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The reactivity of the *N*-Boc protecting group: an underrated feature

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1. Introduction

Among the large array of protecting groups, the *tert*-butoxycarbonyl (Boc) substituent is considered to be one of the most useful. In particular, it has gained an indisputable popularity owing to its role in solid phase synthesis. In fact, even though this strategy is being supplanted in this field by Fmoc (fluorenylmethoxycarbonyl),[1] the Boc group is still one of the most widely used in synthetic organic chemistry when it is required to protect primary or secondary amines. This utility is clearly due to the ease of introducing and removing Boc and to the fact that it can be perfectly orthogonally associated with many other protecting groups.

An important feature of the *N*-Boc group is seldom taken into account namely its propensity to react intramolecularly with nucleophiles as well as electrophiles and, depending on the user's viewpoint, this property may appear as a serious drawback or an interesting synthetic potentiality. It has for example been stated in two excellent authoritative guidebooks that: (i) the Boc group is not hydrolysed under basic conditions and is inert to many other nucleophilic reagents,[2] and (ii) the Boc group… is extremely resistant towards basic and nucleophilic reagents.[3] There is nothing wrong with those sentences, but, as this Report will demonstrate, the reluctance shown by the *N*-Boc group towards nucleophiles is restricted to the intermolecular mode. Moreover, this group is very sensitive to electrophilic reagents and it can play a specific part in many reactions in which they are involved. In this connection, it has already been observed that noteworthy stereochemical controls can

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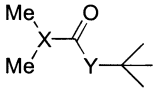
Table 1. AM1 calculations on compounds **1a–d**

	Charge on carbonyl C	Charge on carbonyl O	LUMO energy (eV)	C coefficient on LUMO
Carbamate **1a**	0.395	−0.404	1.71	0.762
Ketone **1b**	0.236	−0.295	0.957	0.765
Ester **1c**	0.313	−0.361	1.338	0.773
Amide **1d**	0.304	−0.366	1.42	0.745

be exercised by nitrogen-protecting groups, thus enlarging the scope of their use.[4]

The aim of the present review is to focus on various aspects of the electrophilic and the nucleophilic reactivity of the *N*-Boc group, with special emphasis being placed on the latter aspect, for which the synthetic utility is much more pronounced. This report does not, however, seek to encompass all of the *N*-Boc chemistry but rather to present an overview of this field of research.

Before getting to the heart of the matter, it is of interest to become acquainted with some basic theoretical data in order to compare the electronic structure of the *N*-Boc group considered as a moiety of a particular carbamate **1a** (X=N, Y=O) with those of the corresponding ketone **1b** (X=CH, Y=CH_2), ester **1c** (X=CH, Y=O) and amide **1d** (X=N, Y=CH_2) molecules. Semi-empirical AM1 calculations[5] were performed with this aim and the most relevant results of the study are collected in Table 1.



1a-d

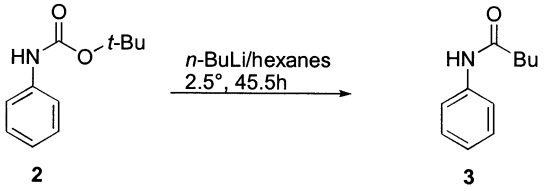
From this study, three main conclusions may be drawn: (i) the carbamate **1a** presents properties which are commensurate with the others, (ii) considering the LUMOs, the various coefficients on the carbonyl carbons of the molecules **1a–d** are very similar and their values are large but the carbamate function should be the least reactive towards nucleophiles due to the relatively high level of its LUMO energy, and (iii) considering the charges, the C=O bond in the carbamate **1a** is the most polarised with a substantial negative charge localised on the oxygen atom.

2. Electrophilic reactivity

Although the formation of methylated amines via $AlLiH_4$ reduction of an *N*-Boc group is a classical process,[6] the first observations of reactions occurring between nucleophilic moieties and the *N*-Boc group were unexpected. Albeit interesting with regard to the understanding the phenomenon which comes into play, they were often found undesirable. In addition to the fact that these reactions take place with an extreme efficiency, the resulting products may, in many cases, be of considerable interest and have attracted attention for synthetic applications especially in relation to the formation of chiral oxazolidinones and imidazolidinones.

2.1. Organolithium reagents

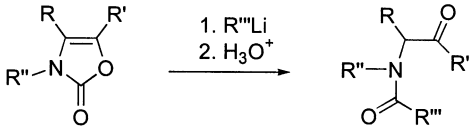
Paradoxically, powerful nucleophilic reagents such as Grignard or organolithium reagents are not reported to react with *N*-Boc groups. An exception can be found in the work of Stanetty et al.[7] who observed the formation of the amide **3** (21% yield) when *N*-Boc aniline **2** was treated with *n*-butyllithium in hexanes (Scheme 1). This was clearly an undesirable feature since the study was aimed at examining the main reaction parameters which favour the lithiation of the aromatic ring; in fact, it had been known that the *N*-Boc group is a very useful *ortho*-directing substituent in lithiation reactions.[8]



2 **3**

Scheme 1.

As previously mentioned, the high level of the carbamate **1a** LUMO may account for this low electrophilic reactivity and the steric hindrance due the *tert*-butyl substituent is also likely to explain this fact. It is really surprising to note, however, that, to the best of our knowledge, there are no further published reports on the reactions of organolithium reagents with any other carbamates. It should nevertheless be noted that Gompper[9] observed in 1957 that these compounds react with 2-oxazolones **4**, i.e. unsaturated cyclic carbamates (Scheme 2).



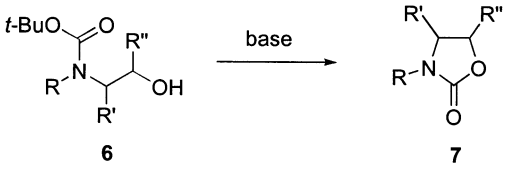
4 **5**

Scheme 2.

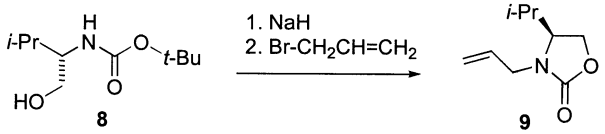
2.2. Transcarbamation reactions

A host of published works describe the effect of an alkoxide moiety on a neighbouring *N*-Boc group. As a result, the *tert*-butoxy appendage is expelled from the substrate **7**, giving rise to the oxazolidinone **7** (Scheme 3). Since Evans' oxazolidinones[10] enjoy a wide use as highly versatile chiral auxiliaries, this great number of works is by no means surprising.

Taking advantage of this intramolecular reaction, Huwe and Blechert[11] have reported a one-pot protocol for the synthesis of *N*-derivatised 2-oxazolidinones via a sodium hydride



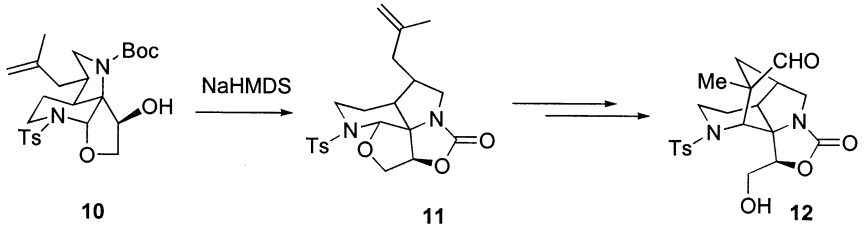
Scheme 3.



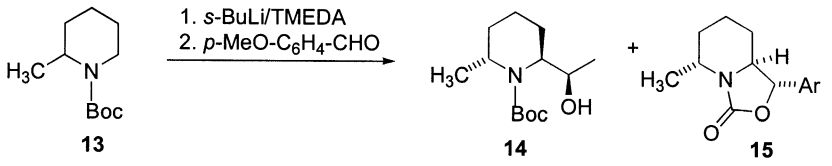
Scheme 4.

core of the marine alkaloid **12** via the intermediates **10** and **11** (Scheme 5). Analogous cyclisations have been observed for *N*-Cbz[13] and N-CO_2Me protecting groups.[14]

Oxazolidinone formation can also be achieved from alkoxy moieties resulting from the addition of an *N*-Boc α-lithiated species onto a carbonyl compound. In this field, Beak and Lee[15] reported that the lithiation of *N*-Boc 2-methylpiperidine **13** with *s*-BuLi, followed by reaction with electrophiles provides *trans*-2,6-disubstituted piperidines as a mixture of *syn* and *anti* isomers. When the electrophile is an aromatic aldehyde, a cyclisation occurs within the *syn* isomer affording the oxazolidinone **15** (Scheme 6). Cyclisation from the *anti* isomer **14** does not take place because the resulting oxazolidinone would be more hindered with a *cis*-4,5-disubstitution pattern.



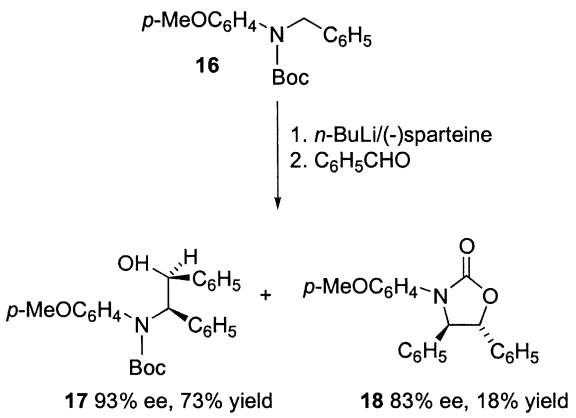
Scheme 5.



Scheme 6.

treatment followed by a nucleophilic substitution on an electrophile (see Scheme 4, in which the oxazolidinone derived from the *N*-Boc derivative **8** reacts with allyl bromide affording compound **9**).

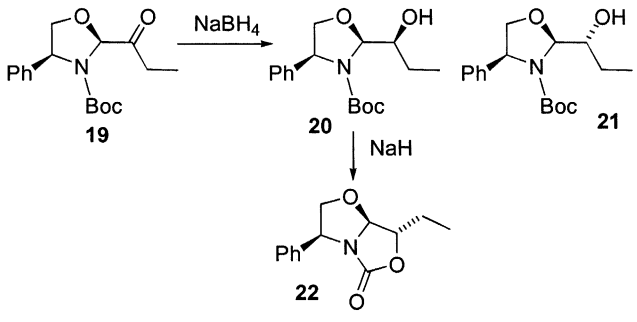
Much more complex structures can be synthesised through such a transcarbamation reaction, which has, for example, been used by Overman et al.[12] to construct the diazatricyclic



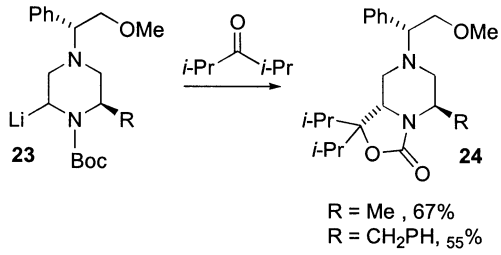
Scheme 7.

The same behaviour was observed by Beak et al.[16] in acyclic series during a sparteine-mediated enantioselective α-lithiation of the *N*-Boc-protected amine **16** followed by reaction with benzaldehyde (Scheme 7) which eventually affords the aminoalcohols **17** and **18**.

A similar stereochemical discrimination took place[17] during the reduction ($NaBH_4$) of the *N*-Boc 2-acyl oxazolidine **19**. This reduction affords two epimeric alcohols **20** and **21** of which only **20** is cyclised when treated with NaH (Scheme 8) and produces compound **22**.

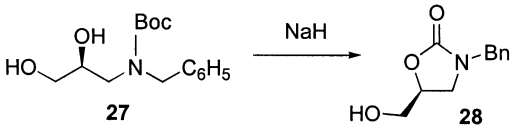


Scheme 8.



Scheme 9.

Scheme 10.



Scheme 11.

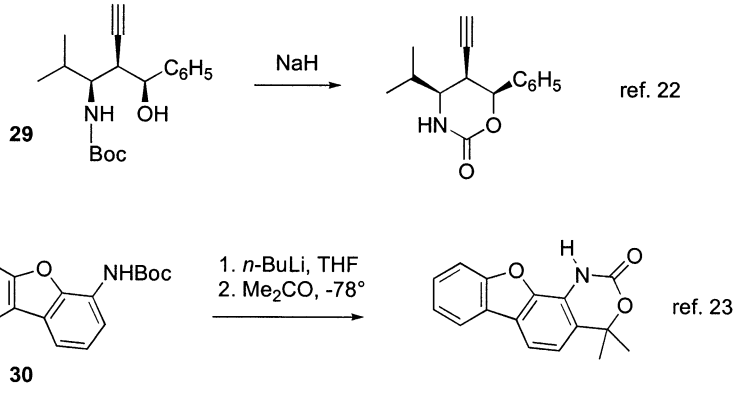
The oxazolidinone **24** was produced from the reaction between a lithiated *N*-Boc piperazine **23** and a ketone (i.e. diisopropyl ketone), and not an aldehyde as in the above reactions described by Beak et al.[15,16] (Scheme 9). In contrast, the use of benzaldehyde instead of diisopropyl ketone led to the expected secondary alcohol without cyclisation. It is worthy of note that, in the former case, a hindered tertiary alkoxide acts as the nucleophile, thus displacing another tertiary alkoxide, the *tert*-butoxy group.[18] Clearly the intramolecularity of this reaction is the driving force for this otherwise odd substitution.

Sharpless et al.[19] have observed the formation of the oxazolidinones **26** as a result of the asymmetric dihydroxylation of the bis-*N*-Boc allylic amines **25** and, as shown in the example depicted in Scheme 10, both the yield and enantiomeric excess are excellent.

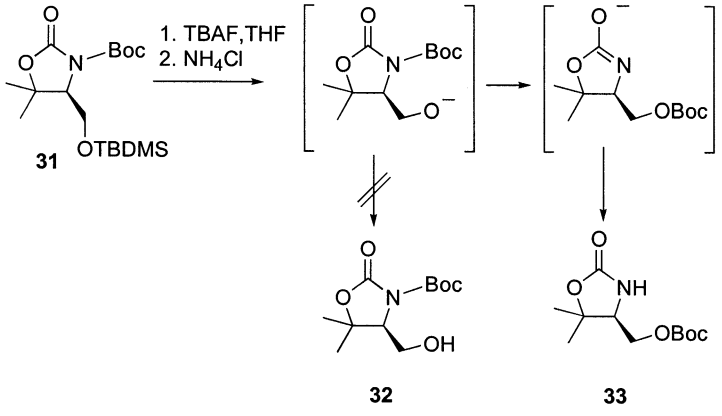
Is this process able to yield tetrahydrooxazinones, i.e. the 6-membered heterocycles? The following results address this point. Treatment of the compound **27** by a base offers two ways for the cyclisation to occur (Scheme 11):[20] production of the oxazolidinone **28** shows that the formation of the 5-membered ring is favoured over the tetrahydrooxazinone production. The selectivity is in agreement with many other experimental facts which have in particular sustained Baldwin's rules.[21]

It has, however, been shown that, when a more favoured pathway is absent, cyclisations leading to 6-membered rings are productive.[22,23] Scheme 12 depicts examples of such cyclisations from the substrates **29** and **30**.

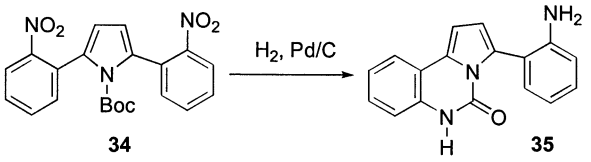
Obviously such nucleophilic attack may sometimes be a real problem. Davies et al.,[24] for example, have observed



Scheme 12.



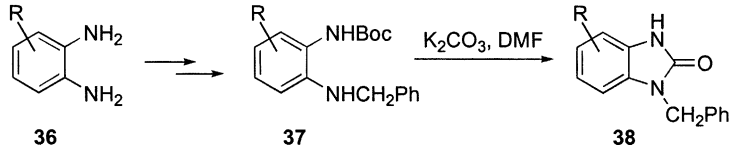
Scheme 13.



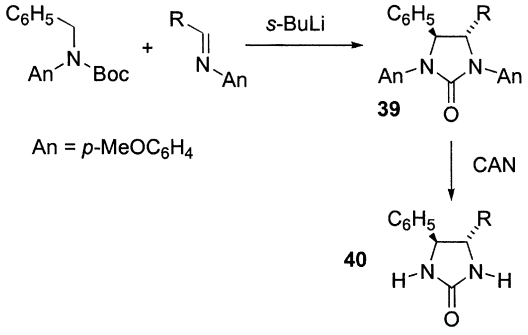
Scheme 14.

diamino compound formed during the hydrogenation of 2,5-bis(*o*-nitrophenyl)pyrrole **34** (Scheme 14).

In the course of a study[26] aimed at evaluating the 5-HT3 receptor antagonist ability of piperazinylbenzimidazoles, the two primary amine moieties in compound **36** were transformed, respectively, into the *N*-Boc-*N*-Bn derivatives **37**. A



Scheme 15.



Scheme 16.

a rapid N–O Boc transfer (Scheme 13) within the oxazolidinone **31**, thus affording the product **33**. Such chiral auxiliaries thus appeared to be unsuitable for the attachment to polymers, since, as in the unavailable oxazolidinone **32**, an unprotected hydroxy group is necessary to permit linkage of the auxiliary to the solid phase.

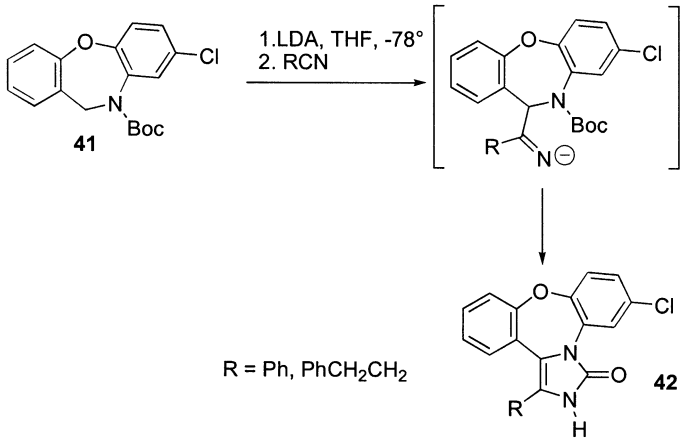
2.3. Nitrogen nucleophiles

2.3.1. Amines. Primary amines are prone to react intramolecularly with a neighbouring *N*-Boc moiety. It was observed,[25] for example, that the compound **35** results from a room temperature cyclisation of the intermediate simple base treatment converted the diprotected diamine **37** into the corresponding benzimidazolone **38** (Scheme 15). Although this hypothesis was not suggested by the authors, an isocyanate intermediate (see below) may be involved during the cyclisation.

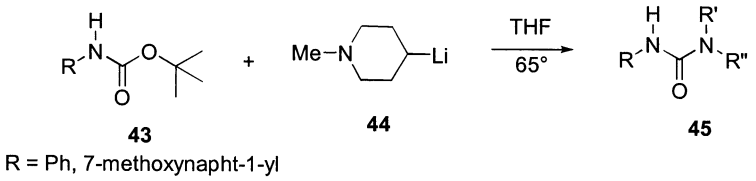
2.3.2. Amide ions. Not surprisingly, amide ions are still more able than amines to react in this mode. Such reactions allowed the discovery of a new synthetic route to chiral 1,2-diamines, which are frequently utilised in enantioselective reactions.[27] The imidazolidinones **39** are conveniently made by the reaction between an *N*-Boc-*N*-Bn aniline (reactive under its deprotonated form) and imines derived from *p*-anisidine (Scheme 16). Upon reaction with ceric ammonium nitrate, the required deprotected ureas **40** are obtained in high yields.

In situ reaction of a nitrile with the lithiated form of the oxazepine **41** was reported to give the fused imidazolidones **42** (Scheme 17).[28] This is reminiscent of the above-mentioned cyclisation within the adducts which result from the reaction between carbonyl compounds and *N*-Boc-protected amines (Schemes 7–9).

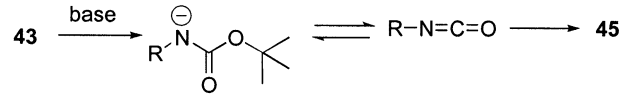
The *N*,*N*′-unsymmetrical ureas **45** can be synthesised very efficiently through the action of a lithiated base (mainly lithium methylpiperazide **44**) on the *N*-Boc-protected primary amines **43** (Scheme 18). The authors[29] stated that



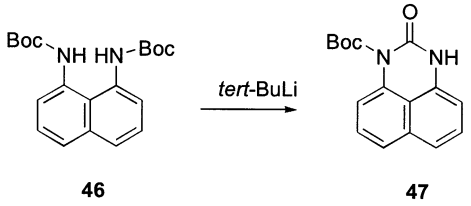
Scheme 17.



Scheme 18.



Scheme 19.

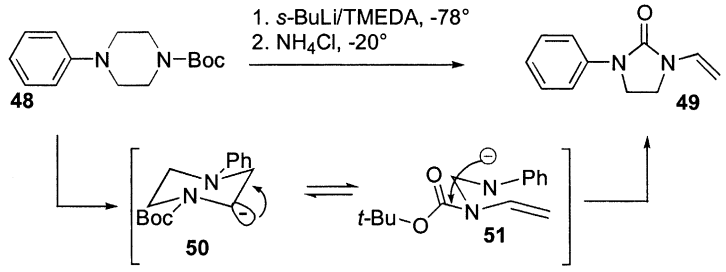


Scheme 20.

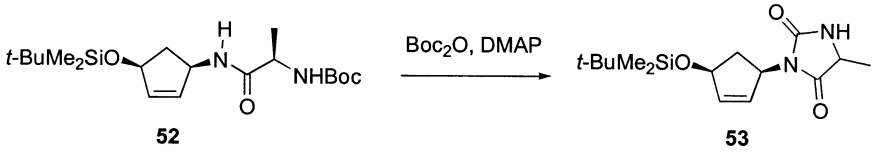
mechanism involves an equilibrated isocyanate formation (Scheme 19).

In many cases, however, reactions involving amide ions and *N*-Boc groups, may be really undesirable, e.g. the *tert*-butyllithium-mediated *ortho*-lithiation of compound **46**, which failed because of the formation of the carbamate **47** (Scheme 20).[30]

The intriguing transformation of the *N*-Boc-protected substrate **48** into the imidazolidinone **49**, depicted in Scheme 21, was reported by Garrido et al.[31] and a convincing explanation for the ring-opening and ring-closing sequence was suggested by the authors which assumes that a lithiated species **50** (stabilized by coordination of the lithium ion by the carbonyl group of Boc) affords compound **49** via the rearranged intermediate **51**.

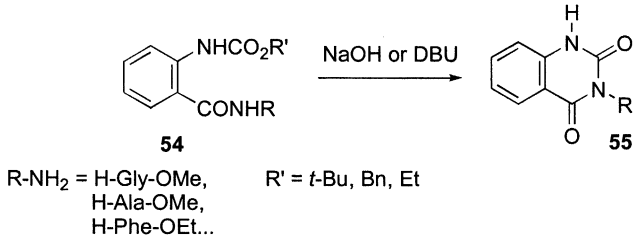


Scheme 21.



Scheme 22.

$(Boc)_2O$ could thus be employed as a safer alternative to the use of triphosgene or as a more stable and easier-to-handle substitute of carbonates. An elegant experiment that used a deuterium-labelled reagent showed that, most likely, the

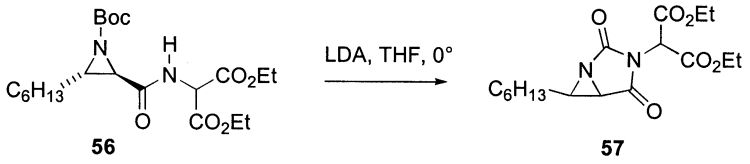


Scheme 23.

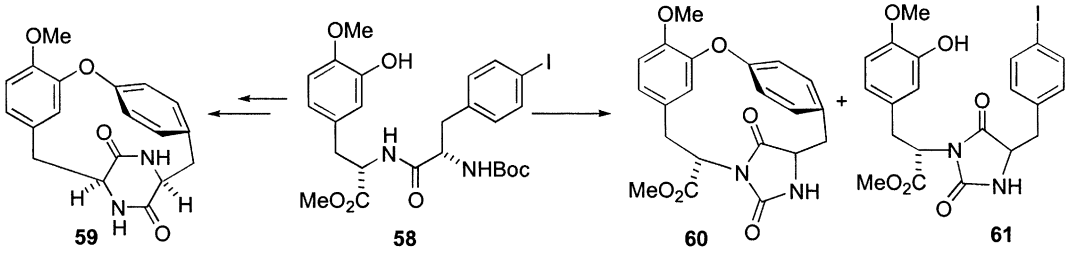
2.3.3. Amides. Ghosh and Miller[32] attempted to achieve the *N*-Boc protection of the compound **52** but what was actually obtained was the unexpected derivative **53**. Optimisation of this process allowed a successful new access to this class of hydantoins that are analogues of 5′-nor carbocyclic nucleosides (Scheme 22).

Another reaction involving an amide as nucleophile is depicted in Scheme 23 which shows that the quinazoline-2,4-diones **55** can be produced from the urethane anthranilides **54**. This synthetic pathway was extended in the solid phase in order to produce libraries of quinazoline-2,4-diones.[33]

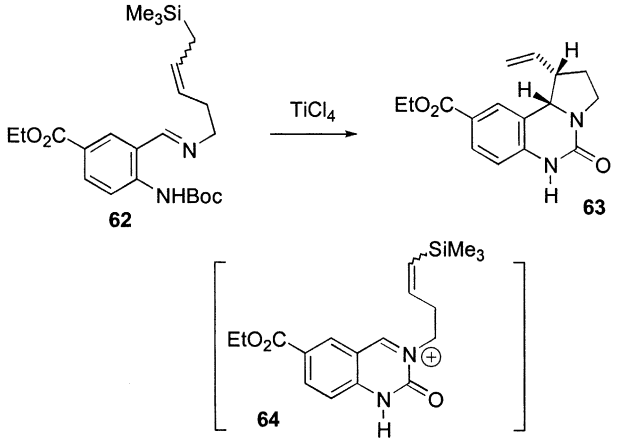
A related urea formation involving the Boc group was



Scheme 24.



Scheme 25.



Scheme 26.

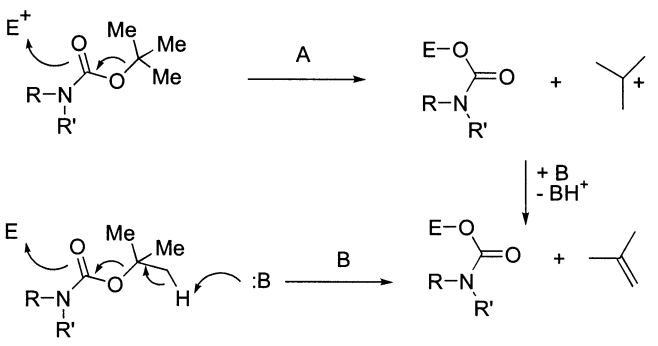
described using the compound **56**. When this substrate was treated under kinetically controlled reaction conditions (Scheme 24),[34] the cyclisation affords a very interesting bicyclic derivative **57**, with the aziridine moiety being retained in the product.

Boger and Zhou[35] have described a total synthesis of (+)-piperazinomycin in which the key-step is an Ullmann macrocyclisation performed on a derivative of the compound **58**. In a preliminary study, an alternative strategy was envisioned in order to obtain the cyclised compound **59** directly from the substrate **58**. The formation of compound **59** was, however, unsatisfactory due to the competitive formation of the side products **60** and **61** which resulted from the amide acylation of the *N*-Boc carbamate moiety (Scheme 25).

2.3.4. Imines. A cyclisation leading to an imidazolidinone was used as a key step during an elegant synthesis of the tricyclic core of martinellines.[36] The highly selective process displayed in Scheme 26 implies the transient formation of an acyliminium ion **64** which reacts with the allylsilane moiety via a classical ene-iminium pathway in order to produce the desired product **63**. This acyliminium ion was actually produced from a reaction between the imine moiety and the *N*-Boc group of compound **62** under the action of $TiCl_4$.

3. Nucleophilic reactivity

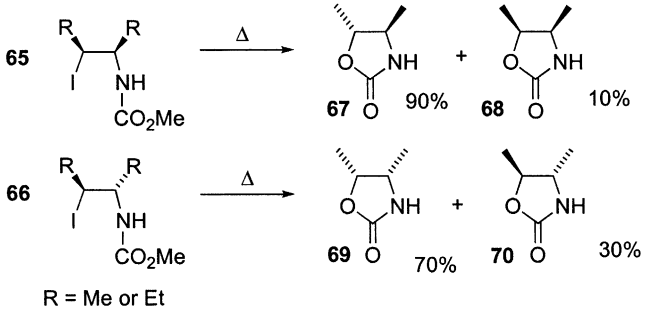
Not only can the *N*-Boc group act as an electrophile, as exemplified above, but it also demonstrates a nucleophilic reactivity which is due to two main factors: (i) the fractional negative charge on the carbonyl oxygen is sizeable (see Table 1 in the Section 1), and (ii) under the action of an electrophile, the *tert*-butyl fragment of the Boc moiety is expelled as a cation. The feasibility of this elementary step is well-known (cf the AAL1 mechanism[37] involved in the



Scheme 27.

acid-catalysed hydrolysis of *tert*-butyl carboxylic esters or the classical acid-catalysed dealkylation of *tert*-butyl phenyl ethers[38]) and, in the present example, any general base induces the further evolution of the *tert*-butyl cation in order to eventually produce isobutene (path A in Scheme 27). Both steps (departure of the cation and deprotonation) can, of course, be concerted (path B in Scheme 27).

In this context, two pioneering investigations should be discussed. In 1963, Heathcock and Hassner[39] presented the first report of an oxazolidinone formation via the pyrolysis of *N*-ethoxycabonyl β-iodoamines. Foglia and Swern[40] considerably extended these observations and provided a mechanistic explanation through a study of the stereoselectivity of the reactions when they are performed with suitably substituted substrates. As shown in Scheme 28 for the synthesis of oxazolidinones **67**–**70**, the stereoselectivity is moderate and depends on the relative configuration of the starting β-iodocarbamates. Intrigued by this absence of stereospecificity since the reaction appears to be a simple S_N2 process, the authors assumed that there is an iodide ion-mediated equilibrium between the *erythro* and the *threo* diastereomeric substrates **65** and **66**. This assumption would explain the lower stereoselectivity observed in the cyclisation of the *threo*-iodocarbamate **66**: this isomer has to suffer from a higher degree of steric hindrance in approaching the transition state for the formation of the oxazolidinone **69**.

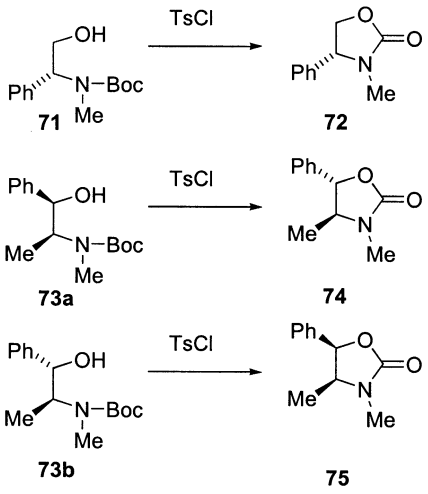


Scheme 28.

These early observations are really innovative[41] but, since this field only began to be thoroughly explored some 20 years after this work, they are too often overlooked. As exemplified thereafter, this type of reaction became of considerable interest from a synthetic viewpoint when the N-linked methoxycarbonyl substituent used in the Foglia and Swern experiments was replaced by a *tert*-butoxycarbonyl group, i.e. when an *N*-Boc moiety became the nucleophilic reagent.[42,43]

3.1. Sulfonic esters

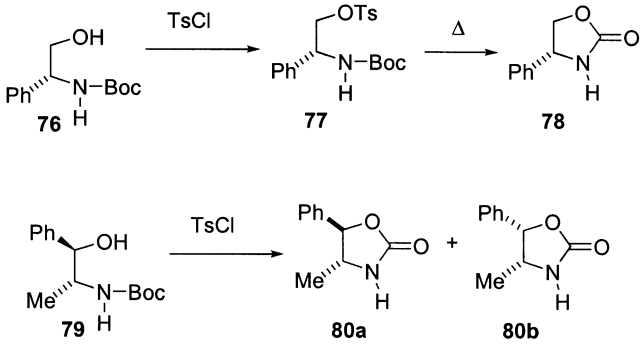
In 1993 it was reported[44] that a simple treatment of *N*-Boc-*N*-methyl-(*R*)-phenylglycinol **71** with TsCl at 0 °C in pyridine led to the oxazolidinone **72** (Scheme 29); however in the derivatives of the *N*-methylephedrine family **73a**–**b**, however, the electrophilic centre is more hindered and the reaction had to be performed at room temperature. In every example, an inversion of the reactive carbon centre was



Scheme 29.

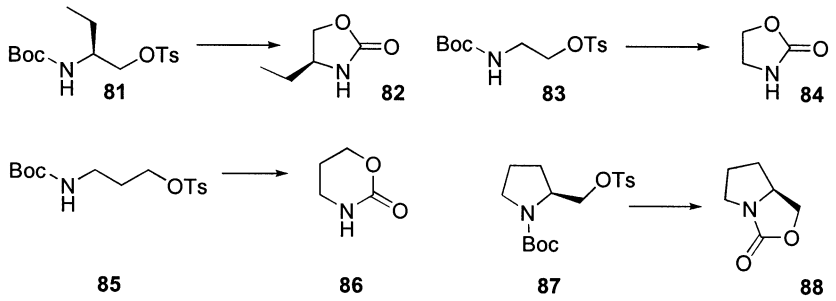
observed and this is consistent with an S_N2 process consisting of nucleophilic attack of the benzylic carbon centre. It is clear that an intermediate tosylate is involved during this process and, most likely, the pyridine solvent is the basic component mentioned in Scheme 27.

When starting from the substrate **76**, the intermediate tosylate **77** has been isolated and was smoothly converted to the oxazolidinone **78** by heating it at 60 °C (Scheme 30). Not only are the *N*-Boc derivatives of primary amines less prone to be cyclised but, with the derivatives of pseudoephedrine, the reaction no longer appears to be stereospecific (as above) since both isomers **80a** and **80b** (80:20 respective ratio) were obtained from the *N*-Boc aminoalcohol **79**. The *N*-methyl substituent therefore exerts a dramatic influence over the reactivity of the substrates and this can be related to a Thorpe–Ingold effect (this point will be addressed later).



Scheme 30.

Since the publication of this study, many papers have appeared which report similar cyclisations and which sometimes enlarge the scope of this reaction. Curran et al.[45] used a refluxing $CHCl_3$ solution of diisopropylethylamine to effect the transformations displayed in Scheme 31; in these experiments, tosylates **81**, **83**, **85** and **87** were formed exclusively from primary alcohols and the resulting cyclisations (leading the oxazolidinones **82**, **84**, **86** and **88**) do not present any stereochemical consequences.



Scheme 31.

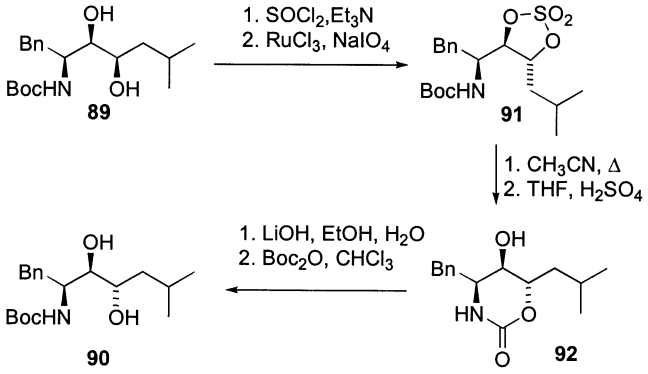
Advantage was readily taken of the inversion of the reactive carbon configuration and this methodology was applied to the transformation of a *syn*,*syn*-3-amino-1,2-diol array as in compound **89** into the *syn*,*anti* structure **90**, which is contained in a class of rennin inhibitors. Scheme 32 shows how this transformation was effected via the intermediates **91** and **92**.[46]

Joullié et al.[47] have made use of this method of inversion of a hydroxyl-bearing carbon in the course a very elegant synthesis of (2*S*,3*S*)-3-hydroxyleucine **98** from (*R*)-serine **93** which was first transformed into the derivative **94** (Scheme 33). In this case, a triflate leaving group was used in order to perform the oxazolidinone **96** formation from the *N*-Boc-protected aminoalcohol **95**. The deprotected aminoalcohol **97** led easily to the desired target molecule **98**.

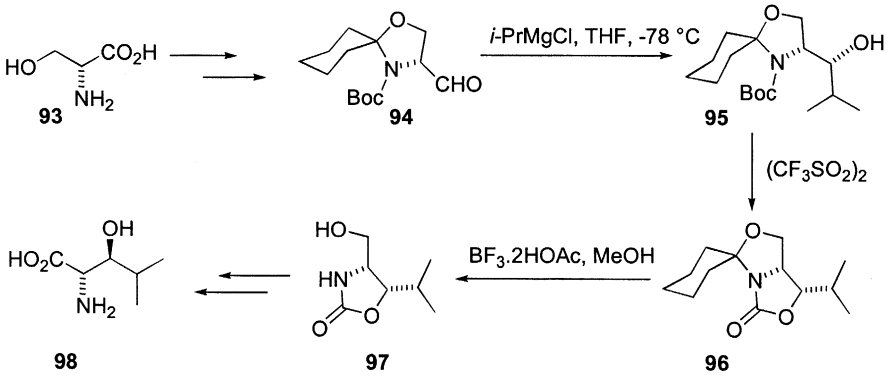
Other observations of such cyclisations, such as those depicted in Scheme 34 leading to the oxazolidinones **103–106** from the substrates **99–102**, have been reported with the inversion phenomenon being observed[48] or not[49] (Scheme 34).

This mode of oxazolidinone formation was used at the start of a synthesis of (−)-xenovenin **110** (Scheme 35) which has been achieved by Lhommet et al.[50] This synthesis involves the prior formation of the oxazolidinone **108** from the *N*-Boc derivative **107** and the intermediate formation of the aminoalcohol **109**. These authors have demonstrated that such methodology provides a versatile stereoselective access to various *trans*-2,5-disubstituted pyrrolidine derivatives.

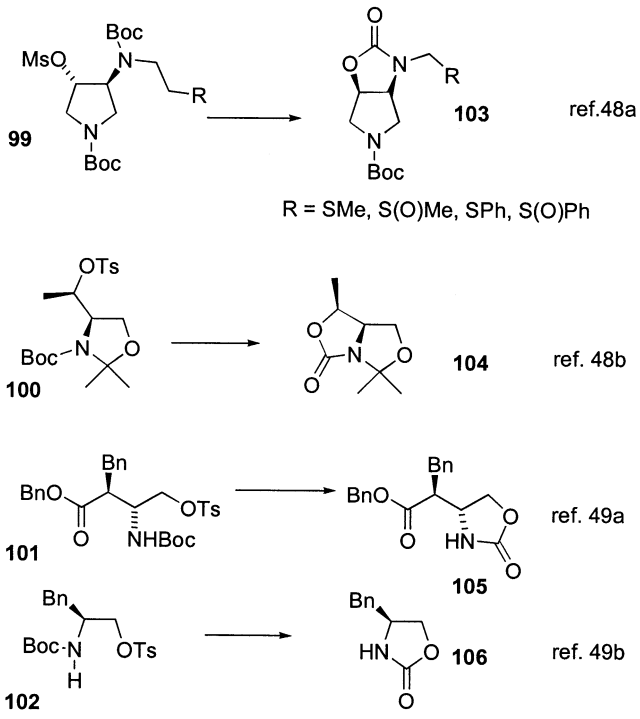
The fact that sulfonate esters of secondary alcohols are



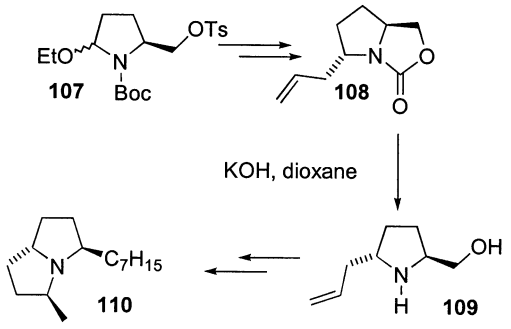
Scheme 32.



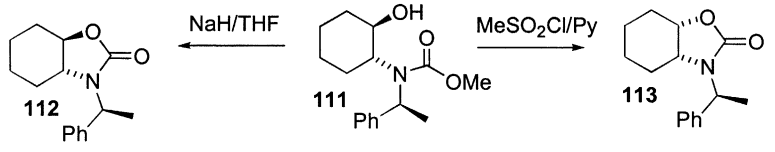
Scheme 33.



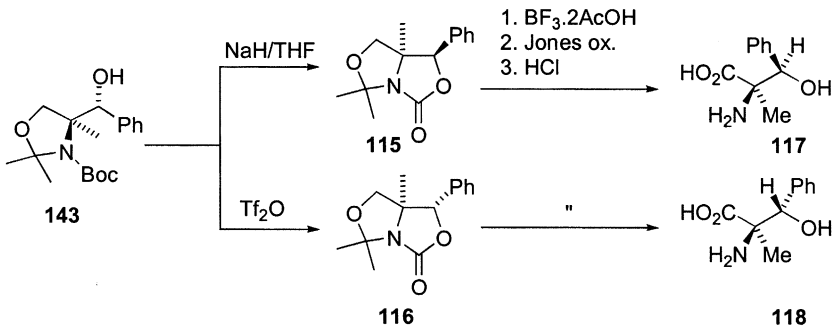
Scheme 34.



Scheme 35.



Scheme 36.



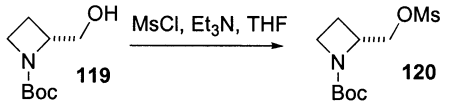
Scheme 37.

stereospecifically cyclised with inversion is of great interest. This is obvious when this evolution is compared to the retention which was observed in the case of nucleophilic alkoxy moieties acting on *N*-Boc groups (see the trans-carbamation reactions in Section 2.2). As regards the stereochemistry of such oxazolidinone formations, the two approaches are complementary. This dual mode of cyclisation was first illustrated in a publication by Juaristi et al.[51] which brings together these two modes of stereoselective cyclisations with *N*-methoxycarbonyl-substituted substrates (Scheme 36).

The formation of oxazolidinone **112** involves a nucleophilic attack of the alkoxide anion on the carbamate whereas the oxazolidinone **113** is formed via a nucleophilic attack of the carbamate onto an intermediate mesylate. As expected, the stereochemical outcomes are opposite.

Such complementary modes of cyclisation were reported recently with an *N*-Boc-containing substrate and, in this way, all isomers of α-methyl-β-phenylserine were synthesised in enantiopure form.[52] Scheme 37 delineates the main reactions which allow the synthesis of both (2*R*,3*R*) and (2*R*,3*S*)-α-methyl-β-phenylserine from the same substrate, the *N*-Boc oxazolidine **143**.

In addition to these studies in which the cyclisation leads to an oxazolidinone by virtue of the *N*-Boc nucleophilic reactivity towards sulfonates, there are some reports[53] in which such a reaction was unexpected and considered as undesirable. In this respect it is worth noting that Lynch et al.[54] apprehended that an oxazolidinone could be formed during mesylation of the azetidine substrate **119**. The unwanted cyclisation did not, however, occur (Scheme 38) with this compound, an early intermediate used in the synthesis of the analgesic ABT-594, and a simple substitution led to mesylate **120**. Obviously, the [4,5] bicyclic system (which would have been produced from the *N*-Boc/mesylate reaction) is too strained and cannot be reached in this way.

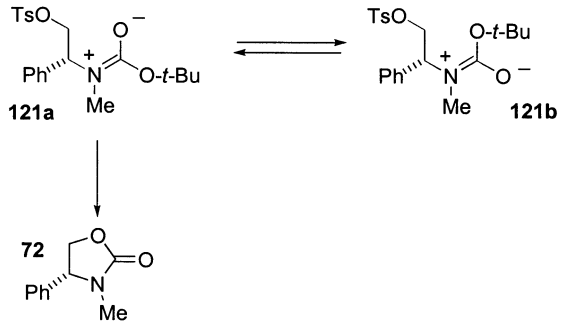


Scheme 38.

3.2. Effect of an *N*-methyl substituent

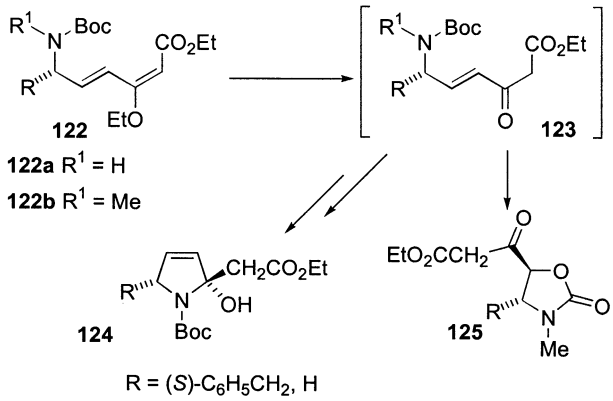
As mentioned above (see Scheme 29), the presence of an *N*-methyl substituent promotes an important rate enhancement when *N*-Boc moieties react as nucleophiles with neighbouring tosylates,[44] this taking place when *N*-methyl secondary amines (and not primary amines) are at the beginning of the process. This phenomenon can be related to the well-documented Thorpe–Ingold effect, which, in fact, has almost always been described for cyclisations being favoured by a *gem*-substitution of a carbon atom. The fact that, in the present examples, the substitution involves a nitrogen atom should not be a radically different illustration of this effect.

It has been very convincingly suggested that, in many cases, this effect can be accounted for by an increasing population of a more reactive conformer induced by the higher level of substitution.[55] Applied to this cyclisation, this hypothesis would be consistent with a larger proportion of the *E*-conformer **121a** over the *Z*-isomer **121b** (Scheme 39). AM1 calculations were performed[56] in order to check this possibility and they show unambiguously that the proportion of the *Z*-conformer **121a** is always predominant whatever the degree of substitution of the nitrogen atom. In agreement with the classical explanation for the Thorpe–Ingold effect, however, the *N*-methyl substitution leads to a compression of the internal C–N=C angle (122.0 and 117.7° for N–H and N–Me moieties, respectively).



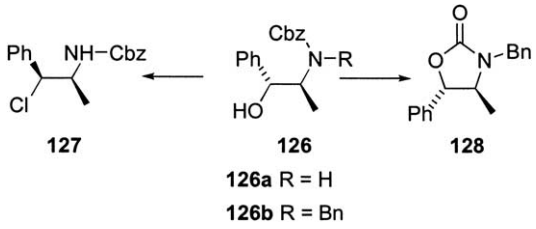
Scheme 39.

A similar feature was noted when the *N*-methyl-*N*-Boc hexadienoates **122** were treated with sulfuric acid supported on silica gel at 0°C. As displayed in Scheme 40, these substrates may either lead to a pyrrole derivative **124** (via a nitrogen atom 1,2 addition on the carbonyl moiety of the intermediate enone **123**) or to an oxazolidinone **125** (via an oxygen 1,4 addition on enone **123**).[57] In agreement with the preceding results, the oxazolidinone formation was highly promoted by the presence of a methyl substituent on the nitrogen of substrate **122b** whereas substrate **122a** (which derives from a primary amine structure) leads to pyrrole **124**. In this example, a conformational effect analogous to that mentioned above was invoked in order to explain this regioselectivity.



Scheme 40.

In the course of an investigation on the PPh_3/C_2Cl_6-mediated synthesis[58] of oxazolidinones, an analogous Thorpe–Ingold effect was assumed[59] to explain why the NH substrate **126a** was simply chlorinated, affording **127**, whereas its *N*-Bn analogue **126b** led to the oxazolidinone cyclised product **128** (Scheme 41). It is worth noting that the nitrogen bears a Cbz-protecting group and not a Boc group as in the previous examples.[60]



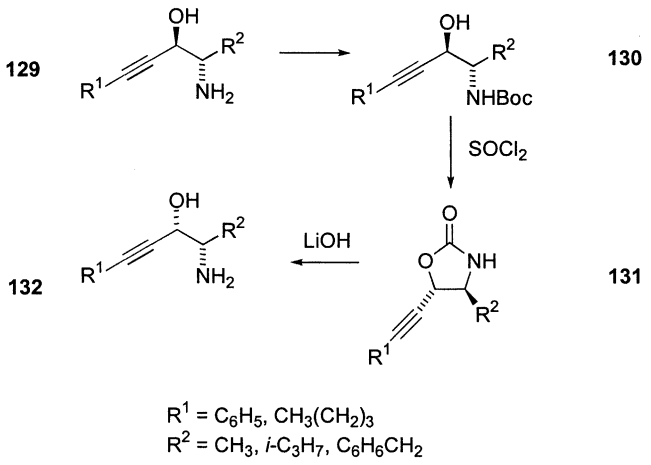
Scheme 41.

These *N*-alkyl substituent effects will be addressed once more in connection with the formation of *N*-carboxyanhydrides, which constitutes a feature of the utmost importance to be taken into account when synthesising peptides from *N*-methyl amino acids.

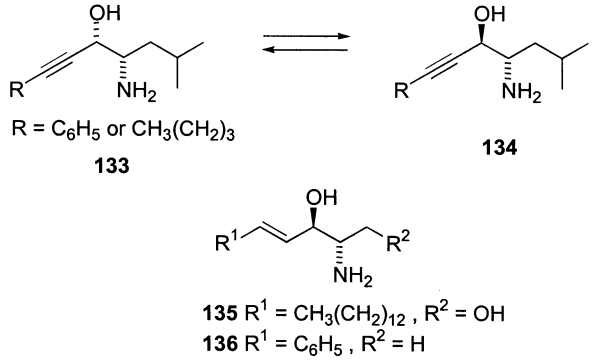
3.3. Sulfinic esters

Kano reported a very interesting method of inverting the configuration of the carbinol carbon of a β-aminoalcohol.[58] This method consists of: (i) converting the aminoalcohol **129** into its *N*-Boc (or *N*-Cbz) derivative **130**, (ii) treating this compound with thionyl chloride and, (iii) treating the resulting oxazolidinone **131** with a base (Scheme 42). The aminoalcohol **129** can therefore be smoothly transformed into its diastereomer **132**.

This method has been used[61] for the interconversion of the *threo* **133**/*erythro* **134** forms of 1-alkynyl-2-aminoalcohols which may allow an easy access to unsaturated aminoalcohols of biological interest, such as sphingosine **135** and merucathine **136** (Scheme 43).

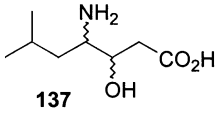


Scheme 42.



Scheme 43.

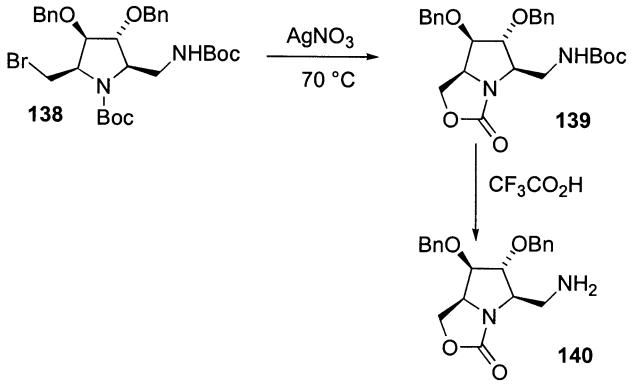
This methodology allowed Kano et al.[62] to report an efficient stereocontrolled synthesis of the four stereomers of statin **137**: the 3*S*,4*S* and 3*R*,4*R* isomers were first synthesised by adapting well-known procedures and were converted by the afore-mentioned method into the 3*R*,4*S* and the 3*S*,4*R* diastereomers.



Matsunaga et al.[63] have described a completely different route for the preparation of 4-substituted 2-oxazolidinones via a cycloaddition reaction; in order to perform a chemical correlation, they have ascertained the structures of their oxazolidinones by synthesising them using the Kano method.

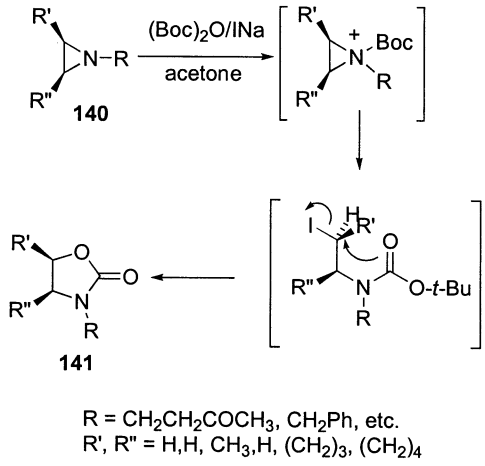
3.4. Alkyl halides

The compound **140** is an interesting homosugar with a masked hydroxyl function at C-1. It results from the deprotection of the *N*-Boc group present in **139** which was easily synthesised by heating the iminoglucitol **138** in the presence of silver nitrate.[64] The formation of the cyclic carbamate **139** therefore reveals that a Lewis acid (Ag^+)-promoted substitution of bromide by the nucleophilic Boc group is feasible (Scheme 44).



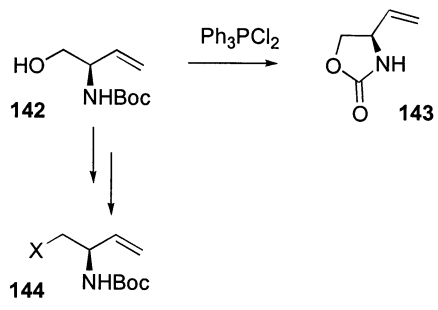
Scheme 44.

With an iodide leaving group, there is no need for electrophilic assistance by a Lewis acid,[65] and the oxazolidinone **141**, for example, was obtained when the aziridine **140** was treated with $(Boc)_2O$ in the presence of sodium iodide, whereas the *N*-Boc protected compound could be cyclised when sodium bromide or chloride were used (Scheme 45).

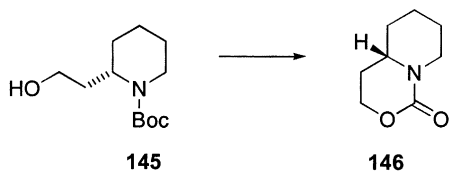


Scheme 45.

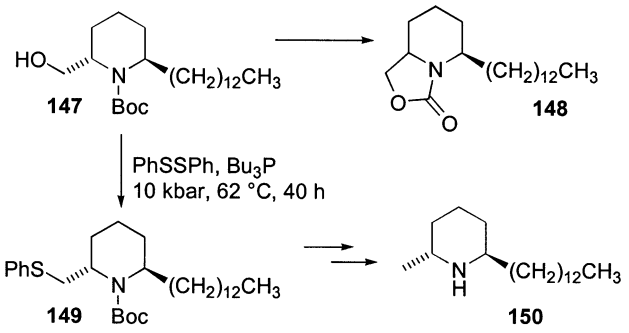
Chlorination of the *N*-Boc aminoalcohol **142** with dichlorotriphenylphosphorane[66] in CH_2Cl_2 at 0°C gave the oxazolidinone **143** in high yield.[67] This reaction corresponds to an attack of the nucleophilic Boc moiety on an activated form of the alcohol function (Scheme 46). The same work reports that the corresponding halides **144** (X=Br or I) are stable at room temperature.



Scheme 46.



Scheme 47.



Scheme 48.

With the aim of studying structure–activity relationships of non-peptidic GnRH receptor antagonists, De Vita et al.[68] have prepared a series of quinolones which are *O*-alkylated with *N*-Boc aminoalcohol derivatives. During the course of their work, they observed that treatment of the substrate **145** with the classical CBr_4/PPh_3 reagent led to the cyclised compound **146** (Scheme 47). They ascribed this cyclisation to displacement of a bromide ion, the bromide corresponding to the alcohol **145** being detected in trace amounts by TLC. This hypothesis is hardly convincing, however, and, most likely, the substitution involves the intermediate alkoxyphosphonium ion.

In the present situation, there are reports of such cyclisations that are considered to be undesirable.[69] What appears to be the most troublesome example has been reported by Kotsuki et al.[70] who faced this problem during the final stage of their synthesis of (−)-solenopsin B **150**. The intermediate compound **147**, under a variety of conditions, led to the undesired cyclic carbamate **148** (Scheme 48). The authors finally obviated this difficulty by synthesising the phenylsulfide **149** using a high-pressure technique. The compound **149**, after desulfurization and *N*-Boc deprotection, afforded the required target molecule, **150**.

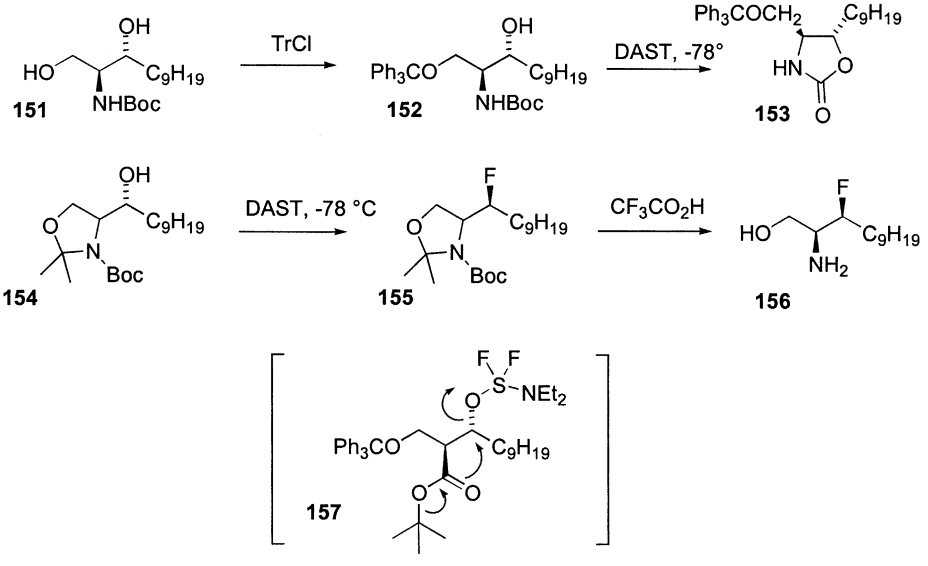
The formation of an oxazolidinone during an attempt to fluorinate the *N*-Boc O-Tr-protected aminoalcohol **152** belongs to this class of reactions.[71] Treatment of the compound **152** with the DAST reagent (Et_2NSF_3) did not afford the expected fluoro derivative but gave the oxazolidinone **153** instead (Scheme 49). The target molecule **156** (a potential inhibitor of dihydroceramide desaturase) was eventually obtained when the starting aminoalcohol **151** was protected as an *N*-Boc oxazolidine **154** and DAST treatment of this new substrate, leading to the oxazolidinone **155**, was successful with no oxazolidinone being produced.

It can be assumed that the cyclisation, leading to the oxazolidinone **153**, occurs within the compound **157** which is an intermediate during the DAST fluorinating process.

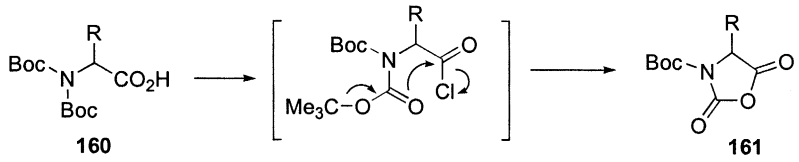
3.5. Carboxylic acid derivatives

N-Carboxy-α-amino acid anhydrides (NCAs) **158** have long been known as α-amino acid derivatives, which are both amine-protected and carboxylic acid-activated. They therefore present an important utility in peptide synthesis, especially when this is performed in the solid phase.

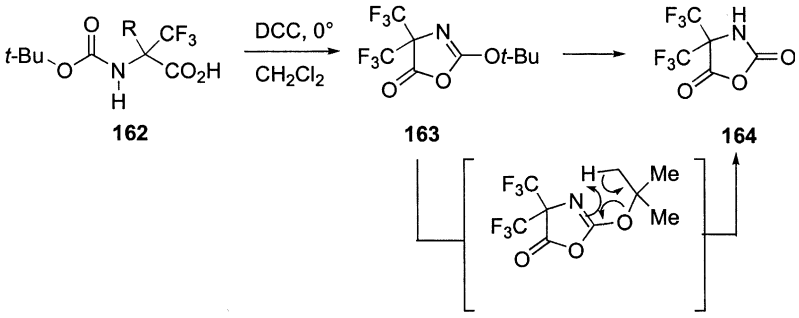
Bodanszky et al.[72] reported in 1975 that treatment of an *N*-Boc amino acid with various reagents which are able to activate the carboxylic acid moiety (DCC, ethyl



Scheme 49.



Scheme 50.



Scheme 51.

chloroformate, etc.) affords the NCA derivative of the amino acid **158**. This compound, however, is rather unstable and decomposes to yield by-products which essentially comprise the initial amino acid and its *tert*-butyl ester. In the same paper, the authors stated that no such cyclisation occurs in the case of *N*-Cbz-protected α-amino acids. Incidentally, it was shown[73] shortly afterwards that *N*-Cbz phenylalanine can be cyclodehydrated under the action of various reagents ($SOCl_2$, $POCl_3$, PCl_5 etc) affording the 5(4*H*)-oxazolone **159**.

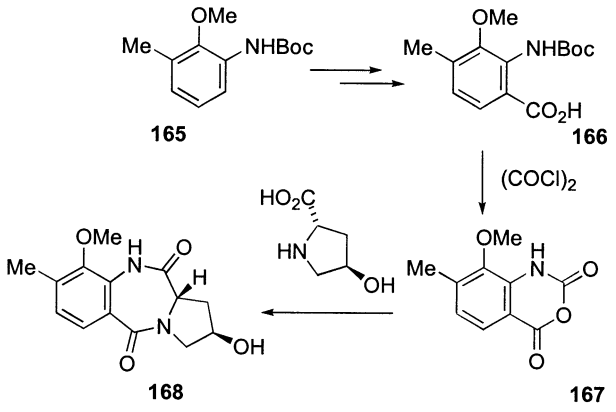
Many preparations of NCAs have been published in which urethane-protected as well as unprotected α-amino acids were the starting materials.[74] A special class of NCAs has been described by Wakselman et al.[75] who have shown that the *N*-Boc NCAs **161** are obtained when the N,*N*-Boc-diprotected amino acids **160** are treated with the $SOCl_2$/DMF Vilsmeier reagent (Scheme 50). The absence of epimerisation (i.e. retention of the stereochemical integrity)[76] was demonstrated during both the formation of these NCAs and their coupling under conditions of peptide synthesis, this feature making the *N*-carboxyanhydrides still more worthwhile.

With regard to peptide synthesis, there is, however, a drawback that must be underlined. Coste et al.[77] have observed that, when using *N*-methyl-*N*-Boc α-amino acids, NCAs are formed with extreme ease under activation of the carboxylic acid moiety with the PyBrop or PyCloP reagents. No analogous reactions were detected when the Cbz- or Fmoc-protected α-amino acids were activated. The same authors observed that peptide coupling was low yielding when *N*-methyl NCAs were employed and advised against using them in this field.

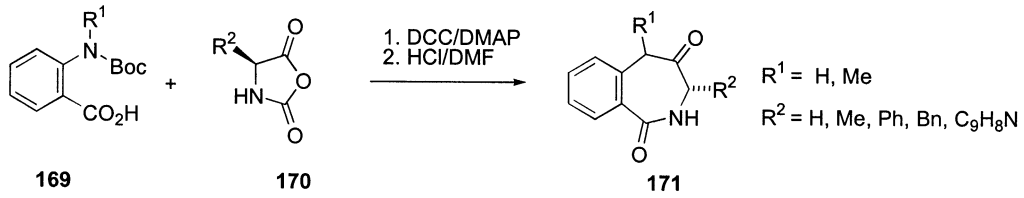
Using DCC for activating the carboxylic acid moiety, the α-trifluoromethyl-substituted *N*-Boc amino acids **162** are cyclised to give the 5(4*H*)-oxazolones **163** (Scheme 51) which were used by Hollweck and Burger[78] in order to synthesise dipeptides. These authors reported a noteworthy observation, namely that the 5(4*H*)-oxazolones decompose spontaneously to afford the NCAs **164**. A retro-ene mechanism was suggested in order to interpret the latter reaction.

This report is interesting because: (i) it demonstrates that 5(4*H*)-oxazolones are involved as intermediates during NCAs formation, and (ii) it offers an alternative explanation (the retro-ene process)[79] for the relative facility shown by the *tert*-butyl moiety to be eliminated even in a neutral medium.

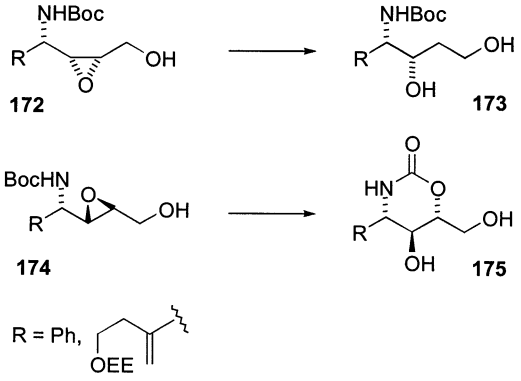
Not only are the NCA derivatives useful in peptide chemistry, but they may also be involved in general synthetic organic chemistry. In the course of their study on *ortho*-metallation, for example, Reed and Snieckus[80] have prepared the anthranilic acid derivative **166** by subjecting the substrate **165** to *tert*-butyl lithium metalation and carboxylation.



Scheme 52.



Scheme 53.



Scheme 54.

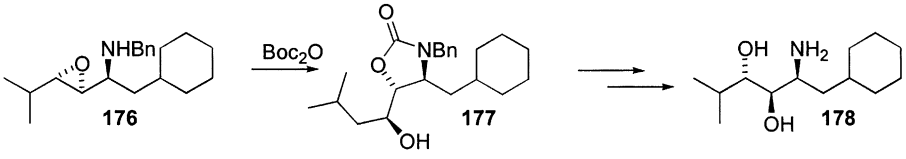
Treated with oxalyl chloride, the compound **166** was smoothly transformed into the fused NCA **167**. This methodology allows a very efficient synthesis of the anthramycin **168** which was easily obtained from the reaction of NCA **167** with *trans*-4-hydroxy-L-proline (Scheme 52).

Another mode of production of benzodiazepin-2,5-diones **171** which presents some similarities with the preceding method has been proposed by Viallefont et al.[81] This methodology consists of the reaction of the NCA **170** (classically prepared from the corresponding *N*-Boc amino acid) with the *N*-Boc-protected anthranilic acid derivative **169**. This reaction involves deprotection of the *N*-Boc group, ring expansion and decarboxylation (Scheme 53).

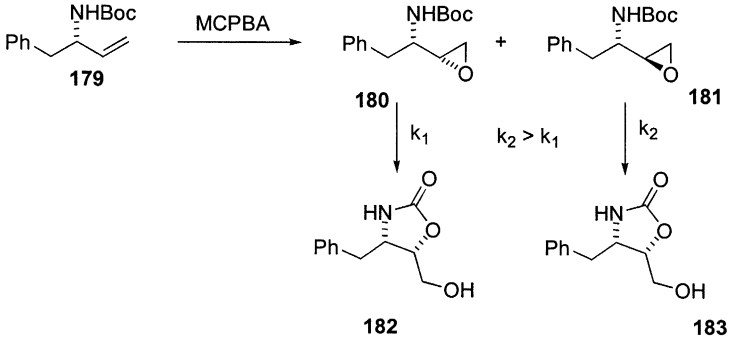
3.6. Epoxides

Whilst testing the $LiAlH_4$ reduction of the *N*-Boc amino epoxides **172** and **174**, Sato et al.[82] observed a very interesting phenomenon (Scheme 54). Whereas the *syn*/*cis* epoxides such as **172** can be transformed in good yield into the corresponding aminoalcohol **173**, its *anti*/*trans* diastereomeric form **174** afforded the tetrahydrooxazinone **175** which resulted from a nucleophilic attack of the epoxide moiety by the Boc substituent (the heterocycle **175** can also be produced by treating the substrate **174** with a Lewis acid [$TiOiPr_4$]. Considerations of steric interactions were convincingly invoked in order to explain this difference in reactivity between the epoxides **172** and **174**.

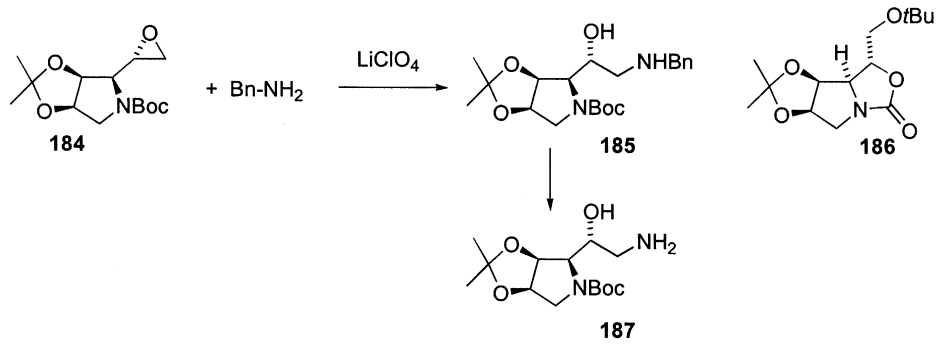
The proclivity towards intramolecular reactivity of amino epoxides having an *anti*/*trans* relative configuration was also observed by Hadad and Larcheveque[83] who made use of this when they synthesised the aminodiol **178** which is a dipeptide isostere subunit (Scheme 55). The key step in this synthesis consisted of the treatment of the aminoepoxide **176** with Boc_2O, in a neutral medium. The oxazolidinone **177** was produced via the intramolecular reactivity of the *tert*-butoxycarbonyl group, the regioselectivity being opposite that observed by Sato et al.[82]



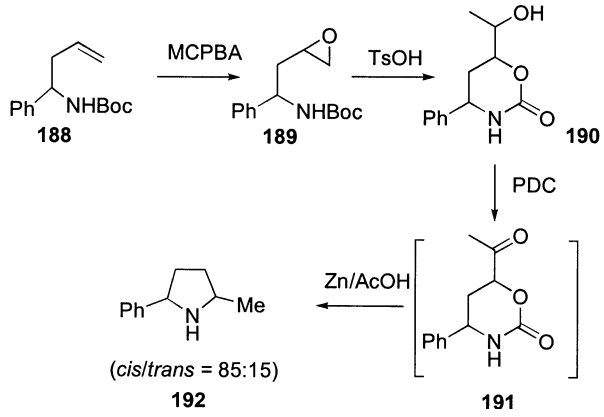
Scheme 55.



Scheme 56.



Scheme 57.



Scheme 58.

In connection with the above observations, Romeo and Rich have reported a noteworthy example of dynamic diastereomeric resolution.[84] During the MCPBA epoxidation of the allylic amine **179**, they observed an increase in the stereoselectivity, favouring the production of the epoxide **180** vs **181** with a protracted reaction time (Scheme 56). The oxazolidinone **182** was therefore formed at the expense of its isomer **183**.

The reason for this time-dependent stereoselectivity stems from a higher rate of cyclisation leading to the corresponding oxazolidinone **183** in the case of the epoxide **181**. By a judicious choice of conditions, it was therefore possible to efficiently obtain the epoxide **180** which has been used in the synthesis of several enzyme inhibitors.

The oxazolidinone **186** was observed as an importunate by-product when the epoxide **184** reacted with $LiClO_4$ (it is worth noting here that the *tert*-butyl group migrates on the alkoxy moiety formed).[85] This reaction actually takes place in the synthesis of the trideoxy-D-mannitol derivative **187**, a potential inhibitor of α-mannosidase (Scheme 57). In order to avoid the formation of the undesired oxazolidinone **186**, it was simply necessary to mix the epoxide **184** and benzylamine prior to the addition of $LiClO_4$ and, under these conditions, the aminoalcohol **185**, an intermediate in the synthesis of the target molecule **187**, was produced in 92% yield.

A new approach to pyrrolidines from homoallylic amines has been developed by Lhommet et al.[86] in which the formation of oxazinones was advantageous. Scheme 58 depicts one application of this methodology.

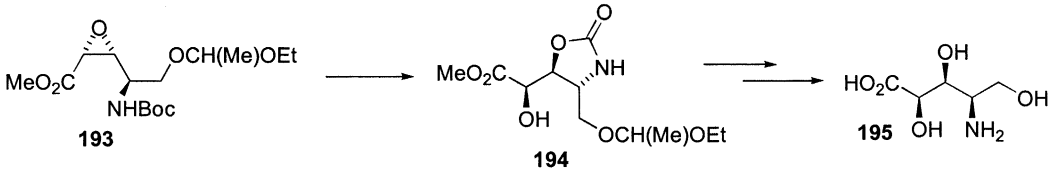
The epoxide **189** derived from the compound **188** was treated with *p*-toluenesulfonic acid to give the oxazinone **190**, oxidation of which afforded the non-isolated intermediate aminoketone **191**. Finally, in situ reductive amination of the latter compound afforded the substituted pyrrolidine **192**.

A regio- and stereoselective ring opening of epoxides by neighbouring Boc groups was the key step in a method which provides an entry to valuable precursors of *syn*/*syn*-3-amino-1,2-diol units related to the compound **195** (Scheme 59).

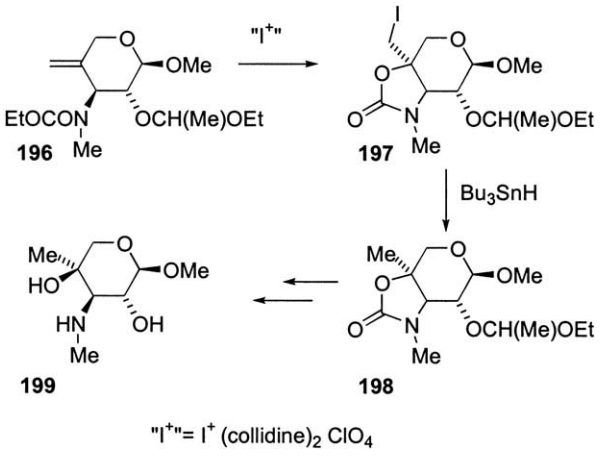
Langlois and Moro[87] observed, for example, that the compound **193** was transformed into the oxazolidinone **194** when it was adsorbed on silica gel (the primary alcohol function was not deprotected under these mild conditions).

3.7. Halonium ions

Intramolecular reaction of a urethane unit with a halonium ion is reminiscent of the well-known and very useful halolactonisation reaction. For a urethane acting as the nucleophile, we are faced with another type of transcarbamation reaction. Clearly, the intramolecular nature of such transformations is a favourable feature and oxazolidinones or oxazinones may easily be attained in this way. It should



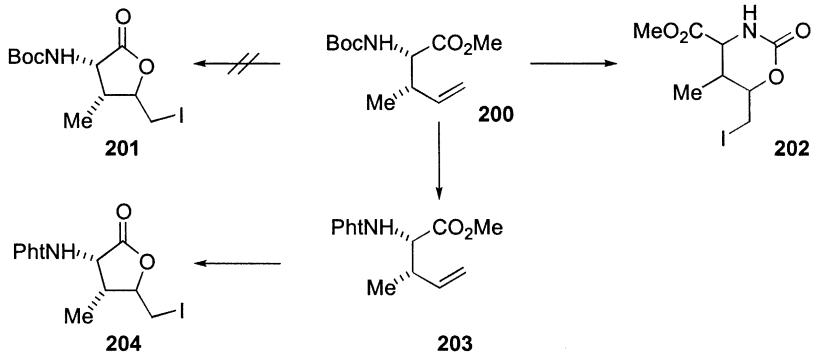
Scheme 59.



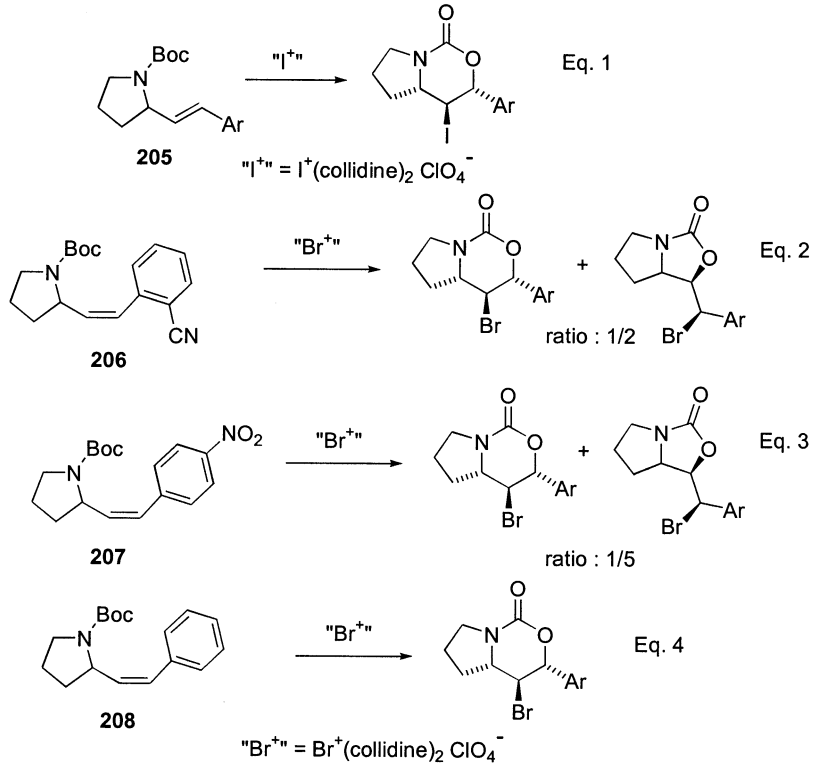
Scheme 60.

be noted that, in these reactions, interesting problems of both regio- and stereoselectivity arise, owing to the fact that halonium compounds are almost always dissymmetrical and that two stereocenters are simultaneously created. These features explain why these reactions may be considered as the most useful application of the nucleophilic reactivity of the *N*-Boc group.

To our knowledge, Pauls and Fraser-Reid[88] were the first authors to describe such a process in order to create *cis*-hydroxyamino moieties in amino sugars (Scheme 60). The *N*-ethoxycarbonyl substrate **196** was treated with iodonium dicollidine perchlorate as a source of iodonium ion. Formation of the oxazolidinone **197** shows that the trans-carbamation took place with a complete regio- and stereo-control. After reduction to **198**, removal of the O-protecting group, and final hydrolysis with potassium hydroxide afforded **199**, the methylglycoside of α-L-garosamine,



Scheme 61.



Scheme 62.

which is a key component of an important class of antibiotics.

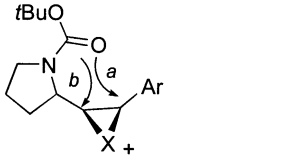
Shortly afterwards, this *cis*-oxyamination route to aminosugars was successfully applied to the synthesis of holacosamine.[89] Following these pioneering studies, many similar reactions were reported in which the nucleophilic urethane moiety most often was the *N*-Cbz group.[90] The first description of an *N*-Boc fragment involved in a halonium ion-mediated transcarbamation was reported by Bartlett et al.[91] During an attempted iodolactonisation with the compound **200** (Scheme 61), the expected molecule **201** was not obtained, this failure being due to competitive cyclisation of the carbamate moiety affording the cyclic carbamate **202**. In order to prevent this undesired transcarbamation, it was necessary to protect the amino group as a phthalimide (*N*-Pht) and the corresponding substrate **203** was indeed cyclised via iodolactonisation to give the lactone **204**.

Parker and O'Fee[92] have reported an extensive study of the steric and electronic parameters able to control the regio- and stereochemistry of these halonium-initiated cyclisations. They first observed that *N*-Boc allylic amines with an *E* geometry of the double bond always afforded oxazinones (see the compound **205** in Scheme 62). For the *Z* isomer the situation is more complex: (i) the presence of an electroattractive substituent on the phenyl group, as in the substrates **206** and **207**, favours the formation of the oxazolidinone (Eqs. (2) and (3) in Scheme 62), (ii) in the absence of such substituents, only the 6-membered heterocycle, i.e. the oxazinone, is obtained (see the *N*-Boc derivative **208** in Scheme 62). These authors have additionally determined the stereochemistry of the heterocycles produced and were able to demonstrate that the bromocarbamation reaction is stereospecific.

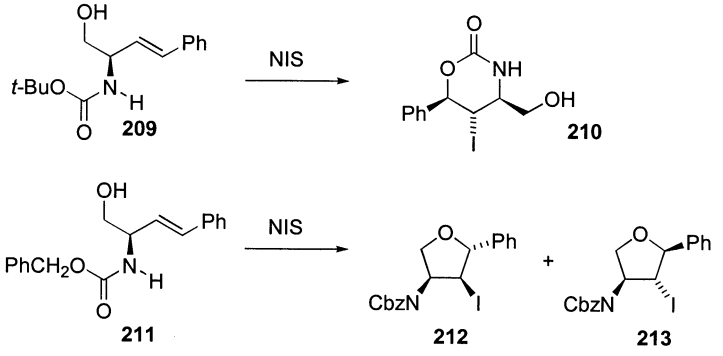
The explanation suggested to account for this dramatic change of regioselectivity was that the regiochemistry should be governed by a nucleophilic attack on an intermediate halonium ion at the site of greater positive charge. This means that Path *a* in Scheme 63 is predominant when there is no electroattractive substituent on the aromatic moiety, whereas competition between Paths *a* and *b* occurs when such a substituent is present.

An intriguing case of chemoselectivity has been raised in recent investigation reported by Sepulveda-Arques et al.[93] Whereas the *N*-Boc-protected aminoalcohol **209** undergoes an iodonium-mediated halocarbamation leading to cyclised derivative **210**, its *N*-Cbz analogue **211**, under the same conditions, reacts via a nucleophilic attack of its hydroxyl group to afford a mixture of the tetrahydrofurans **212** and **213**. These results were rationalised by calculations which indicate that the substrates **209** and **211** should present a different conformation due to a π-stacking effect between the phenyl groups in **211**. Another explanation can, however, be put forward that the *N*-Boc moiety would be more reactive than its *N*-Cbz counterpart. The easy transformation of the potential *tert*-butyl cation into an isobutene molecule is a very substantial factor which could justify this difference of reactivity (Scheme 64).

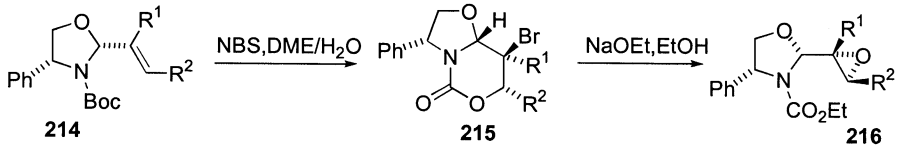
This type of halocarbamation has been invoked to account for a highly diastereoselective functionalisation of the enantiopure *N*-Boc 2-alkenyloxazolidines **214**.[94] The first step in this process is a bromonium ion-mediated



Scheme 63.



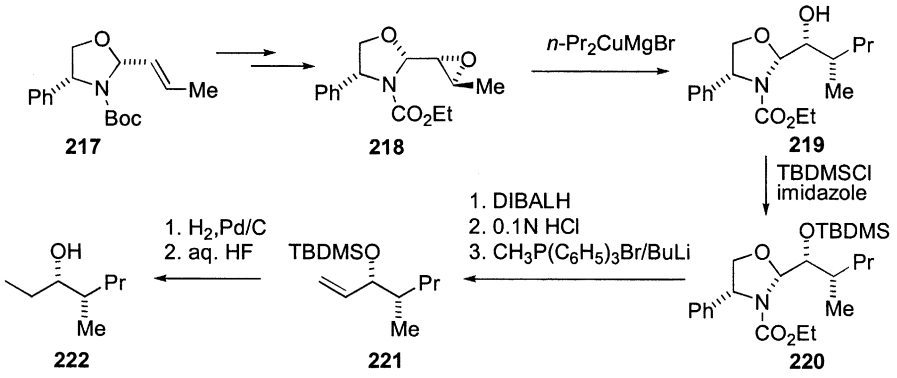
Scheme 64.



R^1 = H, Me

R^2 = Ph, *n*-C_3H_7, -CH=$CHCH_3$ (*E*), C_2H_5

Scheme 65.



Scheme 66.

transcarbamation, leading to the corresponding bromooxazinones **215** which were then transformed into the epoxyoxazolidines **216** by treatment with sodium ethoxide (Scheme 65). This transformation, which actually consists of two successive transcarbamation reactions, was realised with various substrates according to the nature of the R^1 and R^2 substituents.

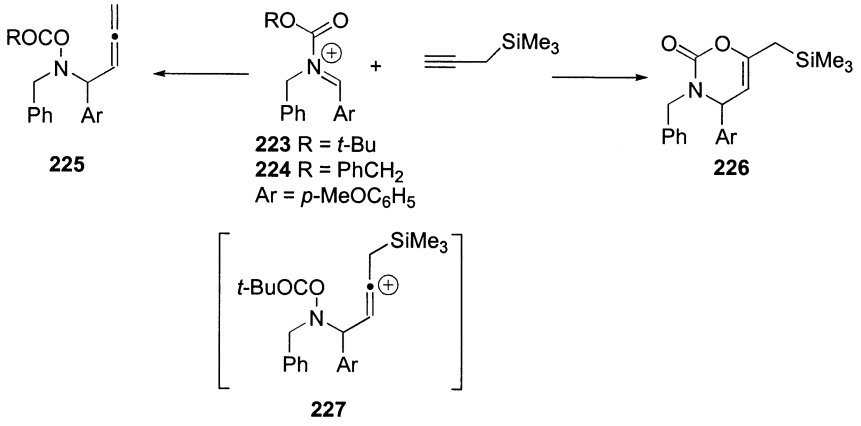
This methodology has been applied to the asymmetric synthesis of some natural products. As an example, Scheme 66 depicts the synthesis of (3*S*,4*S*)-4-methyl-3-heptanol **222**, a beetle pheromone, from the epoxyoxazolidine **218**, which was synthesised from the substrate **217** via the intermediates **219**–**221**.[95]

The diastereoselectivity which was observed during the bromocarbamation reaction (Scheme 65) was rationalised on the basis of conformational effects that direct the stereochemistry of the intermediate bridged bromonium ion before its reaction with the urethane moiety.[96] With regard to the regioselectivity which controls the bromonium ion attack as well as the epoxide opening, the nucleophilic attack in both reactions occurs at the electrophilic center which is more distant from the oxazolidine ring. AM1 calculations showed that the value of positive charge is larger on this centre, which was due to the electroattracting effect of the *N*-urethane-substituted oxazolidine ring.

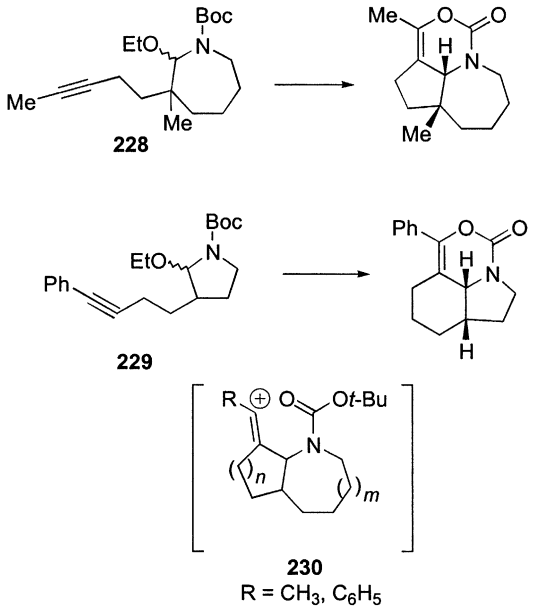
3.8. Carbenium and carbonium ions

With such powerful electrophiles, the nucleophilic reactivity of the *N*-Boc group is unquestionably magnified. The first example of this type was reported by Speckamp et al.,[97] who observed that the reaction of propargyltrimethylsilane with the *N*-Boc iminium ion **223** does not afford the expected allene derivative **225** but exclusively the oxazinone **226**. This results from an attack of the nucleophilic *N*-Boc group on the transient vinylic cation **227** (Scheme 67). It is interesting to note that, under the same conditions, the related iminium ion **224** (the nitrogen atom of which bears a Cbz and not a Boc group) yields both the oxazinone and the allenic products. This is another result which shows that the *N*-Boc moiety is especially nucleophilic.

Intramolecular cyclocondensations from unsaturated *N*-(acyloxy)iminium ion substrates were extensively studied by Fisher and Overman[98] who described a new route to heterotricyclic systems. Azepine, as well as pyrrolidine, substrates possessing tethered alkyne or alkene moieties underwent such cyclocondensation reactions under the influence of $SnCl_4$ which initiates the formation of a reactive iminium ion. Scheme 68 shows two examples of such impressive transformations the mechanism and stereochemistry of which were examined in detail. A stepwise sequence proceeding via a transient carbenium ion **230**



Scheme 67.



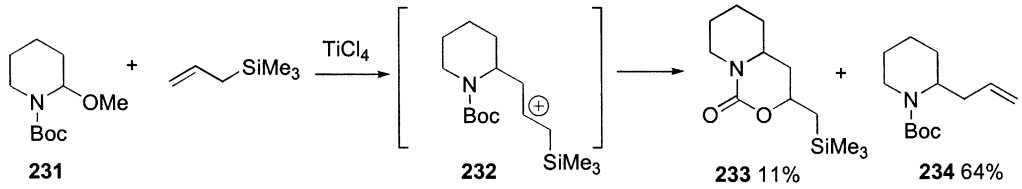
Scheme 68.

can be invoked in order to explain the *N*-Boc involvement in the cyclisations of the substrates **228** and **229**.

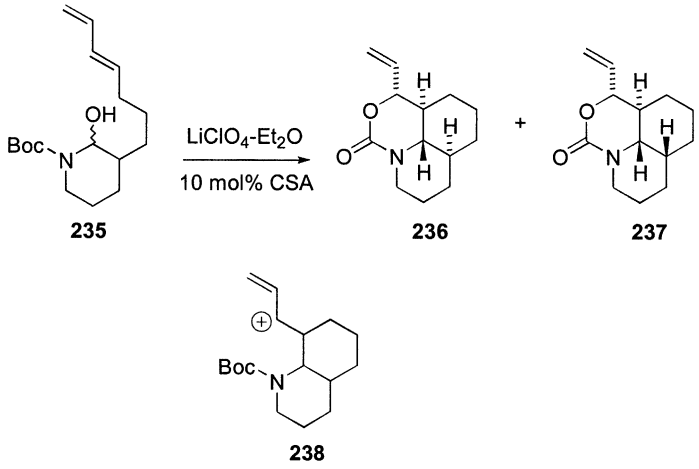
In connection with the reactions of cations resulting from unsaturated silanes reacting with an iminium bond, the oxazinone **233** was reported to be formed, via carbocation **232**, along with the expected homoallylic amine **234**, when the *N*-Boc aminoether **231** was treated with $TiCl_4$ (Scheme 69).[99] In this paper it was indicated that, in accordance with what has often been stated in the present review, other carbamate moieties are unable to afford such oxazinone compounds

In a study aimed at examining intramolecular imino Diels–Alder reactions, Grieco and Kaufman[100] were surprised to observe the formation of the oxazinones **236** and **237** (in a 5:1 ratio) instead of the expected tricyclic amine when they treated the substrate **235** (Scheme 70). Clearly, here again, an intermediate cation **238** is responsible for this reaction.

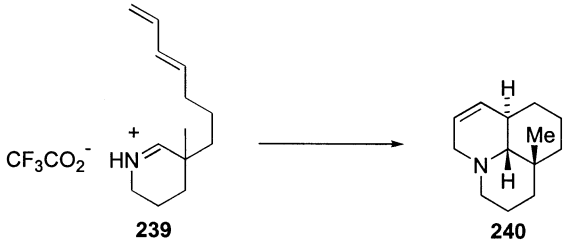
These authors eventually attained their goal by replacing the Boc 'protecting' group by the TEOC (2-(trimethylsilyl)-



Scheme 69.



Scheme 70.



Scheme 71.

ethoxycarbonyl) fragment (Scheme 71) in a methyl-substituted analogue of the piperidine **234**. After deprotection of the nitrogen by the action of fluoride ion and formation of the trifluoroacetic salt of the imine **239**, treatment of this salt simply by heating in aqueous solution afforded the required tricyclic amine **240**.

4. Conclusions

Given the great variety of reactions in which the *N*-Boc

group can be involved, it now appears that its reactivity should be well recognised. Consequently, two points need to be emphasised: (i) careful attention should be paid when this group is chosen as a protective moiety, since it is able to react intramolecularly with both nucleophiles and electrophiles, provided that they are in its vicinity, and (ii) this group allows very efficient synthesis of interesting heterocycles via reactions of many types. It seems, therefore, that the reactivity of this group holds great promise and many elegant syntheses have already been described, particularly in relation to its nucleophilic reactivity. It is expected that further studies may uncover other aspects of the synthetic utility of the *N*-Boc moiety which surely should not be considered only as a protecting group. Substantially more work is required to fully explore and exploit the possibilities of this function in organic synthesis, but, in view of the great variety of reactions that are presented in this review, it can already be stated the *N*-Boc reactivity cannot be qualified as 'underrated' any longer.

Acknowledgements

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