance with this, research in synthetic chemistry has concentrated very successfully in the last few decades on all aspects of selectivity – on highly selective reagents and catalysts as well as on various techniques – to manipulate the structure and the conformation of substrates and to prepare them for a reliably directed approach with all kinds of reaction partners.

This resulted in an impressive arsenal of highly selective reagents and catalysts and also disclosed a manifold of methods to achieve a high degree of chemoselectivity, regioselectivity, diastereoselectivity, and enantioselectivity.

All this has been compiled in review articles and books and can easily be obtained from data banks and synthesis programs.

We believe, therefore, that a general treatment of selectivity is by far beyond the frame of a publication such as this and that we would just duplicate all the information that can easily be collected from electronic data anyway. If it comes to directed selectivity, however, retrieval is not that easy.

We use the term directed selectivity in those cases where a set of transformations will lead to both or all possible sterically defined entities from one single starting material by simply changing reagents, reaction conditions, or the reaction sequence.

This approach is of particular value if the chosen starting material such as a chiral pool compound or an industrial bulk product is cheap or easily available, and if one is aiming at libraries of isomers or stereoisomers to study biological activities or other properties in a quite special group of compounds.

While aiming at directed selectivity, the search for relevant data can sometimes be quite frustrating, since the results of interest may be ''hidden'' in a by-product,

by-pass, or dead end of a synthetic investigation, in a passage of product optimization not mentioned in the abstract, in a mechanistic exercise, or in the optimization of a catalyst.

From various sources of this kind, we have collected numerous references over a period of 15–20 years as contributions to workshops for synthetic chemists.

The presentation starts with a compilation of the most important methods to manipulate the approach and the interaction of reagents with substrates.

This can be done either by changing the constitution or the conformation of the substrate, by varying the electronic nature or space demand of the reagent or catalyst, by changing the reaction mechanism, or by kinetic versus thermodynamic control.

In the second part, we present applications of these options in selective transformations of various synthetically useful functional groups that are generally present in a majority of starting materials or intermediates.

Whenever possible, quite simple and hopefully easy-to-generalize examples are selected; we have rarely included highly developed and very specialized structures, such as advanced intermediates from a total synthesis, since in these quite unique cases transfer to standard type molecules could create problems.

There will also be no general discussion of the reactions presented and no treatment of mechanistic proposals.

Since there is general agreement that in a synthetic venture one should make sure to introduce the correct configuration as soon as possible, reliable and highly flexible selective transformations are mandatory at this early stage of a synthetic enterprise.

Finally, it has to be stressed that we have not made any effort to reach complete coverage. In our selection of topics and examples, we were strongly guided by our own experiences in selective synthesis and our personal judgment on the most annoying difficulties in this field and on the possibilities to solve these problems.

We hope that this very personal selection of examples will properly describe the key challenge in directed selectivity, and we very much apologize to all colleagues who were not cited although they certainly have contributed substantially to this field too.

Leipzig
April 2013

Tanja Gaich
Ekkehard Winterfeldt

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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].

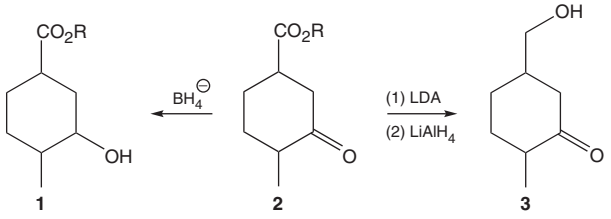
The majority of the problems here have been solved to date, mainly with the help of protecting groups.

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].

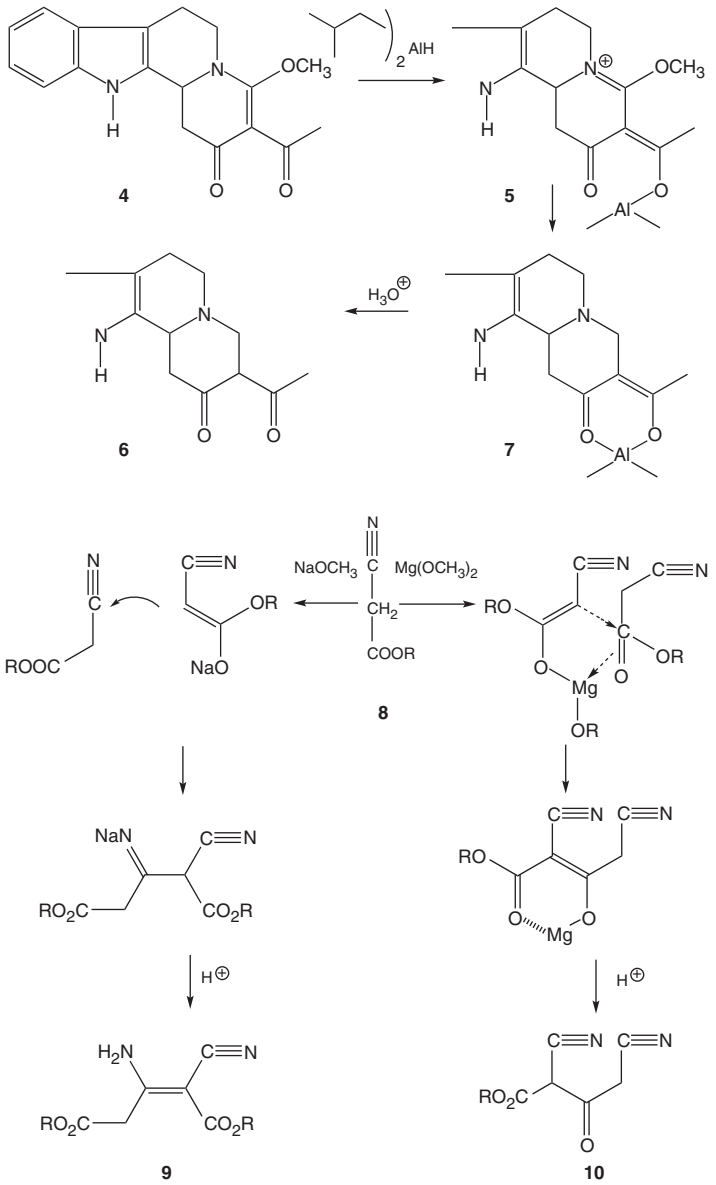


While the higher $\delta \oplus -$ character of the keto group in ketoester **2** allows for mild borohydride reduction to yield hydroxyester **1**, this may lead to preferential enolate formation followed by selective hydride reduction of the ester group to generate hydroxyketone **3**.

Directed Selectivity in Organic Synthesis: A Practical Guide, First Edition. Tanja Gaich and Ekkehard Winterfeldt.

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.

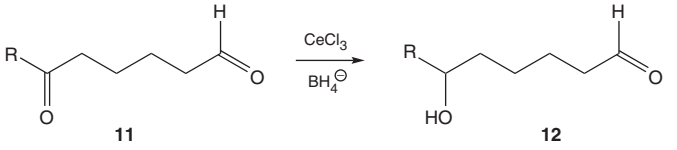
This is nicely demonstrated with the selective diisobutylaluminum hydride (DIBAL)-reduction of β-dicarbonyl compound **4** [6].



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].

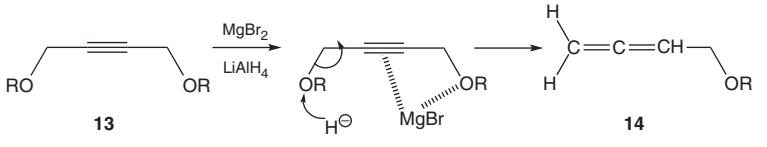
While deprotonation with sodium methoxide leads to nitrile attack forming enamine **9**, the employment of magnesium methoxide favors chelation of the Claisen intermediate, giving rise to the 1,3-dicarbonyl compound **10**.

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



11 **12**

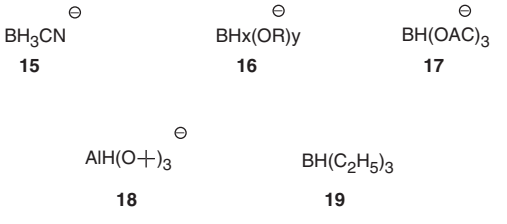
as well as in the allene formation from the butynediol derivatives **13** [9].



13 **14**

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**.



15 **16** **17**

18 **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.

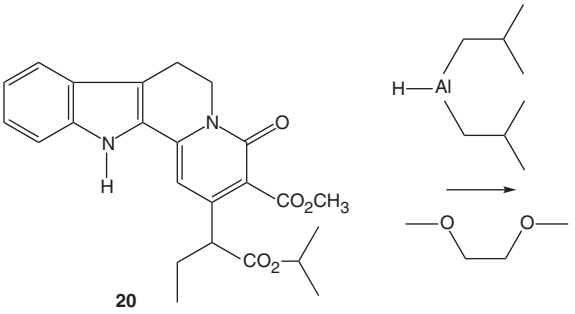
In both cases, only three hydride anions are displaced, leading in the case of complex **18** to not only a very mild but also a space-demanding reducing agent.

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.



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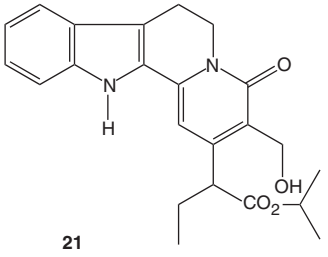

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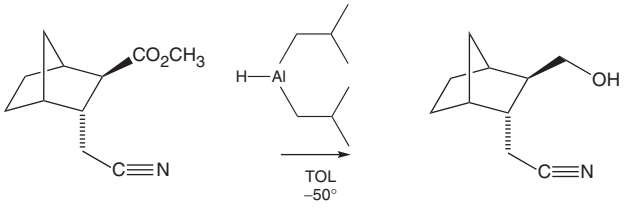


22 **23**

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].

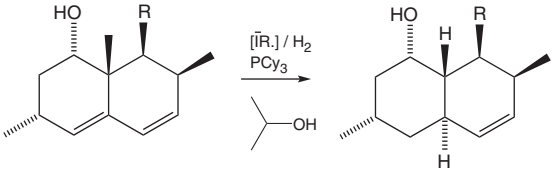
While the polarization of carbonyl groups and the Lewis base capacity of hydroxy groups offer a number of options for complexation, the situation is quite different with carbon–carbon double bonds.

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**

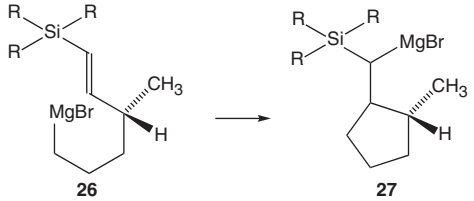
With example **24**, one should not overlook that the higher substituted double bond is hydrogenated and that the chemoselectivity of this process is accompanied by excellent diastereoselectivity. In addition, it turned out that the presence of isopropyl alcohol is mandatory for high chemoselectivity. 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.

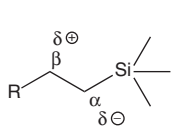
While alkyl substituted double bonds under normal conditions do not intervene in Grignard reactions, the trialkylsilane-substituted olefin **26** nicely forms a five-membered ring (**27**), generating a silicon–magnesium intermediate, which, representing an equivalent of a bis-anion, shows very high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



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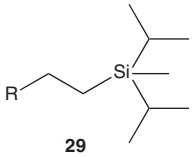

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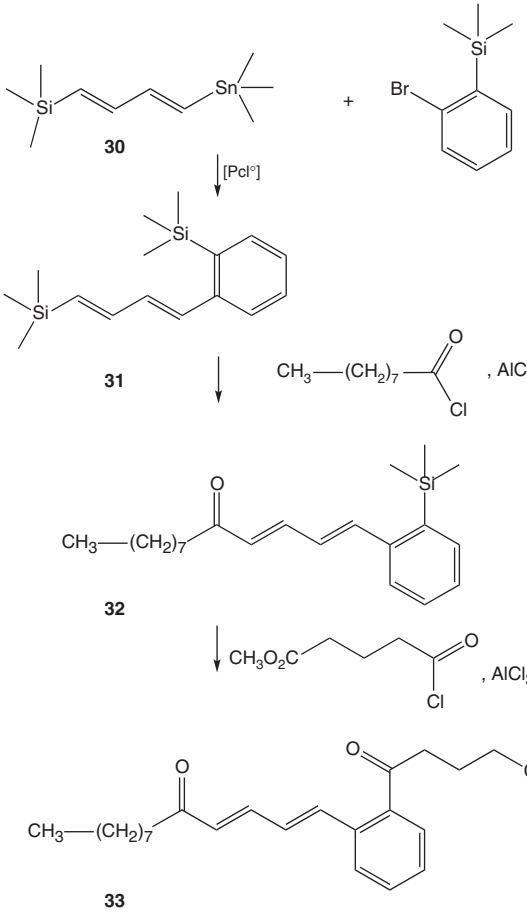


30

31

32

33

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.

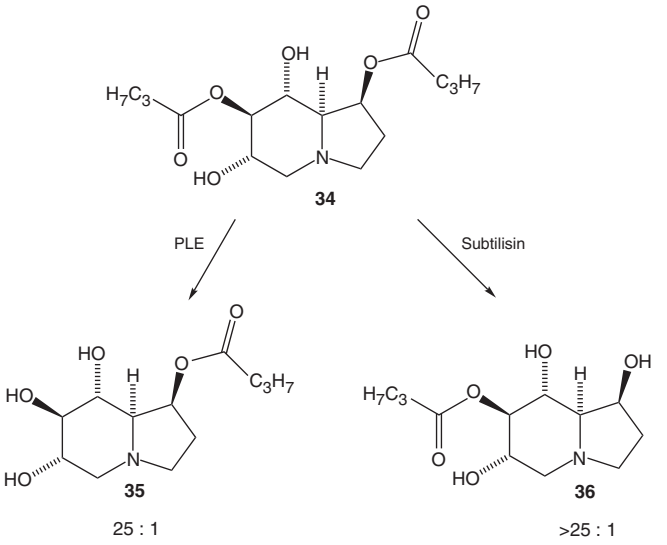
Chemoselectivity poses particularly demanding problems if the same functional group is present at different positions of a molecule as in sugars or glycosides.

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

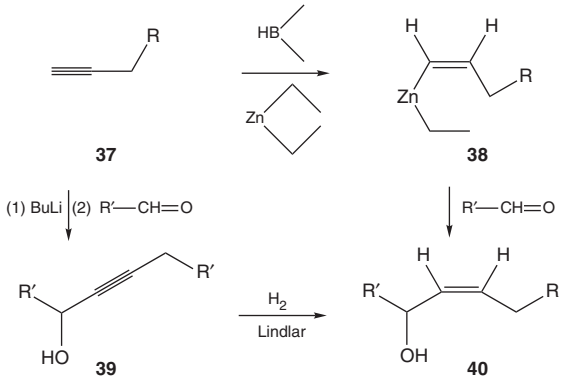
structures of ketones, as well as unsaturated carbonyl groups (1,2- vs 1,4-addition). In addition, there are a number of aromatic and heteroaromatic compounds posing various problems with regard to regioselective substitution.

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].



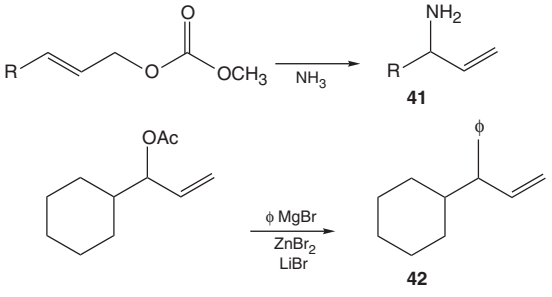
While acetylenes add directly to aldehydes and ketones to give rise to the propargylic systems **39**, which lend themselves for hydrogenation, the vinyl anions of type **38** lead directly to the corresponding allylic alcohols **40**.

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″.

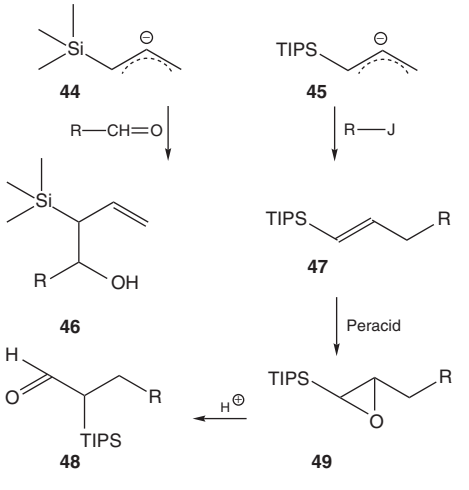
Under these circumstances, the electrophiles may not properly differentiate between α- and γ-positions.

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].

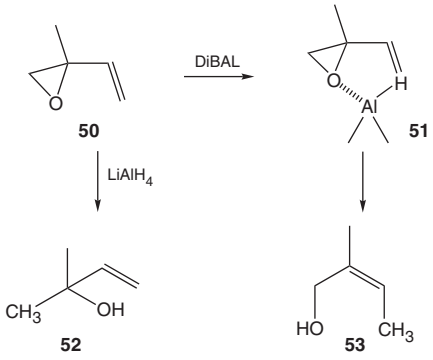


It is noteworthy that in the course of this sequence both carbon atoms of the double bond become substituted in a highly selective and predictable manner.

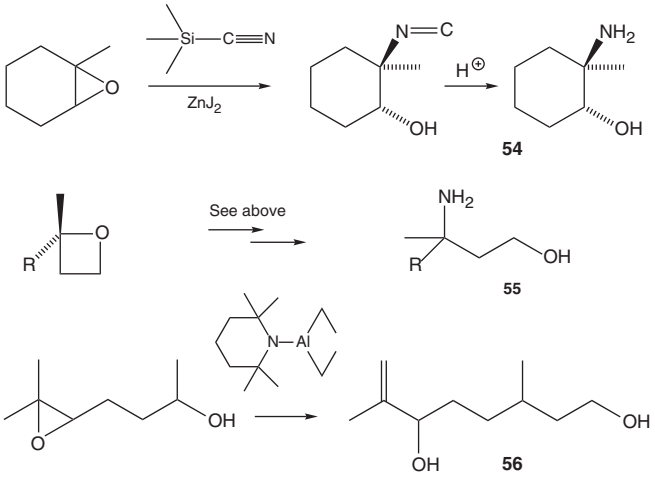
In this case, we deal with the electronic effect of a neighboring silicon substituent, but simply properly chosen reaction conditions can efficiently determine the outcome of epoxide ring openings too.

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.

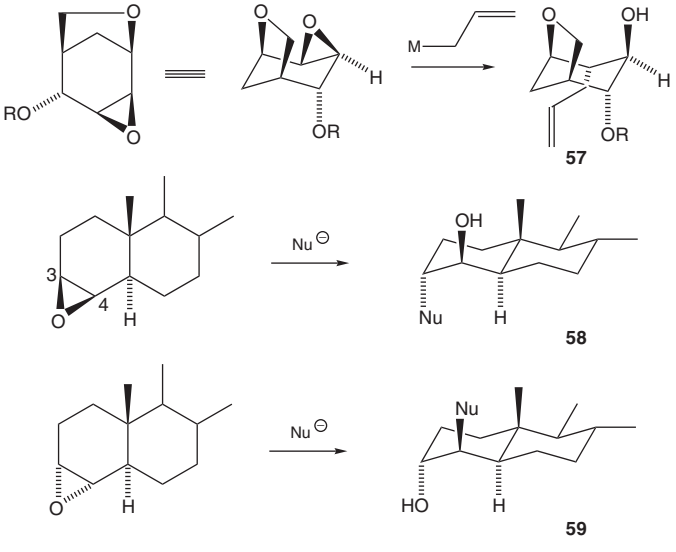


The first case is demonstrated by the regioselective formation of the highly substituted amines **54** and **55** [25].

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].

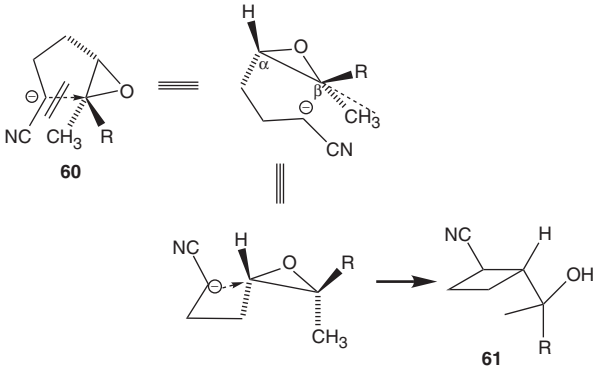


In accordance with the rule, the 3,4-epoxides of steroids or terpenes determine the regioselectivity of nucleophilic attack. Nucleophiles show up in the 3-position (**58**) with β-epoxides while the corresponding α-epoxides undergo nucleophilic ring opening at the 4-position (**59**).

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].

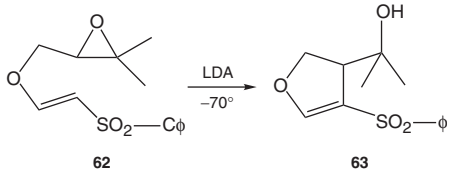


At first glance and ignoring stereochemistry, one is tempted to predict cyclopentane formation, but in this event the cyclobutane **61** is mainly formed.

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.

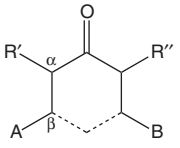
One has to realize that the stereochemical effect (axial substituents) as well as ring strain considerations are completely overruled by overlap necessities.

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_N2-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

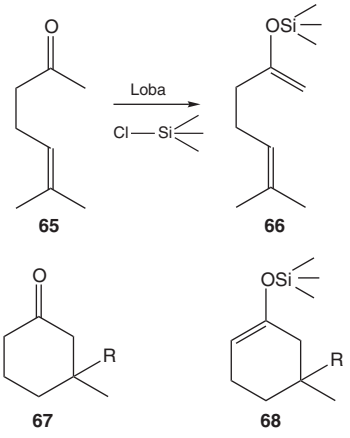
They range from number, size, and electronic properties of α- or β-substituents (see **64**) via ring size and rigidity to various derivatives of the carbonyl group such as oximes, alkylated oximes, and all types of hydrazone derivatives.

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].

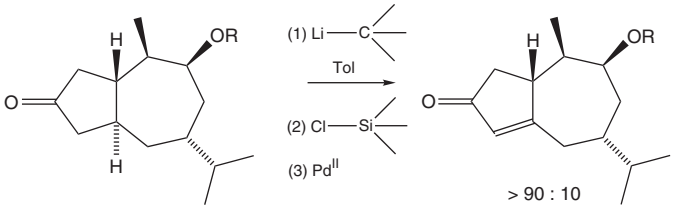


65 **66**

67 **68**

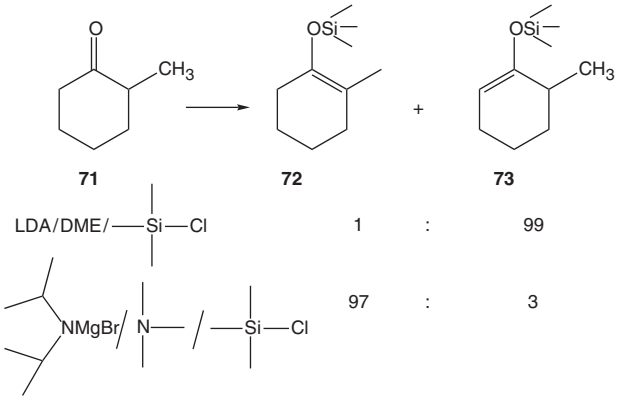
Although this certainly meets our expectations – if not to a large extent – the deprotonation of hydroazulene-ketone **69** with lithiumtriphenylmethyl leading to mainly one enolsilylether is really remarkable [32].

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.



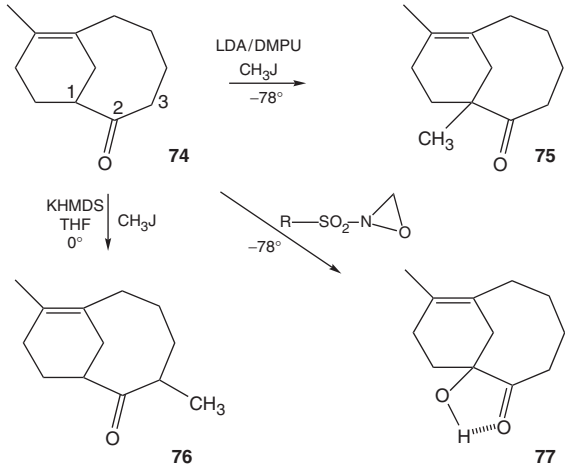
69 **70**

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]



71 **72** **73**

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].



74 **75** **76** **77**

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**.

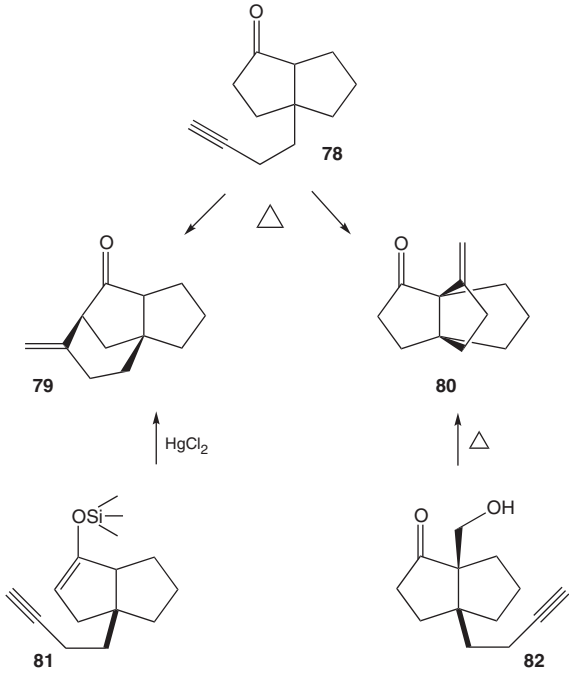
If the deprotonation is done under thermodynamic conditions, the 3-methyl derivative **76** results from the methylation process.

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**.

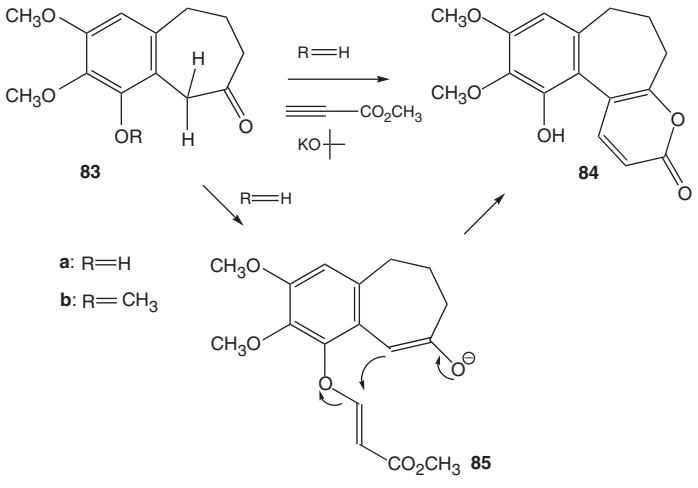
If one starts with the separately prepared enolsilylether **81**, mercury-catalyzed cyclization gives a high yield of **79**, while the easy-to-make aldol **82** leads to **80** after a thermal retro-aldol process [34].



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.



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].

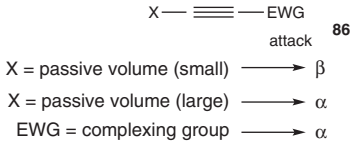
Obviously, the methyl group in **83b** is not bulky enough to completely divert the electrophile from the benzylic position, thus giving rise to mixtures. To achieve complete shielding of this center, highly space-demanding groups such as pivalate, TIPS-ether, or maybe even the triphenylmethyl group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

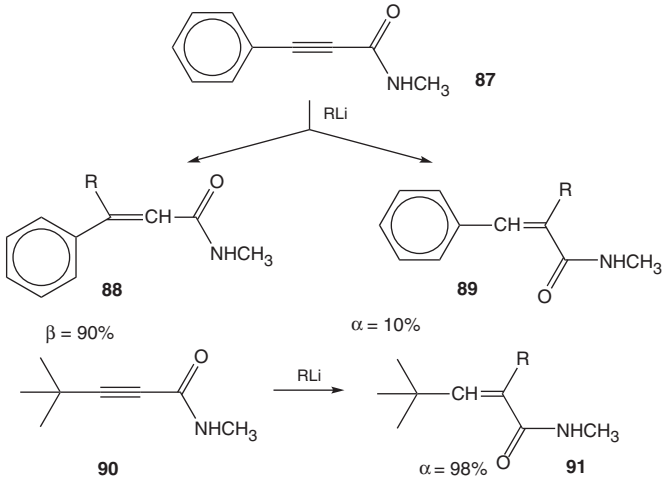
Under these circumstances, the generation of the "wrong" enolate will be of no consequence as long as enolate equilibration is guaranteed. The capture of the electrophile, in this case, represents a Michael addition to an acceptor-substituted acetylene, and this brings us to another subtopic in the carbonyl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



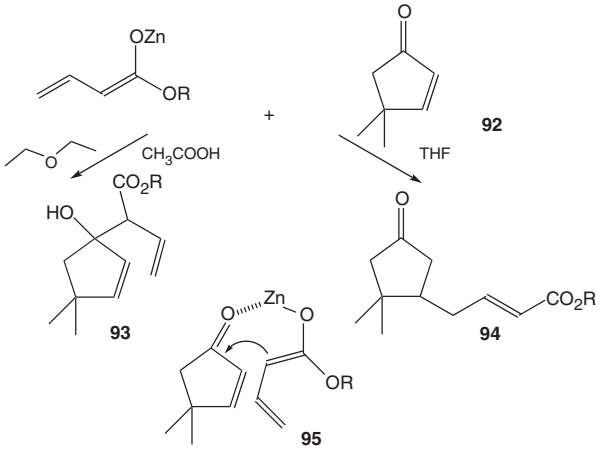
Although the complexing amide is of assistance for the α-addition, the phenyl group diverts the nucleophile only to an extent of 10% to the α-position (see **89**).

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

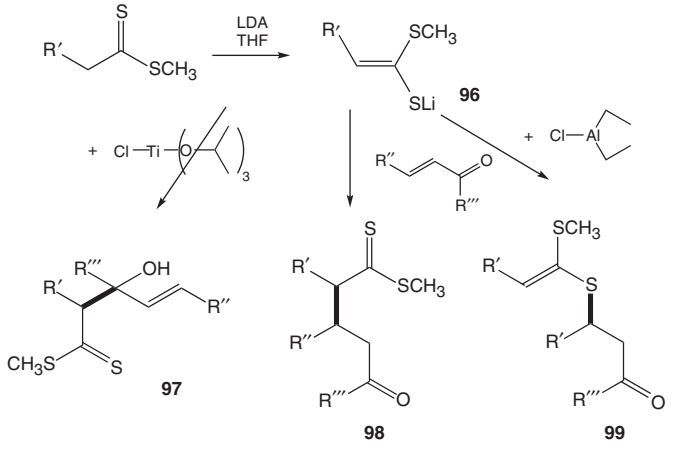
As different studies on the directing power of various passive volume groups have shown (see chapters 1 and 3 on stereochemistry), branched saturated substituents proved to be more space demanding than a phenyl group.

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**).