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CHIRAL ACETALS IN ASYMMETRIC SYNTHESIS

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I. INTRODUCTION

During recent years, a growing number of papers dealing with chiral acetals have demonstrated the usefulness of these auxiliaries in asymmetric synthesis. Of particular interest are acetals prepared with diols having a C_2 axis of symmetry[1]. In these cases, the acetal carbon is prochiral rather than chiral. In a simple aldehyde, without any other stereogenic center, there is no differenciation between the si and the re face of its carbonyl group (Scheme 1). By reaction with a C_2 axially symmetric chiral diol a single acetal is formed. However, in its most stable conformation, for example in the case of a dioxane ring, this acetal has, now, one axial and one equatorial R substituent. It is on these subtle effects that the si and re faces of what was a carbonyl group are, now, differentiated[2].

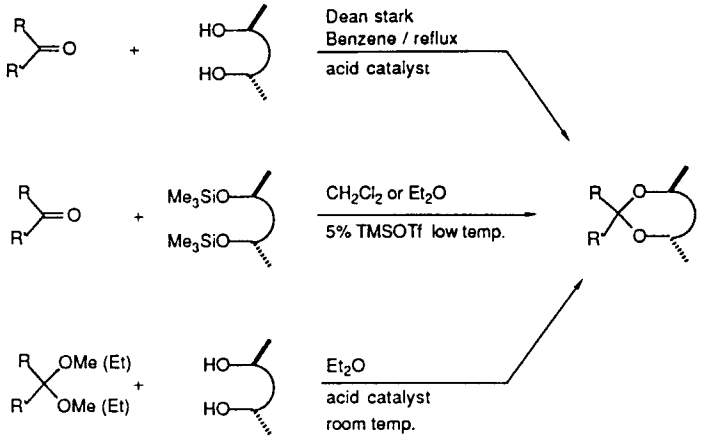
Scheme 1

These acetals may undergo cleavage reactions of the acetal ring, or they may be used near a prochiral center to control its reactivity and stereoselectivity. The two sections of this review deal with each of these two aspects[1,3].

Chiral acetals and ketals are routinely prepared by reacting an aldehyde or a ketone with the chiral diol with azeotropic removal of water in a Dean-Stark trap[4]. Alternatively, Noyori's procedure[5], with disilylated

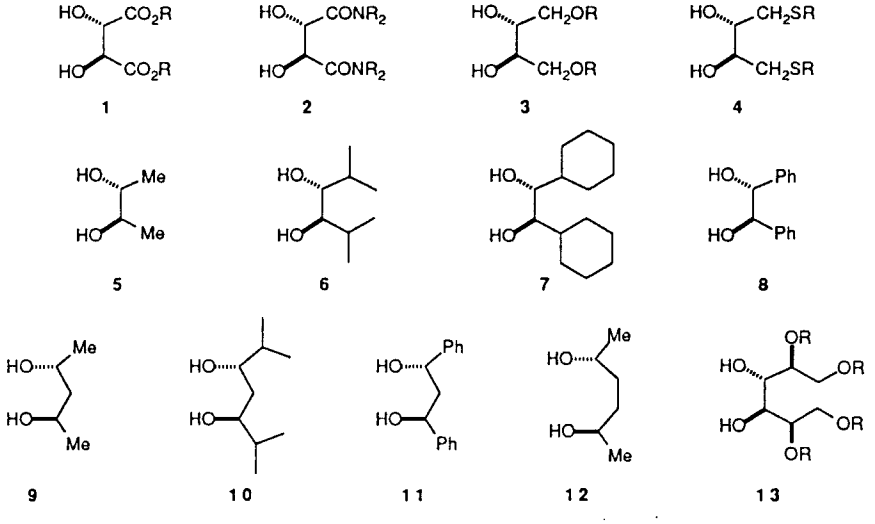
diols, can be applied when migration of the double bond of α,β-enones is a serious problem (Scheme 2). Finally transacetalization[4] is also a useful process when an acyclic acetal is the starting material and the corresponding carbonyl compound rather unstable.

Scheme 2



On the other hand most of the chiral diols are commercially available. The prices go from the very cheap tartaric acid or mannitol **13**, to the more expensive 2,4-pentanediol. Several simple methods exist, however, for their easy preparative synthesis. Scheme 3 summarizes the most commonly encountered diols and their method of preparation.

Scheme 3



1 **2** **3** **4**

5 **6** **7** **8**

9 **10** **11** **12** **13**

From tartaric acid : **1** , **2** , **3** , **4** , **5** ref 6
From microbial transformation : **5** ref 7 , **11** ref 8 , **12** ref 9
From asymetric hydrogenation : **9** , **10** ref 10
From Sharpless osmylation : **7** , **8** ref 11

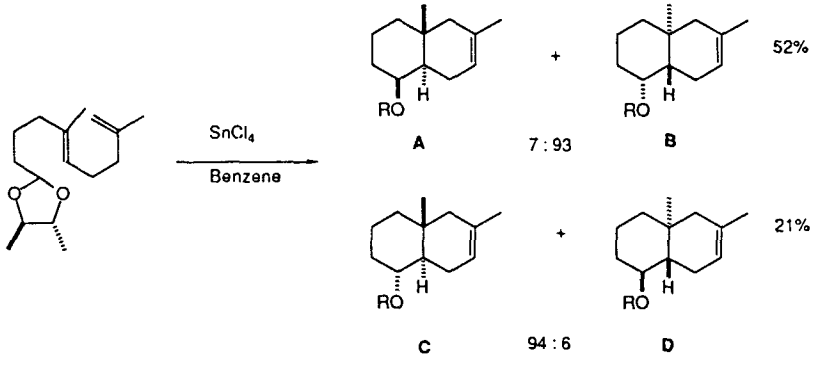
There are also other general methods[12] and some of more specific interest. Thus, **7** was prepared by hydrogenation of **8**[13], which, in turn, was obtained by reduction of benzoin or benzil, followed by resolution[14]. Matteson *et al* prepared **6** through borane chemistry[15]. Chiral or racemic diepoxybutane may be opened twice by an organometallic reagent[16]. Finally, a large array of chiral racemic *d,l* -1,2-diols may be obtained by pinacol type reductive dimerization[17]. These are useful for test studies and may be resolved by standard methods[18].

II. CLEAVAGE OF ACETALS

Acetals and ketals are among the most used protective groups for aldehydes and ketones[4]. However, under appropriate conditions, particularly in the presence of a strong Lewis acid, they may be attacked by nucleophiles or they may undergo electrophilic substitution reactions[19].

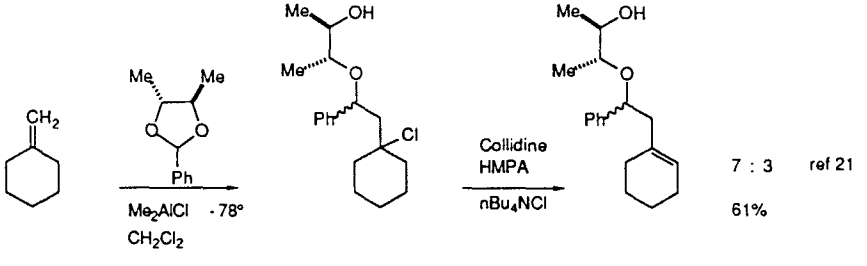
Pioneering in the field of chiral acetals, W.S. Johnson's group[20] used an acetal of R,R-2,3-butanediol **5** in their cationic biomimetic cyclisation. Of the four stereoisomers, obtained in this $SnCl_4$ catalyzed reaction, the two major ones, **B** and **C** (Scheme 4) have the same absolute configuration at what was the acetal carbon. That represents a very high degree of diastereoselectivity in the reaction process (d.e. 86%). Removal of the chiral auxiliary, by degradation, allowed the determination of the absolute configuration.

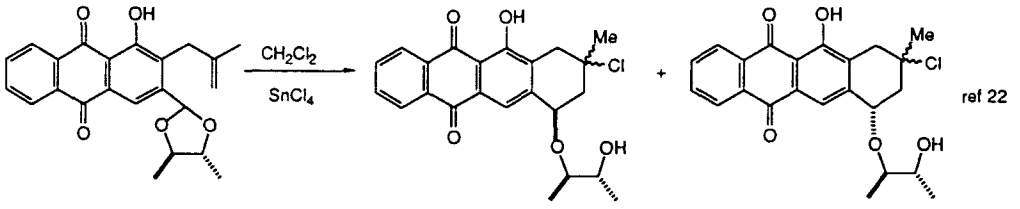
Scheme 4



The *intramolecular* nature of the above reaction may be crucial for such a high selectivity. A later *intermolecular* example by Snider *et al*[21] was less successful (Scheme 5). The same ratio (7 : 3) of diastereoisomers is obtained with 2,3-butanediol and with 2,4-pentanediol as chiral auxiliary. The absolute configuration of the new stereogenic center was not determined. More recently, another example of the same kind of reaction also gave only moderate diastereoselection[22] (Scheme 5).

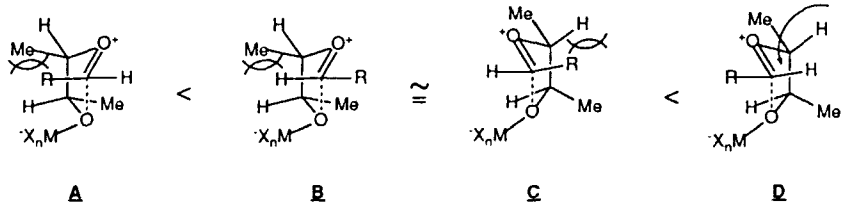
Scheme 5





Chiral acetals of , usually, 2,3-butanediol and 2,4-pentanediol, have also been cleaved, diastereoselectively by a variety of nucleophiles, in the presence of a Lewis acid. However, before going on, let's examine in more detail what are the reasons behind the observed diastereoselectivity, and what are the factors which can govern the stereochemical course of the reaction. From all the following results, a rationalization of the stereochemical outcome of such reactions can be drawn. As shown by NMR investigations[23], at low temperature, upon complexation of the acetal with the Lewis acid, there is no cleavage of the dioxane or the dioxolane ring. However, there are modifications of the molecule with elongation of one of the two C-O bonds and formation of a pseudo-oxocarbonium ion. In a dioxolane ring four possible transition states may be considered[24] (Scheme 6).

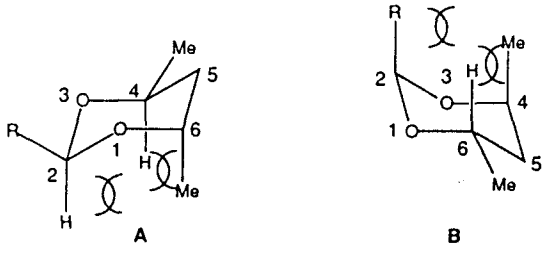
Scheme 6



Assuming that the nucleophile attacks in an S_N2 manner, anti to the departing oxygen, it seems plausible that structure **D** (Scheme 6) is the most favorable since it is the less hindered one. That leads exactly to the experimentally observed stereochemical result.

With the more rigid dioxane ring, in its chair conformation, this explanation finds even more support. Acetals of 2,4-pentanediol, for example, exist, largely if not exclusively, in conformation **A** (scheme 7) where only two 1,3-diaxial interactions H↔Me are present. Conformation **B** (Scheme 7) is destabilized by one R↔Me and by one H↔Me diaxal interaction.

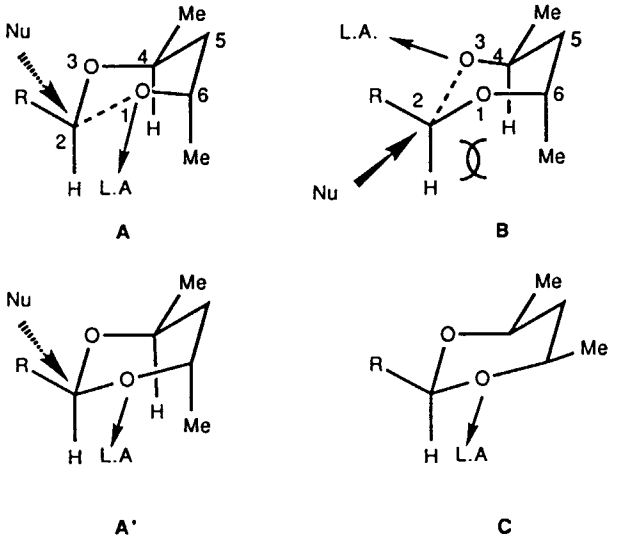
Scheme 7



Compared to a cyclohexane ring, these interactions are much stronger in such dioxane rings. Indeed, the C-O bond is shorter than the C-C bond, and thus the distance between the Me group in position 6 and the H in position 2 is 1.94 Å instead of 2.29 Å in cyclohexane[3a,25].

Chelation of this acetal with a Lewis acid gives a single complex, as has been shown by NMR investigation[23]. This is quite understandable, if we consider the two possible complexes (Scheme 8). In complex A the Lewis acid chelates to O^1, next to the axial Me group. Therefore, the C^2-O^1 bond is elongated, and conversely, by anomeric effect, the C^2-O^3 bond is shortened. Such a situation is quite favorable since the elongation of the C^2-O^1 bond increases the distance between the H in position 2 and the Me in position 6, thus releasing part of the strain of this molecule. On the other hand, in complex **B** (Scheme 8), the C^2-O^3 bond is elongated, and, by anomeric effect, the C^2-O^1 bond is shortened. That increases the 1-3 interaction between the H in position 2 and the Me in position 6, making the formation of such a complex quite unlikely.

Scheme 8



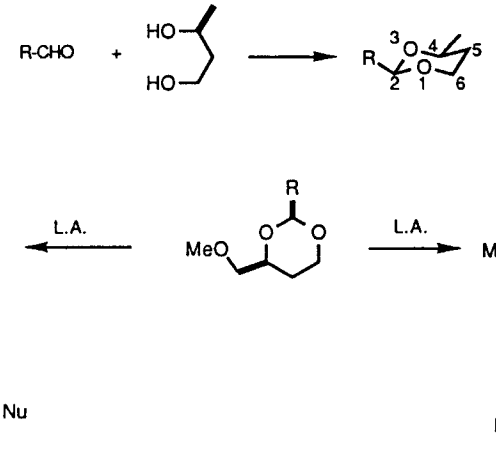
According to the most recent stereochemical[26] and NMR investigations[23,27] on these acetals it may be assumed that, upon coordination with the Lewis acid, the oxygen atom rehybridizes toward sp^2, giving a planar or weakly pyramidal complex. In this trigonal-like configuration, the Lewis acid is more sterically hindered by an equatorial group than by an axial one. Thus, the preferential formation of complex A' (Scheme 8) is easily understood, as well as the very poor reactivity of a meso acetal[28], with two equatorial Me groups, which can hardly form complex C (Scheme 8).

Once the chelate is set, the nucleophile is then able to attack, in *anti* manner, the weakened C-O bond. Most of the following stereochemical results can be accounted for by an $S_N 2$ reaction on chelate A or A'. Moreover, better selectivities are, generally, obtained with the more rigid six membered dioxane ring rather than with the dioxolane ring which is conformationaly more flexible.

Some other acetals, which lack the above detailed axis of symmetry, have also been utilized with success ; particularly acetals arising from 1,3-butanediol. In this case, the acetal carbon is chiral ; however during

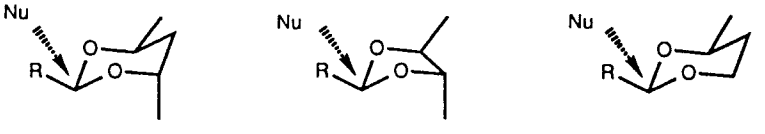
the preparation of such acetals, under thermodynamic control, a single isomer, in which the two substituents are in equatorial position, is formed (> 99%) [25] (Scheme 9). Upon cleavage, the less hindered C^2-O^1 bond is selectively, or exclusively, broken, with concomitant *anti* substitution by the nucleophile. However, in the case of such functionalized acetals, it was recently shown that a bidentate Lewis acid is able to reverse this regioselectivity[29] (Scheme 9).

Scheme 9



In summary, for both the dioxane and dioxolane rings we may say that the cleaved C-O bond is, usually, the one next to the axial, or pseudoaxial, Me group, with *anti* entry of the nucleophile (Scheme 10).

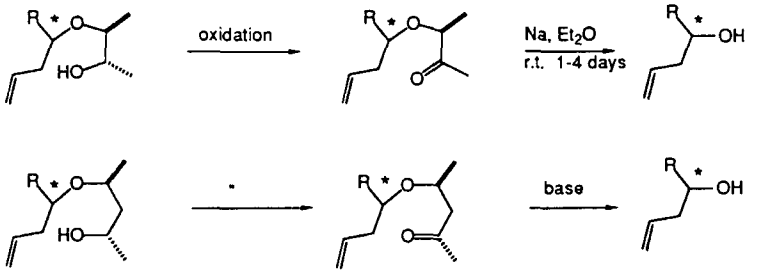
Scheme 10



II. 1. Reactions with allylic silanes.

The Lewis acid promoted reaction of acetals with allylic silanes is a well established and high yielding process[30]. The first chiral version appeared in 1982, when McNamara and Kishi[31] reported the diastereoselective (83 : 17) reaction of benzaldehyde/2,3-butanediol acetal with allyltrimethylsilane, in the presence of $SnCl_4$. A few weeks later, Johnson *et al* [24] described analogous results with $TiCl_4$ as Lewis acid (see scheme 12). They pointed out the strong advantages of 2,4-pentanediol over 2,3-butanediol, not only on the diastereoselectivity of the reaction, but also on the removal of the chiral auxiliary. Indeed, the first stage of this process is oxidation of the free alcohol by standard oxidant (Swern, PCC ...), followed by, α or β elimination respectively (Scheme 11).

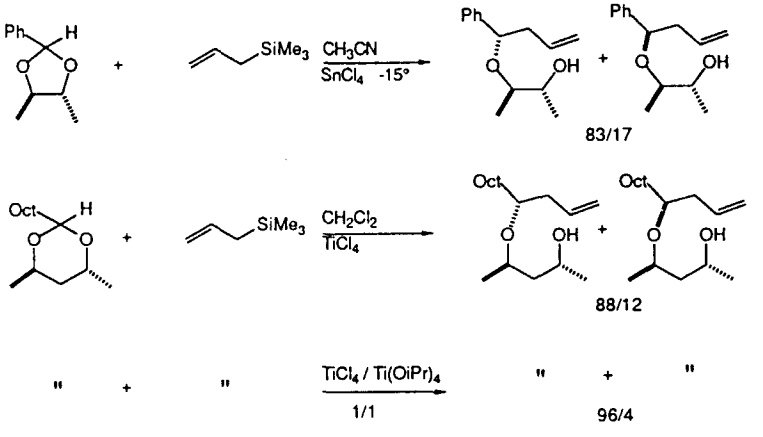
Scheme 11



The α elimination is achieved with Na in Et_2O at room temperature for 1-4 days, a method which is not really convenient, especially if other sensitive functionalities are present. On the other hand the β elimination can be performed even with weak bases, under very mild conditions.

Johnson *et al*[32] have also found that the cleavage reaction is even more diastereoselective with milder Lewis acid, *viz* a combination of $TiCl_4$ and $Ti(OiPr)_4$ in various ratios (Scheme 12). Moreover, in this last case, a very slow addition of the Lewis acid also improves the ratio (96 : 4).

Scheme 12



The intramolecular version of this reaction, was considered by Johnson and his group[33,34]. Again the results emphasize the higher diastereoselectivities attained with 2,4-pentanediol[33]. It should be noted that in these cases a propargylic silane is involved.

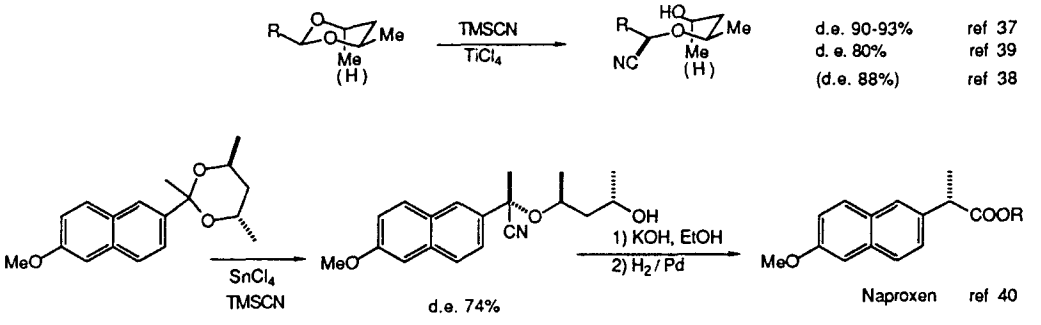
Although not dealing with acetals, similar reactions (with C_3H_5-$SiMe_3$ / $TiCl_4$) were also performed on chiral dioxolanones[35a] and dioxanones[35b] with more or less success, as well as with aldehydes in the presence of a chiral alcohol[36].

II. 2. Reactions with cyanotrimethylsilane and alkynyl silanes.

Instead of allylic silanes, cyanotrimethylsilane can be employed as nucleophile. The stereochemical results are in agreement with the general mechanistic scheme shown above. Both 2,4-pentanediol[37] and 1,3-butanediol[38] were equally successful (Scheme 13) and have been used in the synthesis of natural products, such

as β-adrenergic blocking agents[39]. This method was also applied to a *ketal* [40], a situation which is not as clear cut as with *acetals*. Indeed, in the former case, conformer **B** (Scheme 7) is not as disfavored as for the latter.

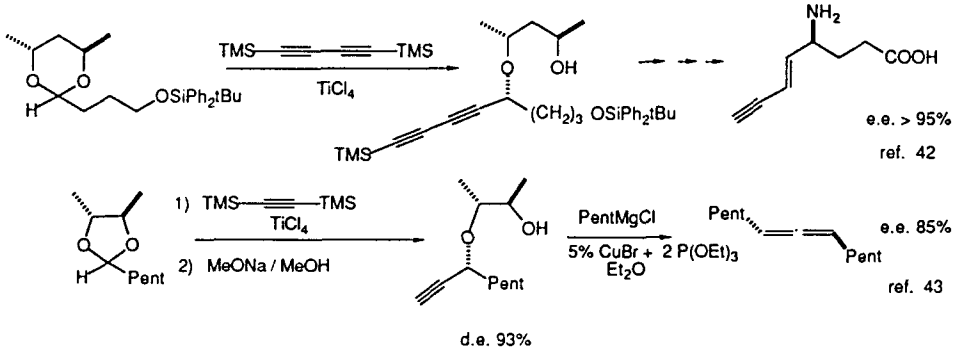
Scheme 13



The chiral auxiliary may be removed as usual, leading to a chiral cyanohydrin, a useful precursor to α-hydroxy acids, aldehydes or amines[37]. This approach was used for the synthesis of an important part of deltamethrine, one of the most potent insecticides[38]. Alternatively, the chiral auxiliary may be removed without destruction, by hydrogenolysis, with concommitent deoxygenation of the product[40], leading to the formation of Naproxen (Scheme 13).

The reaction of alkynyl silanes with chiral acetals affords propargylic ethers and, hence, is a source of chiral propargylic alcohols[41]. The diastereomeric excesses are usually over 90%. This method was used for the synthesis of γ-aminobutyric acid (GABA) derivatives [42] (see Scheme 14). On the other hand, propargylic ethers can be used directly for the synthesis of chiral allenes[43]. In this latter case the chiral auxiliary is released in the last step.

Scheme 14

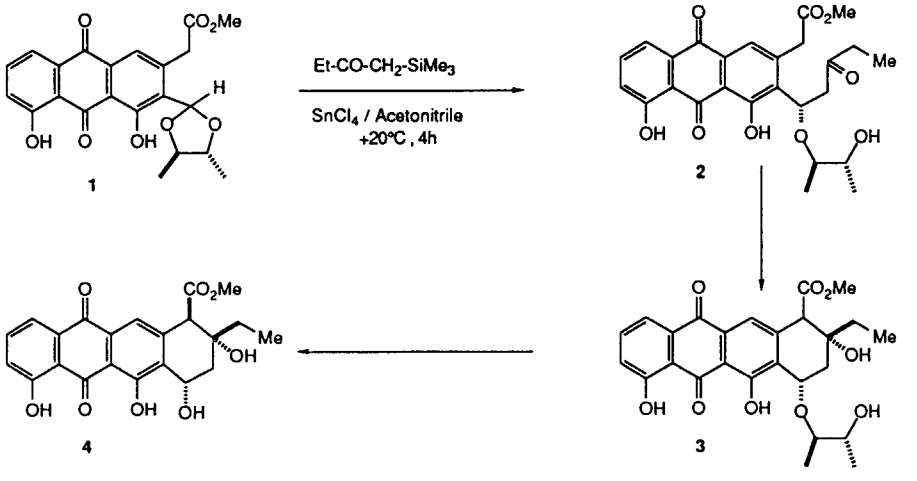


II. 3. Reactions with silyl enolates.

Silyl enolates are another type of silicon derivative , either as enol ethers or α-silyl carbonyl compounds. They are also known to cleave acetals in the presence of a Lewis acid[44]. Kishi *et al*, in their work on asymmetric synthesis of aklavinone, were first to disclose the use of chiral acetals in aldol-type reactions[31,45,46].

Open chain acetals, with *l*-menthol gave a rather low asymmetric induction (1.5 : 1), whereas with the cylic acetal **1**, obtained from 2,3-butanediol, a 10 : 1 ratio of diastereoisomers was observed (Scheme 15). An even better ratio (17 : 1) was obtained in the 11-deoxydaunomycinone series[45].

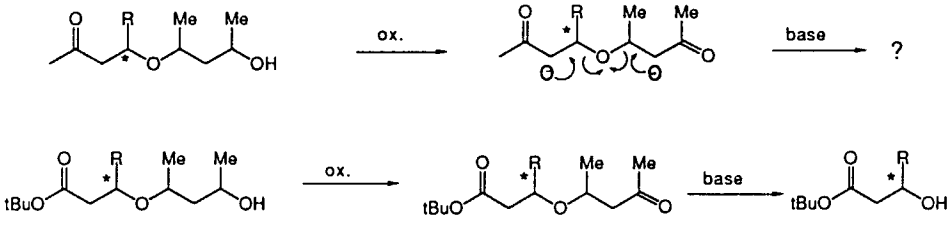
Scheme 15



The removal of the chiral auxiliary was facilitated by the benzylic position of the new chiral center in **2**. Thus, treatment with trifluoroacetic acid gave directly the desired alcohol **4** without racemization. Alternatively, a multistep procedure was also described : *a)* PCC oxidation ; *b)* mCPBA ; *c)* pTSA.py / MeOH.

In simpler model acetals, Kishi et *al* [31], found a much lower diastereoselectivity (1 : 1 to 3.5 : 1) when the starting aldehyde was not aromatic. However, employing six-membered ring acetals, Johnson *et al*, were able to attain a very high degree of selectivity (d.e. > 90%). Enol silyl ethers and α-silyl ketones behave similarly[47], as well as silyl ketene acetals[48]. In this way they synthesized chiral α-Lipoic acid. However, the main problem in using 2,4-pentanediol as auxiliary lies in its removal, once the cleavage reaction is done. The usual method (scheme 11) involves an oxidation followed by a β-elimination. In the present case two carbonyl groups are concerned, not only one (Scheme 16).

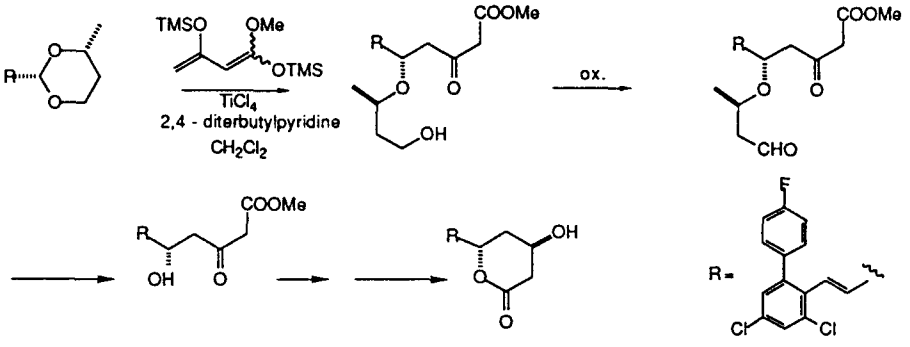
Scheme 16



When one carbonyl group is an ester (cleavage reaction performed with $CH_2=C(OtBu)OSiMe_3$) a mild base (piperidinium acetate) is enough for the discrimination.

A way to avoid such problems is to turn to acetals of 1,3-butanediol. Being also six-membered rings, they are as diastereoselective as acetals of 2,4-pentanediol[49], in the present reaction. Upon oxidation , for the removal of the auxiliary, they afford an aldehyde which then undergoes a smooth β-elimination with dibenzylammonium trifluoroacetate[50]. Through this approach, Johnson *et al* synthesized Mevinolin analogues[51] (Scheme 17) as single enantiomers.

Scheme 17



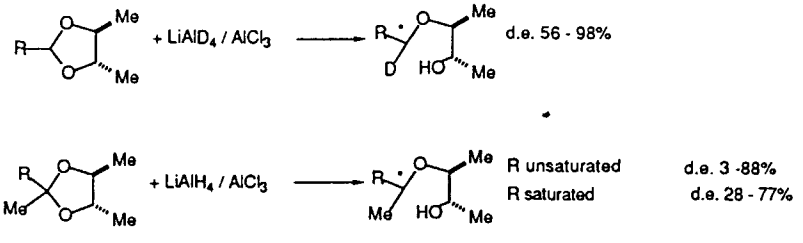
In the present case, as well as in most of the other ones, the cleavage of 1,3-butanediol derived acetals is not only diastereoselective, but also regioselective : only the less substituted C-O bond is broken (see above Scheme10).

All the above results were obtained with silicon derivatives as nucleophiles. However, a recent report showed that zinc enolates, particularly the Reformatsky reagent, (in the presence of $TiCl_4$) are also able to cleave acetals. Among the tested diols (1,3-butanediol, 2,4-pentanediol and dimethyl tartrate) the best diastereoselectivity was attained with the C_2 symmetric 2,4-pentanediol (11.5 : 1)[52,53].

II. 4. Reduction by hydrides.

Acetals are easily cleaved and reduced by hydrides having a Lewis acid character, such as aluminum or boron hydrides. This methodology is routinely used in carbohydrate chemistry[54], for monodeprotection of vicinal diols. However, in these examples the interest lies on the diol part of the acetal and not on the aldehyde part. Chiral acetals with a C_2 axial symmetry were first studied by Richter in 1981[55]. Acetals and ketals of 2,3-butanediol were cleaved by $LiAlD_4/AlCl_3$ reagent. Although the stereochemical outcome of the reaction was not ascertained, since the diol was racemic, the d.e. could be measured (Scheme 18).

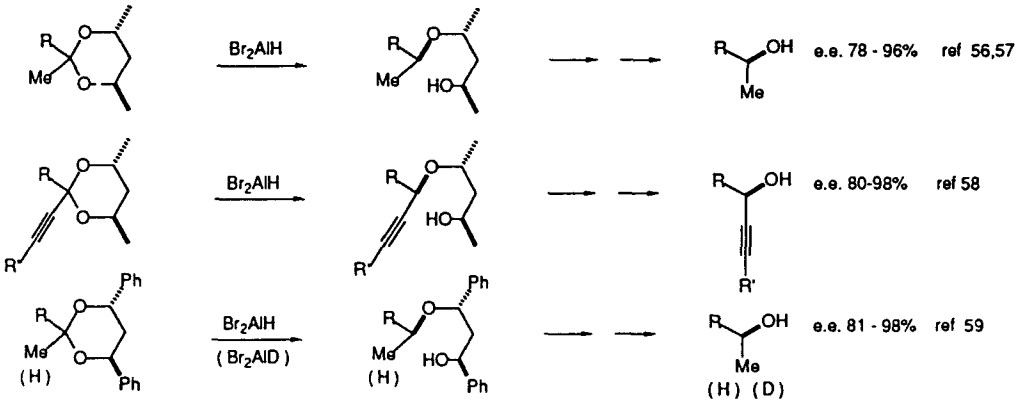
Scheme 18



With *ketals*, the two conformers **A** and **B** (Scheme 7) differ much less, energetically, and both may react. That might explain the considerable drop in diastereoselectivity (d.e. 28-77%) as compared to *acetals* . More importantly, with unsaturated methyl ketones, as starting carbonyl compounds, the d.e. is almost negligible, the lowest being with R = HC≡C-.

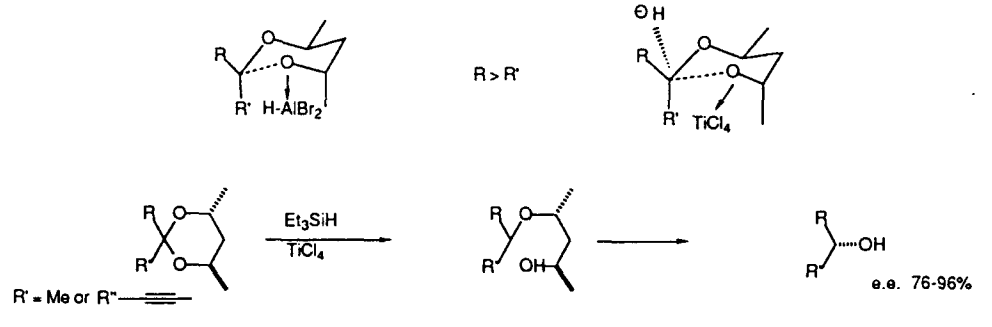
In the case of *ketals* the ring size becomes of crucial importance. H. Yamamoto *et al* reported, in 1983, that with ketals of 2,4-pentanediol the diastereoselectivity is boosted to 78-96%[56]. Not only aryl-methyl ketones can be used, but also alkyl-methyl[57] and, more interestingly, alkynyl-alkyl ketones[58]. Other dioxane systems are possible with equal success, such as the ones deriving from 1,3-diphenylpropane-1,3-diol[59] (Scheme 19).

Scheme 19



The stereochemical outcome of these reductions was determined by the usual oxidation-β-elimination sequence (Scheme 11). Interestingly, in these reductions with X_2AlH, the stereochemistry of the final chiral secondary alcohol was found to be completely reversed to what was expected (Scheme 8). In fact this result can be easily explained if one takes into account the fact that the Lewis acid and the nucleophile are the same reagent. Thus, the stereospecific coordination of the organoaluminum reagent to the oxygen next to the axial methyl group is followed by the attack of the hydride *syn* to the cleaved carbon-oxygen bond (Scheme 20). The normal stereochemical outcome can be restored with a binary reagent, R_3SiH / Lewis acid[60,61]. This last reaction is also highly diastereoselective with *ketals* of methyl-alkyl ketones and of alkynyl-alkyl ketones (Scheme 20).

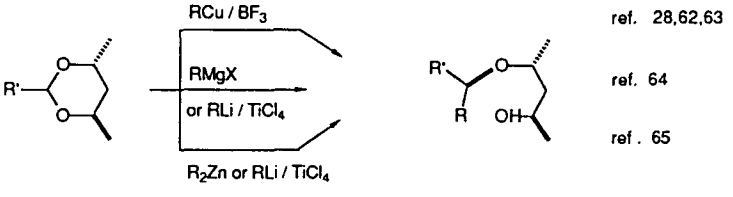
Scheme 20



II. 5. Reactions with organometallic reagents.

During our studies on organocopper reagents, we found that RCu/BF_3 reagents were able to cleave orthoformates, acetals and epoxides[62]. In the same way chiral acetals were also cleaved in a highly diastereoselective manner[28a,63]. The stereochemical outcome is the same as for binary systems (scheme 9). A comparison between dioxolane (from 2,3-butanediol), dioxane (from 2,4-pentanediol) and dioxepine (from 2,5-hexanediol) confirmed the higher diastereoselectivity of the six-membered rings (d.e. 67%, 91% and 86% respectively , for benzaldehyde acetals). Dioxolane acetals from aliphatic aldehydes always gave only one detectable diastereoisomer ! Closely related reactions were also published by Johnson's group[64] with acetals of 2,4-pentanediol (dioxanes). The Lewis acid is $TiCl_4$ and the organometallic reagent RLi, RMgX or R_2CuMgX. Even a *ketal* is diastereoselectively cleaved (d.e. 78%). Yamamoto's group also disclosed similar results with $R_2Zn/TiCl_4$ or $RLi/TiCl_4$[65] (Scheme 21). With Me_3Al alone, however, dioxane acetals are cleaved with a low diastereoselectivity[57].

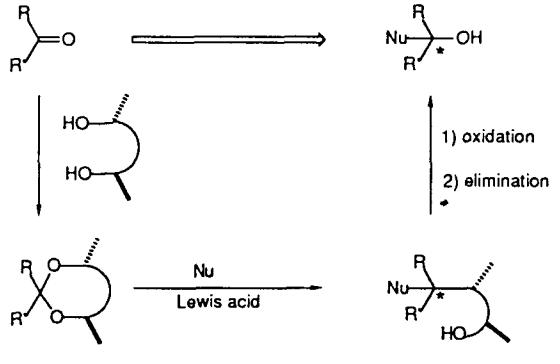
Scheme 21



These reactions are quite general for various R groups (Me, Bu, Ar,Allyl, R-C≡C[43]) and they are also very chemoselective : the acetal group is preferentially cleaved in the presence of a ketone or an ester.

In fact all the above results permit the indirect preparation of chiral secondary alcohols either by hydride attack on a ketone, or an alkyl or allyl attack on an aldehyde. In this process the chiral auxiliary diol is destroyed : it is an immolative enantioselective synthesis (Scheme 22). Nevertheless, the value of the target chiral alcohol may overrule the cost of the auxiliary diol. It should be recalled that 2,3-butanediol is easily accessible from tartaric acid[6], 2,4-pentanediol is conveniently prepared, in both enantiomeric forms, by asymmetric reduction of acetonylacetone[10] and that the recently discovered enantioselective osmylation, by Sharpless[11], greatly helps in the synthesis of various chiral 1,2-diols.

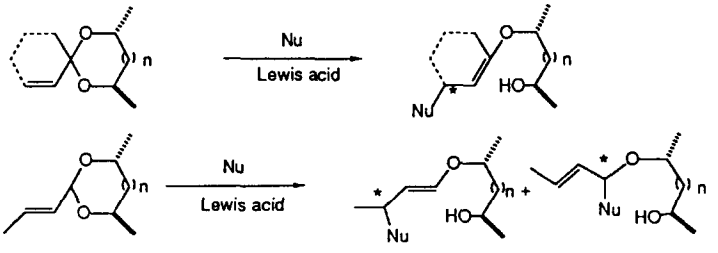
Scheme 22



II. 6. Reactions of α,β-ethylenic acetals and ketals.

α,β-ethylenic acetals have a dual reactivity. They may be cleaved by direct nucleophilic attack (S_N2) or by attack at the γ position, with allylic rearrangement (S_N'). *Ketals* react always regioselectively, by S_N', whereas *acetals* may afford a mixture of both attacks under uncontrolled conditions (Scheme 23).

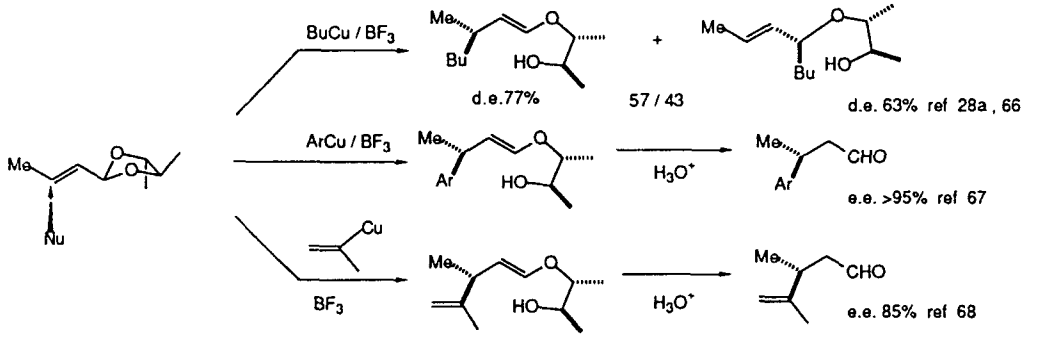
Scheme 23



Nu / Lewis acid : RCu / BF_3 or R_3Al

For example, the reaction of crotonaldehyde acetal and BuCu/BF_3, representative of *alkyl*copper reagents, is not regioselective, although diastereoselective[66]. On the other hand, *aryl* [67] and *alkenyl* [68] copper reagents are completely regioselective and highly diastereoselective. The degree of diastereoselectivity is increased (d.e. > 95%) when a good ligand of copper is used : PBu_3 for example[67]. Dioxolanes and dioxanes behave similarly (Scheme 24). However, when the starting diol contains other functionalities, chelation problems might arise which alter or even invert the diastereoselectivity[28a,67].

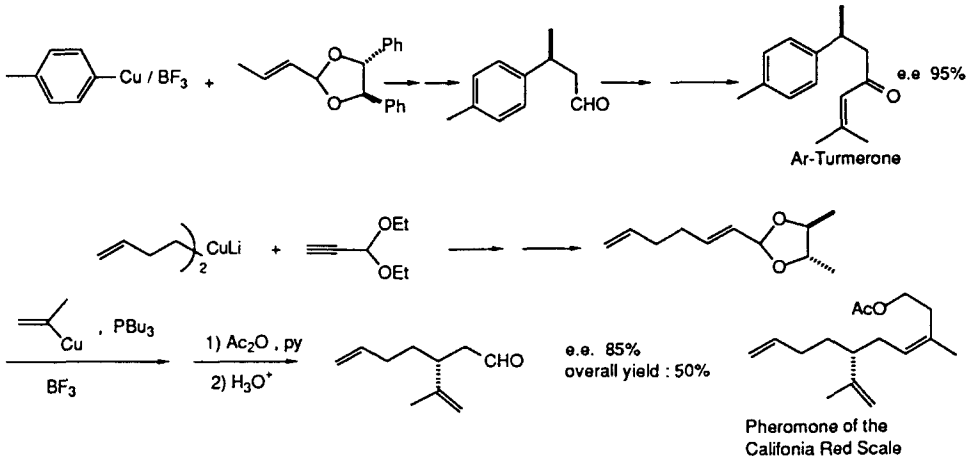
Scheme 24



The stereochemistry of the double bond of the starting acetal is quite important. Thus, working with Z- crotonaldehyde acetal instead of the E-one, affords a final product of reverse absolute configuration, with the same degree of diastereoselection[68]. As for the stereochemical outcome of these reactions, they obey to the general rule (scheme 9) although a γ-attack (S_N') is involved.

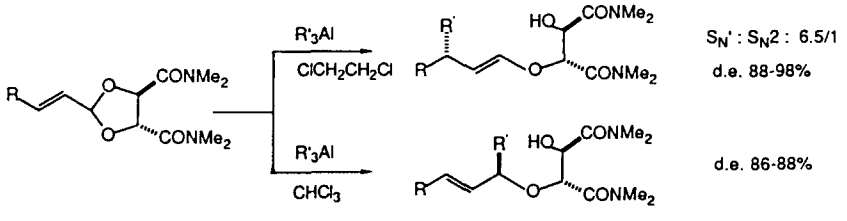
These reactions were applied to the synthesis of some natural products, such as the pheromone of the California Red scale[68] or Turmerone[69], a natural fragrance (Scheme 25).

Scheme 25



α,β-Ethylenic acetals are also cleaved by R_3Al reagents. However acetals from 2,3-butanediol or 2,4-pentanediol are not suited for that purpose, as only the direct (S_N2) attack is observed with loss of diastereoselectivity. Acetals formed with N,N,N',N'- tetramethyltartaric acid diamide are far superior[70]. Moreover, the regioselectivity may be controlled by a simple change of the polarity of the solvent. In $CHCl_3$, exclusive S_N2 attack occurs, with a d.e. as high as 88%, whereas in less polar solvents ($ClCH_2CH_2Cl$, PrCl, toluene) the S_N' adduct becomes the major product (6.5 : 1 to 1.5 : 1). The diastereoselectivity is also excellent : d.e. 88-98% (see Scheme 26). It should be noted, however, that only E acetals are good candidates in this reaction ; Z acetals gave both regioisomers in a non-diastereoselective manner. As for the stereochemical result, there is a clearcut difference between the S_N' adduct and the S_N2 adduct. The former obeys to the general rule (Scheme 9) exactly as do RCu/BF_3 reagents (Scheme 24), whereas the latter arises from a *syn* attack, in a similar way as for the $HAlBr_2$ reagent (Scheme 20).

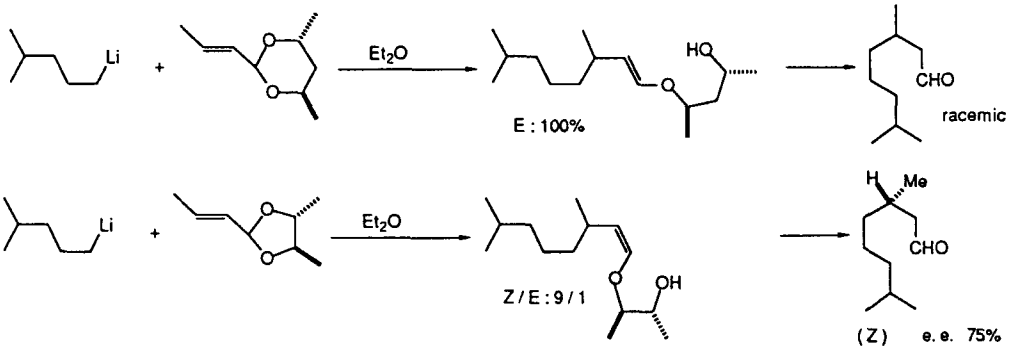
Scheme 26

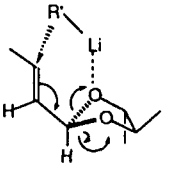


In both cases where a Lewis acid is involved (RCu/BF_3 or R_3Al) the resulting enol ether has a double bond of E-geometry (Schemes 24 and 26) which indicates that the α,β-ethylenic acetal has reacted in its transoid conformation. This is not the case when such acetals are cleaved by a purely nucleophilic reagent such as RLi. Indeed, the acetal of crotonaldehyde and 2,3-butanediol affords, with BuLi, exclusively the S_N' product, having, mainly, the Z-stereochemistry. A cyclic transition state where a cisoid conformation is involved, and with *syn*

delivery of R, may account of this result (Scheme 27). The corresponding acetal with 2,4-pentanediol cannot adopt such a cyclic transition state ; it gives only the E enol ether, but with no diastereoselectivity at all[71].

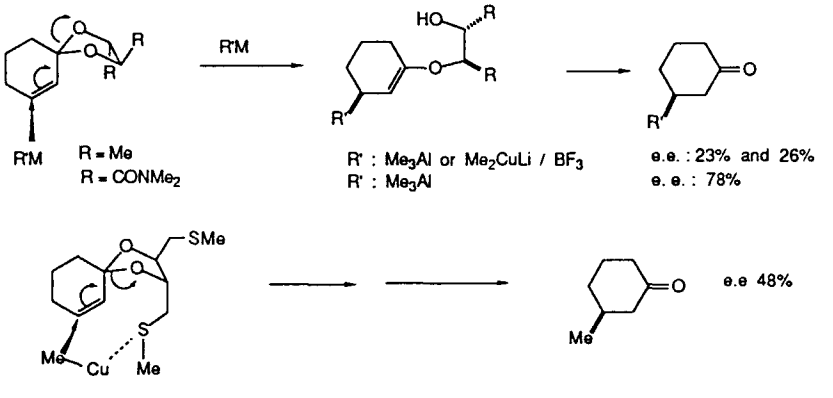
Scheme 27





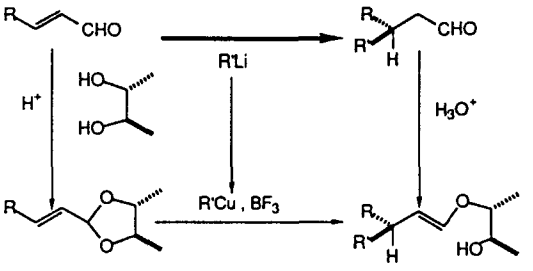
The diastereoselective S_N' cleavage of *ketals* is achieved with R_3Al reagents, only when N,N,N',N'-tetramethyltartaric acid diamide is used as chiral auxiliary. Ketals of 2,3-butanediol or 2,4-pentanediol give a low diastereoselectivity either with R_3Al[72] or RCu/BF_3 reagents[63]. Such a result is quite understandable in view of the possible reaction of both conformers **A** and **B** (Scheme 7). Chelation effects may reverse the sense of induction since only one conformer has the appropriate geometry to allow them[73] (scheme 28).

Scheme 28



The overall result of all the above reactions may be viewed, formally, as a conjugate addition to α,β-unsaturated carbonyl derivatives. Indeed, the enol ether obtained are easily hydrolyzed back to the aldehyde or the ketone, with recovery of the chiral auxiliary diol (Scheme 29).

Scheme 29

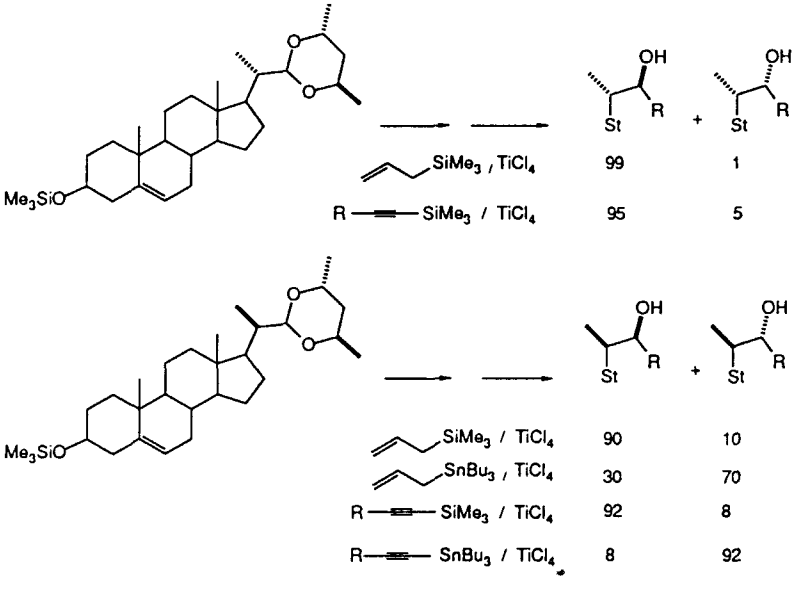


II. 7. Directing strength of the acetal template.

In all the above examples the chirality of the starting auxiliary diol are responsible for the observed high diastereoselectivity. There are no other stereogenic centers in the acetal which may perturb the sense of induction. This situation is not always encountered, particularly in natural product syntheses.

An alkyl substituent β to the acetal ring does not affect at all the expected diastereoselectivity[74]. In the α position, however, a situation may arise where the Cram rule and the acetal template are antinomic[75]. In matched pairs high induction is observed, whereas in unmatched pairs the Cram rule predominates with allyltrimethylsilane/$TiCl_4$. The nucleophile is, here, of crucial importance, since with allyltributyl stannane/$TiCl_4$, the acetal template again imposes its influence. The same trend was also observed with alkynyl silanes and stannanes[75,76] (Scheme 30).

Scheme 30

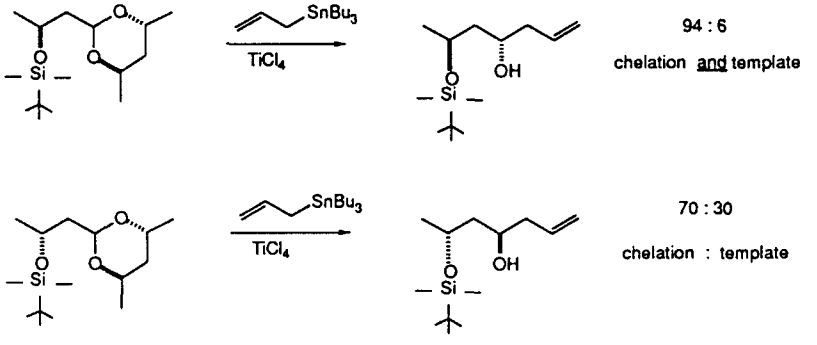


This different behaviour of silicon and tin nucleophiles clearly indicates the importance of the timing in the bond breaking and bond making processes. The organometallic reagents with low nucleophilicity, such as silicon, presumably react after the bond breaking process and, thus, the chiral induction is dictated primarily by

the Cram rule. On the other hand, the tributylstannyl derivatives possess higher nucleophilicity and therefore react simultaneously with bond breaking.

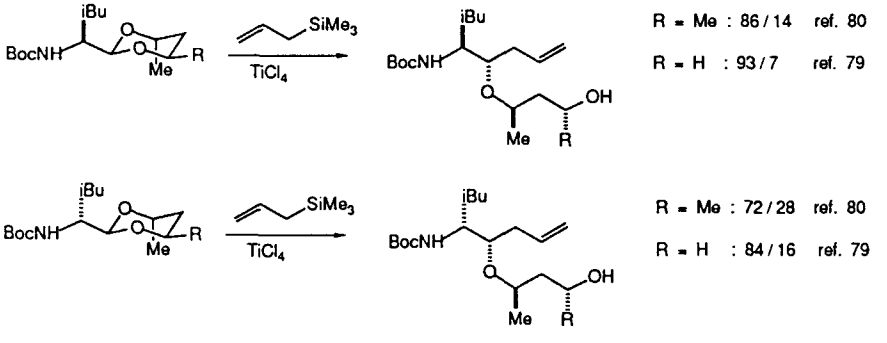
The presence of an heteroatom on the aldehyde precursor may also alter the diastereoselectivity. Thus, an alkoxy group β to the acetal ring imposes its influence through chelation with the Lewis acid[77]. In this case the acetal template is in fact useless (Scheme 31).

Scheme 31



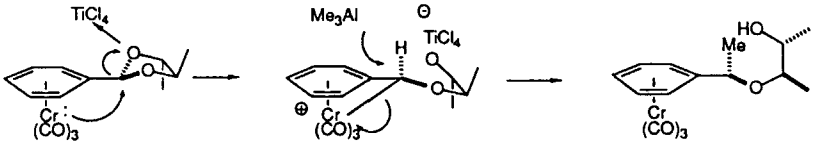
In contrast, with a heteroatom in the α position, it seems that the acetal template competes efficiently, although the diastereoselection is not as high as in the simple cases. Modifications of the Lewis acid[78] or of the acetal[79,80] allow some improvements (Scheme 32).

Scheme 32



Neighbouring group participation is also observed in arene chromium derivatives[81]. The acetal template serves, here, to allow a high degree of diastereoselectivity (100 : 1). However, the absolute configuration of the final product is the reverse of the expected one ! The chromium atom participates in the stabilization of the cation (Scheme 33).

Scheme 33

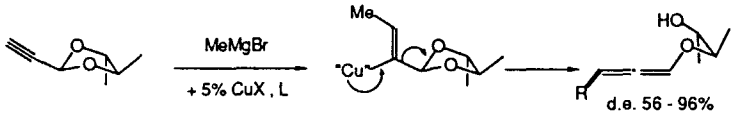


By appropriate choice of acetal and reagents, it is, thus, possible to obtain high degree of diastereoselectivity. In most cases, the separation of the diastereoisomers is easily accomplished during the purification steps allowing of enantiomerically pure compounds to be obtained.

II. 8. Miscellaneous cleavages.

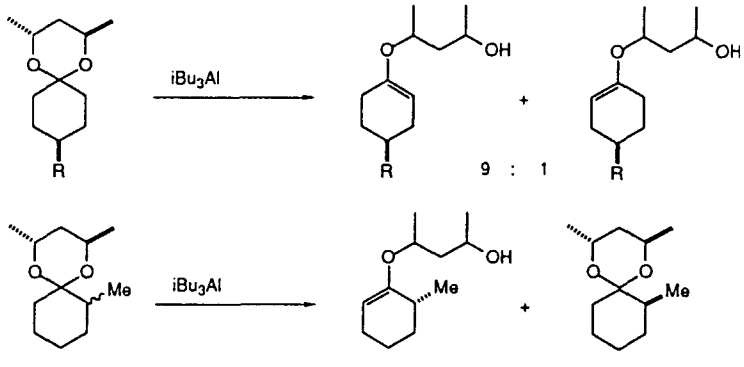
Chiral alkoxy-allenes have been obtained from propargylic acetals[28a,82]. Dioxolanes are, here, superior to dioxanes, in contrast to most previous examples. The reaction proceeds through the *syn* addition of an organocopper intermediate to the triple bond, followed by an *anti* elimination with cleavage of the C-O bond next to the axial Me group (Scheme 34).

Scheme 34



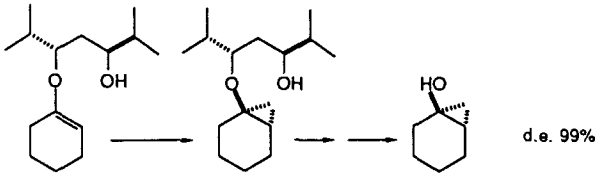
Another example of cleavage of acetal by an elimination rather than by a substitution was observed in the reaction between cyclic ketals and triisobutylaluminum or an aluminum amide. Asymmetrisation of meso ketones was, thus, achieved[83]. The same kind of reagent serves also for the kinetic resolution of α substituted cyclic ketals[84] (Scheme 35). In these cases, iBu_3Al acts as Lewis acid and as a base for the abstraction of a proton to afford the enol ether.

Scheme 35



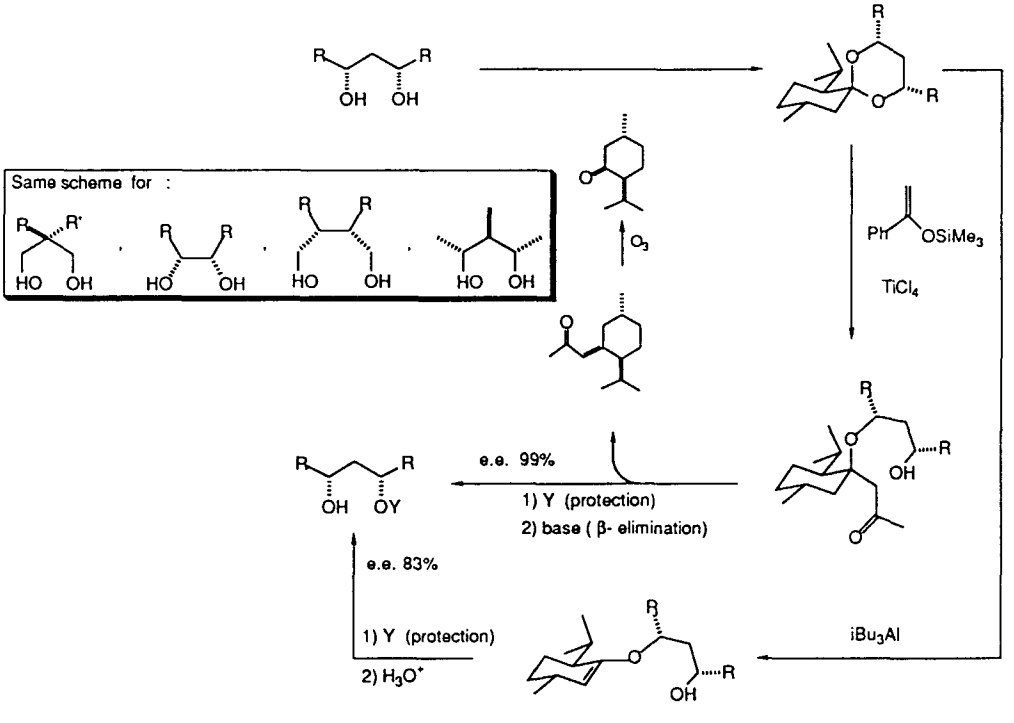
Although not dealing directly with acetals, enol ethers of the kind shown above (scheme 35) were excellent substrates for an asymmetric Simmons-Smith reaction[85,86]. Almost pure cyclopropanes were thus obtained starting from a non chiral cyclic ketone (Scheme 36).

Scheme 36



The principles which govern the diastereoselective cleavage of chiral acetals were applied in another kind of acetals where a transformation of the starting diol is sought. Thus, in a series of papers, Oku *et al* [87-91] have prepared ketals of *l*-menthone and a meso diol. In most cases, only one diastereoisomer is mainly formed. When subjected to cleavage conditions (iBu_3Al[88] or $CH_2 = C(Ph)OSiMe_3/TiCl_4$[87-91]), the axial C-O bond is selectively cleaved with formation of an enol ether (with iBu_3Al) or the S_N2 adduct (with $CH_2=C(Ph)OSiMe_3$ / $TiCl_4$). Protection of the free hydroxy functionality and cleavage of the ether one, affords the starting diol in a monoprotected form with a new chiral center (Scheme 37). In both cases the starting menthone can be regenerated and used again.

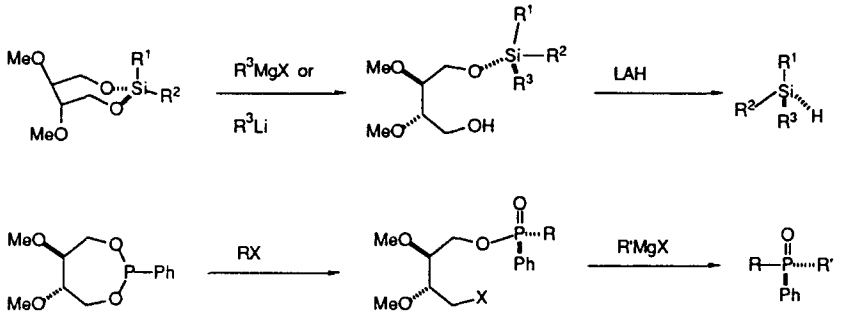
Scheme 37



Chiral diols with a C_2 axis of symmetry were employed for the asymmetric synthesis of silicon and phosphorus derivatives. Thus, silicon acetals were cleaved by a first nucleophile (RMgX or RLi), without the assistance of any Lewis acid ; the second nucleophile, a hydride H^-, cleaves the remaining Si-O bond by *anti*

process affording a chiral silicon hydride[92] (Scheme 38). The highest reported e.e. was 70%. In the phosphorus series, the first step is a diastereoselective Arbuzov reaction. Its diastereoselectivity varies from 11 to 99%. The resulting phosphinate is further reacted with a Grignard reagent, with inversion at phosphorus, affording a chiral phosphine oxide[93] (Scheme 38).

Scheme 38



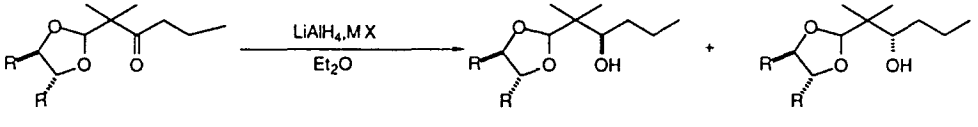
III. REACTIONS WITHOUT RING CLEAVAGE

The formation of a cyclic chiral acetal may serve other purposes than a diastereoselective cleavage reaction. The chiral environment, thus created, should influence the face selectivity of a proximal prochiral center. Steric as well as chelation factors account for the observed selectivities, and the nature of the diol plays a crucial role. A large array of chemical transformations have been investigated, with the acetal auxiliary in various relative positions to the prochiral center, either on the nucleophile or on the electrophile.

III. 1. Chiral acetals on the electrophile.

Perhaps, the most simple conceptual approach to such reactions is the attack of a carbonyl group next to a chiral acetal. Reduction, with $LiAlH_4$, of a ketone, β to a non functionalized dioxolane ring affords one major diastereomeric alcohol (d.e. 66%). However, addition of $MgBr_2$ gives the epimeric alcohol (d.e. 82%)[94]. Changing to a dioxolane having chelating heteroatoms on the ring improves the d.e. to 98%[95]. In this case, addition of MgX_2 salts does not change the selectivity (Scheme 39). This method was applied to a short synthesis of (+) Pedamide[95].

Scheme 39

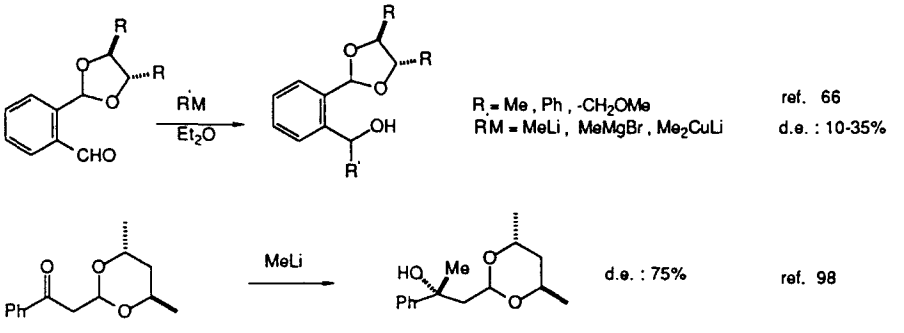


R = Me or Ph	$LiAlH_4$	83	17
	$LiAlH_4$ / $MgBr_2$	9	91
R = -CH_2OMe	$LiAlH_4$	99	1

This salt effect is observed again, even with functionalized acetals, when the ketone is α to the acetal ring[96]. It allows a high diastereoselection on cyclic diketone monoketals ($LiAlH_4$: 96/4 ; $LiAlH_4/MgBr_2$: 10/90). The best diol for this purpose is 1,4-dimethoxy-2,3-butanediol. A short synthesis of both enantiomers of 3'-methoxy-4'-O-joubertiamine uses this approach[97].

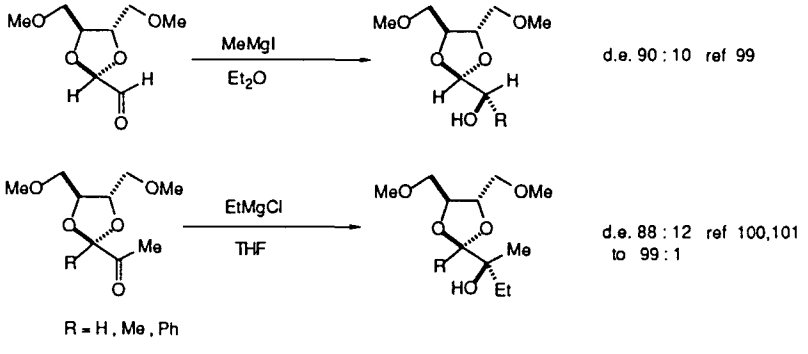
Reactions with organolithium and Grignard reagents have also been attempted. The acetal in β or γ[66,98] position does not affect significantly the C = O face selectivity of the attack (Scheme 40), except in one case[98] (RLi has to be used, and not RMgX).

Scheme 40



When the carbonyl group is located next to the acetal, much higher diastereoselectivities have been commonly attained. A number of papers deal with such a situation. Monoacetal of glyoxal, the most interesting case of the series, affords, at best, 80% d.e.[99]. When the carbonyl group is a ketone d.e.'s as high as 99% were obtained[100,101] (Scheme 41). Salt effects are quite important, with Grignard reagents being usually the best ones.

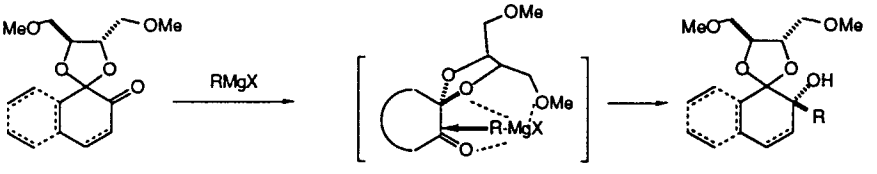
Scheme 41



Chelation of Mg by one of the methoxy groups of the acetal ring seems to direct the face selectivity. The same situation is encountered in the cyclic series, with monoketals of cyclic diketones[102,103]. Thus, efficient syntheses of (-)-7-deoxydaunomycinone[104] and (-)-γ-rhodomycinone[105] have been achieved.

Instead of an aldehyde or a ketone, an aldoxime functionality may lie next to the acetal ring. In this case, high chemical yields and excellent diastereoselectivities were obtained only with organocerium reagents[106]. The face selectivity is rationalized in the same way as for keto-ketals (Scheme 42). After reductive removal of the auxiliary diol, a chiral amine is thus obtained (for example (-) N-acetyl-amphetamine).

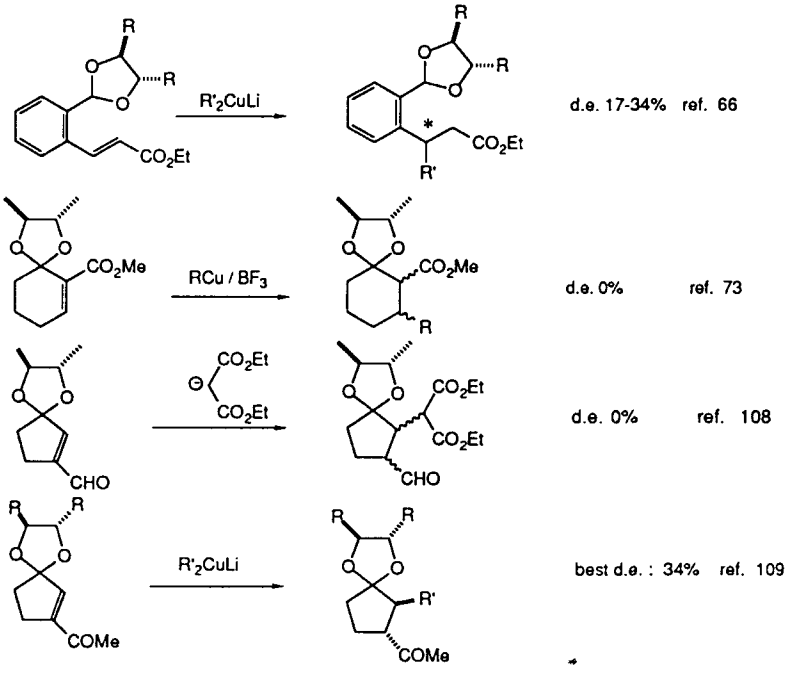
Scheme 42



Other nucleophiles, such as lithium enolates, have been described as being non-diastereoselective[107] on an aldehyde, β to a dioxane ring. No other, such examples were reported.

Double bond, activated by an electron-withdrawing group, is another kind of prochiral center. However, conjugate additions to enones or enoates bearing an acetal or ketal auxiliary, in various relative positions, met with little success (Scheme 43).

Scheme 43

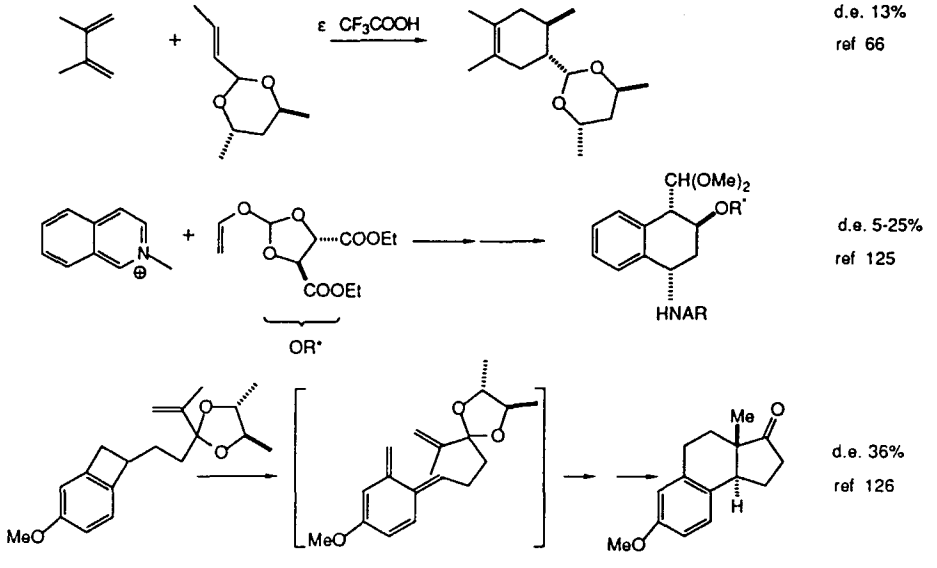


Thus, the activation of the C=C bond by an electron withdrawing group does not seem to be beneficial. Far better results were attained with simple α,β-ethylenic acetals and ketals, in, for example,

The cyclic ketones may be of any ring size, from 5 to 16 carbons, the best being medium and large rings (ratio 20 : 1)[123]. The method was applied to the synthesis of several natural products, (-)-modhephene[117,118], (R)-Muscone[119], Propellanones[120], (+)-β-Eudesmol[121] and (-)-Chokol A[122] (Scheme 45).

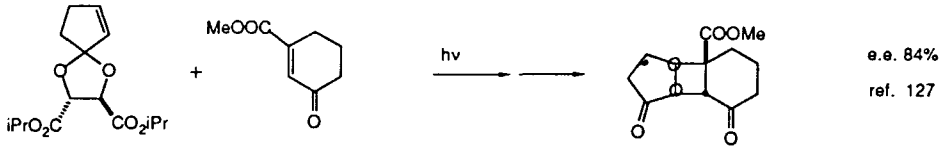
The Diels Alder reaction is another type of cyclisation reaction. However, in most cases, low to moderate selectivities were observed. Thus, activation of an α,β-ethylenic acetal, according to Gassman[124], was attempted on chiral acetal and dimethyl-2,3-butadiene. A high yield of cycloadduct was obtained but with a 13% d.e.[66] only. Condensation of isoquinolium salts with chiral vinyl orthoesters resulted in the formation of chiral tetralins[125]. The intramolecular version of the Diels-Alder reaction met also with little success, as far as chiral induction is concerned[126] (Scheme 46).

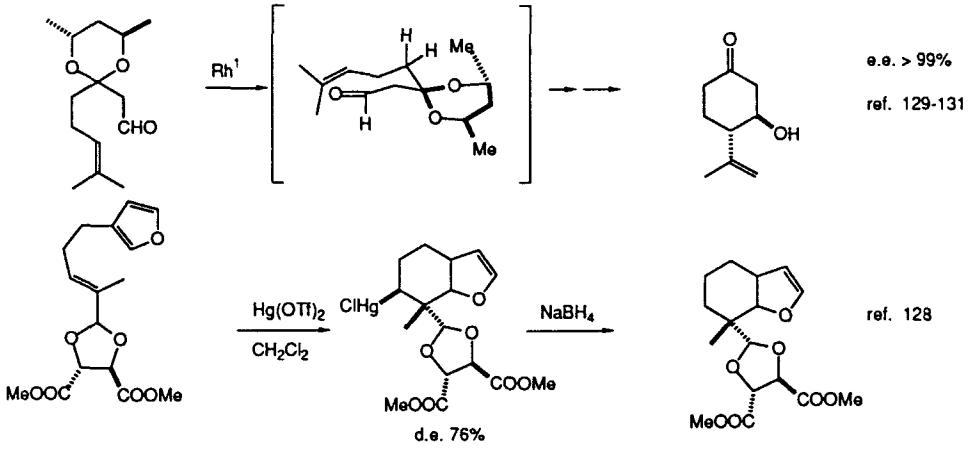
Scheme 46



Better diastereoselectivities were attained in other cyclization reactions, involving chiral acetals. A photochemical 2 + 2 addition employing an α,β-ethylenic ketal gave a d.e. = 84% ; the best auxiliary being diisopropyl tartrate[127] (Scheme 47). Again a tartaric ester was found to be the best one for an intramolecular Hg(II) promoted cyclization. The ratio of diastereomers (d.e. 76%) was determined before the reductive demercuration[128] (Scheme 47). In a different way, a Rh(I) catalyzed intramolecular cyclisation of a chiral ketal afforded a single diastereomer. A conformationnally rigid dioxane ring, arising from, 2,4-pentanediol, serves to maintain a tight transition state throughout the whole process[129-131] (Scheme 47).

Scheme 47

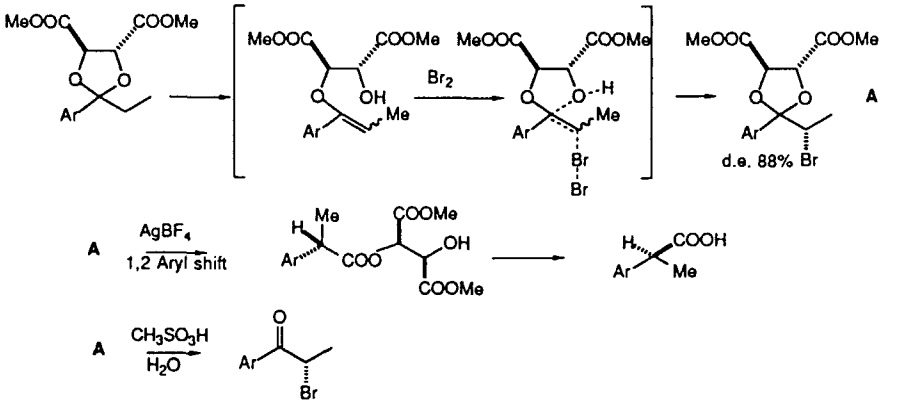




α,β-Ethylenic acetals and ketals have been used also in epoxidation and dihydroxylation of the double bond. The epoxidation of crotonaldehyde acetal (from 2,3-butanediol) with mCPBA gave an inseparable 1 : 1 mixture of both possible diastereomers[132]. On the other hand the OsO_4 catalyzed dihydroxylation, gave a 3 : 1 mixture of diastereomeric diols, which were very easy to separate by column chromatography[133,134].

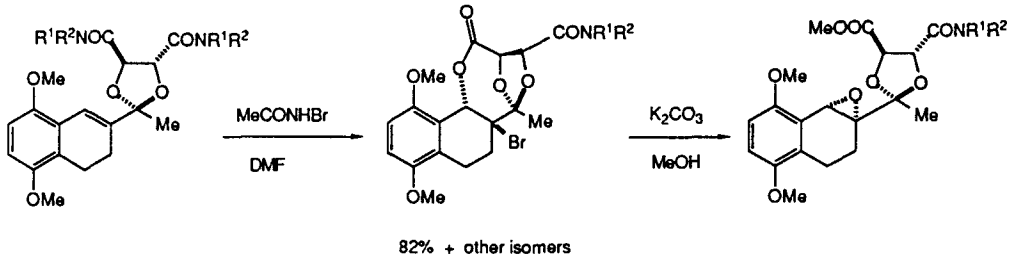
In all the above examples, the chiral acetal is not cleaved but directs the stereochemical course of the reaction, through chelation or steric effects. There are reactions in which, the acetal participates in the reaction process, but where the final product is again an acetal. Thus, bromination of the chiral ketal of an aryl alkyl ketone, afforded the α-bromo ketal with high diastereoselection[135]. The reaction probably proceeds through an enol ether (scheme 48). Careful hydrolysis of the ketal furnishes an optically active α-bromoketone[136], which can serve for the synthesis of chiral 2-alkyl-2-arylacetic acids[137], such as S(+)-Naproxen[138] and S(+)-Ibuprofen. It should be noted that this synthesis has been scaled up into an industrial process by the Zambon Group. Thus Naproxen is one of the very few examples in the world of a large scale asymmetric synthesis. An analogous bromination sequence on a phosphonoacetal, allows the synthesis of chiral Fosfomycin[139].

Scheme 48



Optically active anthracyclinones were obtained via bromolactonisation of a chiral α,β-ethylenic ketal. The chiral auxiliary was a tartaric acid diamide which, again, participates in the reaction process. Formation of the epoxide releases the ketal ring[140-142] (Scheme 49).

Scheme 49

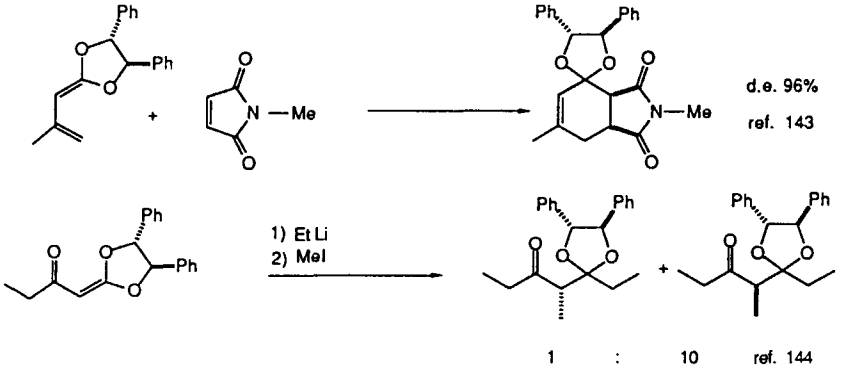


82% + other isomers

III. 2. Chiral acetals on the nucleophile.

The diastereoselective reaction of a chiral nucleophile having an acetal appendage, are very scarce. Thus, ketene acetals have been used in asymmetric synthesis, with diphenyl 1,2-ethanediol seeming to be the best auxiliary in cycloaddition reactions[143], as well as in conjugate addition-enolate trapping reactions[144]. In this latter case the diastereoselective step is the reaction of the formed enolate, the chiral acetal lying on the nucleophile (Scheme 50).

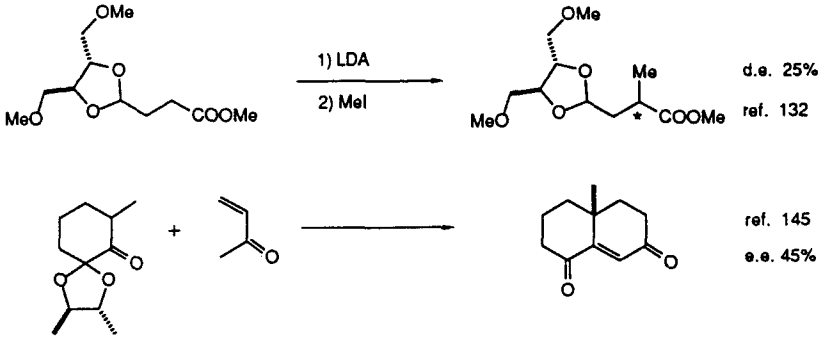
Scheme 50



1 : 10 ref. 144

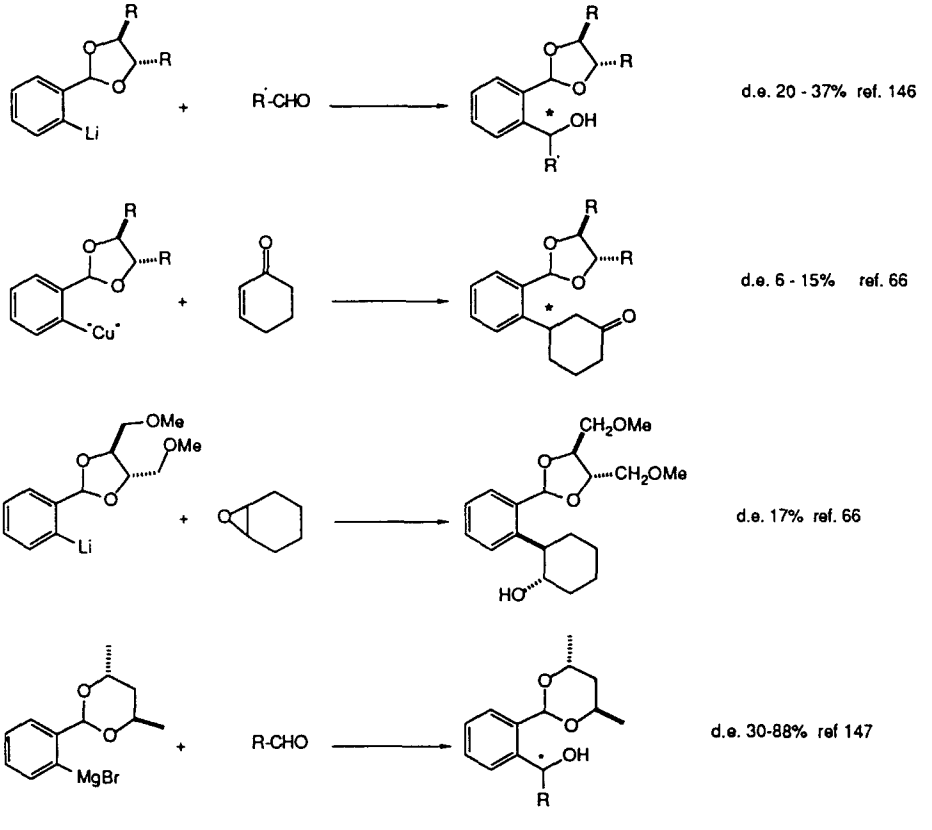
In such enolates, the chiral acetal ring has to be in a close proximity, for a better diastereoselection (possibly through chelation effects). However when the acetal is in β-position[132] chelation factors are not enough for that purpose. The E- or Z-geometry of the enolate should also play a role, and a stereodefined cyclic enolate, in a Robinson annellation, leads to a much better outcome (Scheme 51).

Scheme 51



Other organometallic derivatives than enolates have been tested. The most studied is a phenyl metal derivative bearing, in the ortho position, a chiral acetal auxiliary[66,146,147]. The diastereoselectivity depends, now, not only on the type of acetal, but also on the substrate (generally an aldehyde) and on the kind of metal. The examples shown in Scheme 52 are illustrative.

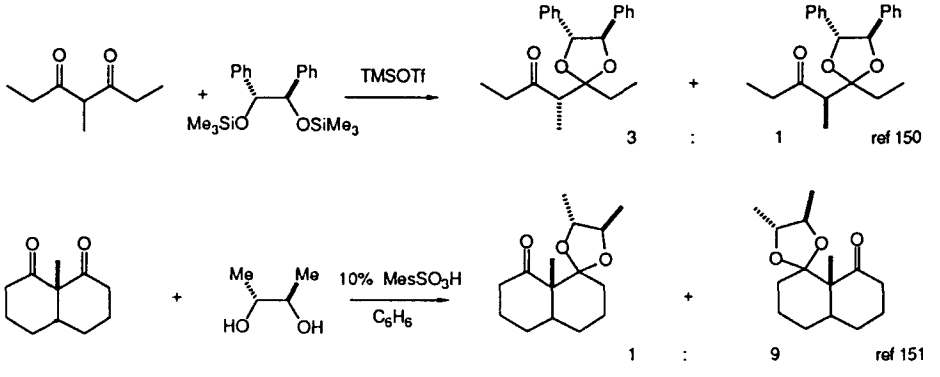
Scheme 52



III. 3. Miscellaneous uses of chiral acetals.

The acetalization reaction can be used by itself with a homochiral diol and a chiral racemic carbonyl compound. Although conceptually attractive, the method has met with limited success[148,149]. Closely related is the enantiotopic differentiation of prochiral diketones through monoacetalization. Two remarquable examples[150,151], are shown in Scheme 53. It should be pointed out that these selectivities are sensitive to many factors such as the acidity of the catalyst, the diol and the method of acetalization.

Scheme 53

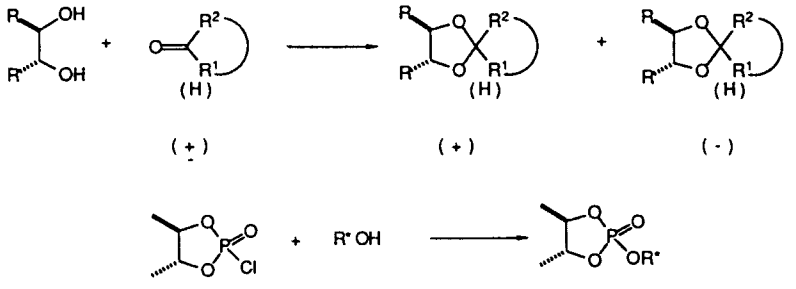


The formation of a chiral acetal can be useful for goals other than asymmetric induction. Thus, resolution of ketones has been achieved through their transformation into the diastereoisomeric ketals, with a chiral diol. After separation by crystallisation, or gas or liquid preparative chromatography, each diastereomer gives back the starting ketone in an optically pure state. Depending on the ketone, 2,3-butanediol[152-154], 1,4-dimethoxy-2,3-butanediol[155,156], 1,2-diphenyl ethanediol[148] or diethyl tartrate[157] have been proposed as the best diol. Although this approach seems efficient in some cases, no general rule can be drawn from the above results. These diasteromeric ketals or acetals, may also serve for analytical purposes. Hence a method for the determination of the enantiomeric excess of chiral ketones or aldehydes (and even some lactones[158] !). Indeed, when a chiral cyclanone is ketalized with (R,R) 2,3-butanediol, the diastereomeric ketals are easily distinguishable by ^{13}C NMR[159] (Scheme 54). Moreover it is also possible to assign the absolute configuration[149].

This method met with a large success and is routinely used nowadays. However, *ketals* of acyclic ketones[160] and *acetals*, do not give always a clean baseline separation of NMR peaks. In some cases, the use of (R,R) 2,4-pentanediol permits a separation of the diastereomeric ketals[72] or acetals[70,161,162] on G.C., and allows a more accurate value of purity. Finally, 1,4-dimethoxy-2,3-butanediol seems also useful for certain ketones[155] or aldehydes[163].

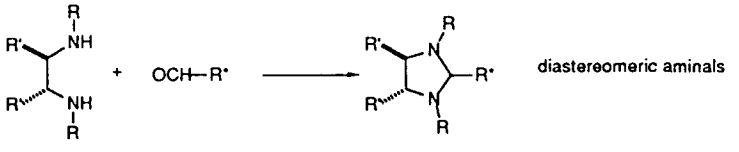
Another analytical use of chiral acetals, but this time on phosphorus, has been described for the determination of enantiomeric excess of chiral alcohols (scheme 54). The method is based on the formation of diastereomeric phosphates which are easily distinguished by ^{31}P NMR, where no other signals than those of phosphorous may interfere on the spectrum[164].

Scheme 54



From the above overview it seems clear that chiral acetals evolved rapidly as useful auxiliaries even when they are immolated in favor of more valuable chiral compounds. The presence of a C_2 axis of symmetry in the acetal, to which this review has been restricted, greatly helps the chemist in his conceptual strategy as well as in practical handling of the molecules. It is from these considerations, and by analogy to acetals, that the authors developed the nitrogen analogues, *viz* chiral aminals with a C_2 axis of symmetry (Scheme 55), which appear to be also excellent auxiliaries in asymmetric synthesis[146,163,165-170].

Scheme 55



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