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Allylic Protecting Groups and Their Use in a Complex Environment
Part I : Allylic Protection of Alcohols

François Guibé

Institut de Chimie Moléculaire d' Orsay, Laboratoire des Réactions Organiques Sélectives, associé au CNRS, Bât. 420, Université Paris-Sud, 91405 Orsay (France)

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1. GENERAL INTRODUCTION

The first mention of allylic protecting groups dates back to 1950 when C. M. Stevens and R.Watanabe reported on the use of the allyloxycarbonyl (Alloc) group for protection of amino groups in aminoacids[1]. At that time unfortunately, no specific methods were available for the selective cleavage of the Alloc group[1,2].

E-mail: fraguibe@icmo.u-psud.fr *FAX: (33) 1 69 15 46 80*

As a result, the Alloc group did not appear to offer any definite advantage[2] over other carbalkoxy entities, especially over the already popular carbobenzyloxycarbonyl (Cbz)[3] group and these preliminary investigations were not followed by further applications.

The real starting point of allylic protective chemistry took place in the mid-sixties when R. Gigg proposed[4] to use the allyl (All) group for protection of hydroxyl groups in oligosaccharides. The specifically designed[4] deprotection strategy was based on prior prop-2-enyl (allyl) to prop-1-enyl isomerisation followed by cleavage of the enol ether thus formed under usually mild conditions. According to Rudinger's terminology[5], the allyl group thus belongs to the class of safety-catch protecting entities, which means that an initially quite stable protecting group is converted, through a specific reaction, to a more labile one as a prelude to the final cleavage step. The term relay-deprotection[6] has also been applied to this methodology.

Another impetus to allylic protective chemistry was given around 1980 by the introduction of catalytic palladium π-allyl chemistry for direct cleavage of allylic entities[7]. At this time, palladium-catalysed allylic alkylation reactions[8] were already in full development in synthetic organic chemistry, due to the work of several groups, chiefly those of J. Tsuji and B. M. Trost. One of the main consequences of the eruption of the Tsuji-Trost reaction in protective group chemistry was to extend the use, on a wide and still growing scale, of allylic protection strategies in the fields of peptide and nucleotide chemistry.

Together with some cleavage procedures based on the use of *stoichiometric* quantities of palladium salts, the two deprotection methods mentioned above are by far the most common strategies for allylic groups removal. Their specificity and, in most cases, the mildness of their reaction conditions make them highly tolerant of other functionalities or protecting groups. Conversely, the allylic protecting groups are, on the whole, quite robust and withstand the removal conditions of many other protecting entities. An obvious limitation is their incompatibility with reagents which do not respect the ethylenic bonds, which include among others, many oxidizing agents as well as some reducing agents. For instance, the hydrogenolytic procedures used for the removal of benzylic goup usually results in partial cleavage and in partial reduction to propyl groups[1,2,6].

It should also be pointed out, at the outset, that the two main methods for allylic group removal differ in their scope and limitations. Direct palladium catalysed cleavage works only for those allyl-protected functions that possess sufficient leaving group ability to allow formation of a π-allyl palladium intermediate. Allyl derivatives of carboxylic acids and phenols and allyloxycarbonyl derivatives of alcohols and amines satisfy this criterion. For such compounds, π-allyl palladium based procedures, which are generally more straightforward and easy to carry out, seem by now to have more or less superseded the isomerisation methods. On the other hand, those latter ones remain mandatory (and very useful) for such important allyl derivatives as allyl amides and, above all, allyl ethers.

In accordance with the above considerations, this review is divided in two parts. The present one essentially deals with allyl ethers and other allyl protected derivatives which are not, as a rule, amenable to deprotection through *catalytic* palladium π-allyl methodology. The second one, which will be published later, will be devoted to catalytic palladium π-allyl allylic deprotection and will include a detailed survey of the applications of allylic protective group chemistry to the peptide and nucleotide fields.

The deprotection procedures of allyl amines which are either similar to those of allyl ethers or involve catalytic palladium π-allyl chemistry are accordingly dealt with in Part I and Part II respectively.

Allyl ether protecting groups are of great importance in carbohydrate chemistry, being especially used as temporary protections in the presence of permanent benzylic ethers . Allylic protection strategies in this field have already been the subject of several comprehensive articles[8]. Consequently, they are not specifically treated in this report and only selected examples are given in the section devoted to allyl ethers and allyl amines deprotection.

2. PART I : ALLYLIC PROTECTION OF ALCOHOLS

2.1. FORMATION OF ALLYL ETHERS.

This section will be limited to the introduction of the simplest and by far the most widely used allyl (All) group. The introduction of other more elaborate allylic protections will be discussed in section 2.4.

2.1.1. **Reaction of alkalinometal alkoxides with allyl halides**

The most obvious method of preparing allyl ethers is to react alkalinometal alkoxides with allyl bromide or iodide. This reaction is best carried out in a polar solvent, usually DMF[10].

Two main disadvantages are, however, associated with the Williamson synthesis: the strongly basic conditions involved which limit its scope, and the fact that it does not allow any reasonable chemo- (mono *versus* polyalkylations) or regioselectivity when dealing with polyhydroxycompounds. Two methods offer the possibility to overcome partially these difficulties. The first one, which is based on the use of tin alkoxides, is not limited to allylation reactions but applies to alkylation reactions in general and to reactions with other electrophiles as well such as acylating or sulfonylating agents. The second one is specific for the allyl group and involves palladium-catalysed extrusion of CO_2 from allylic carbonates.

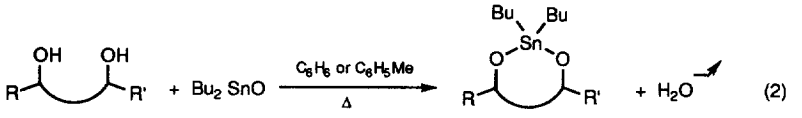
2.1.2. **The tin methods**[11]

. Hydroxy groups may be alkylated, without the need of any added base, after prior conversion to tributylstannyl ethers or, in the case of diols, to dibutylstannylidene acetals.

Tributylstannyl ethers are readily prepared[11a] by heating alcohols and bis(tributyltin)oxide in benzene or toluene with azeotropic removal of water (eq. 1), or in toluene or acetonitrile[12] in the presence of molecular sieves.

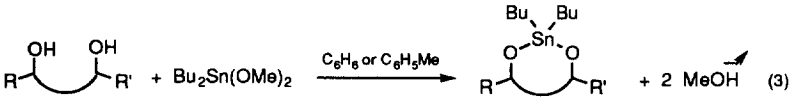
$$2\ ROH + Bu_3SnOSnBu_3 \xrightarrow[\Delta]{C_6H_6 \text{ or } C_6H_5Me} 2\ ROSnBu_3 + \overset{-}{H_2O} \quad (1)$$

Cyclic dibutylstannylidene acetal derivatives of diols are similarly prepared by use of polymeric dibutyltin oxide[11a] (eq. 2). Preparation of such derivatives under microwave heating has recently been reported.[13]



(2)

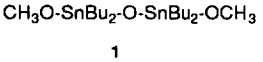
It has also been recently emphasized that dibutylstannylidene acetals are obtained more rapidly and under milder conditions if commercially available dibutyltin dimethoxide is substituted for Bu_2SnO[14] (eq. 3).



(3)

Dibutylstannylidene acetals have also been prepared by heating diols and Bu_2SnO in anhydrous methanol followed by evaporation of the solvent, in which case the true stannylating species is believed to be the intermediate **1** [11a]. There are some indications that under such conditions concomitant methanolysis of ester functions, when present in the molecule, may occur[15].

Alkoxytributyltin compounds are very sensitive towards hydrolysis, readily giving back the alcohol and bis(tributyltin)oxide. Dibutylstannylidene acetals, on the contrary, are usually more stable; indeed, some of them (*e.g.* **2**) may even be recrystallized from methanol.[16]



1

2

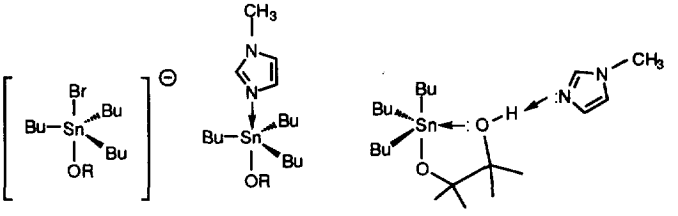
Tin alkoxides are readily acylated with acyl chlorides, but alkylation reaction are much more sluggish. Alkylating tributyltin ethers typically requires prolonged heating (several days) in toluene or in the alkylating agent without solvent. Dibutylstannylidene acetals are still less reactive and alkylation is possible only in polar solvents (usually DMF).

To facilitate the reaction, a most useful technique, first introduced by Veyrières, is catalysis by such species as tetrabutylammonium halides[17, 18], cesium fluoride[14] or *N*-methylimidazole[19-21]. This method works for tributyltin ethers and for stannylidene acetals as well and the latter species may then be alkylated in non-polar (usually aromatic) solvents.

It was firstly proposed that the catalytic effect of tetrabutylammonium halides could involve the formation of very reactive tetrabutylammonium alkoxides according to equilibrium reactions of eq. 4[13].

$$ROSnBu_3 + X^- N^+Bu_4 \rightleftharpoons [ROSnBu_3X]^- N^+Bu_4 \rightleftharpoons RO^- N^+Bu_4 + Bu_3SnX \quad (4)$$

Another and probably more likely explanation is that the reactive species are anionic or neutral pentacoordinated tin species such as **3** (already proposed in eq. 4, but as a non-reactive intermediate on the way to tetraalkylammonium alkoxides), **4**[21] or **5**[21]. Similar activation processes through the formation of penta- or hexacoordinated species are well recognized in tin[22] as well as silicion[23] chemistry.

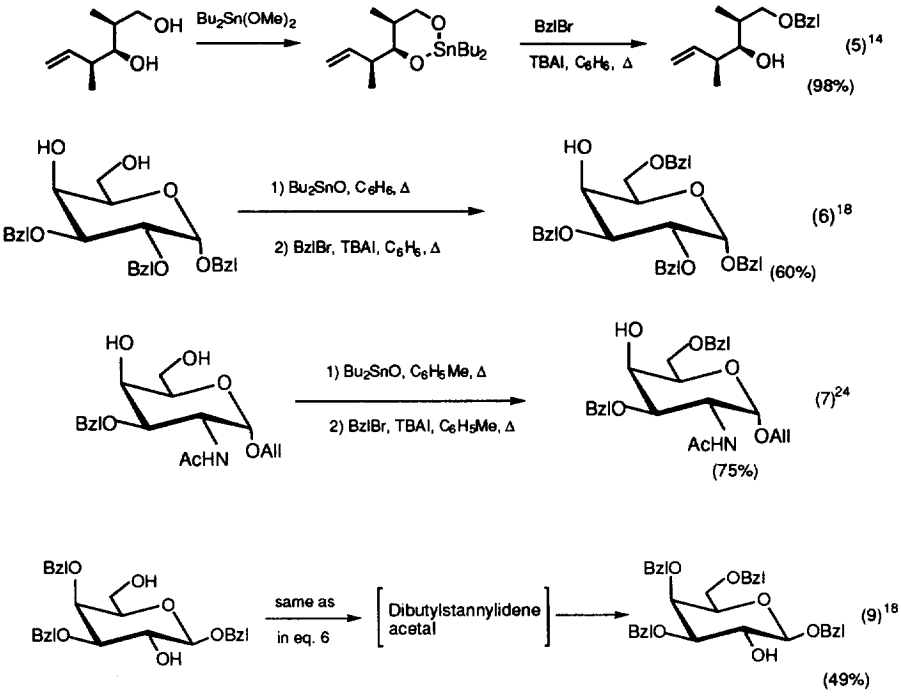


3 **4** **5**

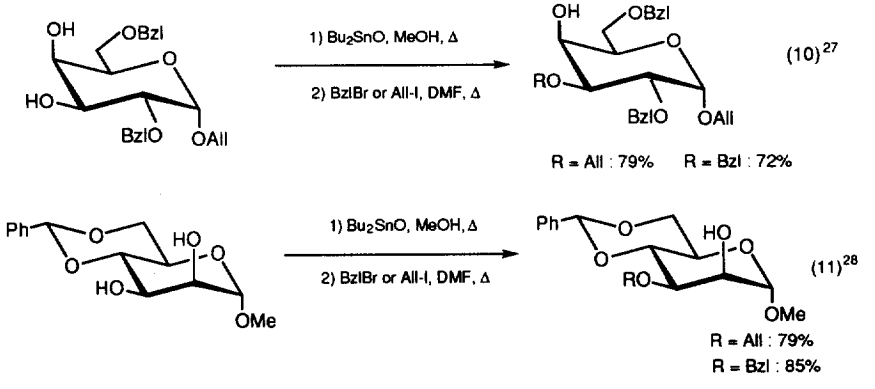
The alkylation of alkoxytin derivatives undoubtly occurs under much milder conditions (in terms of basicity) than those of the classical Williamson synthesis and is compatible for instance with the presence of azido groups[14], *O*-TBDMS groups[14] or acetamido groups[24]. More importantly, they may also allow chemo- and regioselective introduction of alkyl group on polyhydroxy compounds. As such, they have been extensively used in the carbohydrate field. A complete survey of the literature on that subject is outside the scope of the present review and only the essential features of this chemistry will be given here. Neither will we enter into a full discussion of the interpretations of the observed selectivities which may be found in various reviews or articles[11,21,25,26]. It is however important to note, at the outset, that the selectivities observed not only depend on the structure of the polyhydroxylic substrate but are also strongly influenced by the reaction conditions such as the use or not of solvents or of catalysts, and that finding optimum conditions is not always straightforward.

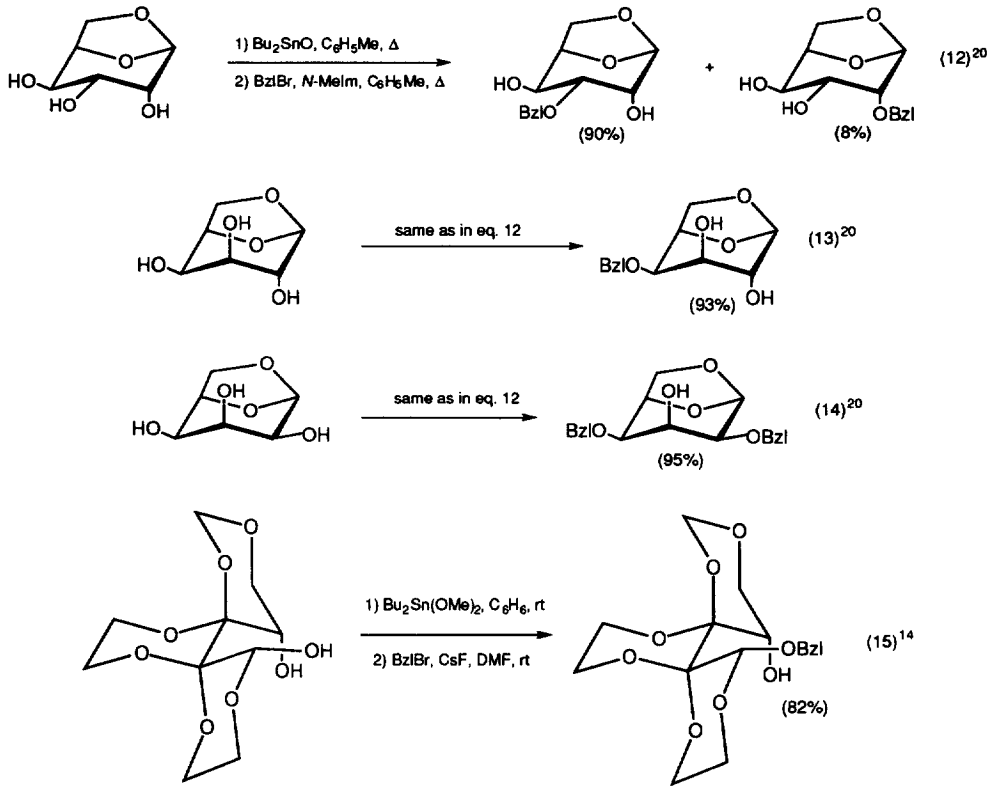
Roughly speaking, it may be said that the tin methodologies tend to increase the inherent differences of reactivity of hydroxy groups towards electrophilic species, which is in the order: 1° OH > 2° eq. OH > 3° ax. OH. When comparisons can be made, there does not seem to be significant differences in selectivities between benzylation and allylation reactions. Therefore, references to both types of reactions will be made in the following discussion.

Dibutylstannylidene acetals derived from mixed 1°-2° alcohols are alkylated at the 1° position. Illustrative examples featuring an acyclic diol and several galactosyl derivatives are given in eq. 5-9[14,18,24]. In the benzylation of benzyl 3,4-di-*O*-benzyl-α-D-galactopyranoside, a boat conformation has been suggested for the intermediate dibutylstannylidene acetal[18].

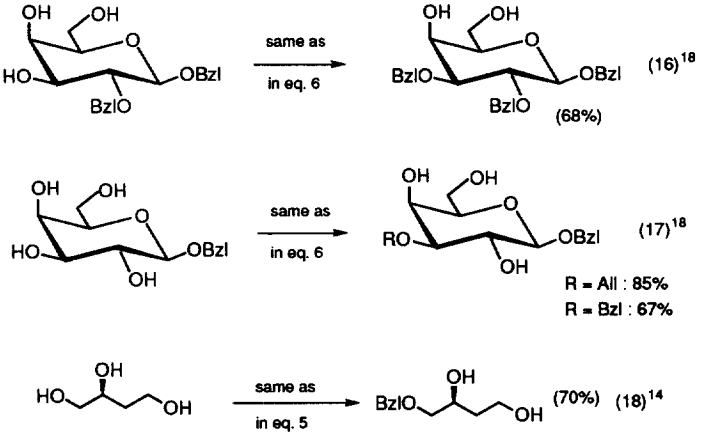


Cyclic dibutylstannylidene derivatives of *cis*-1,2-cyclohexanoid diols are selectively alkylated at the equatorial position[14, 20, 27-29] as illustrated in eq. 10[27] for the galactose and eq. 11[28] for the mannose series and in eq. 12-14 for several 1,6-anhydro-β-D-hexapyranoses[20]. Note the bis-alkylation of 1,6-anhydro-β-D-talose in which the two hydroxy group at C(2) and C(4) are "activated" by the same hydroxy group at C(3) (eq. 14). Eq.15[14] features an interesting case in which the two hydroxyl groups of the axial-equatorial pair belong to two different six-membered cycles.

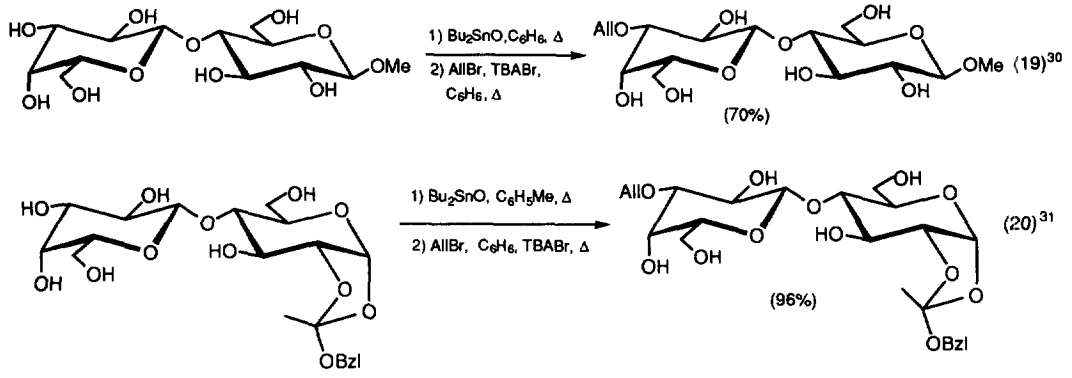




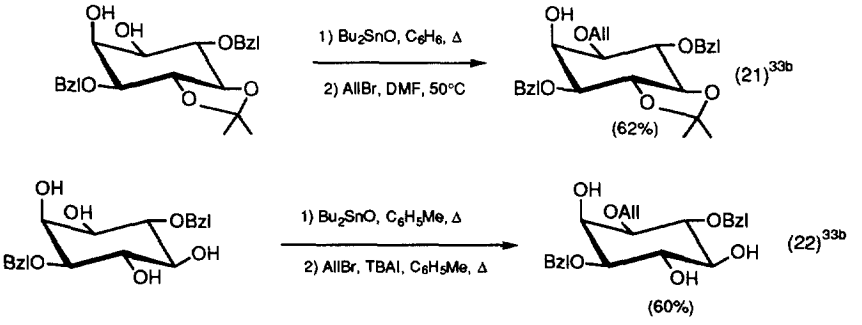
Five-membered cyclic stannylidene acetals are quite stable species and their formation is highly favoured. As a result, very good regioselectivities may be obtained, even if extra OH groups, including 1° ones, are present in the molecule, as illustrated[18] in eqs. 16-17 (see also eq. 12). This also applies to acyclic compounds, as exemplified[14] in eq.18.



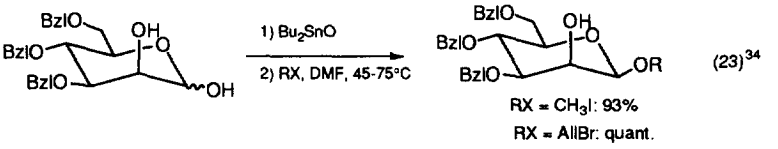
Most impressive examples[30-32] are the selective *O*-allylation of the largely unprotected disaccharides represented in eqs. 19 and 20.



Selective allylation of *myo*-inositol derivatives have been extensively studied by Nashed and Anderson[27] and by Gigg and coworkers[10,33] (eqs. 21-22).

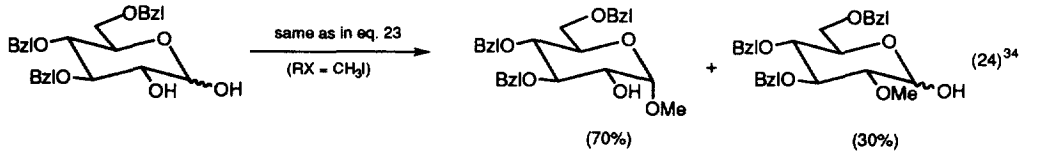


The stannylidene method has also been used for introduction of alkyl groups at the anomeric hydroxyl group. Thus, the otherwise difficult to prepare β-D-mannopyranosides have been obtained from β-D-mannopyranoses derivatives having a free OH group at C(2) (eq. 23)[34].

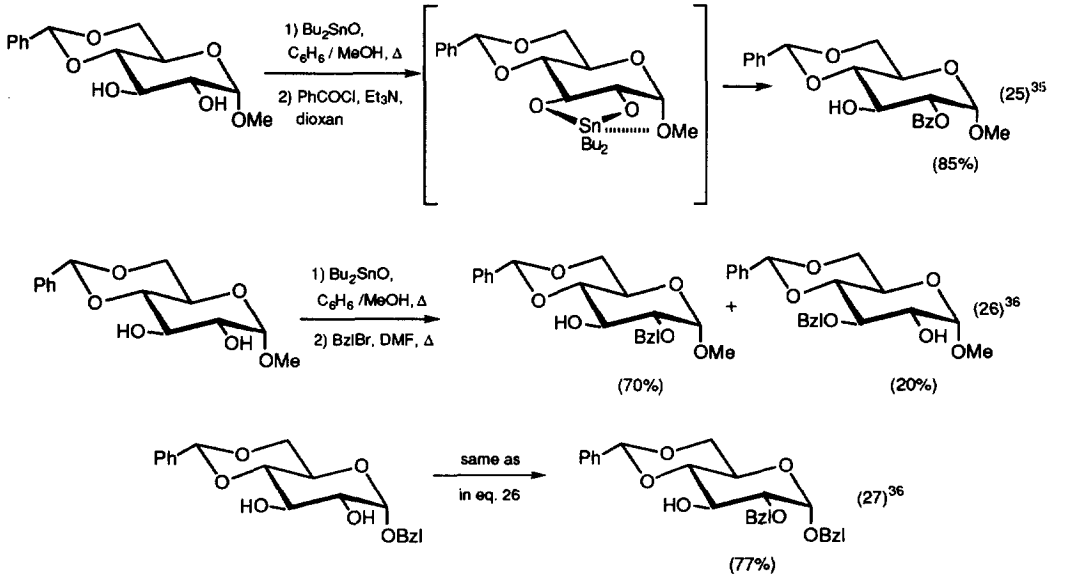


In the glucose series the reaction is no longer regiospecific and gives a mixture of 3,4,6-tri-*O*-benzyl-2-*O*-methyl-D-glucopyranose and methyl 3,4,6-tri-*O*-benzyl-α-D-glucopyranoside (eq. 24)[34]. In this case

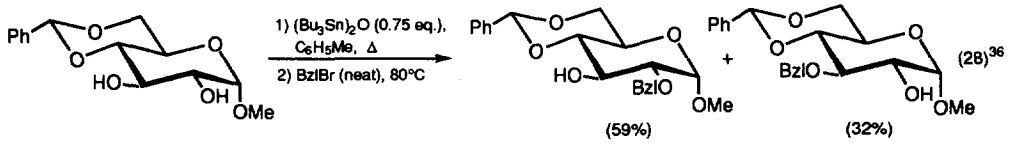
presumably, the anomeric oxygen atom adopts an axial orientation in the intermediate stannylidene derivative and its nucleophilicity is enhanced by electronic factors related to the anomeric effect.

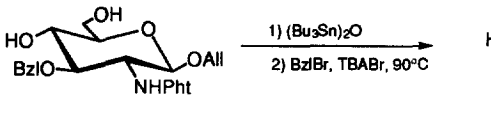


Stannylidene acetals derived from equatorial-equatorial *trans*-1,2-cyclohexanoid diols do not exhibit such good regioselectivities in alkylation reactions as their *cis* axial-equatorial congeners. Nevertheless, if one of the oxygen atoms engaged in the dioxastannolane ring is vicinal to a third axially orientated oxygen site, reasonable selectivities in its favor are generally observed, as illustrated in eq. 25[35] (which features an acylation reaction) and in eqs. 26-27[36]. This has been accounted for[35] by a labilization of the corresponding tin-oxygen bond through coordination of the tin atom to the neighbouring oxygen.

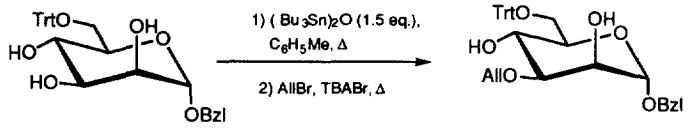


When polyols are reacted with a limited amount of bis(tributyltin) oxide, preferential stannylation may occur at some sites and selective alkylation will ensue[17, 36-41]. Some examples of alkylation reactions of such partially stannylated polyols are given in eqs. 28-35.

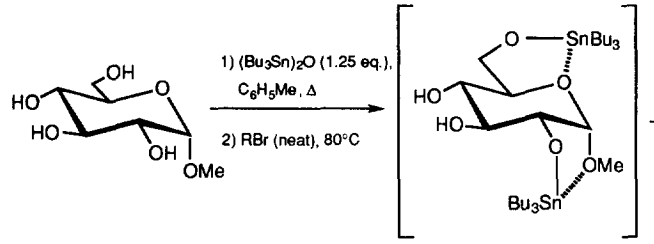




(29)[37]



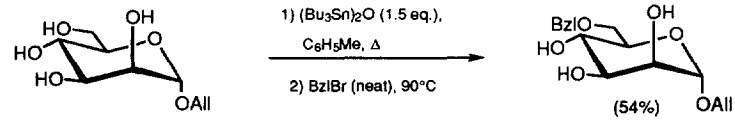
(30)[17]



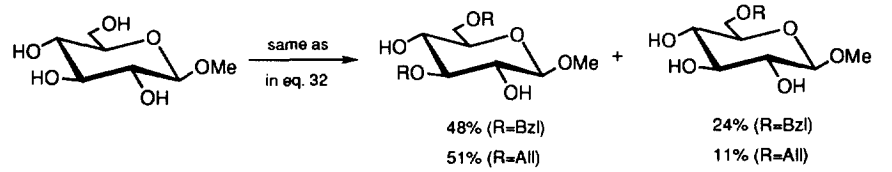
(31)[38b]

RX = AllBr: $R^1=R^2=All$, $R^3=R^4=H$: 42%; $R^1=R^3=All$, $R^2=R^4=H$: 8%; $R^1=All$, $R^2=R^3=R^4=H$: 23%

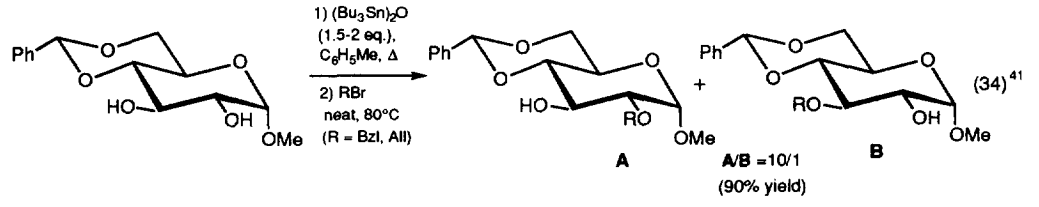
RX = BzlBr: $R^1=R^2=Bzl$, $R^3=R^4=H$: 31%; $R^1=R^3=Bzl$, $R^2=R^4=H$: 5%; $R^1=R^4=Bzl$, $R^2=R^3=H$: 6%; $R^1=Bzl$, $R^2=R^3=R^4=H$: 49%



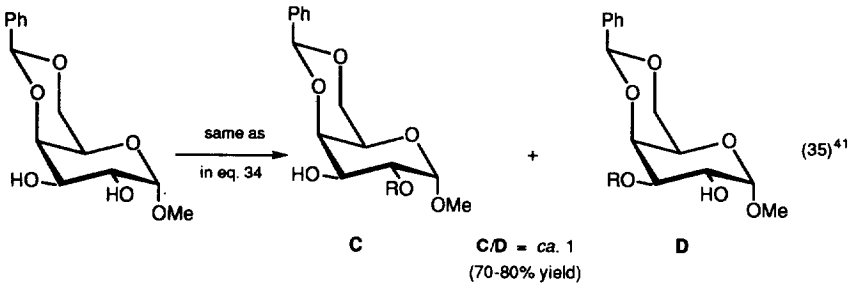
(32)[39]



(33)[40]



(34)[41]



From these examples, it may be seen that the tributyltin alkoxide method favours primary hydroxyl groups. It also favours secondary equatorial hydroxyl groups when a vicinal axially orientated oxygen is present. Particularly instructive in that respect is the comparison[41] of the regioselectivity of alkylation of 4,6-*O*-benzylidene-α-D-gluco- and galacto-pyranosides (eqs. 34-35). The regioselectivity in favor of 2-substitution is excellent for the glucoside but not for the galactoside in which both equatorial OH are "activated" by a vicinal axially orientated oxygen function. A comparison can be drawn between the stability of the five membered coordination ring system **6** formed in the tributyltin method and that of stannylidene acetals derived from axial equatorial *vic* diols **7**.

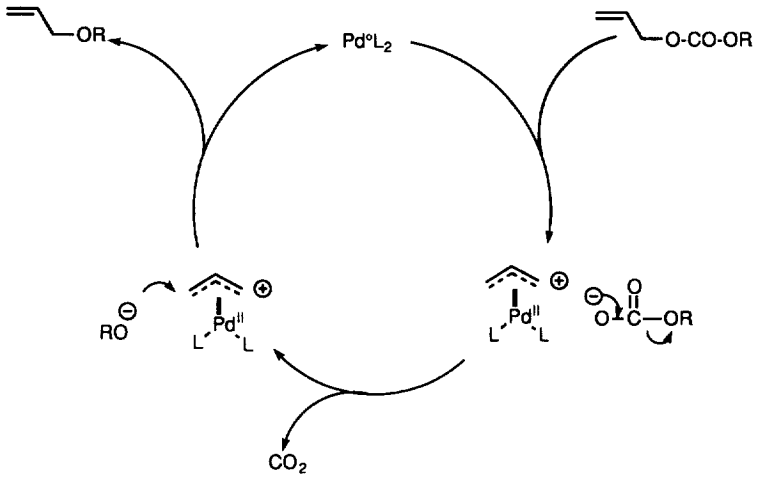
6 **7**

The selectivities offered by the tin alkoxide method are, on the whole, not so clear-cut as those derived from stannylidene acetals (see for instance eqs. 26 and 28), but it should be borne in mind that the selectivities are also highly dependent on the exact reaction conditions (compare for instance eqs. 26, 28 and 34, all of which involving benzylation of 4,6-*O*-benzylidene-α-D-glucopyranosides). Furthermore, the scopes of application of the two methods are not identical. Note for instance the selective alkylation at O(6) without concomitant alkylation at O(3) of the unprotected mannopyranoside of eq. 32 or the direct dialkylation at O(3) and O(6) of methyl glycopyranoside (eq. 33). In particular, the tin alkoxide method constitutes a useful complement in cases when the desired selectivity cannot be attained through stannylidene acetals derived from suitable *cis* axial-equatorial dihydroxyl systems.

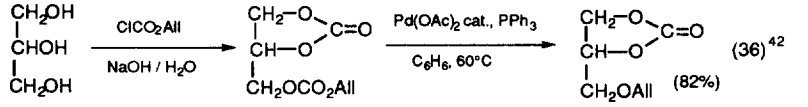
2.1.3. **Palladium catalysed decarboxylative rearrangement of mixed allyl alkyl carbonates**

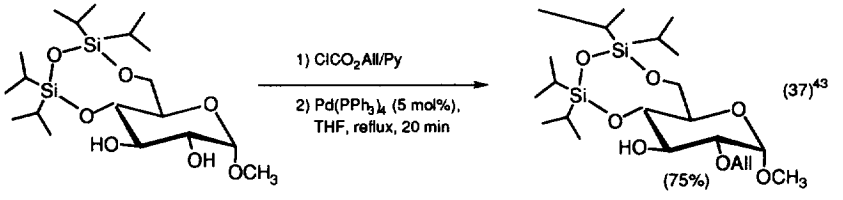
Alkyl allyl carbonates undergo decarboxylative rearrangement[42] when heated at 50-70 °C in the presence of palladium catalysts. This reaction, whose mechanism is represented on fig. 1 occurs under

Fig. 1

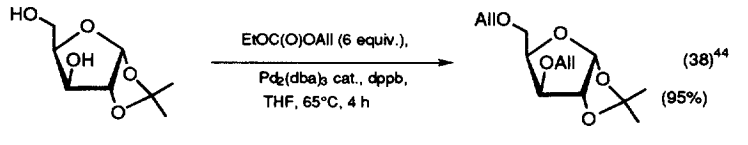


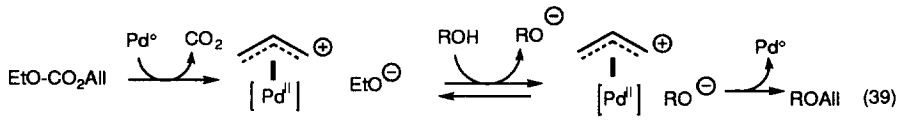
only moderately basic conditions since the concentration of alkoxide species cannot excede that of the catalyst and may very well be much lower if the rate determining step of the catalytic cycle is not its condensation reaction with the π-allyl palladium entity. Therefore, conversion of alcohols to allyl carbonates, followed by palladium catalysed extrusion of CO_2, constitutes a milder alternative to the classical Williamson-type procedure. It has been successfully applied to base sensitive substrates (eqs. 36-37[42,43]), especially to 1,1,3,3-tetraisopropyldisiloxane-1,3-diyl (TIPS) derivatives of carbohydrates (eq. 37[43]).



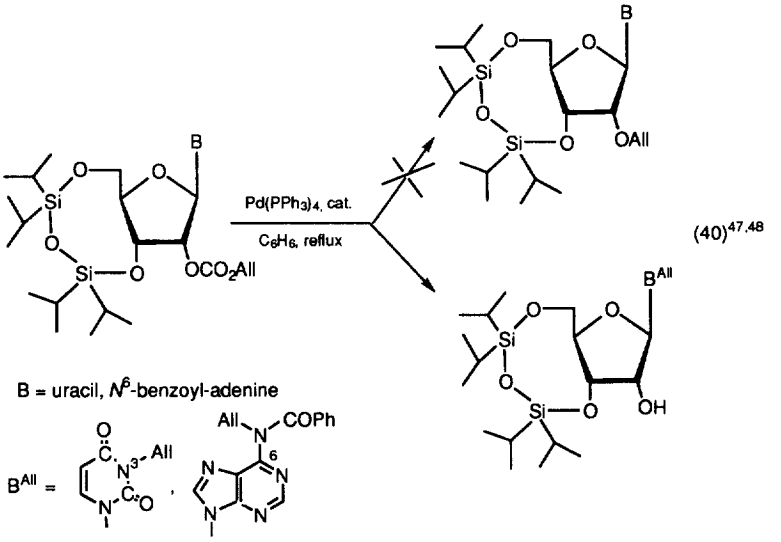


It has been further demonstrated by Sinou and co-workers[44, 45] that allyl ethers may be obtained directly by reacting alcohols with ethyl allyl carbonate in the presence of catalyst, as shown for instance in eq. 38. This procedure must involve a proton exchange between the first formed ethoxy palladium π-allyl intermediate and the alcohol substrate (eq. 39).





Owing to the existence of such prototropic processes, formation of allyl ethers from allylcarbonates with conservation of the regiochemistry in molecules bearing extra free OH groups can hardly be expected[46]. The example of eq. 37[43] constitutes an exception which can be explained by the fact that the reactivity of the 3-OH group is reduced by the vicinity of the bulky TIPS group. Prototropic equilibria also prevented the selective allylation of the 2'-hydroxy function of ribonucleosides through catalytic decarboxylation of 2'-*O*-Alloc-3', 5'-*O*-TIPS precursors[47, 48]. In these reactions, allyl transfer to the nucleobase instead of the 2'-OH group was observed, as exemplified in eq. 40. Selective transfer to the 2'-OH in the case of these two nucleosides could nevertheless be achieved after respective *N*-3 protection and N^6, N^6-bisprotection, by the benzoyl group, of the uracil and adenine residues.

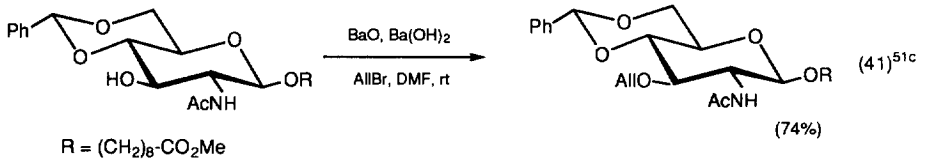


Intra- and intermolecular competitive experiments carried out by Sinou and co-workers[49] on Alloc derivatives of carbohydrates having free hydroxyl groups led to the conclusion that preferential allyl group transfer occurs in the order: primary hydroxyl< secondary hydroxyl <anomeric hydroxyl groups.

Finally, mention should be made that palladium catalysed decarboxylative rearrangement of *O*-allyl *S*-alkyl dithiocarbonates to thioallyl ethers has also been reported[50].

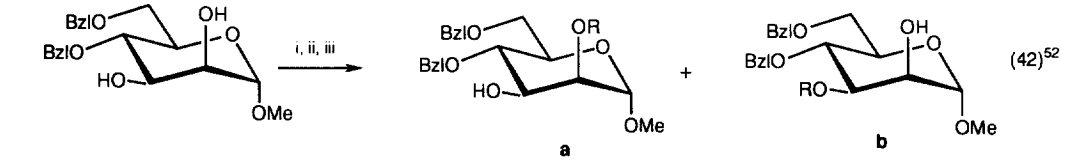
2.1.4. **Miscellaneous**

Alcohols may be alkylated after conversion to their barium salts. This technique is employed in the case of *N*-acyl derivatives of aminosugars[51] (eq. 41) to avoid any risk of alkylation at nitrogen which would accompany the use of sodium hydride as the base.

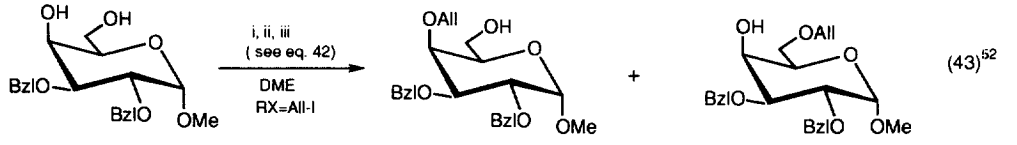


(41)[51c]

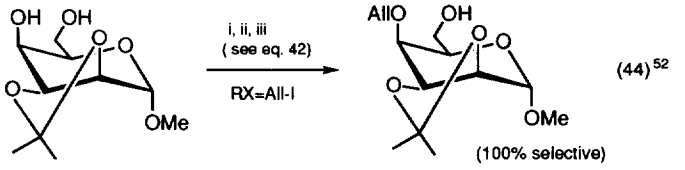
Diols have also been alkylated as their copper(II) salts[52] (eqs. 42-43). Under such conditions, chemoselectivity towards formation of the monoalkylated product is high. Furthermore, good regioselectivities towards alkylation at the 4-OH position are usually obtained with 4-OH, 6-OH free monosaccharide derivatives.



(42)[52]



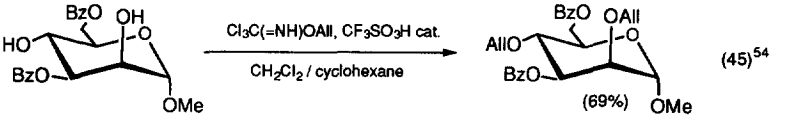
(43)[52]



(44)[52]

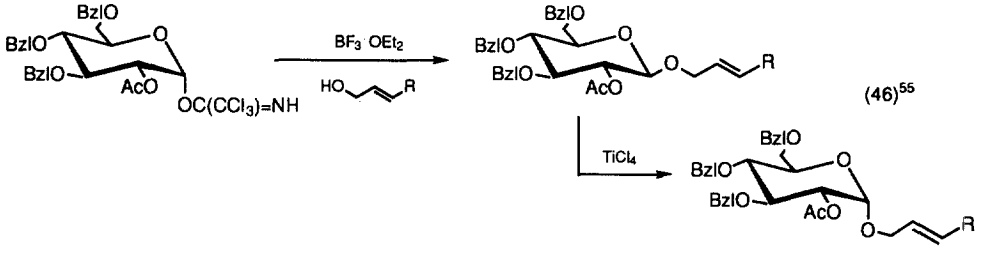
Partial substitutions of hydroxyl groups in carbohydrate chemistry have been carried out under phase transfer catalysis[53]. In hexapyranosides, preferences for 2- and 6-substitution are usually shown, but, as far as alkykation reactions are concerned (BzlBr, tetrabutylammonium hydrogenosulfate, aqueous NaOH, CH_2Cl_2), the regioselectivities are not very pronounced.

The allyl group may be introduced on alcohols, under acidic conditions, by the trichloracetamidate method[54] (eq. 45).



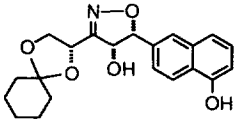
(45)[54]

Substituted allyl glycosides may be obtained from glycosyl trichloroacetamidates[55].



(46)[55]

The phenol alcohol **8** has been successfully bisallylated (80% yield) by treatment with allyl bromide and potassium fluoride adsorbed on alumina. These mild conditions were used to avoid the competitive Beckmann fragmentation of the isoxazoline ring observed under classical Williamson conditions[56].



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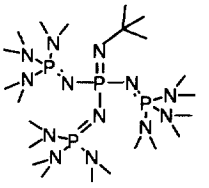
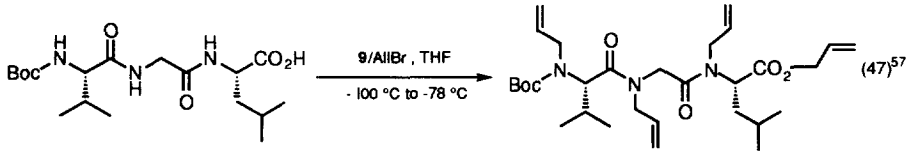


9

Recently, Seebach and coworkers[57] were able to achieve *N*-perallylation and *N*-perbenzylation of the amide bonds of oligopeptides by reaction with allyl or benzyl bromide in the presence of the very strong, newly introduced, P4-phosphazene base **9** (eq. 47).



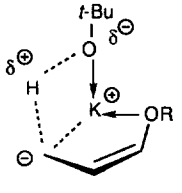
(47)[57]

2.2. MAIN METHODS OF DEPROTECTION OF ALLYL ETHERS AND SOME RELATED DERIVATIVES

Most methods of deprotection of allyl ethers involve prior isomerisation, either base or transition metal catalysed, to labile prop-1-enyl ethers which may then be cleaved under generally mild conditions. Direct allylic cleavage is also possible by use of stoichiometric amounts of some palladium salts or complexes.

2.2.1. **Base-mediated isomerisation of prop-2-enyl derivatives to prop-1-enyl derivatives and cleavage of prop-1-enyl derivatives.**

The base-mediated isomerisation of alkenes in general[58] and of allyl ethers in particular[59,60] has been the subject of detailed investigations. In the rearrangement of allyl ethers to vinyl ethers, conversions as high as 98-99% are obtained, which shows that the process is thermodynamically highly favorable. The reactions, initially carried out under rather drastic conditions[59], are greatly facilitated in a strongly polar aprotic medium[60]. Use of potassium *tert*-butoxide in DMSO seems to be the best choice[60]. Using this system, allyl phenyl ethers may be isomerised at room temperature and the reaction is usually rapid at 100°C with alkyl allyl ethers. The potassium *tert*-butoxide induced isomerisation, whether conducted in apolar (DME, neat) or polar (DMSO) media is highly stereospecific and leads to Z-prop-1-enyl ether with selectivity up to 90-100% [59-61], well beyond the thermodynamic value of *ca.* 65-75%[59-60]. To account for this selectivity, it has been proposed[59,60], that coordination of the ether oxygen atom to the potassium cation imposes a *cis*-configuration of the allylic carbanionic moiety during alkoxide mediated proton transfer (see **10**). In this respect, it is worth mentioning that geometrically constrained allylic ethers that cannot lead to *cis*-prop-1-enyl derivatives are resistant towards base-catalysed isomerisation. Such is the case of 3-*n*-propyloxy-cyclohexene **11**, while 2,5-dihydrofuran **12**, on the contrary, readily rearranges to 2,3-dihydrofuran **13**[59].



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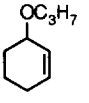
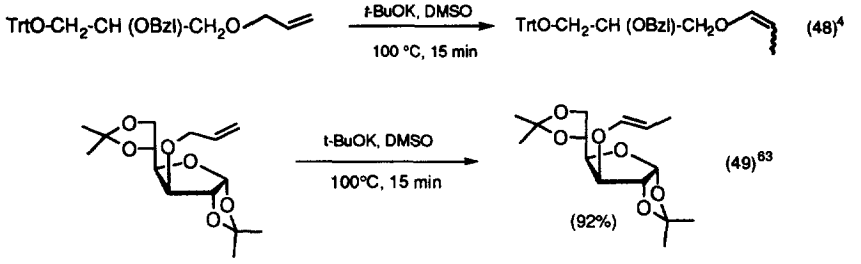


11

12

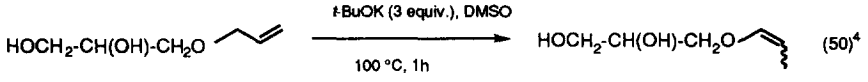
13

On the basis of the above data, the allyl group was first adopted[4] as a means of protection and then extensively studied by R. Gigg and co-workers[4,9,10,33,62-82]. Some early examples of isomerisation to prop-1-enyl derivatives are given below (eqs. 48, 49). Complete rearrangement was observed within 15 min at 100 °C by using 1 equiv. per allyl group of potassium *tert*-butoxide as a 0.5 M solution in DMSO[4, 63].

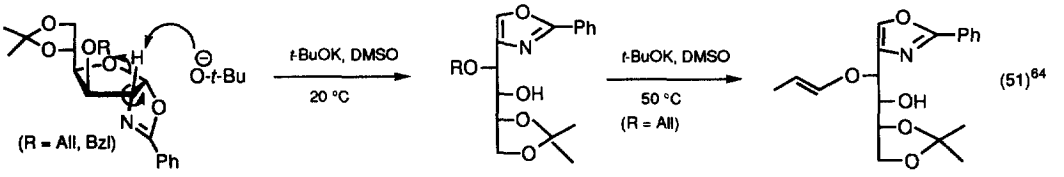


Allyl glycoside may similarly be converted to prop-1-enyl glycosides[63].

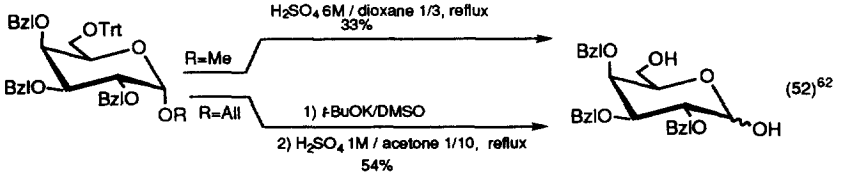
When free hydroxyl groups are present in the molecule, the reaction is somewhat slower and an excess of potassium *tert*-butoxide has to be used (eq. 50)[4].



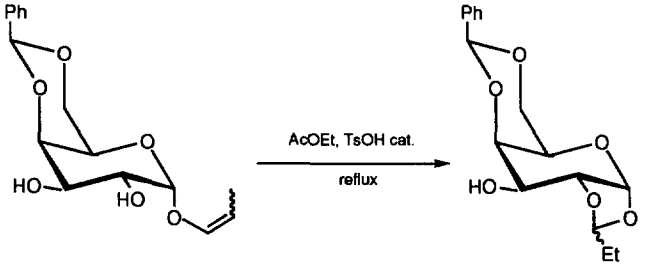
Many protecting groups of wide use in sugar chemistry are stable under the basic conditions of allyl ether isomerisation. Those include the benzyl group, the trityl group, ketal functions and the benzamido and acetamido groups of protected aminosugars [51b,63,64]. Oxazoline derivatives at C(1)-C(2), on the other hand, are ring-opened[64]. This process is triggered by removal of the proton at C(4') of the oxazoline ring (eq. 51).



Prop-1-enyl ethers may be cleaved by acidic hydrolysis. A typical procedure is to use HCl or H_2SO_4 *ca.* 1N in water-acetone 1/9 v/v at reflux[4,62]. These conditions are milder than those required for hydrolysis of the glycosidic linkage. In an early example, better selectivities were thus obtained in the cleavage of an allyl glycoside as compared to its methyl analogue[62] (eq. 52).

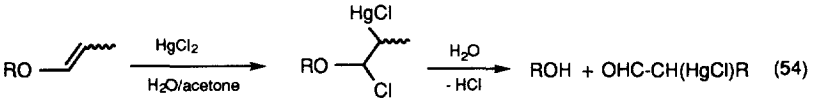


Provided that a free properly orientated hydroxyl group is present in the molecule, prop-1-enyl derivatives may be converted, under anhydrous acidic conditions, to propylidene acetals, a useful protection for diols[4,64] (eq. 53).



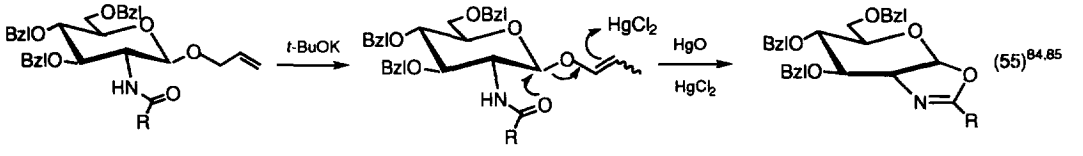
(53)[62]

Since many protecting groups or functions commonly encountered in oligosaccharide chemistry are acid sensitive, other more specific methods were devised for cleavage of prop-1-enyl derivatives. A currently used one, introduced by R. Gigg[82], consists of mercuric(II) chloride assisted hydrolysis. Markovnikov addition of $HgCl_2$ to the double bond (mercuration reaction[83]) leads to a chloroketal which further breaks down to the free alcohol and α-chloromercuripropionaldehyde[64] (eq. 54). The reaction is usually carried out in the presence of mercuric oxide, which acts as an HCl scavenger and regenerates $HgCl_2$.



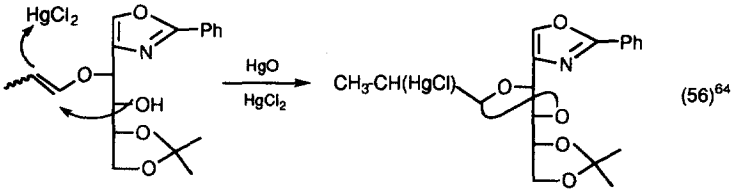
(54)

By treatment with $HgCl_2$/HgO under anhydrous conditions, prop-1-enyl-β-glycosides of *N*-acyl-glucosamines and *N*-acyl-galactosamines have been cyclized to oxazolines which are useful glycosylating agents[84,85]. This procedure fails with α-anomers, which shows that the cyclisation reaction is a concerted process (eq. 55) rather than a stepwise transformation with intermediate formation of a glycosyl cation.



(55)[84,85]

Competition between hydrolytic cleavage and formation of an α-chloromercuric-ketal (eq. 56) has been observed on a prop-1-enyl derivative with a free vicinal hydroxyl group[62].

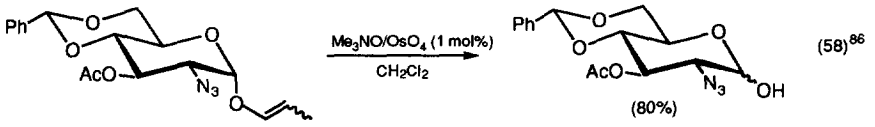


(56)[64]

Various oxidative methods, combined with hydrolysis, are also available for clevage of prop-1-enyl ethers. Sodium permanganate oxidation[4] in basic medium brings about dihydroxylation of the double bond, leading to an unstable hemiketal which immediately liberates the free alcohol (eq. 57). There is, however, some indications that the $KMnO_4$/NaOH method may also cause some loss of benzyl groups through benzylic hydroxylation[63].

$$\text{R-O-CH=CH-CH}_3 \xrightarrow{KMnO_4 / OH^-} [\text{R-O-CHOH-CHOH-CH}_3] \longrightarrow \text{ROH} \quad (57)$$

Dihydroxylation through catalytic osmylation with trimethylamine oxide as the reoxidizing agent has been successfully used as a milder alternative to the permanganate procedure[86] (eq. 58). This method is highly tolerant of both acid and base labile substituents.

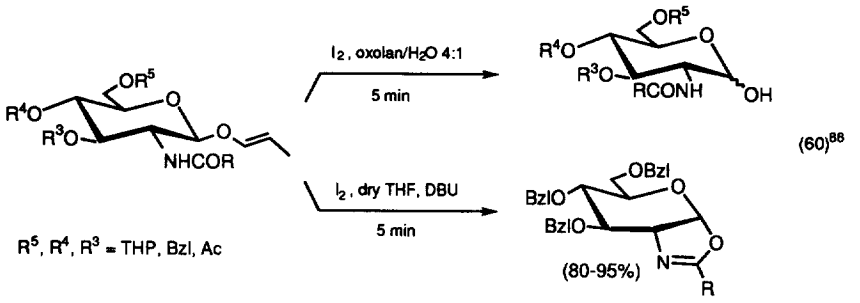


(58)[86]

Oxidative cleavage of prop-1-enyl ethers has also been achieved by ozonolysis followed by base catalysed deformylation[4, 87] (eq. 59) and by treatment with I_2 in an aqueous-organic medium[88](eq. 60).

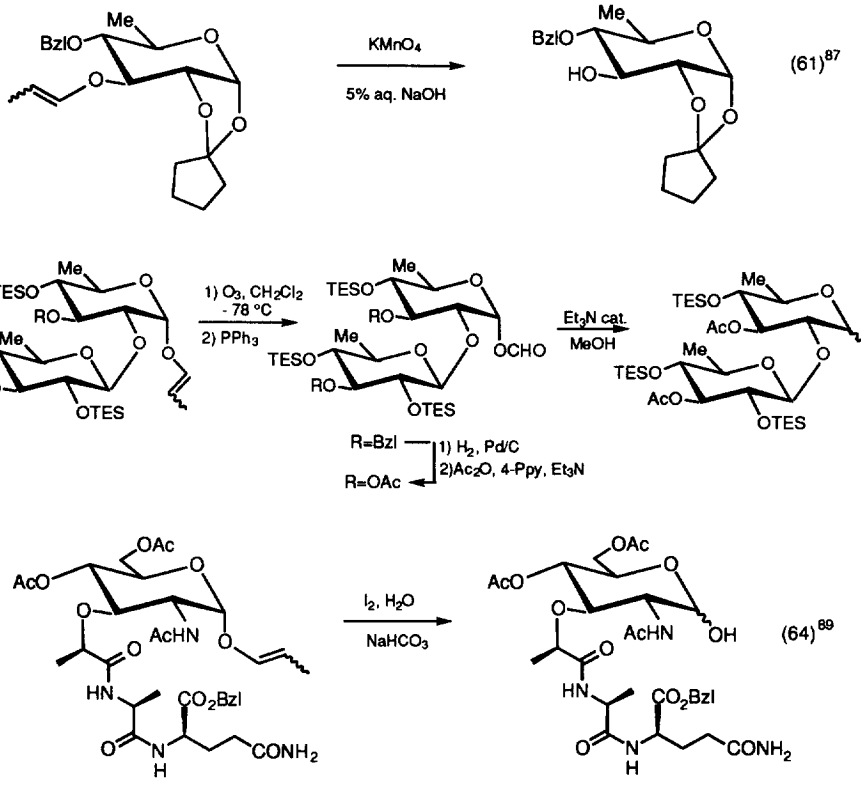
$$\text{R-O-CH=CH-CH}_3 \xrightarrow{O_3} \text{R-O-HC}\underset{O}{\overset{O-O}{\diagdown\diagup}}\text{CH-CH}_3 \xrightarrow{PPh_3} \text{R-O-CH=O} \xrightarrow[H_2O,\ EtOH]{\text{Base (cat.)}} \text{ROH} \quad (59)$$

When treated with iodine in anhydrous THF, prop-1-enyl β-glycosides of *N*-acyl glucosamines readily lead to oxazoline derivatives[88] (eq 60). This method appears to be superior to the already mentioned $HgCl_2$/HgO procedure[84,85].



(60)[88]

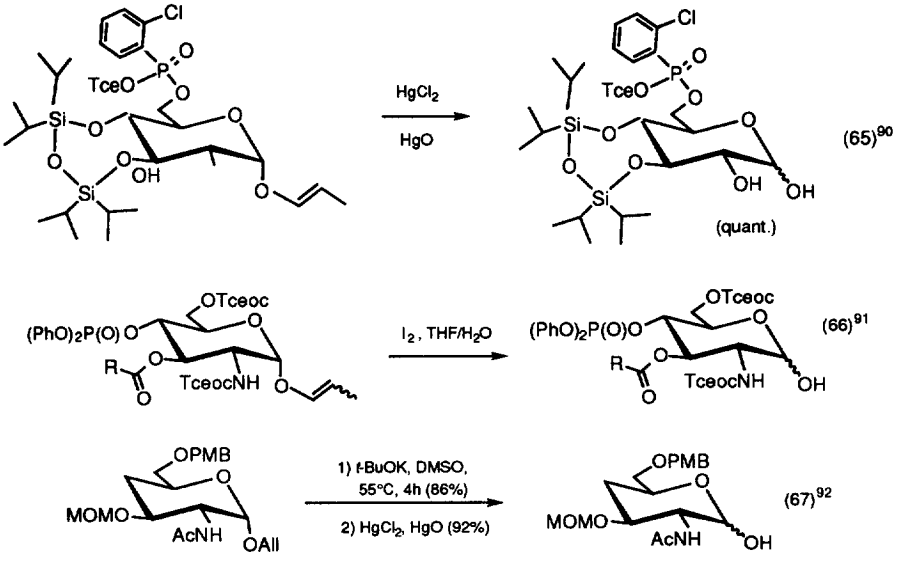
Some additional examples[63,87,89-92] of prop-1-enyl clevage according to the various methods described above are presented in eqs. 61-67.



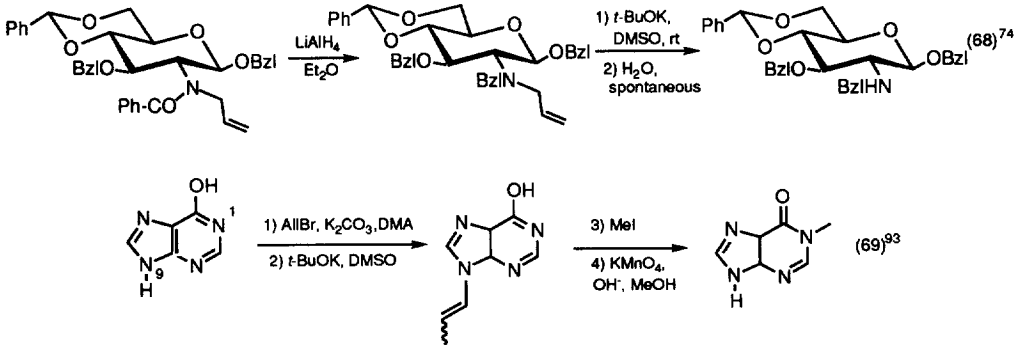
(61)[87]

(63)[87]

(64)[89]



Base catalysed isomerisation of allylamimes is also possible, leading to enamines which are usually readily hydrolysed. Temporary *N*-allyl protection has been used by Gigg[74] (eq.68) in the synthesis of monobenzyl derivatives of 2-amino-2-deoxyderivatives of sugars. Montgomery and Thomas[93] have used temporary prop-1-enyl blockade of the *N*-9 position of purines for selective introduction of alkyl substituents at the *N*-1 position (eq. 69).



2.2.2. Transition-metal catalysed isomerisation of prop-2-enyl to prop-1-enyl derivatives

A number of transition metal complexes catalyse double-bond migration in olefinic compounds. These catalytic processes, which in many cases occur under neutral or near-to-neutral conditions, represent a precious alternative to the *tert*-butoxide mediated rearrangement.

Two major possible mechanisms are recognized for the transition metal catalysed migration of olefinic bonds[94]. Both are schematically reproduced in fig. 2 and fig. 3 in which [M] represents the metal surrounded by its ligands (which are omitted for the sake of clarity) and ▭ a vacant site of the coordination sphere of the metal.

Fig. 2

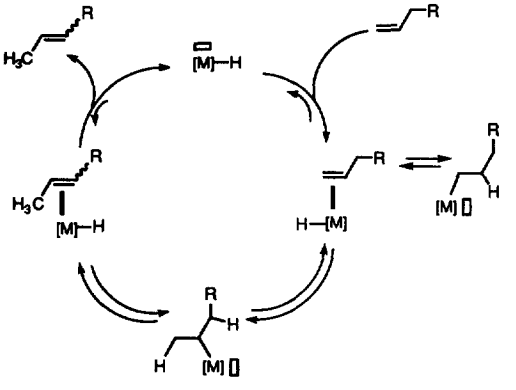
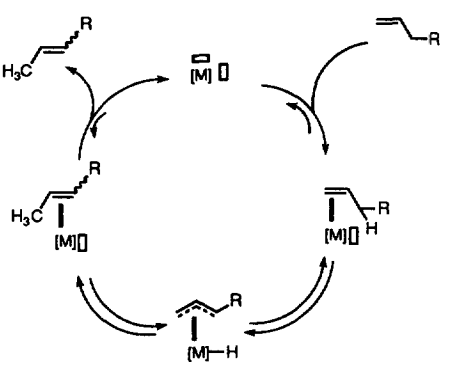


Fig. 3



In the first one (the addition-elimination mechanism of fig. 2), a metal hydride, after prior coordination to the olefin, adds to the double bond. The metal alkyl intermediate thus formed may then, by β-hydrogen elimination, either revert to the original metal coordinated olefin or give a new isomer in which the double bond is now located on an adjacent position.

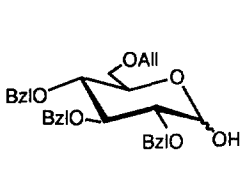
The second one (fig. 3) involves the formation of a π–allyl hydrido intermediate and is associated with a 1,3-hydrogen shift intead of the 1,2-hydrogen shift of the addition-elimination mechanism. The distinction between the two mechanisms may therefore usually be made on the basis of deuterium labelling experiments. Among the catalysts which work according to the addition-elimination mechanism are various hydrido-complexes of cobalt ($HCo(CO)_4$)[95], ruthenium ($RuHCl(PPh_3)_3$)[96] or platinum (*e.g.* $PtH(ClO_4)(PPh_3)_3$)[97]. Similar mechanisms are also encountered with non-hydrido complexes including several nickel complexes such as $Ni[P(OEt)_3]_4$[98], $Ni(H_2C{=}CH_2)[P(o\text{-tolyl})_3]_2$[99] and several rhodium complexes such as $RhCl_3$[100,101], $[RhCl(H_2C{=}CH_2)_2]_2$[102,103], $RhCl(PPh_3)_3$ (Wilkinson catalyst)[103]. The transition metal hydrido species is then formed *in situ*, for example by protonation of the starting complex ($Ni[P(OEt)_3]_4$, $[RhCl(H_2C{=}CH_2)_2]_2$) by an acid co-catalyst, by reduction with H_2 ($PtCl_2(PPh_3)_2SnCl_2$)[104] or by hydride transfer from the solvent[105].

On the contrary, iron complexes such as $Fe(CO)_5$[106], $Fe_3(CO)_{12}$[107], palladium complexes such as $PdCl_2(PhCN)_2$[100] or the cationic iridium complexes[108] $[Ir(cod)(PMePh_2)_2]^+ PF_6^-$ or BF_4^- isomerize olefins according to the π-allyl hydrido mechanism. $RhCl(PPh_3)_3$ may behave similarly when reaction conditions do not allow *in situ* formation of an hydrido species[109].

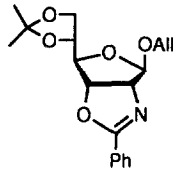
The isomerisation catalysts which have been used for the rearrangement of prop-2-enyl derivatives may belong to either of the two above categories and include rhodium, palladium, iridium and ruthenium complexes. Before going to a detailed survey, it should be noted at the outset, that some isomerisation

catalysts, especially those which work according to the addition-elimination process, may also act as hydrogen-transfer catalysts in the reduction of ethylenic compounds and of other functionalities[110] and may thus lead to unwanted side-reactions.

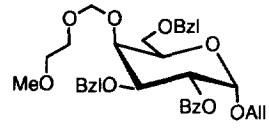
In 1973, Corey and Suggs[111] reported that allyl ethers of methanol, 1-decanol and cholesterol are readily isomerised in the presence of the Wilkinson catalyst $RhCl(PPh_3)_3$. Conversions of *ca.* 95% were obtained within 3 hrs in ethanol/water at reflux and in the presence of DABCO. Other catalysts were also tested and the order of efficiency was found to be $RhCl(PPh_3)_3 > RhCl_3 > PdCl_2$, $RuCl_3$, $IrCl_3$. The role of the base is to prevent any premature hydrolysis of the prop-1-enyl ether to alcohol and propionaldehyde which could bring about poisoning of the catalyst[112]. Indeed, $RhCl(PPh_3)_3$ readily abstracts carbon monoxide from aldehydes[113] and is converted to $RhClCO(PPh_3)_2$, a much less effective[109] catalytic species. The complex $Rh(PPh_3)_4H$ has also been used[114, 115] under acidic conditions (*ie.* in the presence of trifluoroacetic acid) instead of the Wilkinson catalyst. Although few data are available, the rhodium catalysed isomerisation is apparently not stereoselective and leads to a mixture of *E*- and *Z*-prop-1-enyl ethers[61,73]. Several representative examples[68,81,116-121] **14-21** of allylic substrates, most of them bearing base labile substituents, which have been successfully isomerized by the rhodium catalysed process are represented below. The fact that the reaction applies[68] to the free sugar **14** is worthy of note. It shows that, contrary to aldehydes, free sugars do not undergo[68, 81] CO abstraction by the Wilkinson catalyst. For fear of possible deleterious effects on the free sugar, the isomerisation on **14** was also conducted without added base. Although seemingly slowed down by the propionaldehyde formed under such conditions, the reaction was nevertheless found to go to completion. With **21**, spontaneous intramolecular cyclisation of the intermediate deprotected phenol leads to the *cis*-hydridobenzofuran **22** (eq. 70)[121].



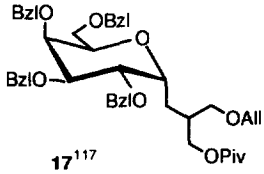
14[68]



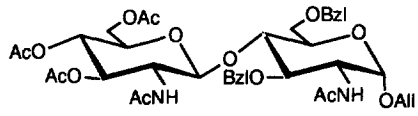
15[81]



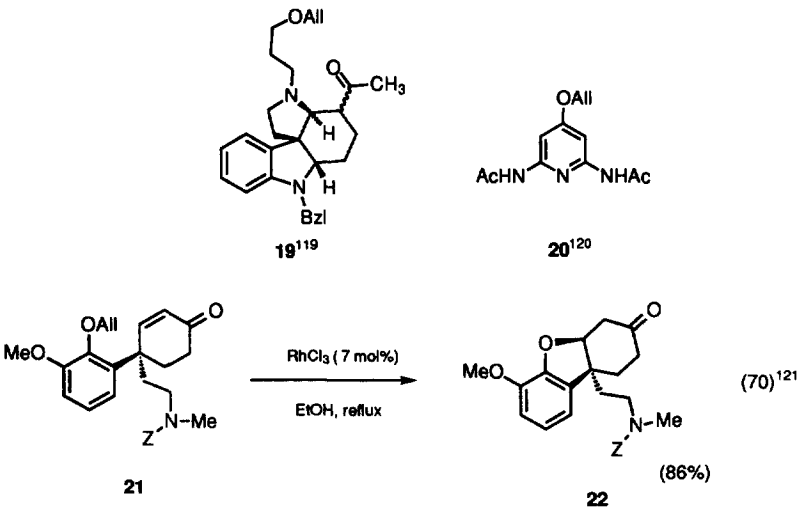
16[116]



17[117]

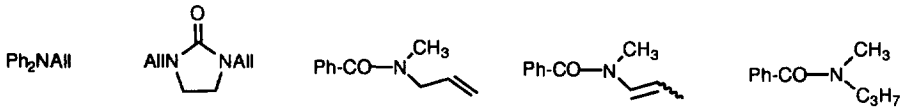


18[118]



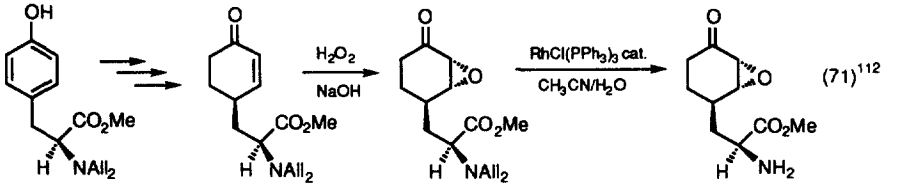
Recently[122], a catalytic system obtained by reacting the Wilkinson catalyst with *n*-butyl lithium has been recommended as especially efficient for the isomerisation of unsubstituted and substituted (see section 2.4) allyl ethers of carbohydrates.

The rhodium catalysed process also applies to the isomerisation of *N*-allyl amines, amides or urea **23-25** [75,112,114,123-125]. With allylamines, the free amine is directly obtained, the intermediate enamine being readily hydrolysed under the reaction conditions.

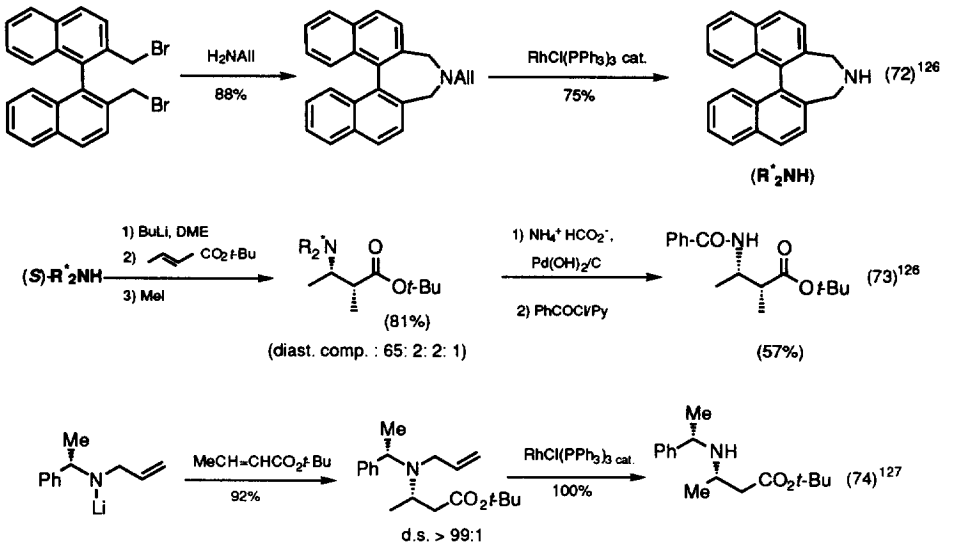


23[123] **24**[123] **25**[123] **26** **27**

A synthesis of anticapsine has been achieved, starting from *N*, *N*-diallyl-L-tyrosine (eq. 71)[112]. *N*-allyl protection was necessary to avoid intramolecular condensation reaction at the enone stage.



Eqs 72-73 and 74 present recent examples[126,127] of the utilization of *N*-allyl protection, in connection with enantioselective synthesis of β-aminoesters[127] and α-substituted β-aminoesters [126].

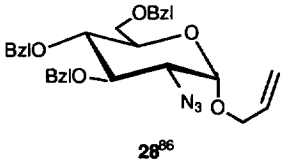


A drawback of the rhodium processes is the possible occurence of competitive reduction of the double bond, which occurs through catalytic hydrogen transfer[110,128,129] from the solvent which is usually ethanol (eq. 75). Besides alcohols, cyclic ethers, especially dioxan and THF, and cyclic amines also display high

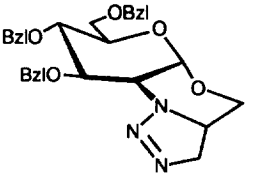
$$CH_3\text{-}CH_2OH + RCH{=}CH\text{-}R' \xrightarrow{RhCl(PPh_3)_3\ cat.} CH_3\text{-}CHO + R\text{-}CH_2\text{-}CH_2\text{-}R' \qquad (75)$$

hydrogen-donating abilities in these catalytic reactions[128]. Side reduction of prop-1-enyl derivatives has been observed in the reaction of **16** (*ca.* 10%), **18** (to a small extent), **25** and in other instances. The extent to which this side reduction may occur is strongly dependent on the reactions conditions. Thus[123], **25** leads to a 1:1 mixture of isomerised **26** and reduced **27** products with $RhCl(PPh_3)_3$ in EtOH, while clean and selective isomerisation to **26** was achieved with $RhCl_3$ in EtOH or with $RhCl(PPh_3)_3$ in dioxan, although the reaction was much slower in the latter case.

Another limitation stems from the occasional need for rather prolonged heating which may result in unwanted side-reactions. For instance, the allyl 2-deoxy-2-azido glycoside **28** mainly gives the intramolecular 1,3-dipolar cycloadduct **29**[86]. First attempts to deprotect the allyl amine **30-a** with catalytic amounts of the rhodium hydride $Rh(PPh_3)_4H$ in ethanol at 100 °C led to a mixture of the desired deprotected compound (**30-b**) and of the product of thermal rearrangement **31**[114]. Satisfactory results were

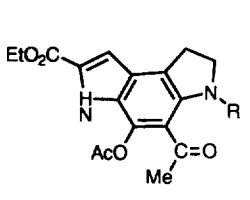


28[86]

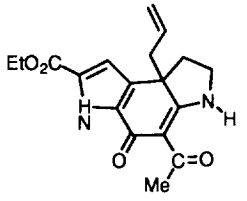


29

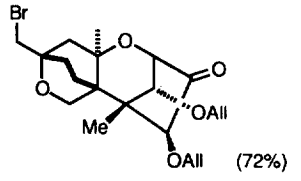
finally obtained by increasing the amount of catalyst to 0.25 molar equiv. and by running the reaction in refluxing ethanol in the presence of 1 equiv. of trifluoroacetic acid. On another hand, replacement of the *N*-allyl by a *N*-benzyl protecting group (*i.e.* **30-c**) was found unsuitable because of the facile dehydrogenation of the indoline ring in the presence of debenzylation catalysts. The $Rh(PPh_3)_4H$ /CF_3CO_2H procedure was also applied to diallylether **32**[115]. Under these acidic conditions, the intermediate prop-1-enyl ether is cleaved



30[114] **a** R=All
b R=H
c R=Bzl



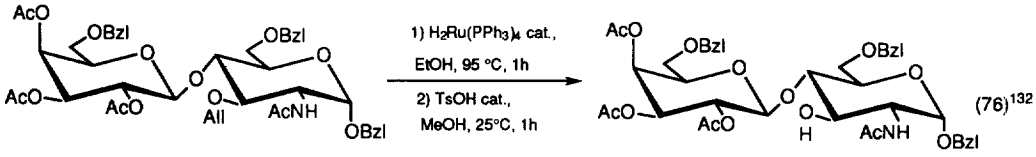
31



32[115]

in situ to give the alcohol. With more simple substrates such as cholesteryl allyl ether, the reaction works equally well with less catalyst (3×10^{-2} molar equiv.)[115].

Ruthenium catalysed isomerisations[130,131] of allyl ethers and *N*-allyl amides or imides[125] have been used in synthetic organic chemistry, but, to the best of our knowledge, only one example pertains to protecting group chemistry[132] (eq. 76).



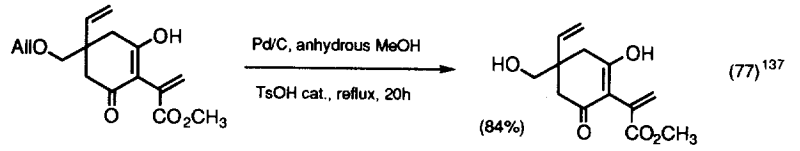
(85%)

Rearrangement of allyl ethers with $RuCl_2(PPh_3)_2$, reduced *in situ* by $NaBH_4$, gives a mixture of *Z*- and *E*-vinyl ethers. It has been further demonstrated that this system also catalyses *Z*/*E*-interconversion[130]. Finally, caution should be exercised in using $RuH_2(PPh_3)_4$ as this complex is able to catalyse hydrogen transfer from alcohols, typically 2-propanol, to olefinic substrates under mild conditions[133]. $RuCl_2(PPh_3)_4$ has also been shown to catalyse hydrogen transfer reduction, albeit at higher temperature, of aldehydes[133], ketones[134,135] and α,β-unsaturated compounds[136].

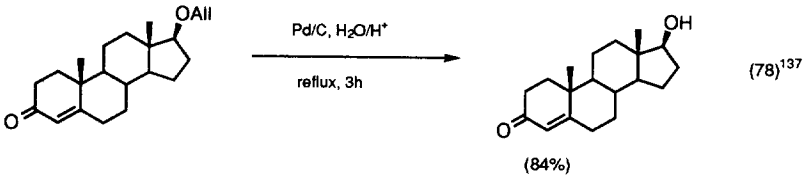
The palladium catalysed isomerisation of allyl ethers has been carried out both under heterogeneous and homogeneous conditions.

In the Boss-Scheffold[137] procedure, the allyl ether is heated with palladium on charcoal in anhydrous methanol or mixed aqueous organic solvents, and a catalytic amount of perchloric or *p*-toluenesulfonic acid, which allows the *in situ* hydrolysis or methanolysis of the prop-1-enyl derivative.

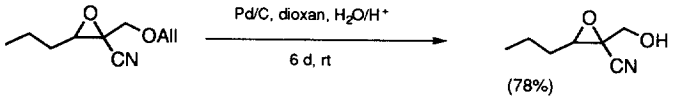
In the procedure devised by H. A. J. Careless and D. J. Haywood[138] the reaction is carried out in anhydrous solvents such as benzene or toluene and stops at the prop-1-enyl stage. A *ca.* 7/3 mixture of *Z*- and *E*- isomers is obtained. Both methods seem highly tolerant of various functionalities (eq. 77-81)[87,137,138].



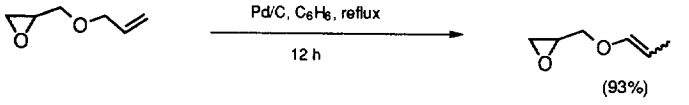
(77)[137]



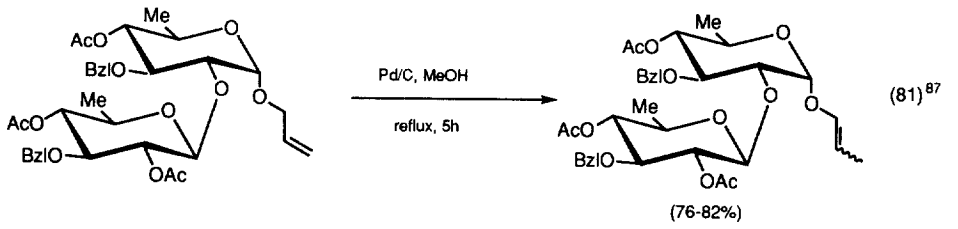
(78)[137]



(79)[137]



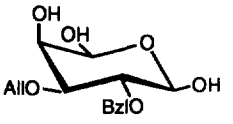
(80)[138]



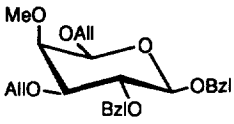
(81)[87]

Mention should be made that Pd/C may catalyse, albeit under rather drastic conditions, hydrogen tranfer from alcohols to conjugated enones[139].

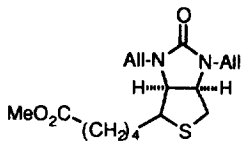
Pd/C isomerisation in acidic EtOH has been used by Gigg and co-workers[10, 33a] for the deprotection of *myo*-inositol derivatives having a large number of free or allyl protected hydroxyl groups such as **33** or **34**. On the other hand, the Pd/C procedure failed in the case of the biotin derivative **35**[123], probably owing to catalyst poisoning by sulfur.



33[10] (81% deallylation yield)

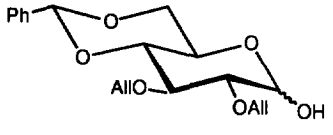


34[10]

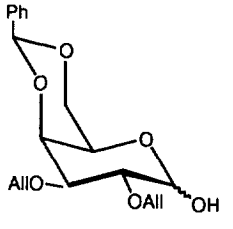


35[123]

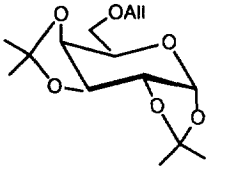
Several soluble palladium complexes has been tested by Bieg and Szeja[140] for the rearrangement of allyl ethers of carbohydrates under homogeneous conditions. Best results were obtained by use of *trans*-$[Pd(NH_3)_2Cl_2]$ in refluxing *tert*-butanol. With this system, the prop-1-enyl derivatives are first formed in a *Z*/*E*-ratio close to 60/40 and are subsequently cleaved to free OH. This second, slower, reaction is also catalysed by *trans*-$[Pd(NH_3)_2Cl_2]$. Various sugar derivatives such as **36** and **37** (α- and β-anomers) were deprotected by this method in *ca.* 90% isolated yield. Bulky groups may slow down the isomerisation, as in the case of 6-*O*-allyl-1, 2, 3, 4-di-*O*-isopropylidene-α-D-galactopyranoside **38**.



36[140] (90% deallylation yield)

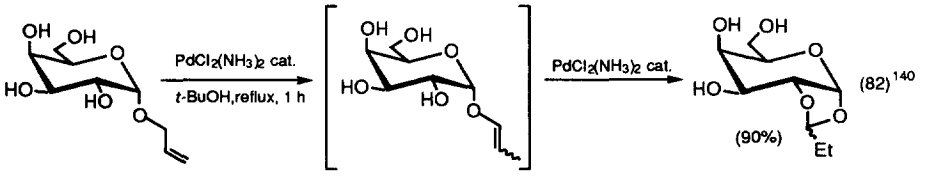


37[140] (90% deallylation yield)

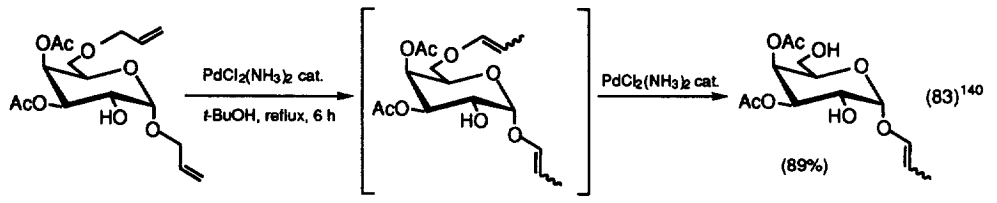


38[140]

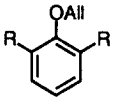
Allyl derivatives of carbohydrates with unprotected hydroxyl groups in a suitable position can be transformed directly into propylidene acetals (eq. 82).



The prop-1-enyl aglycon appears to be much more stable to the action of *trans*-$[Pd(NH_3)_2Cl_2]$ than prop-1-enyl groups in other positions of the molecule; it is therefore possible to remove various allyl groups in allyl-protected allyl glycosides while maintaining the prop-1-enyl group on the anomeric hydroxyl group (eq. 83).



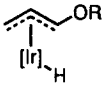
$PdCl_2(PhCN)_2$ catalysed isomerisation of allyl phenyl ethers **39-a,b** in boiling benzene gives quantitatively phenyl prop-1-enyl ethers with predominence of the *cis*-isomers[141]. Despite the fact that



39[141] **a** R = H
b R = CH_3

$PdCl_2(PhCN)_2$ is known to catalyse Cope rearrangement[142], no competitive Claisen rearrangement was observed in these reactions.

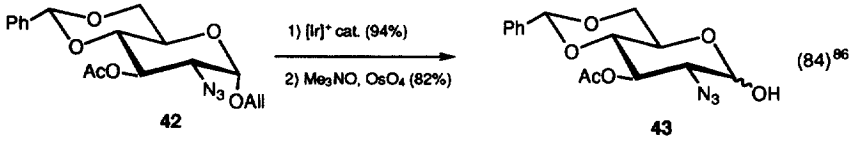
The cationic iridium complex $[Ir(cod)(PPh_2Me)_2]^+ PF_6^-$, has been shown by Baudry, Ephritikhine and Felkin in 1978 to be a very efficient catalyst for the isomerisation of allyl alcohol to saturated aldehydes or ketones[143] and for the isomerization of allyl ethers to prop-1-enyl ethers[108]. Since then, due to its selectivity and its mildness , this method has found increasing use in protecting group chemistry. Before reaction, the iridium catalyst is activated under H_2 atmosphere whose role is not to produce a metal-hydrido species but probably to generate a very active coordinately unsaturated iridium species through reduction of the 1,5-cyclooctadiene (cod) ligand. Isomerisation reactions are typically conducted under an inert (N_2, Arg) atmosphere in THF at room temperature and in the presence of 10^{-3} to 10^{-1} molar equivalents of catalyst. In contrast with most other catalytic isomerisations, they display a very high stereoselectivity in favor of the *E*-isomer ($E/Z > 30$), whose separation and characterization are therefore greatly facilitated. As shown by deuterium labelling experiments, the reaction most likely involves a π-allyl hydrido iridium intermediate. The observed stereoselectivities may therefore be explained on the ground that, for steric reasons, the π-allyl hydrido species is more stable in its *syn*- **40** than in its *anti*- **41** configuration[108] (the *syn*,*anti* denomination referring to the position of the substituent at C(1) with respect to the C(2) hydrogen).



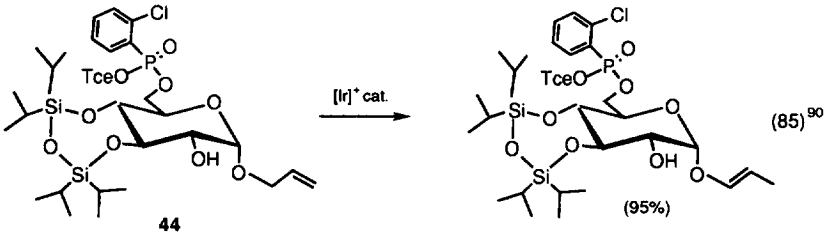
40

41

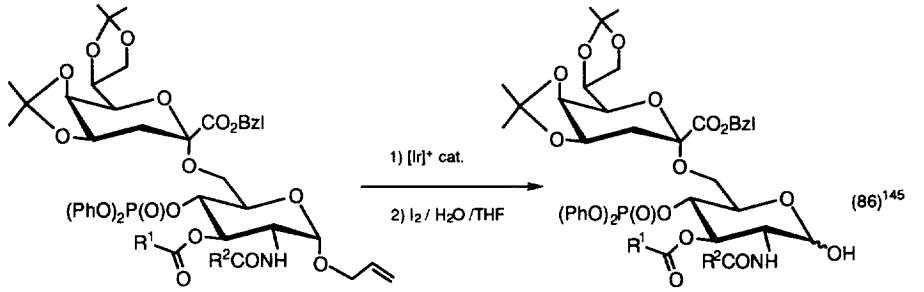
The iridium procedure was successfully applied to the isomerisation of a series of α-allyl 2-deoxy-2-azido-glucosides[86] such as **28**, or **42** (eq. 84), for which all other methods (base catalysis, transition-metal catalysis or (see below, section 2.3) use of stoichiometric amounts of $PdCl_2$) had failed, due to thermally induced competitive formation of intramolecular 1,3-dipolar cyclisation adducts (see **29**).



J. H. van Boom and co-workers[90] have tested the iridium method on particularly sensitive sugar derivatives, for instance on the glucose derivative **44** containing the tetraisopropyldisiloxane-1,3-diyl and the *O*-(2-chlorophenyl)-*O*-(2, 2, 2-trichloroethyl)-phosphoryl groups (eq. 85; for cleavage of the resulting prop-1-enyl ether see eq. 65). An attempted isomerisation on **44** with $RhCl(PPh_3)_3$ resulted not only in reduction of the double bond but also in degradation of the phosphotriester function.

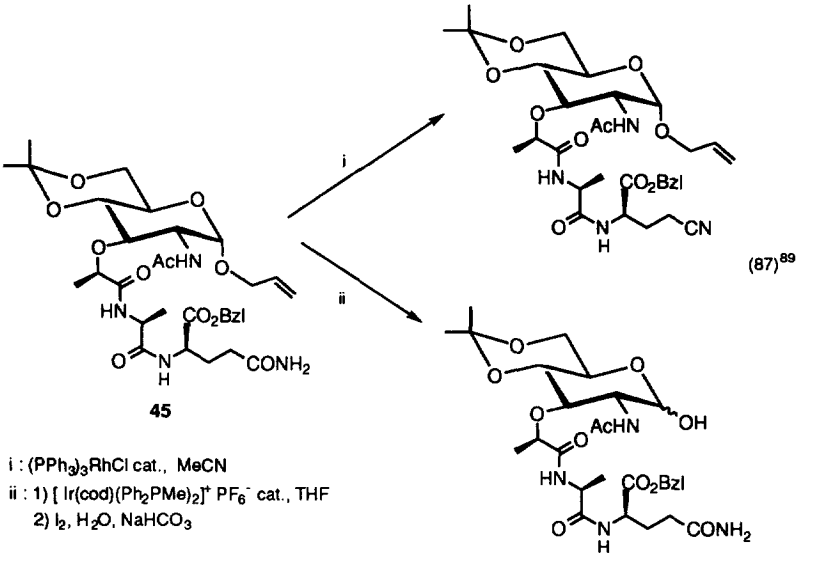


T. Shiba and coworkers[91,144,145] have systematically used allyl protection of anomeric hydroxyl groups in the synthesis of lipo-di- and trisaccarides. Selective removal of the allyl aglycon was successfully achieved, in the presence of a variety of other protecting groups, by iridium catalysis followed by I_2 induced prop-1-enyl cleavage (eq. 86)[145].

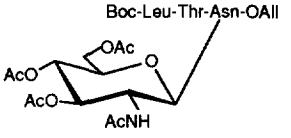


Compound **45** (eq. 87) was also successfully deprotected[89] by the Baudry-Ephritikhine-Felkin method whilst the use of rhodium catalyst (in acetonitrile as the solvent) caused the dehydratation[146] of the carboxamide group to nitrile.

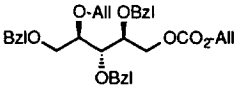
Other catalysts are known to catalyse the isomerisation of allyl ethers, for instance $Ni(H_2C{=}CH_2)[P(o\text{-tolyl})_3]_2$[99], $Fe(CO)_5$ with near-UV irradiation[106] and several platinum hydride complexes[97]. None of them, however, seem to have been used in protecting group chemistry.



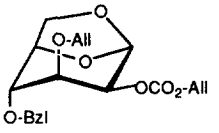
Before closing this section, mention should be made that, besides allyl ethers, amines and amides, allyl carboxylates may also be cleaved through transition metal (especially $RhCl(PPh_3)_3$) catalysed isomerisation[147]. Compounds **46-49** are representative examples of allyl esters and carbonates to which such



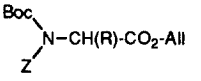
46[147a]



47[147d]



48[147d]



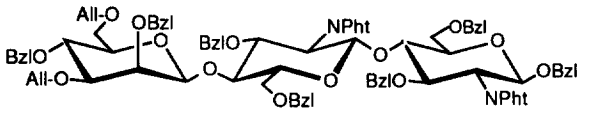
49[147e]

methods have been applied. As already mentioned, however, procedures based on catalytic π-allyl palladium chemistry, are usually easier to carry out , more rapid and less prone to catalyst poisoning, and they tend now to be preferred.

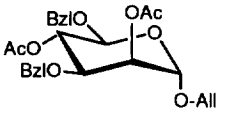
2.2.3. Direct palladium mediated allylic cleavage and some related methods

$PdCl_2(PhCN)_2$, used in stoichiometric amount, allows direct cleavage of allyl phenyl ethers to phenols in 85-95%yield[148]. This reaction tolerates a wide range of substituents in the *meta* or *para* position including Me, CHO, COMe, CO_2Me, OH, OMe.

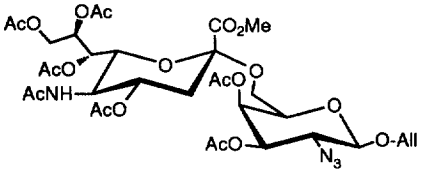
Another powerful and selective method of cleavage of allyl ethers based on the use of stoechiometric amounts of palladium salts has been devised by Ogawa and has found extensive use in carbohydrate chemistry[37,87,92,149-156]. In this method, the substrate is reacted with equimolar (or often excess) amounts of $PdCl_2$ in aqueous acetic acid and in the presence of sodium acetate at temperatures ranging from 25°C to 70°C. The free alcohol is obtained directly. Compounds **50-55**, which include polysaccharides, are representative examples of substrates to which the $PdCl_2$ mediated allylic cleavage has been applied. Note that the azido group in the β-glucoside **52**[153] remains unaffected but it should be remembered that under such conditions allyl 2-deoxy-2-azido-α-glycosides give the 1,3 dipolar cycloadduct (**28** → **29**, see above)[86]. The $PdCl_2$/AcONa/AcOH-H_2O method was also applied to the allyl glycoside of eq. 81 to give the deallylated product in 89% yield[87]. Cleavage of allyl ethers has also been successfully carried out, for example on **54**[29], in methanol at room temperature and in the presence of substoeichiometric (*ca.* 20 mol%) amounts of $PdCl_2$ in MeOH[29,157].



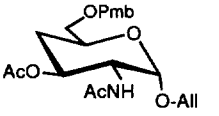
50[37] (58%, bis-deallylation yield)



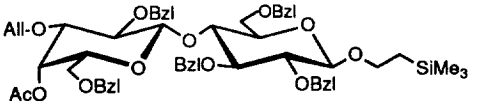
51[150] (64% deallylation yield)



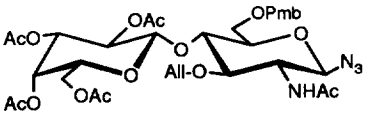
52[153] (79% deallylation yield, mixture of α– and β– isomers)



53[92]
(93% deallylation yield)



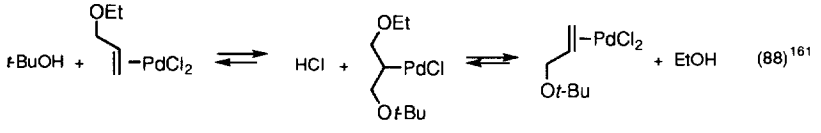
54[29] (76% deallylation yield)



55[156] (55% deallylation yield)

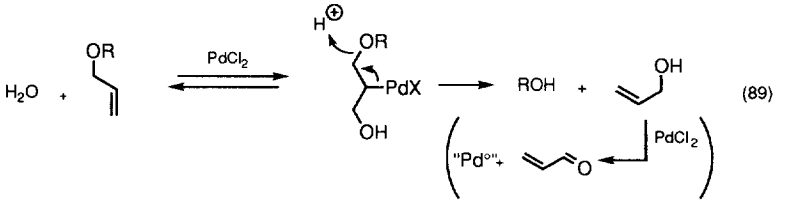
The mechanism of allyl group removal by stoechiometric $PdCl_2$ has not been thoroughly investigated and the by-products of the reaction are not known with certainty, but the reaction is not likely to involve a

simple migration of the double bond as was the case with the aforementioned methods. As suggested for the cleavage of *N*-allylamides under similar conditions[158], direct allylic cleavage could result in the formation of a π-allyl chloropalladium dimer $[(allyl)PdCl]_2$ which in turn would undergo nucleophilic attack by H_2O or AcO^- ultimately leading to oxidative degradation of the allyl framework[159]. Other mechanisms have also been conceived. For instance, oxidative degradation of the allyl group could take place through a series of acetoxy- or chloro-palladation reactions[160] (somewhat analogous to the mercuration reaction of eq. 54) coupled with β-hydrogen elimination processes[160]. Wenzel has recently shown[161] that ethyl allyl ether in *tert*-butanol in the presence of a Wacker-type catalytic system ($PdCl_2(CH_3CN)_2$, CuCl, $CuCl_2$) mainly undergoes, through *anti*-Markovnikov *tert*-butoxypalladation of the double bond followed by β–alkoxy-elimination, an exchange reaction leading to *tert*-butyl allyl ether (eq. 88) and ethanol. Oxidation



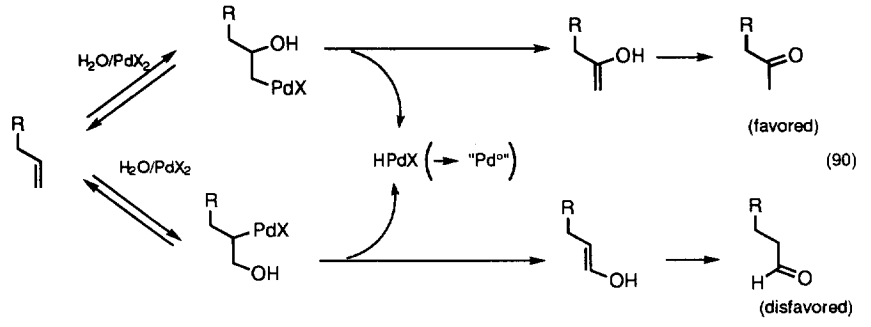
(88)[161]

products (aldehyde and ketones) are formed only in minor amounts. By analogy with eq. 88, another mechanism, based on *anti*-Markovnikov hydroxypalladation followed by β-alkoxy cleavage, may also be considered for allylic deprotection under Ogawa conditions (eq. 89). The allyl alcohol formed in the process

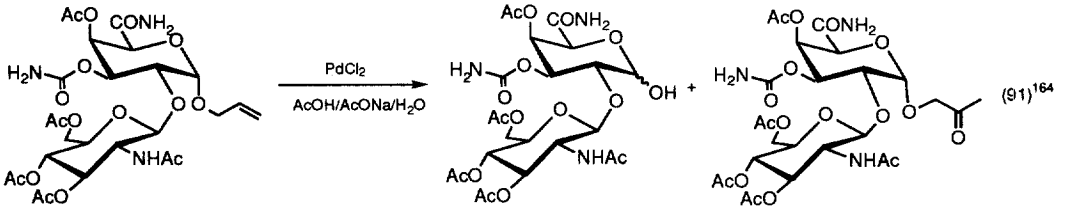


(89)

would then progressively reduce palladium salts to zerovalent palladium with formation of oxidized by-products such as acrolein[162]. The hydroxypalladation of double bonds occurs mainly according to the Markovnikov mode, with the well-known consequence that Wacker oxidation of terminal alkenes[163] leads to methyl ketones in strong preference to aldehydes (eq. 90). Although this is in contrast to the the *tert*-butoxypalladation of eq. 88, hydroxypalladation is a reversible process and the mechanim of eq. 89 cannot be discarded on this ground. Furthermore, recent data shows a less marked regioselectivity in the Wacker

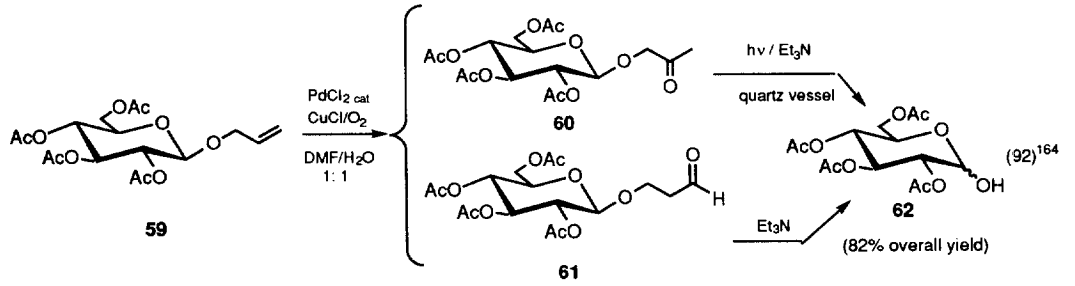


oxidation of allyl glycoside as compared to that of other olefins. Indeed the observation that deprotection of the allyl glycoside **56** under Ogawa conditions gave, together with the cleavage product **57**, a substantial amount of the oxidation product **58** (eq. 91), prompted Welzel and co-workers[164] to explore a new



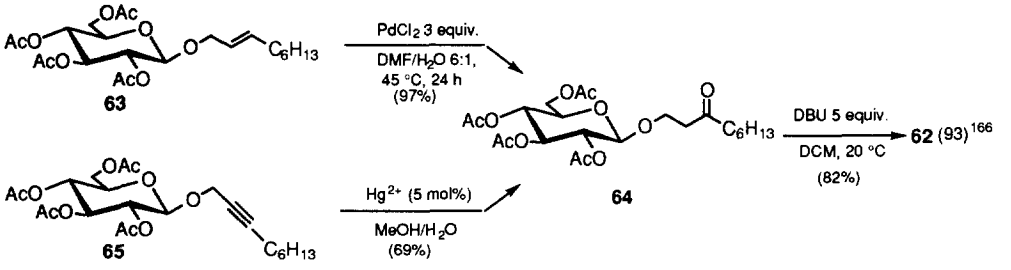
56 **57** (44%) **58** (30%)

deprotection method based on Wacker oxidation[165]. Thus, for instance, under typical Wacker conditions, the peracetylated allyl glycoside **59** was found to give a 1.4: 1 mixture of ketonic and aldehydic compounds **60** and **61**. The 2-oxopropyl group in **60** was then cleaved by photochemical irradiation (mercury lamp) in the presence of triethylamine while simple exposure to the same amine was found to be enough to achieve removal of the 3-oxopropyl group of **61**. The deprotected product **62** could thus be obtained in 82% overall yield from **59** (eq. 92)[164].

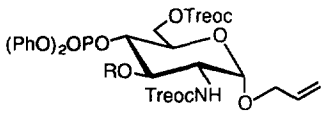


59 **60** **61** **62**

More recently and with the aim of conferring increased lipophilicity to protected molecules, the same authors have introduced[166] the *E*-non-2-enyl group and the non-2-ynyl group for protection of the anomeric position of carbohydrates. Interestingly, Wacker oxidation of the nonenyl glycoside **63** was found to lead regioselectively to the 3-oxononyl derivative **64** from which the hydroxy free compound **62** could be obtained in 82% yield by treatment with DBU. Compound **64** was also obtained from the nonynyl glycoside **65** by Hg^{2+} catalysed hydratation of the triple bond (eq. 93).



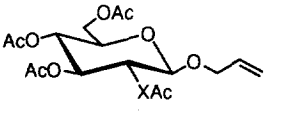
Another method for deprotection of allyl glycosides, devised by Kusama and co-workers[167] and successfully applied for instance to compounds **66** and **67** consists of heating the protected derivative in acetic acid in the presence of palladium tetrakis(triphenylphosphine). The amount of catalyst required is rather high



66

deallylation yield: 75-80%

R = CO-CH2-CH(O-CO-(CH2)12-CH3)-(CH2)10-CH3



67

deallylation yield: 78% (X =O),
96% (X = NH)

(*ca.* 30 mol%), but this procedure, nevertheless, constitutes a rare example of the utilization of catalytic palladium π-allyl methodology (see part II) for the deprotection of allyl derivatives of non-acidic functions.

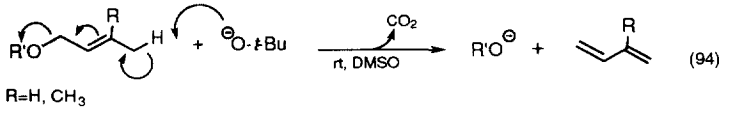
2.2.4. **Substituted allylic protecting groups and their removal**

Besides the allyl group itself, the γ,γ-dimethylsubstituted and all the regioisomeric monomethylsubstituted analogues have been tested, mainly by R. Gigg and co-workers, for the protection of hydroxyl groups. But-2-enyl ethers[64,65] (crotyl ethers) are prepared by alkylation of metal alkoxides with crotyl bromide. Commercially available crotyl bromide is a *ca.* 85: 15 equilibrium mixture of crotyl bromide itself and of 1-methylallyl bromide. However, both isomers are in rapid equilibrium in the conditions of alkylation reactions and since crotyl bromide is much more S_N2 reactive than 1-methylallyl bromide, only

crotyl ethers are formed. A disadvantage of the crotyl derivatives is that they exist as a mixture of *E*-and *Z*-isomers in *ca.* 85: 15 proportion[141].

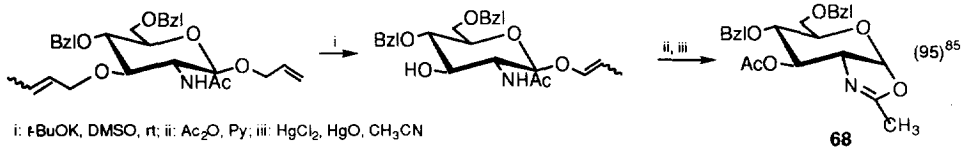
1-Methyl-prop-2-enyl (3-buten-2-yl) ethers[65] are obtained by alkylation with 1-methylallyl chloride. This compound is not as prone to allylic transposition as the corresponding bromide and reacts with metal alkoxides only in a S_N2 (as opposed to S_N2') manner. 2-Methyl-prop-2-enyl (2-methylallyl ethers)[66] and 3-methyl-but-2-enyl) ("γ,γ-dimethylallyl"or "prenyl") ethers[73] are prepared from the corresponding bromides.

The crotyl and the prenyl groups are readily removed[65,73] in DMSO/*t*-BuOK through γ-hydrogen elimination reactions (eq. 94). These reactions are faster than the allyl to prop-1-enyl isomerisation but the



(94)

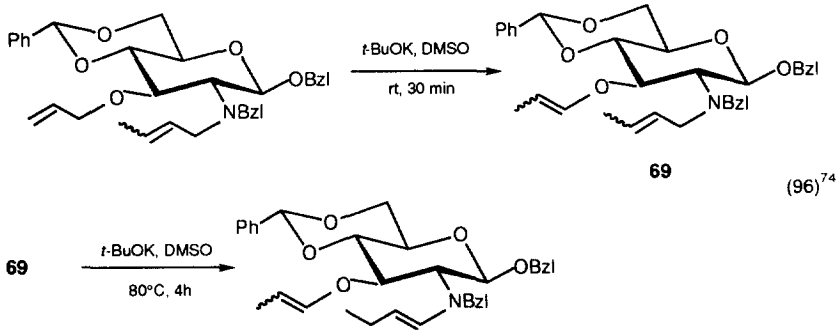
difference in rates does not appear to be sufficient to allow good selectivities[65]. On the other hand, it is possible to effect in a single step removal of a crotyl group and isomerization of an allyl group. Since *tert*-butanol is formed in the removal of the crotyl group, the isomerization proceeds slower than under strictly aprotic conditions[60,65]. Concomitant crotyl group removal and allyl isomerisation have been used[85] in the synthesis of oxazoline derivatives of sugars, as represented in eq. 95. The 3-*O*-acetyl derivative **68**



(95)[85]

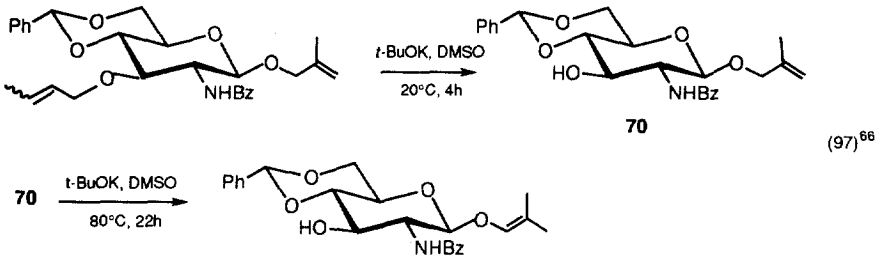
68

is a useful building block in the synthesis of oligosaccharides containing internal β–*N*-acetylglucosaminyl linkages[51a,84,85,168]. In contrast to but-2-enyl ethers, tertiary *N*-but-2-enylamines are not cleaved by potassium *tert*-butoxide in DMSO but isomerised to but-1-enylamines. Selective isomerisation of *O*-allyl ethers in the presence of *N*-but-2-enyl groups is possible as exemplified in eq. 96[74].



(96)[74]

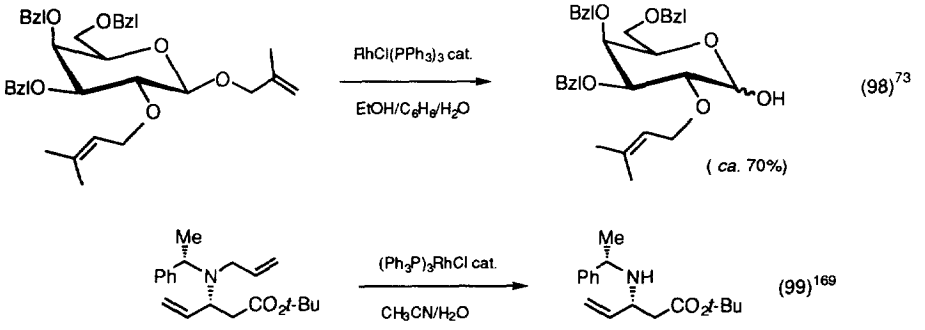
The base-catalysed isomerisation of 2-methylallyl ethers to 2-methyl-prop-1-enyl derivatives is much slower than that of allyl ethers and it is now possible to remove a crotyl group, used as a temporary protection, in the presence of a 2-methylallyl group used as a permanent one, as shown in eq. 97[66]. Despite this illustration, little attention has apparently been paid to such a strategy of differential protection, probably because the base-catalysed isomerisation of 2-methylallyl derivatives requires too harsh conditions (prolonged heating in *t*-BuOK/DMSO, eq. 97). Transition metal catalysis could however offer a valuable



alternative. As a rule, methyl substitution of the allylic framework either slows down or even inhibits its transition-metal catalysed isomerisation[81,108,138,141], but this effect is minimal in the case of substitution at the 2-position and 2-methylallyl ethers are still readily isomerised in the presence of Pd/C[138], $RhCl(PPh_3)_3$[81] or of the iridium catalyst $[Ir(cod)(PMePh_2)_2]^+ PF_6^-$ [108].

The iridium catalyst is also effective for the isomerisation of *E*-but-2-enyl ether while $PdCl_2(PhCN)_2$ was found to give uncomplete reactions[141]. Compared to its *E*-isomer, the *Z*-but-2-enyl group is much more difficult to isomerize, probably because of the unfavorable *anti*-configuration (methyl *endo* with respect to the metal)[141] of the π-allyl hydrido metal intermediate formed in this case.

The prenyl group is completely stable towards $RhCl(PPh_3)_3$[73] and $[Ir(cod)(PMePh_2)_2]^+ PF_6^-$ [108] and the Wilkinson catalyst has been used for selective removal of the allyl (or 2-methylallyl) group in its presence (eq. 98)[73]. Another example of selective isomerisation of an allyl group in the presence of another substituted one is represented in eq. 99[169].



To sum up, the use of methyl-subtituted allyl groups opens the way to various differential protection strategies based on the following possibilities:

-the selective isomerisation (and removal) of allyl groups in the presence of prenyl groups.

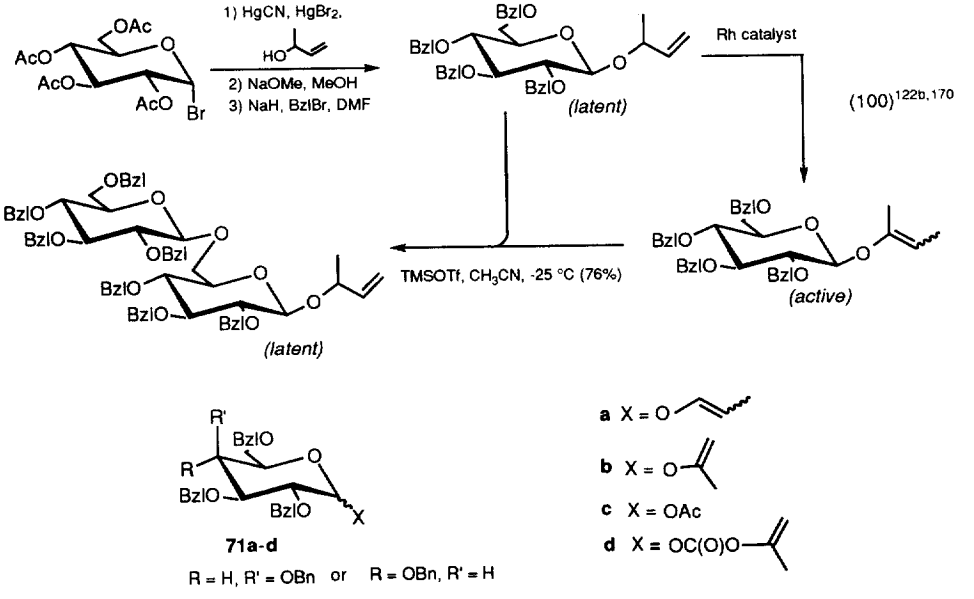
-the selective removal of but-2-enyl or prenyl groups in the presence of 2-methylallyl groups.

-the concomitant removal of but-2-enyl or prenyl groups and isomerisation of allyl groups to prop-1-enyl groups.

Such possibilities do not appear to have been fully exploited.

The protection of anomeric hydroxyl groups by the *E*-non-2-enyl group and the non-2-ynyl groups [166] has already been referred to (see paragraph 2.3).

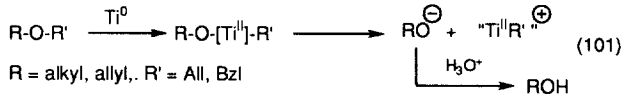
3-But-2-enyl (α-methylallyl) glycosides are isomerised, through rhodium catalysis, to 2-buten-2-yl glycosides, which in turn may be used as glycosyl donors in the presence of Lewis acids (TMSOTf). This "latent/active" glycosylation strategy allows the synthesis of oligosaccharides in a convergent manner[122b,170] as exemplified in eq. 100. Prop-1-enyl glycosides **71-a**, obtained by isomerisation of the corresponding allyl derivative, had already been tested for the same purpose by Sinaÿ and co-workers[171], but with limited success. On the other hand[171], isopropenyl glycosides **71-b**, obtained by reacting the corresponding anomeric acetate **71-c** with the Tebbe reagent, and isopropenyl glycosyl carbonates **71-d**, obtained by acylation of the free anomeric hydroxyl group with isopropenyl chloroformate, are also efficient glycosyl donors in the presence of Lewis acids.



3. OTHER METHODS OF CLEAVAGE OF ALLYL ETHERS

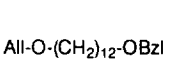
Allyl (and benzyl) ethers may be cleaved under Lewis acidic conditions; a recent example involves the use of the reagent combination $AlCl_3$/*N*, *N*-dimethylalinine[172]. $Ac_2O/BF_3 \cdot Et_2O$[173] converts allyl alkyl ethers to alkyl acetates which may in turn be cleaved, for instance, by sodium methoxide in methanol.

Allyl,[174] benzyl,[174] and propargyl[175] ethers are cleaved by Ti(0) species, *in situ* formed from $TiCl_3$ and Mg in THF at reflux. These deprotection reactions are thought to proceed through oxidative addition of a Ti(0) species to the substrate followed by cleavage of the titanium-oxygen bond (eq. 101).

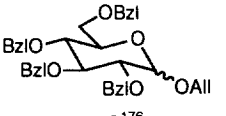


(101)

The oxidative addition process occurs more readily with the allyl group and selective deprotection of allyl ethers in the presence of benzyl ethers (*e.g.* on compound **72** , 87% deprotection yield) is therefore possible. Selective deprotection of allyl ethers in the presence of benzyl ethers (*e.g.* on compound **73**, 91% deprotection yield) is also possible with the zirconium dicyclopentadienyl species ($ZrCp_2$)[176] prepared *in situ* from zirconocene dichloride and butyl lithium. This reagent, which tolerates the presence of acid labile

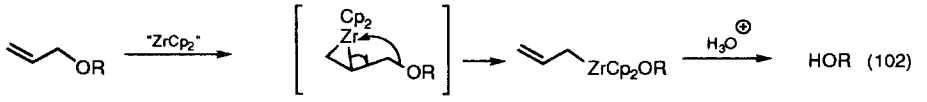


72[174]



73[176]

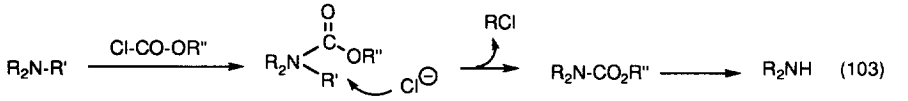
protecting groups (*O*-tetrahydropyranyl, *O*-isopropylidene) also cleaves allyl amines but much more sluggishly, which allows selective deprotection of allyl ethers in the presence of allyl amines. The mechanism of the reaction first involves coordination of the $ZrCp_2$ fragment on the double bond followed by β-elimination of the alkoxy group (eq. 102). Another closely related system associates Grignard reagents and $Ti(O\text{-}i\text{-}Pr)_4$[177].



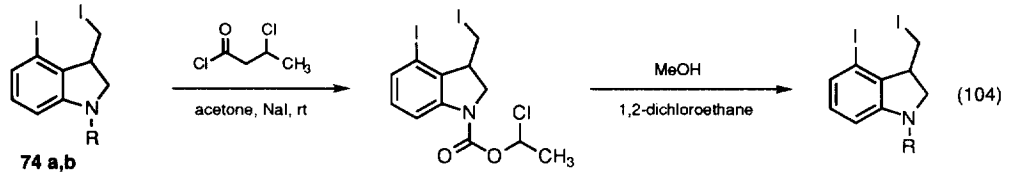
(102)

$SmCl_3$-catalysed electrochemical cleavage of allyl ethers has recently been reported[178]. The presence of $SmCl_3$ (10 mol%) probably facilitates the transfer of electrons to the system via its reduction to a Sm(II) species. $SmCl_3$ could in addition assist the cleavage process by Lewis acid coordination of the ether function.

Tertiary amines can be selectively dealkylated to secondary amines upon treatment with chloroformates (eq. 103)[179]. This procedure is most effective for *N*-debenzylation and *N*-deallylation. It has

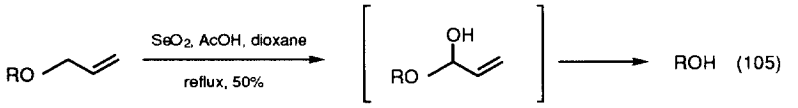


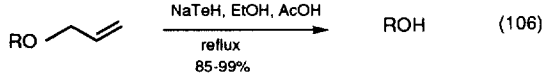
recently been used[180] for the deprotection of the *N*-benzyl and *N*-allyl subtituted indolines **74** (eq.104), in the latter case in preference to methods based on transition metal catalysed migration of the double bond. Use of



1-chlorethyl chloroformate[181] as the chloroformate reagent allows cleavage of the intermediate carbamate under especially mild conditions.

Allyl ethers may be also cleaved through SeO_2 induced allylic oxidation[182] and by use of sodium telluride[183] (eqs. 105 and 106).





List of abbreviations: Ac: acetyl; All: allyl; AllBr, AllI: allyl bromide, iodide; Alloc: allyloxycarbonyl; Bzl: benzyl; cat: catalyst; Cbz (or Z): benzyloxycarbonyl; cod: 1,5-cyclooctadiene; Cp: cyclopentadienyl; DABCO: diazabicyclooctane; dba: dibenzylideneacetone; DBU: diazabicycloundecene; DMA: dimethylacetamide; DME: dimethoxyethane; DMF: dimethylformamide; DMSO: dimethylsulfoxide; dppb: 1,2-bis(diphenylphosphino)butane; *N*-MeIm: *N*-methyl-imidazole; MOM: methoxymethyl; Pht: phthaloyl; Piv: pivaloyl; Pmb: *p*-methoxybenzyl; 4-Ppy: 4-pyrrolidinopyridine; TBABr, TBAI: tetrabutylammonium bromide, iodide; Tce: trichloroethyl; Tceoc: trichloroethoxycarbonyl; TES: triethylsilyl; TIPS: tetraisopropyl-disiloxane-1,3-diyl; THF: tetrahydrofuran; THP; tetrahydropyranyl; TsOH: *p*-toluenesulfonic acid; Z (or Cbz): benzyloxycarbonyl.

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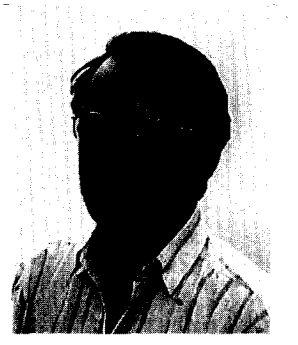
Biographical Sketch



François Guibé

François Guibé is a Director of Research in the French "Centre National de la Recherche Scientifique" (CNRS). He was born on January 1, 1946 in Caen (France). He graduated from the Ecole Normale Supérieure (Ulm, Paris). After PhD studies at the University of Paris-Sud with Professors M. Vilkas and G. Bram, dealing with solvents effects in organic chemistry, he pursued his scientific education as a post-doctoral fellow (1974-1975) at the University of California (Berkeley) with Professor A. Streitwieser, working on carbon acidity. Returning to France, he joined the "Groupe de Recherche n° 12" of the CNRS centre at Thiais, which was mainly involved with the study of organic reactions mechanisms, and whose director was the late Ms. B. Tchoubar. In 1982, he moved to the University of Paris-Sud (Orsay).

His current research interests centre on catalytic transition metal chemistry (palladium π-allyl chemistry, olefin metathesis ...) and heteroelement chemistry (silicon, boron and tin compounds) and their applications to various fields of organic synthesis, particularly in protecting group chemistry and peptide and aminoacid synthesis.