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Allylic Protecting Groups and Their Use in a Complex Environment Part II: Allylic Protecting Groups and their Removal through Catalytic Palladium π-Allyl Methodology[1,2]

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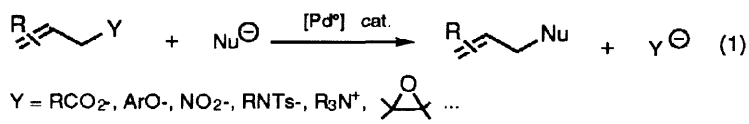
1. GENERAL CONSIDERATIONS ON PALLADIUM CATALYSED ALLYLIC SUBSTITUTION REACTIONS AND THEIR MECHANISM.

A number of electrophilic allylic derivatives which do not behave as allylating agents under usual S_N2 conditions, may do so, provided that catalytic amounts of appropriate soluble palladium(0) complexes are present in the medium (eq. 1). Such catalytic allylic alkylation reactions constitute a very useful tool for

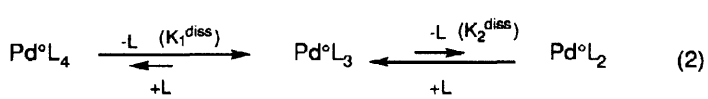


synthetic organic chemistry[3]. Aside from the fact that these electrophilic allylating reagents are more readily available and handled than allyl halides, they also display unique regiochemical and stereochemical characteristics. The use of optically active ligands on palladium also permits enantioselective allylic alkylations.[3e,3h]

Many nucleophiles may participate in catalytic allylation reactions including both carbon nucleophiles such as enolates derived from β-dicarbonyl compounds and organometallics (Mg, Zn...) as well as heteronucleophiles such as amines and azides.

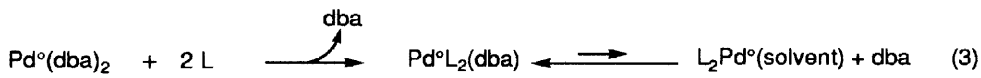
The mechanism of the palladium catalysed allylic substitution reaction (the Tsuji-Trost reaction) is by now well understood, at least in its main features. The question of the exact nature of the active catalytic species is a rather complex matter. With some approximation, it may be said that they are coordinatively unsaturated zerovalent palladium entities of general structure $Pd^{\circ}L_2$ or PdL_2X^- (X^- being Cl^-, AcO^-.. depending on the nature of the anionic species present in the medium).[4,5] The ligands L on palladium are generally tertiary phosphines -typically triphenylphosphine- or phosphites. The active species may be formed *in situ* in several ways:

(a) - by ligand dissociation from coordinatively saturated palladium zerovalent complexes (eq. 2); for

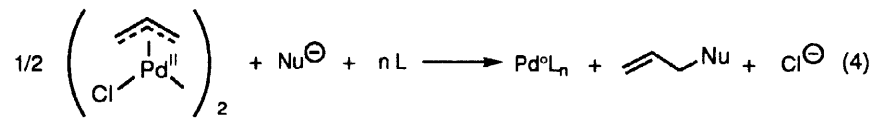


L=PPh_3, NMR spectroscopy and kinetic and voltamperometric studies[4] have led to the conclusion that the first equilibrium is largely in favor of the tricoordinated species while the dissociation of $Pd(PPh_3)_3$ to $Pd(PPh_3)_2$ and PPh_3 ,on the contrary, occurs only to a very small extent (for instance, K_2^{diss} = 1.5x 10^{-5} M in the presence of chloride ion in THF).

(b) -From air-stable palladium dibenzalacetone (dba) complexes such as $Pd(dba)_2$ or $Pd_2(dba)_3$. $CHCl_3$, by ligand exchange with phosphines. Recent studies[6] (L= PPh_3) have shown that, in this process, most of the resulting complex retains one molecule of dba in the coordination sphere of the metal. The active catalytic species however results from further deligation of dba from palladium (eq.3).

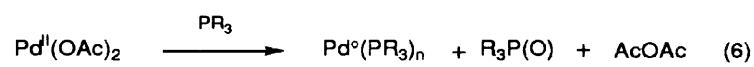


(c) -From nucleophilic attack on the π–allyl palladium(II) chlorodimer in the presence of ligands[7] (eq. 4).



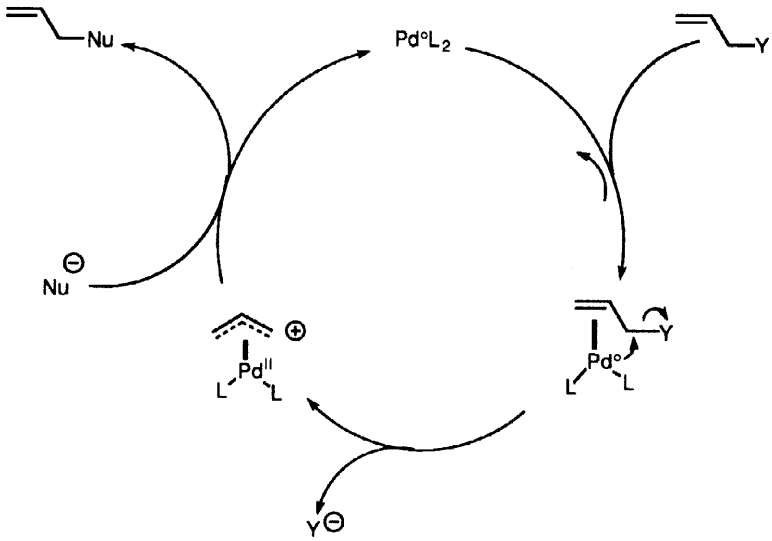
(d) -By reduction of air stable divalent complexes $Pd^{II}L_2X_2$ (X=Hal) by various chemical reagents including organometallic reagents (Grignard reagents, organoaluminum compounds...)[8] or hydride donors such as formic acid, borohydrides or tributyltin hydride. Electrochemical reduction is also possible.[4b,8]

(e) -By reduction[9] of palladium(II) diacetate in the presence of phosphine (eq. 6).

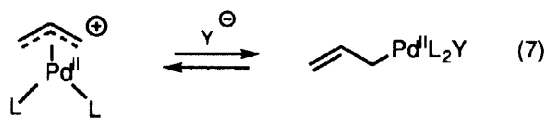


The catalytic cycle of allylic alkylation reactions (fig. 1) involves two major steps, in which the PdL_2 fragment acts successively as a nucleophile (while in its zerovalent state) and then as a leaving group (once in its divalent oxidation state). In the first step, after prior coordination to the double bond, the $Pd°L_2$ fragment displaces the leaving group Y, leading to a π-allyl complex. Except for some very specific cases[10], this process occurs with inversion of configuration at the carbon atom bearing the Y group and may be roughly considered as an intramolecular S_N2 process. From the point of view of organometallic chemistry, it constitutes an oxidative addition process[11] in which the formal oxidation state of palladium is raised by two. The question as to whether the π-allylpalladium complex exist mostly as a cationic species with a 16-electron outer shell for the metal or as a neutral 18-electron species with the Y leaving group coordinated to palladium has not been definitely resolved[12] and its structure can in fact depend on many factors such as the nature of the ligand L, the solvent and the leaving group. The picture is further complicated by the fact that the π-allyl complex is in rapid equilibrium with σ-allyl forms as represented in eq. 7. Most of the time and for the

Fig 1



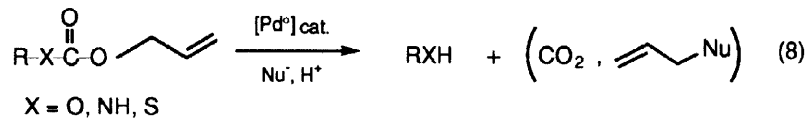
sake of simplicity, we will assume in the following review that the only reactive species in the medium is the presumably more electrophilic cationic complex.



The second step of the catalytic cycle is the attack of the nucleophile on the π-allyl complex. From the organometallic point of view, this corresponds to a reductive elimination process[11] in which the PdL_2 fragment is restored to its initial zerovalent oxidation state. Mechanistically speaking, this step may occur in two ways:[13-14] soft nucleophiles, especially enolates derived from β-dicarbonyl compounds, react directly at the allylic carbon site from the face opposite to palladium (*anti* mechanism). Hard nucleophiles, typically organozinc compounds, organomagnesium compounds or hydride species tend to coordinate first to the palladium, leading to neutral π-allyl or σ-allyl complexes. Reductive elimination then occurs through internal delivery of the nucleophilic entity from palladium to carbon. The distinction between these two mechanisms is usually made on the basis of stereochemical studies.[13,14] The first (*anti*) mechanism entails inversion at carbon. Given the first inversion of configuration during formation of the π-allyl palladium species, overall retention of configuration is therefore observed. By way of contrast, the second (*syn*) mechanism occurs with retention of configuration and results in overall inversion of configuration for the whole process.

The reaction of eq.1 may be seen as the deprotection of a Y function initially protected as its allylic derivative. A necessary condition for successful removal of the allyl group is that the Y function possesses sufficient leaving group ability to allow the formation of the π-allyl complex. Carboxylic acids, phenols, phosphoric and phosphonic acids are among the main functional goups which fulfill this conditions, but the deprotection reaction of eq.1 has also been applied to other compounds such as allylated oximes, imides, quaternary allylammonium ions, and allylamines in their protonated form.

Contrastingly, allyl ethers, thioethers, and allylamines in their basic form are not cleaved by a Pd° catalyst. This difficulty may be circumvented by using the allyloxycarbonyl group instead of the allyl group for protection. The allylic cleavage is then usually accompanied by decarboxylation (eq.8).



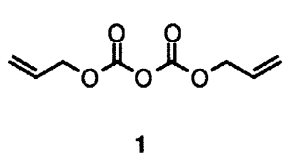
(8)

Many nucleophilic species have been used as allyl acceptors in the deprotection reactions of eq. 1 or 8. From the outset, an important distinction can be made between reversible allyl group scavengers, which, once allylated, may revert back to π-allyl complex, and irreversible ones which do not. Before reviewing them however, we will first deal with the main methods of formation of allyl carboxylic esters, carbonates and carbamates. Some general comments on possible side reactions in the deprotection of allyl carbamates will also be made.

2. MAIN METHODS OF FORMATION OF ALLYL CARBOXYLATES, CARBONATES AND CARBAMATES.

As with most alkyl esters of carboxylic acids, allyl carboxylates may generally be obtained[2d,2e] by one of three main procedures: i) direct acid catalysed esterification of the carboxylic acid with allyl alcohol; ii) reaction of allyl alcohol with an activated carboxy-derivative; iii) nucleophilic displacement of allyl halides with carboxylates salts. Allyl carbonates or carbamates are usually obtained by the reaction of the alcohols or amines with allyl chloroformate in the presence of base.

More sophisticated reagents for the introduction of the allyl or the allyloxycarbonyl group include diallyldicarbonate **1**[15], allyl isopropenyl dicarbonate **2**[16], 1-(allyloxycarbonyl)tetrazole **3**[17] and allyl 1-benzotriazolylcarbonate **4**.[17]



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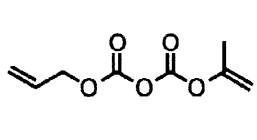

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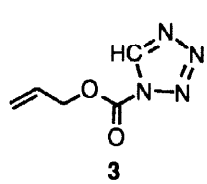

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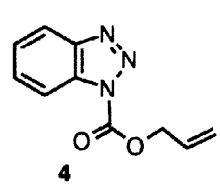
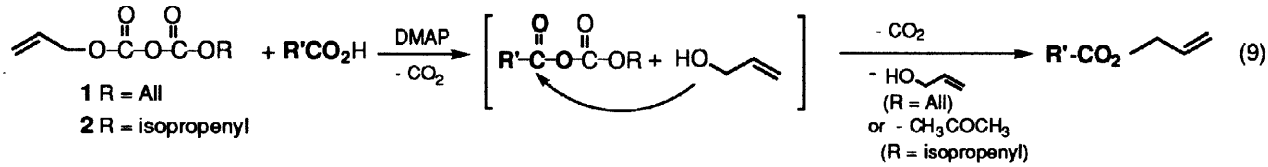


4

4 has been used for the preparation of *O*-Alloc derivatives[18] of carbohydrates and **1**, **3** and **4** for the preparation of *N*-Alloc or *O*-Alloc protected forms of nucleobases[17] or related entities[17,19] in nucleosides (see section 6). **1** and **2** have been used in the DMAP mediated esterification of carboxylic acids[16,20] (eq. 9).



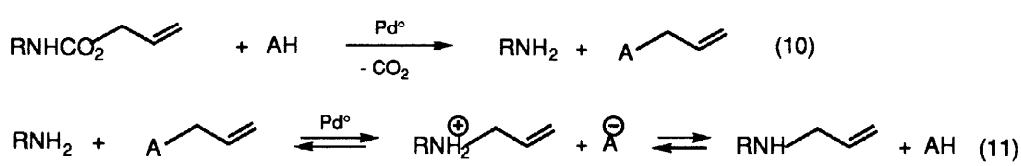
(9)

3. THE PROBLEMATIC SIDE REACTION OF ALLYLAMINE FORMATION DURING PALLADIUM CATALYSED DEPROTECTION OF ALLYL CARBAMATES.

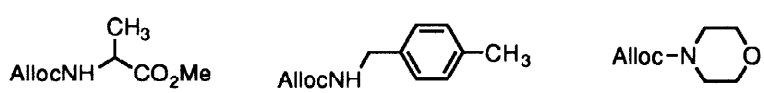
The formation of allylamines as a side reaction during palladium catalysed deprotection of allylcarbamates is a matter of serious concern and may occur in different ways.

Firstly, the deprotected amine may compete with the nucleophilic allyl group scavenger in the trapping of the π-allyl palladium complex. Therefore, it is better to use deprotection systems which lead to the amine in protonated or other masked non nucleophilic forms, or to use the allyl scavenger in large excess.

With protonic reversible allyl group scavengers AH (eq. 10), allylamine may also be formed through the equilibration process of eq. 11 .



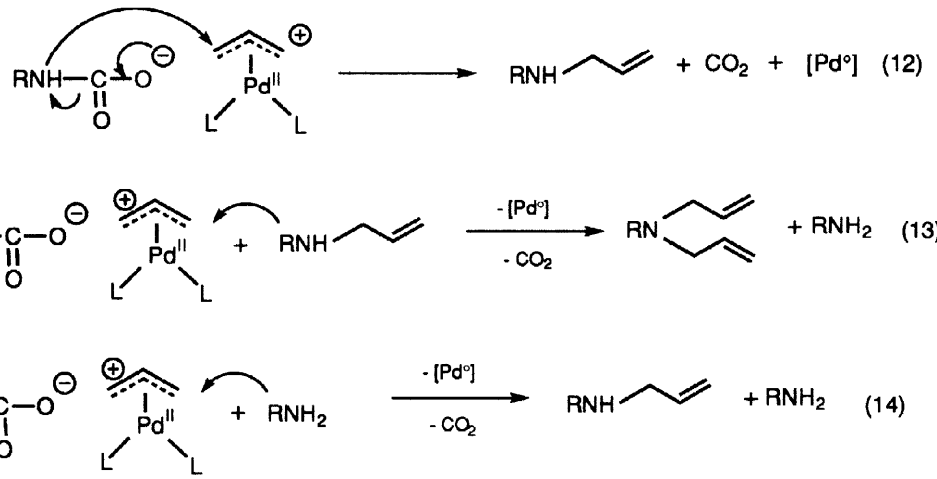
Finally, Alloc derivatives of amines in the presence of palladium catalysts and without any added nucleophile are known to undergo decarboxylative rearrangement to allyl amines. The rapidity of the process is highly dependent on the nature of the amine. In general, secondary amines rearrange faster than primary ones.[21-24] The following half-life times have been determined[23] for carbamates **5**, **6**, **7** (25 °C, 0.25 M solution in dichloromethane containing 2 mol% of $Pd(PPh_3)_4$): **5**, 58 min.; **6**, 16 min.; **7**, < 5 min.



5 **6** **7**

The *N*-Alloc to *N*-allyl conversion must involve an intra-molecular (intra-ion pair) decarboxylative condensation between the cationic π-allyl entity and its carbamato counter-anion[22] (eq.12, see also paragraph 4-5). In the case of Alloc derivatives of primary amines, the free monoallylamine, once formed, may react

intermolecularly with the π-allyl complex and self-propagation of the process becomes possible by way of eqs 13 and 14.



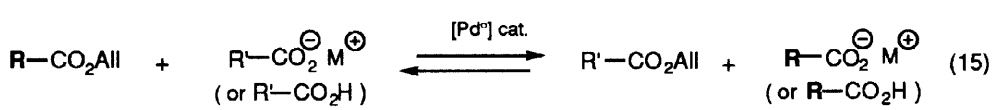
Allyl carbonates also undergo decarboxylative rearrangement leading to allyl ethers in the presence of palladium catalyst . However, alcohols and alkoxides are rather poor nucleophiles towards π-allyl palladium complexes and side formation of allyl ethers is generally not observed during deprotection of allyl carbonates in the presence of allyl scavengers. Acylation with allyl chloroformate followed by palladium catalysed decarboxylative rearrangement is a useful method for introducing allyl groups on alcohols under moderately basic conditions (see part 1, paragraph 1-3).

4. NUCLEOPHILIC SYSTEMS USED IN PALLADIUM-CATALYSED REMOVAL OF ALLYLIC PROTECTING GROUPS.

A large variety of nucleophilic species have been employed as allyl group scavengers in eqs 1 and 8 and these include oxygen, nitrogen, carbon and sulfur nucleophiles, as well as hydride donors.

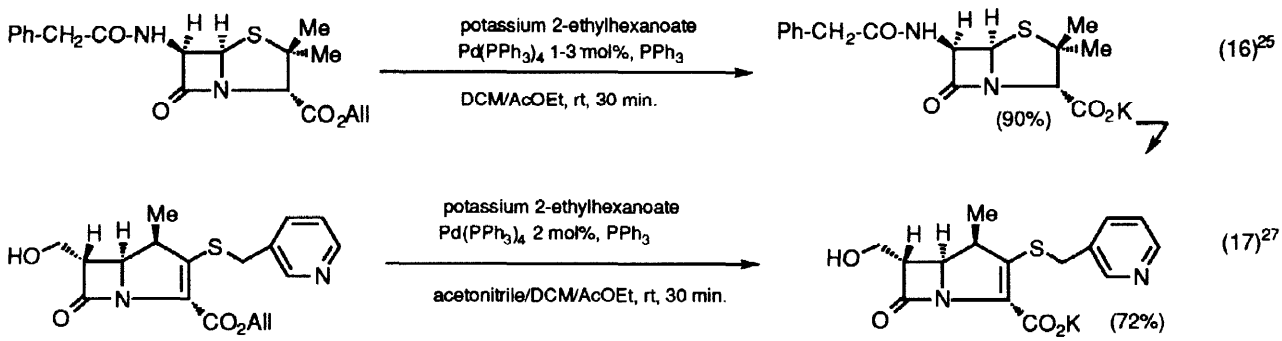
4.1 **Oxygen nucleophiles**

Carboxylic acids and carboxylate anions may act as allyl goup scavengers (eq.15). These reactions



are of course equilibrated and conditions must be devised to displace the equilibrium in the sense of the desired deprotection reaction. As early as 1982, Jeffrey and Mc Combie[25] proposed to use potassium 2-ethyl-hexanoate. This salt is highly soluble in organic media and the deprotected product is obtained by selective precipitation of its potassium salt. This mild near-to-neutral procedure has been used more specifically for deprotection of allyl carboxylates on base-sensitive β-lactam compounds[25-27] (eqs 16, 17).

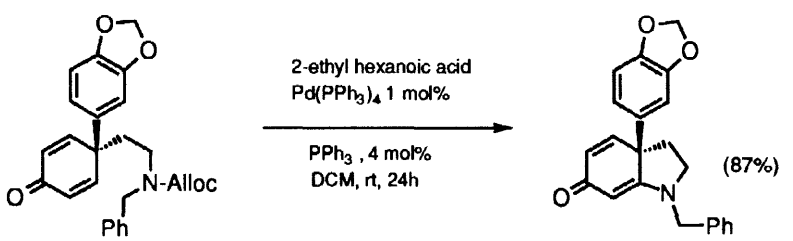
2-ethylhexanoic acid was similarly tested for the deprotection of allyl carbamates, but



(16)[25]

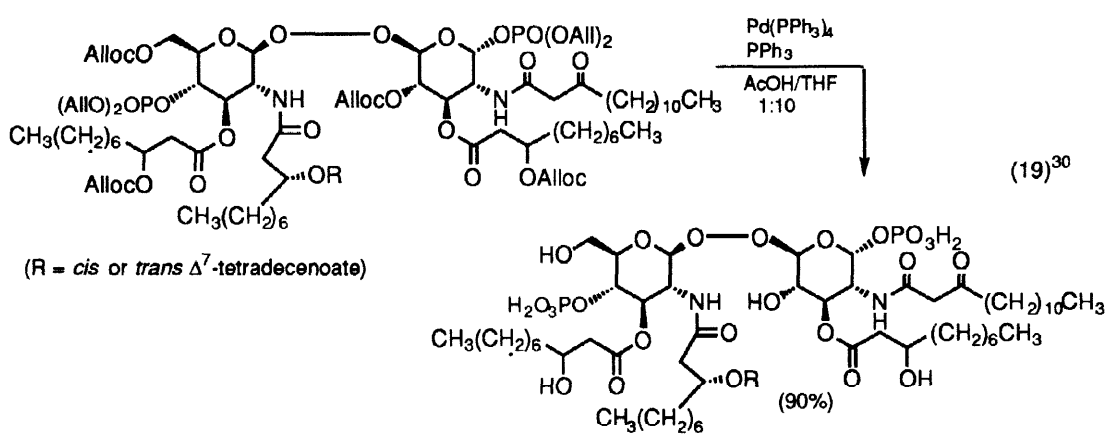
(17)[27]

the formation of allyl amines as a significant side reaction was observed both in the aromatic[25] and the aliphatic[28] series. The procedure was nevertheless used successfully in the deprotection reaction of eq. 18,[29] perhaps because in this particular case the deprotected amino group is immediately trapped through intramolecular condensation onto the enone moiety.



(18)[29]

Acetic acid in large excess has recently been used in the deprotection of the allyl phosphates and allyl carbonates[30] (eq. 19); it should be noted however that these two allylic functionalities are especially prone[31] to cleavage by palladium(0) complexes. When applied to allyl carbamates,[28,32] the same procedure was found to lead to sluggish reactions, either incomplete[28], or necessitating continued additions



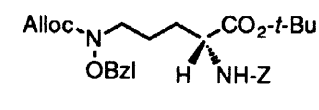
(19)[30]

of further catalyst.[32] More rapid reactions are possible through association of acetic acid with a base such as morpholine and *N*-methylmorpholine (see paragraph 4-2).

The reaction of the bis-protected (*N*-Alloc, *O*-Bzl) hydroxylamine **8** with $Pd(PPh_3)_4$ / AcOH (4 equiv.) was found[33] to give a mixture of the desired deprotected product and of its N-allyl derivative **9**, probably through the equilibrium process depicted in eq. 11. Clean deprotection could be achieved by using *O*-benzyl hydroxylamine as the allyl acceptor[33] (see paragraph 4.2).

As already mentioned (see part I , paragraph 2.3), cleavage of an allyl glycoside has been achieved with palladium (tetrakis)triphenylphosphine (30 mol%) in hot acetic acid.[34]

The highly nucleophilic *N*-hydroxysuccimide[35] (in association with formic acid) and hydroxybenzotriazole[36-37] (HOBt) has been used as the allyl acceptor in aminoacid and peptide chemistry (see section 5).



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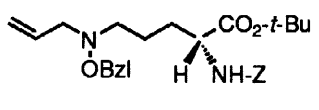

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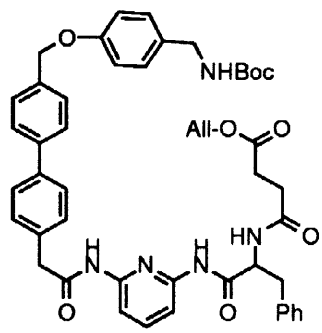
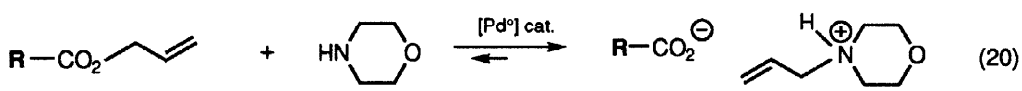


10

Finally, despite the fact that water is a notoriously poor nucleophile in palladium catalysed allylic substitutions[38], allyl ester **10** has been successfully deprotected in water/dioxane.[39]

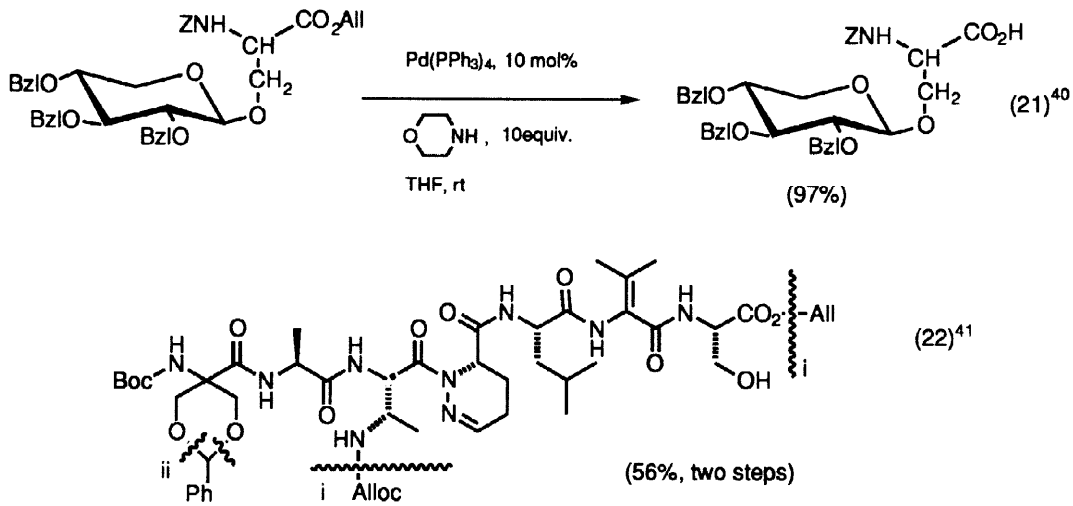
4.2 **Nitrogen nucleophiles**

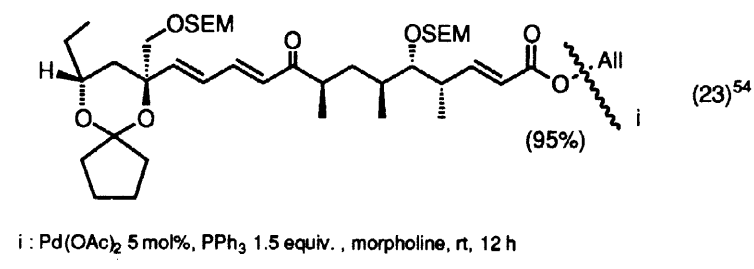
In 1984, Kunz and coworkers[40] described the use of morpholine in the palladium catalysed deprotection of allyl esters of amino-acids and glycopeptides (eq. 20). Since allylammonium species are able to transfer their allyl group to palladium zerovalent compounds (see paragraph 4.3), this reaction cannot be considered as truly irreversible, and the use of an excess[40] of scavenger is therefore highly recommended.

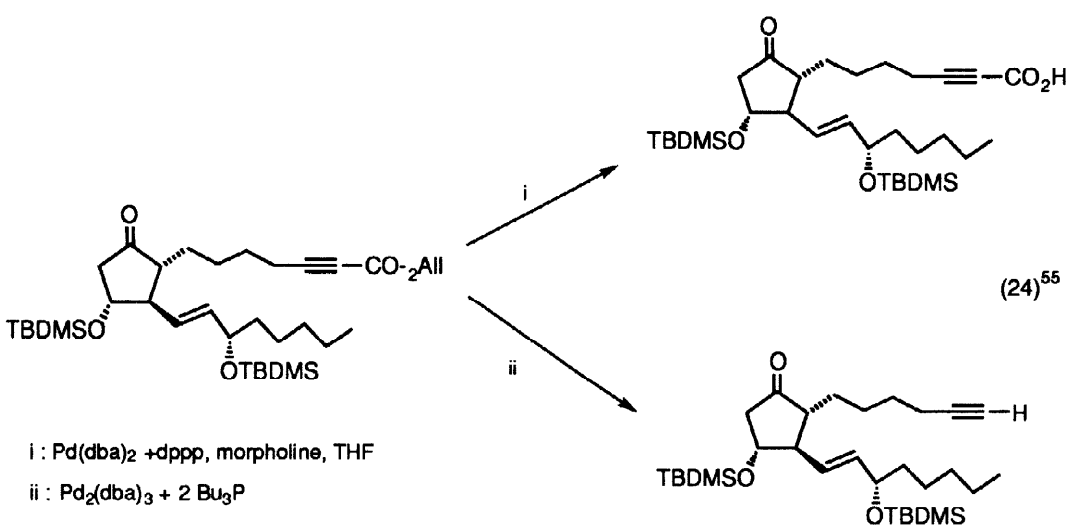


(20)

Since Kunz' original report, many amines, especially secondary ones, have found service as allyl acceptors not only in the cleavage of allyl carboxylates or phosphates, but also, albeit more rarely, in the deprotection of allyl carbamates. [24,41-44] In this case also, the scavenger is used in excess in order to avoid kinetic competitive allyl trapping by the liberated amine. Morpholine itself has been routinely used in the aminoacid,[45,46] peptide,[47,48] and glycopeptide field, [2a,49-52] as well as in other areas[53-55] (eqs 21-24). As exemplified in eqs 21, 23, 24, the deprotection procedure is compatible with the presence of labile *O*-serine anomeric linkages and *O*-SEM and *O*-TBDMS protections. In the deprotection of alkynoic allyl esters[55] (eq.24), use of a chelating diphosphine ligand- namely dppb- is mandatory. With the monophosphine



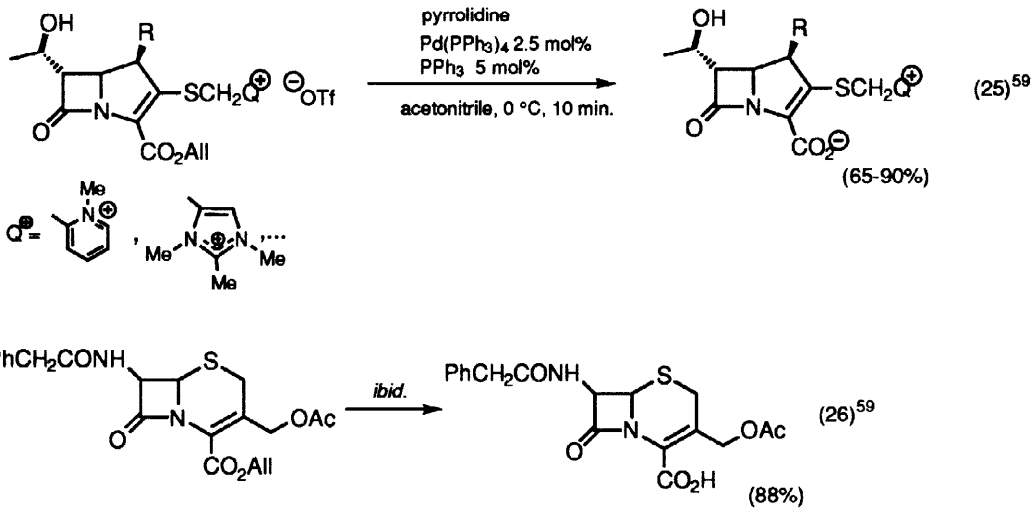




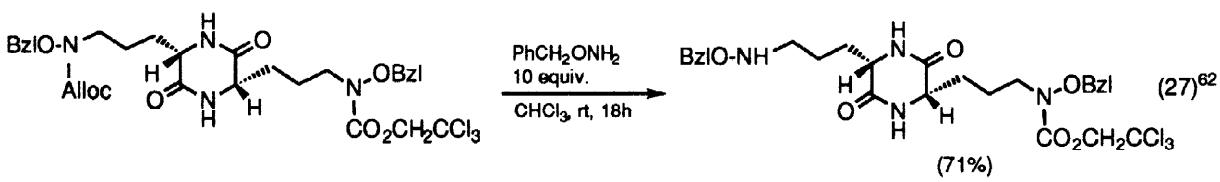
PBu_3 as the ligand, concomitant decarboxylation, which is made possible by ligand decoordination[55] during the catalytic process, was found to take place.

A multicomponent system consisting of DMSO/THF/0.5M aqueous HCl 2/2/1 v/v and morpholine (in *ca.* threefold excess over HCl) has been devised by Albericio, Giralt and coworkers for the cleavage of All and Alloc groups on resin-bound peptides.[56-58] The more basic and more nucleophilic pyrrolidine has been used in the deprotection of quaternized carbapenems[59] (eq. 25), for which neither morpholine nor potassium

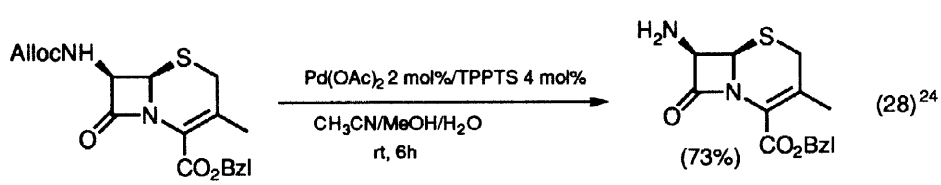
2-ethyl-hexanoate were found to be satisfactory. In the deprotection reaction of eq. 26,[59] the allyl carboxylate is selectively cleaved and the acetoxy group, which also forms part of an allylic system, but with a tetra-



substituted double bond, is retained in the process. Pyrrolidine or piperidine have also been utilized in the aminoacid and peptide field.[60,61] Miller and coworkers have repeatedly resorted to *O*-benzyl hydroxylamine as the allyl scavenger with good results[33,62,63] (eq. 27). Palladium catalysed deprotection of monoallyl



phosphotriesters with Pd/*n*-BuNH$_2$ and Pd/Et$_2$NH has been carried out by Hayakawa and Noyori on model dinucleotides.[64] More recently, the same authors have employed diethylammonium hydrogenocarbonate in the deprotection of allyl and allyloxycarbonyl derivatives of nucleobases[65] (see section 6). A procedure for deprotection in an aqueous organic medium (H_2O/CH_3CN) or in two-phase system (H_2O/Et_2O) has been devised by Genêt and coworkers[24,43,44], using dimethylamine as the allyl scavenger and the water-soluble catalytic system Pd(OAc)$_2$ + TPPS (eq.28)[24] (TPPS: 3,3',3''-phosphinetriylbenzenesulfonate).



Palladium catalysed cleavage of allyl carbonates in water using the same water-soluble catalytic system and sodium azide as the allyl scavenger has recently been reported.[66]

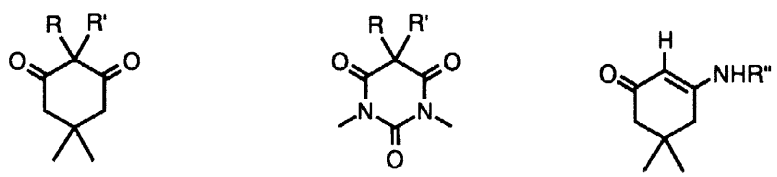
N-methylaniline (NMA) is another potent allyl acceptor which has been used for instance in β-lactam chemistry[67]and for removal of the Paloc[68] (see paragraph 7-1) group . Due to its low basicity, NMA offers

the very significant advantage, especially in peptide chemistry, and over other secondary amines including the albeit relatively weakly basic morpholine[57], of being compatible with Fmoc protection.[69,70]

Another way to ensure Fmoc compatibility has been to use *N*-methyl-morpholine (NMM), a tertiary amine of low basicity, either in DMSO/THF/HCl 0.1N[71] 2/2/1 v/v (NMM in 100% excess over HCl) or in $CHCl_3$/AcOH 95/05 v/v (AcOH in 100% excess over NMM).[57, 72-74] The latter system has been specifically designed for deprotection of both allyl esters and carbamates during solid phase peptide synthesis in a continuous flow apparatus.[57,74]

4.3 **Carbon nucleophiles**

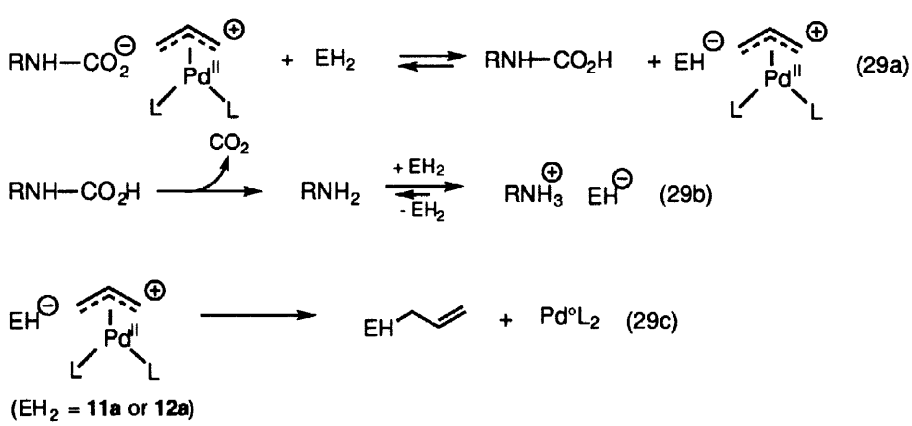
Dimedone **11a**[75] and *N, N*-dimethylbarbituric acid (NDMBA) **12a**[76] are both β-dicarbonyl compounds of high acidity (pK_a= 5.3 and 4.7 respectively) which have been introduced by Kunz and coworkers as allyl group scavengers in the deprotection of allyl carbamates. The allyl transfer processes which lead to the mono- and di-C-allyl derivatives **11b,c** and **12b,c** may be considered as irreversible.[77] At the start, they are likely to



11a-c **12a-c** **13**

a : R=R'=H; b : R=H, R'=All; c: R=R'=All

involve a prototropic exchange between the carbamato π-allyl intermediate and the β-dicarbonyl compound EH_2, leading to the corresponding enolate EH^- and the carbamic acid which then undergoes decarboxylation to amine, while irreversible condensation of the enolate species with the π-allyl palladium complex allows regeneration of the Pd° catalyst, thus completing the catalytic cycle (eq. 29a-c).[78] Of course, as the reaction proceeds , the concentration of the enolate species in the medium increases steadily as a result



(29a)

(29b)

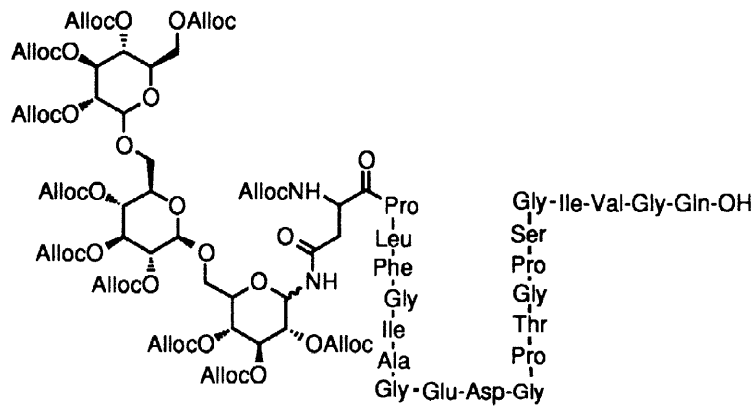
(29c)

(EH_2 = **11a** or **12a**)

of proton exchange between the liberated amine and the scavenger. A possible complication[76,79] when using the Pd/dimedone combination is the formation of the hydrolytically stable[80] ketoenamine **13** by reaction

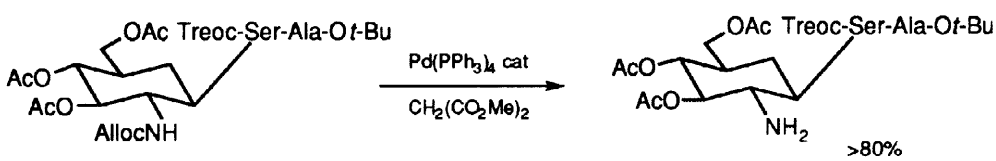
between the liberated amine and dimedone. For this reason, the use of NDMBA , whose "carbonyl" groups are unreactive, seems more advisable.

The Pd/dimedone and Pd/NDMBA systems have been extensively employed, in the glycopeptide area[75,76,81-83] (see paragraph 5-1) as well as in other fields.[84-87] An impressive example concerns the simultaneous removal (55% yield) of the *N*-Alloc and of the ten *O*-Alloc groups of compound **14**.[87]

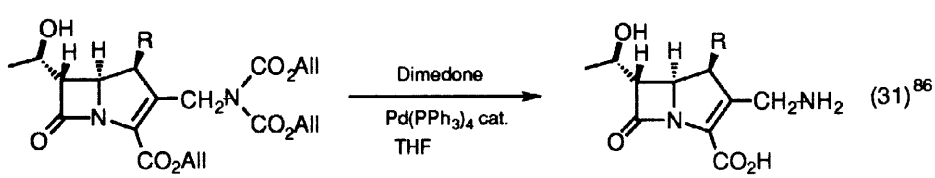


14[87]

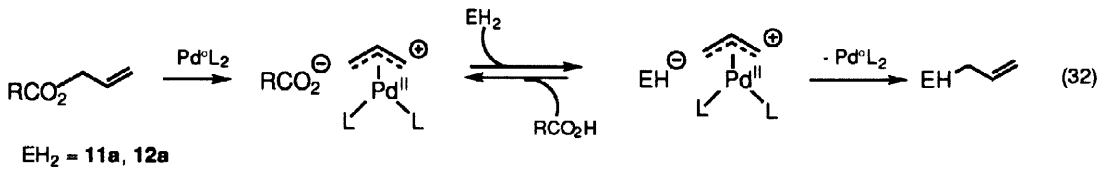
Thanks to the irreversible nature of the reactions, their relative rapidity, and the fact that the liberated amine is protonated by the allyl scavenger (used, as a rule, in excess), the side-formation of allylamine during deprotection of allyl carbamates by the Pd/dimedone or the Pd/NDMBA systems is highly improbable and has, in fact, never been reported. Furthermore, as we shall see below, allylamines are themselves cleaved by the Pd/NDMBA system. Instead of dimedone or NDMBA, dimethyl malonate, a β-dicarbonyl compound of much weaker acidity has also been occasionnaly used[88-92](eq. 30). Simultaneous

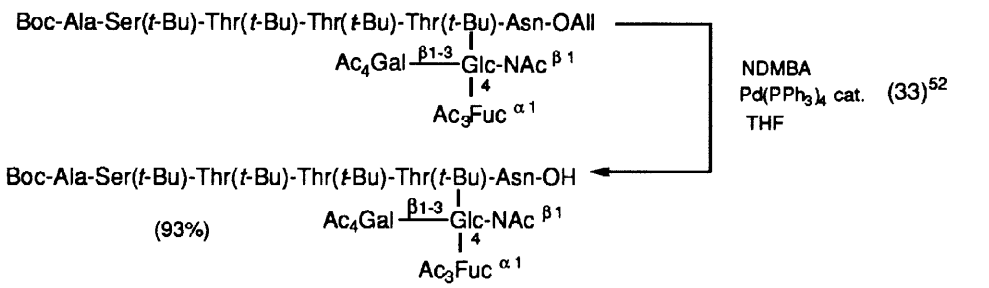


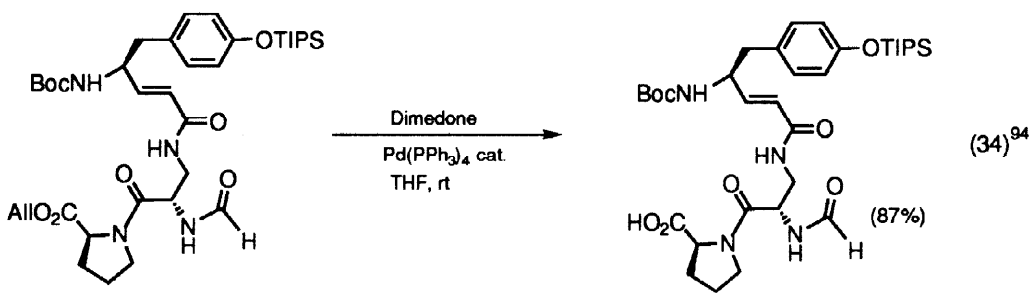
deprotection of allyl esters and allyl carbamates[86] (eq. 31) with dimedone, as well as the deprotection of allyl



esters in the presence of the preformed enolate of dimedone[93] have also been reported. Other literature data[52,94] however, seem to indicate that dimedone or NDMBA are, in fact, acidic enough to allow deprotection of allyl esters without the need for an extra base (eq. 32), as for example in eqs 33 and 34.





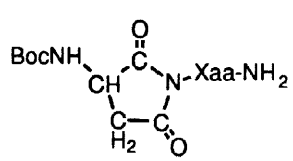


Such a procedure may be helpful when basic conditions must be avoided. This point is well illustrated in the deprotection of the dipeptides **15**, **16** and **17**.[95] Selective and quantitative deprotection is achieved

Boc-Asp(OAll)-Phe-NH_2
15

Boc-Asp(OAll)-Gly-NH_2
16

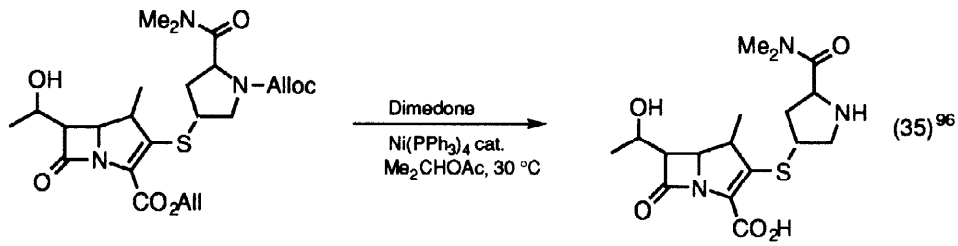
Boc-Asp(OAll)-Ser-NH_2
17



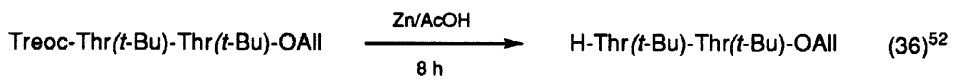
18 Xaa = Gly, Ser

by the use of dimedone as the allyl scavenger. However, with the more basic morpholine, in the case of the sensitive Aps-Gly and Asp-Ser sequences, partial formation -6% and 2% respectively- of the aminosuccinyl (ASU) derivative **18** has been noted. This reaction, which involves an intramolecular nucleophilic condensation on the β-carbalkoxy group of the Asp residue, is commonly encountered in aspartyl peptide chemistry.

Simultaneous deprotection of allyl esters and carbamates with dimedone in the presence of catalytic amounts of zerovalent *nickel* complexes (eq. 35) has been described in a patent.[96,97] The trichloroethoxycarbonyl group (Treoc) can be selectively removed in the presence of allyl esters[52,98] (eq. 36) and

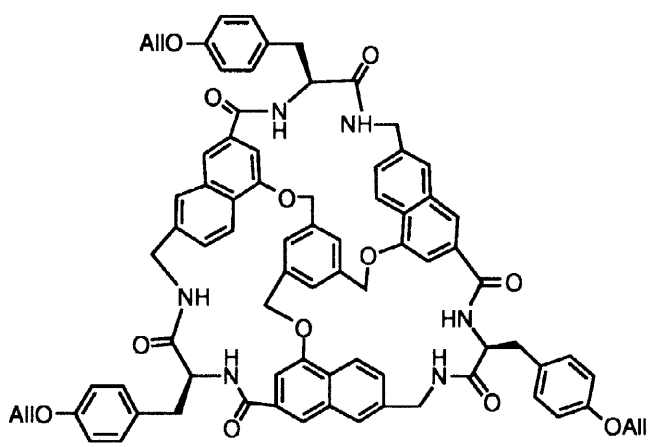


(35)[96]



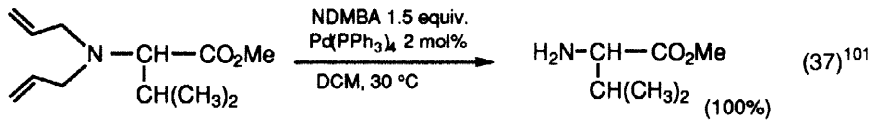
(36)[52]

carbamates.[98] Since the reverse is also true (eqs 27, 30), the All, Alloc groups on the one hand, and the Tre (trichloroethyl) and Treoc groups on the other, are orthogonal. The cleavage of allyl aryl ethers with palladium and dimedone under neutral conditions has been recently reported on compound **19** but without any details concerning the reaction conditions.[99] Previous attempts to perform deprotection of allylic phenolic ethers of tyrosine derivatives under similar conditions, were unsuccessful.[100] The problem of the compatibility of dimedone or NDMBA enolates with Fmoc protection has apparently not been thoroughly examined.

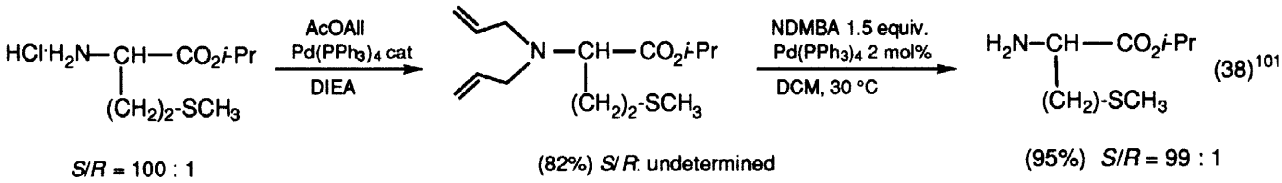


19[99]

As mentioned above, the Pd/NDMBA system allows deallylation of allylamines under mild conditions.[101] This reaction is possible because, once protonated by NDMBA, the allylamine is sufficiently electrophilic to react with the Pd° catalyst and generate the π-allyl palladium complex. The whole process may thus be considered as a palladium mediated transfer of the allyl group from the protonated allyl ammonium species to its enolate counterpart. Some examples are given in eqs 37 and 38. The deprotection of the methionine derivative was found to occur with little or no racemization (<2%).



(37)[101]

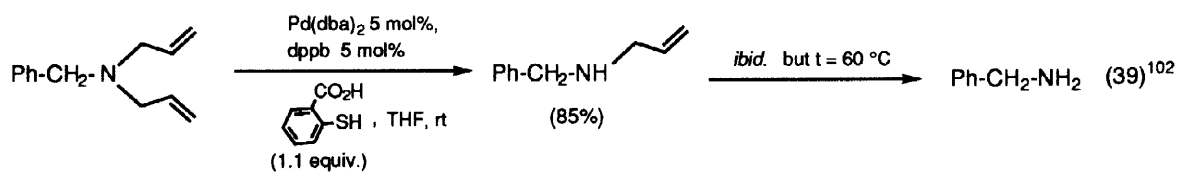


(38)[101]

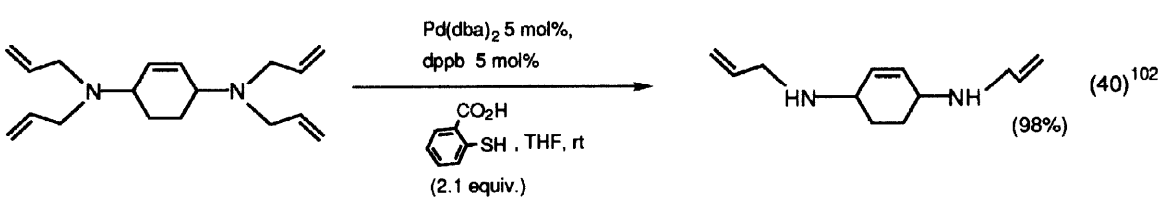
Allyl and diallyl amines, as volatile and inexpensive compounds, can be used in large excess on a practical scale and should therefore constitute useful Gabriel synthons for the synthesis of primary amines. This procedure has been illustrated[101] in the conversion of (chloromethyl)polystyrene into aminopolystyrene, a functionalized polymer of wide use in solid phase peptide synthesis.

4.4 Sulfur nucleophiles

Genêt and coworkers have recently advocated[24,102] the use of 2-thiobenzoic acid as an allyl group scavenger. The corresponding thioallyl ether, which is the by-product of reaction, is readily eliminated by a simple extraction into aqueous alkali. The scope of utilization of 2-thiobenzoic acid is rather similar to that of acidic carbon pronucleophiles such as dimedone and NDMBA, and has been applied to the deprotection of allyl carbamates[24] and to the deallylation of allylamines.[102,103] By taking advantage of the different

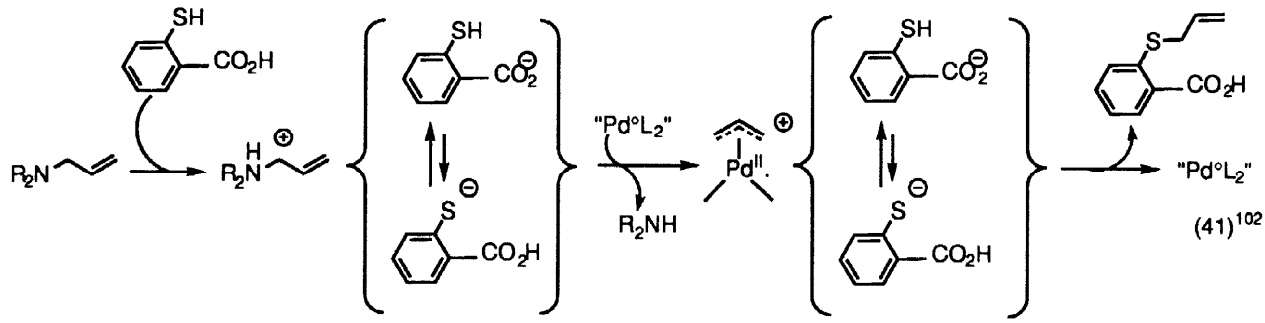


(39)[102]



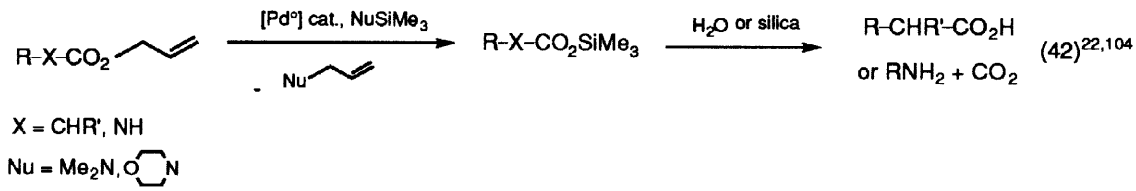
(40)[102]

reactivity of secondary and tertiary allylamines, Genêt and coworkers have been able to achieve selective removal of one allyl group from diallyl amines (eqs 39, 40). The mechanism of deprotection of allylamines, as proposed by the authors, is reproduced in eq. 41.

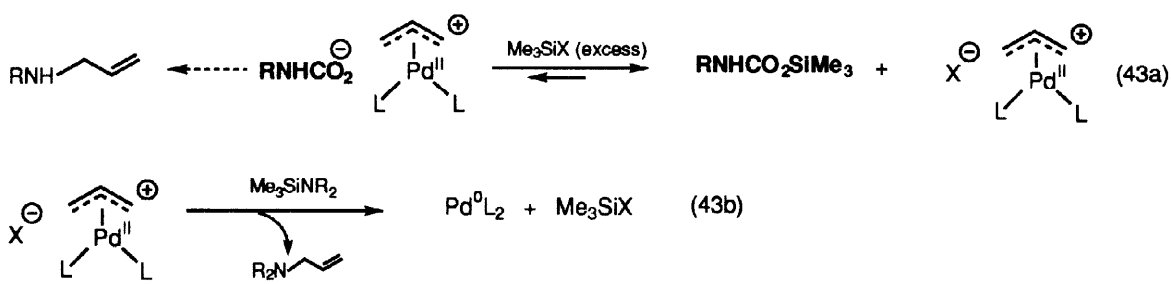


4.5 Silylated derivatives of nucleophiles.

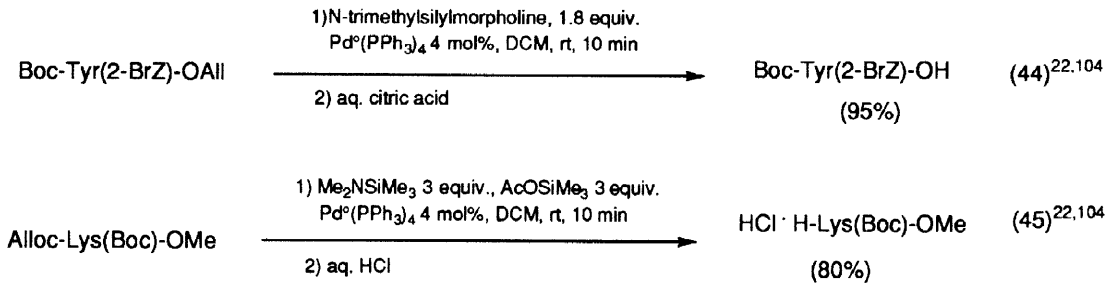
Clean deprotection reactions of allyl esters or carbamates has been observed through use of N-trimethylsilylated secondary amines as allyl group scavengers (eq. 42).[22,101,104] The products of reaction are the corresponding trimethylsilylated carboxylates which can be instantaneously converted to the parent unprotected functional groups under neutral conditions simply by adding water or silica.



Since allyl carbamates are converted to trimethylsilylcarbamates and not directly to the free amines, these latter ones cannot compete for trapping of the π-allyl entity . In spite of this, formation of allylamines was observed in some cases, most likely as a result of direct intra-molecular (or intra ion-pair) decarboxylative condensation within the intermediate carbamato π-allyl palladium intermediate (see eq. 12). This side reaction may be completely suppressed by carrying out the reaction in the presence of a mild silylating electrophile such as trimethylsilyl acetate, trifluoroacetate or mesylate. The role of the electrophilic silylating agent is probably to displace the π-allyl entity from its carbamato counter-anion through a fast transilylation process. The risk of decarboxylative condensation is therefore minimized, while the allyl trapping process, which now takes place at the new [π-allyl palladium]$^{+}$, X^{-} ion pair , remains fundamentally unaffected (eq. 43a, 43b).



The Pd^0/R_2NSiMe_3 systems are perfectly tolerant towards the Boc and *t*-Bu groups and also towards the 2-bromobenzyloxycarbonyl group which is widely used for protection of the phenolic hydroxyl group of tyrosine (eqs 44, 45). Unfortunately, Fmoc groups are readily cleaved by N-trimethylsilylated secondary amines. Allyl aryl ethers are not cleaved by the Pd^0/R_2NSiMe_3 systems, even in the presence of electrophilic silylating agents.



G. Shapiro and coworkers[105] have advocated the use of trimethylsilyl azide in association with tetrabutylammonium fluoride whose role is to facilitate the π-allyl trapping process through anionic activation[106] of trimethylsilyl azide.[107] The $Pd/MeSiN_3/Bu_4NF$ has been sucessfully used, *inter alia*, in solid phase peptide synthesis for removal of N^{α}-Alloc terminal groups on base labile serine phosphopeptides and for deprotection of allyl derivatives of phosphonopeptides (see paragraph 5.1)

The use of silicon hydrides in palladium catalysed allylic cleavage is dealt with in section 4.6.d

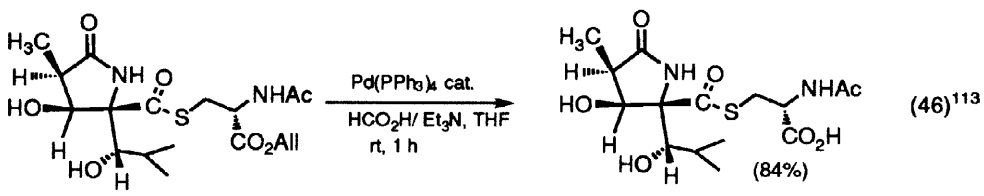
4.6 **Hydrides donors**

Hydride donors which are active in palladium-catalysed allylic substitution reactions[108] include silicon hydrides, tributyltin hydride, borohydrides and formic acid. In the presence of these reagents, Pd(II) pre-catalysts such as $PdCl_2(PPh_3)_2$ or $Pd(OAc)_2$ + PPh_3 are readily reduced *in situ* and may be advantageously used instead of the usually more fragile Pd° catalysts. Futhermore, by doing so, the ligand concentration in the medium is kept at low level, which usually results in increased palladium catalytic activity. Stereochemical studies have shown that palladium catalysed allylic reductions occur with inversion of configuration at carbon.[109] With the possible exception of formic acid for which an alternative mechanism may also be proposed[109c,d] (*vide infra*), they are therefore very likely to go through the intermediacy of hydrido palladium species.

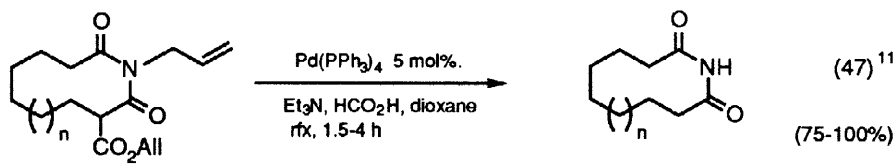
4.6.a ***Formic acid***

Formic acid was the first allyl group scavenger to be used in palladium catalysed allylic cleavage[110]. It acts as a hydride donor, leading to propene as the by-product. The palladium/HCO_2H system, which was further developped essentially by Tsuji and coworkers [31,108,109] and, in the oligonucleotide field, by Noyori, Hayakawa and coworkers (see section 6), has been used for deprotection of allyl aryl ethers,[110] allyl carboxylates,[111-115] carbonates,[116-120] carbamates,[21,117,121,122] oximates,[123] imides[112] and phosphates.[117,121, 124-127] These reactions, which are faster and cleaner if formic acid is used in association with amines (ammonia, triethylamine, pyridine, n-butylamine), generally require heating at *ca* 70-80°C, but

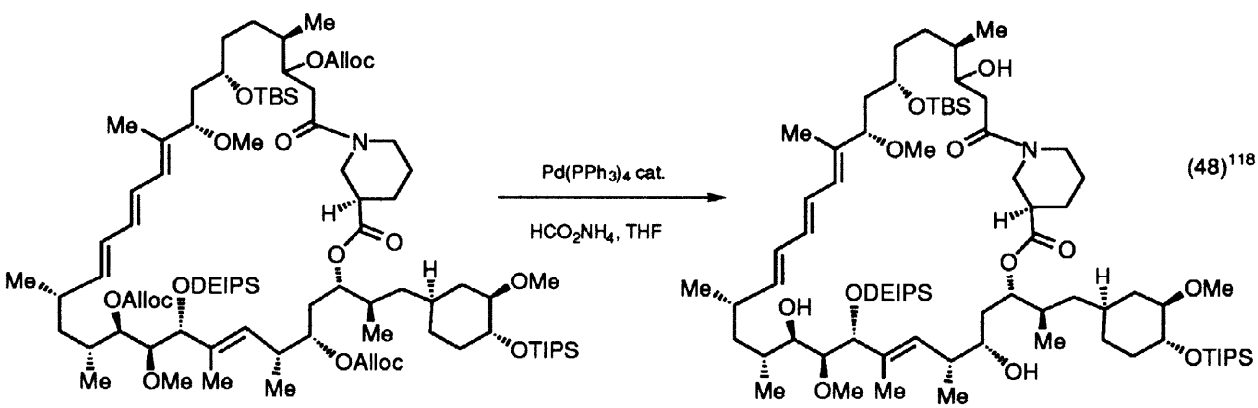
deprotection at room temperature has also been reported.[113,115] In those latter cases, the question may be raised as to whether the deprotection is truly a hydrogenolytic process, or simply an allyl group exchange between the substrate and formic acid or butylamine. Some examples of deprotection by the Pd/HCO_2H or the Pd/HCO_2H/amine systems are given in eq. 46-49. The simultaneous removal of the carboxylato and the imido allyl groups in eq. 47 is noteworthy.



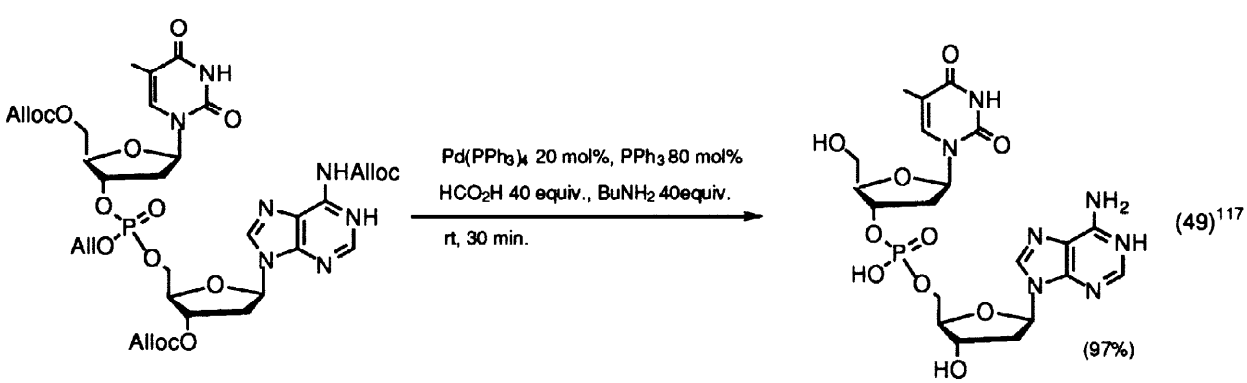
(46)[113]



(47)[112]

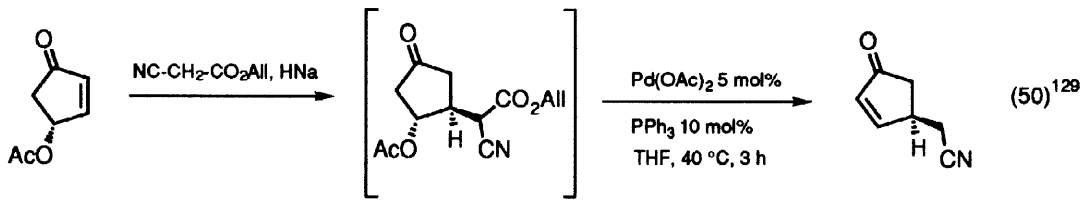


(48)[118]

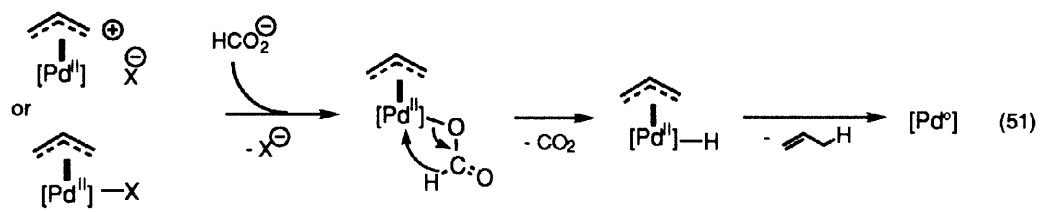


(49)[117]

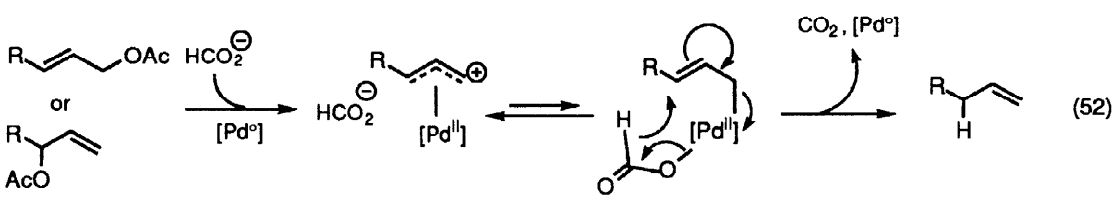
When applied to allyl β-ketoesters or β-cyanoesters, the hydrogenolytic process is accompanied by decarboxylation. Such decarballyloxylation reactions, which occur under much mild conditions have proven useful in synthesis[2f,31a,b,128-131] (eq. 50).



The more currently accepted mechanism (see for instance ref 3g) for palladium-catalysed allylic hydrogenolysis with formic acid involves the formation of a formato-π-allyl palladium complex by ligand exchange from the initial X-π-allyl complex. The formato complex then undergoes β-hydrogen elimination with loss of CO_2 leading to the transient π-allyl hydrido complex which decomposes to propene and Pd^0L_2 through reductive elimination (eq. 51). Strong support for this mechanistic proposal has been given

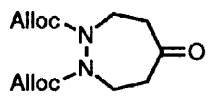


by Shimizu, Yamamoto and coworkers[132] who were able to isolate and characterize some formato π-allyl palladium complexes and to study their chemical properties. More recently however, an alternative mechanism involving a concerted 8-electron 7-center electrocyclic reaction (eq. 52) has been invoked by Tsuji, Mandai and coworkers.[109d,133] This seems to account better for the regiospecific formation of terminal olefins from unsymmetrically substituted allyl carboxylates or carbonates.



Rather surprisingly, palladium catalysed deprotection of allyl carbamates with formic acid are not always exempt from side-reactions leading to allyl amines.[21,35,134] Such was the case for instance in the deprotection of N^{α}-cinnamyloxycarbonyl derivatives of aminoacids by the Pd/HCO_2H/pyridine system. The formation of cinnamylamine could nevertheless be almost completely suppressed by adding nucleophilic

N-hydroxysuccinimide as an additional allyl scavenger[35]. Attempted deprotection (HCO_2H (10 equiv.), ($Pd(PPh_3)_4$, + PPh_3) cat.) of *N,N'*-diallyloxycarbonylhydrazine **20** led to diallylhydrazine **21** in 49% yield.[134,135]



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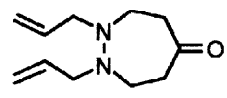
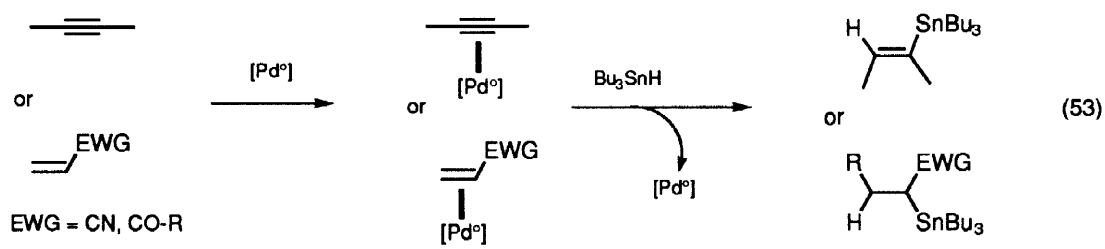


21

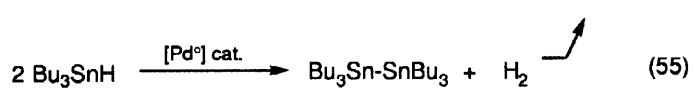
4.6.b ***Tributyltin hydride***

Palladium catalysts such as $Pd(PPh_3)_4$ or $PdCl_2(PPh_3)_2$ increase to a considerable extent the reducing properties of tributyltin hydride towards functional groups which are able to strongly interact with Pd^0L_2 species.[136] Thus electron poor olefins[137,138] and alkynes[139-141] which coordinate readily to palladium to form π-alkene or π-alkyne complexes are readily hydrostannylated, while acyl chlorides[142] and allylic halides[143] or esters[109a,b,144] which give oxidative addition products, respectively acyl-chloro palladium complexes and π-allyl complexes are rapidly reduced (eqs 53, 54). Most of these reactions are almost instantaneous (*ca* 1 min.) at room temperature. Other potentially reducible functions which do not interact



with palladium are left unreacted under these conditions. Such is the case of nitro compounds, inactivated olefins, non conjugated carbonyl compounds and aldehydes.

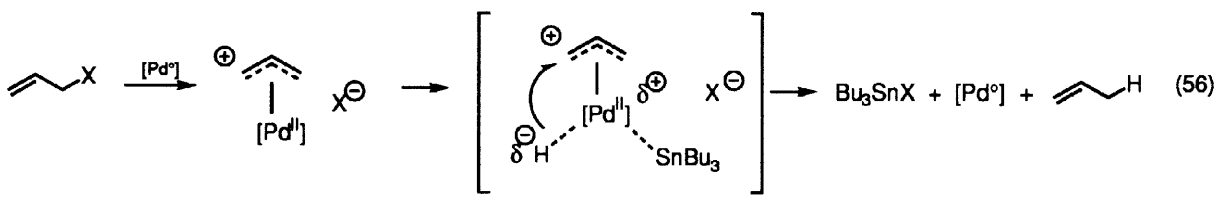
In the presence of a palladium complex (and of palladium metal as well) and in the absence of suitable substrates, tributyltin hydride itself decomposes rather rapidly into hexabutyldistannane and dihydrogen (eq. 55). This may constitute an additional advantage for selectivity since tributyltin hydride, if present in



(55)

excess, will be readily converted to the even more inert hexabutyldistannane. On the other hand, if the desired reduction is too sluggish, for instance as a result of unfavorable steric factors, this decomposition reaction into hexabutyldistannane may become troublesome.

All available data[109a,136-143] regarding chemo-, regio-and stereoselectivity, are in favor of a polar (as opposed to radical) mechanism for the palladium catalysed hydrostannylation and hydrostannolytic reactions of equations 53, 54. The exaltation of the intrinsically quite poor hydride donor properties of tributyltin hydride is therefore likely to occur by formation of a transient hydrido palladium complex through oxidative addition to palladium, as represented in a schematic and probably oversimplified manner in equation 56 for the cleavage of allylic derivatives.



(56)

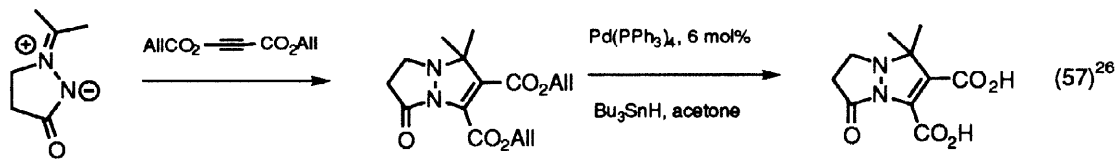
The almost instantaneous hydrostannolytic cleavage of allyl carboxylic esters,[109a,144] allyl carbamates[144] (no side formation of allylamines), allyl carbonates,[116,144,145] and mono or diallylphosphates[146] by $PdCl_2(PPh_3)_2/Bu_3SnH$ or $Pd(PPh_3)_4/Bu_3SnH$ may be carried out in a wide variety of solvents, polar or non polar, including benzene, toluene, diethylether, THF, acetone, ethyl acetate and DMF. However, acetonitrile is not suitable since tributyltin hydride is insoluble in that solvent. With the exception of allyl carbonates which are converted to tributyltin alkoxides with loss of CO_2, all of the above-mentioned allyl protected functions are converted to the corresponding tributyltin derivatives from which the free functional groups may be obtained by reaction with an acid such as HCl. In the case of an allyl carbamate, the hydrostannolytic reaction is best carried out in the presence of a weak acidic species such as acetic acid or *p*-nitrophenol, whereby the free amine is directly obtained.[144]

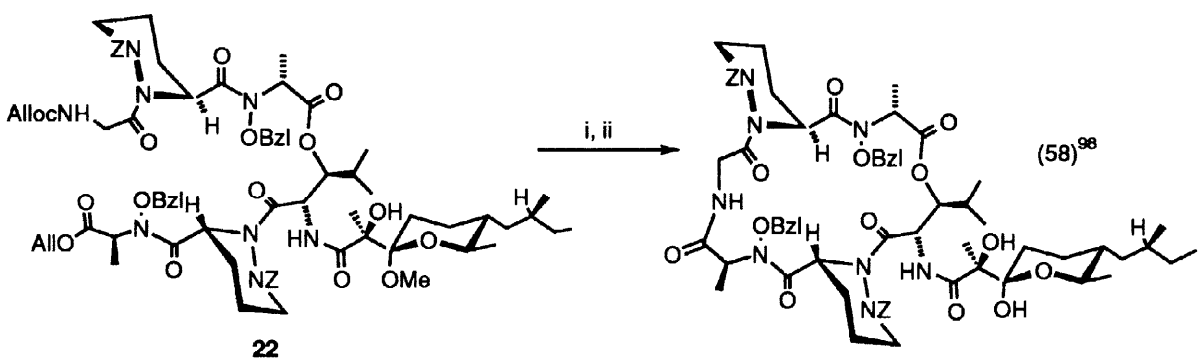
Tributyltin salts of strongly acidic phosphoric acid derivatives are not easily protonolysed. They are conveniently converted to inorganic phosphates by treatment with chloroboronates $ClB(OR)_2$ followed by hydrolysis of the mixed phosphoric-boronic anhydride. Both of these reactions are instantaneous at room temperature.[146]

The separation of the deprotected compounds from tin by-products - hexabutyldistannane and the products resulting from protonolysis of the intermediate tin salts- deserve some comment.[147] While hexabutyldistannane is readily eluted (R_f close to one with pentane as the eluent), tributyltin halides (Cl, Br, I) and acetate tail on chromatography, irrespective of the support or the eluent. It should also be noted that, in the presence of tributyltin halides, carboxylic acids cannot be separated by the usual extraction into aqueous alkali because alkali-metal carboxylates are immediately reextracted in the organic phase as their tributyltin salt. If the deprotected compound is insoluble or poorly soluble in hexane or other hydrocarbons, but soluble in acetonitrile, straigtforward separation from tin compounds is possible by partition between these two solvents systems. Another widely used technique[148] is to convert tributyltin halides, by reaction with sodium fluoride, into tributyltin fluoride which precipitates, in a polymeric form, to the extent of *ca* 80-90%.

Maximum precipitation is obtained from acetonitrile or acetone solution. Since Bu_3SnF is retained on silica, the remaining unprecipitated material may then be eliminated by short column chromatography.

The hydrostannolytic cleavage of allyl and allyloxycarbonyl groups from aminoacid derivatives has been the subject of a detailed study[144] including side chain functionalized derivatives such as Alloc-Arg(Tos)-OH, Alloc-Trp, Alloc-Lys(Z)-OH, Alloc-Lys(Boc)-OH, Boc-Lys(Alloc)-OH, Alloc-Ser(*t*-Bu)-OH, Alloc-Tyr(Alloc)-OH, Alloc-Cys(Alloc)OH. In the two last examples, both Alloc groups are removed. The reaction does not induce any racemisation at the C^{α} center and is perfectly tolerant of the presence of Boc, *t*-Bu and Z, Bzl protections. No poisoning of the catalyst is observed by the sulfide group of methionine or by the thiol group of cysteine. Further studies have shown that the hydrostannolytic procedure is compatible with the presence of Fmoc groups. Several applications of this method in peptide synthesis are described in section 5. Hydrostannolytic cleavage of allyl esters has been used during the synthesis of a bicyclic pyrazolidinone derivative[26] (eq. 57). The hydrostannolytic procedure has also ben used[98] for simultaneous

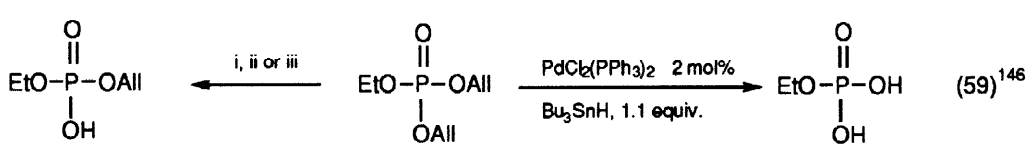




22

i) $Pd(PPh_3)Cl_2$, Bu_3SnH, DCM, H_2O
ii) [*n*-PrP(O)O]$_3$, DMAP, DCM, high dilution (10^{-4} M)

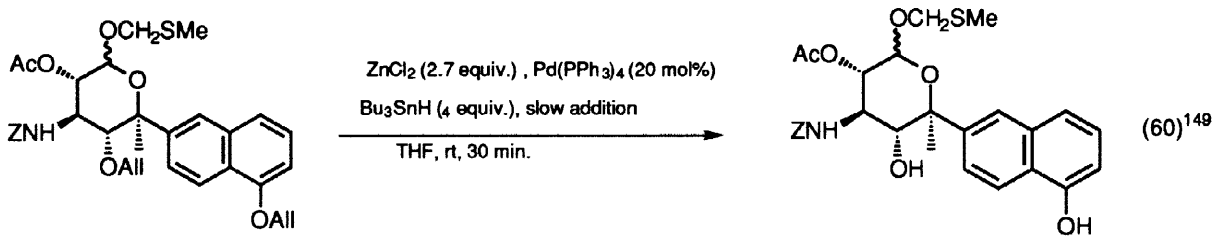
removal of the terminal All and Alloc groups of the depsipeptide **22** before cyclisation (eq. 58). Interestingly, during this process, the methyl pyranoside entity was converted to the hemiketal. Model studies on mixed allyl alkyl phosphoric esters have led to the conclusion that the allyl group is orthogonal to the widely used *p*-chlorophenyl, trichloroethyl and β-cyanoethyl protecting groups[146] (eq. 59).



i) TBAF (R = *o*-ClPh); ii) Zn/Cu in DMF (R = CH_2-CCl_3); iii) Py/*i*-Pr_2NH (R = CH_2-CH_2-CN)

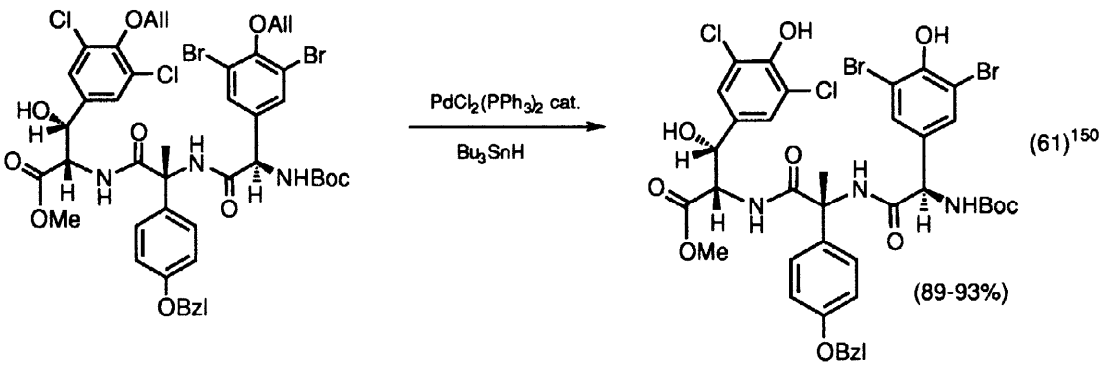
The hydrostannolytic procedure also applies to allyl aryl ethers such as phenolic allyl ether derivatives of tyrosine[144] provided that tributyltin hydride is slowly added to the reaction mixture in order to minimize

the competitive decomposition of tributyltin hydride into hexabutyldistannane (eq. 55). The deprotection reaction is further facilitated by the presence of weak acids such as acetic acid or *p*-nitrophenol whose role is probably to assist the formation of the π-allyl complex through prototropic exchange. Anhydrous $ZnCl_2$ is also a very efficient promoter of the reaction, as exemplified by the reaction shown in eq. 60 which is taken from[149] Franck's synthesis of Nogalamycin and which, to the best of our knowledge, constitutes, with the



(60)[149]

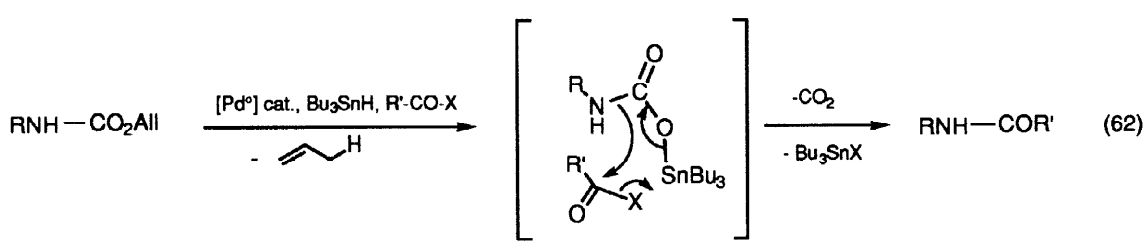
aforementioned cleavage of allyl glycosides with Pd^0/AcOH[34] (see part I, paragraph 2.3) the only example of cleavage of alkyl allyl ethers involving *catalytic* π-allyl methodology. Other examples of hydrostannolytic cleavage of aryl allyl ethers may be found in the synthesis of antibiotics of the vancomycin family[150] (eq. 61). In this deprotection reaction, no competitive hydrogenolysis of aromatic chlorine and bromine substituents



(61)[150]

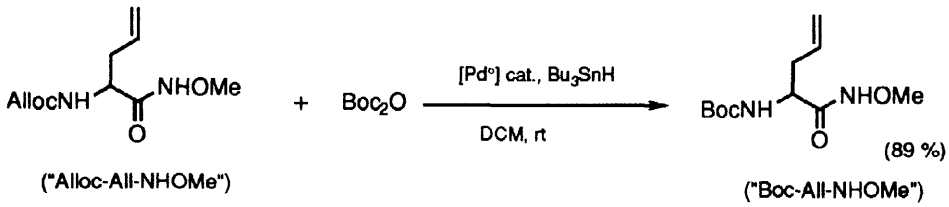
was observed, presumably because the oxidative addition of bromo and chloroaryl derivatives to Pd° is sufficiently slow when compared with the formation of the π-allyl complex and also with the decomposition of tributyltin hydride to hexabutyldistannane.

Hiemstra, Speckamp and coworkers[151,152] found that when the palladium-catalysed hydrostannolysis of allylcarbamates is carried out in the presence of acylating agents such as carboxylic acid anhydrides, or *N*-hydroxysuccinimide, pentafluorophenyl or HOBt esters (the latter formed *in situ* from carboxylic acids, DCC and HOBt), direct transacylation takes place, probably according to the concerted mechanism of eq 62.

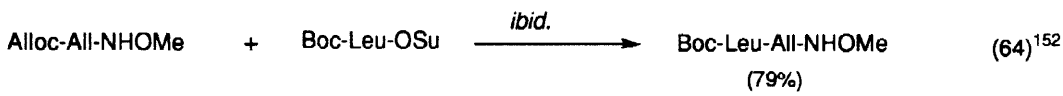


(62)

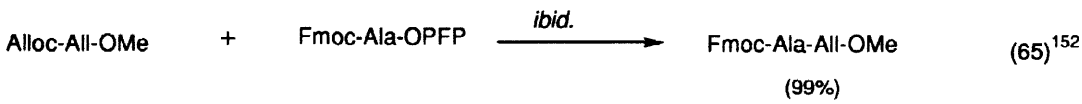
Thus, one pot transprotection reactions (eq. 63) and tandem deprotection-couplings (eq. 64-66) have been achieved under virtually neutral conditions, with very satisfactory yields and conservation of enantiomeric purity at the chiral centers.



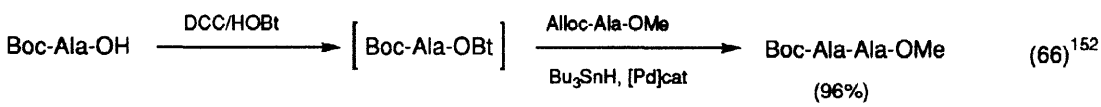
(63)[151]



(64)[152]

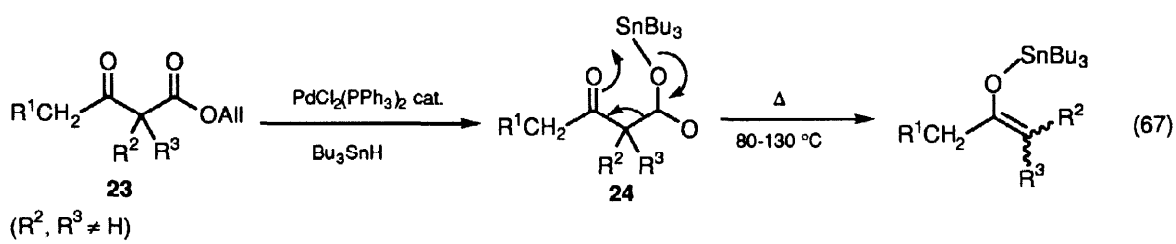


(65)[152]



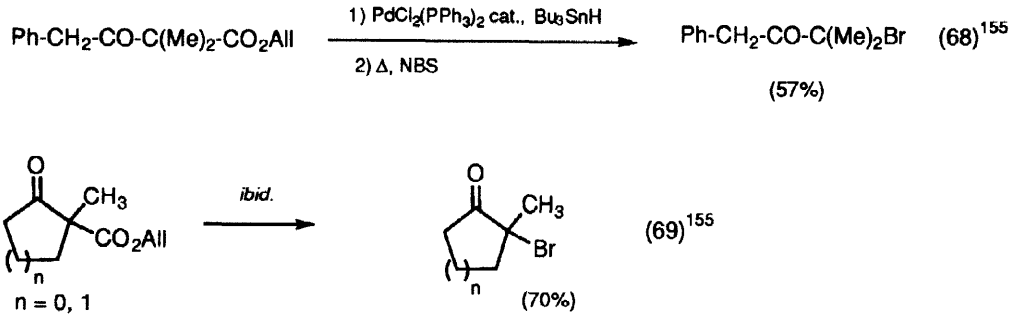
(66)[152]

Polysubstituted allyl β-ketoesters of general formula **23** (R^2 and $R^3 \neq H$), are readily prepared through classical Claisen condensations or β-ketoester mono- or dienolate alkylation reactions and are easily converted by Pd/Bu_3SnH to the corresponding tributyltin β-ketoesters **24**, which, in turn, may be decarboxylated at moderate temperature (80-120°C). The regiospecific tetrasubstituted tin enolates thus formed (eq. 67) may subsequently be trapped as enol acetates or trimethylsilyl enol ethers.[153] By way of



(67)

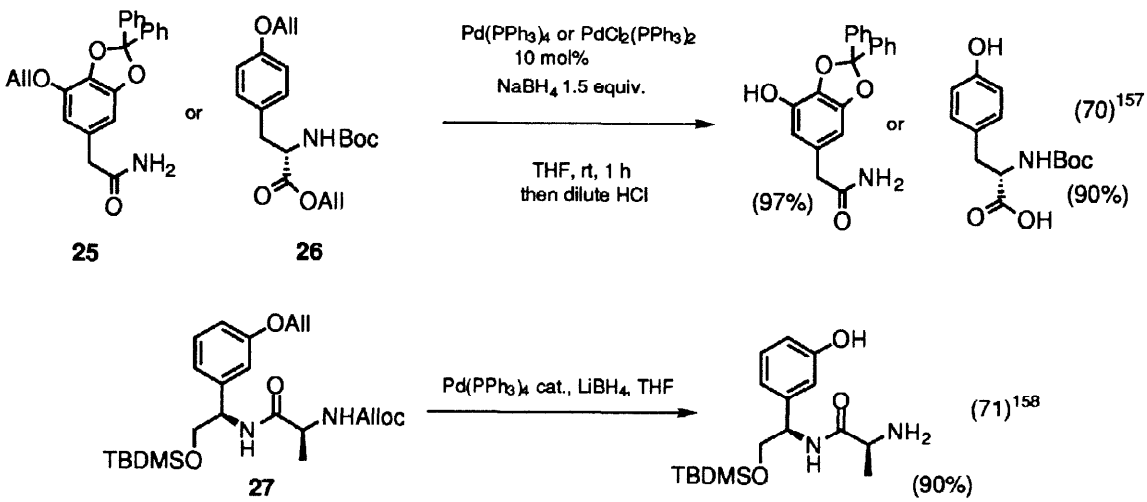
comparison, the silatropic rearrangement of trimethysilyl β-ketoesters takes place only at temperatures around 240-470 °C.[154] If the thermal conversion of tributyltin β-ketoesters is carried out directly in the presence of Ac_2O or NBS, tetrasubstituted enol acetates or α-bromo-α,α-disubstituted ketones respectively are obtained in both cases with total regioselectivity and in moderate to good yields[155] (eqs 68-69).



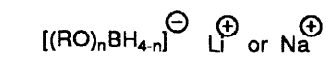
4.6.c. ***Borohydrides***

Hutchins and coworkers[156] reported in 1980 that allylic acetates are cleaved by Pd°/$NaBH_4$ or Pd°/$NaBH_3CN$ in THF.

The Pd°/$NaBH_4$ or $LiBH_4$ systems have recently been used[157,158] for deprotection in high yields of aryl allyl ethers such as **25**, **26** or **27** (eqs 70 and 71). The reaction is faster with $PdCl_2(PPh_3)_2$ than with



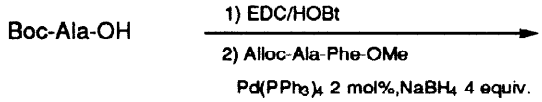
$Pd(PPh_3)_4$ as the catalyst. Since allyl carboxylates react more readily than allyl aryl ethers, this allows for their selective deprotection (for instance in compounds such as **26**). Aryloxy- or acyloxyborates **28**[159] are the probable primary products of these reactions. As in the case of the hydrostannolytic method, direct trans-



28 (R = acyl, aryl)

acylation reactions (transprotection and peptide bond formation) are possible by carrying out the hydrogenolytic process in the presence of acylating agents. These acylating agents must however be sufficiently mild in order to avoid direct reaction with the reducing agent. As far as coupling reactions are

concerned, HOBt esters (formed *in situ)* seem to be the best choice (eq. 72).



4.6.d.Silicon hydrides

Various silicon hydrides behave as hyride donors towards allylic esters in the presence of a palladium catalyst.[160] In most cases, these reactions are unfortunately much slower than the hydrostannolytic process with tributyltin hydride. Attempts for instance to use Ph_2SiH_2 in the palladium catalysed deprotection of allyl carbamates resulted in extensive rearrangement to allylamines.[79]

On the basis of an earlier report[160] by Keinan and Greenspoon on the fast reductive cleavage of allylic carboxylates with $Pd(PPh_3)_4/PhSiH_3$(phenyltrihydrosilane), the use of this system in protective group chemistry was nevertheless reinvestigated.[161]

It has thus been found that $Pd(PPh_3)_4/PhSiH_3$ allows the deprotection of allyl carboxylates and carbamates within a few minutes at room temperature and, in the case of carbamates, without concurrent formation of allylamines . Aryl allyl ethers are also totally cleaved, albeit more slowly (*ca* 20-40 min at room temperature). When the hydrosilylolytic procedure is carried out in the presence of an acylating agent, allyl carbamates are transacylated. Such reactions have been carried out with a large array of acyl-activated species, including acetic anhydride, di-*tert*-butyl dicarbonate, *N*-hydroxysuccinimide or pentafluorophenyl esters of aminoacids, Fmoc-aminoacid fluorides and *N*-protected (Z, Boc, Fmoc) *N*-carboxyanhydrides (UNCAs). Some results[161b] concerning peptide bond formation are collected in Table 1. In contrast to tributyltin hydride, $PhSiH_3$ seems indefinitely stable in the presence of the Pd catalyst. Owing to its rapidity,

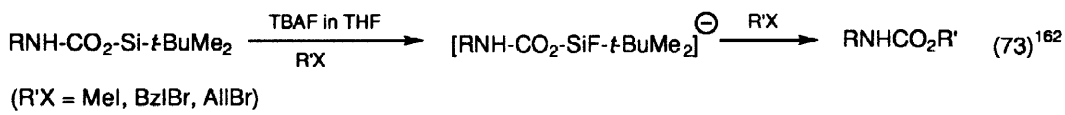
Table 1

Entry	Alloc derivative	Acyl-activated derivative	Coupling product	Yield (%)
1	Alloc-Phe-OMe	Fmoc-Ala-OPfp	Fmoc-Ala-Phe-OMe	100
2	Alloc-Pro-OMe	Fmoc-Ala-OPfp	Fmoc-Ala-Pro-OMe	86
3	Alloc-Pro-OMe	Boc-Ala-OSu	Boc-Ala-Pro-OMe	73
4	Alloc-Leu-OMe	Fmoc-Ala-F	Fmoc-Ala-Leu-OMe	90
5	Alloc-Aib-OMe	Fmoc-Ala-F	Fmoc-Ala-Aib-OMe	77
6	Alloc-Leu-OMe	Z-Ala-NCA	Z-Ala-Leu-OMe	94
7	Alloc-Aib-OMe	Z-Ala-NCA	Z-Ala-Aib-OMe	85

Reactions conditions : $Pd(PPh_3)_4$, 2 mol%; $PhSiH_3$ 2 mol. equiv.; acylating agent, 1.2 equiv.; DCM, room temperature, ten min. to a few hours.

neutral conditions, high tolerance towards many other protective or functional groups, and the possibility of achieving transacylation reactions with a variety of acyl activated compounds, the $Pd(PPh_3)_4/PhSiH_3$ system appears very promising, especially for peptide chemistry.

Ohfune and coworkers[162] have found that allyl esters and carbamates are converted to the corresponding silyl carboxylates by treatment with triethylsilane or *tert*-butyldimethylsilane in the presence of catalytic amounts of $Pd(OAc)_2$. These reactions which can also be applied to benzyl esters and carbamates are unlikely to involve π-allyl intermediates . Indeed, in a recent publication,[152] Speckamp, Hiemstra and coworkers note that allyl carbamates are not cleaved by triethylsilane in the presence of $Pd(PPh_3)_4$. The hydrolytic stability of *tert*-butyldimethylsilyl carboxylates is sufficient to allow their isolation through conventional extractive work-up.[162] They are conveniently cleaved by sequential treatment with anhydrous tetrabutylammonium fluoride and with aqueous NH_4Cl. From *tert*-butyldimethylsilyl carbamates, various alkyl carbamates may be obtained by carrying out the fluoride anion induced cleavage in the presence of alkylating agents (eq. 73). Z to Boc transprotection has also been achieved by reacting benzylcarbamates with $Pd(OAc)_2/Et_3SiH$ in the presence of di-*tert*-butyl dicarbonate.[163]



5. ALLYLIC PROTECTING GROUPS IN PEPTIDE SYNTHESIS.

The relative robustness of allylic carboxylates, the selective and mild conditions of π-allyl palladium based procedures for allyl group removal and the compatibility of these procedures with the presence of sulfur derivatives combine to favour the utilization allylic protection in peptide synthesis. Allylic protecting groups may be used for temporay as well as permanent protection, and allylic handles have been devised for peptide anchoring onto solid supports.

5.1 **Allylic groups as temporary, semi-permanent or permanent protections.**

The possibility of using the Alloc group for transient protection of the terminal α-amino groups during peptide chain elongation has been illustrated[144] by a linear solid phase peptide synthesis (SPPS), using exclusively N^{α}-Alloc aminoacids derivatives as buiding blocks, of substance P **29**, a neuropeptidamide of eleven residues.

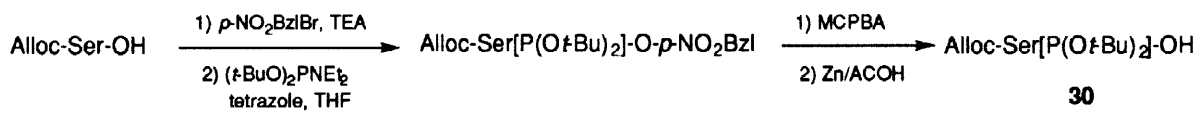
Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-NH_2

29

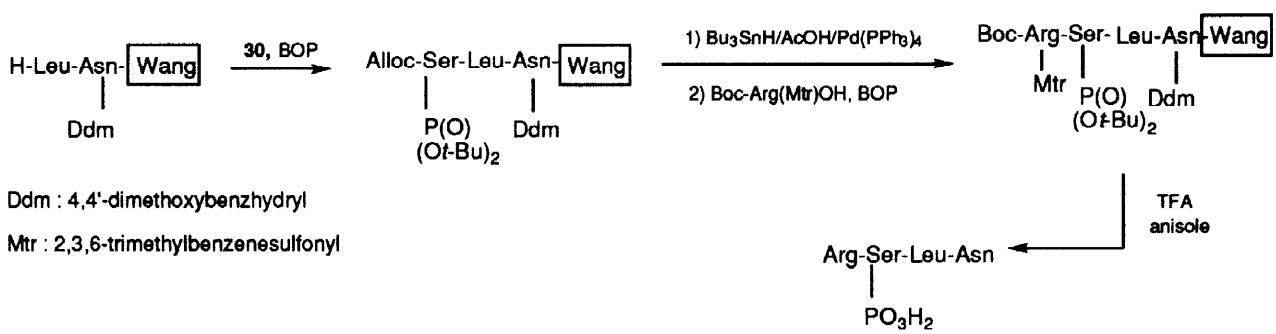
Conventional DCC/HOBt coupling reactions were used throughout the synthesis, except for the N^{α}-Alloc-Gln residues which were coupled as their *p*-nitrophenyl esters. For Alloc removal, the hydrostannolytic procedure $Bu_3SnH/PdCl_2(PPh_3)_2$ in the presence of acetic acid was chosen on account of its rapidity. Final detachment of the peptide chain from the MBHA resin and removal of the permanent side-chain protections (benzyl group for lysine and tosyl group for arginine) were achieved by conventional treatment with liquid hydrogen fluoride in the presence of carbocations scavengers. After chromatographic purification, **29** was obtained in 25% unoptimized yield and with full biological activity.

N^{α}-Alloc temporary protection, together with its hydrostannolytic removal, has found use in the synthesis of base-sensitive *O*-phosphoserine peptides.[164] In this case, N^{α}-Fmoc protection was first considered but found inconvenient because *O*-phosphoserine derivatives are readily converted into α,β-dehydro-derivatives under basic conditions. Alloc-Ser[P(O)(O*t*-Bu)$_2$]-OH **30** was synthetized in four steps from Alloc-Ser-OH as shown in Scheme 1 and then incorporated, by SPPS, on an acid labile *p*-alkoxybenzyl (PAC, Wang) resin, in tetrapeptide sequences as represented in scheme 2. A similar approach has been used by Shapiro and coworkers.[105] In this work (scheme 3) selective cleavage of the Alloc group was achieved by the ternary system Pd° cat./ N_3SiMe_3/ $F^- {}^+N(Bu)_4$ (see paragraph 3.5)

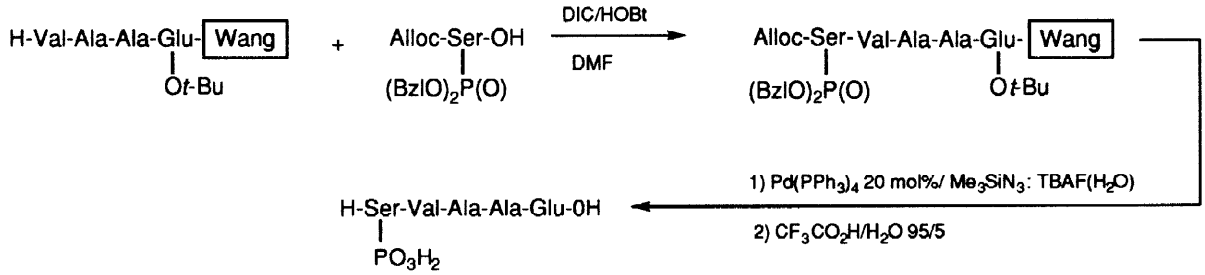
Scheme 1[164]



Scheme 2[164]

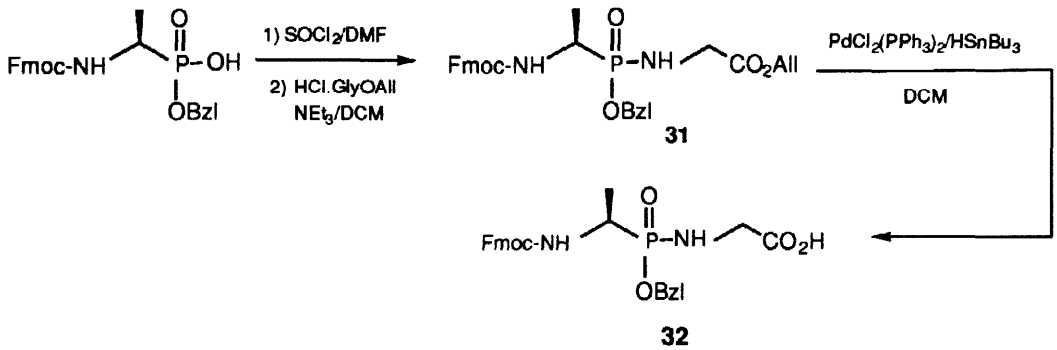


Scheme 3[105]



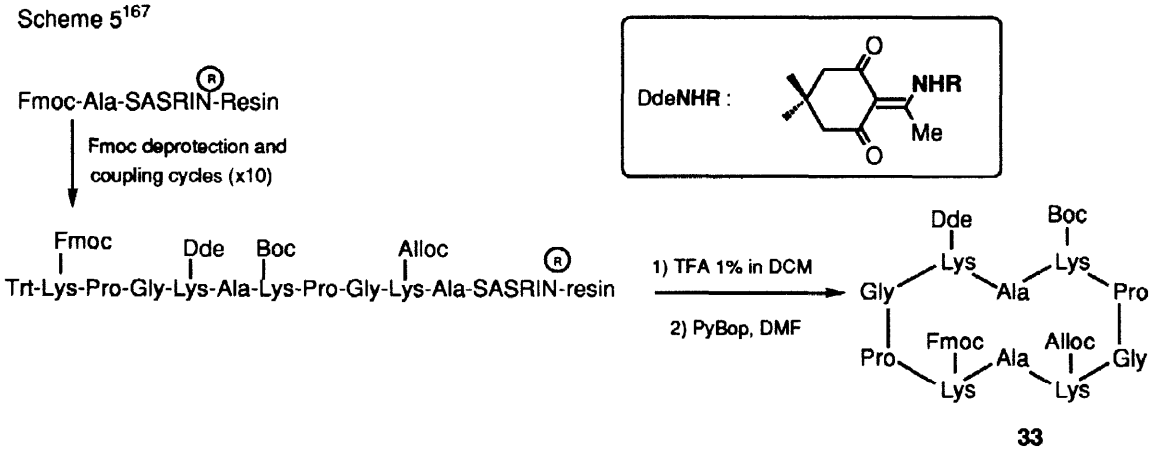
Temporary allyl protection of α-carboxy groups has been used in a synthesis of phosphonamido pseudopeptides[165](scheme 4). The fully protected pseudodipeptide **31** incorporating allyl α-carboxy protection, Fmoc N^{α}-amino protection and *O*-benzyl phosphoprotection was first prepared. By selective palladium-catalysed hydrostannolysis, **31** was converted to carboxy-free pseudopeptide **32**, which was then in turn incorporated into various oligopeptidic sequences by SPPS based on a temporary Fmoc protection and BOP-DIEA coupling.

Scheme 4[165]



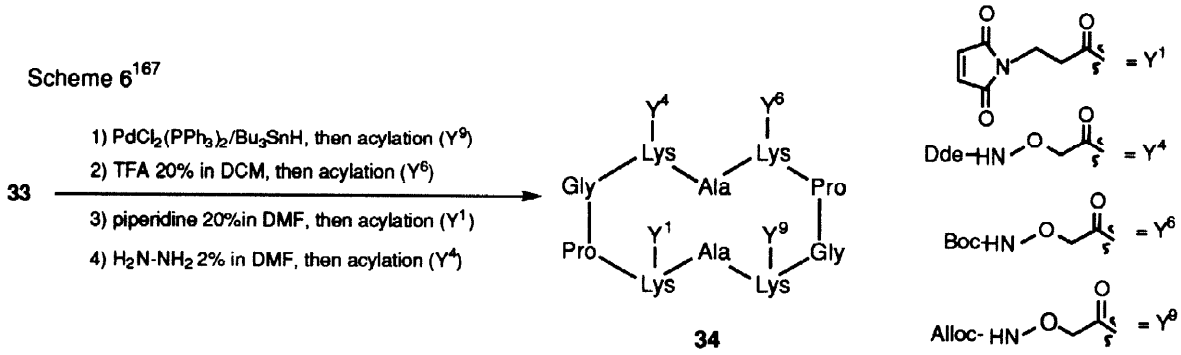
For the *de novo* design of proteins according to the TASP[166] (Template Assembled Synthetic Proteins) concept, a RAFT (Regioselectively Adressable Functionalized Template) molecule with four selectively adressable sites has recently been devised by Dumy, Mutter and coworkers.[167] Towards this end

Scheme 5[167]



(scheme 5), in the first step, the cyclic decapeptide template **33** was prepared, incorporating two Pro-Gly motifs (in order to induce β-turns) and four lysine residues differentially protected on their N^{ε}-amino groups by the three Alloc, Boc, Fmoc groups to which was added the recently introduced[168] hydrazinolysable Dde ([1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)ethyl]) group. The linear peptidic chain was first assembled according to the temporary Fmoc strategy on a highly acid labile SASRIN handle, the last N^{ε}-Fmoc residue being introduced as its N^{α}-trityl protected derivative. After concomitant detritylation and cleavage from the handle, cyclisation, which was probably facilitated by the preference for a quasi-cyclic conformation of the linear peptide, was achieved with remarkable efficiency by the use of PyBOP coupling reagent in DMF at high dilution. The cyclopeptidic template **33** was further derivatized, as summarized in scheme 6, by

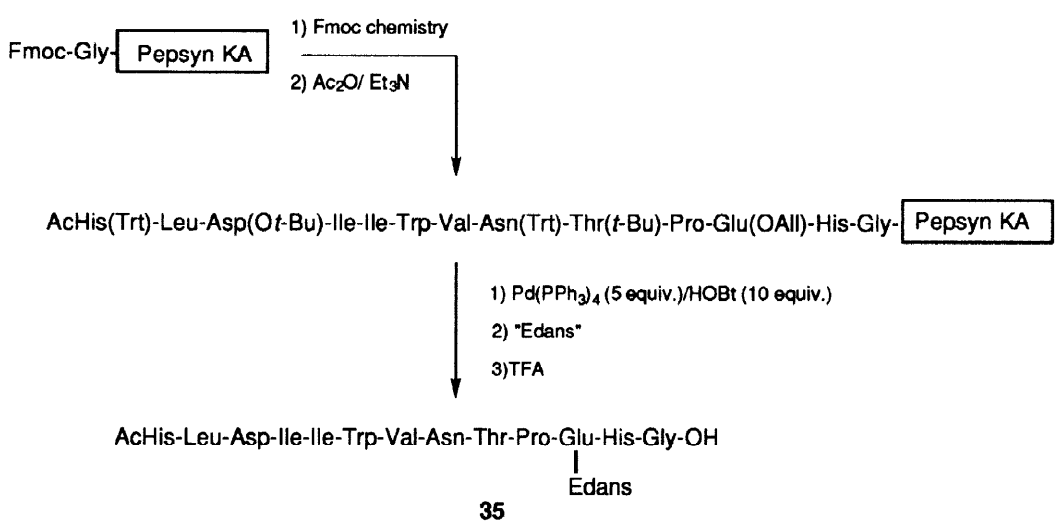
Scheme 6[167]



successive and selective deprotection reactions, each of them being followed by acylation with orthogonally protected maleimido or aminoxy entities.[169] The RAFT molecule **34** thus formed is able to accomodate up to four different peptide blocks by chemoselective ligation to the aminoxy and maleimido ends.

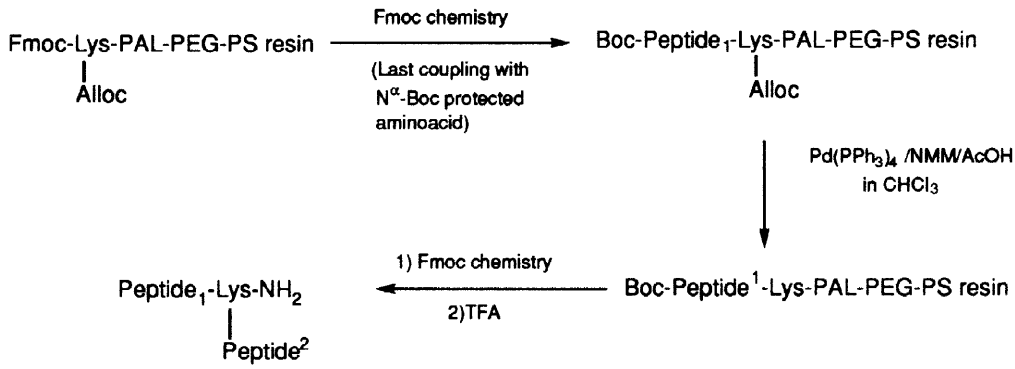
A striking example of the use of allyl groups for semi-permanent protection can be found in the synthesis[37], by Handa and Keech, of the tridecapeptide **35**, a substrate of the endothelin converting enzyme bearing the fluoroquencher group 5-(2-aminoethylamino)-1-naphtalene sulfonic acid (Edans group) on the side-chain of the Glu residue. The SPPS of **35** required selective manipulation of the Glu side-chain carboxyl group in the presence of Asp, Thr and His. A first synthesis, by Van Goldern and coworkers, performed on a Merrifield resin, involved temporary Boc N^{α}-protection, permanent benzyl protection for Asn and Thr and Fm (9-fluorenylmethyl) semi-permanent protection for Glu. After final cleavage from the resin, **35** was obtained in 2.5% yield. By switching to the allyl group for Glu protection, Handa and Keech were able to use a trifluoroacetolysable anchoring on a Pepsin KA resin together with trifluoroacetolysable protection (O-*t*-Bu, *t*-Bu and Trt) for the side-chains of the Asp, Thr and His residues. Peptide chain elongation was achieved in a continuous flow synthetizer with temporary Fmoc N^{α}-protection. Under these conditions, **35** was obtained in 31% yield (scheme 7).

Scheme 7[37]

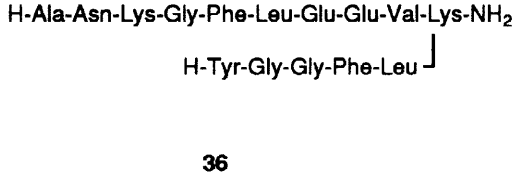


Another example of Alloc semi-permanent protection concerns the synthesis of branched peptides on Fmoc-Lys(Alloc)-resin[57] (scheme 8). In a similar way to that just described, substitution by Alloc for Boc for N^{ε}-protection of lysine opened up the possibility of using temporary Fmoc/permanent *t*-Bu, Boc chemistry

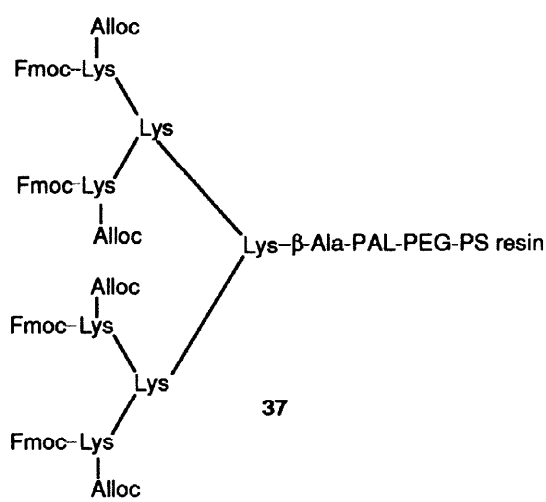
Scheme 8[57]



and an automated continuous flow synthetizer for the successive assembly of the two peptide chains. This strategy was illustrated by the synthesis of the branched dipeptidamide prothrombin$^{1\text{-}9}$-Lys-(Leu-enkephalin)-NH_2 **36**.



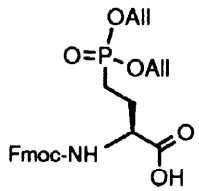
36



37

A MAP (multiantigen peptide resin) conjugate of prothrombin and Leu-enkephalin has been similarly prepared from a resin-bound two-epitope octavalent lysine-core matrix **37**.

Shapiro and coworkers have synthetised[170] the allyl protected N^{α}-Fmoc derivative **38** of L-2-amino-4-phosphonobutanoic acid ("Abu(P)"), an isostere of phosphoserine. **38** was subsequently[171] incorporated into various aminoacid sequences such as **39**, related to a partial sequence **40** of neuromodulin , by SPPS using a Wang (PAC) resin and temporary Fmoc/ permanent trifluoroacetolysable protections. The allyl groups on the



38

H-Thr-Lys-Ile-Gln-Ala-Abu(P)-Phe-Arg-Gly-OH

39

-Thr-Lys-Ile-Gln-Ala-Ser-Phe-Arg-Gly-His-Ile-

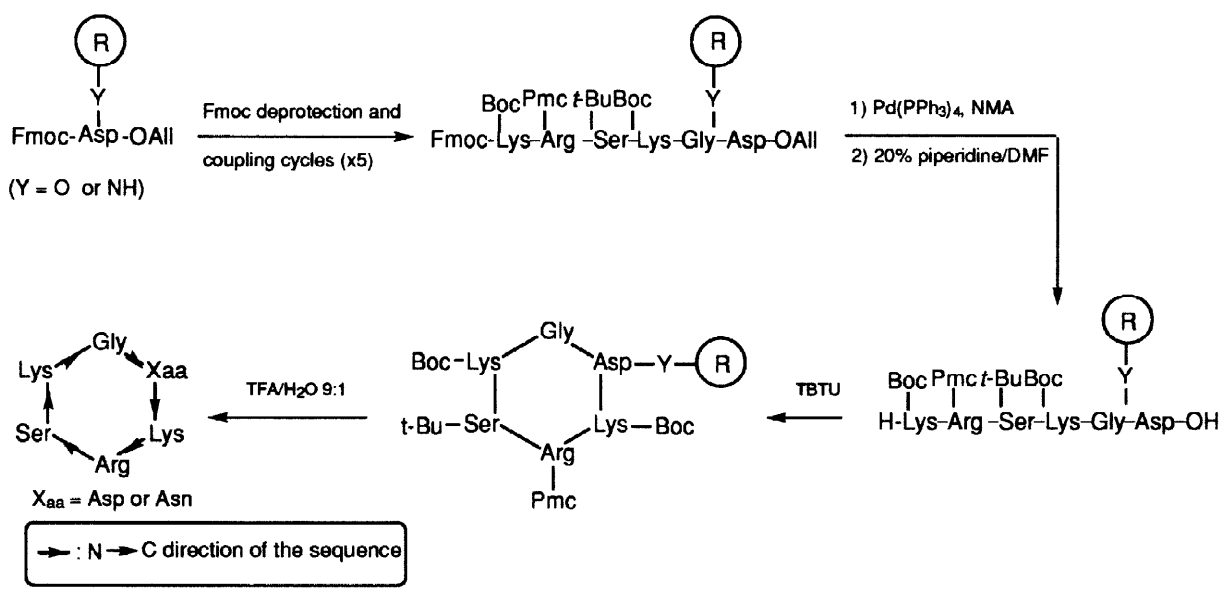
40

phosphonate function were selectively removed, in the presence of the N^{α}-terminal Fmoc protection by an adaptation of the Noyori procedure ($Pd(PPh_3)_4$ 20 mol%, butylamine 4 equiv., formic acid 16 equiv., THF, 50 °C, 16 h), under which conditions the trifluoroacetolysable linker was left intact.

The synthesis of cyclic peptides is a difficult task and requires the use of multicomponent sets of orthogonal protecting entities. Several strategies involving allylic protections in solution or solid phase synthesis have been described in recent years. In all SPPS the cyclisation step was carried out on the resin-bound peptide chain, so as to take advantage of the pseudodilution effect offered by this technique.

In the synthesis of head to tail cyclized peptides described by Trzeciak and Bannwarth[172] (scheme 9), an Fmoc-Asp-OAll residue was first attached, through its carboxylic side-chain function, to a *p*-hydroxymethyl-phenoxy (PAC) resin for final release as an Asp residue or (presumably) to a PAL ((5-(4-aminomethyl-3,5-dimethoxyphenoxyvaleryl) resin for final release as an Asn residue. Chain elongation was

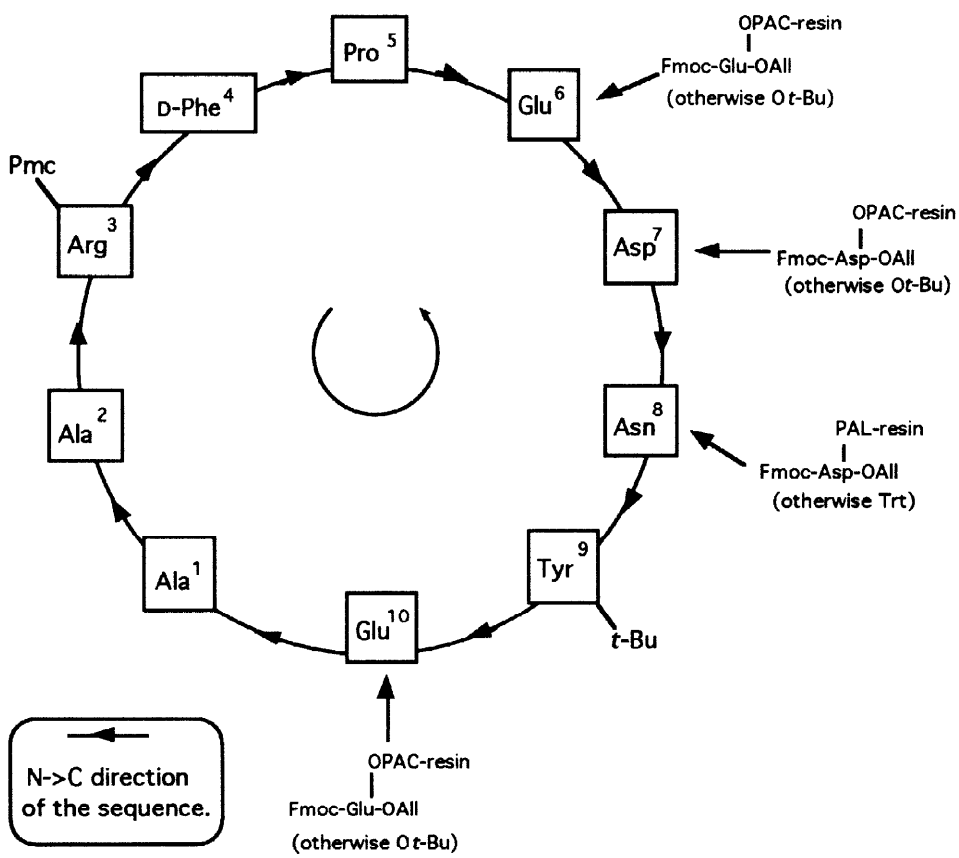
Scheme 9[172]



carried out by the temporary Fmoc strategy, incorporating trifluoroacetolysable *t*-Bu, Boc and Pmc groups for the side-chain protections of the Ser, Lys and Arg residues respectively. Following successive removal of the allyl group ($Pd(PPh_3)_4$, NMA in THF/DMSO/0.5N HCl) and of the Fmoc group, cyclisation was achieved on the support by TBTU activation. Simultaneous release from the support and removal of the side-chain protections were ultimately performed in TFA/H_2O 9:1

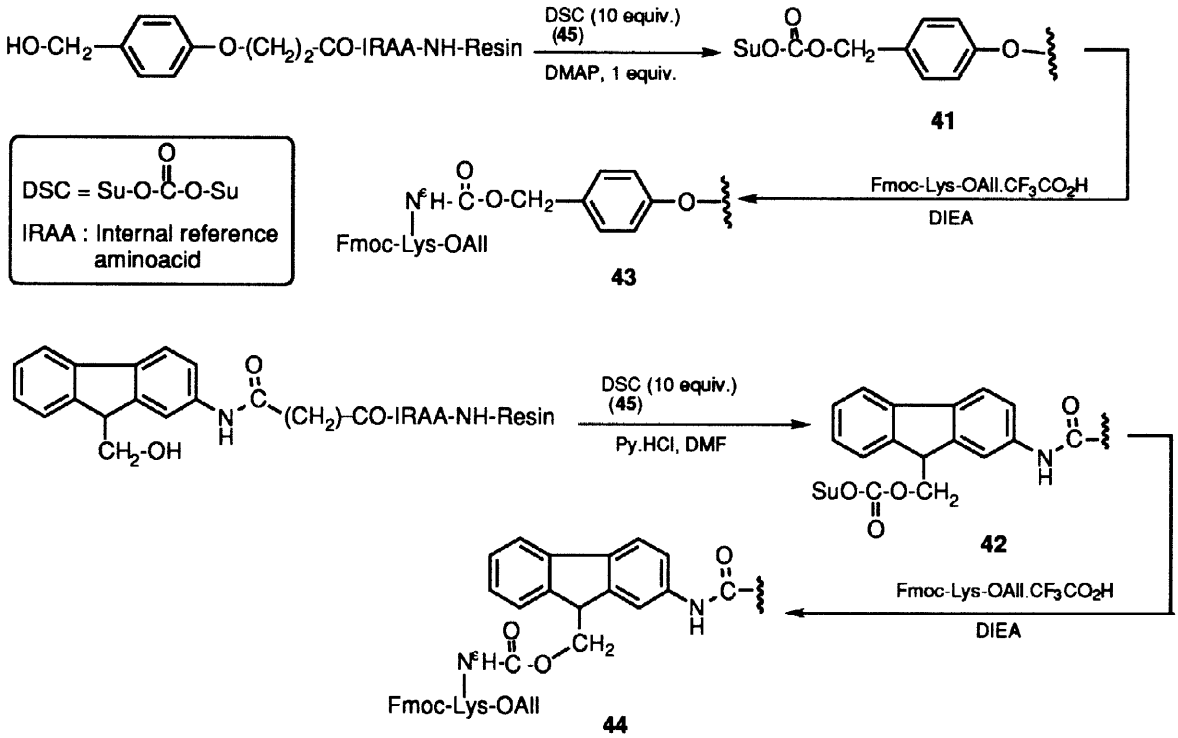
A similar three-dimensional orthogonal protection scheme has been used by Albericio and coworkers[58] for the synthesis of *cyclo*(Ala-Ala-Arg-D-Phe-Pro-Glu^6-Asp^7-Asn^8-Tyr-Glu^{10}) (scheme 10). Four possible variations of this strategy could be considered, depending on which of the (future) Glu^6, Glu^{10}, Asp^7, or Asn^8 was selected for initial attachment to a PAC (Glu^6, Glu^{10} or Asp^7) or a PAL (Asn^8) resin. All of them were tested and peptide chain elongation was carried out in the usual C→ N direction (internal arrow on scheme 10) on a continuous flow synthetizer. The Ser, Glu and Asp residues were protected, on their side chains as their *tert*-butyl ether or ester derivatives and the Arg and Asn residues respectively as their Pmc and Trt derivatives. Once the sequences were completed, the allyl ester group was cleaved with $Pd(PPh_3)_4$/morpholine in DMSO/THF/0.5 N HCl. After Fmoc removal, cyclisation was achieved by use of BOP/HOBt/DIEA. Reagent R (TFA-thioanisole-β–mercaptoethanol-anisole 90:5:3:2) was used for final cleavage from the linker and for removal of the permanent side-chain protections. The best results in terms of yield and purity were obtained by the Asn^8 strategy.

Scheme 10



The synthesis of head-to-tail cyclic peptides has also been achieved through lysine (instead of apartic or glutamic acid) side chain anchoring[56]. The key-problem here was to devise a convenient method for

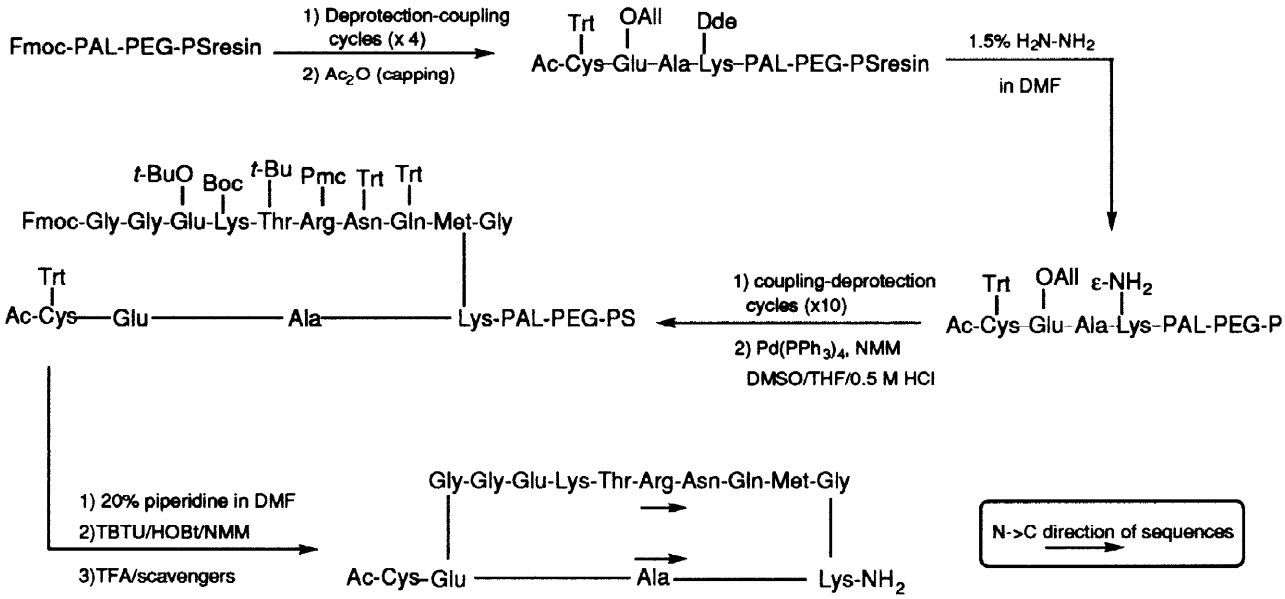
Scheme 11[56]



preparation of the required Fmoc-Lys-OAll N^{ε}-carbamato resins **43** and **44**. A convenient solution, which avoids the hazardous and potentially troublesome use of phosgene, was found by resorting instead to *N,N'*-disuccinimidyl carbonate (DSC) **45** (scheme 11). **45** was used for the synthesis of the intermediate acyl activated succinimidylcarbonato-resins **41** and **42** on which N^{α}-Fmoc-lysine allyl ester was subsequently condensed. As an illustration of the lysine side-chain anchoring methodology, Albericio and coworkers have synthesized, on resin **43** and according to the Fmoc/*t*-Bu protocol, the cyclic peptide *cyclo*(Val-Phe-Sar-Tyr-D-Trp-Lys).

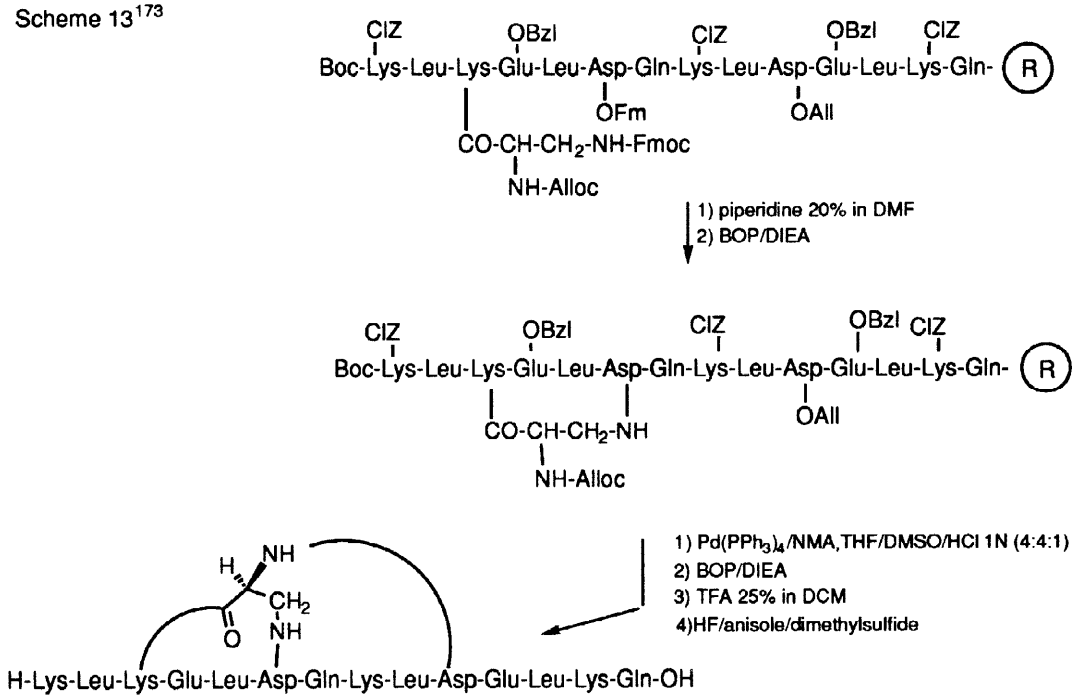
For the synthesis of branched cyclopeptides, Bloomberg and coworkers[71] have used the conventional combination of temporary base labile (Fmoc)/ permanent trifluoroacetolysable (Boc, *t*-Bu) protections, to which were associated two additional levels of orthogonality: a semi-permanent Dde group for ε-aminoprotection of lysine in order to allow the formation of the branched lysine peptide, and a semi-permanent allyl group for protection of the γ–carboxyl function of the Glu residue involved in the cyclisation step. The overall strategy adopted by the authors is summarized in scheme 12.

Scheme 12[71]



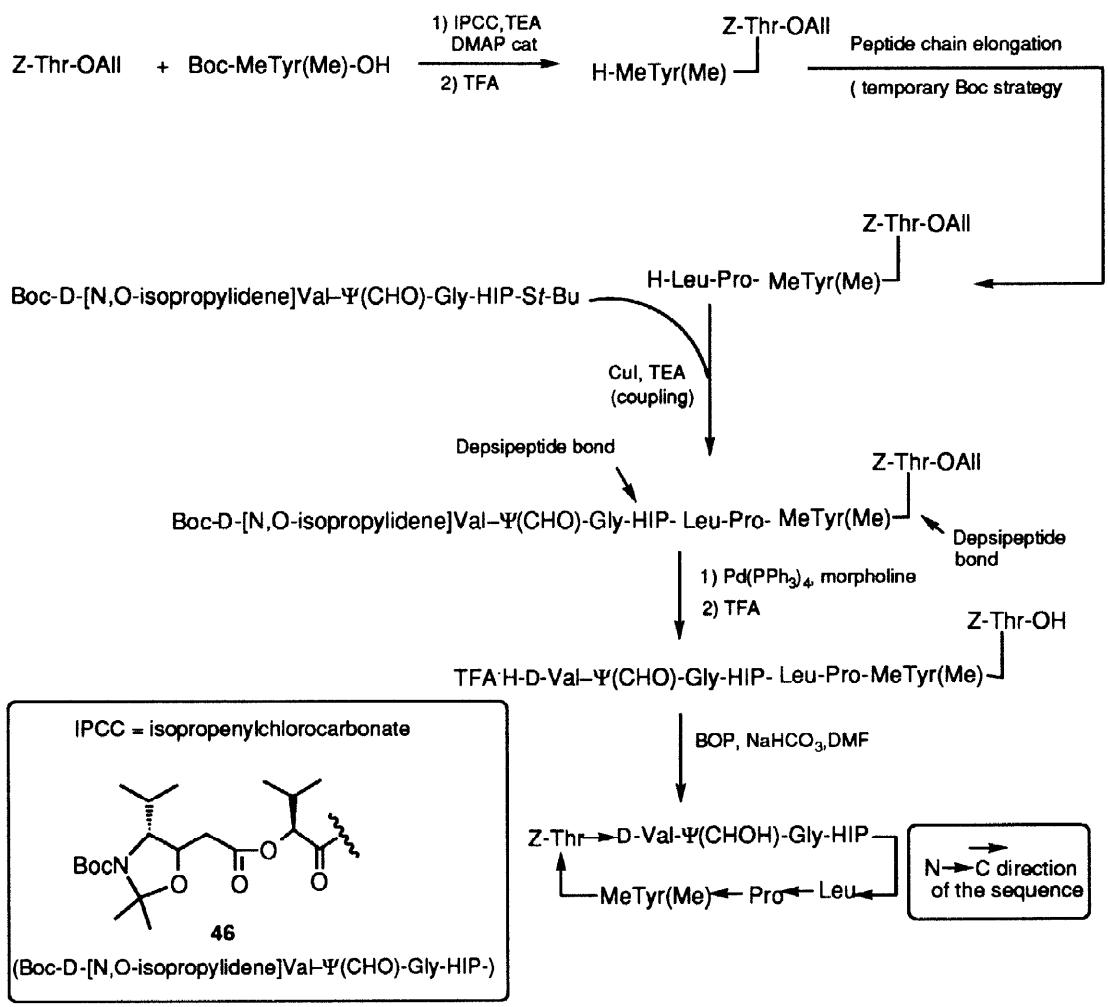
Standard Boc/Bzl method on Merrifield resin together with orthogonal Fmoc/Fm and Alloc/All protections has recently been used in the synthesis of a bicyclic peptide with a tripodal side-chain bridge (scheme 13).[173]

Scheme 13[173]



A solution phase synthesis of the cyclodepsipeptide nordidemnin B featuring semi-permanent allyl protection of the α-carboxy group of a threonine residue has been described by Jouin and coworkers[47]. The choices of the hydrogenolysable Z group for N-protection of threonine and of the allyl group for its carboxy-protection were guided by the two following requirements: first the N-protecting group of threonine had to be resistant to the acidic conditions of deprotection of the Boc-D-[N,O-isopropylidene]Val-Ψ(CHO)Gly moiety (see **46**) of the linear peptide before cyclisation; secondly, both protecting groups had also to be removable under conditions compatible with the presence of the depsipeptide bonds. The main steps of this synthesis, relevant to allylic protection, are represented in scheme 14.

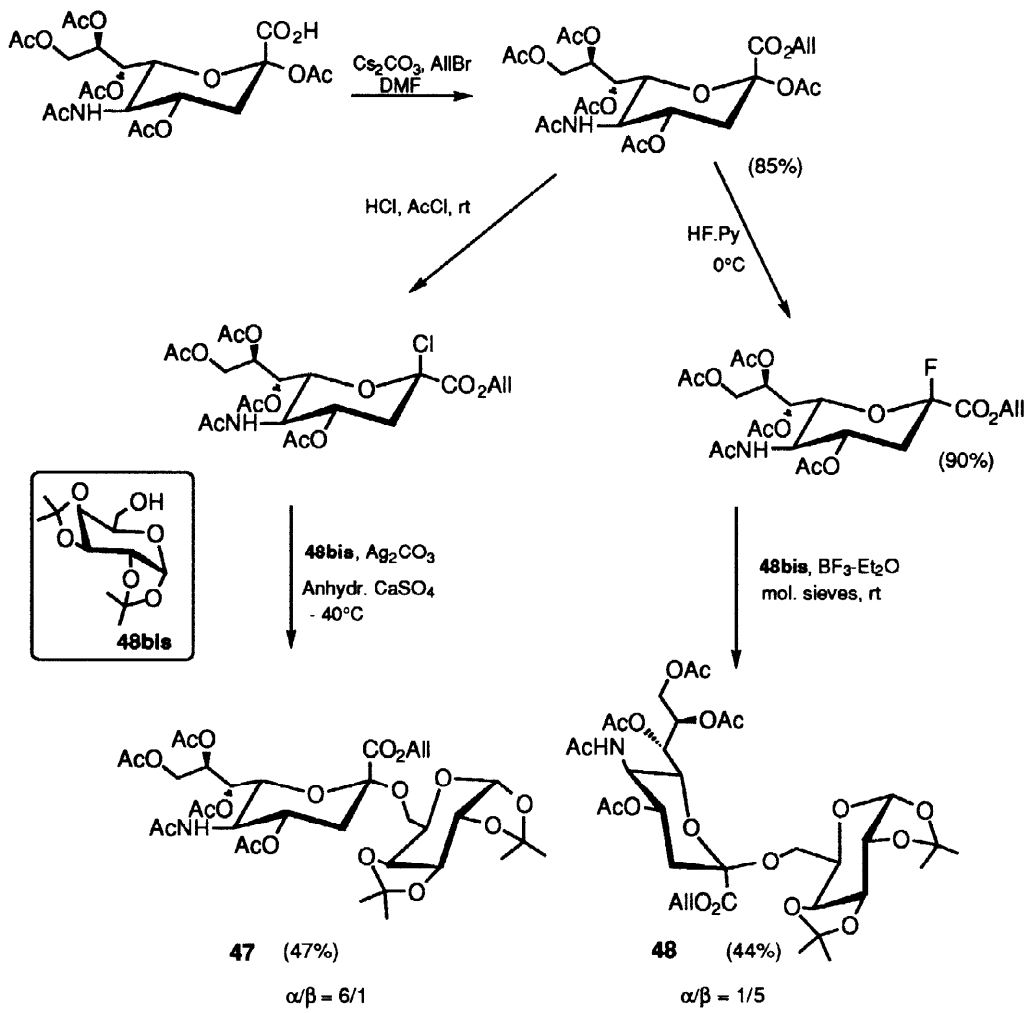
Scheme 14[47]



An example[98] of convergent solution phase synthesis of a cyclodepsipeptide involving simultaneous removal of the All and the Alloc groups of the terminal α-carboxy and α-amino functions before the cyclisation step has already been mentioned (eq. 57, paragraph 3.6). A similar strategy has been used in the synthesis of the cyclopeptide cyclotheonamide B.[174]

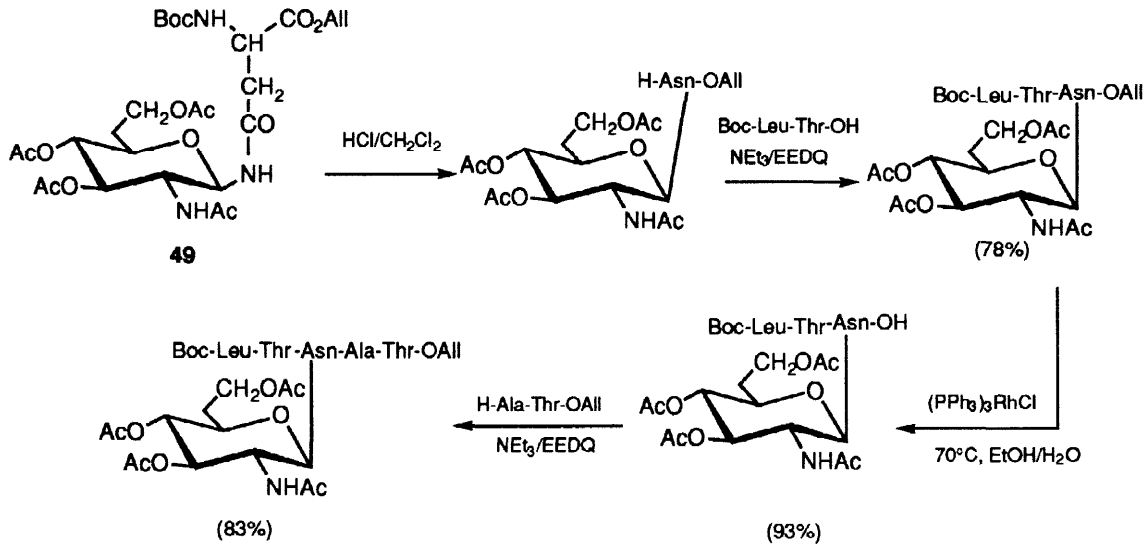
Allylic protections in glycopeptide chemistry have been introduced and extensively developed by Kunz and associates.[175] Their particular helpfulness in this field stems from the fact that allyl carboxylates are at the same time stable under the conditions of most glycosidation procedures, and cleaved under conditions mild enough to preserve the often fragile *O*-glycosyl linkages. These two points are particularly well illustrated in the chemistry of neuraminic acid derivatives described in scheme 15.[50] Final treatment of both anomeric mixtutes **47** and **48** with $Pd(PPh_3)_4$/morpholine in THF, allowed quantitative deprotection of the allyl ester groups without side reactions.

Scheme 15[50]



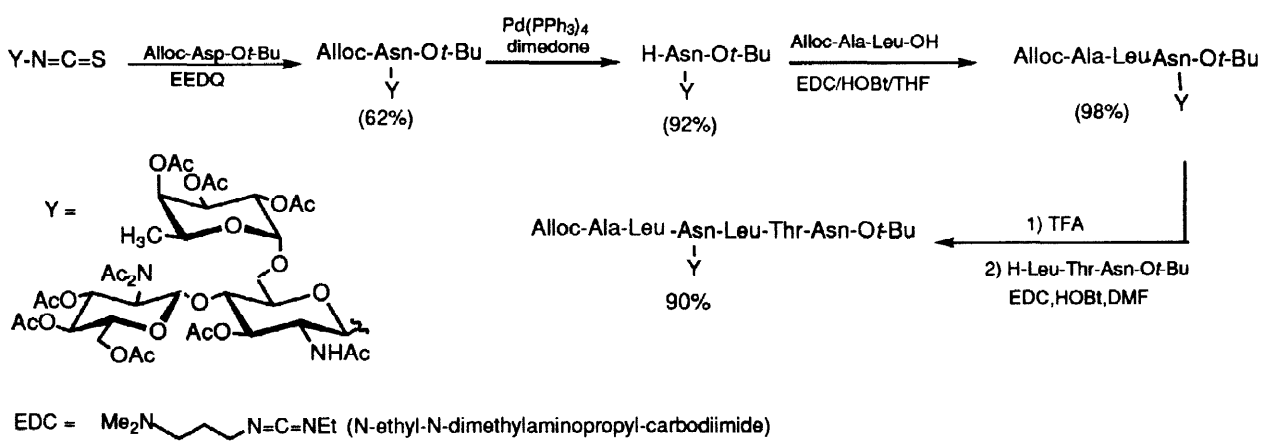
Kunz and Waldmann have used allyl protection of α-carboxy groups in combination with Boc protection of α-amino groups in the synthesis of N-glycopeptides[176] (scheme 16). According to this strategy and starting from the Boc, All differentially protected asparagin glycoconjugate **49**, the allyl group is used

Scheme 16[176]



successively as a permanent and as a temporary protection, while peptide chain elongation is, at the same time, carried out successively in the C→N and in the N→C direction. Removal of the allyl group was effected through rhodium catalysed isomerisation to a prop-1-enyl derivative (see part I). A more recent illustration of this strategy can be found in the synthesis of *N*-glycopeptides containing two Lewis^x antigen side-chains.[177] A related strategy, based this time on the association of *t*-Bu ester and *N*-Alloc protections, has been used[82] in the synthesis of a fucosyl-chitobiose glycopeptide (scheme 17). The unusual

Scheme 17[82]

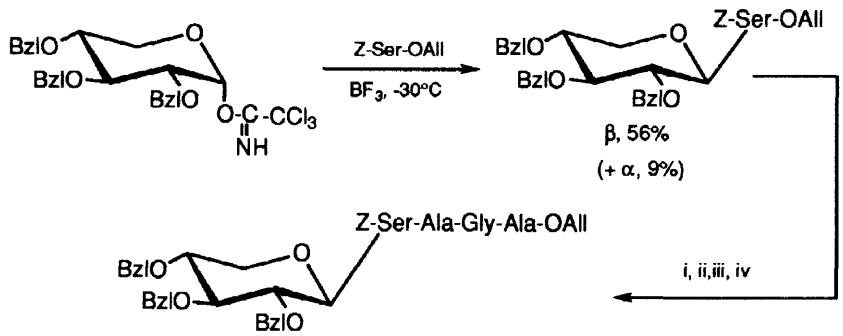


stability of the ficoside bond towards trifluoroacetic acid has been attributed to a shielding effect by the acetyl groups present on the glycosyl moiety. Another differentially protected Alloc/*t*-Bu glycosyl-asparagine conjugate (β-mannosyl-chitobiosyl-asparagine) has been prepared more recently by Günther and Kunz.[178]

For the synthesis of more labile *O*-glycoserine peptides, allylic protection was reserved to α-carboxy groups, together with Z-permanent α-amino protection and peptide chain elongation in the N→C

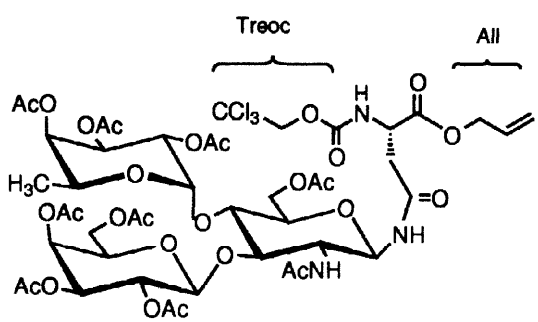
direction[2a, 40,51] (scheme 18). A similar strategy, relying on Boc permanent α-amino protection, was used in the synthesis of several Asn *N*-glycopeptides.[49]

Scheme 18[41,50]

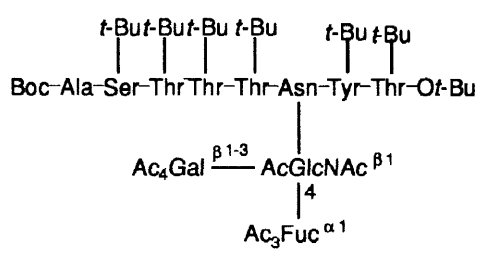


i) $Pd(PPh_3)_4$, morpholine, 97% ii) HCl . H-Ala-Ala-OAll, NEt_3, EEDQ, DCM (87%)
iii) same as i), 97%; iv) HCl · H-Gly-Ala-OAll, NEt_3, EEDQ, DMF (61%)

In all of the above examples, the All and Alloc groups are used in combination with Z, Bzl or Boc, *t*-Bu protections. In recent work, Kunz and coworkers have also focussed on the combination of allylic and Fmoc or trichlorethoxycarbonyl (Treoc) protecting groups. Kunz and März[52] have prepared the differentially deprotectable asparagine glycoconjugate **50**, with a Lewis[a] antigen side chain, and used it in the synthesis[52] of protected glycopeptide **51** whose aminoacid sequence corresponds to a fragment of the envelope



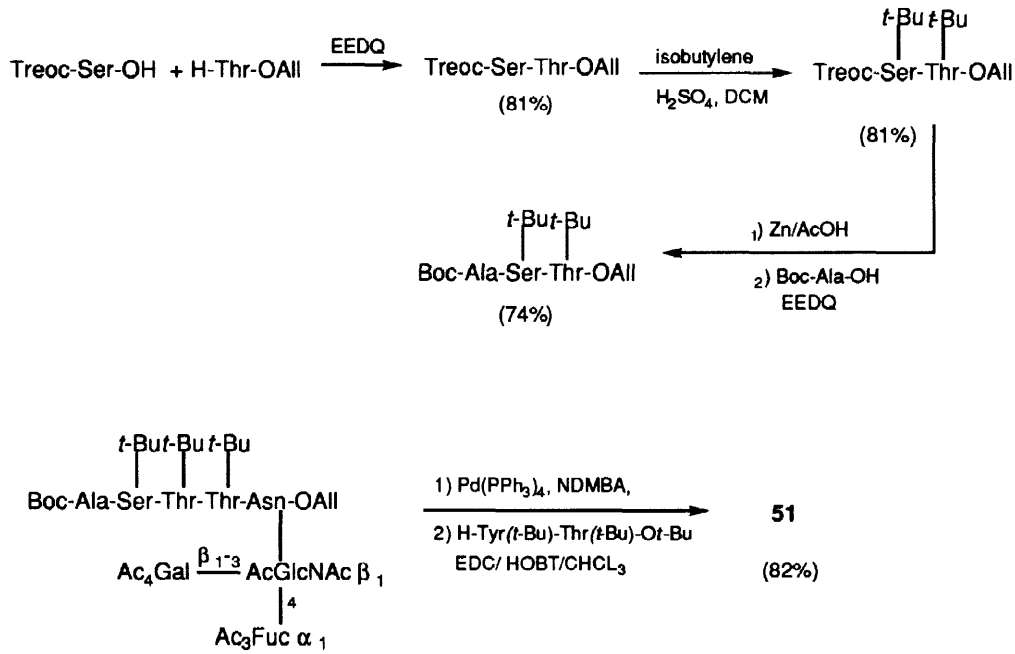
50



51

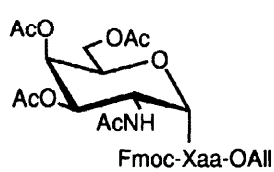
glycoprotein gp 120 of HIV-1. Selection of the orthogonal All and Treoc group was guided by the fact that both of them may be removed under conditions mild enough to allow *O*-acetyl protection of the carbohydrate part; as already pointed out, such *O*-acetyl protection confers increased stability to the intersaccharide bonds towards acids.[82] In this work, the C-terminal moiety Boc-Ala-Ser(*t*-Bu)-Thr(*t*-Bu)-Thr(*t*-Bu)-Thr(*t*-Bu)-OH and the N-terminal moiety H-Tyr(*t*-Bu)-Thr(*t*-Bu)-O*t*-Bu were first synthesised and then successively condensed with the differentially protected glycoconjugate **50**. Successive removal from **51** of the *t*-butyl groups (TFA) and of the *O*-acetyl protections (dimethylethylamine/water, pH 9) completed the synthesis. Some selected steps of this synthesis are represented in scheme 19. Note, in the building of the

Scheme 19[52b]



peptidic fragment, the introduction of the *t*-Bu side chain at the dipeptide level, which was made possible by the stability of both the All and Treoc groups to acids.

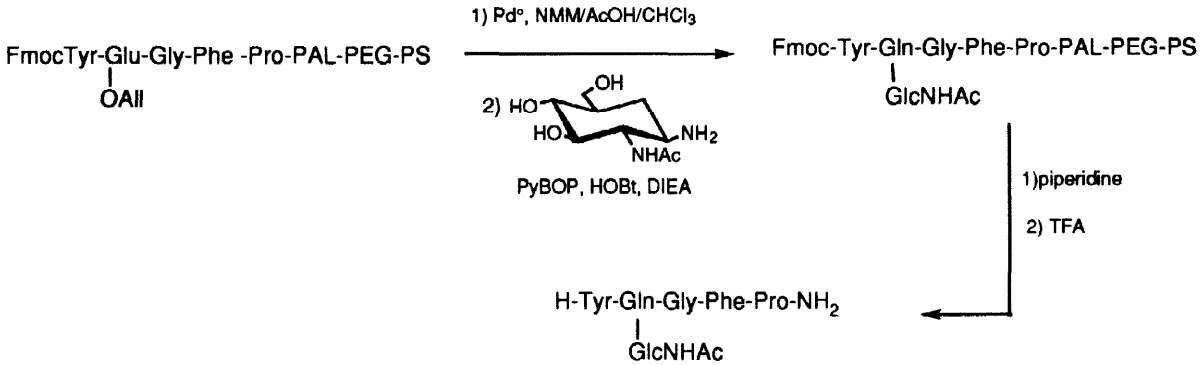
In an analogous manner, Fmoc/allyl differentially protected serine or threonine glycoconjugates **52** have been used[69] in the synthesis of glycopeptides related to human glycophorin A.



52 (Xaa = Ser, Thr)

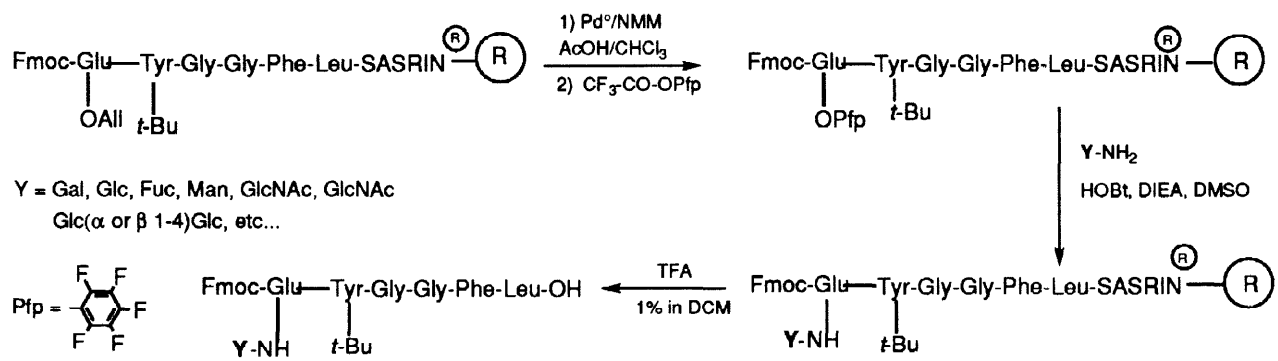
The Fmoc/All combination has recently been used in a different way in the solid phase synthesis of glycopeptides by Albericio and coworkers[72](scheme 20). Peptide chain elongation was first carried out according to Fmoc chemistry in a continuous flow synthesiser, using a polyethylene glycol-polystyrene graft resin (PEG-PS) derivatized with a TFA cleavable PAL handle. Palladium catalysed removal of All side chain protections of Asp or Glu residues was then achieved and the post-synthetic glycosidation was subsequently performed on the resin bound peptide. The final steps of the synthesis consisted of the cleavage of the N^{α}-terminal Fmoc group and the release of the peptide chain from the resin. A similar strategy has recently

Scheme 20[72]



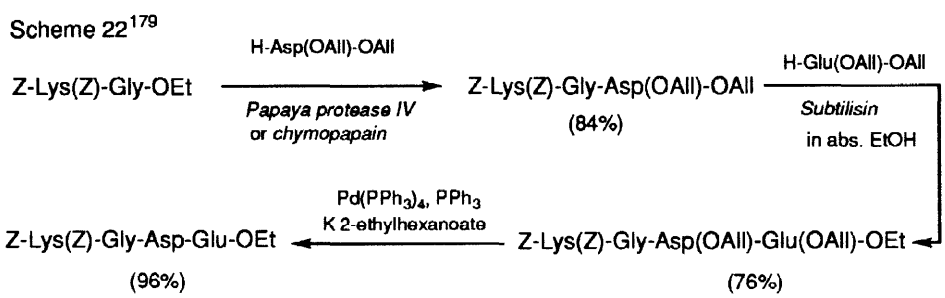
been utilised by Vetter, Gallop and coworkers[73] who were able to devise a procedure of wide applicability for post-synthetic N-glycosylation based on condensation of glycosamines with the pentafluorophenyl (Pfp) activated β- or γ-carboxy groups of aspartic or glutamic residues (scheme 21).

Scheme 21[73]



Before concluding this section, mention must be made of the recent use of glutamic and aspartic bisallyl esters in the enzymatic synthesis of oligopeptides according to a minimal protection strategy.[179] The allyl group was chosen on the grounds that, in contrast to their *tert*-butyl analogues, α-carboallyloxy groups of α-amino-esters behave as acyl donors in protease-catalysed coupling reactions. Therefore no deprotection is needed before the coupling step. Some selected reactions of this enzymatic synthesis are represented in scheme 22.

Scheme 22[179]



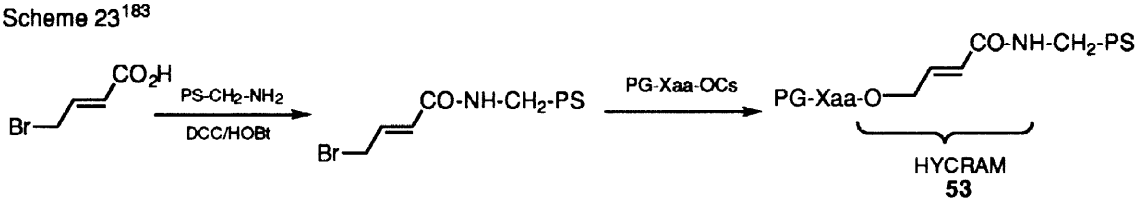
The problem of permanent allylic side-chain protection of aminoacids is discussed more specifically in section 4.3.

5.2 **Allylic linkers for use in solid phase peptide synthesis.**

The development of SPPS in general and, in the recent years, of convergent SPPS[180,181] which entails the synthesis of fully protected fragments for subsequent use in block condensation reactions has stimulated the invention of a wide array of handles (linkers) in order to facilitate and diversify the anchoring of the peptide chains to the solid supports. The criteria for "good" handles are basically the same as those for any protecting groups.[182] In particular, they must be removable under mild and selective conditions in order to ensure maximum compatibility with other functional groups or protecting entities, but, at the same time, have good stability under as wide a range of conditions as possible in order to ensure maximum flexibility in the choice of permanent side-chain protection and methods for peptide chain elongation. In both respects, allylic handles, due to their orthogonality with many other protective groups are obviously of high potential utility.

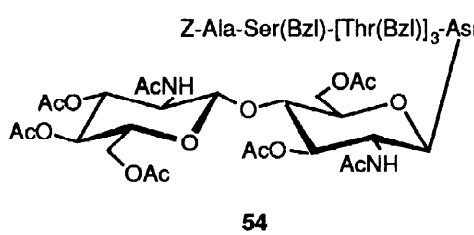
Allylic handles so far devised are structurally simple and readily accessible. They all incorporate, at one end, an allylic halide or hydroxyl group for anchoring the peptide chain, while at the other terminus, attachment to the support is achieved through the carboxyl group. 2-bromocrotonic acid was the first of these to be proposed, by Kunz and Dombo[183] in 1988 and has the shortest possible structure of this kind. 2-bromocrotonic acid was condensed onto an aminomethyl resin by the DCC/HOBt procedure. Attachment of the C-terminal aminoacid on the bromoallyl resin was then achieved by the caesium salt (Gisin) method (scheme 23). As a first illustration[183] of use of the Hycram (hydroxycrotonylamide) resin **53**, several model

Scheme 23[183]

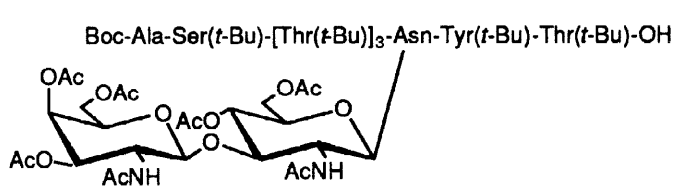


53

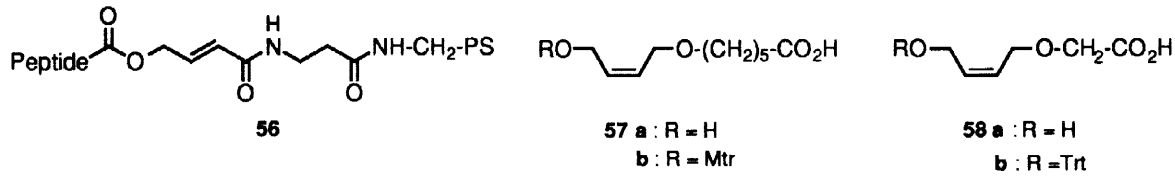
protected peptides were synthetized by the Boc-temporary strategy such as Z-Tyr(Bzl)-Gly-Gly-Phe-Leu-OH or the glycopeptide Boc-Leu-Asn(Ac_3GlcNAc)-Ile-OH. Allylic cleavage from the resin was achieved with morpholine in large excess and in the presence of palladium tetrakis(triphenylphosphine) (10 mol% based on allylic substitution of the resin). Since then, the more complex glycopeptides **54** and **55** have been successfully synthesised[184] according to the Boc strategy and the Fmoc strategy respectively, and by the use



54



55

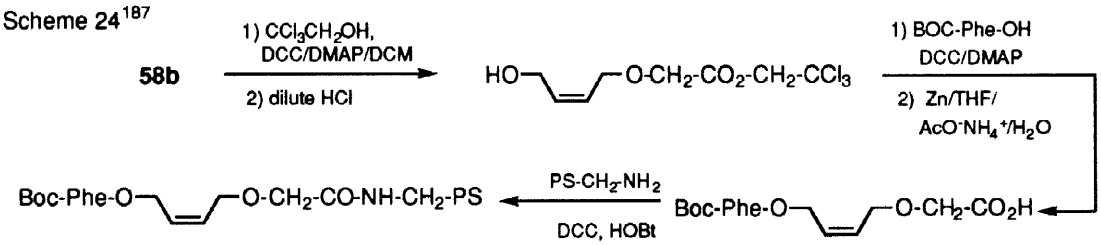


56 57 a : R = H b : R = Mtr 58 a : R = H b : R = Trt

of the modified β-Hycram resin **56** which incorporates between the crotonyl unit and the support, a β-alanine fragment, used both as a spacer and an internal reference. With the temporary Fmoc strategy however, difficulties seem to have been encountered in other cases,[185] possibly because in basic medium the crotonyl unit, a Michael acceptor, is too prone to undergo nucleophilic attacks

6-(4-hydroxy-*Z*-but-2-enyl-1-oxy)-hexanoic acid **57a** and (4-hydroxy-*Z*-but-2-enyl-1-oxy)-acetic acid **58a,** are readily available from *Z*-2-butene-1,4-diol and 6-bromohexanoic or bromoacetic acid. Handle **57**[36] was condensed, as its 4-*O* -(4'-methoxytrityl) derivative **57b** on cellulose disc supports by MSNT-mediated (MSNT: 1-mesitylenesulfonyl-3-nitro-1,2,4-triazole) esterification in pyridine.[186] After removal of the methoxytrityl group (3% dichloroacetic acic in DCM), the C-terminal aminoacid was condensed onto the free allylic OH as its symmetrical anhydride or as its HOBt ester in the presence of DMAP. Handle **58**[187] was condensed, as its 4-*O*-trityl derivative **58b**, to aminomethyl-polystyrene by the DCC/HOBT method; the trityl group was then removed (HCO_2H/ CH_2Cl_2, then H_2N-NH_2·H_2O/DMF) and the free hydroxy group esterified by the C-terminal aminoacid in the presence of DCC and DMAP. In another option, the hydroxyallyl resin was converted to chloroallyl resin by treatment by TsCl/DMAP and the first amino acid attached by the Gisin (caesium salt) method. A third option ("preformed handle approach") , which minimizes the risk of racemisation at the C-terminal residue, involves prior attachment of the C-terminal aminoacid to the free linker in solution, and subsequent anchoring to the support (scheme 24).

Scheme 24[187]



Handles **57** and **58** have been used in the synthesis of fully protected peptide fragments according to either the temporary Boc or temporary Fmoc strategies.

Model protected peptides **59**[187] and **60**[188] for instance, which are related to the sequences of LHRH and uteroglobin respectively, were synthetized according to the Boc-strategy. In the first case, cleavage from

<Glu-His-Trp-Ser(Bzl)-Tyr(Dcb)-OH **59**

Boc-Leu-Thr(Bzl)-Glu(Oc-Hx)-Lys(2-ClZ)-Ile-Val-Lys(2-ClZ)-Ser(Bzl)-Pro-OH **60**

the resin was effected by the hydrostannolytic procedure ($PdCl_2(PPh_3)_2$, 0.02 mol. equiv., Bu_3SnH, 1.5 equiv. based on allylic substitution of the resin) while several systems were investigated for **60**.[188] Excellent results

(>95%cleavage yields) were obtained by using an excess of morpholine in polar medium such as THF/DMSO/0.5M HCl. **60** was also prepared under similar conditions and in comparable yields on a Hycram resin.[188]

The obtention of fully protected peptidic fragments by the Fmoc strategy is more challenging because the choice of allyl scavengers is limited to those whose basicity is sufficiently low to avoid competitive removal of the N^{α}-terminal Fmoc group. The problem here is more acute than for the selective deprotection of simple All or Alloc groups because allylic linkers, with their disubstituted double bonds, are not so easily cleaved. In their synthesis[36] on cellulose disk supports with handle **57a**, Blankemeyer-Menge and Franck used HOBt as the allyl scavenger in the presence of large amounts of catalyst ($Pd(PPh_3)_4$, 2 equiv. based on allylic substitution of the support) for final allylic cleavage. By this method, good yields (65-83%) were obtained of several fully protected peptide fragments such as Fmoc-[Glu(O*t*-Bu)]$_n$-OH (n=4,5) or Fmoc-Cys(S-*t*-Bu)-Arg(Mtr)-His(Bum)-Trp-Lys(Boc)-Gln-Cys(*t*-Bu)-Met-OH.

The syntheses of the protected peptidic fragments **60**, **61** and **62** related to the sequence of uteroglobin have been recently investigated[70] (**60** and **61** differing only by the nature of the side-chain protecting groups). Peptides **60** and **61** were prepared on a polystyrene resin containing the (4-oxy-2-butenyloxy)-acetyl linker **58**. The same handle, but on a PEG-polystyrene resin was used for synthesis of fragment **62**. After completion of the aminoacid sequences, final cleavage from the resin was accomplished at room temperature, either hydrostannolytically or by allyl transfer to the weakly basic NMA (50 equiv) in DMSO/THF/ 0.5 M HCl 2:2:1. In the first case, tributyltin hydride was slowly and continuously added over a period of 30 min.; in the second one, a 12 hour reaction time was applied. The results thus obtained are summarized in Table 2

Fmoc-Leu-Thr(*t*-Bu)-Glu(O*t*-Bu)-Lys(Boc)-Ile-Val-Lys(Boc)-Ser(*t*-Bu)-Pro-OH

61

Fmoc-Gln(Trt)-Thr(*t*-Bu)-Thr(*t*-Bu)-Arg(Pmc)-Glu(O*t*-Bu)-Asn(Trt)-Ile-Met-Lys(Boc)OH

62

Table 2

Peptide	Cleavage yields	
	Method A[a]	Method B[b]
60	63/28[c]	70
61	91	80
62	87	86

(a) $PdCl_2(PPh_3)_2$, 3.3 x 10^{-2} mol. equiv.; Bu_3SnH 3 equiv., DMF/DCM 1:1
(b) $Pd(PPh_3)_4$, 3.3 x 10^{-1} mol. equiv, NMA 30 equiv., DMSO/THF/0.5 M HCl 2:2:1
(c) lower yield obtained when Bu_3SnH was added all at once.

Irrespective of the method, high cleavage yields were obtained with fragments **61** and **62** while only fair results were obtained with fragment **60**. It was further observed that the cleavage yields for **55** by the hydrostannolytic method dropped dramatically when tributyltin hydride was added in one single portion. Obviously, under such conditions, the palladium catalysed decomposition of tributyltin hydride into hexabutyldistannane (eq. 55) becomes preponderant. Although other reasons may be invoked, the

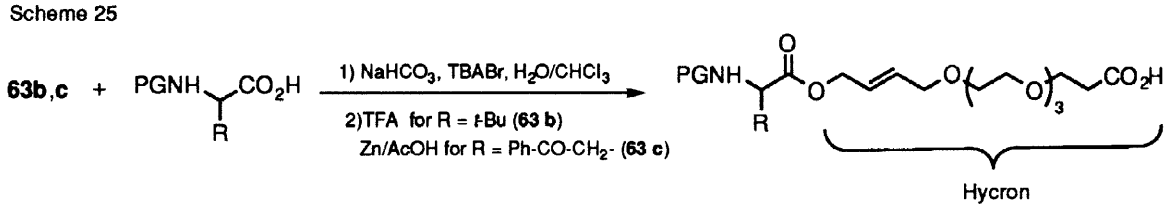
unsatisfactory results obtained with **61** are likely to be the consequence of the lack of accessibility of the allylic reactive site to the bulky $Pd(PPh_3)_n$ catalytic species (first step in fig. 1); the high yields obtained with fragment **62** for which a PEG spacer was used are in accordance with this explanation.

Kunz and coworkers have recently described[185] a new allylic linker (Hycron) **63** in which a polyether fragment is inserted between the allylic and the carboxylic ends. **63b** is readily obtained by Michael addition

63 a : R = H
b : R = *t*-Bu
c : R = Ph-CO-CH_2-

of triethyleneglycol on *tert*-butyl acrylate, followed by condensation of the Michaël adduct with 1,4-dibromobutene. To minimize the risk of racemisation, loading of the polymer is best achieved by the preformed handle approach (scheme 25). With the Hycron resin, Seitz and Kunz were able to synthesise

Scheme 25



the fully protected O-glycosylated peptides **64** and **65** in high yields by the Fmoc strategy. Allylic cleavage from the resin was achieved by palladium catalysed allylic transfer to NMA.

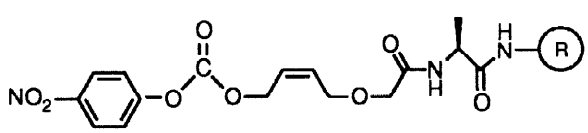
Fmoc-Ala-Ser(*t*-Bu)-Thr(αAc3GalNAc)-Thr(*t*-Bu)-OH

64

Ac-Ala-Pro-Asp(O*t*-Bu)-Thr(αAc3GalNAc)-Arg(Mtr)-Pro-Ala-Pro-Gly-OH

65

Recently[189], the allylic resin **66** in the activated (4-nitrophenylcarbonate) form has been prepared and used in the SPPS of Pseudoargiopinine III. A cleavage yield of 92% was obtained for detachment of the peptide from the resin by the hydrostannolytic procedure.



66

-HN-(R) : 4-methylbenzhydrylamine-polystyrene resin

From all the above results, it may be concluded that allylic anchors allow SPPS of fully protected fragments both by the Boc and by the Fmoc temporary protection strategy. Final cleavage from the resin may sometimes cause problems, probably due to the difficulty of access of the catalytic species to the reactive allylic site. To circumvent this problem and facilitate the formation of the π-allyl palladium complex, use of polyethyleneglycol spacers appears highly advisable; it is also believed that the recently introduced allyl scavenger $PhSiH_3$,[161] due to its high reactivity and its non-basic character, could be advantageously used for allylic cleavage from the resin. Finally, mention should be made that a possible drawback in the use of allylic linkers is their relatively pronounced tendency to lead to DKP formation at the third aminoacid introduction stage. This fact which is attested by several observations[185,70] (see also " notes added in proof") is in accordance[190] with the relatively high acidity[191] of allylic alcohols.

5.3 **Permanent allylic side-chain protection of aminoacids.**

The two main strategies in current use in the SPSS of fully protected peptide fragments[180,181] rely on temporary Boc/ permanent Bzl or temporary Fmoc/permanent *t*-Bu,Boc protection schemes. In the first one, TFA-stable linkers are used, which may be cleaved by bases, nucleophiles or by photochemical means. In the second approach, base stable, highly acid sensitives handles are usually involved. The acidic conditions required for final removal of benzylic or *tert*-butylic side-chain protecting groups may bring about various unwanted side-reactions. In that respect, their replacement by allylic protecting groups could constitute an interesting alternative. Besides, the use of allylic side-chain protection could open the way to new possibilities in the choice of the handles and of the temporary terminal N^{α} protecting group. Finally, due to the small size of the allyl group, allylic protected fragments could well display better solubilities in a polar medium than their benzylic or *tert*-butylic congeners and thereby contribute to alleviate one of the most acute difficulties[180,181,192] encountered in fragment condensations.

In order to take full advantage of allyl based permanent side chain protection strategy, we would require however a full array of allylic protecting groups which span the entire set of side chain functionalities of natural aminoacids. As shown in the following section, this condition cannot be considered as fulfilled at the present time.

In Table 3 is given a list[193,194] of all the All or Alloc side-chain protected N^{α}-Boc and N^{α}-Fmoc aminoacids derivatives prepared so far, with the exception of allyl derivatives of histidine (*vide infra*). With the exceptions of Fmoc-L-Cys(Alloc)-OH and Fmoc-L-Thr(Alloc)-OH, all of them are crystalline, either as such or, for some N^{α}-Boc derivatives, as their dicyclohexylammonium salts. In scheme 26 are represented some selected procedures for their obtention.[193-196] All- and Alloc side-chain protected derivatives of *N*-urethane-*N*-carboxyanhydrides, namely Boc-Asp(OAll)-NCA, Boc-Lys(Alloc)-NCA, Fmoc-Asp(OAll)-NCA and Fmoc-Lys(Alloc)-NCA, have also been prepared and incorporated in oligopeptidic sequences.[197]

Table 3 : All or Alloc side-chain protected amino-acid derivatives[a,b]

N^{α}-Boc-derivatives	N^{α}-Fmoc-derivatives
Boc-L-Arg(Alloc)$_2$-OH.DCHA	Fmoc-L-Arg(Alloc)$_2$-OH
Boc-L-Asp(OAll)-OH	Fmoc-L-Asp(OAll)-OH
Boc-L-Cys(Alloc)-OH	Fmoc-L-Cys(Alloc)-OH[d]
Boc-L-Glu(OAll)-OH	Fmoc-L-Glu(OAll)-OH
Boc-L-His(Alloc)-OH[e]	Fmoc-L-His(Alloc)-OH[e]
Boc-L-Lys(Alloc)-OH.DCHA	Fmoc-L-Lys(Alloc)-OH
Boc-L-Ser(Alloc)-OH.DCHA	Fmoc-L-Ser(Alloc)-OH
Boc-L-Thr(Alloc)-OH.DCHA	Fmoc-L-Thr(Alloc)-OH[d]
Boc-L-Trp(Alloc)-OH.DCHA[c]	Fmoc-L-Trp(Alloc)-OH[c]
Boc-L-Tyr(All)-OH.DCHA	Fmoc-L-Tyr(OAll)-OH

(a) taken from ref. 193b unless otherwise specified; (b) crystalline material unless otherwise specified

(c) ref 194; (d) oil; (e) mixture of N^{π}- and N^{τ}-regioisomers , see scheme 26, eq. d.

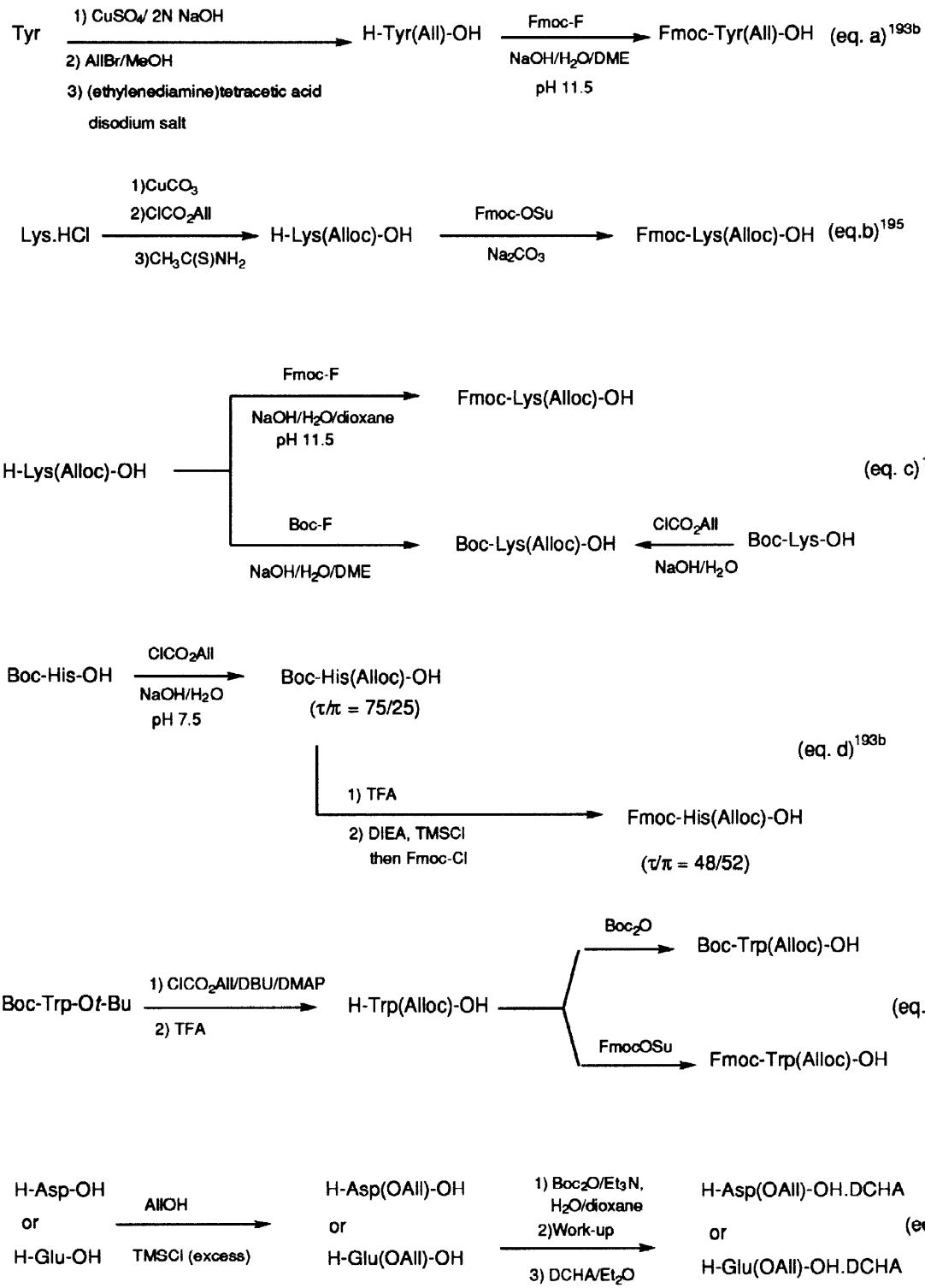
It has been shown that by use of the hydrostannolytic procedure (Bu_3SnH, $PdCl_2(PPh_3)_2$), all All or Alloc protections in the compounds listed in Table 3 are selectively and almost instantaneously removed,[198] with the exception of the allyl derivatives of tyrosine. In this case, slow addition of tributyltin hydride is required to ensure complete deprotection.

If all of the allylic protections displayed in Table 3 are stable under the conditions of Boc/*t*-Bu removal, this is not always the case under the basic conditions of Fmoc removal. Alloc derivatives of serine, cysteine, histidine[193] and tryptophan[194] are cleaved or may undergo unwanted rearrangements in the presence of piperidine, and Boc-Arg(Alloc)$_2$-OH is converted to Boc-Arg(Alloc)-OH[193] through loss of one Alloc group. Replacement of piperidine by a still basic but less nucleophilic amine may be helpful. Trzeciak and coworkers[194] have found that the *N*-Alloc group on the indole ring of tryptophan is stable to 2% DBU, a system which nevertheless allows Fmoc removal. They were consequently able to carry out Fmoc-SPSS of several peptides incorporating Trp residues such as Gly-Gly-Ala-Lys-Ala-Trp-Trp-Trp-Ser-Pro-Gly-Gly-NH_2. Better results were obtained by incorporating Alloc protected rather than unprotected tryptophan residues. A similar strategy was used in the synthesis of the phosphorylated peptide **67**, for which side-chain protection was mandatory in order to avoid oxidative degradation of the indole nucleus during I_2 oxidation of a phosphite intermediate.

Trp-Ala-Ser(OPO_3H_2)-Gly-Glu

67

Scheme 26


Tyr
1) CuSO4/ 2N NaOH
2) AllBr/MeOH
3) (ethylenediamine)tetracetic acid disodium salt
H-Tyr(All)-OH
Fmoc-F
NaOH/H2O/DME
pH 11.5
Fmoc-Tyr(All)-OH (eq. a)193b
Lys.HCl
1)CuCO3
2)ClCO2All
3)CH3C(S)NH2
H-Lys(Alloc)-OH
Fmoc-OSu
Na2CO3
Fmoc-Lys(Alloc)-OH (eq.b)195
H-Lys(Alloc)-OH
Fmoc-F
NaOH/H2O/dioxane
pH 11.5
Fmoc-Lys(Alloc)-OH
Boc-F
NaOH/H2O/DME
Boc-Lys(Alloc)-OH
ClCO2All
NaOH/H2O
Boc-Lys-OH
(eq. c)193b
Boc-His-OH
ClCO2All
NaOH/H2O
pH 7.5
Boc-His(Alloc)-OH
(τ/π = 75/25)
1) TFA
2) DIEA, TMSCl
then Fmoc-Cl
Fmoc-His(Alloc)-OH
(τ/π = 48/52)
(eq. d)193b
Boc-Trp-Ot-Bu
1) ClCO2All/DBU/DMAP
2) TFA
H-Trp(Alloc)-OH
Boc2O
Boc-Trp(Alloc)-OH
FmocOSu
Fmoc-Trp(Alloc)-OH
(eq. e)194
H-Asp-OH
or
H-Glu-OH
AllOH
TMSCl (excess)
H-Asp(OAll)-OH
or
H-Glu(OAll)-OH
1) Boc2O/Et3N, H2O/dioxane
2)Work-up
3) DCHA/Et2O
H-Asp(OAll)-OH.DCHA
or
H-Glu(OAll)-OH.DCHA
(eq. f)196

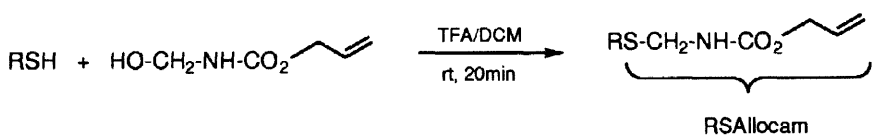
Kunz' work[95] concerning the deprotection of allyl esters of aspartyl dipeptide amides has already been discussed (see section 3.3)

The problem of allylic protection of serine, threonine and cysteine

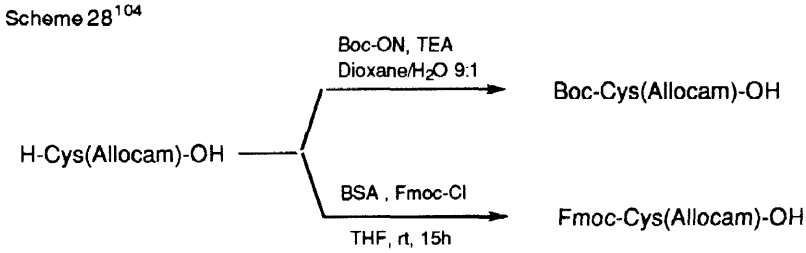
The allyl group cannot be used for OH or SH protection of serine, threonine or cysteine; indeed, allyl ethers or thioethers do not lead to π-allyl complexes in the presence of zerovalent palladium catalysts (see section 1). The allyloxycarbonyl derivatives are also unsuitable, because as with most other alkoxycarbonyl derivatives, *O*- or *S*-Alloc derivatives of serine threonine or cysteine are prone to undergo intramolecular nucleophilic attack by the neighbouring α-amino group under the basic conditions of Fmoc removal or even during coupling processes.[193]

In an effort to circumvent these problems, a new form of allylic protection, the allyloxycarbonyl (Allocam) group, specific for thiols in general and cysteine in particular has been devised.[199] Allocam derivatives of thiols are readily obtained by condensation of thiols and allyl *N*-hydroxymethylcarbamate in acidic medium (scheme 27). The *S*-Allocam derivative of cysteine prepared by this method is easy to further derivatise into Boc-Cys(Allocam)-OH and Fmoc-Cys(Allocam)-OH by conventional procedures (scheme 28).[104] Several allyl group scavengers -NDMBA, *N*-trimethylsilyldimethylamine, $PhSiH_3$, Bu_3SnH-

Scheme 27[199]

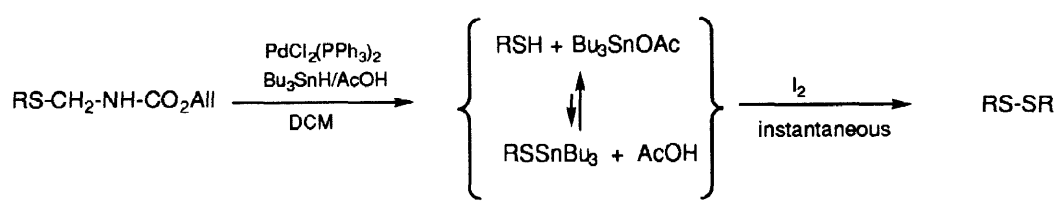


Scheme 28[104]



known to be efficient in the deprotection of allyl carbamates in general were tested in the deprotection of Allocam derivatives of thiols. Only the hydrostannolytic procedure carried out in the presence of acetic acid was found to be satisfactory. For the sake of convenience, the deprotected thiols were isolated in their oxidized disulfide form, after treatment with iodine of the crude reaction mixtures (scheme 29). Under these conditions 98-100% conversions and 65-100% yields of isolated products were obtained. All other

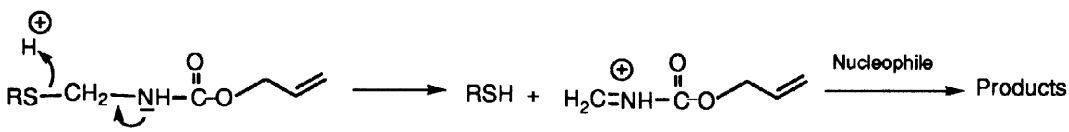
Scheme 29[199]



deprotection systems were unsatisfactory, due to poisoning of the catalyst at an early stage (*ca* 20% conversion) of the reaction. The success of the hydrostannolytic process is probably imputable to its very high rate and to the presence of acetic acid which prevents the formation of poisonous thiolato[200] (RS^-) species in the medium.

S-Allocam derivatives of thiols are perfectly stable in DMF/piperidine but display only marginal stability in DCM/CF_3CO_2H, with, for instance a 2% loss per cycle of Boc deprotection for the Allocam derivative of Fmoc-cysteine. Not surprisingly, *O*-Allocam derivatives of alcohols are still more labile under acidic conditions than their thio analogues. These degradation reactions are likely to involve a proton induced fragmentation process, leading to the transient *N*-allyloxycarbonyl-acyliminium[201] (scheme 30). A possible answer to this problem could be to devise more sophisticated protecting groups, **68** or **69**, derived from

Scheme 30



Allocam by introduction of an additional electronwithdrawing group at the nitrogen or the carbon atom.

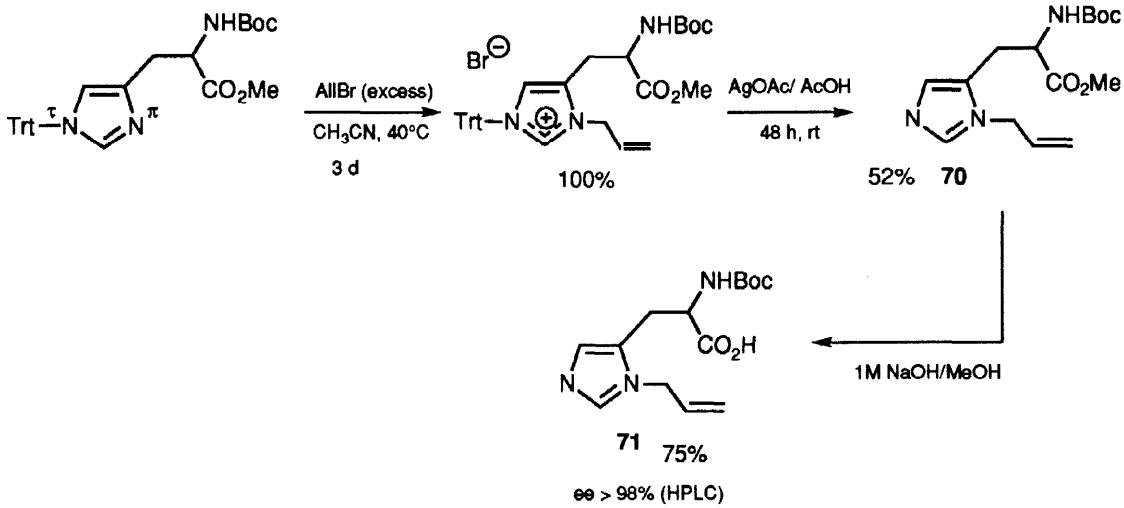
68 **69**

Allyl protection of histidine

The basic and nucleophilic properties of the imidazole ring of histidine may be the source of various complications; preeminent among them is the risk of racemisation associated with the carboxyactivation of *im*-unprotected histidine derivatives.[202,203] Therefore, masking the imidazole ring of histidine, if not strictly imperative, is nevertheless highly advisable. As far as allylic protection is concerned, the Alloc group is of little help because, as with most other acyl derivatives, *im*-Alloc derivatives of histidine are too labile towards nucleophiles. In view of recent results,[204] allyl protection of histidine, on the other hand, seems promising. Since the allyl group is devoid of electron-withdrawing character and its deactivating effect on the imidazole ring can only be of a steric nature, regiospecific allyl substitution at the N^{π} site is however imperative to ensure efficient resistance towards recamisation.[203]

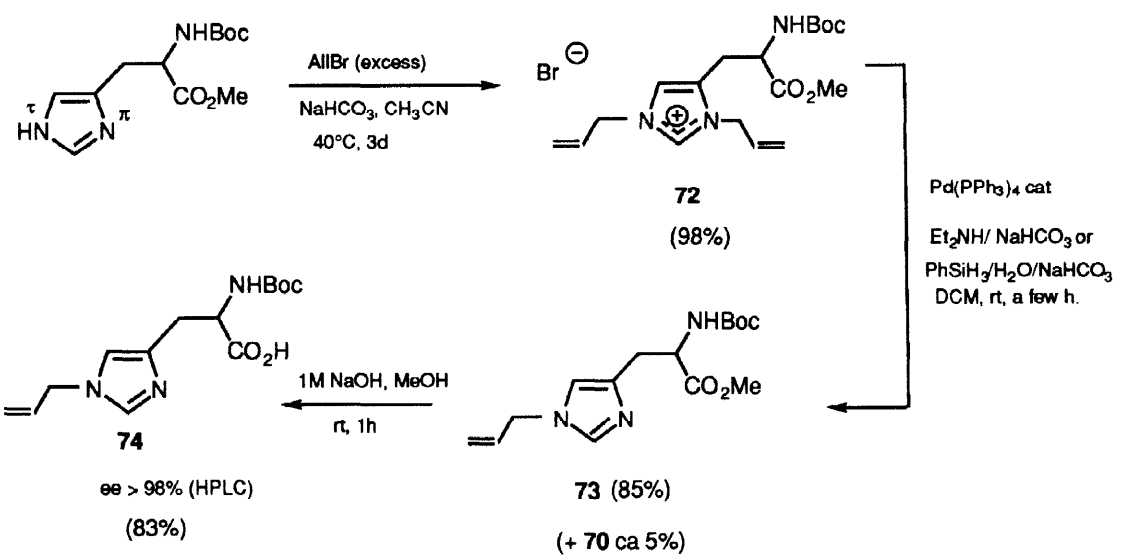
N^{α}-Boc-N^{π}-allyl-L-histidine **71** is easily synthetised from N^{α}-Boc-N^{τ}-trityl-L-histidine methyl ester[203] according to well-documented methodologies (scheme 31). As to the N^{τ}-analogue **74**, it may be

Scheme 31[204]



obtained with good regioselectivity by palladium catalysed chemoselective monodeallylation of the diallylammonium precursor **72** (scheme 32). Quite surprisingly, this reaction displays high selectivity towards removal of the N^{π}-allyl group (S>90:10). The N^{α}-Boc-N^{π}-and N^{α}-Boc-N^{τ}-allyl derivatives of histidine methyl esters **70** and **73** may be separated by flash chromatography.

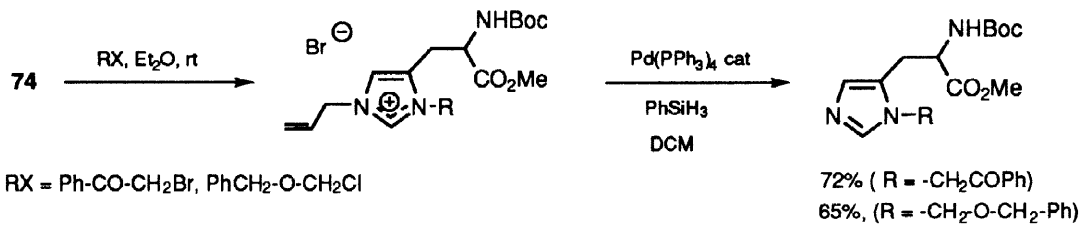
Scheme 32[204]



The resistance of **71** and **74** towards racemization has been investigated by using DCC mediated coupling with prolinamide as the test[203] reaction. Extensive racemisation was observed with the N^{τ}-derivative **74** while almost totally optically pure dipeptide (ds>96%) was obtained with the N^{π}- regioisomer **71**. N^{π}- and N^{τ}-allyl histidine derivatives **70** and **73** are readily deallylated by palladium catalysed allyl tranfer to NDMBA, a procedure which is also efficient for deallylation of allylamines in general (see section 3.3) or by palladium catalysed hydrosilylosis with $PhSiH_3$ in the presence of acetic acid or acetic anhydride.

Finally the allyl group at the τ–position may be used, in a way similar to the trityl group, as a temporary blocking group in the regioselective preparation of N^{π}-substituted derivatives (scheme 33).

Scheme 33[204]



RX = Ph-CO-CH_2Br, $PhCH_2$-O-CH_2Cl

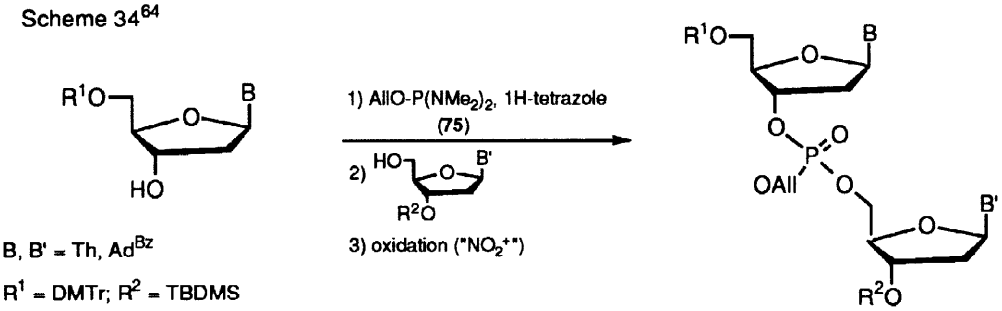
72% (R = -CH_2COPh)
65%, (R = -CH_2-O-CH_2-Ph)

6. ALLYLIC PROTECTING GROUPS IN OLIGONUCLEOTIDE SYNTHESIS

The use of allylic groups for protection of internucleotide linkages and nucleobases has been introduced and developed essentially by Noyori, Hayakawa and coworkers.

In the first report[64], allyl protected dinucleoside phosphates **76** were obtained by stepwise condensation of 3'-OH and 5'-OH free nucleosides with the *O*-allyl phosphoramidite reagent **75**, followed by oxidation of the resulting phosphite triester by NO_2^+ (scheme 34). Selective removal of the allyl group was then carried out by use of Pd°/$BuNH_2$ or Pd°/$BuNH_2$/HCO_2H.

Scheme 34[64]



B, B' = Th, Ad^{Bz}

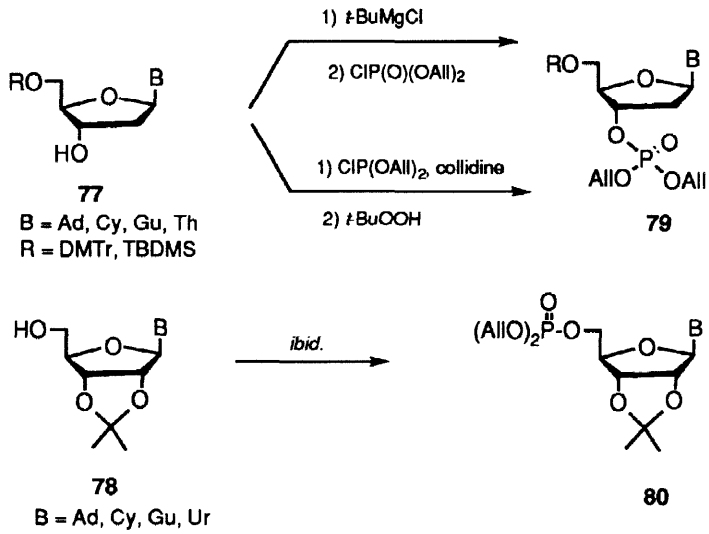
R^1 = DMTr; R^2 = TBDMS

76

Bis(allyloxy)diisopropylaminophosphine, another phosphonylating agent has also been used for the phosphorylation of hydroxyl groups in nucleosides and in aminoacids derivatives (Ser, Tyr, Thr).[127]

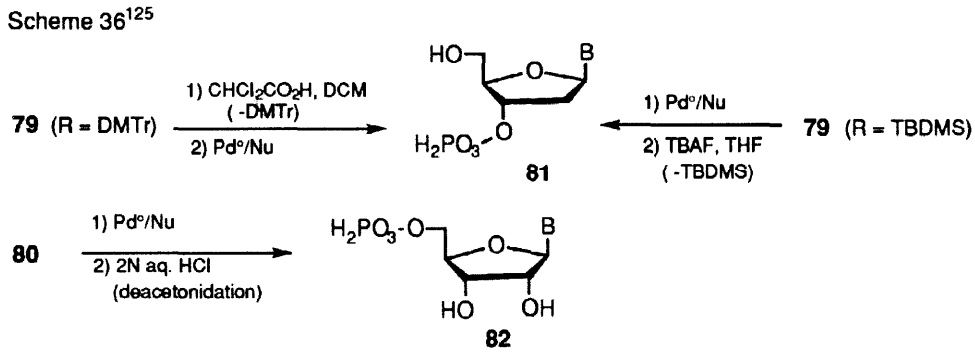
3'-*O* and 5'-*O*-diallylphosphato derivatives of nucleosides, **79** and **80**, have been prepared[125] by reaction of **77** and **78** with di-*O*-allyl phosphochloridate or with di-*O*-allyl phosphochloridite followed by oxidation (scheme 35).

Scheme 35[125]



Removal of the allyl protecting groups ($Pd^0/BuNH_2/HCO_2H$) and of other protection in **79** and **80** leads to free 3'- and 5' monophosphates **81** and **82** which are key intermediates in the synthesis of biologically important nucleoside di- and triphosphates (scheme 36).

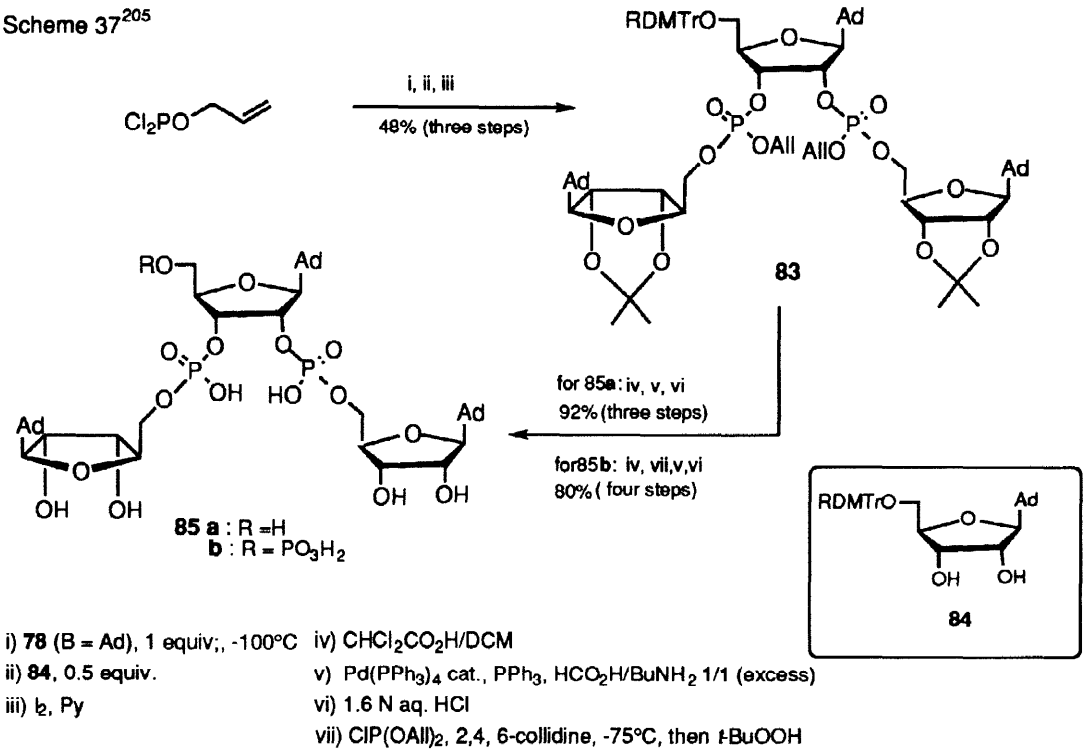
Scheme 36[125]



"Pd^0/Nu = $Pd(PPh_3)_4$ cat., PPh_3, $HCO_2H/BuNH_2$ 1:4 (excess)

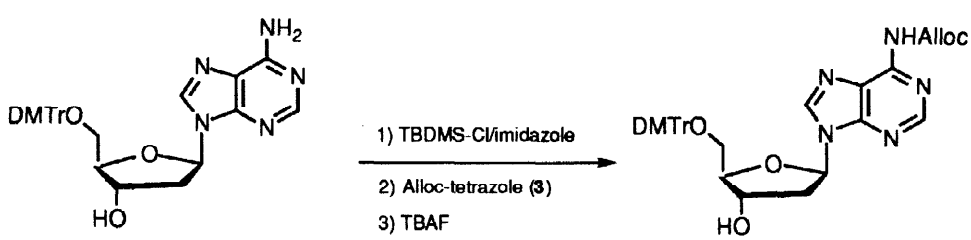
An expeditious way to 2'-5', 3'-5' linked triadenylates **83** has been devised[205] (scheme 37), which involves direct bis-adenylation of the 2' and 3' hydroxyl groups of 5'-*O*-dimethoxytrityladenosine **84** with an *in situ* formed allyl protected adenosine 5'-phosphochloridite (derived from acetonide **78**, B=Ad), followed by oxidation. The allyl protected intermediate **83** is readily convertible to **85a**. Alternatively, selective removal of the dimethoxytrityl group followed by phosphorylation and deallylation leads to the 5'-phosphate **85b**.

Scheme 37[205]



The same authors have also worked out specific conditions for introduction of the Alloc group on nucleobases.[17] These conditions differ depending on the nucleobase structure. The N^6-Alloc-5'-*O*-(*p*, *p'*-dimethoxy)trityl derivative **86** of 2'-deoxyadenosine was obtained (scheme 38) *via* transient *tert*-butyldimethylsilyl protection of the 3' hydroxyl group and allyloxycarbonylation with 1-[(allyloxy)carbonyl]-tetrazole **3** (see section 2).

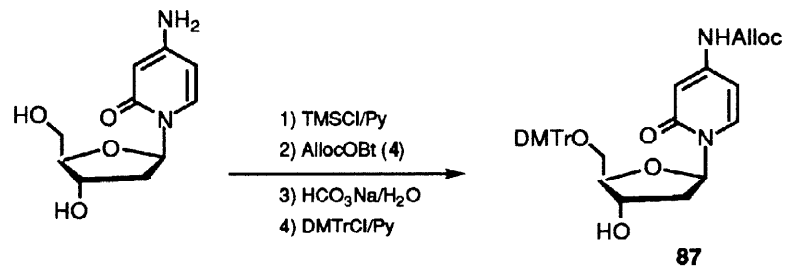
Scheme38[17]



86

To prepare the N^4-Alloc-5'-*O*-(*p*, *p'*-dimethoxy)trityl derivative **87** of 2'-deoxycytidine, 2'-deoxycytidine was first trimethylsilylated on its 3' and 5' hydroxyl groups and subsequently reacted with allyl 1-benzotriazolyl carbonate (AllocOBt) **4** (see section 2). The silyl groups were then removed and the (*p*, *p'*-dimethoxytrityl group introduced (scheme 39).

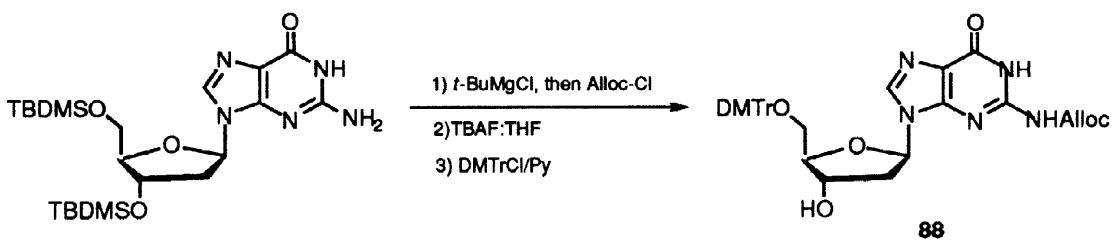
Scheme 39[17]



87

N^2-Alloc-5'-*O*-[(*p*, *p'*-dimethoxy)trityl]-2'deoxyguanosine **88** was prepared by the action of allyl chloroformate on 3',5'-bis(*O*-*tert*-butyldimethylsilyl)-2'-deoxyguanosine (scheme 40).

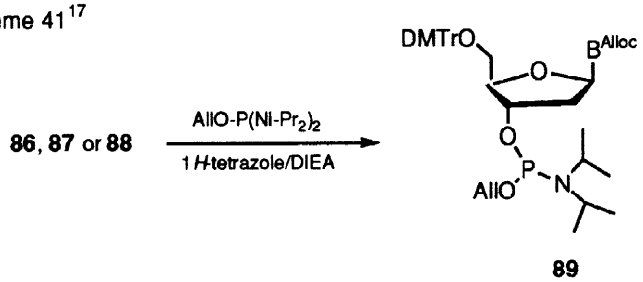
Scheme 40[17]



88

All of the above schemes in the present section show that the Alloc groups on nucleobases and the allyl groups on phosphates are stable to the conditions of *O*-*tert*-butyldimethylsilyl as well as *O*-monomethoxy- or *O*-dimethoxytrityl cleavage. Conversely, they are readily and selectively cleaved by use of palladium π-allyl chemistry.[17,64,125,127,205] Noyori and Hahakawa's work on nucleotide allylic protection culminated in the solid phase synthesis[17] of oligodeoxyribonucleotides (32-, 43- and 60mers) in which the All group was used for permanent protection of phosphate internucleotidic linkages and the Alloc group for permanent protection of the nucleobases adenine, cytosine and guanine; thymine was left unprotected. The oligonucleotidic chains were assembled on controlled pore glass supports, to which they were attached, through a succinato linker and a long-chain alkylamine spacer by the 3'-OH group of a thymidine or a N^6-Alloc-adenosine residue. The 3'-phosphoramidite monomers **89** were synthetised as represented in scheme 41. The 5'-*O*-DMTr groups were cleaved with 3% trichloroacetic acid in DCM and coupling reactions

Scheme 41[17]

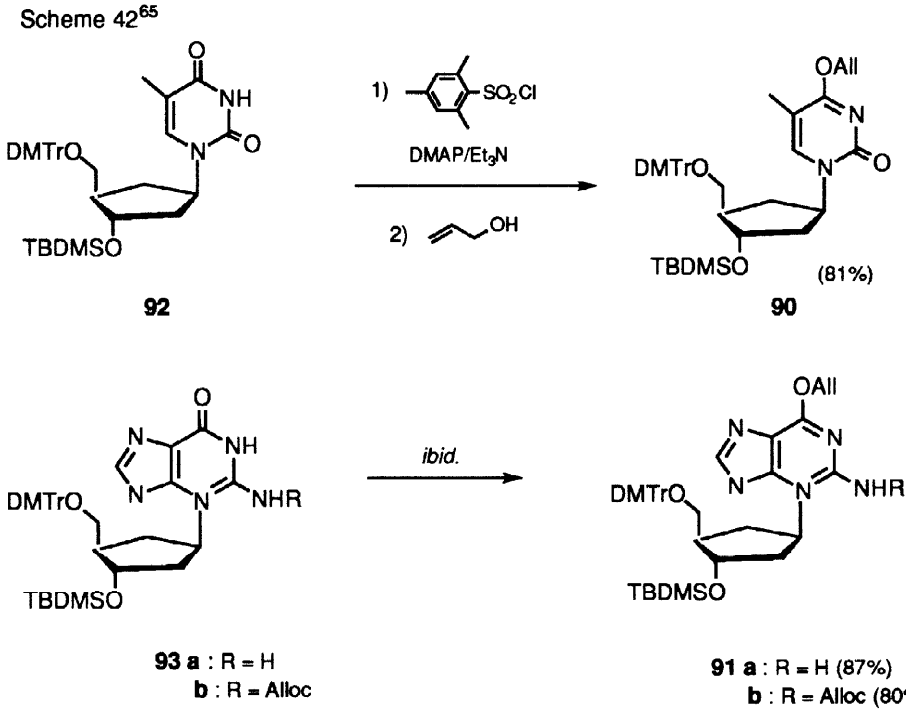


89

were carried out in the presence of (4-nitrophenyl)tetrazole. Each coupling step was followed by oxidation of the newly formed phosphite bridge with *tert*-butyl hydroperoxide. After completion of the sequences, the allylic protecting groups were removed from the nucleotidic chain still attached to the support. In all cases, $Pd_2(dba)_3$-$CHCl_3$ was used as the catalyst (2.5 equiv. per allyl group), in the presence of triphenylphosphine (25 equiv./allyl group) and a large excess of 1:1 butylamine/HCO_2H. The reactions were run in THF at 50°C for 0.5 to 1 h . After allylic group cleavage, the CPG supports were washed with several solvent systems, including an aqueous solution of sodium *N,N*-diethyldithiocarbonate, used as a complexing agent to ensure complete elimination of palladium. For the sake of comparison, the same 32-,43- and 60mers were also synthesised by a conventional method which involved *N*-benzoyl protection for adenosine, *N*-isobutyryl protection for thymine and cytosine while the internucleotidic linkages were protected by the 2-cyanoethyl group. In terms of yields, and of purity as attested by the bio-image chromatograms[17] of the crude synthetic DNAs , impressively better results were obtained by the new allyl strategy. Such success has been attributed[17] to the much milder conditions required for Alloc group removal, as compared to the rather harsh alkaline conditions involved in the elimination of the isobutyryl and benzoyl groups.

More recently, methods have been devised for *O*-allyl protection of thymidine and guanine[65] (scheme 42). The O^4-allyl derivative **90** of thymidine, and the O^6-allylderivative of N^2-unprotected and N^2-Alloc guanosine **91a** and **91b** may be obtained in two steps by reaction of **92**, **93a** or **93b** with mesitylenesulfonyl chloride followed by alcoholysis of the resulting sulfonate with allyl alcohol. Application of the Mitsunobu reaction (allyl alcohol, DEAD, PPh_3) to unprotected thymidine was found to lead not to

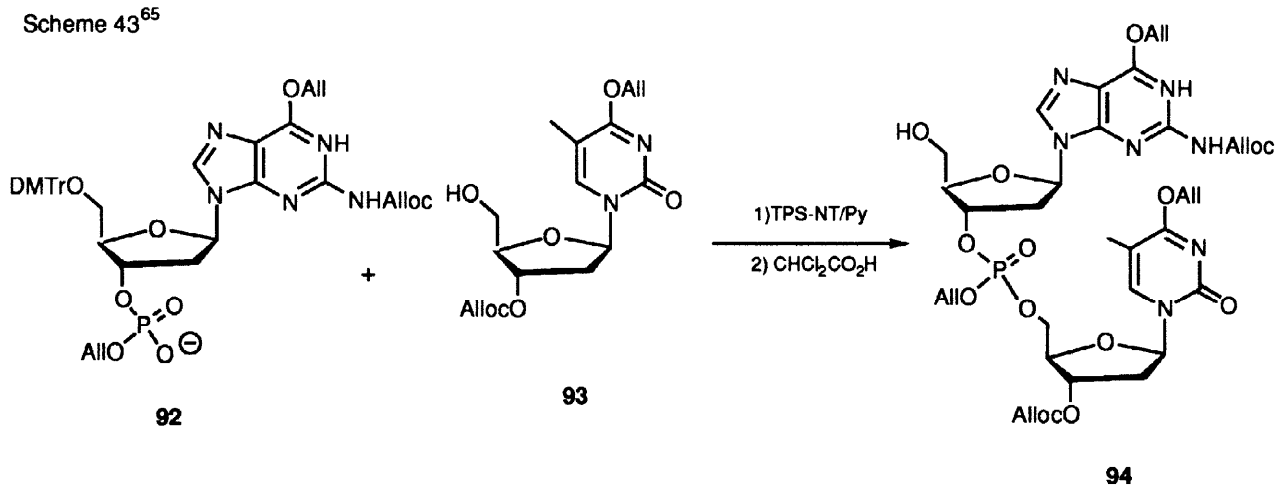
Scheme 42[65]



the O^4-, but to the N^3-allyl derivative.[65] The N^3-allyl derivatives of uridine may also be synthesised by allylation with allyl bromide under phase transfer conditions.[206]

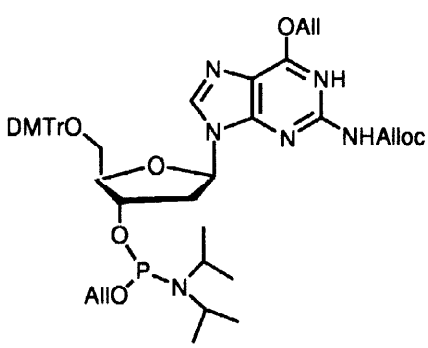
O-allyl protected derivatives **90**, **91a** and **91b** are stable under the conditions of *O*-TBDMS or *O*-DMTr removal at the C-3' or C-5' positions of the sugar. They are very rapidly cleaved through palladium π-allyl methodology ($Pd(PPh_3)_4$ 5 mol%, PPh_3 3 mol%, triethylammonium hydrogenocarbonate in excess). However, the N^3-allyl derivative of thymidine is left unchanged under such conditions. Condensation of the N^2-Alloc-O^6-allyl-deoxyguanosine-3'-phosphodiester **92** with the 5'-*O*-free 3'-*O*-Alloc-O^4-allyl-thymidine derivative **93** using 1-(2,4,6-triisopropylbenzene sulfonyl)-3-nitrotriazole (TPS-NT) in pyridine was found to cleanly afford the dinucleoside phosphate **94** in 69% yield after removal of the dimethoxytrityl group (scheme 43)[65]. No competitive triazolylation at the thyminyl-O^4 or guanyl-O^6 positions

Scheme 43[65]

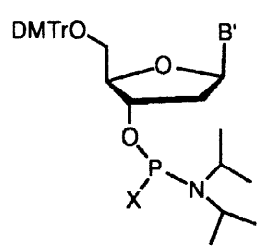


92 **93** **94**

could be detected as is often the case in the absence of O-protection. **94** was also obtained in 95% yield by 1-*H*-tetrazole-assisted coupling of **93** with phosporamidite **95** followed by phosphorus oxidation with *tert*-butylhydroperoxide and detritylation. Cleavage of all allylic groups in **94** with palladium catalyst and diethylammonium hydrogenocarbonate in DCM was achieved in 98% yield.



95



96

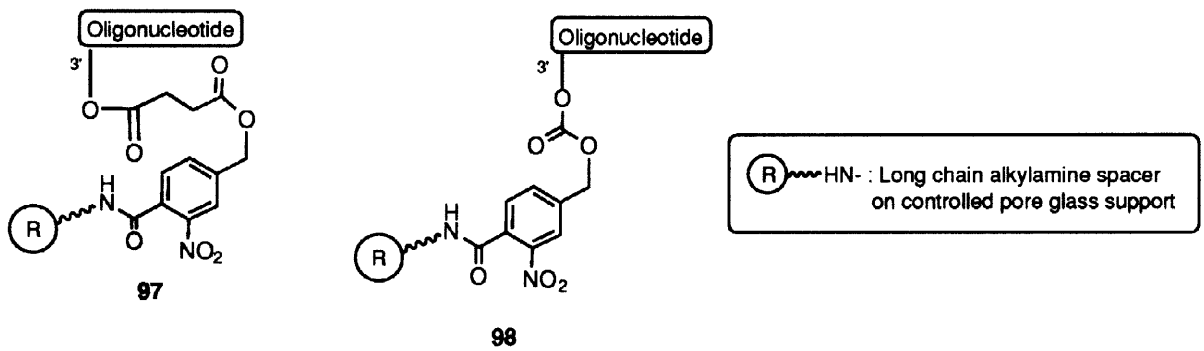
B' = Ad^{Alloc}, Cy^{Alloc}, Th, Gu^{Alloc}, $Gu^{All,Alloc}$

X = OMe, OEt, O*i*-Pr, OPh, CH_3, Ph

Oligodeoxyribonucleotides in which some "natural" internucleotidic phosphodiester linkages have been replaced by nonionic phosphonodiesters or phosphotriester bridges constitute in many respects an interesting and promising class of compounds. Because the basic conditions needed for removal of the usual *N*-acyl (benzoyl, isobutyryl) protectors of adenine, cytosine and guanine are not compatible with such base-

labile nonionic phospholinkages, *N*-Alloc protection of the nucleobases offers a unique opportunity to achieve the synthesis of modified DNAs of this kind. Using phosphoramidites of general structure **96** as building blocks, Noyori, Hayakawa and coworkers have recently been able to synthesise[207] a number of phosphonodiester- or phosphotriester analogues of oligodeoxyribonucleotides, such as d[5'Tp(R)CGAT3'] with R=CH_3, C_6H_5, OCH_3, OC_2H_5 and OC_6H_5 or d[5'GACACp(R)CCAAT3'] with R=C_6H_5, OCH_3, OC_2H_5 and OC_6H_5.

The SPS of oligodeoxyribonucleotide on photolabile linkers **97** or **98** and using All/Alloc protected phosphoramidites **89** as building blocks has been reported by Greenberg and Gilmore[122]. Due to the full

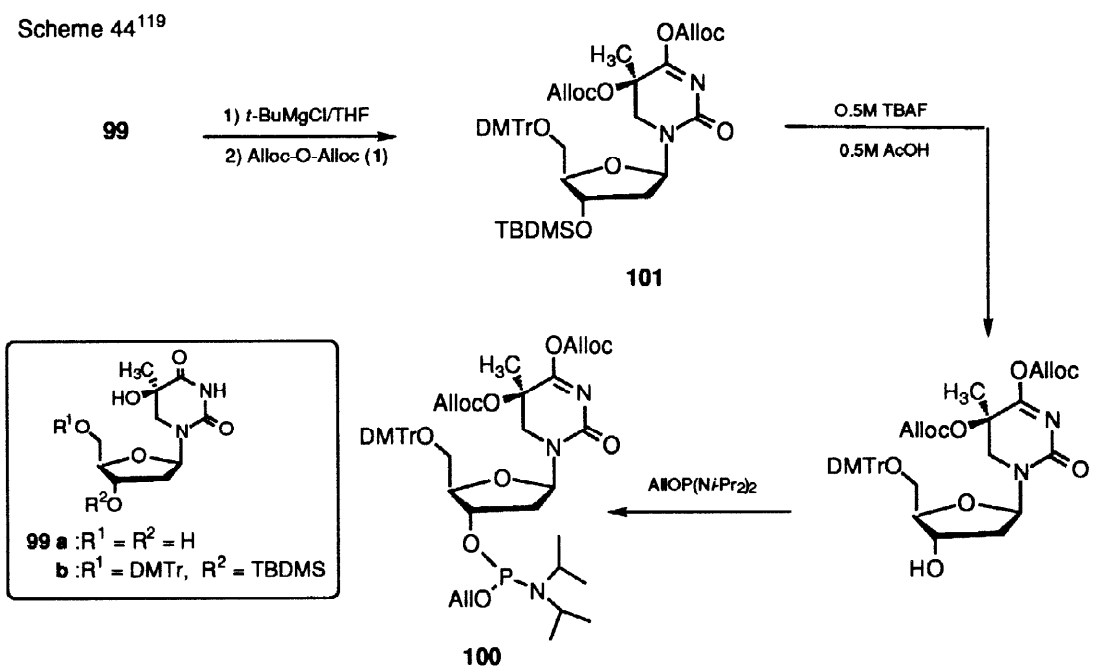


97 **98**

orthogonality of allylic groups and the linkers, it was found that removal of allylic protection could be accomplished equally well either before or after detachment from the resin.

Matray and Greenberg[19] have recently resorted to All/Alloc protection for site-specific incorporation of the base-labile (5*R*)-5,6-dihydro-5-hydroxythymidine **99a** in oligoDNAs. The required protected phosphoramidite building block **100** was prepared as represented in scheme 44: the di-*O*-Alloc derivative **101** was obtained by reaction of diallyl pyrocarbonate **1** (see section 5) with the dianion of **99b**. In order to

Scheme 44[119]

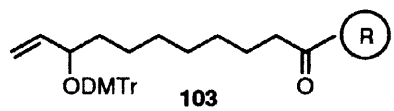


prevent any cleavage of the allyl carbonate function in **101**, subsequent desilylation was carried out with buffered tetrabutylammonium fluoride (TBAF/AcOH 1:1): the desilylated compound was finally condensed with bis(diisopropylamino)-allyloxyphosphine to give **100**. An octamer **102** containing a **100** residue was synthesised using a photolabile linker and Noyori and Hayakawa's All/Alloc protection strategy.

d[5'(CAT A100G CAT GTA GCT GAT3']

102

A secondary allylic linker (9-*O*- (4,4'-dimethoxytrityl)-10-undecenyl **103** for use in DNA and RNA automated synthesis has also been recently proposed.[208]



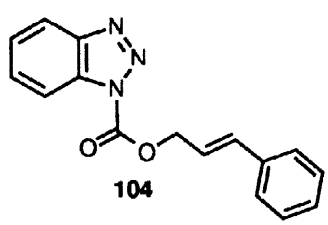
103

7. ALLYLIC FUNCTIONALITY OTHER THAN THE ALLYL AND ALLYLOXYCARBONYL GROUPS.

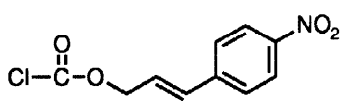
7.1 **The cinnamyloxycarbonyl and other structurally related groups.**

The cinnamyloxycarbonyl group ("Coc" group[35]) has been used, in a way similar to the Alloc group, for protection of amino groups in aminoacids derivatives. It is conveniently introduced by the use of crystalline 1-(cinnamyloxycarbonyl)-benzotriazole **104** (Coc-OBt). Deprotection of cinnamyl carbamates has been performed with Pd°/HCO_2H/pyridine, in the presence of HOBt to avoid side-formation of cinnamylamine.

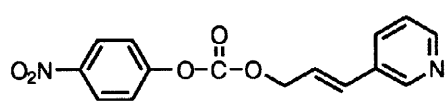
The *p*-nitrocinnamyloxycarbonyl ("Noc") group, proposed by Kunz and März [76], is more stable to acidic conditions than the allyloxycarbonyl and the cinnamyloxycarbonyl group and is conveniently introduced by use of the corresponding chloroformate **105**. Many *N*-Noc derivatives of aminoacids are



104



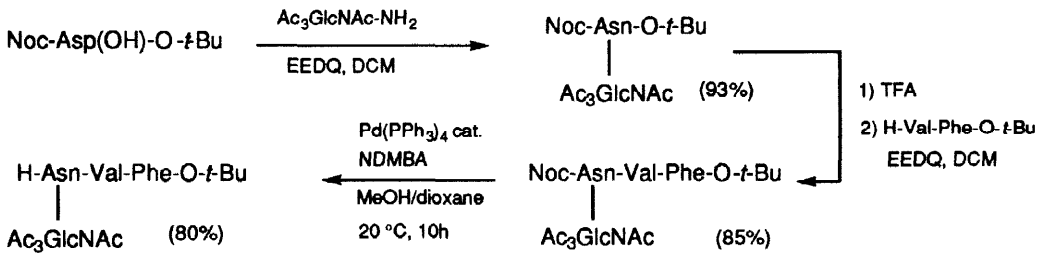
105



106

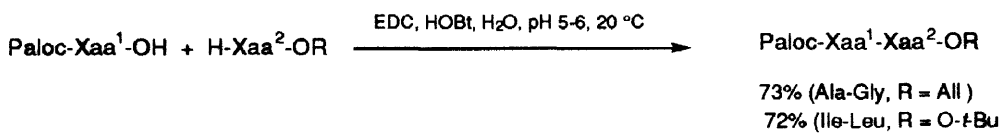
crystalline, and the strong UV absorption of the nitrophenyl ring allows easy monitoring of the deprotection reactions. These deprotections require a longer time than that of the Alloc group, and are best achieved by use of NDMBA as the nucleophilic acceptor. The orthogonality between the *tert*-butyl and the Noc group has been exploited in the synthesis of various oligopeptides and oligoglycopeptides (scheme 45).

Scheme 45[76]



The Paloc group (3-(3-pyridyl)allyloxycarbonyl group) proposed by Kunz and van dem Bruch[68] is introduced by use of its 4-nitrophenyl carbonate derivative **106**. Its hydrophilicity, similar to that of the parent 2-(4-pyridyl)-ethoxycarbonyl (Peoc) group[209] allows peptide bond formation in aqueous medium (scheme 46).

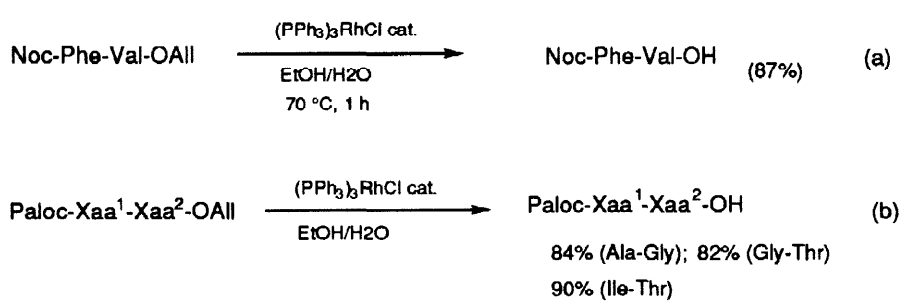
Scheme 46[68]



tert-Butyl esters may be selectively cleaved (HCl/Et_2O/DCM, room temperature) in the presence of Paloc groups. The Paloc group has been removed by palladium catalysed transfer to NMA in THF at room temperature.

For obvious thermodynamic reasons, the Coc, Noc and Paloc groups are stable towards transition metal catalysed migration of the double bond. Selective removal of simple allyl groups in their presence is therefore feasible, as exemplified[76] in scheme 47 (eqs a and b)

Scheme 47[76]



7.2 The γ,γ -dimethylallyl group

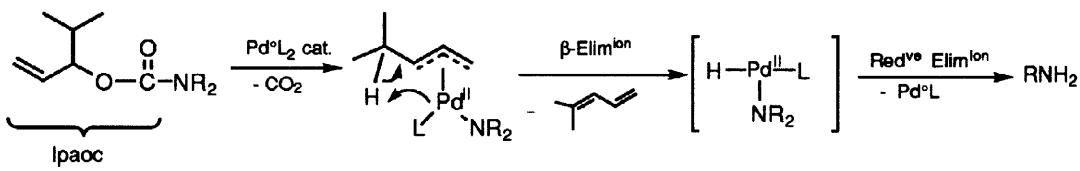
The rate of allylic cleavage of allylic esters by zerovalent palladium complexes is in the order allyl> cinnamyl> γ,γ dimethylallyl. As a result, selective deprotection of allyl carboxylates in the presence of

γ,γ-dimethylallyl carboxylates may be readily achieved. On the other hand, the difference of reactivity between cinnamyl and allyl esters is not sufficiently great to allow satisfactory selectivity in deprotection.[44]

7.3 Allylic groups removable by palladium induced β-elimination

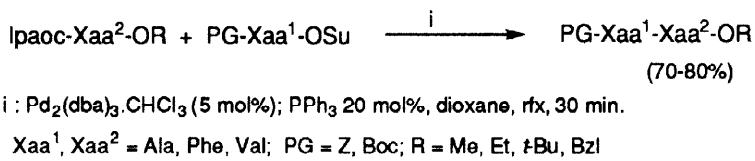
The 1-(isopropyl)-allyloxycarbonyl group (Ipaoc)[210] has been proposed by Tsuji for the protection of amines. Its removal may take place in the presence of palladium catalyst alone (without added nucleophile) through a β-elimination process (scheme 48), but the conditions under which this reaction takes place (100°C, several hours) are rather drastic.

Scheme 48



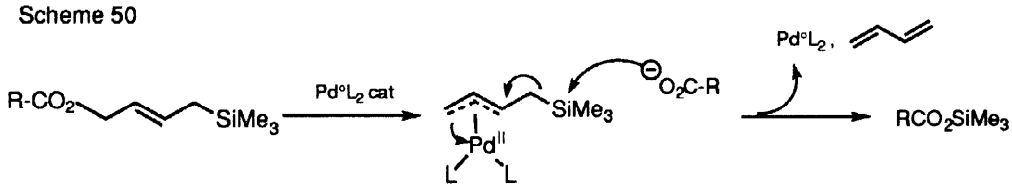
Direct peptide bond formation has been achieved by conducting Ipaoc group removal in the presence of N-hydroxysuccinimide esters of aminoacids (scheme 49).

Scheme 49

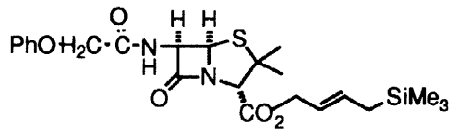


The 4-(trimethylsilyl)-2-buten-1-yl and the 4-(trimethylsilyl)-2-buten-1-oxycarbonyl groups proposed by Mastalerz[211] and which are the vinylogues of the 2-(trimethylsilyl)ethyl and the 2-(trimethylsilyl)ethoxycarbonyl groups[2c] are cleaved under especially mild conditions in the presence of a palladium catalyst alone and at room temperature. According to this ingenious procedure, the expelled carboxylato species participates in its own deprotection by ensuring regeneration of the catalyst through desilylation of the intermediate π-allyl complex to butadiene and palladium(0) (scheme 50). This method has

Scheme 50



been successfully applied to very sensitive substrates such as the allylic ester of penicillin V **107**.



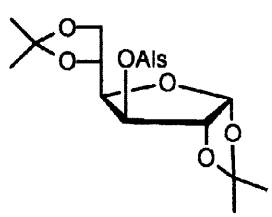
107

4-(Trimethylsilyl)-2-buten-1-yl carbamates (prepared from isocyanates by reaction with 4-(trimethylsilyl)-2-buten-1-ol) are deprotected in the same manner. Unfortunately, no method has been proposed for the direct introduction of the 4-(trimethylsilyl)-2-but-1-enoxycarbonyl group on amines.

4-(trimethylsilyl)-2-but-1-enyl carboxylic esters are stable under the acidic conditions used for cleavage of *O*-TBDMS ethers (1N aq. HCl/MeOH 1/5, 5°C)

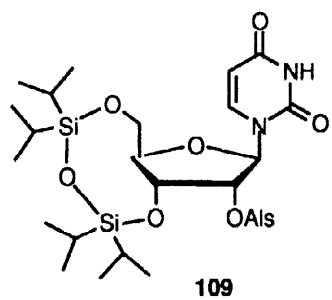
7.4 The allylsulfonyl (Als) group

As already pointed out, allyl ethers are, in general, not amenable to deprotection through catalytic π-allyl palladium methodology. Allylcarbonates are readily cleaved by palladium, but use of the Alloc group in the protection of polyols in general and carbohydrates in particular is seriously limited, owing to the risk of transacylation reactions and side formation of cyclic carbonates.[212] In an effort to circumvent these problems, Kunz and Brill have devised the allylsulfonyl (Als) group.[213] The Als group is introduced by reacting alcohols with allylsulfonyl chloride in the presence of a tertiary amine (pyridine, 2,6-lutidine, collidine) at low temperature (*ca* -30 °C). Compounds **108-110** represent some examples of Als derivatives prepared in this way. The Als groups in **108-110** were found to withstand the conditions required for deacylation, desacetalization and desilylation. No Als migration was observed during such processes.

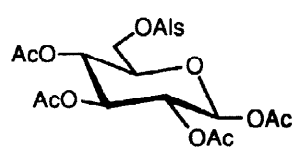


108

Als = 



109

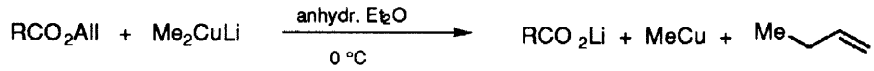


110

The Als group may be removed for instance by the palladium/morpholine system. A serious drawback of the procedure however is that it must be conducted in the presence of aqueous formaldehyde, in order to prevent poisoning of the catalyst by the sulfur dioxide liberated in the process.

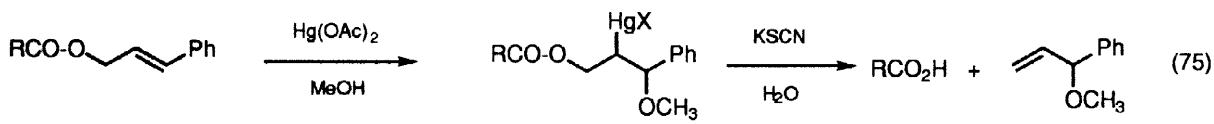
8. MISCELLANEOUS

Allyl esters can be deprotected by reaction with lithium dimethyl cuprate[214] (eq. 74). Cinnamyl esters are cleaved by successive methoxymercuration and demercuriocarboxylation (eq. 75).[216] The presence of the



(74)

phenyl group in the cinnamyl moiety is necessary to ensure the proper regiochemistry of the methoxymercuration step.



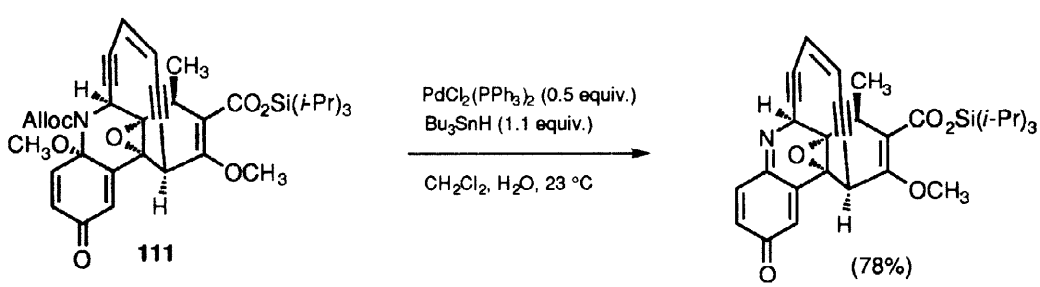
(75)

Allyl carbonates and carbamates are cleaved by reaction with excess nickel tetracarbonyl in DMF and in the presence of *N,N'*-tetramethylenediamine.[216] 2-methylallyl esters are cleaved in refluxing 90% formic acid.[217]

Notes added in proof

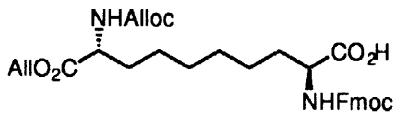
The deprotection of allyl 2,6-dichloro- or 2,6-diaryloxy-substituted phenoxides has been successfully achieved by use of a palladium/morpholine system.[218] To the best of our knowledge, this constitutes, together with the case of the deprotection of compound **19** with dimedone,[99] the only example of the deprotection of allyl aryl ethers with an allyl group scavenger other than a hydride donor. The palladium catalysed hydrostannolytic procedure has been successfully applied[219] to the removal of the Alloc group in compound **111** which contains a strained ene-diyne core and a partially protected quinoneimine functionality (scheme 50).

Scheme 50[219]

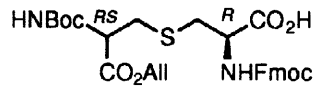


New examples of the use of semi-permanent allylic protecting groups in the synthesis of cyclopeptides[220,221] or a pseudo-cyclopeptide[222] may be found in the recent literature. A semi-permanent allylic protecting group strategy has also recently been involved[223] in a procedure for the reversal of peptide orientation[224] on a solid support. An asymmetric synthesis of an Fmoc/All orthogonally protected derivative of (*2S,9R*)-2,9-diaminodecanedioic **112**, for further use in the synthesis of conformationally constrained peptides, has been described.[225] The obtention of a Fmoc/Boc/All orthogonally protected derivative of

lanthionine **113**, as a mixture of separable *RS* and *RR* diastereoisomers, has similarly been reported.[226] A solution phase synthesis in aqueous medium of di, tri- and tetrapeptides based on temporary Alloc protection has been reported by Genêt and coworkers.[227]



112



113

IN SPPS, it has been shown that tandem deprotection-coupling (see sections 4.6.b,c,d) of N^{α}-Alloc-protected dipeptide resins with N^{α}-Fmoc-aminoacyl fluorides in the presence of palladium catalyst and of phenylsilane as the allyl group scavenger allows the suppression of diketopiperazine formation in cases when this reaction is troublesome. Thus, the tripeptide resin Fmoc-Leu-D-Val-Pro-AB-Ile-MBHA could be obtained from the corresponding Alloc-D-Val-Pro resin and Fmoc-Leu-F without any DKP formation.[228] A full report[229] on the use of the Hycron allylic linker in glycopeptide synthesis has recently been issued, in which the preparation of the anchor conjugate of the starting Z-, Boc-, and Fmoc-N^{α}-protected aminoacids is described. This study also confirms the tendency towards DKP formation (see section 4.2) exhibited by allylic linkers, especially with the temporary Fmoc-strategy. In a recent communication, Habermann, Kunz and Seitz[230] report that the DKP problem is efficiently circumvented by using N^{α}-Boc protection for the second aminoacid. After trifluoroacetolysis, coupling of the third aminoacid is directly carried out, without a prior neutralisation step, using newly introduced pentafluorophenyluronium coupling reagents in the presence of DIEA/collidine.

Finally, mention should be made that diallyl dicarbonate has been successfully used for the enantioselective enzymatic protection of amines and gives much better results than its dimethyl or diethyl analogues.[231]

List of abbreviations: Abu(P): L-2-amino-4-phosphonobutanoic acid; All: allyl; Alloc: allyloxycarbonyl; dba: dibenzylidene-acetone; Boc: *tert*-butyloxycarbonyl; Boc-ON: 2-(*tert*-butyloxycarbonyloxyimino)-2-phenylacetonitrile; BOP: Benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate; 2-BrZ: 2-bromobenzyloxycarbonyl; BSA: bis(trimethylsilyl)acetamide; *t*-Bu: *tert*-butyl; Bum: *tert*-butyloxymethyl; Bzl: benzyl; Cbz (or Z): benzyloxycarbonyl; ClZ or 2-ClZ: 2-chlorobenzyloxycarbonyl; Coc: cinnamyloxycarbonyl; DCC: dicyclohexylcarbodiimide; DCM: dichloromethane; Dde: 1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)ethyl; Ddm: 4,4'-dimethoxybenzhydryl; DEIPS: diethylisopropylsilyl; DIC: diisopropylcardodiimide; DIEA: Diisopropylethylamine; DMAP: 4-dimethylaminopyridine; dppb: bis(diphenylphosphino)butane; DNA: desoxyribonucleic acid; DSC: disuccinimidyl carbonate; EDC: 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide; EEDQ: *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline; Fm: 9-fluorenylmethyl; Fmoc: 9-fluorenylmethoxycarbonyl; Fuc: fucosyl; Gal: galactosyl; Glc: glucosyl; <Glu: pyroglutamyl; HOBt: 1-hydroxybenzotrazole; HYCRAM^{TM}: hydroxycrotonylaminomethyl resin; Ipaoc: 1-(isopropyl)-allyloxycarbonyl; IPCC: isopropenylchlorocarbonate; IRAA: internal reference aminoacid; LHRH: luteinizing hormone-releasing hormone; Man: mannosyl; MAP: multiantigen peptide resin; MBHA: *p*-methylbenzhydrylamine; Mtr: 4-methoxy-2,3,6-trimethylbenzenesulfonyl; NBS: *N*-bromosuccinimide;

NDMBA: N,N'-dimethylbarbituric acid; NMA: *N*-methylaniline; NMM: *N*-methylmorpholine; MSNT: 1-mesitylenesulfonyl-3-nitro-1,2,4-triazole; OSu: *N*-oxysuccinimido; PAC: *p*-alkoxybenzylalcohol (resin); PAL: peptide amide linker (5-(4-aminomethyl-3,5-dimethoxyphenoxy)valeric acid); Paloc: 3-(3-pyridyl)allyloxycarbonyl; PEG: polyethyleneglycol; Peoc: 2-(4-pyridyl)-ethoxycarbonyl Pfp: pentafluorophenyl; PG: protecting group; Pmc: 2,2,5,7,8-pentamethylchroman-6-sulfonyl; PS: polystyrene; PyBop: benzotriazol-1-yloxy-tris-pyrrolidino-phosphonium hexafluorophosphate; RAFT: regioselectively adressable functionalized template; SASRIN^{TM}: super acid-sensitive resin (2-methoxy-4-alkoxybenzyl alcohol resin); SPPS: solid-phase peptide synthesis; SPS: solid-phase synthesis; TASP: template assembled synthetic protein; TBAF: tetrabutylammonium fluoride; TBDMS: t*ert*-butyldimethylsilyl; TBTU: 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate; TFA: trifluoroacetic acid; TIPS: triisopropylsilyl; TPPS: 3,3',3"-phosphinetriylbenzene-sulfonate; TPS-NT: 1-(2,4,6-triisopropylbenzene sulfonyl)-3-nitrothiazole; Tre: trichloroethyl; Treoc: trichloroethoxycarbonyl; Trt: triphenylmethyl (trityl); Ts: tosyl; UNCA: urethane-*N*-carboxyanhydride; Z (or Cbz): benzyloxycarbonyl.

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Footnotes and references

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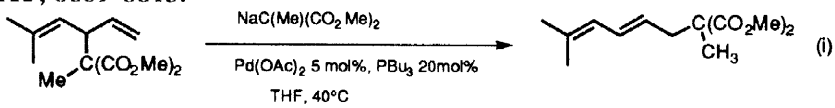

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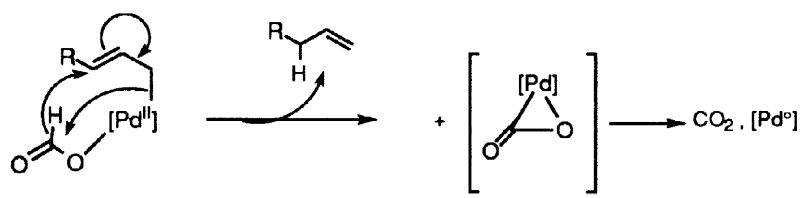

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Biographical sketch

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.