N,N-DIPROTECTED DEHYDROAMINO ACID DERIVATIVES: VERSATILE SUBSTRATES FOR THE SYNTHESIS OF NOVEL AMINO ACIDS

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Abstract. *Non-proteinogenic amino acids are an important class of organic compounds that can have intrinsic biological activity or can be found in peptides with antiviral, antitumor, anti-inflammatory or immunosuppressive activities. This type of compounds is also important in drug development, in the elucidation of biochemical pathways and in conformational studies. Therefore, research towards efficient methods that allow the synthesis of these compounds constitutes an important area of peptide chemistry. In our laboratories we have developed a new and high yielding method for the synthesis of N,N-diprotected dehydroamino acid derivatives using tert-butyl pyrocarbonate and 4-dimethylaminopyridine. These compounds were used as substrates in several types of reactions, allowing the synthesis of a variety of new amino acid derivatives. Some of these new compounds are heterocyclic systems or contain heterocyclic moieties such as pyrazole, indole, or imidazole. Thus, several nitrogen heterocycles were reacted with N,N-diprotected dehydroalanine to give new β-substituted alanines and dehydroalanines. Furanic amino acids were obtained treating the methyl ester of N-(4-toluenesulfonyl), N-(tert-butoxycarbonyl) dehydroalanine with carbon nucleophiles of the β-dicarbonyl type having at least one methyl group attached to one of the carbonyl groups. Treatment of these furanic amino acids with trifluoracetic acid afforded pyrrole derivatives in good to high yields. A N,N-diprotected 1,4-dihydropyrazine was obtained reacting the methyl ester of N-(4-toluenesulfonyl), N-(tert-butoxycarbonyl)dehydroalanine with 4-dimethylaminopyridine and an excess of potassium carbonate. Tetrahydropyrazines were synthesized by reaction of this 1,4-dihydropyrazine derivative with nucleophiles or by electrochemical reduction. Cleavage of the N-protecting groups from the 1,4-dihydropyrazine gave a disubstituted pyrazine. This review covers the synthesis of N,N-diprotected dehydroamino acids and their application as precursors for the synthesis of new compounds.*

Contents

1. Introduction

Non-proteinogenic amino acids can be found in biologically active peptides of several sources such as marine sponges and tunicates, fungi, bacteria and lower animal forms. The biological activities of these compounds include antimicrobial, antiviral, insecticidal, antitumor, anti-inflammatory or immunosuppressive actions. These types of compounds are also used as drugs or as lead compounds in drug discovery and are useful in the elucidation of biochemical pathways. Non-proteinogenic amino acids when inserted into peptides affect their conformations and biological activities. These include, among others, β-amino acids, α,α-disubstituted amino acids, α,β-dehydroamino acids and β-substituted amino acids. Several approaches are available for the synthesis of these compounds namely, amination of α-halo-acids, Strecker synthesis, multicomponent Ugi or Petasis reactions and addition reactions to dehydroamino acids.

Dehydroamino acids can be found in several yeasts and bacteria, in which they contribute with a catalytic role in the active sites of some enzymes, as well as in a variety of peptide antibiotics of bacterial origin that include the lantibiotics (nisin, epidermin, subtilin, gallidermin).[1] Since they affect both chemical reactivity and conformation, dehydroamino acids have been introduced into peptides for structure-function relationship studies and have also been used as linkers in solid phase peptide synthesis.[2] Another important application for dehydroamino acid derivatives is their use as substrates for the synthesis of new amino acids.[3] Owing to the wide variety of biological activities and uses found among the known compounds and also to the economical importance of many of them, α,β-dehydroamino acids are promising synthons for exploration of new compounds with new biological properties and applications. A key step to progress in this area is the production of α,β-dehydroamino acid derivatives suitable for incorporation into peptide sequences or, otherwise, a method for dehydration of appropriate peptidic precursors.

β-Substituted, α,α-disubstituted amino acids and α-aminoglycines can have biological activity, can be used in the synthesis of peptides more stable towards proteolytic degradation and also for introducing chemical diversity into bioactive peptides. Thus, several β-substituted alanines exhibit important biological activities: β-(pyrazol-1-yl)alanine has hypoglycaemic properties;[3] quisqualic acid possesses neuroexcitatory activity;[4] *S*-substituted cysteines have cytotoxic activity.[5] The β,β-dimethoxyalanine derivatives have been used in a variety of synthetic transformations namely, the synthesis of ifetroban, a cardiovascular drug and of several capreomycins and tuberactinomycins.[6] Pyrazines can be obtained from dehydroamino acids and are found in the luminescent chromophores of certain marine organisms, in cephalostatins which are powerful anticancer agents, and in foods as potent flavour components.[7] Pyrazinamide is one of the front agents against *M. Tuberculosis*.[8] 1,4-Dihydropyrazines are found in certain redox active biological molecules like flavin coenzymes and in certain marine luciferins.[9] These compounds are also interesting electron-donors in conducting charge transfer complexes. Certain dihydropyrazines such as 2,3-dihydro-5,6-dimethylpyrazine show DNA strand-breaking activity in plasmid[10] and tetrahydropyrazines have been used in the synthesis of a HIV protease inhibitor.[11] α-Aminoglycines are used in the synthesis of retro-inverso-peptides more stable towards proteolytic degradation.[12]

2. Synthesis of α,β-dehydroamino acid derivatives

2.1. Introduction

The main biosynthetic route to α,β-dehydroamino acid derivatives has been described as β-elimination reactions from precursors containing serine, cystein and threonine residues to give the corresponding dehydroalanine (ΔAla) and dehydroaminobutyric acid (ΔAbu) derivatives.[2a] Other possible biosynthetic routes to dehydroamino acid derivatives are the dehydration of *N*-hydroxyamino acids obtained by *N*-hydroxylation of amino acids or peptides and of α-hydroxyamino acids obtained by condensation of α-keto acids and amides or by direct oxidation of amino acids.[2a]

The chemical synthesis of α,β-dehydroamino acids and their derivatives has been attempted through several methods. Those that follow the biosynthetic routes involving elimination reactions of β-hydroxyamino acids, β-mercaptoamino acids and *N*-hydroxyamino acids are the most important. However, other methods can be used, namely, condensation reactions of α-ketoacids with amides or nitriles,[13] Hofmann degradation of α,β-diaminopropionyl residues,[14] reduction of α-azidoacrilates and α-azidocarboxilates[2c] and hydrolysis of unsaturated oxazolinones.[15]

2.2. Elimination reactions

Elimination reactions using β-substituted or α-amine substituted amino acids as starting materials have been the most widely used approach to the chemical synthesis of dehydroamino acid derivatives. For the synthesis of dehydroalanines and dehydroaminobutyric acids, serine and threonine have been the main substrates and several reactants have been used to promote elimination reactions. Thus, triphenylphosphine with diethylazodicarboxylate were used to dehydrate the methyl esters of *N*-acylserine and threonine, however, the yields were moderate (55%-69%) and led to a 1:1 mixture of *Z* and *E*-isomers in the case of the dehydroaminobutyric acid derivatives.[16] Higher yields could be obtained when the methyl esters of *N*-benzyloxycarbonylserine and threonine were treated with disuccinimido carbonate and triethylamine in acetonitrile.[17] The yields in dehydroalanine and dehydroaminobutyric acid derivatives were 90% and 70%, respectively, and in the case of the latter, the reaction was stereoselective towards the *Z*-isomer. Reaction of *N*-benzyloxycarbonylserine and threonine esters with diethyl chlorophosphate in the presence of sodium hydride in THF gave the corresponding *N*-benzyloxycarbonyldehydroamino acid esters in good yields.[18] This method is also stereoselective towards the *Z*-isomer of the dehydroaminobutyric derivative. Goodall and Parson used several haloacetyl chlorides and triethylamine to react with serine and threonine derivatives giving dehydroamino acids in yields from 39% to 89%, however the reaction was not stereoselective with the threonine derivatives.[19]

Dehydroalanine derivatives have also been obtained from cysteine. *N*-Acylcysteine derivatives suffer β-elimination reactions when treated with silver oxide (I), silver carbonate (I), mercury oxide (I) and ferric salts.[2a] Synthesis of *N*-(4-chlorobenzyloxycarbonyl) dehydroalanine has also been carried out by treatment of *N*-(4-chlorobenzyloxycarbonyl) cysteine with DCC.[20]

The elimination of *O*-arylsulfonate derivatives of β-hydroxyamino acids in the presence of a base has been used for the preparation of dehydroamino acids and dehydropeptides.[2a] Several side reactions occur, namely, formation of oxazolinones, aziridines and hydantoines, thus reducing the yield in the wanted products.

β-Halogenated amino acid derivatives have been used as precursors of dehydroamino acids, however in most cases the elimination reactions occur in drastic conditions.[2a]

Selective synthesis of *Z* and *E*-dehydroaminobutyric acid from L- and L-*allo*-threonine, respectively was carried out *via* the formation of a selenoether followed by oxidative elimination by treatment with hydrogen peroxide.[21]

N-Substituted amino acids can also suffer elimination to yield dehydroamino acid derivatives. Thus, *N*-chloroamino acids obtained by treatment of *C*-protected amino acids with *tert*-butylhypochlorite, eliminate hydrogen chloride in the presence of base giving rise to the corresponding enamine.[2c]

Treating *N*-hydroxyamino acids with triethylamine in dry benzene at room temperature for 24 hours gave dehydroamino acid derivatives.[22] The replacement of triethylamine for DBU significantly reduces the reaction time to approximately 1 hour.[23] Alkyl esters of *N*-acyl, *N*-hydroxyamino acids and *N*-acyl, *O*-acylhydroxyamino acids by treatment with triethylamine eliminate water and acid, respectively giving dehydroamino acids.[2c] Alkyl esteres of *N*-acyl, *N*-hydroxyamino acids can also be converted to dehydroamino acids by treatment with 4-toluenesulfonyl chloride and triethylamine.

Some of the above methods are usually low yielding, multistep processes requiring tedious purifications to remove side products. In the case of dehydroaminobutyric acid derivatives the work-up procedures can be complicated by the formation of two stereoisomers. Thus, there is still a need for developing simple and efficient approaches to these compounds.

2.3. Synthesis of *N,N*-diprotected dehydroamino acids

Our initial strategy for the synthesis of α,β-dehydroamino acids was based on Berkowitz and Pederson's method for simultaneous amine and carboxyl protection of amino acids with benzyl chloroformate in the presence of 4-dimethylaminopyridine (DMAP) and triethylamine.[24] We found that under these conditions, serine undergoes elimination; the only product isolated being the corresponding fully protected dehydroalanine derivative (Z-ΔAla-OBzl, Table 1, **10**) in a yield of 51%.[25] Applying the same procedure to several amino acids protected either at their *N*-terminus with *tert*-butoxycarbonyl (Boc), benzyloxycarbonyl (Z), 4-nitrobenzyloxycarbonyl [Z(NO_2)] and 4-toluenesulfonyl (Tos) (Table 1, **2**-**5**) or at both the *N*- and the *C*-terminus (Table 1, **6**), the yields in dehydroamino acid derivatives were within the range of 56-76% (Table 1, **11**-**13**).

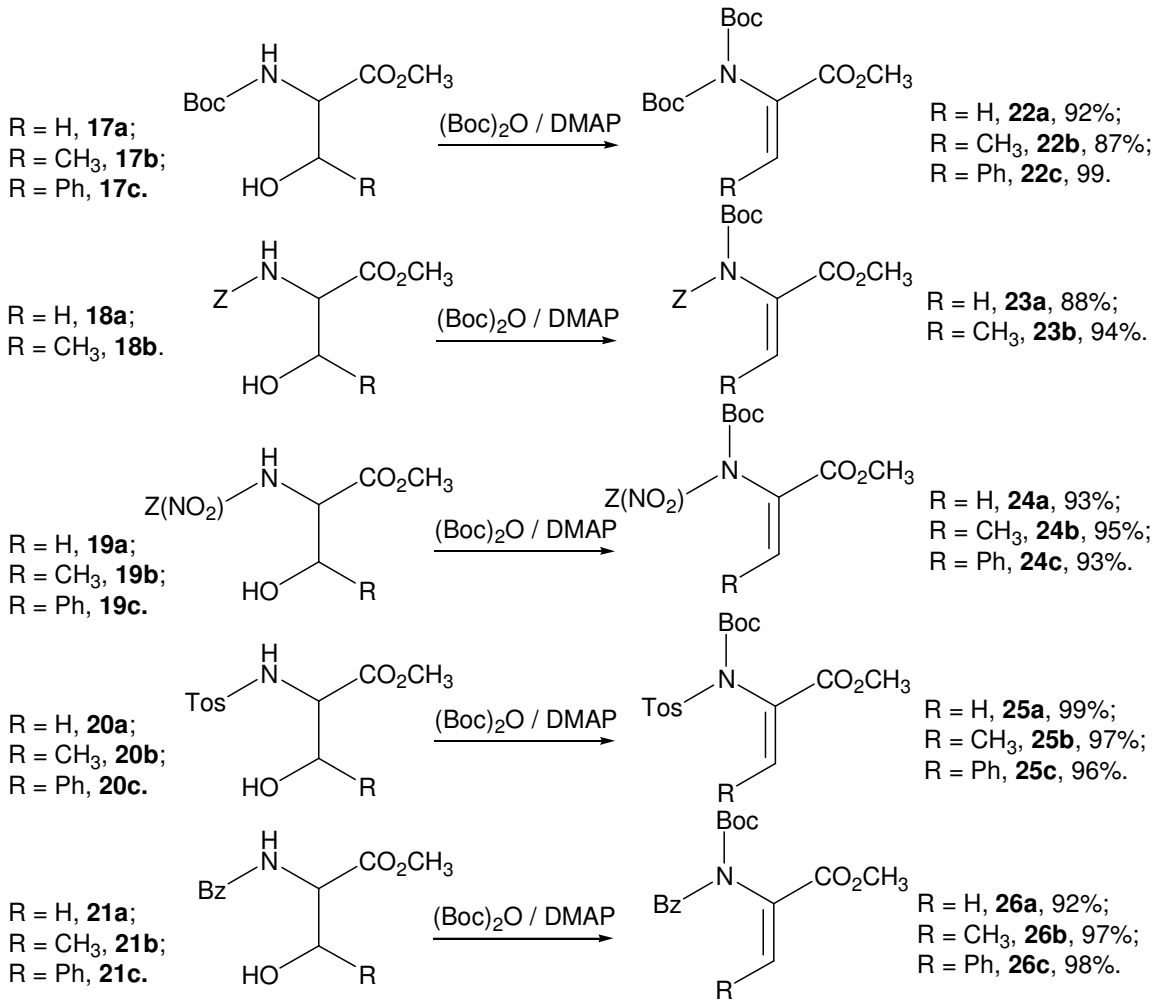
Table 1. Results obtained in the synthesis of dehydroalanine derivatives.[25]

Reagent	**Product**	**Yield / %**
H-Ser-OH, **1**	Z-ΔAla-OBzl, **10**	51
Boc-Ser-OH, **2**	Boc-ΔAla-OBzl, **11**	58
Z-Ser-OH, **3**	Z-ΔAla-OBzl, **10**	56
Z(NO_2)-Ser-OH, **4**	Z(NO_2)-ΔAla-OBzl, **12**	74
Tos-Ser-OH, **5**	Tos-ΔAla-OBzl, **13**	76
Tos-Ser-OBzl, **6**	Tos-ΔAla-OBzl, **13**	68
Z-Gly-Ser-OMe, **7**	Z-Gly-ΔAla-OMe, **14**	54
Z-Ala-Ser-OMe, **8**	Z-Ala-ΔAla-OMe, **15**	61
Z-Phe-Ser-OMe, **9**	Z-Phe-ΔAla-OMe, **16**	57

The method could also be applied to the dehydration of serine containing dipeptides (Table 1, **7**-**9**). With a threonine derivative, although all the starting material was consumed, we failed to obtain any pure product and NMR spectroscopy of the reaction mixture was consistent with the presence of two isomers of dehydroaminobutyric acid.

Nugent has patented a method for dehydration of *N*-acyl, β-hydroxyamino acid esters by treatment with an excess of acetic anhydride in the presence of pyridine.[26] In this reaction an acetyl group was introduced at the amide function to give the *N*-acetyl, *N*-acyldehydroamino acid esters. The second acyl group bonded to the nitrogen atom helps formation of the new double bond and the reported yields were approximately 60%. However, the product thus obtained is of limited value, once the acetyl group cannot be easily removed.[2b]

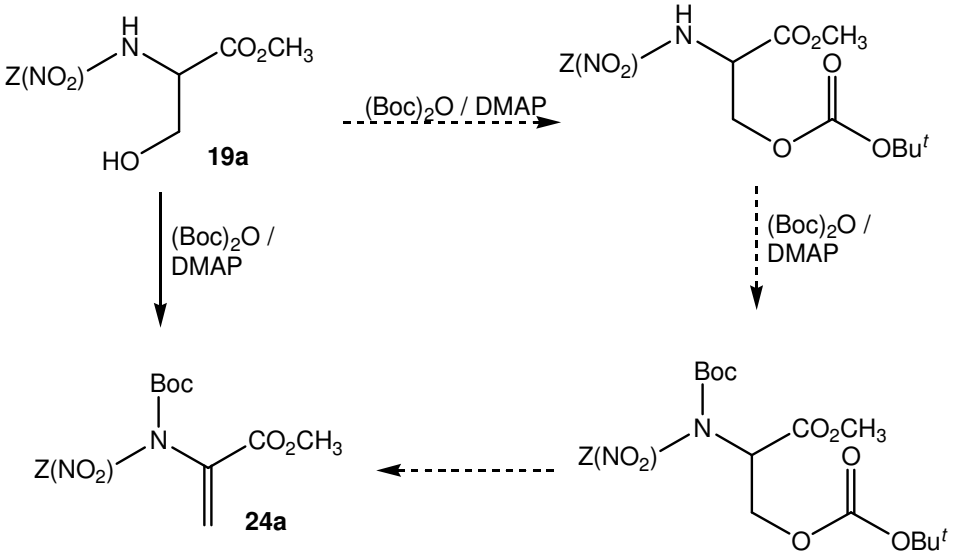
In view of these results, we considered introducing a more bulky second group at the nitrogen atom of the *N,C*-diprotected β-hydroxyamino acids in order to facilitate β-elimination and thus improve the reaction yields. The *tert*-butoxycarbonyl group is easily introduced by reaction of the previously *N*-protected amino acid with *tert*-butyl pyrocarbonate [$(Boc)_2O$] in the presence of DMAP as catalyst, according to Ragnarsson's method for *tert*-butoxylation of amides.[27] The reaction of β-hydroxyamino acids with *tert*-butyl pyrocarbonate in the presence of DMAP resembles significantly the method we had taken advantage of previously to prepare Z-ΔAla-OBzl (**10**).



Scheme 1

The use of two equivalents of $(Boc)_2O$ would thus suit both tasks, *i.e.* further acylation and dehydration. Thus serine, threonine or β-hydroxyphenylalanine methyl esters protected with one of the following groups: *tert*-butoxycarbonyl (Scheme 1, **17a**-**c**), benzyloxycarbonyl (Scheme 1, **18a**, **b**), 4-nitrobenzyloxycarbonyl (Scheme 1, **19a**-**c**), 4-toluenesulfonyl (Scheme 1, **20a**-**c**) and benzoyl (Scheme 1, **21a**-**c**) were reacted in dry acetonitrile with *tert*-butyl pyrocarbonate in the presence of DMAP as catalyst. In these conditions the only products isolated were the corresponding ΔAla [Scheme 1, **(22**-**26)a**], ΔAbu [Scheme 1, **(22**-**26)b**] or dehydrophenylalanine (ΔPhe) [Scheme 1, **22c**, **(24**-**26)c**] derivatives.[28]

The increased bulkiness created at the nitrogen atom assisted elimination during the dehydration step, giving as the only product isolated the corresponding dehydrated diacylamino acid ester in almost quantitative yields. By sampling the reaction mixture throughout the preparation of compound $Z(NO_2)$-ΔAla(*N*-Boc)-OMe (**24a**), it was found that the reaction proceeds with formation of a *tert*-butylcarbonate, which undergoes *β*-elimination to the final product after a *tert*-butoxycarbonyl group is bound to the amine function (Scheme 2).



Scheme 2

In an attempt to use a *N*-trityl serine derivative (Trt-Ser-OMe) as substrate for β-elimination, the only product obtained was Trt-Ser(*O*-Boc)-OMe. In this case, the steric hindrance of the trityl group prevented further reaction at the nitrogen atom. The absence of dehydration suggests that a second acyl group is essential as a driving force for elimination.

With both threonine and β-hydroxyphenylalanine derivatives (threo type) the reaction was stereoselective, giving only the *Z*-isomer. This selectivity seems again to result from the bulkiness of the groups bound to the nitrogen atom, which would force and thus facilitate a *trans* E_2-elimination. This is in agreement with results obtained by Srinivasan *et al.* who have reported that base induced *β*-elimination of *N*-acyl-DL-Thr(*O*-Tos)-OMe (threo type) proceeds *via* a *trans* E_2-elimination to give the *Z*-isomer.[29]

DMAP catalysed esterifications with dicarbonates have been described by Takeda *et al.*.[30] With the aim of simplifying our procedure by saving one of the two otherwise required protection steps, *N*-Boc serine and threonine derivatives having a free carboxyl function were reacted with 3 eq. of *tert*-butyl pyrocarbonate in the presence of DMAP. As expected, both dehydration and esterification occurred to give the *tert*-butyl

ester of the *N,N*-bis(*tert*-butoxycarbonyl) dehydroamino acid. However, the reactions were more sluggish and the yields slightly lower when compared to those of dehydration of the corresponding methyl or benzyl esters. We have also investigated the direct dehydration of the methyl ester of serine. The reaction of this amino acid derivative with 3 eq. of *tert*-butyl pyrocarbonate allowed the preparation of the *N,N*-bis(*tert*-butoxycarbonyl) dehydroalanine methyl ester in 82% yield.

The applicability of our methodology to the dehydration of peptides containing β-hydroxyamino acids was also investigated.[28b,31] Thus, dipeptides containing serine, threonine or β-hydroxyphenylanine in either the amine or the carboxyl terminus (Table 2, **27**-**36**) were reacted under the previously described conditions. In these reactions, 3 eq. of *tert*-butyl pyrocarbonate were used, *i.e.* 2 eq. for acylation of both amide nitrogen atoms and a third equivalent to generate the carbonate at the β-carbon atom. The yields in dehydrodipeptides (Table 2, **37**-**46**) were high and again, peptides containing threonine and β-hydroxy-phenylanine gave only one of the two possible geometric isomers. In the case of a dipeptide containing both threonine and serine (**35**) and of another containing two residues of threonine (**36**), simultaneous dehydration of both amino acid residues was achieved (**45** and **46**, respectively).

Table 2. Results obtained in the synthesis of dehydropeptide derivatives.[28b,31]

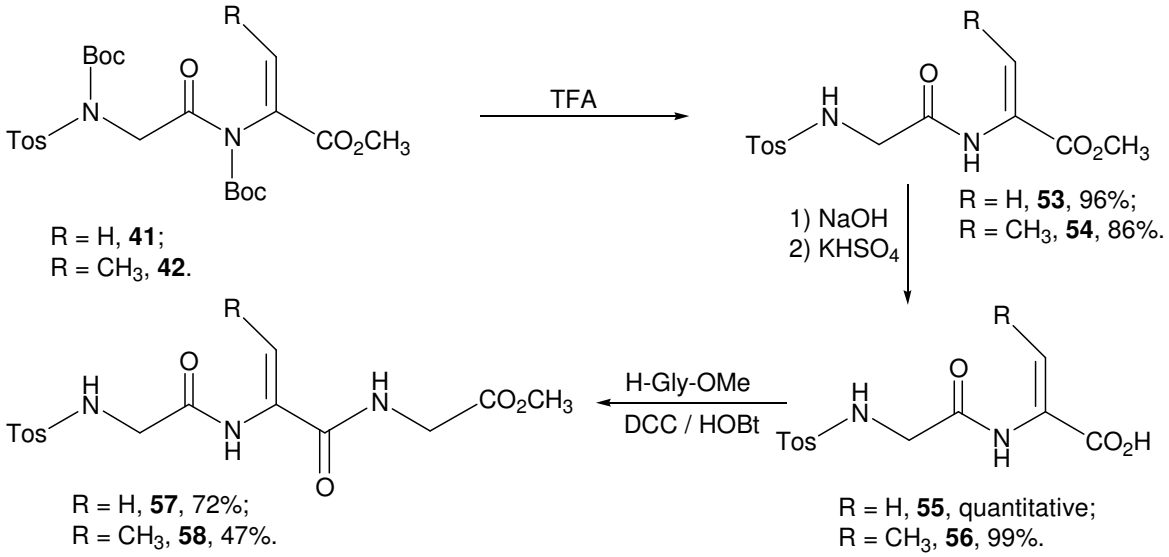
Reagent	Product	Yield / %
$Z(NO_2)$-Ser-Phe-OEt, **27**	$Z(NO_2)$-ΔAla(*N*-Boc)-Phe(*N*-Boc)-OEt, **37**	93
Boc-Ala-Ser-OMe, **28**	Boc-Ala(*N*-Boc)-ΔAla(*N*-Boc)-OMe, **38**	91
Z-Thr-Gly-OMe, **29**	Z-*Z*-ΔAbu(*N*-Boc)-Gly(*N*-Boc)-OMe, **39**	81
Boc-Ala-Thr-OMe, **30**	Boc-Ala(*N*-Boc)-*Z*-ΔAbu(*N*-Boc)-OMe, **40**	84
Tos-Gly-Ser-OMe, **31**	Tos-Gly(*N*-Boc)-ΔAla(*N*-Boc)-OMe, **41**	96
Tos-Gly-Thr-OMe, **32**	Tos-Gly(*N*-Boc)-*Z*-ΔAbu(*N*-Boc)-OMe, **42**	91
Boc-Gly-Thr-OMe, **33**	Boc-Gly(*N*-Boc)-*Z*-ΔAbu(*N*-Boc)-OMe, **43**	82
Tos-Gly-Phe(β-OH)-OMe, **34**	Tos-Gly(*N*-Boc)-*Z*-ΔPhe(*N*-Boc)-OMe, **44**	96
Boc-Thr-Ser-OMe, **35**	Boc-*Z*-ΔAbu(*N*-Boc)-ΔAla(*N*-Boc)-OMe, **45**	83
Boc-Thr-Thr-OMe, **36**	Boc-*Z*-ΔAbu(*N*-Boc)-*Z*-ΔAbu(*N*-Boc)-OMe, **46**	74

All of the protecting groups used were intended to allow the investigation of their cleavage from dehydroamino acids using mild reaction procedures. One such method is electrolysis[32] which offers a clean, non-polluting alternative to the classical methods of reduction. Thus, both $Z(NO_2)$ and Tos were selectively removed from compounds **24a**,**b** and **25a**,**b**, by electrolysis at controlled potential to give the methyl ester of the respective *N*-(*tert*-butoxycarbonyl)dehydroamino acid (**49**, **50**) in yields ranging from 73% to 88% (Table 3). However, when electrochemical equipment is not available selective cleavage can still be achieved by reduction with an appropriate metal.[33] Thus, the $Z(NO_2)$ group was cleaved from compounds **24a** and **b** by selective reduction with mercury activated aluminum to give the methyl ester of the respective *N*-(*tert*-butoxycarbonyl)dehydroamino acid in high yields (**49**, **50**). Selective cleavage of the Boc group with trifluoroacetic acid (TFA) gave *N*-protected, *C*-protected dehydroamino acid derivatives (**47**, **48**). Saponification of the methyl esters allowed the preparation free carboxyl dehydroamino acid derivatives (**51**, **52**).

Table 3. Results obtained in selective cleavage of protecting groups from *N,N*-diprotected dehydroamino acid derivatives.[28b,31]

Reagent	Deprotecting method	Product	Yield / %
Z(NO_2)-ΔAla(*N*-Boc)-OMe, **24a**	e^-	Boc-ΔAla-OMe, **49**	88
Z(NO_2)-*Z*-ΔAbu(*N*-Boc)-OMe, **24b**	e^-	Boc-*Z*-ΔAbu-OMe, **50**	88
Tos-ΔAla(*N*-Boc)-OMe, **25a**	e^-	Boc-ΔAla-OMe, **49**	73
Tos-*Z*-ΔAbu(*N*-Boc)-OMe, **25b**	e^-	Boc-*Z*-ΔAbu-OMe, **50**	78
Z(NO_2)-ΔAla(*N*-Boc)-OMe, **24a**	Al/Hg	Boc-ΔAla-OMe, **49**	87
Z(NO_2)-*Z*-ΔAbu(*N*-Boc)-OMe, **24b**	Al/Hg	Boc-*Z*-ΔAbu-OMe, **50**	95
Z(NO_2)-*Z*-ΔAbu(*N*-Boc)-OMe, **24b**	TFA	Z(NO_2)-*Z*-ΔAbu-OMe, **47**	85
Z-*Z*-ΔAbu(*N*-Boc)-OMe, **23b**	TFA	Z-*Z*-ΔAbu-OMe, **48**	87
Z(NO_2)-*Z*-ΔAbu-OMe, **47**	NaOH	Z(NO_2)-*Z*-ΔAbu-OH, **51**	78
Z-*Z*-ΔAbu-OMe, **48**	NaOH	Z-*Z*-ΔAbu-OH, **52**	77

The *C*-deprotected dehydroamino acid derivatives could be coupled with *C*-protected amino acids to give *N,C*-diprotected dehydrodipeptides. Saponification of *N,C*-diprotected dehydrodipeptides and subsequent coupling with a *C*-protected amino acid derivative gave *N,C*-diprotected dehydrotripeptides (Scheme 3, **57**, **58**).[31]



Scheme 3

3. *N,N*-Diprotected dehydroamino acids as precursors of novel amino acid derivatives

3.1. Introduction

Non-natural amino acids can show pharmacological activities and can also be used to reduce the rates of degradation of several pharmaceuticals in living organisms. Dehydroamino acid derivatives are versatile synthetic precursors since they can be readily transformed into various natural and non-natural amino acids due to the presence of a double bond.

Although Michael addition is one of the most powerful and widely used synthetic tools, there are only a few reports on Michael addition of nucleophiles to dehydroamino acids. The limited use of these

compounds in Michael addition can be assigned mainly to the fact that dehydroamino acids are only fairly reactive Michael acceptors.

Zahn has reported a 96.5% yield in the synthesis of a β-substituted alanine by the addition of N^{α}-acetyl-L-lysin to the ethyl ester of *N*-acetyldehydroalanine in the presence of sodium hydroxide.[34] Morin and Labia prepare a α,β-diaminopropionic acid derivative in a 55% yield by reacting a dehydroalanine with an excess of benzylamine in methanol.[35] The preparation of cysteine derivatives by sulfenylation using P_4S_{10} in benzene at reflux of *N*-formyldehydroamino acid esters was described by Hruby *et al.*.[36] Moore *et al.* reported the synthesis of a β,β-dialkylcysteine derivative in 80% yield by a Michael addition of 4-methylbenzylmercaptan to a dehydroamino acid unit using a catalytic amount of sodium hydride in toluene.[37] Michael additions of nitrogen nucleophiles to dehydroalanine derivatives using $FeCl_3$ as catalyst have been reported, giving various β-substituted alanine derivatives in yields varying within the range of 13-98%.[38] A orthogonally protected lanthionine derivative was prepared *via* Michael addition of a fully protected cysteine to a dehydroalanine derivative using cesium carbonate as base in acetonitrile (80% yield).[39]

Addition reactions using as substrate the methyl ester of *N*-acetyldehydroalanine and as nucleophiles pyrazole and 1,2,4-triazole in the presence of an inorganic base gave the corresponding β-substituted alanine in 54% and 78% yield, respectively.[40] In order to circumvent difficulties met in attempted solution synthesis, namely difficult purification of the products due to similarity of their solubility to that of the corresponding starting materials, a solid phase strategy was used. Thus, *N*-acetyldehydroalanine was anchored to a Wang resin and reacted with nucleophiles in the presence of potassium carbonate under forcing conditions (6 to 15 eq. of nucleophile were used in 2-day reactions at temperatures within the range 50-60 °C).[40] *N*-Acetyl, β-substituted alanine salts were prepared in good yields by treatment of methyl 2-acetamidoacrylate with several nitrogen heterocycles in the presence of an inorganic base at 60 ºC.[41]

Naidu *et al*. found that the rate of Michael addition of thiols and amines to dehydroalanine amides was greatly accelerated in water. The authors used this method to prepare several β-substituted alanines in good to high yields.[42]

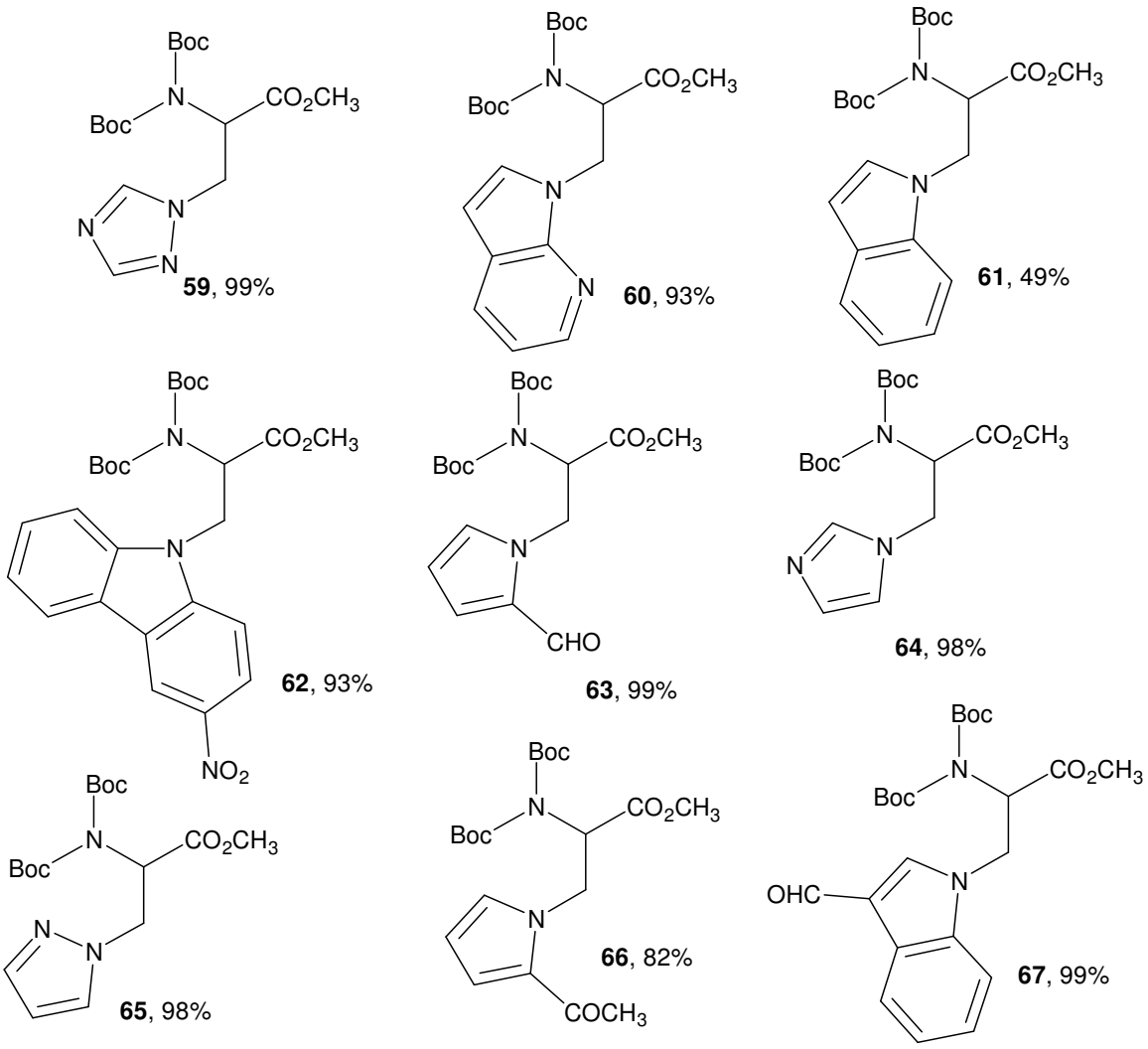
The enantioselective rhodium-catalysed conjugate addition of aryl boronic acids to dehydroalanine derivatives was successfully carried out in the presence of C_2-symmetric aryl diphosphite ligands.[43] This type of reaction can be performed in water with low catalyst loading.[44] Darses and Genet prepared several β-substituted alanines by reacting the methyl ester of *N*-acetyldehydroalanine with potassium trifluoro(organo)borates which are highly stable and easily prepared in the presence of rhodium complexes.[45] The same authors introduced enantioselectivity to this reaction using BINAP as a chiral ligand and guaiacol as a proton donor. The preparation of β-substituted alanines from dehydroalanines and trifluoro(organo)borates was accomplished with enantioselectivities of up to 90%.[46]

Chen *et al.* reported the synthesis of β-benzylsulfanyl-β-trifluoromethyl-α-amino acid esters with moderate to good diastereoselectivies from *Z*-β-substituted-β-trifluoromethyl-α,β-dehydroamino acid esters *via* a Michael addition in the presence of Et_3N and LiBr which acted as a bifunctional catalyst.[47]

3.2. Synthesis of β-substituted amino acids

The high yielding synthesis of *N*,*N*-disubstituted dehydroamino acids developed by us made these compounds available in large amounts and ready for further applications.[28a-b] It was possible to use these

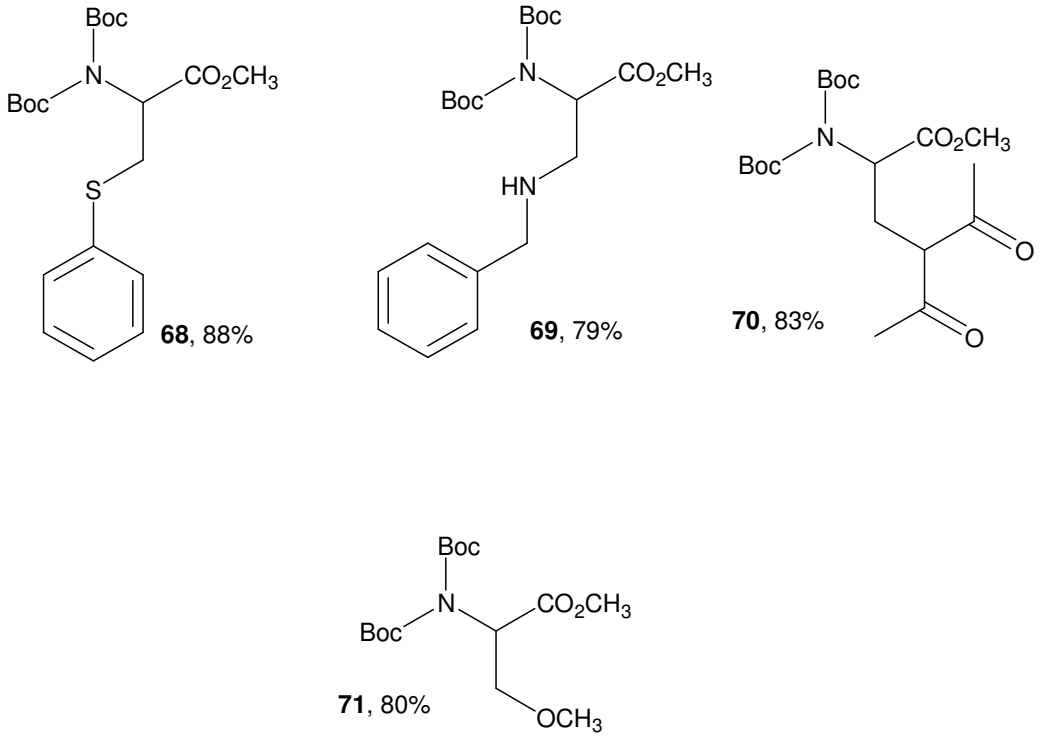
compounds successfully as substrates in Michael addition reactions, since the presence of two substituents at the nitrogen atom greatly increases the reactivity of the β-carbon atom of the dehydroamino acids towards nucleophilic attack. This allowed the use of one equivalent of nucleophile which simplifies the work-up procedures. Thus, using as substrate the methyl ester of *N*,*N*-bis(*tert*-butoxycarbonyl)dehydroalanine (**22a**) and as nucleophiles nitrogen heterocycles we were able to prepare β-heterocyclic alanines (Scheme 4, **59**-**67**).



Scheme 4

It was possible to observe a correlation between the reaction yields and the chemical shift of the nitrogen protons of the heterocycles. Some of the compounds obtained are analogues of tryptophan and histidine. Using as nucleophiles thiols, amines, carbon nucleophiles of the β-dicarbonyl type and oxygen nucleophiles we were able to prepare several other β-substituted alanines in good to high yields (Scheme 5, **68**-**71**).[48] This reaction was also investigated with several dehydroalanine derivatives having unsymmetrical double substitution at their nitrogen atom. In many cases, specially with the 4-nitrobenzoyl group, a large amount of the methyl ester of *N*-*tert*-butoxycarbonyl dehydroalanine (**49**) was detected in the reaction mixture. This may result from competitive nucleophilic cleavage of the substituents at the nitrogen atom of the dehydroalanine derivative in a manner similar to that described by Ragnarsson *et al.*.[49] Cleavage of the protecting groups was carried out. Thus, the Boc groups were easily removed from the *N,N*-diprotected,

β-substituted alanine methyl esters (Table 4, **59**, **60**, **72**) by treatment with TFA, the benzoyl group was removed using 2-(diethylamino)-ethylamine (DEAEA) (**73**) or *N,N,N',N'*-tetramethylguanidine (TMG) (**74**) while 4-nitrobenzyloxycarbonyl and 4-nitrobenzoyl were cleaved by reduction with mercury activated aluminum (**75** and **76**, respectively).[48] Saponification of the *N,N*-bis(*tert*-butoxycarbonyl) amino acid methyl esters (**59**, **60**, **65**, **67**) gave the corresponding *N,N*-bis(*tert*-butoxycarbonyl) amino acids (Table 4, **82**-**85**).[48]

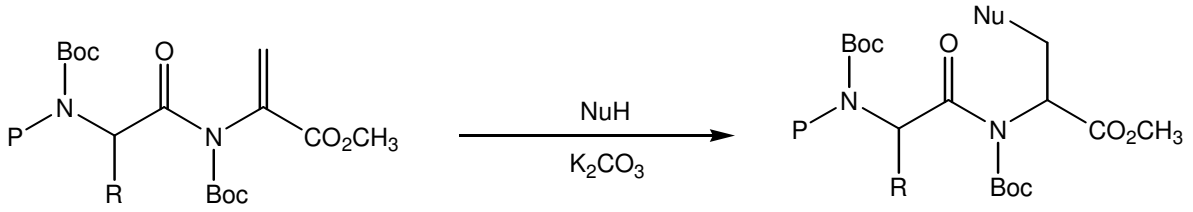


Scheme 5

Table 4. Yields in the selective cleavage of heterocyclic β-substituted alanine derivatives.[48]

Substrate	Deprotection reactant	Product	Yield %
Boc-Ala[*N*-Boc, β-(1,2,4-triazol-1-yl)]-OMe, **59**	**TFA**	H-Ala[β-(1,2,4-triazol-1-yl)]-OMe.2TFA, **77**	80
Boc-Ala[*N*-Boc, β-(7-azaindol-1-yl)]-OMe, **60**	**TFA**	H-Ala[β-(7-azaindol-1-yl)]-OMe .TFA, **78**	85
Boc-Ala[*N*-Boc, β-(carbazol-9-yl)]-OMe, **72**	**TFA**	H-Ala[β-(carbazol-9-yl)]-OMe .TFA, **79**	91
Bz-Ala[*N*-Boc, β-(1,2,4-triazol-1-yl)]-OMe, **73**	**DEAEA**	Boc-Ala[β-(1,2,4-triazol-1-yl)]-OMe, **80**	78
Bz-Ala[*N*-Boc, β-(7-azaindol-1-yl)]-OMe, **74**	**TMG**	Boc-Ala[β-(7-azaindol-1-yl)]-OMe, **81**	74
Z(NO_2)-Ala[*N*-Boc, β-(1,2,4-triazol-1-yl)]-OMe, **75**	**Al/Hg**	Boc-Ala[β-(1,2,4-triazol-1-yl)]-OMe, **80**	86
Bz(NO_2)-Ala[*N*-Boc, β-(1,2,4-triazol-1-yl)]-OMe, **76**	**Al/Hg**	Boc-Ala[β-(1,2,4-triazol-1-yl)]-OMe, **80**	58
Boc-Ala[*N*-Boc, β-(1,2,4-triazol-1-yl)]-OMe, **59**	**NaOH**	Boc-Ala[*N*-Boc, β-(1,2,4-triazol-1-yl)]-OH, **82**	86
Boc-Ala[*N*-Boc ,β-(7-azaindol-1-yl)]-OMe, **60**	**NaOH**	Boc-Ala[*N*-Boc, β-(7-azaindol-1-yl)]-OH, **83**	94
Boc-Ala[*N*-Boc, β-(pyrazol-1-yl)]-OMe, **65**	**NaOH**	Boc-Ala[*N*-Boc, β-(pyrazol-1-yl)]-OH, **84**	91
Boc-Ala[*N*-Boc, β-(3-formylindol-1-yl)]-OMe, **67**	**NaOH**	Boc-Ala[*N*-Boc, β-(3-formylindol-1-yl)]-OH, **85**	89

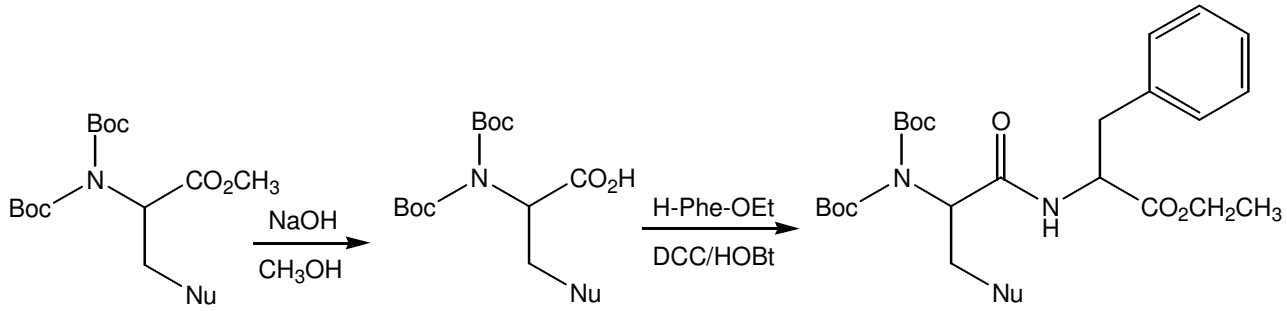
Using as substrates dehydrodipeptides containing dehydroalanine residues, it was possible to obtain several dipeptides containing β-substituted alanines in good to high yields (Scheme 6, **86**-**91**).[48]



P = Tos, R = H, Nu = 1,2,4-triazole, **86**, 76%;
P = Boc, R = CH_3, Nu = 1,2,4-triazole, **87**, 98%;
P = Tos, R = H, Nu = 7-azaindole, **88**, 90%;
P = Tos, R = H, Nu = thiophenol, **89**, 87%;
P = Tos, R = H, Nu = benzylamine, **90**, 53%;
P = Tos, R = H, Nu = 1,3-cyclohexadione, **91**, 60%.

Scheme 6

The synthesis of dipeptides containing β-heterocyclic alanines was also accomplished by cleavage of the methyl ester followed by coupling with an amino acid ester (Scheme 7, **92**, **93**).[31]



Nu = 7-azaindol-1-yl, **60**, 94%;
Nu = pyrazol-1-yl, **65**, 91%.

Nu = 7-azaindol-1-yl, **83**, 94%;
Nu = pyrazol-1-yl, **84**, 91%.

Nu = 7-azaindol-1-yl, **92**, 86%;
Nu = pyrazol-1-yl, **93**, 80%.

Scheme 7

The *N*,*N*-diprotected dehydroaminobutyric acid derivatives, due to the β-substitution, are poorer Michael acceptors when compared with dehydroalanine. It was found that these compounds only react with the stronger nucleophiles such as imidazole and 1,2,4-triazole giving in considerably lower yields the corresponding β-triazol-1-yl and β-imidazol-1-yl aminobutyric acid derivatives as 1:1 diastereomeric mixtures. The dehydrophenylalanine derivatives showed an even lower reactivity and no addition product were obtained using Boc-ΔPhe(*N*-Boc)-OMe (**22c**) and Bz-ΔPhe(*N*-Boc)-OMe (**26c**) as substrates.[48]

The possibility of activating *N*-acyldehydroalanines by electrochemical reduction at an appropriate potential and thus converting them into nucleophiles which could attack other molecules of *N,N*-diacyldehydroalanines was investigated. Thus, the activation potentials of several *N*-acyl- and *N,N*-diacyldehydroamino acid derivatives were determined by cyclic voltammetry and compared with those for the respective β-hydroxyamino acid derivatives (Table 5).[50]

Table 5. Peak potentials obtained by cyclic voltammetry of amino acid and dehydroamino acid derivatives.[50]

	-*Ep* (V *vs* S.C.E.)[a]				
Compound	**P**	**Z(NO_2)**	**Bz**	**Tos**	**Z**	**Boc**
P-Thr-OMe	1.14	2.36	2.50	2.82	[b]
P-Ser-OMe	1.04	2.42	2.48	2.86	[b]
P-Phe(β-OH)-OMe	1.08	2.38	2.53		[b]
P-ΔAbu-OMe	0.97	2.21	2.18	2.34	2.46
P-ΔAla-OMe	1.10	1.91	1.90	2.29	2.12
P-ΔPhe-OMe	1.12	1.87	1.65		1.84
P-ΔAbu(*N*-Boc)-OMe	1.02	2.02	2.12	2.19	2.36
P-ΔAla(*N*-Boc)-OMe	1.04	1.84	1.88	2.04	2.01
P-ΔPhe(*N*-Boc)-OMe	1.02	1.80	1.74		1.84

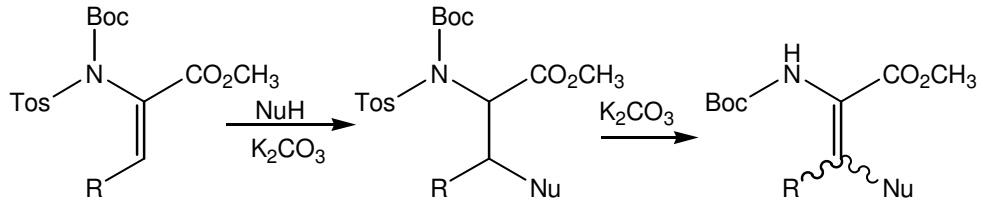
[a] Cathode: vitreous carbon. Solvent: dimethylformamide. Supporting electrolyte: Bu_4NBF_4 0.1 mol dm^{-3}. Substrate conc.: ≈0.005 mol dm^{-3}.
[b] No reduction peak was detected.

The peak potentials found with all the Z(NO_2) amino acid derivatives investigated fell within a fairly narrow range (0.15 V); the reduction potential of this group is not affected by the neighbourhood of either a *tert*-butoxycarbonyl group or a double bond. However, this was not the case of both benzoyl and 4-toluenesulfonyl dehydroamino acid derivatives, which exhibit reduction potentials shifted to significantly less negative values than those of the corresponding β-hydroxyamino acid compounds. We assign this behaviour to stabilisation of the radical anion by conjugation of the aromatic ring of these two groups with the α,β-double bond and with the Boc carbonyl group. This effect is enhanced in the dehydrophenylalanine series by further conjugation with the amino acid β-phenyl ring and markedly weakened in the dehydroaminobutyric acid series, certainly due to the electron donating effect of the β-methyl group. All cyclic voltammograms were consistent with irreversible processes occurring after formation of the radical anions, and previous results obtained in electrolyses of Z(NO_2) and Tos in *N,N*-diacyl-dehydroalanine and dehydroaminobutyric acid derivatives showed that these two protecting groups undergo cleavage at the peak potentials listed in Table 5.[28b] However, cyclic voltammograms for dehydroamino acids mono and diacylated with Boc showed peak potentials between –1.84 and –2.46 V *v*s S.C.E. Since this group is stable to electrochemical reduction,[51] the irreversible voltammograms found for these compounds could not be related to cleavage of Boc. In addition, once the aromatic ring of Z is not conjugated with the rest of the molecule, potential shifts of 0.63 V or more would be related to the α,β-double bond in conjugation with at least two carbonyl groups, and not to the protecting group.

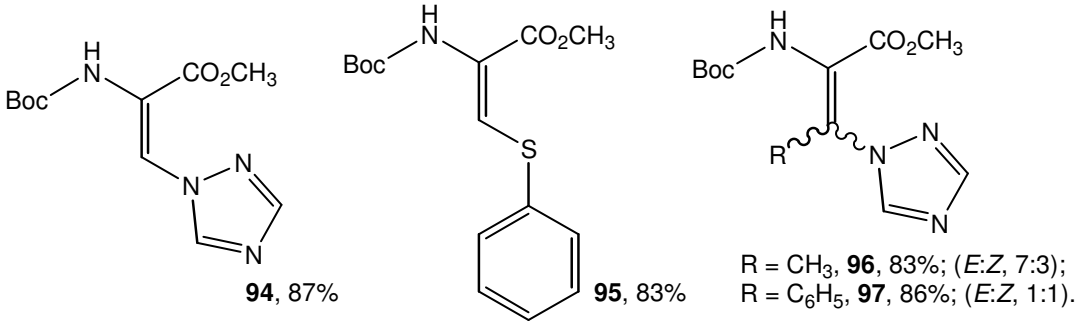
Controlled potential electrolysis of Boc-ΔAla(*N*-Boc)-OMe (**22a**) and Z-ΔAla(*N*-Boc)-OMe (**23a**) at the peak potentials indicated in Table 5 were carried out. With both substrates, a 2,5-diaminoadipic acid derivative was isolated as diastereomeric mixtures in yields of 85% and 78%, respectively.[50] We believe that the reaction proceeds *via* formation of a carbanion at the β-carbon atom, which acts as a nucleophile and adds to a molecule of the starting material. This is supported by the fact that no such reaction occurred with Boc-ΔAla-OMe (**49**) and Boc-ΔPhe(*N*-Boc)-OMe (**22c**), which are known not to be sufficiently strong electrophiles to undergo nucleophilic attack.

3.3. Synthesis of β-substituted dehydroamino acids

When *N*-(4-toluenesulfonyl), *N*-(*tert*-butoxycarbonyl)dehydroamino acids (**25a**-**c**) were reacted with nitrogen heterocycles and thiols the corresponding Michael addition products were obtained. However, these underwent elimination of 4-toluenesulfinic acid giving the corresponding β-substituted dehydroamino acid derivatives in good to high yields (Scheme 8, **94**-**97**). In the case of dehydroalanines the reaction is stereoselective for the *E*-isomer. With the dehydroaminobutyric acid and dehydrophenylalanine derivatives mixtures of the *E* and *Z*-isomers were obtained (Scheme 8).[48c,52]



R = H, **25a**; CH_3, **25b**; C_6H_5, **25c**.
NuH = nitrogen heterocycles and thiols.

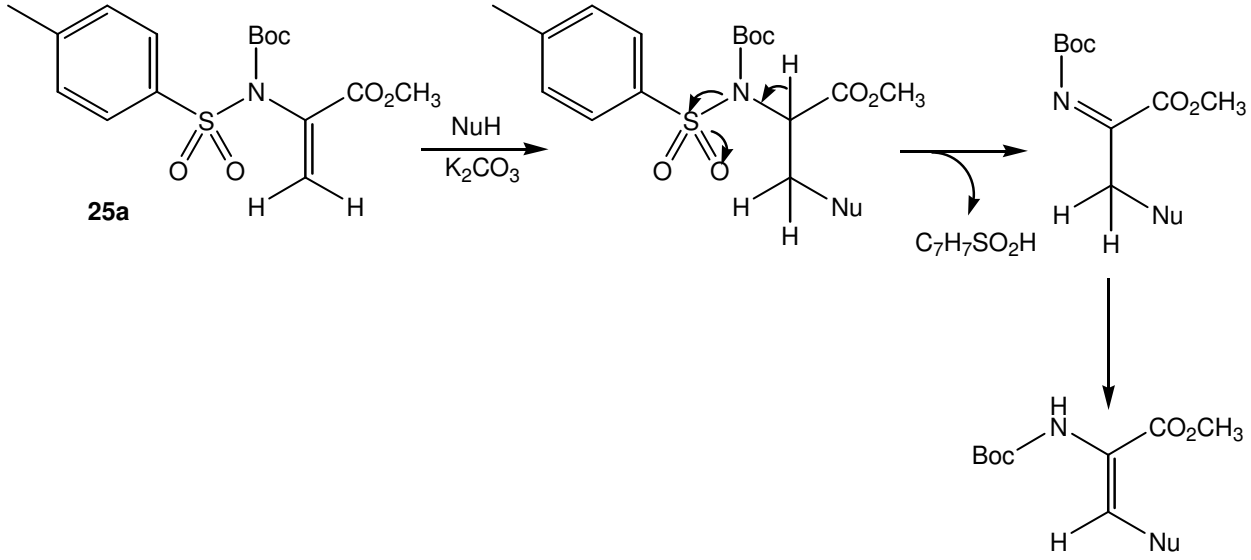


94, 87% **95**, 83%

R = CH_3, **96**, 83%; (*E*:*Z*, 7:3);
R = C_6H_5, **97**, 86%; (*E*:*Z*, 1:1).

Scheme 8

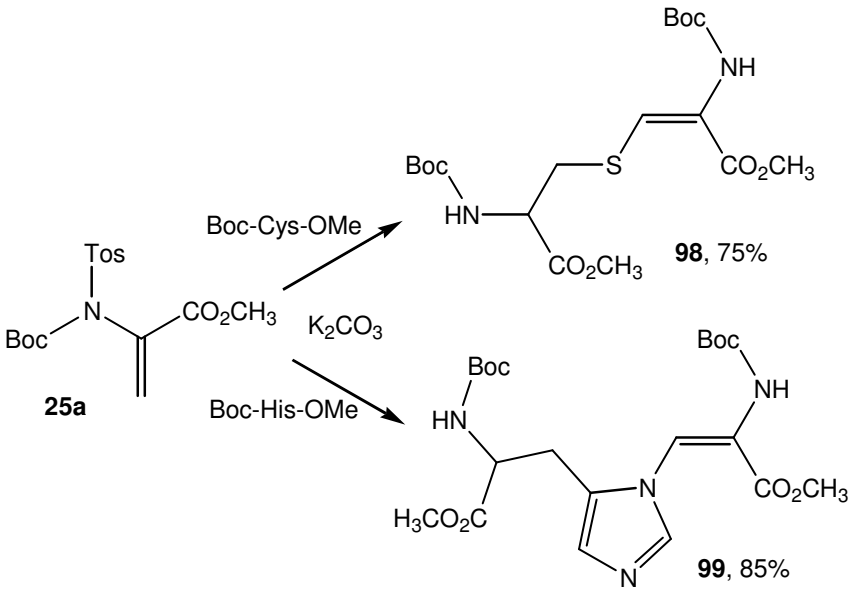
We propose a mechanism for this reaction that involves the elimination from the addition products of the 4-toluenesulfonyl group followed by regeneration of the α,β-double bond (Scheme 9).[48c]



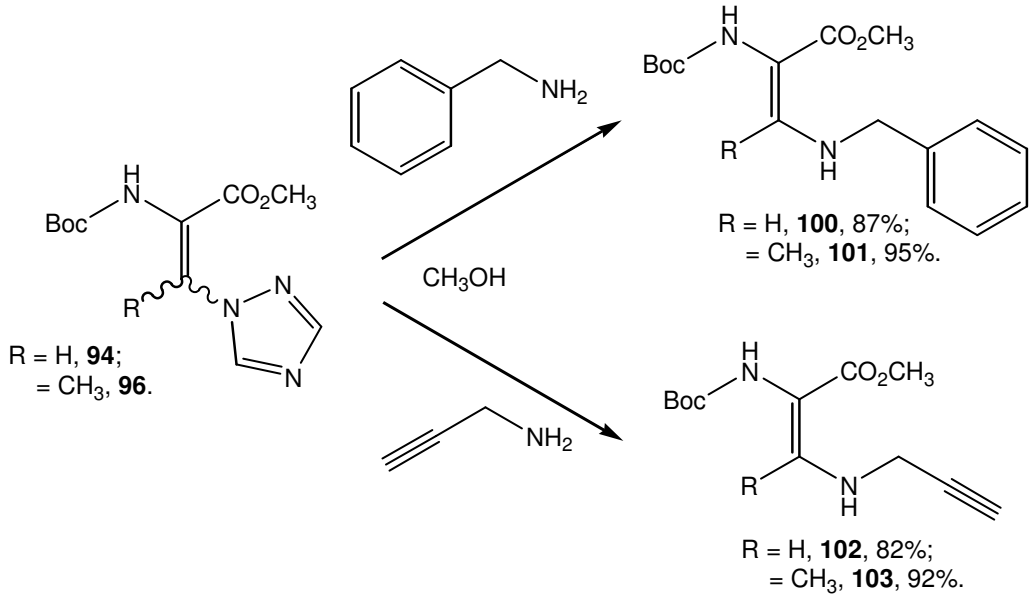
Scheme 9

Using amines as nucleophiles the only products obtained were the corresponding β-substituted alanines. Carbon nucleophiles of the β-dicarbonyl type, such as, diethyl malonate or 1,3-cyclohexadione react with the methyl ester of *N*-(4-toluenesulfonyl), *N*-(*tert*-butoxycarbonyl)dehydroalanine (**25a**) to give β-substituted alanines. Thus, the mechanism proposed in Scheme 9 does not explain why this reaction only occurs with nitrogen heterocycles and thiols and, up until now, the reason for this is not yet clear to us. With carbon nucleophiles having at least one methyl group attached to one of the carbonyl groups, a different reactivity is observed and described later in this review.

The reactivity of *N*-(4-toluenesulfonyl), *N*-(*tert*-butoxycarbonyl)dehydroalanine (**25a**) towards nitrogen heterocycles and thiols was used to synthesize in high yields cross-linked amino acids namely, histidino-α,β-dehydroalanine and dehydrolanthionine derivatives (**98** and **99**, respectively) using as nucleophiles *N*,*C*-diprotected derivatives of histidine and cysteine, respectively (Scheme 10).[53]



Scheme 10

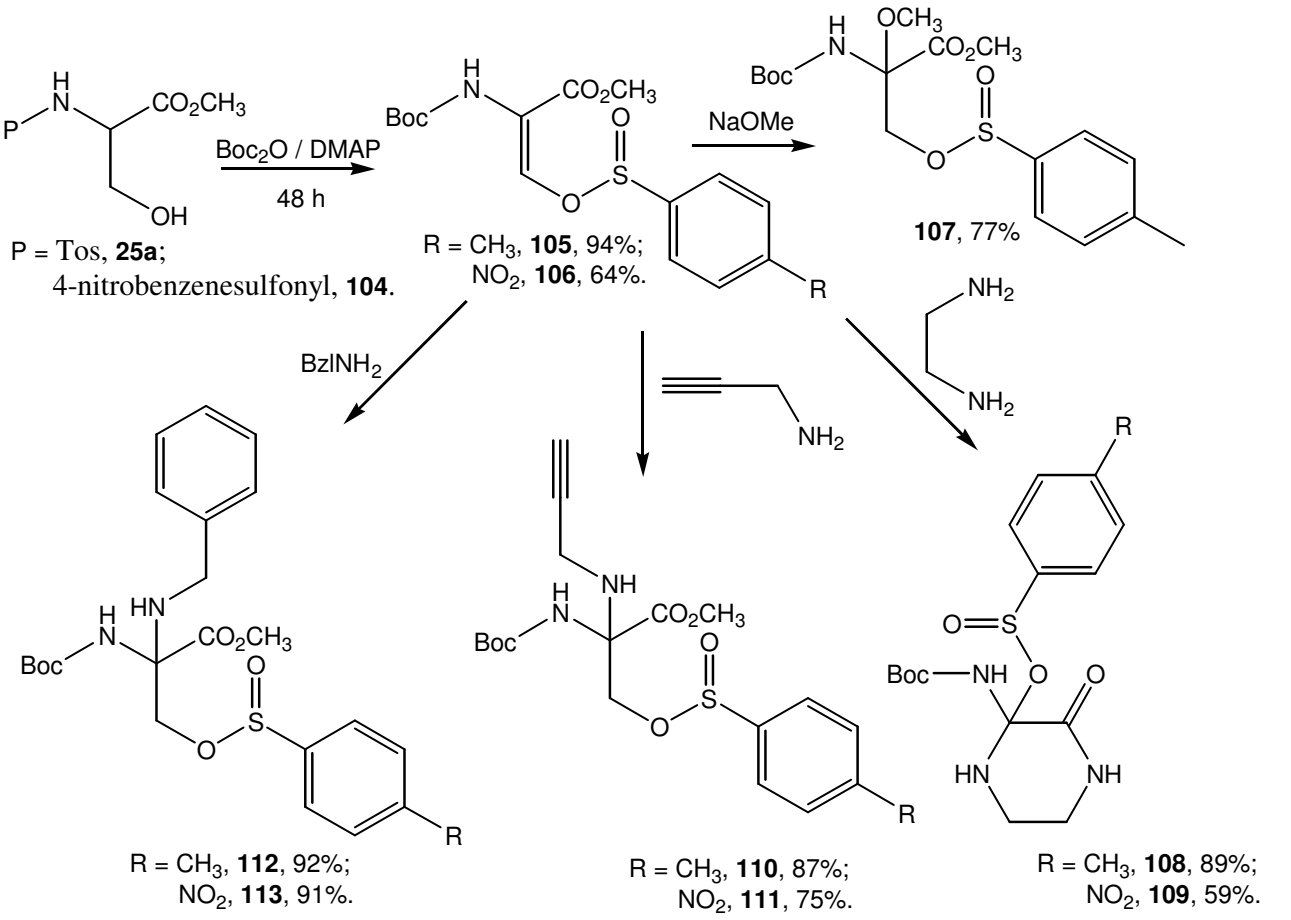


Scheme 11

As referred above, the reaction of compound **25a** with primary amines affords β-substituted alanines. However, the preparation of β-aminodehydroalanines could be carried out by reacting a β-heterocyclic dehydroalanine namely the methyl ester of *N*-(*tert*-butoxycarbonyl), β-(1,2,4-triazol-1-yl)dehydroalanine (**94**) with amines in methanol (Scheme 11, **100** and **102**).[53,54] The same reaction was applied to the dehydroaminobutyric acid derivative (**96**) thus allowing the synthesis of β-aminodehydroaminobutyric acid derivatives (Scheme 11, **101** and **103**). The β-(1,2,4-triazol-1-yl)dehydrophenylalanine (**97**) does not react with amines, possibly due to stabilization of the substrate through conjugation with the aromatic ring.

3.4. Synthesis of α,α-disubstituted amino acids

The methyl esters of *N*-(4-toluenesulfonyl) or *N*-(4-nitrobenzenesulfonyl), *N*-(*tert*-butoxy-carbonyl)dehydroalanine (Scheme 12, **25a** and **104**, respectively) in the presence of base undergo a rearrangement to give the *E*-isomer of *O*-(4-toluenesulfinyl) or *O*-(4-nitrobenzenesulfinyl) dehydroserine derivatives (**105** and **106**, respectively).[53,54] When these compounds were treated with amines and oxygen nucleophiles, addition to the α-carbon occurs to give the corresponding α-substituted, *O*-(arenesulfinyl)serine (Scheme 12, **107**-**113**).

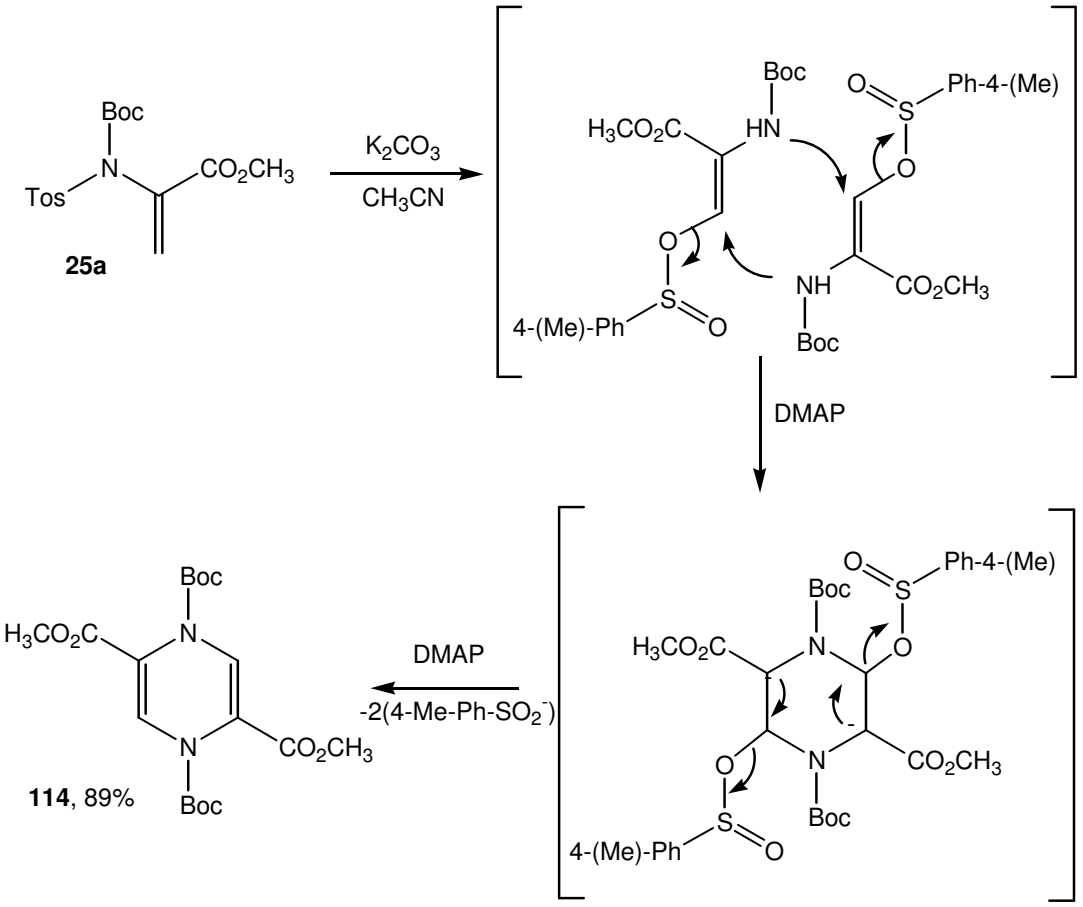


Scheme 12

The strong electron withdrawing effect of the sulfinyl group increases the electrophilic character of the α-carbon atom, when compared with the β-carbon atom, making the former more susceptible to nucleophilic attack. The reaction with 1,2-ethylenediamine gave a piperazine derivative resulting from addition to α-

carbon atom followed by an intramolecular aminolysis (**108**, **109**). However, it was found that the reaction of the *O*-(4-toluenesulfinyl)dehydroserine (**105**) with nitrogen heterocycles and thiols gives by substitution of the *O*-toluenesulfinyl group the corresponding β-substituted dehydroalanines. The same reactivity was observed for the methyl ester of *N*-(4-nitrobenzenesulfonyl), *N*-(*tert*-butoxycarbonyl) dehydroalanine (**106**).[53,54]

A 1,4-dihydropyrazine derivative (Scheme 13, **114**) was obtained reacting the methyl ester of *N*-*tert*-butoxycarbonyl, *O*-(4-toluenesulfinyl)dehydroserine (**105**) with DMAP and potassium carbonate in acetonitrile according to Scheme 13.[55] The presence of electron-withdrawing substitutents on the *N,N*-bis(*tert*-butoxycarbonyl)-2,5-bis-methoxycarbonyl-1,4-dihydropyrazine (**114**) has a stabilizing effect which allowed the preparation and isolation of this compound.

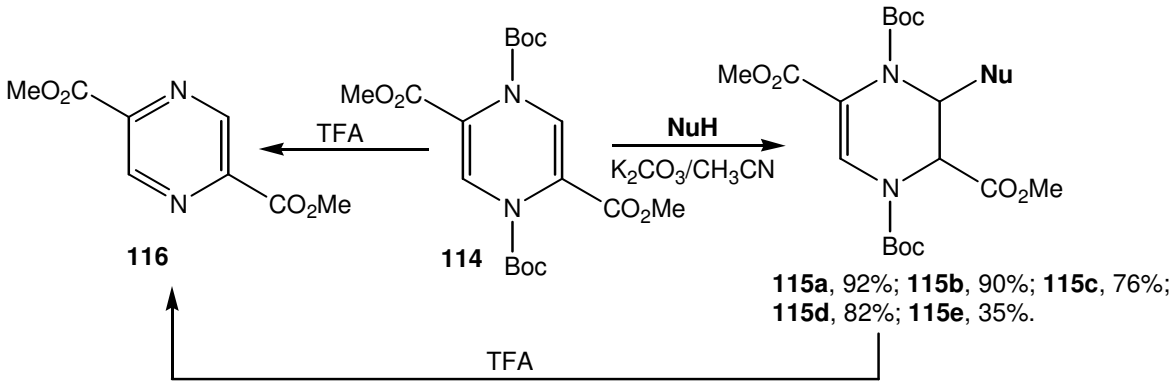


Scheme 13

Using this dihydropyrazine derivative as substrate it was possible to obtain tetrahydropyrazines and a pyrazine. Thus, the reaction of compound **114** with nucleophiles gave 3-substituted, *N,N*-bis(*tert*-butoxycarbonyl)-2,5-bis-methoxycarbonyl-1,2,3,4-tetrahydropyrazines (Scheme 14, **115a**-**e**). The removal of the *tert*-butoxycarbonyl groups with TFA from **114** gave the pyrazine derivative **116** in a 71% yield.[55]

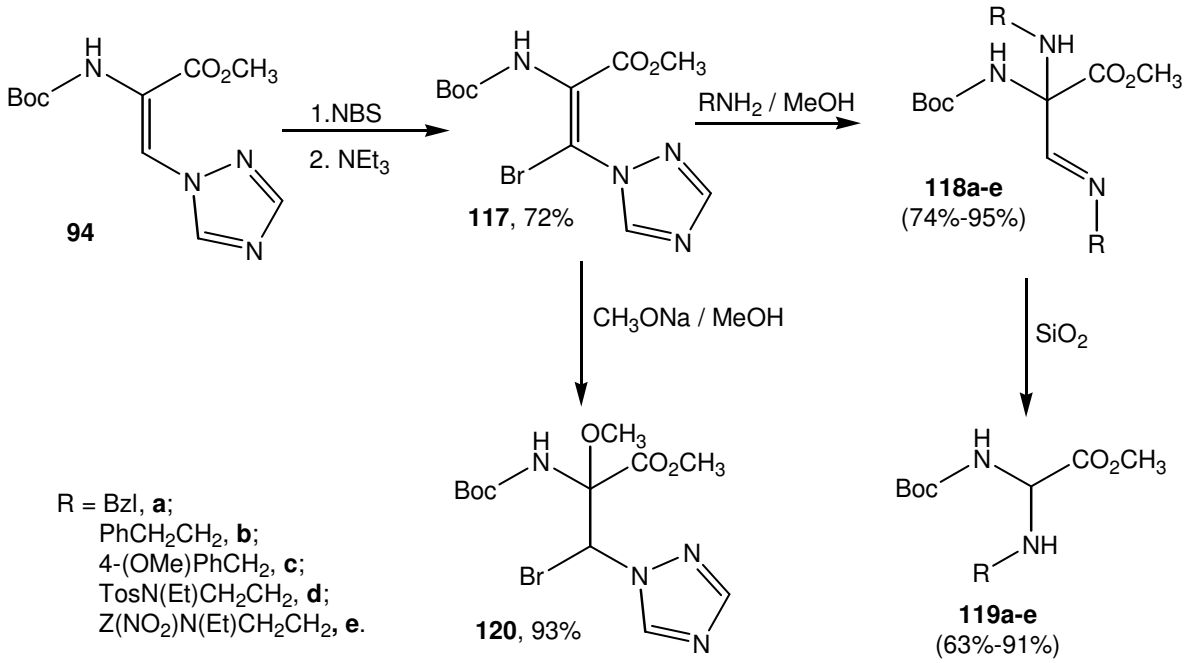
A β-heterocyclic dehydroalanine derivative namely the methyl ester of *N*-(*tert*-butoxycarbonyl), *Z*-β-bromo-β-(1,2,4-triazol-1-yl)dehydroalanine (Scheme 15, **117**) reacts with amines in methanol to give, after α-addition, β-substitution and β-elimination, α-alkylamino-β-alkyliminoalanines in high yields (**118a**-**e**).[56]

Compound **117** was prepared from a β-(1,2,4-triazol-1-yl)dehydroalanine derivative (**94**) by reaction with *N*-bromosuccinimide (NBS), followed by treatment with Et_3N. The α-alkylamino-β-alkyliminoalanines were easily converted into α-aminoglycines in good to high yields by treatment with silica in dichloromethane (Scheme 15, **119a**-**e**). This reaction may involve the addition of water to the imine carbon atom and elimination of an amide. The β-bromo-β-(1,2,4-triazol-1-yl)dehydroalanine (**117**) reacts with oxygen nucleophiles to give α,α-disubstituted amino acids (**120**). The α-addition in this case is due to the electronwithdrawing effect of the groups attached to the β-carbon atom.[56]



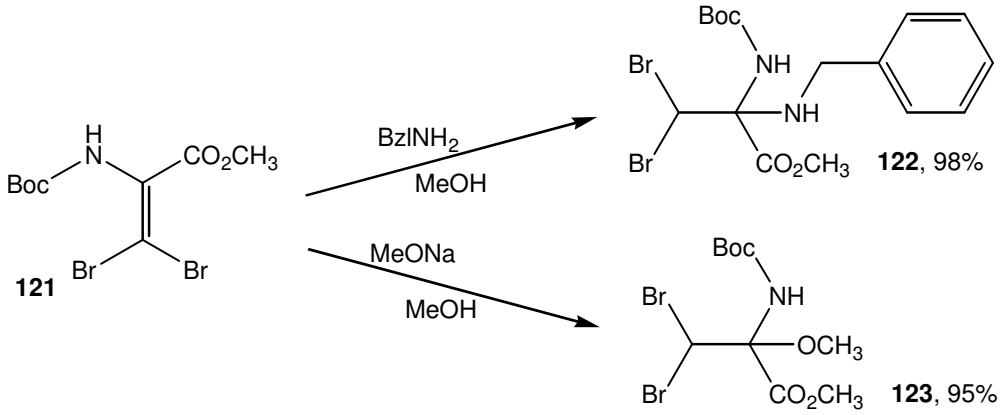
NuH: 1,2,4-triazole, **a**; 3-formylindole, **b**; 4-bromothiophenol, **c**; benzylamine, **d**; sodium methoxide, **e**.

Scheme 14



Scheme 15

α-Addition was also observed when a β,β-dibromodehydroalanine derivative (Scheme 16, **121**) was treated with primary amines and methoxyde in methanol (**122** and **123**, respectively).[56]

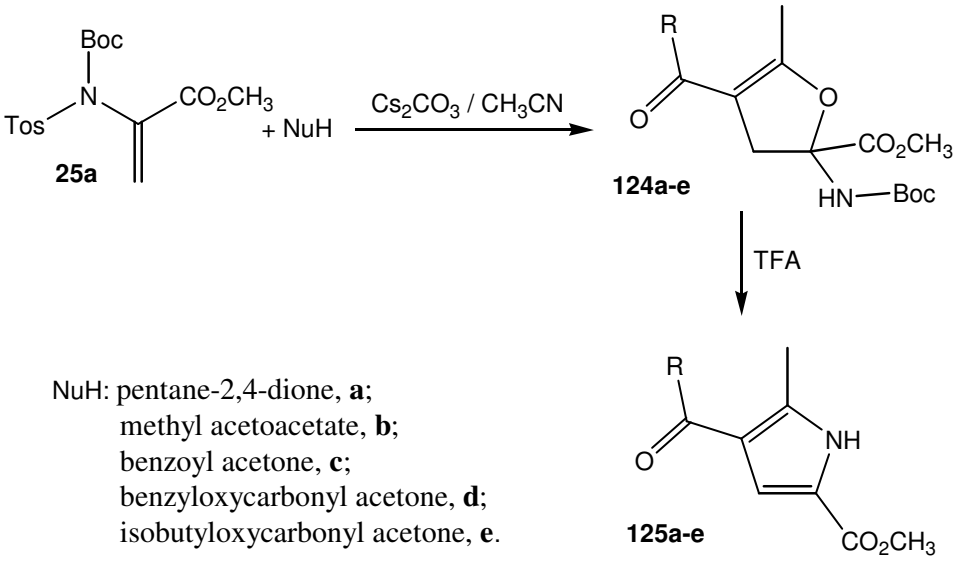


Scheme 16

3.5. Synthesis of dihydrofurans and pyrroles

Cyclic amino acids of the furan type were synthesized in good yields from a dehydroalanine derivative and carbon nucleophiles. These amino acids were converted into pyrroles with TFA.

The methyl ester of *N*-(4-toluenesulfonyl), *N*-(*tert*-butoxycarbonyl)dehydroalanine (**25a**) reacts with carbon nucleophiles with at least one methyl group bonded to one of the carbonyl groups to give the corresponding addition products. These undergo spontaneous elimination of the 4-toluenesulfonyl group followed by cyclization to afford dihydrofurans in good yields (Scheme 17, Table 6, **124a**-**e**).[53,57] These compounds resulted from a rearrangement of the detosylated β-substituted alanines *via* enolization with attack of the enolic oxygen atom on the amino acid α-carbon atom.

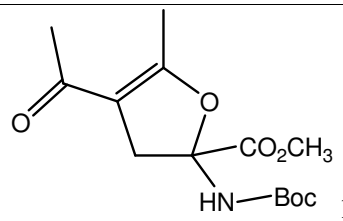
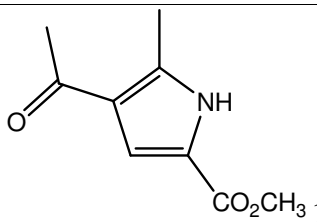
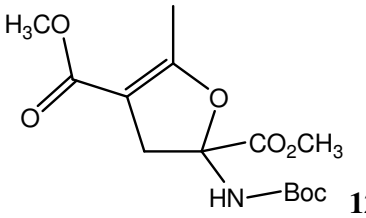
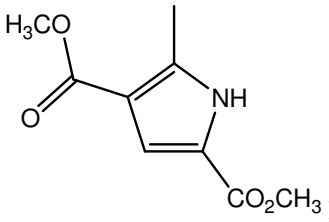
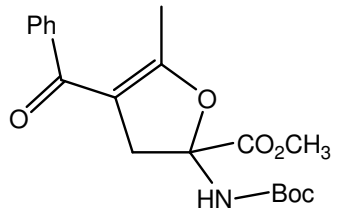
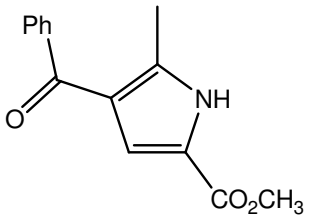
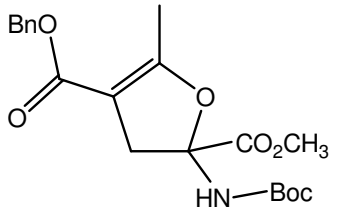
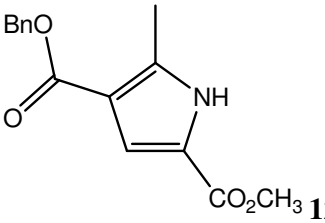
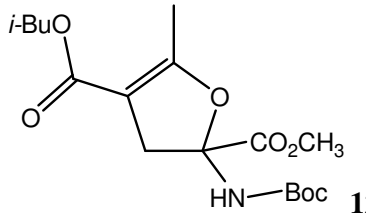
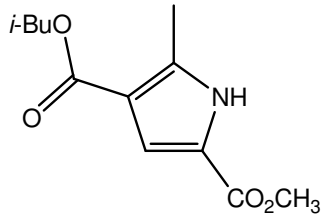


NuH: pentane-2,4-dione, **a**;
methyl acetoacetate, **b**;
benzoyl acetone, **c**;
benzyloxycarbonyl acetone, **d**;
isobutyloxycarbonyl acetone, **e**.

Scheme 17

Cleavage of the *tert*-butoxycarbonyl group from the furanic amino acids with trifluoroacetic acid resulted in a new rearrangement to give the corresponding pyrrole derivatives (Scheme 17, Table 6, **125a**-**e**). This reaction seems to proceed *via* ring opening and subsequent attack of the nitrogen atom of the amine function on the enolic carbon atom.

Table 6. Results obtained in the synthesis of furanic amino acids and pyrroles.[53,57]

Dihydrofurans	Yields / %	Pyrroles	Yields / %
 **124a**	88	 **125a**	92
 **124b**	86	 **125b**	90
 **124c**	80	 **125c**	77
 **124d**	78	 **125d**	79
 **124e**	82	 **125e**	88

4. Conclusions

An efficient and practical method for the synthesis of *N,N*-diacyldehydroamino acids from β-hydroxyamino acids with *tert*-butyl pyrocarbonate and 4-dimethylaminopyridine was developed in our laboratories. The method can be applied to various β-hydroxyamino acids with several *N*- and *C*- protecting groups and also to the synthesis of dehydrodipeptides.

The *N,N*-diprotected dehydroamino acids were versatile synthons allowing the preparation of a large variety of non-proteinogenic amino acids. Thus, *N,N*-diacyldehydroamino acid derivatives were used as substrates in Michael addition reactions allowing the synthesis of β-substituted amino acids. Using as nucleophiles nitrogen heterocycles it was possible to prepare new β-heterocyclic amino acids namely indolylalanines, 1,2,4-triazolylamino acids, pyrazolylamino acids and histidylamino acids. Some of these compounds are analogues of the amino acids histidine and tryptophan others, such as pyrazolylalanine are

known to have biological activity (hypoglicaemic proprieties) or can be used in structure-activity relationship studies or as fluorescent markers (7-azaindolylalanine). When one of the protecting groups was a 4-toluenesulfonyl group and the nucleophiles were nitrogen heterocycles or thiols it was possible to synthesize the corresponding β-substituted dehydroamino acid derivatives. Piperazine derivatives were prepared in good yields by treatment of *O*-(arenesulfinyl)dehydroserines with 1,2-ethylenediamine. A 1,4-dihydropyrazine was obtained reacting the methyl ester of *N*-(4-toluenesulfonyl), *N*-(*tert*-butoxycarbonyl)dehydroalanine with DMAP and potassium carbonate. This compound gave tetrahydropyazines by treatment with nucleophiles, and with TFA gave the corresponding pyrazine. Furanic amino acids can be prepared from *N,N*-diprotected dehydroamino acids and were easily converted into pyrroles with TFA.

This work shows that *N,N*-diprotected dehydroamino acid derivatives constitute excellent substrates for the synthesis of a wide range of heterocyclic amino acids and amino acids containing heterocyclic moieties.

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References

1. (a) Palmer, D. E.; Pattaroni, C.; Nunami, K.; Chadha, R. K.; Goodman, M.; Wakamiyia, T.; Fukase, K.; Horimoto, S.; Kitazawa, M.; Fujita, H.; Kubo, A.; Shiba, T. *J. Am. Chem. Soc*. **1992**, *114*, 5634. (b) Jung, G. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1051. (c) Chatterjee, C.; Paul, M.; Xie, L.; Van Der Donk, W. A. *Chem. Rev.* **2005**, *105*, 633.
2. (a) Schmidt, U.; Hausler, J.; Olher, E.; Poisel, H. *Fortschr. Chem. Org. Naturst.* **1977**, *37*, 251. (b) Noda, K.; Shimohigashi, Y.; Izumiya, N. *The Peptides, Analysis, Synthesis, Biology*; Academic Press: New York, 1983, Vol. 5, p. 286. (c) Schmidt, U.; Lieberknecht, A.; Wild, J. *Synthesis* **1988**, 159. (d) Nomoto, S.; Sano, A.; Shiba, T. *Tetrahedron Lett.* **1979**, *20*, 521. (e) Mazur, R. H.; Pilipauskas, D. R. *Peptides 1982*; de Gruyter, W., Ed.; Berlin, 1983; p. 319.
3. Dunnill, P. M.; Fowde, L. *Phytochemistry* **1965**, *4*, 933.
4. (a) Shinozaki, H.; Konishi, S. *Neuropharmacology* **1974**, *13*, 665. (b) Evans, R. H.; Francis, A. A.; Hunt, K.; Martin, M. R.; Walkins, J. C. *J. Pharma. Pharmac*. **1978**, *30*, 364.
5. Zee-Cheng, K-Y.; Cheng, C. C. *J. Med. Chem*. **1970**, *13*, 414.
6. (a) DeMong, D. E.; Williams, R. M. *Tetrahedron Lett.* **2002**, *43*, 2355. (b) Swaminathan, S.; Singh, A. K.; Lee, W.; Venit, J. J.; Natalie, K. J., Jr.; Simpson, J. H.; Weaver, R. E.; Silverberg, L. J. *Tetrahedron Lett.* **1998**, *39*, 4769.
7. (a) Jones, K.; Keenan, M.; Hibbert, F. *Synlett* **1996**, 509. (b) Cavalier, J.-F.; Burton, M.; De Tollenaere, C.; Dussart, F.; Marchand, C.; Rees, J.-F.; Marchand-Brynaert, J. *Synthesis* **2001**, 768. (c) Lotowski, Z.; Gryszkiewiez, A.; Borowiecka, J. B.; Nikitiuk, A.; Morzycki, J. W. *J. Chem. Res.* **1999**, *(S)*, 662. (d) Fourrey, J. L.; Beauhaire, J.; Yuan, C. W. *J. Chem. Soc., Perkin Trans 1* **1987**, 1841. (e) Shu, C. *J. Agric. Food Chem*. **1999**, *47*, 4332.
8. Seitz, L. E.; Sulling, W. J.; Reynolds, R. C. *J. Med. Chem.* **2002**, *45*, 5604.
9. (a) Brook, D. J. R.; Haltiwanger, R. C.; Koch, T. H. *J. Am. Chem. Soc*. **1992**, *114*, 6017. (b) Brook, D. J. R.; Noll, B. C.; Koch, T. H. *J. Chem. Soc., Perkin Trans. 1* **1998**, 289.
10. Yamaguchi, T.; Eto, M.; Harano, K.; Kashibe, N.; Watanabe, K.; Ito, S. *Tetrahedron* **1999**, *55*, 675.
11. (a) Rossen, K.; Pye, P. J.; Di Michele, L. M.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* **1998**, *39*, 6823. (b) Rossen, K.; Weissman, S. A.; Sager, J.; Reamer, R. A.; Askin, D.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* **1995**, *36*, 6419.

12. (a) Rivier, J. E.; Jiang, G.; Koerber, S. C.; Porter, J.; Simon, L.; Craig, A. G.; Hoeger, C. A. *Proc. Natl. Acad. Sci. USA* **1996**, *93*, 2031. (b) Kirby, D. A.; Wang, W.; Gershengorn, M. C.; Rivier, J. E. *Peptides* **1998**, *19,* 1679. (c) Reubi, J. C.; Schaer, J.-C.; Wenger, S.; Hoeger, C.; Erchegyi, J.; Waser, B.; Rivier, J. *Proc. Natl. Acad. Sci. USA* **2000**, *97*, 13973. (d) Rivier, J.; Erchegyi, J.; Hoeger, C.; Miller, C.; Low, W.; Wenger, S.; Waser, B.; Schaer, J.-C.; Reubi, J. C. *J. Med. Chem.* **2003**, *46*, 5579.
13. (a) Nakagawa, Y.; Tsuno, T.; Nakajima, K.; Iwai, M.; Kawai, H.; Okawa, K. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 1162. (b) Sommerfeld, T. L.; Seebach, D. *Helv. Chim. Acta* **1993**, *76*, 1702.
14. Wieland, F.; Ohnacker, G.; Ziegler, W. *Chem. Ber.* **1957**, *90*, 194.
15. Miller, M. J. *J. Org. Chem.* **1980**, *45*, 3131.
16. Wojciechowska, H.; Pawlowicz, R.; Andruszkiewicz, R.; Grzybowska, J. *Tetrahedron Lett.* **1978**, *19*, 4063.
17. Ogura, H.; Sato, O.; Takeda, K. *Tetrahedron Lett.* **1981**, *22*, 4817.
18. Berti, F.; Ebert, C.; Gardossi, L. *Tetrahedron Lett.* **1992**, *33*, 8145.
19. Goodall, K.; Parson, A. F. *Tetrahedron Lett.* **1995**, *36*, 3259.
20. Kisfaludi, L.; Patty, A.; Low, M. *Acta Chim. Acad. Sci. Hung*. **1969**, *59*, 159.
21. Nakamura, K.; Isaka, T.; Toshima, H.; Kodaka, M. *Tetrahedron Lett.* **2004**, *45*, 7221.
22. Shin, C.-G.; Nanjo, K.; Ando, E.; Yoshimura, J. *Bull. Chem. Soc. Jpn*. **1974**, *47*, 3109.
23. Kolasa, T. *Synthesis* **1983**, 539.
24. Berkowitz, D. B.; Pederson, M. L. *J. Org. Chem.* **1994**, 5476.
25. Ferreira, P. M. T.; Maia, H. L. S.; Rodrigues, L. M. *Peptides 1996*; Mayflower Scientific Ltd.: Kingswinford, 1998; p. 377.
26. Nugent, W. A. PCT Int. Appl. W09616021 (Cl. C07C231/14), US Appl. 340, 781, 17; *Chem. Abs.* **1996**, 143302k.
27. Grehn, L.; Gunnarsson, K.; Ragnarsson, U. *Acta Chem. Scand., Ser. B* **1986**, *40*, 745.
28. (a) Ferreira, P. M. T.; Maia, H. L. S.; Monteiro, L. S. *Tetrahedron Lett.* **1998**, *39*, 9575. (b) Ferreira, P. M. T.; Maia, H. L. S.; Monteiro, L. S.; Sacramento, J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3697.
29. Srinivasan, A.; Stephesen, R. W.; Olsen, R. K. *J. Org. Chem.* **1977**, *42*, 2256.
30. Takeda, K.; Akiyama, A.; Nakamura, H.; Takizawa, S.; Mizuno, Y.; Takayanagi, H.; Harigaya, Y. *Synthesis* **1994**, 1063.
31. Sacramento, J. "Síntese de aminoácidos não proteinogénicos com potencial actividade biológica", *PhD Thesis* **2003**, Department of Chemistry, University of Minho.
32. (a) Grehn, L.; Gunnarsson, K.; Maia, H. L. S.; Montenegro, M. I.; Pedro, L.; Ragnarsson, U. *J. Chem. Res.* **1988**, *(S),* 399; *J. Chem. Res.* **1988**, *(M)*, 3081. (b) Grehn, L.; Maia, H. L. S.; Monteiro, L. S.; Montenegro, M. I.; Ragnarsson, U. *J. Chem. Res.* **1991**, *(S),* 144; *J. Chem. Res.* **1991**, *(M)*, 1501.
33. Nyassé, B.; Grehn, L.; Maia, H. L. S.; Monteiro, L. S.; Ragnarsson, U. *J. Org. Chem.* **1999**, *64*, 7135.
34. Okuda, T.; Zahn, H. *Chem. Ber.* **1965**, *98*, 1164.
35. Labia, R.; Morin, C. *J. Am. Chem. Soc.* **1986**, *51*, 249.
36. Stanfield, C. F.; Cody, W. L.; Hruby, V. J. *J. Org. Chem.* **1986**, *51*, 5153.
37. Yim, N. C. F.; Bryan, H.; Huffman, W. F.; Moore, M. L. *J. Org. Chem.* **1988**, *53*, 4605.
38. Pérez, M.; Pleixats, R. *Tetrahedron* **1995**, *51*, 8355.
39. Probert, J. M.; Rennex, D.; Bradley, M. *Tetrahedron Lett.* **1996**, *37*, 1101.
40. Barbaste, M.; Rolland-Fulcrand, V.; Roumestant, M. L.; Viallefont, P.; Martinez, J. *Tetrahedron Lett.* **1998**, *39*, 6287.
41. Rolland-Fulcrand, V.; Haroune, N.; Roumestant, M. L.; Martinez, J. *Tetrahedron: Asymmetry* **2000**, *11*, 4719.
42. Naidu, B. N.; Sorensen, M. E.; Connolly, T. P.; Ueda, Y. *J. Org. Chem.* **2003**, *68*, 10098.
43. Chapman, C. J.; Wadsworth, K. J.; Frost, C. G. *J. Organomet. Chem*. **2003**, *680*, 206.
44. Chapman, C. J.; Frost, C. G. *Adv. Synth. Catal*. **2003**, *345*, 353.
45. Navarre, L.; Darses, S.; Genet, J.-P. *Eur. J. Org. Chem.* **2004**, 69.
46. Navarre, L.; Darses, S.; Genet, J.-P. *Angew. Chem., Int. Ed*. **2004**, *43*, 719.
47. Enders, D.; Chen, Z-X. *Lett. Org. Chem.* **2005**, *2*, 156-159.
48. (a) Ferreira, P. M. T.; Maia, H. L. S.; Monteiro, L. S.; Sacramento, J. *Tetrahedron Lett.* **1999**, *40*, 4099. (b) Ferreira, P. M. T.; Maia, H. L. S.; Monteiro, L. S.; Sacramento, J.; Sebastião, J. *J. Chem.*

Soc., Perkin Trans 1 **2000**, 3317. (c) Ferreira, P. M. T.; Maia, H. L. S.; Monteiro, L. S.; Sacramento, J. *J. Chem. Soc., Perkin Trans 1* **2001**, 3167.
49. Grehn, L.; Gunnarsson, K.; Ragnarsson, U. *Acta Chem. Scand.*, *Ser. B* **1987**, *41*, 18.
50. Ferreira, P. M. T.; Maia, H. L. S.; Monteiro, L. S. *Tetrahedron Lett*. **2003**, *44*, 2137.
51. Maia, H. L. S.; Monteiro, L. S.; Degerbeck, F.; Grehn, L.; Ragnarsson, U. *J. Chem. Soc., Perkin Trans. 2* **1993**, 495.
52. Ferreira, P. M. T.; Maia, H. L. S.; Monteiro, L. S.; Sacramento, J. *Tetrahedron Lett.* **2000**, *41*, 7437.
53. Ferreira, P. M. T.; Maia, H. L. S.; Monteiro, L. S. *Eur. J. Org. Chem.* **2003**, 2635.
54. Ferreira, P. M. T.; Maia, H. L. S.; Monteiro, L. S. *Tetrahedron Lett.* **2002**, *43*, 4495.
55. Rodrigues, A.; Ferreira, P. M. T.; Monteiro, L. S. *Tetrahedron* **2004**, *60*, 8499.
56. Ferreira, P. M. T.; Monteiro, L. S. *Eur. J. Org. Chem*. **2006**, 3226.
57. Ferreira, P. M. T.; Maia, H. L. S.; Monteiro, L. S. *Tetrahedron Lett.* **2002**, *43*, 4491.