Free-Radical Reactions in the Synthesis of α-Amino Acids and Derivatives

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Received June 21, 1996 (Revised Manuscript Received October 15, 1996)

Contents

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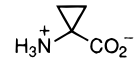
I. Introduction

α-Amino acids are one type of the main building blocks of living systems, being the principal components of all naturally occurring peptides and proteins. Although only 20 compounds of this class occur commonly in biological systems, the group is much more diverse, with over 500 α-amino acids having been identified in nature.[1] These compounds and their derivatives display quite diverse physiological and pharmaceutical activity. As a consequence, methods for their synthesis have attracted a considerable amount of attention.[2−4]

In the past, most of the focus of amino acid synthesis has been on the use of ionic procedures. Until recently, free-radical reactions had received little attention, by comparison, in this and in many other areas of chemistry, because the potential to exploit radical reactions to achieve transformations in a controlled manner had not been recognized. Now, the realization that radical reactions can be accomplished in good yield, with a high degree of regio- and stereocontrol,[5−8] has aroused interest in this area. Often the products of the radical processes are quite distinct from those formed in ionic reactions of the same substrates, and under some circumstances the reagents and reaction conditions used in the free-radical procedures are more compatible with the functional groups present and the stability of the compounds involved.

The purpose of this review is to collate examples of the use of free-radical reactions in the synthesis of α-amino acids and their derivatives. The examples have been categorized according to the methods of generation of the amino acid radicals and the types of reactions that the radicals undergo. Reaction mechanisms and other factors governing the processes have been discussed, in order to draw correlations and reach general conclusions.

Since the emphasis of the review is on the use of radical reactions of amino acid derivatives in synthesis, examples are only included where reaction products have been isolated and the amino acid moieties have remained intact throughout the transformations. Accordingly, spectroscopic studies have not been surveyed and radiation studies, which result mainly in decarboxylation or deamination of amino acids, have not been incorporated. These aspects of the free-radical chemistry of amino acids have been the subjects of earlier reviews.[9−11] Many biochemical reactions involve amino acid radicals.[12] For example, there is strong evidence that free radicals are intermediates in penicillin and cephalosporin biosynthesis[13−26] and in the bioconversion of the cyclopropyl amino acid **1** to ethylene[27] during the maturation of fruits. Although it could be argued that these reactions involve amino acid radicals in synthesis, processes of this type are only discussed in this review when there has been a deliberate attempt to accomplish a transformation of a novel substrate using an enzyme.



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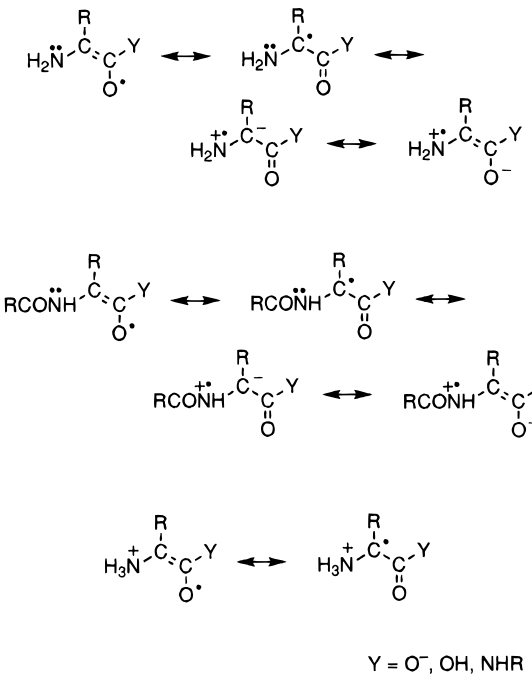


Figure 1. Resonance contributors of α-carbon-centered radicals.

The free radicals that form from amino acids and their derivatives may be divided into three classes: sulfur radicals, aromatic radicals, and aliphatic radicals. Of these, only the aliphatic radicals are characteristic of amino acids and, accordingly, they are the main topic of this review. Reactions involving sulfur radicals, such as those occurring with the thiol and disulfide bonds of cysteine and cystine, respectively, are not included. Material relating to aromatic radicals, such as phenolic coupling, has not been incorporated. Applications of phenolic coupling to the synthesis of peptide secondary metabolites, such as lysobactin and vancomycin, have been discussed recently.[28]

II. α-Carbon-Centered Radicals

The aliphatic radicals which are peculiar to amino acids and their derivatives are α-carbon-centered radicals.[29] When the amino group is present in the free-base form or protected as an amide, there is extensive delocalization of the unpaired spin density in a radical of this type (Figure 1), through the action of the electron-releasing amino or amido substituent and the electron-withdrawing carboxy group. These radicals belong to the class of captodative radicals. The captodative effect was postulated by Viehe *et al.*[30,31] as the combined resonance effect of electron-withdrawing (capto) and electron-donating (dative) substituents on a radical center, leading to enhanced stabilization of the radical. The theoretical basis of this concept was originally formulated by Dewar, in 1952.[32] Analogous concepts of "push−pull" stabilized radicals and merostabilization were independently developed by Balaban[33] and by Katritzky *et al.*,[34−36] respectively.

Much of the interest in this area has been aimed to determine the extent to which the combined stabilization provided by the substituents is synergistic.[37−45] The determination has not been straightforward, as it has been difficult to delineate the effects of radical stabilization from steric and polar effects, and other factors affecting radical formation. Nevertheless, it now seems clear that there is synergistic stabilization of amino carboxy substituted radicals[39,41,42,44−47] and additive, but not synergistic, stabilization of amido carboxy substituted radicals.[47] In any event, the extent of electron delocalization by the substituents is substantial, and the complementary electron-donating and electron-withdrawing effects of the substituents, to delocalize charge and unpaired spin density that develop in reaction transition states facilitate radical formation.[48] By comparison, when the amino group is protonated or quaternized, dative stabilization of a radical centered on the α-carbon does not occur (Figure 1).[46,49] Consequently these radicals are much less stable and much less easily formed. Not surprisingly, therefore, a recent study[50] on the aqueous solution thermochemistry of the radicals of glycine indicated that the α-carbon-centered radicals **2** and **3** are the most stable.

2 **3**

Given their relative instability, it is only as expected that reports of α-carbon-centered amino acid radicals having the amino group protonated or quaternized are rare. There has been a limited number of reports of radicals substituted with free amino groups, but the most common are those involving amido-substituted analogues. Presumably this latter observation is not a reflection of the relative stability of the amino- and amido-substituted radicals, as delocalization of the nitrogen electrons over the carbonyl group would be expected to decrease the extent of dative radical stabilization provided by an amido group. Instead it seems more likely that the predominance of examples of amido-substituted radicals reflects the compatibility of this moiety with the reagents, solvents, and reaction conditions used typically for free-radical transformations. By comparison, the basic conditions required to maintain an amino group in the nonprotonated form are incompatible with free-radical reactions such as halogenation, they limit the range of potential substrates to those that are base-stable, and they lead to competing electron-transfer reactions of amines, which result in deamination.

III. Hydrogen-Transfer Reactions

As mentioned above, free-radical reactions offer particular advantages where they afford products different from those obtained in ionic reactions of the same substrates, or where it is not possible to accomplish the same transformations in ionic processes. One reaction class for which this is particularly pertinent is that of hydrogen atom-transfer reactions. These provide the facility either to introduce a functional group or to form a carbon−carbon bond, by directly substituting for hydrogen at a position which need not be activated by adjacent

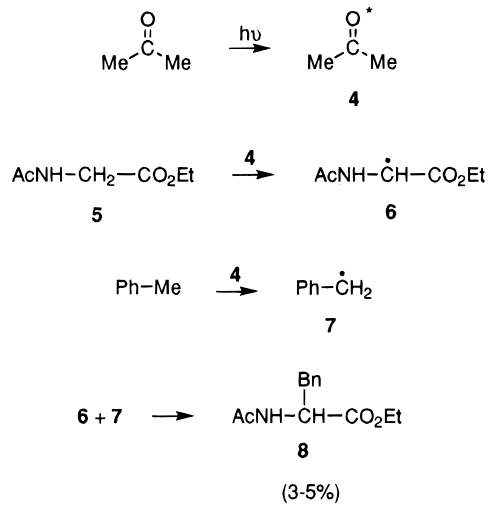
functional groups. The anionic counterparts of these processes involve quite strong bases, and the regioselectivity of proton transfer is typically quite different to that of hydrogen atom transfer, with aliphatic carbanions generally forming most easily at least-substituted positions, while the radicals form more readily at the most-substituted centers.

A. Intermolecular To Give α-Carbon-Centered Radicals

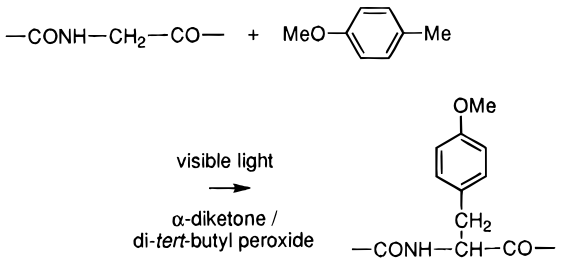
Most intermolecular hydrogen atom-transfer reactions of amino acid derivatives afford mainly α-carbon-centered radicals, presumably as a result of the particular stability of these species, as outlined above. Many examples of these involve hydrogen transfer from derivatives of glycine, the simplest amino acid. They often involve the introduction of an amino acid side chain, with formation of a carbon−carbon bond.

Pioneering work in this area was reported by Elad *et al.*[51−53] This group established that irradiation of a mixture of *N*-acetylglycine ethyl ester (**5**), toluene, and acetone, with ultraviolet light, resulted in the formation of *N*-acetylphenylalanine ethyl ester (**8**), albeit in low yield.[51] A logical mechanism for this reaction is shown in Scheme 1. In the later work,[52,53] it was shown that the reactions could be carried out using visible light instead of ultraviolet light, if an α-diketone, such as biacetyl or camphorquinone, and di-*tert*-butyl peroxide were used in place of acetone. With this combination of reagents, the α-diketone acts as the light-absorbing system, to induce photolysis of the peroxide, and the resultant *tert*-butoxy radicals (and/or methyl radicals produced by *β*-scission of the *tert*-butoxy radicals) act as the hydrogen atom-abstracting species. Using visible light substantially increased the scope of the procedure, to allow both the reaction and production of amino acid derivatives sensitive to ultraviolet light. Accordingly, reaction with 4-methoxytoluene, in place of toluene, resulted in the conversion of glycine derivatives to the corresponding tyrosine derivatives (Scheme 2). In other variations of this procedure, replacing toluene with 4-fluorotoluene, or acetic acid or acetic anhydride, resulted in the conversion of glycine derivatives to the 4-fluorophenylalanine and aspartic

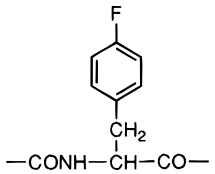
Scheme 1



Scheme 2



acid analogues **9** and **10**, respectively.[52,53] In each of these reactions it was necessary to use a large excess of the alkylating agent, in order to obtain the necessary balance between hydrogen atom transfer from that agent and the glycine derivative.



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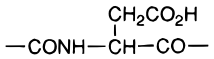

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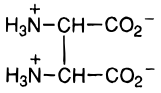
Processes competing with the cross-coupling reactions to give the alkylated glycine derivatives are dimerization of the glycinyl radicals and of the radicals derived from the alkylating species. For example, in the reactions of glycine containing peptides with toluene, biphenyl and 1,2-diaminosuccinic acid (**11**) were identified as components of the products of hydrolysis of the reaction mixtures.[54] These dimers provide good evidence of the radical nature of the reactions. Presumably they are formed only in small quantities because the competing cross-coupling reaction is favored by the different electronegativities of the reacting species.



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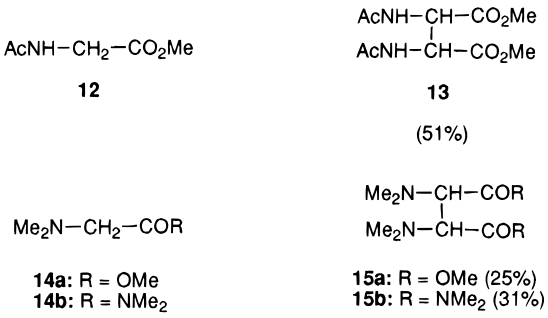
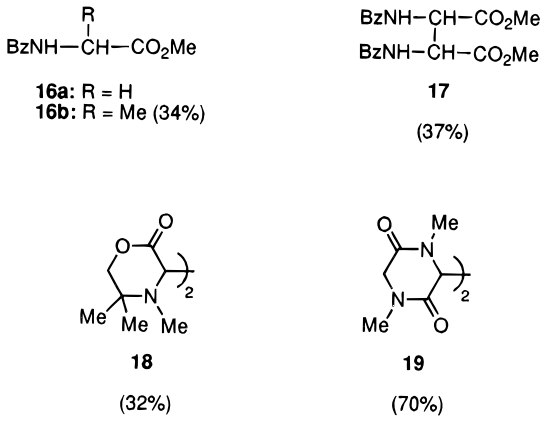
In the absence of an alkylating agent, dimer formation becomes the major reaction pathway, affording cross-linked amino acid derivatives which are of interest in the synthesis of conformationally constrained peptides. Irradiation of a mixture of *N*-acetylglycine methyl ester (**12**) and di-*tert*-butyl peroxide in benzene gave a 1:1 mixture of the diastereomers of the dimer **13**.[55] The reactions can be initiated thermally as well as photochemically, and they proceed when the amino group is present either as a free base or protected as an amide. Accordingly, the glycine derivatives **14a** and **14b** reacted with di-*tert*-butyl peroxide, at 160 °C, to give the corresponding dimers **15a** and **15b**.[30]

As noted above, in reactions with di-*tert*-butyl peroxide, *tert*-butoxy radicals, and/or methyl radicals may be the hydrogen atom-abstracting agents. Methyl radicals are prone to react with the glycinyl radicals, as seen in the photochemical reaction of *N*-benzoylglycine methyl ester (**16a**) to give the corresponding alanine derivative **16b** and a 1:1

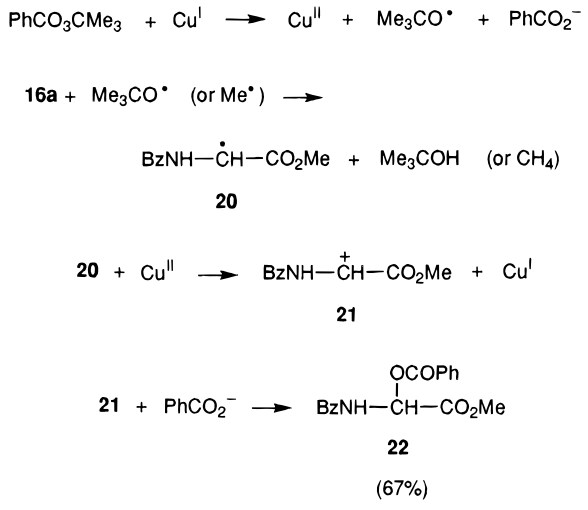


mixture of the diastereomers of the dimer **17**, in approximately equal ratio.[56] Apparently, this process does not detract seriously from the synthetic utility of the dimerization reaction, however, and more recently the method has been used to prepare the dimers **18**[57] and **19**.[47]



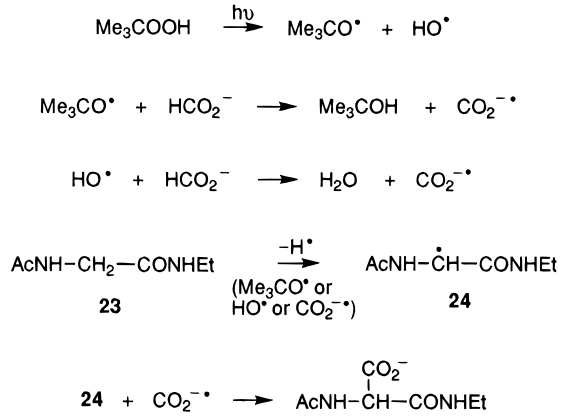
Hydrogen atom-transfer reactions can also be used for the direct introduction of a functional group in place of hydrogen at the α-carbon of a glycine derivative. For example, the copper-catalyzed reaction of *N*-benzoylglycine methyl ester (**16a**) with *tert*-butyl perbenzoate gave the benzoate **22**.[58] This compound has been used in the synthesis of α-substituted and cross-linked amino acid derivatives.[59,60] The probable mechanism[61] of production of the benzoate **22** is outlined in Scheme 3. The electron-

Scheme 3



transfer reaction of the radical **20** indicates the ease of formation of the carbocation **21**. Oxidations of this

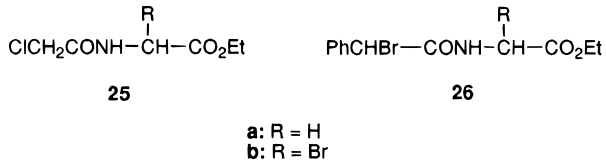
Scheme 4



type are also apparent in a number of other reactions of glycinyl radicals which are discussed in more detail below.

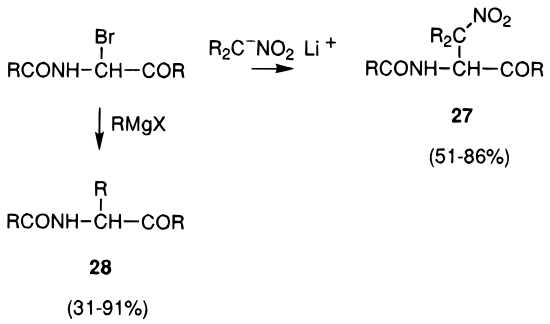
Several alternative procedures for functionalization of glycine derivatives through hydrogen-transfer reactions have been reported. On irradiation with *tert*-butyl hydroperoxide in the presence of formate, glycine derivatives give the corresponding α-carboxy-substituted products, from coupling of the intermediate α-carbon-centered radicals with carbon dioxide radical anion, as illustrated in Scheme 4 for the glycine derivative **23**.[62] This mechanism is more probable than reaction of the amino acid radicals with carbon dioxide, where normally the reverse process of decarboxylation is thermodynamically preferred. This procedure may constitute a biomimetic synthesis of α-carboxyglycine derivatives and indicates that the occurrence of such residues in proteins may be a result of their oxidative degradation.[63]

A far more common approach to the synthesis of α-functionalized glycine derivatives involves free-radical bromination, either with bromine or *N*-bromosuccinimide. In the original report in this area, Lidert and Gronowitz[64] described reactions of the glycine derivatives **25a** and **26a** with the succinimide, to give the corresponding bromides **25b** and **26b**.

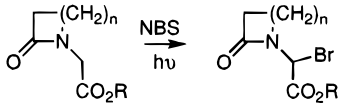


α-Halo amino acids of this type tend to be unstable and for that reason they are isolated only rarely. Nevertheless compounds prepared via halides of this type are usually obtained in high yield, indicating that the bromination is quite practical and efficient. α-Bromoglycine derivatives obtained in this manner have been used extensively in synthesis.[64−76] For example, reactions with Grignard reagents afforded the α-substituted amino acid derivatives **28**,[67] while reactions with lithium alkyl nitronates gave the corresponding *β*-nitro amino acid derivatives **27**[68,75] (Scheme 5). Reactions with higher order cuprates, trimethylsilyl enol ethers, and *β*-dicarbonyl compounds,[69] and arylation of bromoglycine derivatives,[72] have also been reported.

Scheme 5



Scheme 6



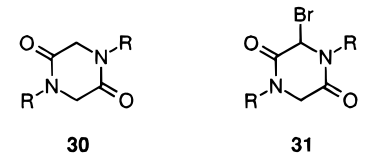
a: n = 1
b: n = 2

The exocylic functionalization of *N*-(alkoxycarbonyl)methyl-substituted *β*- and *γ*-lactams (Scheme 6)[77] is a variation of the bromination procedure. It provides an attractive alternative to the glyoxalate route for the synthesis of *N*-(α-haloalkyl)-substituted lactams,[78,79] which have been used widely in the synthesis of *β*-lactam antibiotics. In the absence of the alkoxycarbonyl substituent, reaction at the exocyclic carbon adjacent to the lactam nitrogen is no longer favored and endocyclic reaction occurs.[80]

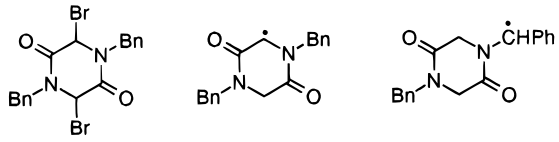
Glycine residues in diketopiperazines have also been converted to the corresponding bromides. The original procedure reported by Trown[81] involved heating the substrate with bromine in *o*-dichlorobenzene at 150 °C. Under these vigorous conditions, it is likely that the transformation could occur via either a radical or an ionic mechanism. More recently, conditions typical of free-radical reactions have been used to promote the same conversions. For example, the diketopiperazine **30a** gave the dibromide **32** in virtually quantitative yield, on treatment with *N*-bromosuccinimide and benzoyl peroxide, at reflux in carbon tetrachloride.[82] The lack of competing reactions of the exocyclic methylene groups is worthy of note, as it demonstrates the relative ease of formation of the radicals **33** and **34**. The brominated diketopiperazines have also attracted interest in synthesis.[82–84]

Contrary to initial indications,[85] it is possible to selectively brominate one glycine residue in a symmetric diketopiperazine, without complications from subsequent reactions.[86,87] The diketopiperazines **30a–c** are each approximately seven times more reactive than the corresponding bromides **31a–c** in reactions with *N*-bromosuccinimide. With a limiting amount of that reagent the monosubstituted species **31a–c** were produced and converted to the corresponding α-methoxyglycine derivatives, in overall yields ranging from 41–61%.[87] The monobromides **31a–c** have particular potential for the asymmetric synthesis of diketopiperazine derivatives.[85,86,88]

The potential to exploit bromoglycine derivatives in synthesis has prompted the use of chiral auxiliaries in order to obtain stereocontrol. Accordingly, the glycine derivatives **35a–41a** gave the corresponding bromides **35b–41b**, each in high yield, on treatment with *N*-bromosuccinimide,[74,89–96] and these bromides **35b–41b** have been used in a variety of asymmetric syntheses.[74,89–106] The regioselectivity of reaction of the glycine derivative **35a** again illustrates the ease of formation of α-carbon-centered amino acid radicals, given that there has been no indication of competing reaction at either of the benzylic positions in this molecule.[89] The bromides **35b–41b** were obtained as various mixtures of diastereomers. It seems likely that the ratios of isomers reflect the thermodynamic equilibria attained through reaction via the corresponding imines or iminium ions, rather than the stereochemistry of bromine incorporation in the reactions of the intermediate radicals. In any event, the stereochemistry of the bromides **35b–41b** is not particularly important as most reactions of these compounds involve intermediates which are planar at the α-carbon. In the case of the bromination of the 8-phenylmenthol derivative **38a**, experiments with deuteriated analogues established a high degree of stereoselectivity in the hydrogen atom transfer to give the intermediate glycinyl radical.[92]

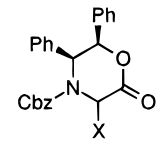


a: R = Bn
b: R = Me
c: R = CH_2Ph-*p*-OMe



The reactions described above involve glycine derivatives which have the amino and carboxyl groups protected in a variety of different forms. However, the effect of these substituents on reactivity toward hydrogen atom transfer can only be delineated where direct comparisons have been made, or where more than one glycine residue is present, for example in a peptide derivative, where there is the possibility of selective reaction. The carboxyl group may be present as either a free acid, a carboxylate anion, an ester, or as is the case with most amino acid residues in peptides and proteins, an amide (or aminocarbonyl group). The relative effects of the methyl ester and *N*-methylamide groups were examined through comparison of reactions of the glycine derivatives **16a** and **42a** on photolysis with di-*tert*-butyl peroxide.[107] The amide **42a** reacted to give the corresponding dimer **43** and the alanine derivative **42b**, in an analogous manner to the reaction of the ester **16a** described above, and in competitive experiments the amide **42a** reacted 2.3 times faster than the ester **16a**.

At first sight, it appears that this activation by the aminocarbonyl group compared to the ester is reflected in the reaction of *N*-benzoylglycylglycine



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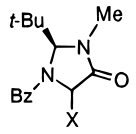

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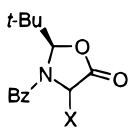

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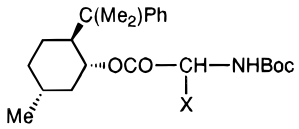

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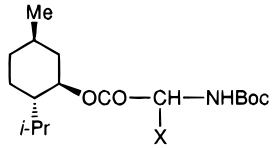

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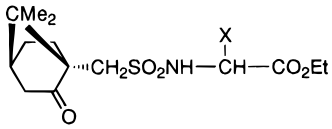

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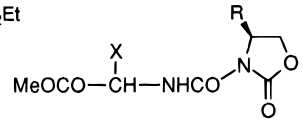
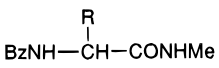


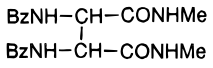
R = *i*-Pr, Bn, *i*-Bu or *t*-Bu

41

a: X = H
b: X = Br



42a: R = H
42b: R = Me (20%)

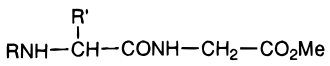


43

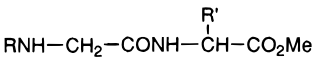
(21%)

methyl ester (**44a**) carried out under similar conditions.[107] The derivatives of alanylglycine **44b** and glycylalanine **45b** were produced in a 10:1 ratio, presumably as a result of the relative ease of formation of the radicals **46a** and **47a**. Likewise, reaction of the dipeptide derivative **44a** with *N*-bromosuccinimide gave the bromide **44c**, and none of the regioisomer **45c** was detected.[108] However, the factors contributing to regioselectivity in reactions of peptide derivatives are more complex. Irradiation of a mixture of *N*-acetylglycylglycine methyl ester (**44d**), toluene, and acetone gave the phenylalanine derivatives **44e** and **45e** in the ratio 52:48, indicating little difference between the relative ease of formation of the radicals **46b** and **47b** in that case.[109,110]

The nature of substitution of the amino group in an amino acid derivative also affects the reactivity toward hydrogen transfer. Reaction of *N*-(trifluoroacetyl)glycylglycine methyl ester (**44f**), as described above for the nonfluorinated analogue **44d**, gave the corresponding phenylalanine derivatives **44g** and **45g** in the ratio 43:57.[109,110] Presumably, the different product ratios obtained in the reactions of the acetamide **44d** and the trifluoroacetamide **44f** reflect the relative ease of formation of the radicals **46b** and **47b**, and **46c** and **47c**. In turn, this can be attributed to the decreased dative stabilization of the radical **46c** by the trifluoroacetamido substituent, compared to the effect of the acetamido group on the radical **46b**. Again the situation is more complicated than

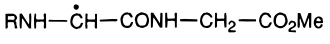


44

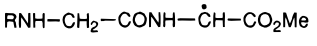


45

a: R = Bz, R' = H
b: R = Bz, R' = Me
c: R = Bz, R' = Br
d: R = Ac, R' = H
e: R = Ac, R' = Bn
f: R = CF_3CO, R' = H
g: R = CF_3CO, R' = Bn
h: R = CF_3CO, R' = CH_2Ph-*p*-OMe
i: R = CF_3CO, R' = CH_2CO_2H



46



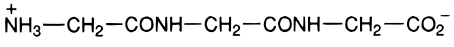
47

a: R = Bz
b: R = Ac
c: R = CF_3CO

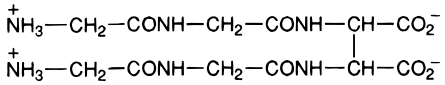
this simple interpretation would indicate; however, as the reaction of *N*-(trifluoroacetyl)glycylglycine methyl ester (**44f**) carried out using visible light, biacetyl, and di-*tert*-butyl peroxide, in place of ultraviolet light and acetone, gave a 1:1 mixture of the phenylalanine derivatives **44g** and **45g**.[52] The obvious difference between these reactions is the nature of the hydrogen atom-abstracting species, but it is not clear why that leads to a change in the ratio of products. Despite their stability, captodative radicals still undergo radical coupling reactions at rates which are diffusion controlled.[50,111] Under these conditions the nature of the alkylating agent should not affect the ratio of products of reactions of the dipeptide derivative **44f**. As expected, therefore, when using visible light, biacetyl, and di-*tert*-butyl peroxide, with *p*-methoxytoluene and acetic acid or acetic anhydride, the derivatives of tyrosine **44h** and **45h** and aspartic acid **44i** and **45i** were each obtained in equal ratios.[52]

The substantially greater activating effect of an amido substituent compared to a protonated amino group on formation of a radical on the adjacent carbon is clearly illustrated in the reaction of triglycine **48** with di-*tert*-butyl peroxide.[112] The dimers **49** and **50** were formed in approximately equal quantities, each as a 1:1 mixture of diastereomers, and glycylglycylalanine (**51**) and glycylalanylglycine (**52**) were formed in a 5:1 ratio. There was no evidence of formation of other dimeric species or of alanylglycylglycine (**53**), indicating that hydrogen atom transfer from triglycine **48** affords the radicals **54** and **55**, in preference to the radical **56**. It is also apparent from these results that the radical **54** forms in preference to the regioisomer **55**.

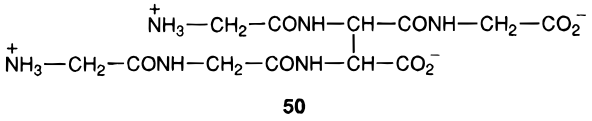
Whereas the reaction of *N*-benzoylglycylglycine methyl ester (**44a**) with *N*-bromosuccinimide gave only the bromide **44c** from reaction of the *N*-terminal glycine residue, the analogous reaction of *N*-phthaloylglycylglycine methyl ester (**57a**) gave only the bromide **57b** from reaction of the *C*-terminal amino acid residue.[108] The regioselectivity of the latter reaction indicates that the α-position of an *N*-phtha-



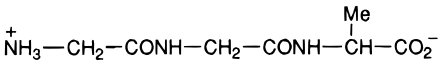
48



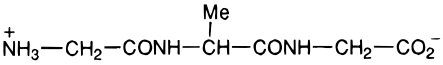
49



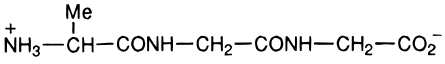
50



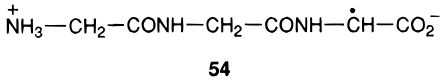
51



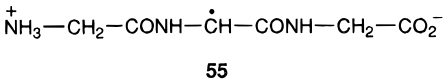
52



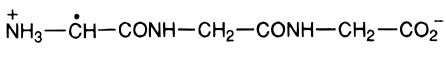
53



54



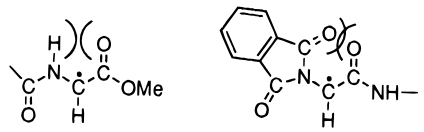
55



56

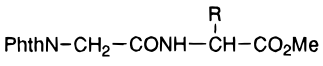
loyl-substituted amino acid derivative is less reactive than that of an *N*-acylamino acid derivative toward hydrogen atom transfer. This may be attributed to the relative stability and ease of formation of the corresponding α-carbon-centered radicals **58** and **59**. Whereas the acylamino-substituted radical **58** can adopt a planar conformation, in which there is good overlap of the π-orbitals of the amido substituent with the semioccupied p-orbital of the radical, steric interactions distort the radical **59** from planarity and limit the extent of orbital overlap in that case (Figure 2). In addition, the π-electrons of the imido substituent are less available to stabilize the radical **59** through resonance. The phthaloyl substituent is also likely to hinder approach of bromine atom to the *N*-terminal glycine residue in the dipeptide derivative **57**.

The relative effects of amido and imido substituents on radical formation are also illustrated in reactions of the diketopiperazines **30b**, **60a**, and **60b**.[113] In competitive experiments, the *N*,*N*-dimethyl-substituted compound **30b** reacted with *N*-bromosuccinimide to the exclusion of the *N*,*N*-diacetyl derivative **60a**. In the case of the asymmetric pip-

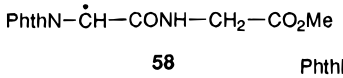


58 59

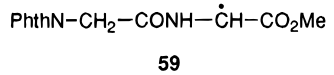
Figure 2. Nonbonding interactions associated with planar conformations of the radicals **58** and **59**.



57a: R = H
57b: R = Br

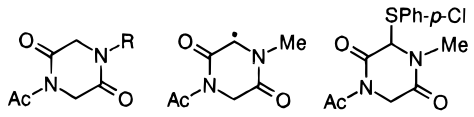


58



59

erazinedione **60b**, a strong preference was observed for reaction via the radical **61**, and a reaction with 1 mol equiv of *N*-bromosuccinimide, followed by treatment with *p*-chlorothiophenol, gave only the product **62**.



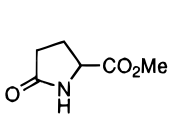
60a: R = Ac
60b: R = Me

61

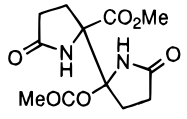
62

(74%)

In each of the reactions described above, the α-carbon-centered amino acid radical was derived by hydrogen atom transfer from a derivative of glycine. Derivatives of many other amino acids also form α-carbon-centered radicals in a similar manner and in some cases these react in an identical way to the corresponding glycinyl radicals. For example, the irradiation-induced reaction of methyl pyroglutamate (**63**) with di-*tert*-butyl peroxide afforded a 1:1 mixture of the diastereomers of the dimer **64**,[55] in a reaction directly analogous to that of the glycine derivative **16a** already discussed. Likewise, reactions of the alanine derivatives **16b** and **42b** with di-*tert*-butyl peroxide gave the corresponding dimers **65a** and **65b**, in a procedure analogous to that for reaction of the glycine derivatives **16a** and **42a**.[107,114] The reactions

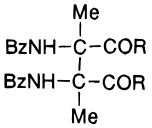


63

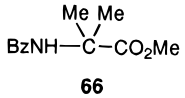


64

(64%)



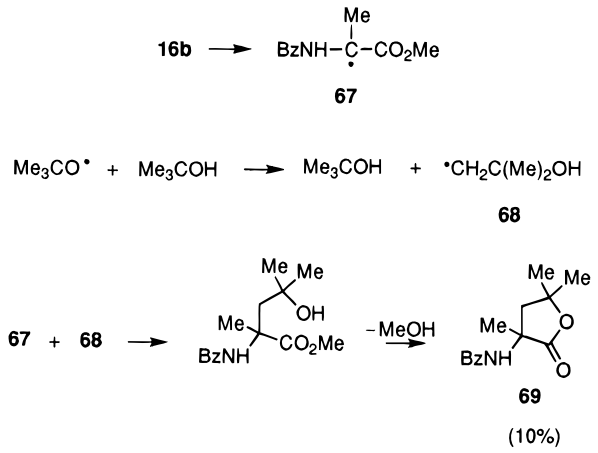
65a: R = OMe (20%)
65b: R = NHMe



66

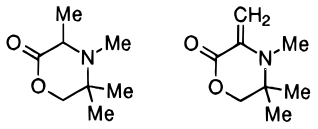
(10%)

Scheme 7



of the alanine derivatives **16b** and **42b** were relatively inefficient, however, and competing reactions were more prevalent. The alaninate **16b** gave more substantial quantities of the α-methyl derivative **66** and the lactone **69** was also produced. A mechanism of formation of the lactone **69** is shown in Scheme 7.

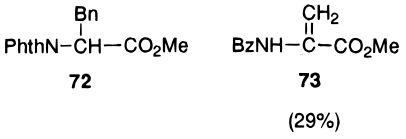
In other cases the presence of the amino acid side chain has a more significant effect on the course of reaction. An abstractable hydrogen at the *β*-position can lead to the formation of an α,*β*-dehydro amino acid derivative from an α-carbon-centered amino acid radical. Treatment of the alanine derivative **70** with di-*tert*-butyl peroxide gave the dehydroalanine derivative **71**.[57] While nickel peroxide often causes



70 **71**

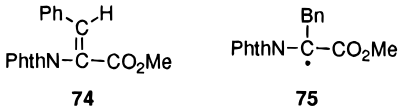
cleavage of α-carbon−nitrogen bonds in amino acid derivatives,[115] the compounds **16b**, **72**, **76a**, and **76b** reacted to give the corresponding unsaturated derivatives **73**, **74**, **77a**, and **77b**, presumably via the radicals **67**, **75**, **78a**, and **78b**, respectively.[116] The regioselective reaction of the *C*-terminal amino acid residue in each of the dipeptide derivatives **76a** and **76b** may reflect the effect of the phthalimido protecting group, described above. Alternatively, the nickel peroxide may selectively complex aspartate residues.

The oxidation of the oxazolines **79** to the respective oxazoles **80**, using either *N*-bromosuccinimide or *tert*-butyl perbenzoate with cuprous bromide, may involve an analogous process of hydrogen atom transfer from the corresponding intermediate radicals **81**. Alternatively, the radicals **81** may be reacting to give the corresponding bromides **82a** and benzoates **82b**, which subsequently undergo elimination to give the oxazoles **80**.[117,118] In any event, incorporation of a functional group at the α-position, in place of hydrogen, is a common mode of reaction for derivatives of other amino acids, as it is for derivatives of glycine. This occurs in the autoxidation of amino acid derivatives, as illustrated by the reactions of the cyclic



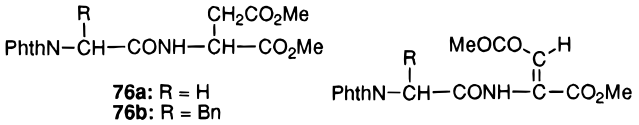
72 **73**

(29%)



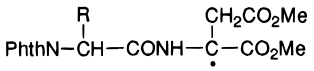
74 **75**

(20%)

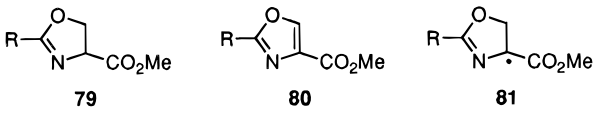


76a: R = H
76b: R = Bn

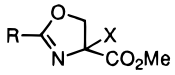
77a: R = H (84%)
77b: R = Bn (27%)



78a: R = H
78b: R = Bn

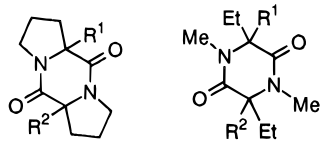


79 **80** **81**



82a: X = Br
82b: X = OBz

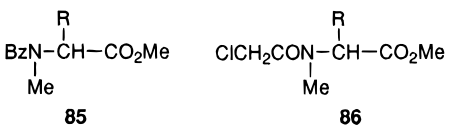
dipeptides **83a** and **84a** to give the corresponding hydroperoxides **83b**, **83c**, **84b**, and **84c**.[119,120]



83 **84**

a: $R^1 = R^2 = H$
b: R^1 = OOH, R^2 = H
c: $R^1 = R^2$ = OOH

Free radical reactions with molecular bromine or *N*-bromosuccinimide result in α-bromination, as illustrated in the reactions of the sarcosine derivatives **85a** and **86a**, to give the halides **85b** and **86b**, respectively.[64,70,121] In these examples, further reac-

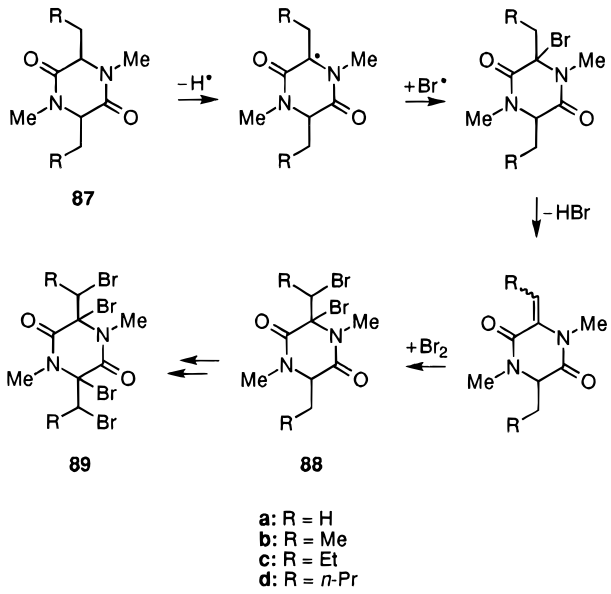


85 **86**

a: R = H
b: R = Br

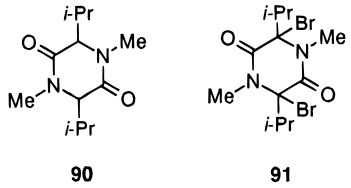
tion through loss of hydrogen bromide is not possible, but where there is an amino acid side chain with a *β*-hydrogen, the ionic elimination process often occurs

Scheme 8



a: R = H
b: R = Me
c: R = Et
d: R = *n*-Pr

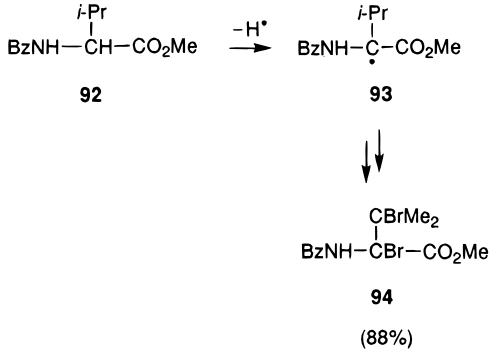
subsequent to the radical bromination, to give dehydro amino acid derivatives which may react by bromine addition. Accordingly, the diketopiperazines **87a**−**d** gave the corresponding dibromides **88a**−**d** and tetrabromides **89a**−**d**, from reaction with 2 and 4 equiv of *N*-bromosuccinimide, respectively,[122] presumably via the reaction sequence shown in Scheme 8. Evidence in support of this sequence is provided from the reactions of related compounds. The valylvaline derivative **90** reacted with 2 equiv of *N*-bromosuccinimide to give the dibromide **91**.[122] In



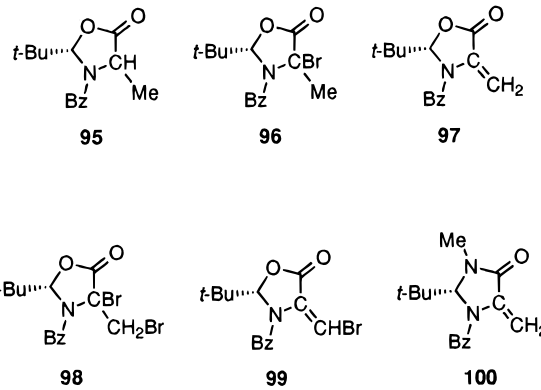
this case the reaction stops at this stage, probably because the elimination of hydrogen bromide is inhibited by steric constraints. The valine derivative **92** afforded the dibromide **94** in a reaction which displayed a deuterium isotope effect of 3.7 for cleavage of the α-carbon−hydrogen bond, indicating reaction via the corresponding α-carbon-centered radical **93**[121,123,124] (Scheme 9).

Often elimination/addition reaction sequences of the type shown in Scheme 8 complicate reactions of

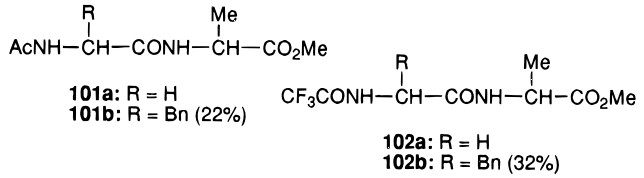
Scheme 9



alanine derivatives with *N*-bromosuccinimide.[64,121] Small changes in reaction conditions affect the relative efficiency of the initial radical reaction and the subsequent ionic processes. As a result, the outcome of reactions of this type tends to be quite variable. Zimmermann and Seebach[94] reported that treatment of the alanine derivative **95** with 1 equiv of *N*-bromosuccinimide afforded the bromide **96**, which underwent base-induced elimination to give the dehydroalanine derivative **97**. Other workers[125] found that elimination/addition reactions of the bromide **96** complicated the preparation of this compound, and found it to be preferable to use 2 equiv of *N*-bromosuccinimide, to extend the reaction to the formation of the dibromide **98**, from which the dehydroalanine derivative **97** was prepared by treatment with sodium iodide in acetone. Even so, the dibromide **98** reacted further to give the bromoalkene **99**,[126,127] unless the radical bromination was particularly efficient and the reaction time was kept short to limit the extent of the subsequent ionic reactions.[128] A similar approach was used to prepare the lactam **100**.[125] These dehydroalanine derivatives **97** and **100** have attracted considerable interest in the asymmetric synthesis of amino acids, using cycloaddition and ionic and free-radical reactions.[94,125−135] The latter are discussed in more detail below.



Where derivatives of different amino acids are present in a system the possibility of selective reaction exists. Under these circumstances glycine residues show particular reactivity in hydrogen atom transfer reactions to give the corresponding α-carbon-centered radicals. This is apparent from the work of Elad *et al*.[52−54,109,110,136−138] In early reports they noted that alkylation of the glycylalanine derivatives **101a** and **102a**, by irradiation in the presence of toluene and acetone, resulted in the selective reaction of the glycine residue in each case, to give the corresponding phenylalanine derivatives **101b** and **102b**.[109,136] Reactions of this type occur without



racemization of other amino acid residues, which can therefore act as chiral auxiliaries in the production

of the new chiral center at the α-carbon of the glycine residue.[54,109,137] Accordingly, synthetic polypeptides consisting of glycine and (*S*)-alanine in a 1:2 ratio showed a preferential reactivity of glycine over alanine of 30:1, and the production of (*S*)- and (*R*)-phenylalanine residues in the ratio 70:30, while peptides containing (*S*)-proline and glycine in a 2:1 ratio formed (*S*)- and (*R*)-phenylalanine in the ratio 38:62.[54,137] Selective reaction of glycine residues in small peptides which also contained leucine, valine, phenylalanine and *O*-methyltyrosine was also reported.[52,110] The degree of selectivity for reaction of glycine residues and the extent of asymmetric induction in the reactions were found to be dependent on the location of the glycine residues in the peptides and to increase as the molecular weight of the peptides increased.[137,138] Selective reaction of glycine residues was also observed in reactions of lysozyme, collagen, gelatin, and ribonuclease.[53] In the case of lysozyme, analysis of the amino acids obtained from hydrolysis of the product of a reaction carried out using ultraviolet radiation indicated that lysine, arginine, aspartic acid, threonine, serine, glutamic acid, proline, alanine, valine, methionine, isoleucine, and leucine were little affected under the conditions required for reaction of glycine, but histidine, cysteine, tyrosine, phenylalanine and tryptophan decomposed. It is likely that the decomposition of the aromatic amino acid residues is at least partly due to the use of ultraviolet radiation and that this could be avoided using the alternative system involving visible light, although results for reaction under these conditions were not reported. In a more recent example of the selective reaction of glycine residues in free-radical reactions of proteins, Koch *et al.*[62] applied the procedure for the carboxylation of glycine derivatives using *tert*-butyl hydroperoxide and formate to the generation of α-carboxyglycine residues in gelatin.

The selective reaction of glycine derivatives to give α-carbon-centered radicals is contrary to the expectation that tertiary radicals are more stable, and should form more easily, than secondary radicals. Studies of reactions of the amino acid derivatives **16a**, **16b**, and **92** with *N*-bromosuccinimide, through formation of the corresponding radicals **20**, **67**, and **93**, have provided an explanation for this anomaly.[124,139] The rate of reaction of the glycine derivative **16a** to give the secondary radical **20** is faster than the rate of reaction of the corresponding alanine derivative **16b** to give the tertiary radical **67**, which is in turn faster than the rate at which the valine derivative **92** reacts to give the radical **93**. The relative ease of formation of the radicals **20**, **67**, and **93** can be attributed to the relative stability of these species. Stabilization of the radicals **20**, **67**, and **93** will result from overlap of their semioccupied p-orbitals with the π-orbitals of the amido and methoxycarbonyl substituents. There will be maximum overlap of these orbitals in planar conformations of the radicals **20**, **67**, and **93** (Figure 3). The alaninyl radical **67** will be destabilized compared to the glycinyl radical **20** due to nonbonding interactions associated with planar conformations, and the valinyl radical **93** will be even less stable due to more severe nonbonding interactions. Consistent with this explanation, the relative rates of reaction of the derivatives of alanine **67** and sarcosine **85a** are nearly identical, since the extent of nonbonding interactions associated with planar conformations of the radicals **67** and **103** is very similar. Methyl pyroglutamate (**63**) reacts faster than the glycine derivative **16a**, because the radical **104** can adopt planar conformations which are relatively free of nonbonding interactions and because formation of the radical **104** is favored by the relief of ring strain and by the release of steric interactions between the methoxycarbonyl substituent and the β-hydrogens.[140−143]

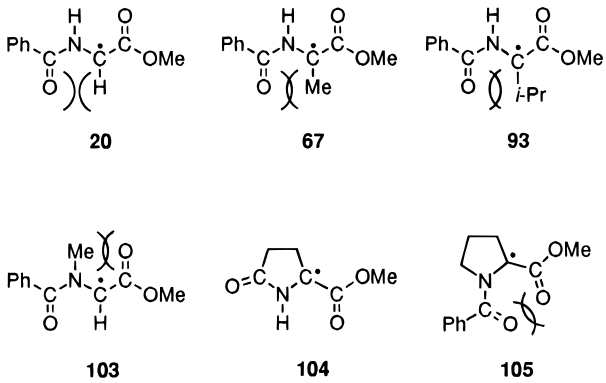
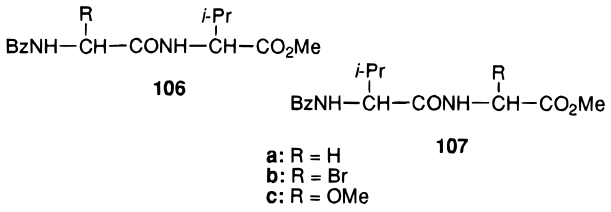
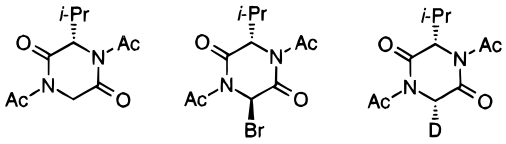


Figure 3. Nonbonding interactions associated with planar conformations of the radicals **20**, **67**, **93**, and **103**−**105**.

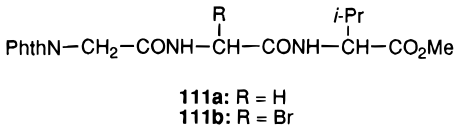
The selectivity for hydrogen atom transfer from glycine residues on treatment of peptides with *N*-bromosuccinimide is illustrated in the reactions of the glycylvaline and valylglycine derivatives **106a** and **107a** to give the corresponding bromides **106b** and **107b,** from which the methoxides **106c** and **107c** were obtained in overall yields of 73% and 65%, respectively.[70,124] Compounds of this type have considerable potential for the asymmetric synthesis of amino acid derivatives, through their use to generate the corresponding reactive *N*-acylimines and electrophilic and radical glycine equivalents.[70,124,144] This use of another amino acid in the peptide as the chiral auxiliary offers several advantages. Normally both enantiomers of the auxiliary are cheap and readily available, and they are easily recovered after reaction, through hydrolysis of the product peptide, for use in subsequent reactions. Reactions of cyclic dipeptide derivatives are of particular interest in this area, due to the relatively rigid spatial arrangement of the chiral and prochiral center. The diketopiperazine **108** gave the bromide **109** from reaction with *N*-bromosuccinimide, due to selective reaction of the glycine residue, and this material was reduced with deuterium over palladium chloride to give the deuteride **110** in 90% enantiomeric excess.[144] Other effects can be exploited in conjunction with the selectivity for reaction of glycine residues, to achieve regioselective functionalization of peptides. On treatment with *N*-bromosuccinimide, the tripeptide derivative **111a** gave only the bromide **111b**, as a result of the effect of the phthaloyl protecting group outlined above.[108]

As an alternative to hydrogen atom transfer, amines and their derivatives also react by electron



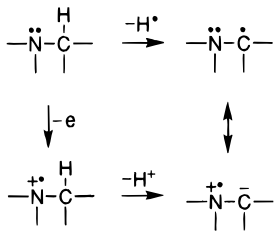


(86%)



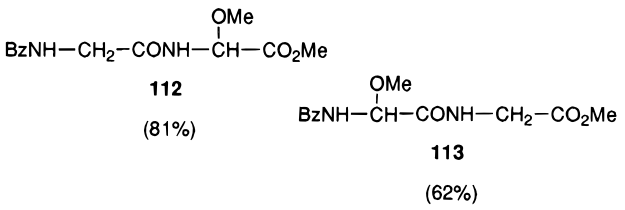
transfer followed by proton loss (Scheme 10). It is possible to form an α-carbon-centered amino acid

Scheme 10

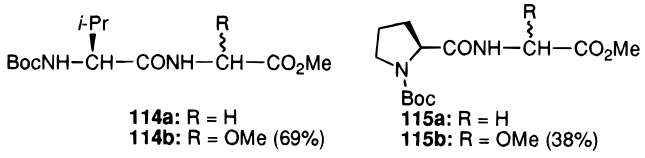


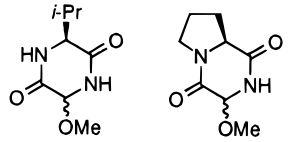
radical by either method, and in some cases there may be ambiguity about which mechanism is involved. The electron-transfer process may be accomplished either using chemical reagents or electrochemically, and a variety of *N*-protected amino acid derivatives react in this manner to give the corresponding imines.[145−151] Depending on the reaction conditions, these may react *in situ* to give α-methoxy[145,147−150] and α-hydroxy[149] amino acid derivatives. The products have the potential to react in similar ways to those described above for other α-functionalized amino acid derivatives.

With dipeptide derivatives, the regioselectivity of reaction depends on the amino acid constituents and the protecting groups. For example, anodic oxidation of *N*-benzoylglycylglycine methyl ester (**44a**) in methanol gave the methoxide **112**, from selective reaction of the *C*-terminal amino acid residue, while reactions of *N*-[(2-nitrophenyl)sulfenyl]-protected dipeptides occurred mainly at the *N*-terminal positions.[152] The regioselectivity of the electrochemical reaction of the dipeptide **44a** is complementary to that of the bromination of the same compound, discussed above. The dipeptide **44a** reacted with *N*-bromosuccinimide and then methanol to give the methoxide **113**,[108] which is isomeric to the oxidation product **112**. Oxidation of the valyl- and prolylglycine derivatives **114a** and **115a** gave the methoxides **114b** and **115b**, respectively.[152,153] Presumably the regioselectivity of these reactions reflects the relative ease of electron



transfer from amides and carbamates. On hydrolysis with formic acid the methoxides **114b** and **115b** gave the corresponding diketopiperazines **116** and **117**, which are of interest in the asymmetric synthesis of amino acid derivatives.



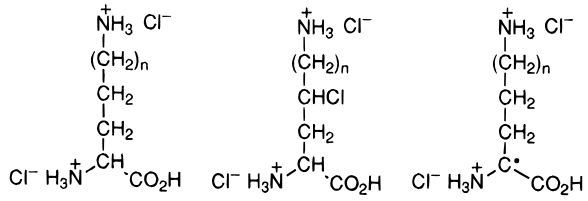


B. Intermolecular To Give Side-Chain Radicals

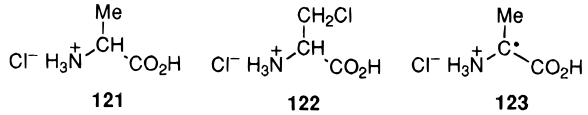
The tendency for hydrogen atom-transfer reactions of amino acid derivatives to give mainly α-carbon-centered radicals is a direct consequence of the stability of these radicals. In order for reaction to occur on the side chain of an amino acid derivative, in a controlled manner, either the side chain radical must be the more stable or other factors must determine the outcome of the radical process. Reactions on amino acid side chains are of particular interest because the chirality of the starting materials can then be exploited in asymmetric synthesis.

Side-chain chlorination of the amino acid derivatives **118**, **121**, **124a**,**b**, and **128** occurred on photolysis of solutions with chlorine in sulfuric acid.[154−157] In these cases the regioselectivity of reaction is determined by the inductive electron-withdrawing effect of the carboxy and protonated amino groups and the inability of the latter to stabilize the corresponding α-carbon-centered radicals **120**, **123**, **126a**,**b**, and **130** through resonance delocalization of the unpaired spin density. In the transition state for hydrogen atom transfer in a free-radical halogenation reaction, an electron-deficient center is formed at the site of hydrogen abstraction, with the result that reactions of the amino acid derivatives **118**, **121**, **124a**,**b**, and **128** occur remote from the inductively electron-withdrawing substituents, to give the corresponding chlorides **119**, **122**, **125a**,**b**, and **129**.[154,156,157] The inductive effect of the substituents is highlighted in the reaction of the isoleucine derivative **128** to give the chloride **129**, via the δ-centered primary radical **131**, instead of the tertiary β- and secondary γ-centered radicals **132** and **133**.[156]

The inductive effect of substituents is also illustrated in the regioselectivity of hydrogen atom-

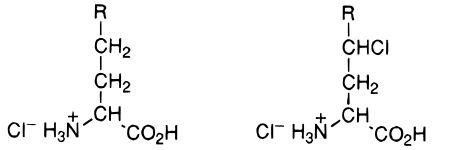


118a: n = 1 **118b:** n = 2 **119a:** n = 1 **119b:** n = 2 (74%) **120a:** n = 1 **120b:** n = 2

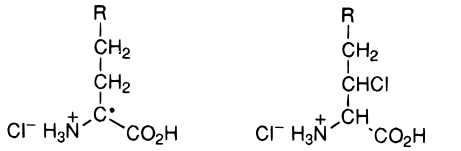


121 **122** **123**

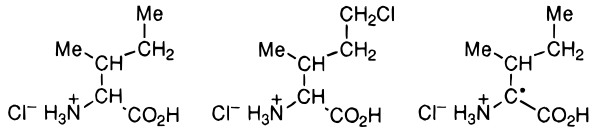
(78%)



124a: R = H **124b:** R = CO_2H **125a:** R = H (40%) **125b:** R = CO_2H (25%)

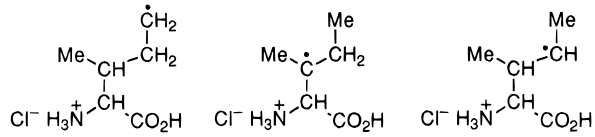


126a: R = H **126b:** R = CO_2H **127a:** R = H **127b:** R = CO2H



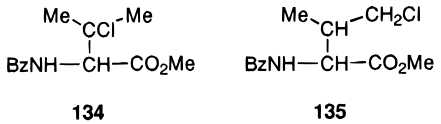
128 **129** **130**

(33%)

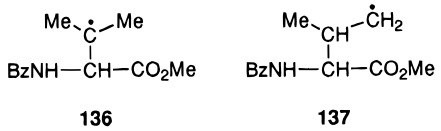


131 **132** **133**

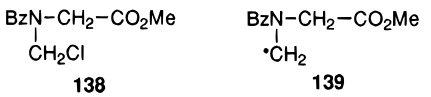
transfer reactions of *N*-benzoylvaline methyl ester (**92**). As indicated above, the valine derivative **92** reacted with *N*-bromosuccinimide via the α-carbon-centered radical **93**. By contrast, radical reactions with sulfuryl chloride afforded the chlorides **134** and **135**, via the radicals **136** and **137**, respectively.[123,158,159] With little carbon−hydrogen bond homolysis in the transition state for hydrogen transfer in the chlorination, the regioselectivity in this case is controlled by the inductive electron-withdrawing effect of the amido and carboxy groups, acting to retard attack at the α-position by electrophilic radicals involved in the hydrogen abstraction. The reaction with *N*-bromosuccinimide is more sensitive to radical-stability effects since there is a greater degree of bond homolysis in the transition state. Further studies indicated that the valine derivative **92** reacted by hydrogen atom transfer to *tert*-butoxy radical to give a mixture of the radicals **93** and **136**.[121] The extent of carbon−hydrogen bond homolysis in the transition state for hydrogen transfer to *tert*-butoxy radical is intermediate between that for chlorination and bromination, with the result that there is a balance between the resonance and inductive effects of the substituents in this case. The contrast in the regioselectivity of the reactions of the valine derivative **92** is reflected in reactions of the sarcosine derivative **85a**.[121] Whereas reaction with *N*-bromosuccinimide gave the α-bromide **85b** via the radical **103**, chlorination afforded the (halomethyl)glycine derivative **138** via the radical **139**. Again, the difference can be attributed to the balance between the resonance and inductive effects of the methoxycarbonyl group.



134 **135**



136 **137**

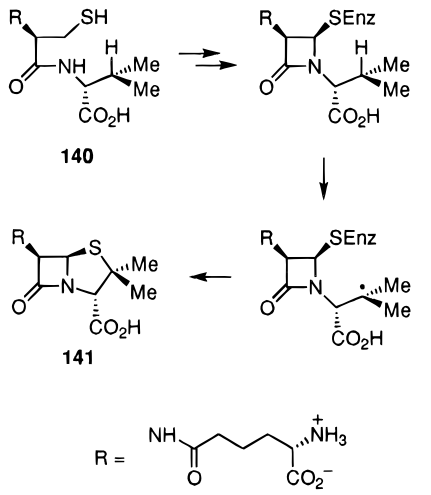


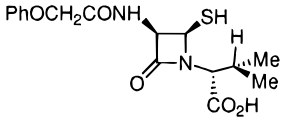
138 **139**

(89%)

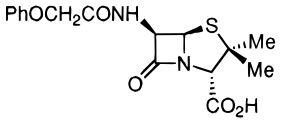
The reactions of the valine derivative **92** indicate that the regioselectivity of hydrogen atom transfer from the valine residue during the biosynthesis of isopenicillin N (**141**) from Arnstein's tripeptide **140** (Scheme 11) can be attributed to polar effects,[158] and the isopenicillin N synthetase enzyme is not essential for regiocontrol. Accordingly, treatment of the β-lactam **142** with Udenfried's reagent [iron(II) sulfate, ascorbic acid, and ethylenediaminetetraacetic acid] in the presence of oxygen gave the penicillin **143**, in the absence of the enzyme.[16] Further evidence that the enzyme does not control the regioselectivity is

Scheme 11





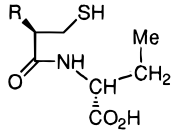
142



143

provided in reactions of modified substrates with the enzyme.[14,160] The α-aminobutyrate derivative **144** gave a mixture of the penam (**147**) and the cepham (**148**), indicating that the radicals **145** and **146** were both produced (Scheme 12).[160] With the modified

Scheme 12



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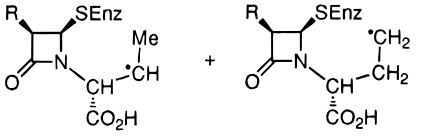
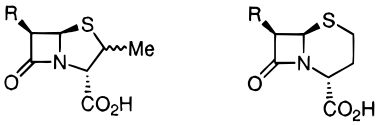
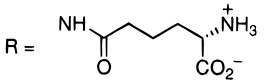


145 146



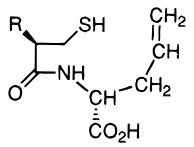
147 148



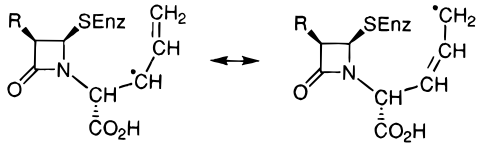
substrates, the balance between the reaction pathways to give penams and cephams appears to be determined primarily by the relative stability of the intermediate side chain radicals.[14,160] The radical nature of the enzyme-catalyzed processes was confirmed through reactions of unsaturated substrate analogues[15,18,161,162] and cyclopropylamino acid derivatives.[23,25,26,163] For example, the allylglycine derivative **149** and the cyclopropylalanine derivative **152** afforded the products **151** and **154**, respectively, from allylic rearrangement and ring opening through the corresponding intermediate radicals **150** and **153** (Schemes 13 and 14).

In addition to the polar effects outlined above, steric effects can lead to reactions occurring on the side chains of amino acid derivatives. Accordingly, the proline derivative **155** reacted to give the radical **156**, instead of by hydrogen transfer from the α-carbon, presumably as a result of the severe nonbonding interactions associated with planar conformations of the radical **105** (Figure 3), distorting that species from planarity and limiting resonance delocalization of the unpaired spin density.[139] The steric and

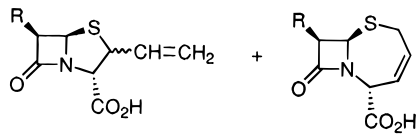
Scheme 13



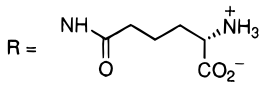
149



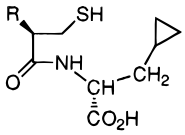
150



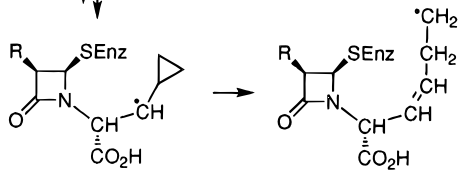
151



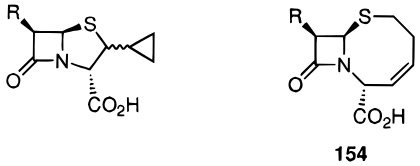
Scheme 14



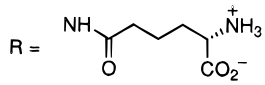
152



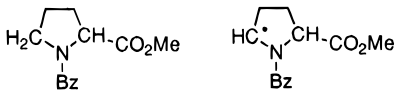
153



154

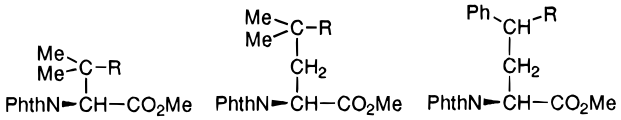


electronic effects of the phthalimido group, illustrated in the reactions of the peptide derivatives **57a** and **111a** described above, also lead to side chain reac-



155 156

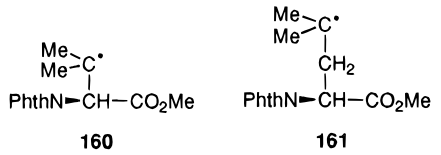
tions of *N*-phthaloyl-protected amino acid derivatives.[108] This is exemplified in the reactions of the amino acid derivatives **157a**−**159a** and **165a** to give the corresponding bromides **157b**−**159b** and **165d**, through reaction with *N*-bromosuccinimide. The reactions occur via the most stable side chain radicals **160**−**163**, and the chiral integrity of the amino acid derivatives **157a**−**159a** and **165a** at the α-position is maintained in the bromides **157b**−**159b** and **165d**. This approach to the side chain functionalization of amino acid derivatives has been used in the stereocontrolled synthesis of dehydro,[164] cyclopropyl,[165] and hydroxy[28,166−169] amino acids.



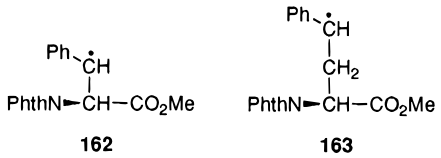
157a: R = H
157b: R = Br (87%)

158a: R = H
158b: R = Br (82%)

159a: R = H
159b: R = Br (69%)

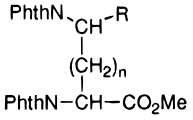


160 161



162 163

While the deactivating effect of the phthalimido group is apparent at the α-position of amino acid derivatives, where the carboxyl group also places steric and electronic constraints on reactions,[48] alone and where the steric constraints are less severe, a phthalimido substituent activates the adjacent carbon toward hydrogen atom transfer. This is indicated in the regioselective side chain bromination of the amino acid derivatives **164a** and **164b**.[48,170] The product bromides **164c** and **164d** are masked imines/aldehydes, and the reaction may therefore have some potential for the oxidative regioselective side chain deamination of diamino acid derivatives.



164a: n = 2, R = H
164b: n = 3, R = H
164c: n = 2, R = Br (74%)
164d: n = 3, R = Br (85%)

Side chain bromination of *N*-phthaloylamino acid derivatives can be accomplished with the carboxyl

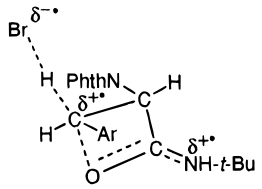
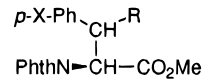
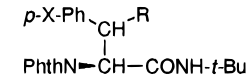


Figure 4. Neighboring group participation in hydrogen atom transfer from the phenylalanine derivatives **166a**−**c**.

group present either as the free acid or protected as an amide or ester. In the reactions of the phenylalanine derivatives **165a**−**c** and **166a**−**c** to give the corresponding bromides **165d**−**f** and **166d**−**f**, the amides **166a**−**c** reacted approximately five times faster than the corresponding esters **165a**−**c**.[171] The



165a: X = H, R = H
165b: X = NO_2, R = H
165c: X = OAc, R = H
165d: X= H, R = Br (83%)
165e: X = NO_2, R = Br (97%)
165f: X = OAc, R = Br (100%)

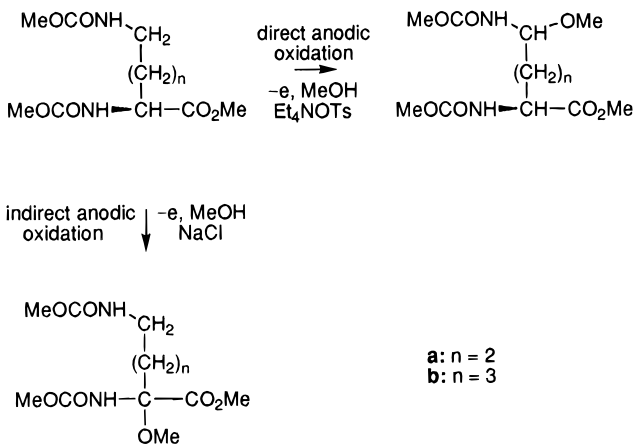


166a: X = H, R = H
166b: X = NO_2, R = H
166c: X = OAc, R = H
166d: X= H, R = Br (100%)
166e: X = NO_2, R = Br (97%)
166f: X = OAc, R = Br (98%)

effect of the aromatic ring substituents indicates that the hydrogen atom transfer occurs through an electron-deficient transition state and the effect of the carboxyl group can be attributed to stabilization of the electron-deficient center through an unusual mode of neighboring group participation (Figure 4).

Electron-transfer reactions of amino acid derivatives can also lead to side-chain functionalization, although the regioselectivity is restricted to reaction at or near an electron-donating group. With derivatives of diamino acids such as ornithine and lysine, oxidation can occur either at the α-position or on the side chain, depending on the conditions used (Scheme 15).[145,172−174] Cyclizations of the side chain-substituted derivatives have been used for the synthesis of optically active piperidine and pyrrolidine alkaloids.[172,173,175,176] In principle, electron transfer from proline derivatives, followed by proton loss, and then addition of methanol to the resultant imines, could afford products methoxylated at either the 2- or 5-position. In practice, the 5-methoxy derivatives are obtained.[177−181] Interest in these compounds in

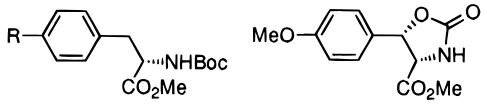
Scheme 15



a: n = 2
b: n = 3

synthesis[181−189] stems from the optical activity of the proline derivatives which is retained in the products.

Oxidation of the tyrosine derivative **167a** with potassium persulfate in the presence of cupric sulfate gave the cyclic carbamate **168**, as a result of reaction at the benzylic position, and it seems likely that this reaction involves electron transfer from the aromatic ring since the corresponding phenylalanine derivative **167b** was unreactive.[190] Benzylic bromination of the

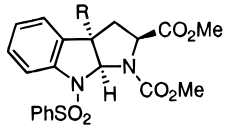


167a: R = OMe
167b: R = H

168

(55%)

tryptophan derivative **169a** gave the bromide **169b**, although it is interesting to note that the reaction was stopped at approximately 90% conversion because attempts to drive the reaction to completion resulted in further reaction of the bromide **169b** at the amino acid α-carbon.[191,192] The amino acid derivative **169a** also underwent benzylic oxidation, to give the alcohol **169c**, on treatment with ceric ammonium nitrate.[191,192] The demethylation of *N*-methylated diketopiperazines on treatment with ceric ammonium nitrate[86] and the *N*-methylation of amino acid carbamates through their copper-catalyzed reactions with *tert*-butyl perbenzoate[58] are also likely to involve electron-transfer processes.



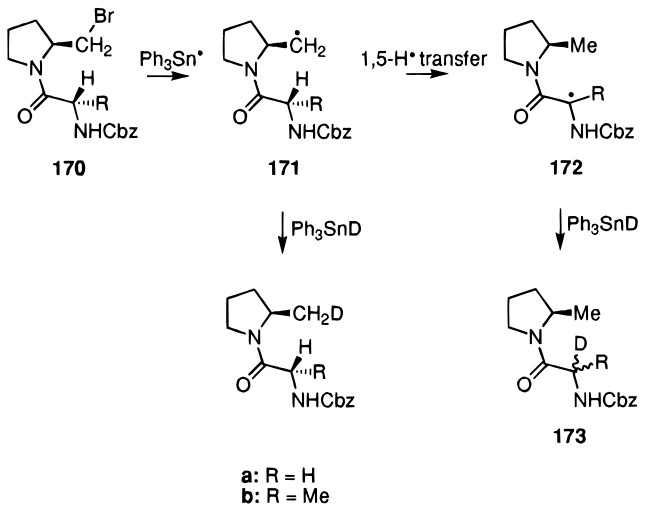
169a: R = H
169b: R = Br (72%)
169c: R = OH (65%)

C. Intramolecular

The reactions described above involve intermolecular hydrogen transfer to give amino acid radicals. Analogous intramolecular processes have also been reported, and while these offer particular opportunities for regiocontrolled synthesis, the reactions are affected by many of the same factors that affect their intermolecular counterparts. Thus, the stability of the product radicals has a major effect on the outome of reactions, and α-carbon-centered radicals are readily formed.

On treatment of the bromides **170a** and **170b** with triphenyltin deuteride, the corresponding deuteriated products **173a** and **173b** were obtained. This indicates that the radicals **171a** and **171b** formed by bromine transfer from the substrates **170a** and **170b**, respectively, each underwent 1,5-hydrogen atom transfer, to give the corresponding α-carbon-centered radicals **172a** and **172b** (Scheme 16).[193] The reactions of the radicals **171a** and **171b** were studied as a model for reactions catalyzed by the enzyme pyruvate formate-lyase.[193] The photochemically induced cyclization of the *N*-(benzoylethyl)glycine derivatives **174** occurred diastereoselectively, in this case via 1,6-

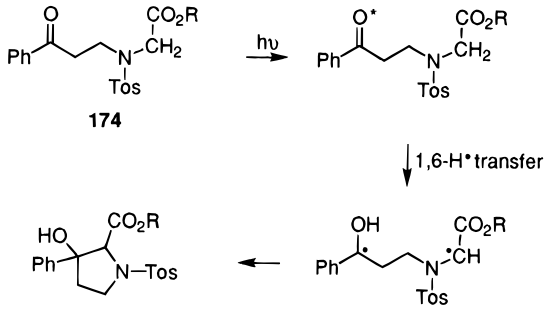
Scheme 16



170 **171** **172** **173**

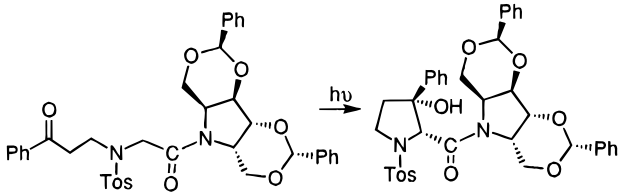
a: R = H
b: R = Me

Scheme 17



174

Scheme 18



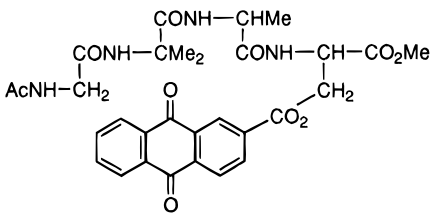
175 **176**

(70%)

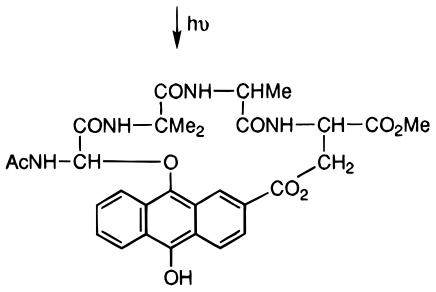
hydrogen atom transfer (Scheme 17).[194,195] Similar products were obtained from reactions of derivatives of alanine and phenylglycine.[194] More recently, reactions of analogous C_2-symmetric pyrrolidine derivatives have been found to occur with a high degree of stereocontrol, as illustrated in the reaction of the glycinamide **175** to give only the stereoisomer **176** (Scheme 18).[196]

While 1,5- and 1,6-hydrogen atom transfer reactions are not unusual, the efficiency of intramolecular hydrogen abstraction tends to decrease as the distance between the origin and terminus of hydrogen migration increases. In this regard the photochemical reactions of oligopeptide-linked anthraquinones, reported by Maruyama *et al.*[197,198] are of special interest. In examples typical of the work, photolysis of solutions of the anthraquinone derivatives **177** and **179**, in acetonitrile, afforded the corresponding cyclized products **178** and **180** (Schemes 19 and 20). These reactions involve 1,19- and 1,21-hydrogen atom-transfer reactions, and they are each highly regioselective for coupling the α-carbon of the glycine

Scheme 19



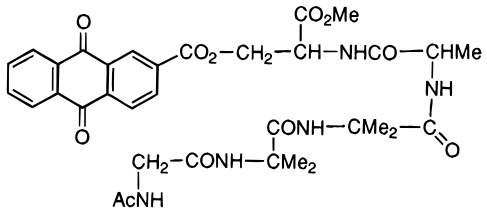
177



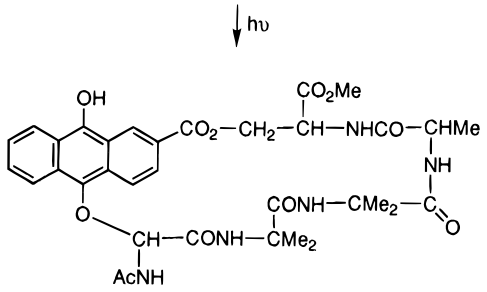
178

(58%)

Scheme 20



179

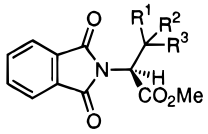


180

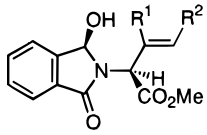
(57%)

residue to a specific carbonyl group of the anthraquinone moiety. In part this must be attributable to the rigid structure of the anthraquinone, but it seems likely that the reactions are also facilitated by the particular stability of α-carbon-centered amino acid radicals.

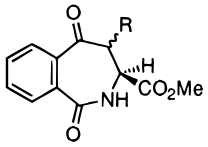
In some cases, geometrical constraints prevent intramolecular hydrogen transfer reactions to give α-carbon-centered radicals, and under these circumstances, side chain radicals are formed. This is the situation with the photolysis of *N*-phthaloylamino acid derivatives,[199,200] where intramolecular reaction of the photochemically excited phthalimide to give an α-centered radical would involve an unusual 1,4-hydrogen atom transfer. In typical photochemical reactions of *N*-phthaloylamino acid derivatives, the esters **157a** and **181a**−**d** underwent a variety of reactions to give the unsaturated amino acid derivatives **182a**−**d**, the ring-expanded products **183a** and **183b**, and the tricyclic amino acid derivative **184**.[199,200]



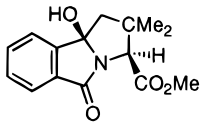
181a: R^1 = Me, R^2 = R^3 = H
181b: R^1 = Et, R^2 = R^3 = H
181c: R^1 = Me, R^2 = Et, R^3 = H
181d: R^1 = R^2 = R^3 = Me



182a: R^1 = R^2 = H (20%)
182b: R^1 = Me, R^2 = H (85%)
182c: R^1 = H, R^2 = Me (15%)
182d: R^1 = Et, R^2 = H (75%)



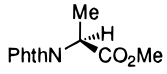
183a: R = H (60%)
183b: R = Me (60%)



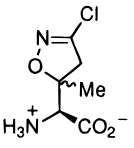
184

(90%)

In each case reaction occurred with retention of stereochemical integrity at the α-position and with high diastereoselectivity. The products **182a**−**d**, **183a**,**b**, and **184** can be attributed to reaction of the first singlet excited state phthalimido group, by 1,6-hydrogen atom transfer. The product diradicals then react by further hydrogen atom transfer to give the alkenes **182a**−**d**, by rearrangement to give the bicyclic products **183a** and **183b**, or by coupling to give the tricyclic species **184**. It is interesting to note that the alanine and phenylalanine analogues **185** and **165a** of the amino acid derivatives **157** and **181a**−**d** did not react on photolysis, indicating that 1,5-hydrogen transfer to the excited state phthalimide does not occur.[199,200] The route outlined above for the preparation of the β,γ-dehydrovaline derivative **182b** has been exploited in the asymmetric synthesis of the amino acid derivative **186**.[201]



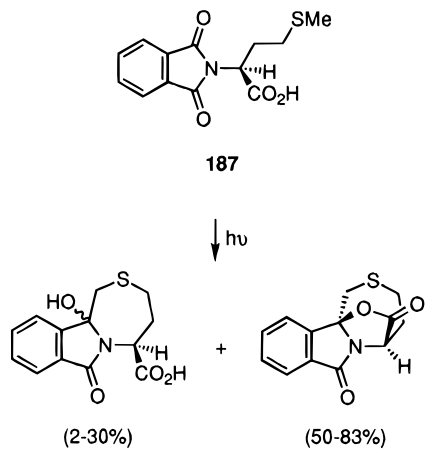
185



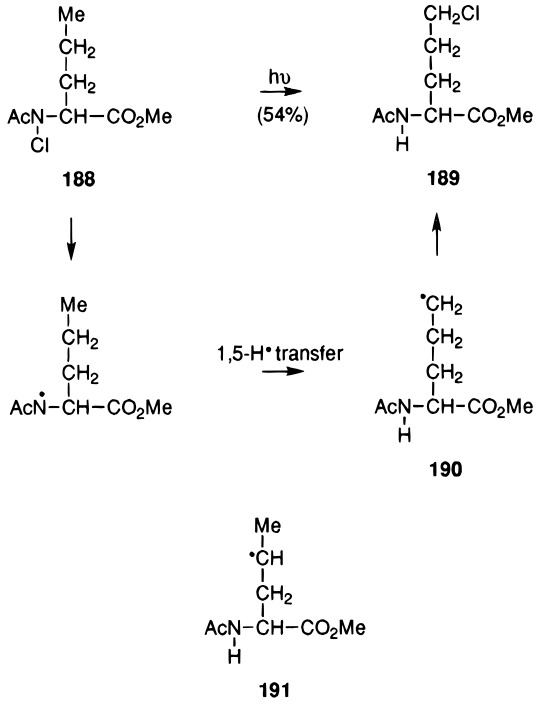
186

For the photochemically initiated hydrogen transfer reactions of *N*-phthaloylamino acid derivatives, the carboxyl group must be protected, otherwise decarboxylation is the predominant reaction.[202,203] Alternatively, electron-transfer reactions sometimes compete effectively with the hydrogen abstraction and decarboxylation processes.[200,203−208] This accounts for the reactions of the methionine derivative **187** (Scheme 21) and analogous reactions of the corresponding methyl ester.[200,203,205] Evidence strongly supporting the electron-transfer mechanism of these reactions comes from the fact that the sulfoxide and sulfone analogues of the sulfide **187** reacted solely by decarboxylation.[209] While the *N*-phthaloylphen-

Scheme 21



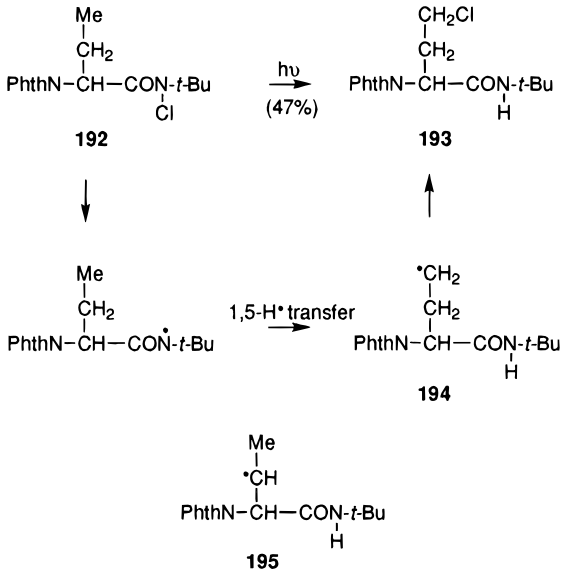
Scheme 22



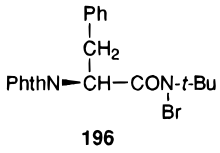
ylalanine derivative **165a** is photochemically inert,[199,200] analogues bearing electron-donating substituents attached to the aromatic ring undergo photocyclization,[210−212] irrespective of protection of the carboxyl group. Again this is consistent with an electron-transfer mechanism.

Amidyl radicals generated by photolysis of *N*-halo amino acid derivatives also react via intramolecular hydrogen atom-transfer to give side-chain radicals. Accordingly the α-amido pentanoate derivative **188** afforded the chloride **189**, while photolysis of the butyramide **192** gave the chloride **193** (Schemes 22 and 23).[213] Presumably, each reaction involves a 1,5-hydrogen atom transfer. Formation of the primary radicals **190** and **194**, in preference to the secondary radicals **191** and **195**, respectively, reflects the relative ease of 1,5-hydrogen transfer compared to the corresponding 1,4-processes. Nevertheless, it appears that the phenylalanine derivative **196** affords a mixture of diastereomers of the bromide **166d**

Scheme 23



through intramolecular 1,4-hydrogen atom transfer.[171]

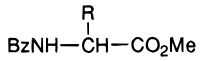


IV. Functional Group Transformations

While free-radical reactions may be used to introduce a functional group or to form a carbon−carbon bond, by substituting for hydrogen, they can also be used to remove or manipulate a functional group and, in a limited number of cases, for the cleavage of a carbon−carbon bond. In the simplest examples, functional groups may be replaced with hydrogen through reaction with tributyl- and triphenyltin hydride. Although the synthetic utility of these reductions is limited, the examples that have been reported show the types of functional groups that may be modified selectively and others that remain unaffected.

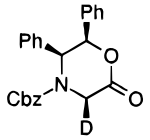
Reactions of this type occur easily at the α-position of amino acid derivatives, due to the stability of the intermediate amino acid radicals. α-Haloglycine derivatives react readily with tributyltin hydride,[70,124] as illustrated by the conversion of the bromide **197a** and the chloride **197b** to the glycine derivative **16a**. The high reactivity of the halides **197a** and **197b** is apparent from the observation that the reductions proceed efficiently, even in potentially reactive halogenated solvents, such as dichloromethane, chloroform, and carbon tetrachloride. The methoxide **197c** and the benzoate **22** were also reduced with tributyltin hydride, in yields of 91 and 92%, respectively.[59] Reactions of the glycine derivatives **22** and **197a**−**c** with hexabutylditin in place of tributyltin hydride gave the dimer **17**,[56,59] providing strong evidence for the radical nature of these processes. Reductions of α-alkylthio-substituted glycine derivatives have also been reported.[60,214]

Tributyltin deuteride may be used as an alternative to tributyltin hydride; then the products are

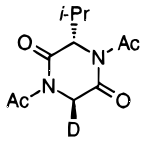


197a: R = Br
197b: R = Cl
197c: R = OMe

chiral α-deuteriated glycine derivatives. In cases where the glycine derivative has been bonded to a chiral auxiliary, generally the diastereoselectivity of deuterium transfer to the intermediate glycinyl radical has been found to be only modest.[95,102,144] The bromides **35a** and **109** gave the corresponding deuterides **198** and **199**, in 60 and 33% diastereomeric excess, respectively.[102,144] The stereoselectivity of these processes is much less than that of the reactions of the bromides **35a** and **109** with deuterium over palladium chloride. Increased stereoselectivity was observed in the reaction of the 8-phenylmenthol derivative **38a** with tributyltin deuteride, which afforded the deuteride **200** in up to 90% diastereomeric excess.[91,92]

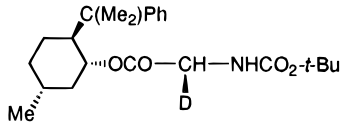


198



199

(55%)

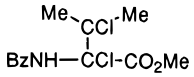


200

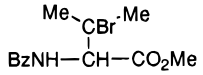
(70%)

The dihalovaline derivatives **94** and **201** each reacted with 1 mol equiv of tributyltin hydride, to give only the corresponding β-halovaline derivatives **202** and **134**.[121,123,124] The regioselectivity of these reactions and the lack of subsequent reactions of the product halides **202** and **134** indicates the relative stability and ease of formation of the α-carbon-centered radicals **203a** and **203b**, compared with the β-carbon-centered radicals **204a**, **204b**, and **136**. In competitive experiments with limiting quantities of the stannane, the haloglycine derivatives **197a** and **197b** reacted to the exclusion of the corresponding dihalovaline derivatives **94** and **201**, indicating the comparative ease of formation of the radicals **20**, **203a**, and **203b**.[121,124] These examples of selective halogen atom transfer from glycine derivatives are analogous to those observed in hydrogen-transfer reactions discussed above, and they can be rationalized in a similar fashion.

While reductions with tin hydrides and deuterides occur most easily at the α-position of amino acid derivatives, efficient reactions also occur on amino acid side chains. The β-chlorovaline derivative **134** reacted with triphenyltin deuteride to give the β-deuteriated valine derivative **205**.[215] Since the chloride **134** was prepared from the valine derivative **92**, and the chlorination and the reduction can be accomplished with optically pure material and without loss

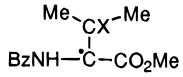


201

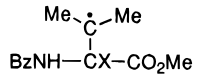


202

(51%)

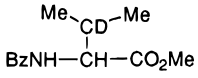


203a: X = Br
203b: X = Cl



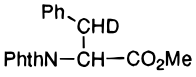
204a: X = Br
204b: X = Cl

of stereochemical integrity, the procedure is applicable to the stereocontrolled synthesis of β-deuteriated valine. The diastereomers of the bromophenylalanine derivative **165d** each reacted with tributyltin deuteride, to give a 3:1 mixture of the diastereomers of the deuteride **206**.[216] The low stereoselectivity observed in these reactions compares with complete retention of configuration in the reactions of the diastereomers of the bromide **165d** with deuterium over palladium on carbon.[217] Tributyltin deuteride has been used to reduce bromocyclopropyl amino acid derivatives to obtain labeled compounds for studies of the mechanism of penicillin biosynthesis.[25,26]



205

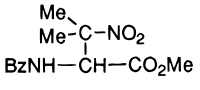
(78%)



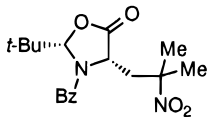
206

(89%)

Often free-radical reductions with tributyltin hydride are used to remove a functional group that has been incorporated in an amino acid derivative as part of an overall synthetic strategy. Accordingly, reactions of the derivatives of nitrovaline **207** and nitroleucine **208** were used to substitute the nitro group for hydrogen, in syntheses of amino acid derivatives using alkyl nitronates.[68,129] Xanthate transfer cyclizations and addition reactions have been used in the synthesis of amino acid derivatives, as discussed in more detail below, and reductive cleavage of the product xanthates has been exploited to increase the utility of these processes.[218,219] Iodides have been reduced with tributyltin hydride, as part of syntheses of constrained hydroxy amino acid derivatives,[220−222] while tris(trimethylsilyl)silane has been exploited in a similar manner for the synthesis of bicyclic amino acid derivatives.[223]



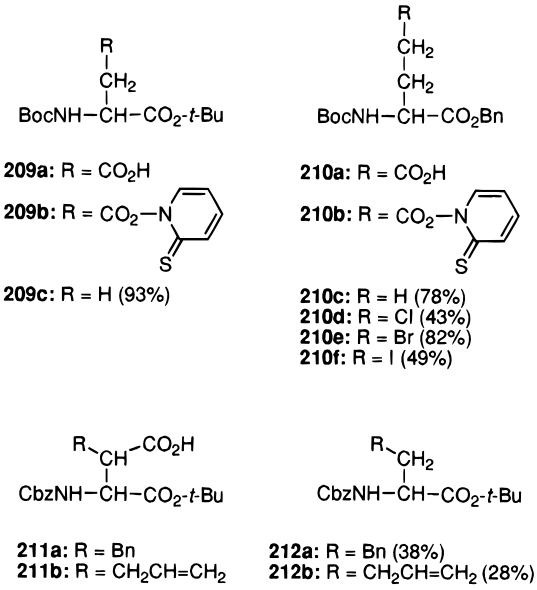
207



208

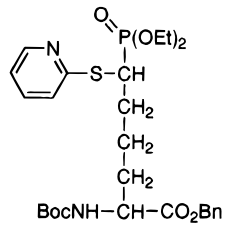
Barton esters of aspartate and glutamate derivatives have been used to remove side-chain carboxyl groups.[224−226] This free-radical methodology is particularly useful, given the lack of ionic alternatives. As examples, the amino acid derivatives **209a** and **210a** were treated with isobutyl chlorocarbonate, then *N*-hydroxypyridine-2-thione to give the corresponding esters **209b** and **210b**. Irradiation of the

esters **209b** and **210b** in the presence of *tert*-butyl mercaptan, as a hydrogen atom source, gave the corresponding derivatives of alanine **209c** and α-aminobutyrate **210c**.[224,225] The method has been applied to the decarboxylation of a glutamate residue in a dipeptide derivative.[225] Side-chain decarboxylation of amino acid derivatives is less facile than loss of the α-carboxyl group, as would be expected from the relative stabilities of the product radicals. In a variation of the decarboxylation procedure, developed for the reactions of α-disubstituted carboxylic acids,[227] the aspartate derivatives **211a** and **211b** were treated with 1-oxa-2-oxo-3-thiaindolizinium chloride, and the products were irradiated in the presence of *tert*-butyl mercaptan, to give the derivatives of homophenylalanine **212a** and butenylglycine **212b**, respectively.[228] Tributyltin hydride has been used to reduce

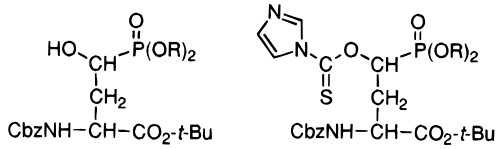


thio- and selenopyridines, such as the phosphonate **213**, as part of synthetic sequences discussed below which involve using Barton esters of amino acid derivatives.[229–231] In a related procedure, radical dehydroxylation of the amino acid derivatives **214a** and **214b** was accomplished by treatment with 1,1-thiocarbonyldiimidazole and then reaction of the products **215a** and **215b** with tributyltin hydride.[232]

By altering the reagents and reactions conditions, many of the free-radical procedures described above for replacing functional groups with hydrogen can be used to interconvert functional groups. In general terms, this involves avoiding hydrogen atom transfer to the intermediate amino acid radicals, by removing the hydrogen source, and providing alternative reaction pathways for these species. In the absence of *tert*-butylmercaptan or another hydrogen atom donor, *N*-hydroxy-2-thio- and 2-selenopyridinone esters of carboxylic acids undergo decarboxylative rearrangement,[233–235] as illustrated in Scheme 24 for the glutamate derivative **216**.[233] Oxidative elimination of the selenopyridine **218** has been used in the synthesis of vinylglycine.[233] Barton esters undergo decarboxylative halogenation when the reactions are conducted in the presence of halogen atom donors, to trap the intermediate amino acid radicals.[224,225,233,235–238] Accordingly, the glutamate de-



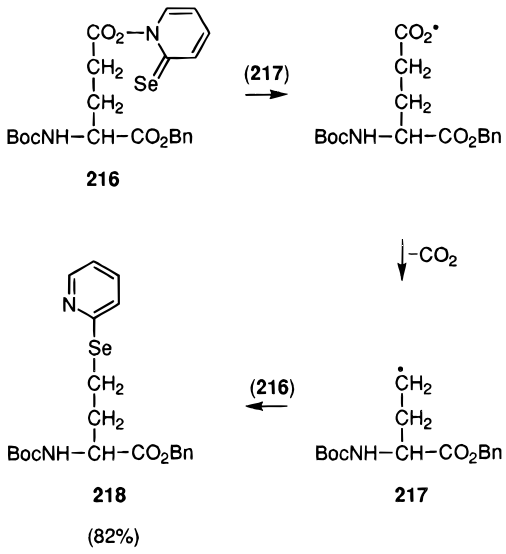
213



214a: R = Me
214b: R = Et

215a: R = Me
215b: R = Et

Scheme 24



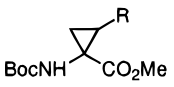
216

218

(82%)

217

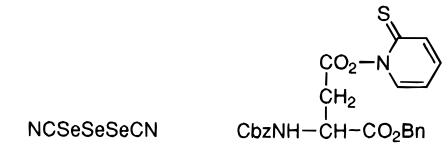
rivative **210a** was converted to the corresponding chloride **210d**, bromide **210e**, and iodide **210f**, when the ester **210b** was irradiated in carbon tetrachloride, bromoform and iodoform, respectively.[225] In this manner it was possible to prepare the bromocyclopropane **219b** from the methanoaspartate derivative **219a** without ring opening.[237] Diselenides and di-



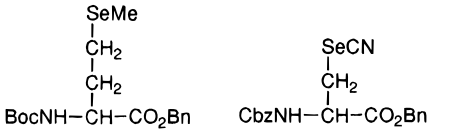
219a: R = CO_2H
219b: R = Br (52%)

cyano triselenide **220** have also been used to trap the intermediate amino acid radicals.[235] For example, the esters **210b** and **221** gave the corresponding methyl selenide **222** and the selenocyanate **223**, when the reactions were carried out in the presence of diphenyl diselenide and the triselenide **220**, respectively. Reactions of this type are of interest in the synthesis of selenomethionine and selenocysteine derivatives.

Functional group interconversions can also be accomplished at the α-position of amino acid deriva-



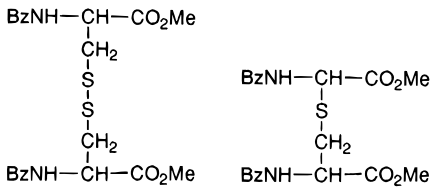
220 **221**



222 **223**

(78%) (73%)

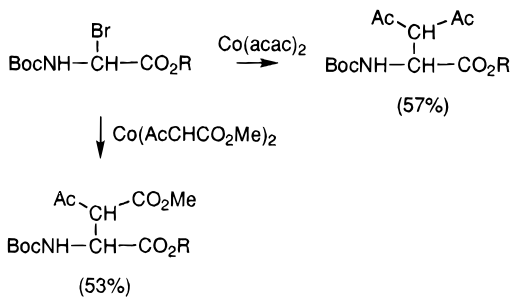
tives. The bromide **197a**, the methoxide **197c**, and the benzoate **22** were each treated with hexabutylditin and dialkyl disulfides, to give α-alkylthio-substituted glycine derivatives, through homolytic substitution reactions of the intermediate glycinyl radical **20**.[59,60] When the cystine derivative **224** was used as the disulfide, the cross-linked amino acid derivative **225** was produced. Bromoglycine derivatives have also been used in reactions with cobalt(II) bis(pentane-2,4-dioate) and cobalt(II) bis(methyl acetoacetate) (Scheme 25).[74] In cases where



224 **225**

(73%)

Scheme 25



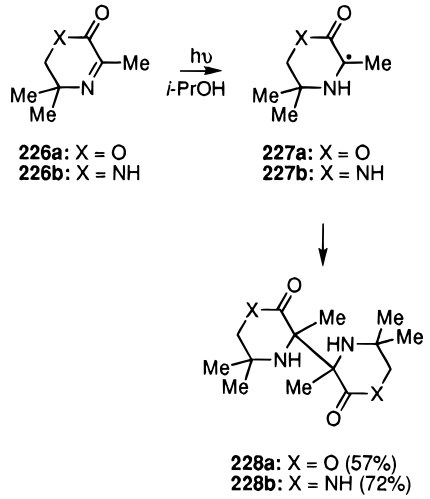
(57%)

(53%)

the glycine carboxyl group was protected as the menthol ester, modest diastereoselectivity was observed.

Photochemical reduction of the imines **226a** and **226b** has been used to produce the dimers **228a** and **228b**, respectively, through coupling of the corresponding α-carbon-centered amino acid radicals **227a** and **227b** (Scheme 26).[38,239,240] The coupling reaction is reversible, and in solution at room temperature, the dimers **228a** and **228b** exist in equilibrium with the corresponding radicals **227a** and **227b**. Through spontaneous carbon−carbon bond homolysis the diastereomers of the dimers **228a** and **228b** interconvert, they undergo oxidation in air to revert to the

Scheme 26

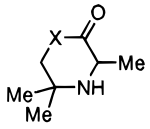


226a: X = O
226b: X = NH

227a: X = O
227b: X = NH

228a: X = O (57%)
228b: X = NH (72%)

imines **226a** and **226b**, and they give mixtures of the imines **226a** and **226b** and the reduced analogues **229a** and **229b** as a result of disproportionation of the corresponding radicals **227a** and **227b**.[240−242]

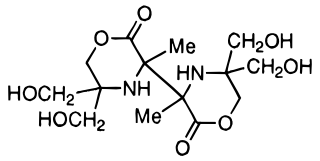


229a: X = O
229b: X = NH

For the diastereomers of the dimer **228a**, the dissociation enthalpy is 11 kcal mol^{-1} in ethanol and 22 kcal mol^{-1} in chloroform.[241] The apparent ease of homolysis of these diastereomers and those of the other dimer **228b** is consistent with the stability of the product radicals **227a** and **227b** although it could result from steric interactions between the monomer units. Elongation of the central bond in the crystal structure of the racemic isomer of the dimer **228a** is consistent with either interpretation.[243] The solvent dependence may reflect the polar nature of α-carbon-centered amino acid radicals (Figure 1) and their stabilization in polar solvents, or it may reflect the disruption of intramolecular hydrogen bonding when the dimers **228a** and **228b** are dissolved in the more polar solvent.

A range of dimers has been obtained,[244] including the diol **230** which has been designed to be soluble in water.[245,246] In a variation of the dimerization procedure, the bis(oxazinone) **231** was used to make macrocycles with coronand structure.[247] The radicals formed by bond homolysis of the dimers act as one electron reducing agents, reflecting the ease of electron transfer from α-carbon-centered amino acid radicals, referred to above. Reductions by the dimers of compounds such as adriamycin and daunomycin have been studied in detail, as models for the *in vivo* manipulation of quinone antitumor drugs.[240,245,246,248−258]

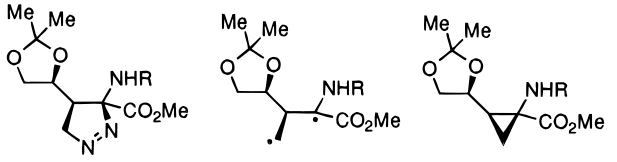
As a final example of the production of amino acid radicals through functional group transformations, photolysis of the pyrazolines **232a**−**c** gave the corresponding cyclopropylamino acid derivatives **234a**−



230 **231**

(50-66%)

c, presumably through homolytic cleavage followed by coupling of the intermediate diradicals **233a**−**c**.[259]



232a: R = Cbz
232b: R = Boc
232c: R = Ac

233a: R = Cbz
233b: R = Boc
233c: R = Ac

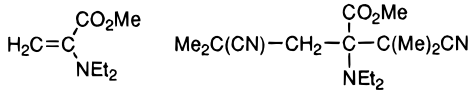
234a: R = Cbz (100%)
234b: R = Boc (100%)
234c: R = Ac (100%)

V. Addition Reactions

The hydrogen atom-transfer reactions and functional group transformations referred to above involve a diverse range of amino acid radicals, and they illustrate the range of processes available to produce these species. Similar radicals are also formed in addition reactions of unsaturated amino acid derivatives, and the amino acid radicals themselves undergo addition and allyl group transfer reactions. These processes are of particular interest in synthesis as they provide a range of opportunities for building the carbon framework of target species.[6]

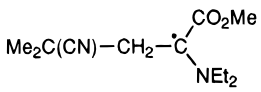
A. Intermolecular

Addition reactions of radicals to α,β-unsaturated amino acid derivatives have been the subject of several investigations. For example, reaction of the dehydroalanine derivative **235** with azobisisobutyronitrile gave the bisadduct **236**.[30] It is reasonable to assume that the mechanism of this process involves radical addition at the β-position of the alkene **235** to give the corresponding α-carbon-centered radical **237**, although the product **236** could have formed through the alternate regioselectivity. In the



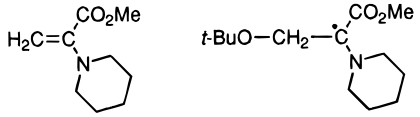
235 **236**

(37%)

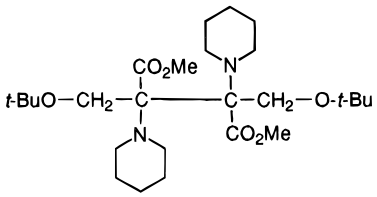


237

reaction of the dehydroalanine derivative **238** with di-*tert*-butyl peroxide, the mechanism is less ambiguous, and formation of the product **240** can be attributed to dimerization of the radical **239**.[260] This regioselectivity can be attributed mainly to steric effects, with radical addition at the less hindered end of the alkene **238**.[261] Stabilization of the adduct radicals has little effect on reactions of this type, although radical additions to alkenes are favored due to polar effects when the alkenes are substituted with electron-withdrawing groups.[6,261] On this basis, it is as expected that vitamin B_{12}-photoelectrocatalyzed addition reactions to *N*-acetyldehydroalanine methyl ester gave similar yields of products to those obtained from the analogous reactions of methyl acrylate,[262] indicating that the acetamido substituent has little effect in this case.



238 **239**

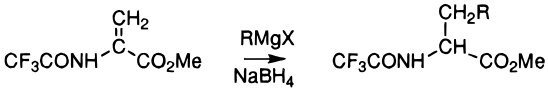


240

(30%)

The *N*-(trifluoroacetyl)dehydroalanine derivative **241** reacted with primary, secondary, and tertiary alkyl radicals, generated by the treatment of alkylmercury halides with sodium borohydride (Scheme 27),[6] but did not react with phenyl radicals.[263] Simi-

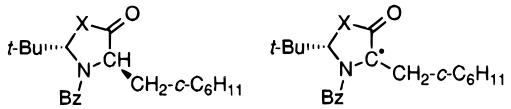
Scheme 27



241 (30-85%)

lar products could not be obtained using tributyltin hydride and alkyl bromides and chlorides, due to competing hydrostannylation of the alkene **241**. In an extension of the work, addition reactions of dehydroalanine residues in di- and tripeptide derivatives were examined.[264] Modest yields of adducts were obtained but the reactions occurred with only poor diastereoselectivity.

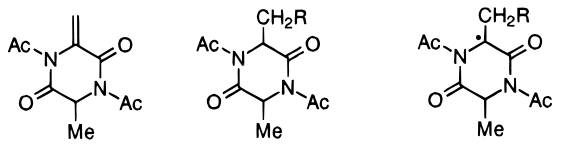
Greater diastereoselectivity was achieved in reactions of the cyclic dehydroalanine derivatives **97** and **100**, with either cyclohexylmercury chloride and sodium borohydride or alkyl iodides and tributyltin hydride. Using either method, the adducts **242a** and **242b** were each obtained in at least 60% diastereomeric excess.[125] The diastereoselectivity of these reactions is anomalous as hydrogen atom is apparently delivered to the respective intermediate radicals **243a** and **243b** *syn* to the *tert*-butyl group. In later



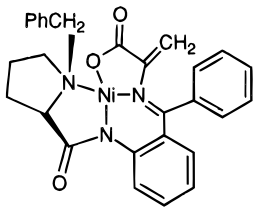
242a: X = O (68%, 73%)
242b: X = NMe (44%, 25%)

243a: X = O
243b: X = NMe

work, the diastereoselectivity of reactions of analogues of the alkene **97** was found to depend on the nature of the nitrogen protecting group, indicating that it is the steric effect of this substituent which determines the stereochemical outcome.[133] From reactions of the unsaturated piperazine-2,5-dione **244** with isopropyl- and cyclohexylmercury chloride in the presence of sodium borohydride, only the *cis*-isomers of the corresponding disubstituted diketopiperazines **245a** and **245b** were isolated.[265] This indicates that hydrogen atom transfer to the intermediate radicals **246a** and **246b** occurs *anti* to the methyl substituent. Diastereoselective radical addition to the chiral Schiff base derivative of dehydroalanine **247** has also been reported.[266]



244 **245a:** R = *i*-Pr (46%) **245b:** R = *c*-C_6H_{11} (49%) **246a:** R = *i*-Pr **246b:** R = *c*-C_6H_{11}

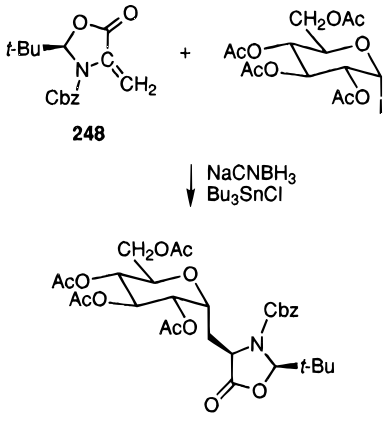


247

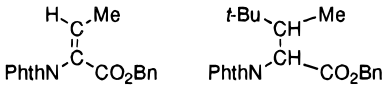
C-Glycopeptides have been obtained through the radical addition of glycosyl halides to dehydroalanine derivatives, using sodium cyanoborohydride and tributyltin chloride.[133,267] In all cases studied the reactions displayed high stereoselectivity for the formation of α-*C*-glycosides. The degree of stereocontrol of bond formation at the α-carbon of the alanine moiety depended on the substrate, however, ranging from very low in reactions of dehydroalanine residues in small peptides[267] to diastereospecific in reactions of the alkene **248** (Scheme 28).[133]

The addition reactions described above each involve dehydroalanine residues, where the lack of a *β*-substituent is likely to favor reaction on steric grounds.[6,261] There has been only one report of radical addition to a *β*-substituted α,*β*-dehydroamino acid derivative.[268] The phthalimide **249** reacted with *tert*-butyl iodide and tributyltin hydride to give a 2.3:1 mixture of the diastereomers of the adduct **250**. Radical addition

Scheme 28



(88%)

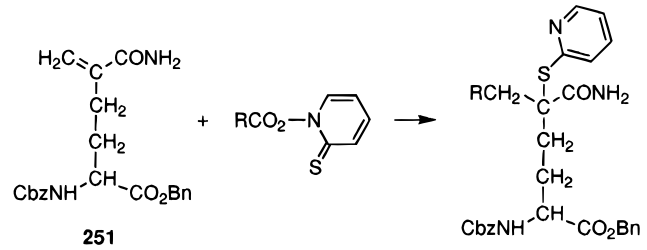


249 **250**

(41%)

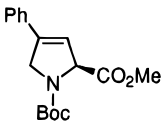
to the less hindered end of the double bond of the *δ*,*ϵ*-dehydro amino acid derivative **251** has also been reported (Scheme 29).[230] This is one of several

Scheme 29



251

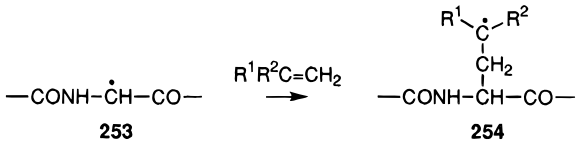
examples of reactions of dehydro amino acid derivatives which proceed via side chain radicals. Others involve reactions of hydrogen bromide, and sulfuryl and phosphoryl radicals, with vinyl- and allylglycine derivatives,[165,269−272] and manganese(III) acetate-catalyzed addition of monomethyl malonate to the proline derivative **252**.[273]



252

The observation that addition reactions of dehydro amino acid derivatives occur irrespective of whether the adduct is an α-carbon-centered radical or a side-chain radical is consistent with the understanding that the stability of the product radical has little effect on the efficiency of these processes.[261] It is also known that the stability of the radical which adds to the alkene has little effect on the ease of addition,[261] explaining why α-carbon-centered amino acid radicals also add to alkenes, despite their stability. The synthetic utility of the photoalkylation procedures developed by Elad *et al.* (Schemes 1 and 2) is significantly enhanced by the ease with which the intermediate glycinyl radicals **253** react with terminal alkenes such as but-1-ene, 2-methylpropene, hex-1-ene, and oct-1-ene (Scheme 30).[51,53,54,109,110,136−138,274,275] Subsequent reactions of the adduct radicals **254** to produce the telomers **255** occurred to only a small extent.[109,110,138,275] By exploiting alkenes in the photoalkylation processes, glycine residues in peptides were selectively elaborated to produce a range of α-substituted amino acid derivatives, with

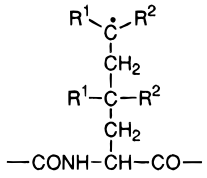
Scheme 30



253 **254**

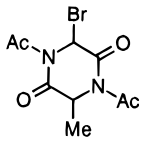
a: R^1 = Et, R^2 = H
b: R^1 = Me, R^2 = Me
c: R^1 = Bu, R^2 = H
d: R^1 = *n*-C_6H_{13}, R^2 = H

a small degree of diastereoselectivity in some cases.[53,109,137,138,275] Glycinyl radicals generated from

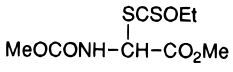


255

the bromide **256**[88] and the xanthate **257**,[219] using tributyltin hydride and di-*tert*-butyl peroxide, respectively, also reacted by addition to alkenes. In the latter case, 1,2-disubstituted alkenes were used as well as terminal alkenes.

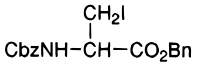


256

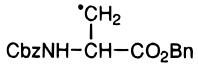


257

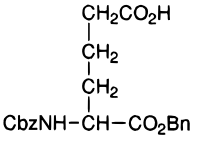
Amino acid side-chain radicals have also been exploited in addition reactions with alkenes. Treatment of the iodide **258** with tributyltin hydride in the presence of acrylic acid afforded the adducts **260** and **261**, from sequential addition reactions of the alaninyl radical **259**.[276] A similar reaction of the bromide **169b** with tributyltin hydride and methyl vinyl ketone has also been reported.[192] Radicals obtained by decarboxylation of aspartate and glutamate derivatives, via the *N*-hydroxypyridine-2-thione esters, have also been used in addition reactions with alkenes.[229−231,234] When the decarboxylations were performed using the corresponding pyridine-2-selenone derivatives, there was no addition to activated



258

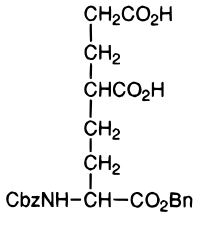


259



260

(30%)



261

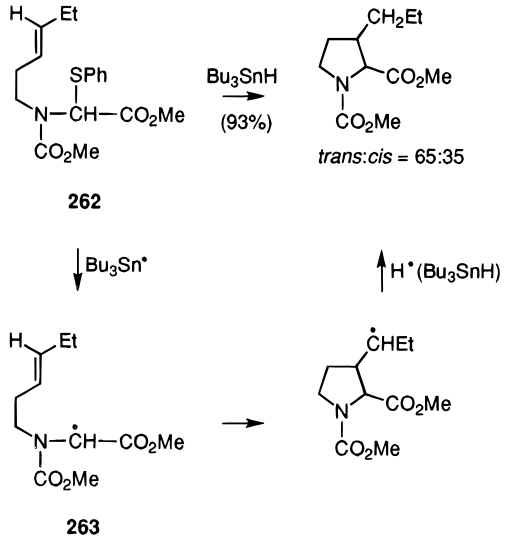
(6%)

olefins, however, and only rearranged products were obtained.[233]

B. Intramolecular

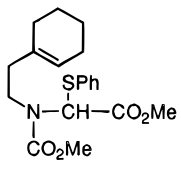
Intramolecular addition reactions of amino acid radicals provide access to cyclized derivatives. The advantage of free radicals in this area is that their characteristic cyclization modes[5,277] are distinct from those of their ionic counterparts. In particular, radicals typically react in the *exo*-mode, as illustrated in Scheme 31 for reaction of the α-(phenylthio)glycine

Scheme 31

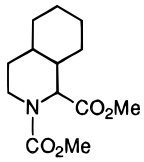


262 **263**

derivative **262** on treatment with tributyltin hydride.[278−280] Subtle geometrical constraints can affect the balance between the *exo*- and *endo*-cyclizations; however, particularly in reactions to give bicyclic compounds, and the cyclohexene derivative **264** reacted in the *endo* mode, to give mainly the ring-fused species **265**.[278,280]



264

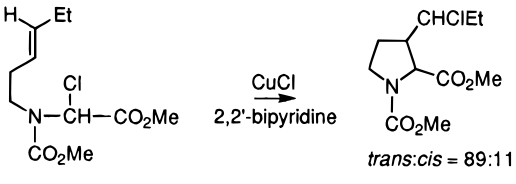


265

(61%)

In a variation of the cyclization procedure, treatment of α-chlorinated glycine derivatives with cuprous chloride in the presence of 2,2′-bipyridine resulted in radical ring closure (Scheme 32).[279,281−283] The advantage of this method is that it avoids the

Scheme 32

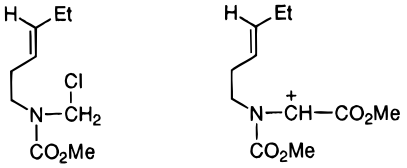


266

trans:*cis* = 89:11

(83%)

reductive termination of the tin hydride process, leaving a functional group in the product for further manipulation. The decarboxylated analogue **267** of the chloroglycine derivative **266** underwent cyclization in the *endo*-mode, presumably in a cationic reaction.[282] The change in mechanism can be at-

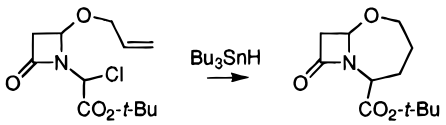


267 **268**

tributed to the effect of the methoxycarbonyl group to stabilize the radical **263** and destabilize the corresponding carbocation **268**. Xanthate transfer reactions have also been used to accomplish cyclizations of glycinyl radicals without reductive termination.[218] Using this method, 1,5- and 1,6-*exo*-cyclizations occurred, whereas the copper-catalyzed reaction of chloroglycine derivatives failed in the latter case.

Glycinyl radical cyclizations have been used in the synthesis of fused bicyclic β-lactams.[284−286] The strain imposed by the preexisting azetidinone ring generally outweighs the normal tendency for reaction in the *exo*-mode, as illustrated in Scheme 33 for

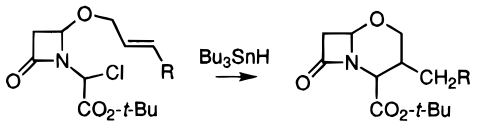
Scheme 33



269 (47%)

reaction of the chloroglycine derivative **269**.[284] *exo*-Cyclization only occurred to a significant extent with the analogues **270** (Scheme 34),[284] where the substit-

Scheme 34



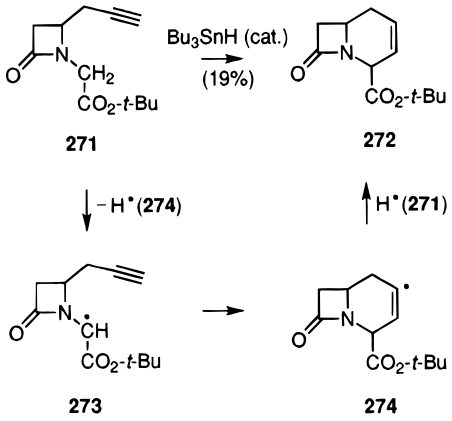
270

a: R = CO_2Me (68%)
b: R = Ph (68%)

uents retard *endo*-cyclization, due to steric effects, and may favor the *exo*-process by stabilizing the cyclized radicals. Prior functionalization of the glycine residue is not essential for reaction, and the β-lactam **271** reacted directly with a catalytic amount of tributyltin hydride to give the carbacephem (**272**, Scheme 35).[287] Presumably, the glycinyl radical **273** is generated in this chain process through hydrogen atom transfer to the bicyclic radical **274**.

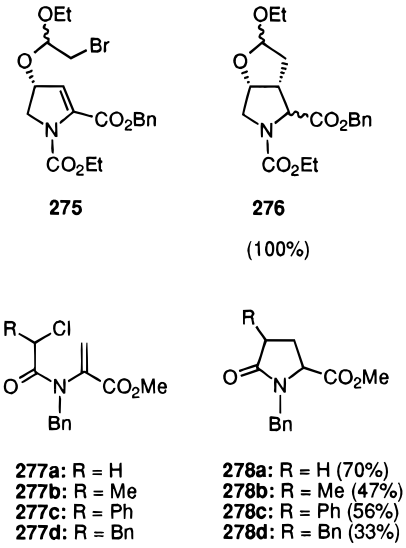
The bromide **275** reacted with tributyltin hydride to give the cyclized derivative **276**,[288] and analogous reactions have been used to produce a range of fused bicyclic species.[289,290] Again this illustrates the preference for 1,5-*exo*-cyclization. By contrast 1,5-*endo*-cyclization is favored over the 1,4-*exo*-process, due to the ring strain associated with the latter. Accord-

Scheme 35



271 **272** **273** **274**

ingly, the chlorides **277a**−**d** reacted with tributyltin hydride to give the pyrrolidinones **278a**−**d**, respectively,[291,292] while cyclization of the imine **279** gave the α-carbon-centered radical **280** (Scheme 36).[293]



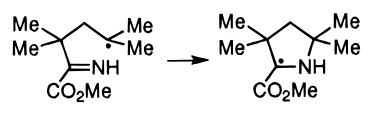
275 **276** (100%)

277a: R = H
277b: R = Me
277c: R = Ph
277d: R = Bn

278a: R = H (70%)
278b: R = Me (47%)
278c: R = Ph (56%)
278d: R = Bn (33%)

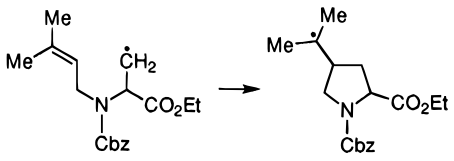
In addition to cyclization reactions of α-carbon-centered amino acid radicals, and reactions to give those species, intramolecular addition reactions involving only side chain radicals have also been reported. In representative examples, the *N*-allyl-substituted β-alaninyl radical **281** reacted by 1,5-*exo*-cyclization to give the proline derivative **282** (Scheme 37),[294−298] whereas reaction of the azetidinyl radical **282** occurred in the 1,6-*endo*-mode (Scheme 38),[299−301] presumably due to the strain associated with the bicyclic system. Thiyl radical additions such as those illustrated in Scheme 39 have been used in the construction of the penam and cepham carbon skeletons, through 1,5-*exo*- and 1,6-*endo*-cyclizations, respectively,[302−308] and thiopyroglutamates and thiopiperidinones have been generated by *exo*-cyclizations of the type shown in Scheme 40.[309] The radicals **283a**

Scheme 36



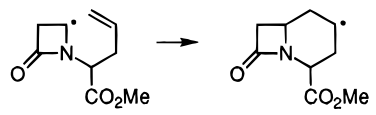
279 **280**

Scheme 37



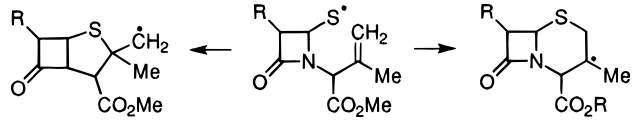
281 **282**

Scheme 38

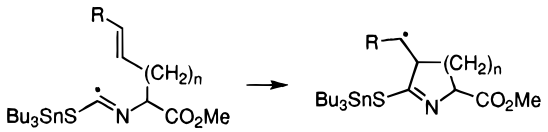


283

Scheme 39



Scheme 40

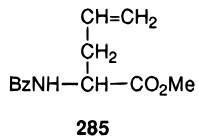


284a: R = Me, n = 2
284b: R = Ph, n = 1,2

and **283b** were produced through addition of tributyltin radical to isothiocyanates, derived from α-amino acids. Analogous thiol-mediated cyclizations of isocyanides have also been reported.[310,311]

C. Allylations and Rearrangements

Allyl group transfer reactions have provided another procedure for the elaboration of amino acid derivatives using free-radical methodology. α-Carbon-centered amino acid radicals readily undergo reactions of this type, as demonstrated by reaction of the bromide **197a** with allylstannanes to produce the corresponding allylglycine derivative **285**.[70,312] The

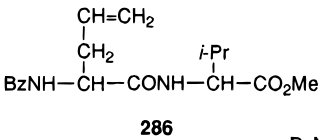


285

(62%, 65%)

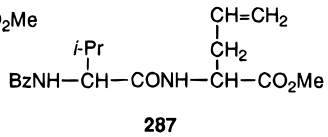
process is not restricted to reactions of bromides, and the alkoxide **197c** and the benzoate **22** also reacted to give the same product **285**.[59] 2-Chloro-, 2-cyano-, and 2-ethoxycarbonyl-substituted allylstannanes reacted in a similar manner, to give the corresponding γ-functionalized allylglycine derivatives.[312] Normally reactions of 1- and 3-alkyl-substituted allylstannanes are complicated by competing elimination reactions,[6,313−315] but difficulties of this type were not encountered in reactions of the bromide **197a**.[316]

The allylation procedure has been used for the elaboration of glycine residues in peptides, as an extension of the selective bromination of those residues.[70] Reactions of the bromides **106b** and **107b** afforded the corresponding products **286** and **287**, as 1:1 and 3:1 mixtures of the diastereomers, respectively. More substantial asymmetric induction was observed in reactions of cyclic dipeptides, and the bromide **109** afforded only the *trans*-diketopiperazine **288**.[144] The bromoglycine derivative **38b** also reacted with allyltributylstannanes with a high degree of asymmetric induction.[104,105] The same substrate **38b** was treated with allenyl- and alkynyl-stannanes but the products obtained in those cases were consistent with an ionic rather than a radical mechanism, involving the glycinyl cation instead of the corresponding radical.[104,105] In the reaction of the bromide **289** with allyltributylstannane, zinc chloride was found to act as a radical initiator and to increase the diastereoselectivity of allyl transfer.[93]



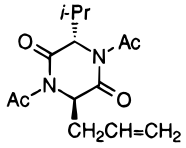
286

(35%)



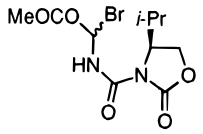
287

(33%)



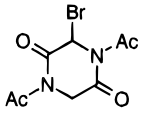
288

(60%)

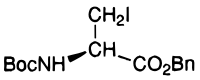


289

In other examples of the allylation procedure which involve α-carbon-centered amino acid radicals, reactions of the bromides **29**[317] and **290**,[88] and an alkylthio-substituted glycine residue in a peptide,[214] with allyltributylstannane have also been reported. In examples which involve side chain radicals, the bromotryptophan derivative **169b**[192] and the iodoalanine derivatives **258** and **291**[315,318] underwent allyl transfer reactions with stannanes. Treatment of



290

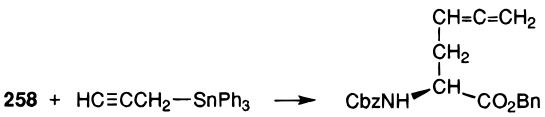


291

haloalanine derivatives with triphenylprop-2-ynylstannane (**292**) afforded allenyl amino acids, as illustrated in Scheme 41 for the iodide **258**.[319]

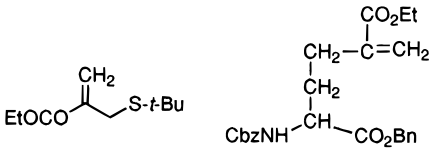
Allyl sulfides can be used as alternatives to allylstannanes, in cases where thiyl radicals can propagate the radical chain processes. Accordingly the

Scheme 41



292 (60%)

Barton ester **221** reacted with the sulfide **293** to give the amino acid derivative **294**.[234] In an intramolecu-

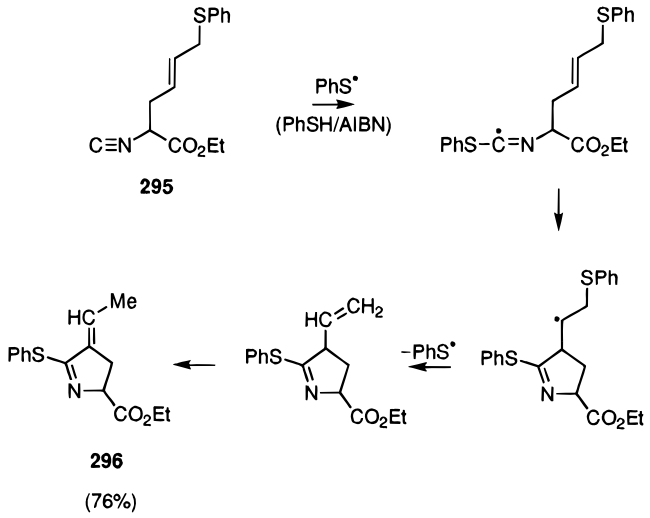


293 **294**

(34%)

lar variation of this type of reaction involving a sulfide, the isocyanide **295** reacted with catalytic amounts of thiophenol and azobisisobutyronitrile to give the pyrroline **296** (Scheme 42).[310]

Scheme 42

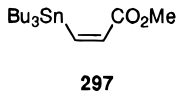


295 **296**

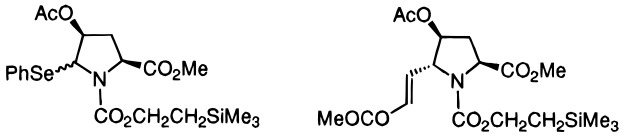
(76%)

Methyl β-(tributylstannyl)acrylate (**297**) was developed as another reagent for alkylation through an addition−elimination radical chain sequence.[320,321] It has been exploited in the reaction of the proline derivative **298** to give the corresponding acrylate **299**.[184] Another type of radical addition−elimination reaction sequence of amino acid derivatives which has attracted attention has involved reactions of the bromoimines **300a**, **300b**, and **303**.[322−326] On treatment with tributyltin hydride, these react by intramolecular addition, with formation of the corresponding cyclopropyl radicals **301a**, **301b**, and **304**, and then β-scission to give the rearranged products **302a**, **302b**, and **305**, respectively. Reactions of this type have been studied as models of biochemical systems involving catalysis by vitamin B_{12}.[327] The rearrangement of the bromo imine **300b** is also catalyzed by vitamin B_{12} *in vitro*,[324] and analogous reactions have been reported using vitamin B_{12} analogues,[328−332] but it is not clear if these processes involve radical or ionic intermediates.

An intramolecular radical addition is also involved in the reaction of the proline derivative **306** with tributyltin hydride (Scheme 43).[333] The cyclization is preceded by an intramolecular 1,5-radical translocation.[334,335] Processes of this type significantly expand the utility of radicals in synthesis because they provide new opportunities for regioselective radical formation.

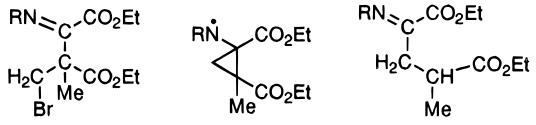


297

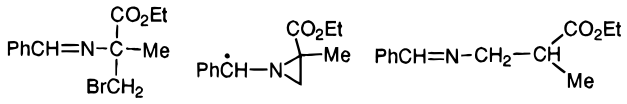


298 **299**

(67%)



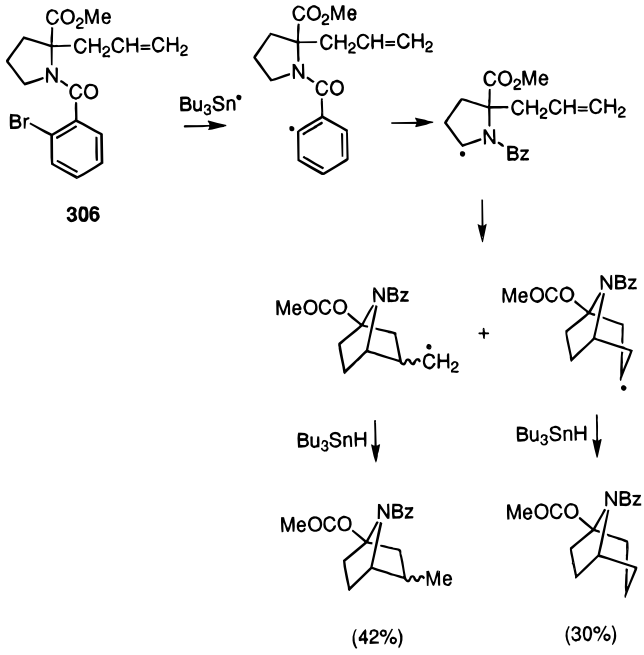
300a: R = Bn **301a:** R = Bn **302a:** R = Bn (80%)
300b: R = Ph **301b:** R = Ph **302b:** R = Ph (56%)



303 **304** **305**

(62%)

Scheme 43



306

(42%) (30%)

VI. Conclusion

The chemistry summarized in this review indicates the extent to which free-radical chemistry has been developed for, and applied to, the synthesis of amino acids and their derivatives. Unique transformations have been accomplished and, in many cases, good product yields have been obtained. Procedures for addition and cyclization reactions, and for the introduction and manipulation of functional groups, have been discussed. These indicate the level of regio- and stereocontrol that can be achieved and highlight the potential utility of radical reactions in this area. The

examples reported to date clearly demonstrate the key role that radical reactions can be expected to play in the continuing search for methods to access these important compounds.

VII. Acknowledgments

This review was partially compiled while the author was on leave in the Department of Chemistry at the University of Otago. The generous support of the Department is gratefully acknowledged. The author's continuing interest in this area has been stimulated by an enthusiastic group of co-workers whose professional contributions and social interactions are greatly appreciated.

Note Added in Proof

While this review was in press, an article by Renaud and Giraud was published,[336] in which they reviewed aspects of the chemistry of amino- and amidoalkyl radicals.

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CR9402844