The Use of *N*-Boc-1,3-Oxazolidines as Chiral Auxiliaries in Asymmetric Synthesis

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This microreview presents the use of 1,3-oxazolidines, prepared from enantiomerically pure β-amino alcohols, as chiral inductors for the stereoselective transformation of adjacent prostereogenic C=C or C=O bonds. After a brief chronological presentation of the major advances in this field, a convenient synthesis of *N*-Boc-2-acyl- and -2-alkenyloxazolidines is presented, together with the use of these heterocycles in asymmetric synthesis. The important role played by the Boc group on the nitrogen of the heterocycle in these transformations is emphasized. In addition to its well known properties as a protecting group, this carbamate actively contributes to the efficiency of this chemistry. Thanks to its bulkiness and chelating properties, it contributes to an efficient stereodifferentiation of the close prostereogenic moiety, but can also directly react with this moiety either as an electrophile or as a nucleophile.
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Introduction

Enantioselective catalysis is still gaining in efficiency and popularity and is clearly the "high road" for the production of enantiopure chiral building blocks. The enormous advantages brought by this methodology have on the way been "officialized" and rewarded by the presentation of the 2001 Nobel Prize for chemistry to Knowles, Sharpless, and Noyori, for their outstanding contributions in this field.[1] From a practical point of view, however, processes based on this methodology often require considerable finalization to produce target compounds with high *ee*s. Furthermore, asymmetric catalysis is necessary in order to achieve perfection, since the produced enantiomers are seldom easily optically enriched by conventional purification techniques. This is the reason why asymmetric syntheses based on the stoichiometric use of a recyclable chiral inductor still gain considerable attention. The flexibility of these methodologies, the facility associated with their being put into practice, the capability for facile elimination of minor undesirable diastereoisomers, and a wide choice of available inductors[2] are convincing qualities that often influence the choice to adopt this technique when a rapid route to a given enantiopure building block is envisioned.

Despite the commercial availability of many 1,3-amino alcohols in both enantiomerically pure forms, the use of

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MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

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1,3-oxazolidines as chiral templates for the diastereoselective functionalization of adjacent C=C or C=O bonds in this field (**2**, **3** in Figure 1) was hampered in the early stages of asymmetric synthesis by two fundamental problems that have progressively found efficient solutions. The first of these problems concerns the control of the diastereoselectivity in the course of the formation of the oxazolidine heterocycle (C-2 stereocenter). This is an important point of course, since this newly created stereocenter is to a large extent intended to control the stereoselective transformation of the adjacent moiety. The second problem is more of a practical nature, but can seriously reduce the efficiency of the process, and relates to the ease of unmasking the aldehyde moiety, with concomitant recovery of the β-amino alcohol. These two problems are in fact connected, since they deal with two closely connected chemical transformations: the formation and the cleavage of the oxazolidine ring. The judicious choice of the group on the nitrogen (R^3 in Figure 1) of the heterocycle is a key parameter in this process and provides solutions to the two problems discussed.

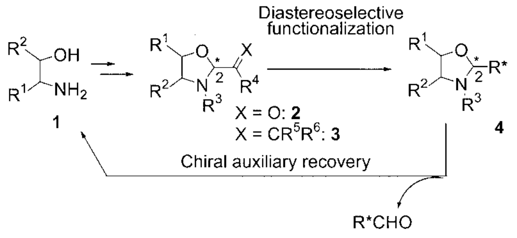
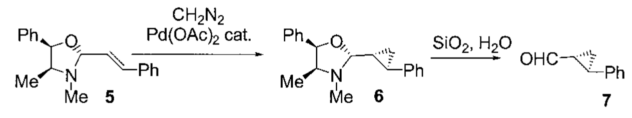


Figure 1. 1,3 Oxazolidines as chiral auxiliaries for the diastereoselective functionalization of adjacent C=C or C=O bonds

The aim of this review is to present the contributions of different groups in this field, placing the emphasis on the advantages brought by the use of the Boc group on the heterocyclic nitrogen in this methodology.

Early Stages of Oxazolidine Chemistry: *N*-Alkyloxazolidines for the Stereoselective Functionalization of Alkenes

The use of 1,3-oxazolidines in asymmetric synthesis begins in the early 1980s, when Carrié and Gree reported the use of an oxazolidine as a chiral inductor for the first time.[3] In this work, palladium-catalyzed cyclopropanation of (1*R*,2*S*)-ephedrine-derived oxazolidine **5**, prepared by condensation between (−)-ephedrine and cinnamaldehyde, occurred stereoselectively (> 90 % *de*) and gave **6** in good yield. Unmasking of the aldehyde under smooth conditions then gave the optically enriched aldehyde **7** (Scheme 1).

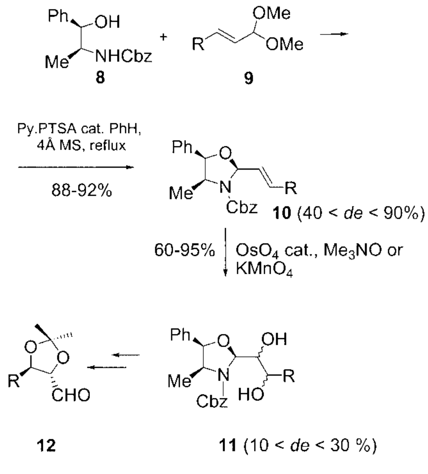


Scheme 1

This seminal paper was then rapidly followed by papers from several other groups: Normant[4] and Berlan[5] shortly afterwards described stereoselective conjugate cuprate additions to α,β-unsaturated ephedrine-derived oxazolidines, and at the same time mechanistic investigations into the stereoselectivity observed during the condensation between aldehydes and ephedrine were reported.[6] Despite these promising new results, however, very few reports[7] on the use of *N*-alkyl-1,3-oxazolidines in asymmetric synthesis followed. This is due mainly to a practical problem: the instability of these heterocycles towards hydrolysis in most cases precludes their purification by flash chromatography. Since the stereoselectivity of the thermodynamically controlled oxazolidine formation seldom exceeds 90 % in favor of the *cis*-2,4 isomer, the enantiomeric excesses of the target aldehydes could not conform to the standards dictated by modern asymmetric synthesis. Since then, the use of *N*-alkyl-1,3-oxazolidines as chiral auxiliaries has been periodically investigated with different β-amino alcohols, such as prolinol[8] or, more recently, piperidin-3-ol.[9]

Later Stages: the Use of *N*-Acyl- and *N*-Tosyl-2-alkenyl-1,3 oxazolidines

In 1985, Scolastico and co-workers described[10] the diastereoselective synthesis of a *N*-CBz-1,3-oxazolidine **10** for the first time, through acid-catalyzed transacetalisation of an allylic dimethylacetal **9**. Although the diastereoselectivities of the ring formation and of the subsequent dihydroxylation of the adjacent alkene moiety were modest, the stability of these heterocycles allowed separation of minor isomers by flash chromatography, which eventually furnished enantiopure aldehyde **12**. This reaction was followed by a two-step cleavage of the oxazolidine involving hydrogenolysis or DIBAL reduction of the CBz carbamate, and subsequent mild acidic hydrolysis (Scheme 2).

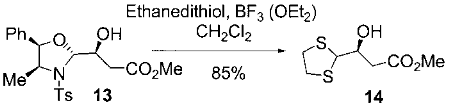


Scheme 2

This pioneering work showed that protection of the nitrogen in the oxazolidines with an electron-withdrawing group allowed purification by flash chromatography, thereby establishing their utility as chiral inductors in asymmetric synthesis. This work was rapidly followed by the publication of other efficient stereoselective transformations of alkenyl moieties adjacent to a *N*-acyl- or *N*-tosyl-oxazolidine heterocycle, such as cuprate,[11] Grignard, and lithium acetylide[12] conjugated additions, epoxidation,[13] Michael addition of alkoxides,[14] radical cyclizations,[15] cyclopropanation,[16] hydrogenation,[17] 1,3-dipolar cycloadditions,[18] and intramolecular Diels–Alder reactions.[19] The problems discussed in the Introduction were to a large extent solved at this stage, since the introduction of an electron-withdrawing group on the nitrogen of the heterocycle allowed the stereoselective synthesis of the *cis*-2,4 isomer with excellent diastereoisomeric excesses,[12] this *cis* isomer being favored both kinetically and thermodynamically.

Most of the work on chiral oxazolidines carried out by Scolastico and Poli deals with *N*-tosyl derivatives. According to the latter author, the choice of this protecting group benefits from the easy availability of the parent *N*-tosylamino alcohols, as well as the crystalline natures of several derivatives. Furthermore, it was found that the thermodynamically controlled Lewis acid-promoted cyclizations of *N*-tosyl-*nor*-ephedrine with several α,β-unsaturated dimethyl acetals were totally stereoselective in favor of the *cis* isomers only in the case of *N*-tosyl substitution. Such a result is consistent with the non-planar structure of the nitrogen atom in these compounds, which is responsible for enhancement of the energetic gap between the *cis* and the *trans* C-2 substituted oxazolidines.[20]

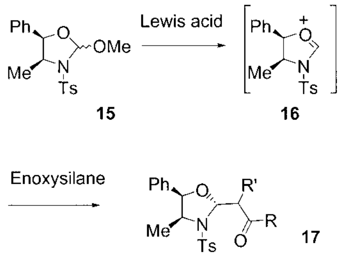
Scolastico et al. also proposed a standard procedure for the recovery of the chiral auxiliary, involving a Lewis acid-catalyzed transthioacetalization, as demonstrated in Scheme 3.[14]



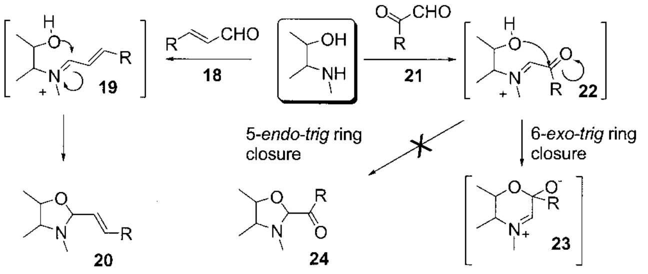
Scheme 3

In the late 1980s, after this fruitful period, oxazolidine chemistry was in expansion, and Hoppe's group also began to publish in this field. Almost simultaneously, Scolastico[21] and Hoppe[22] reported a new stereoselective synthesis of *N*-tosyl-oxazolidines, which takes advantage of the high π-face stereodifferentiation of the oxocarbenium ion **16**. This allowed the preparation of β-acyloxazolidines such as **17**, which were used for diastereoselective aldol reactions,[23] Michael additions,[24] and intermolecular Diels–Alder reactions.[25] (Scheme 4). All these transformations also involved the stereoselective transformation of an intermediate C=C double bond adjacent to the chiral oxazolidine framework.

As outlined below, at the beginning of the 1990s the use of *N*-Cbz- or *N*-tosyl-oxazolidines as chiral auxiliaries for the stereoselective transformation of alkenes became used routinely. This was not the case for ketones, however, since there was no general method available for the stereoselective synthesis of 2-acyloxazolidines of general structure **24** (Scheme 5). As a matter of fact, unlike α,β-unsaturated aldehydes – which give oxazolidines upon condensation with a β-amino alcohol, through 5-*endo*-*trig* ring closure of an intermediate ene-iminium **19** – glyoxal derivatives **21** generate oxo-iminium ions that preferentially cyclize by a 6-*exo*-*trig* pathway.[26] This mechanistic feature restricts the synthesis of 2-acyloxazolidines through direct condensation to the use of phenylglyoxal and *N*-alkyl-β-amino alcohols.[8,9]



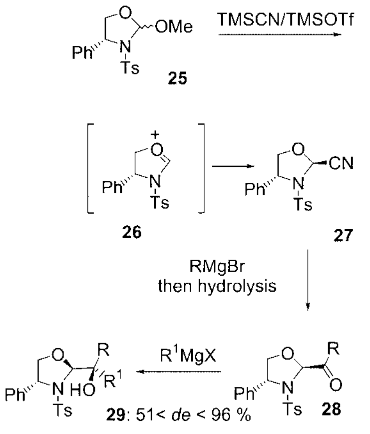
Scheme 4



Scheme 5

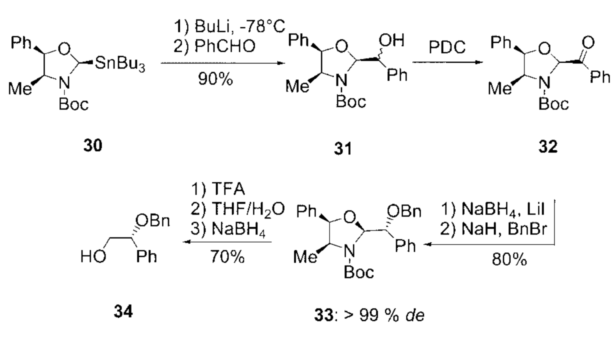
Synthesis and Diastereoselective Reductions of 2-Acyloxazolidines

Hoppe was now the first to provide a convenient and general route to *N*-tosyl-2-acyloxazolidines.[27] In 1993 he described the stereoselective preparation of a 2-cyanooxazolidine **27**, resulting from the Lewis acid-catalyzed addition of TMSCN to oxonium ion **26**, generated from **25**. Treatment of the nitrile moiety with a Grignard reagent cleanly gave the corresponding ketone **28**. Addition of another Grignard reagent occurred stereoselectively to give the α-hydroxyoxazolidine **29** with good selectivity (Scheme 6). Hoppe next described an electrochemical cleavage of the *N*-tosyloxazolidine, which allowed access to an optically enriched α-hydroxy ketone by this methodology.[28] It should be noted that the stereoselective reduction of an ephedrine-derived *N*-tosyl-2-acetyloxazolidine of 2,4-*cis* stereochemistry had previously been studied and optimized by Scolastico,[29] but the synthesis of this ketone was indirect, since it involved the oxidative cleavage of an intermediate alkenyloxazolidine. Furthermore, the transthioacetalisation described above, intended to unmask the aldehyde, failed to produce the α-hydroxythioacetal.[30]



Scheme 6

In 1994, Colombo[31] described the synthesis of an N-Boc-2-acyloxazolidine **32** by anionic chemistry: lithiation of the 2-stannyloxazolidine **30**, obtained in modest yield by an acid-catalyzed transacetalisation, gave, after a quench with benzaldehyde, the α-hydroxyoxazolidine **31** as a mixture of isomers. Oxidation of this alcohol then gave diastereoisomerically pure acyloxazolidine **32**. Diastereoselective reduction of this compound, followed by protection of the hydroxy moiety, afforded **33**. Unmasking of the aldehyde was achieved by conventional N-Boc deprotection (TFA), followed by hydrolysis (THF/H_2O), and eventually gave α-benzyloxyaldehyde **34** (96 % *ee*, Scheme 7). Two very important features in this isolated example should be noted: (i) the excellent level of stereoselection (higher than 100:1) observed for the reduction step, and (ii) the ease of unmasking of the aldehyde. The Boc group, so far curiously absent in the chemistry of oxazolidines, was thus shown as unquestionably worthwhile.

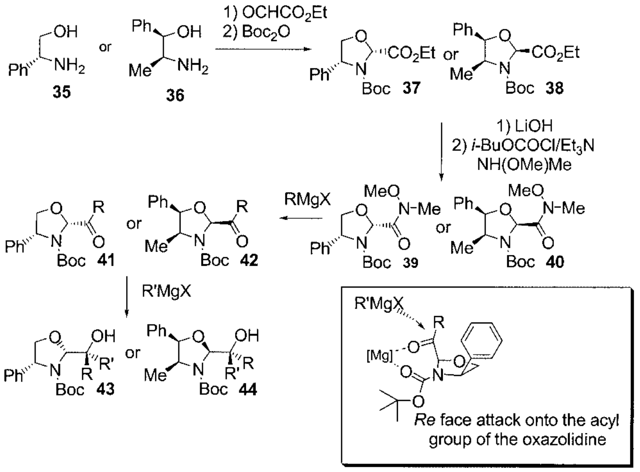


Scheme 7

Two months later, we started to investigate this topic and we reported a convenient and general synthesis of N-Boc-2-acyloxazolidines. The following sections of this microreview place emphasis on the advantages brought by the use of a N-Boc group in oxazolidine chemistry.

Synthesis and Reactivity of *N*-Boc-2-acyloxazolidines

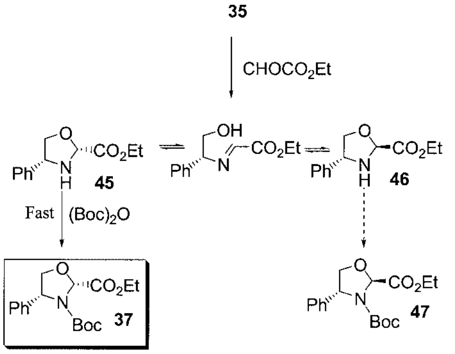
Our methodology developed for the synthesis of N-Boc-2-acyloxazolidines is based on the use of Weinreb amides. Condensation of ethyl glyoxylate with (R)-phenylglycinol **35** or (1R,2S)-norephedrine **36**, followed by treatment with $(Boc)_2O$, stereoselectively affords 2,4-*cis*-2 carboethoxy oxazolidines **37** or **38**.[32] Saponification then gives the carboxylic acids, which were best transformed into the corresponding Weinreb amides **39** or **40** by the mixed anhydride method.[33] Treatment of these amides with Grignard reagents provided the corresponding acyloxazolidines **41** or **42** in good yields, and addition of other Grignard reagents to these compounds was shown to occur through a chelated model (depicted for the reaction involving **41**, Scheme 8), to give tertiary alcohols **43** or **44** with high stereocontrol. The enantiomerically enriched α-hydroxy aldehydes could then be recovered as shown above in Scheme 7.



Scheme 8

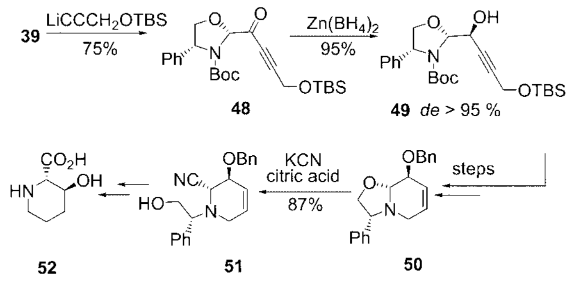
The origin of the stereoselectivity observed in this condensation (C-2 stereocenter) was explained as follows. Condensation of the β-amino alcohol with ethyl glyoxylate is not stereoselective, affording a roughly equimolar mixture of *cis* and *trans* isomers **45** and **46** [as depicted for the condensation involving (R)-phenylglycinol: Scheme 9]. The *cis* isomer **45** is more reactive than the *trans* with regard to the reaction with the bulky acylating reagent Boc_2O, because the reacting lone pair of the nitrogen can be located in a *trans* relationship with respect to the α and α′ substituents in this isomer and is therefore not hindered. As a consequence, its protection is more rapid, and irreversibly gives **37**. Since an equilibrium exists between **45** and **46**, but not between **37** and **47** (the lone pair of the nitrogen is engaged into the carbamate and cannot contribute to the opening of the oxazolidine), this selective protection will drive the equilibrium toward isomer **37**. The diastereoselectivity of the process is thus a consequence of a kinetic dynamic resolution. From a practical point of view, it should be noted that the overall synthetic sequence for the preparation of

Weinreb amide **39** is very convenient. It affords **39** on a large scale in an 80 % overall yield from the β-amino alcohol **35**, with no need for chromatographic purification (the intermediate acid is a crystalline solid that can conveniently be purified by simple trituration). Since Weinreb amides are one of the best precursors to ketones,[34] the convenient preparation of **39** gives access to a wide range of 2-acyloxazolidines in large quantities, so that further chemical transformation can conveniently be performed.



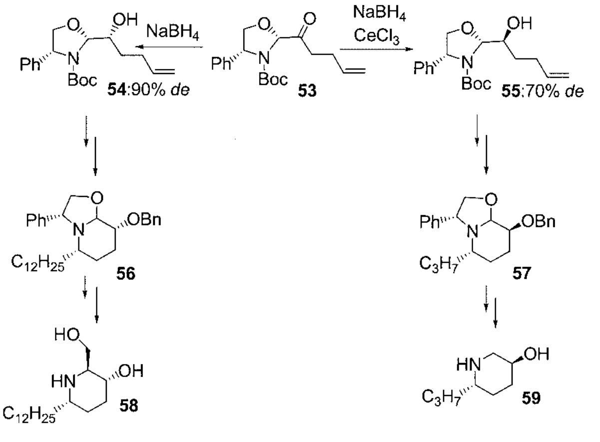
Scheme 9

This methodology proved to be well suited for the enantioselective synthesis of hydroxylated piperidine heterocycles, and it was first applied to the synthesis of (2*S*,3*S*)-3-hydroxypipecolic acid (**52**).[35] The hydroxylated center of this amino acid was created through diastereoselective reduction (NaBH$_4$, CeCl$_3$) of ynone **48**, the result of the addition of a lithium acetylide to Weinreb amide **39**. The stereoselectivity (90 % *de*) of the reduction step could be explained in terms of a chelated model and could be enhanced to > 95 % *de* by use of zinc borohydride as the reducing agent.[36] The other key steps of the synthesis involved: (i) an intramolecular alkylation of the deprotected *N*-Boc-amine in order to give **50**, and (ii) a stereoselective addition of HCN, producing amino nitrile **51** (Scheme 10).



Scheme 10

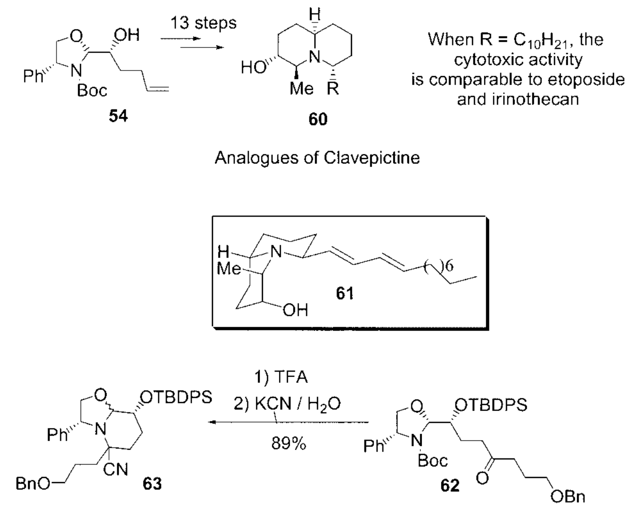
The stereoselectivity of the reduction step of *N*-Boc-2-acyloxazolidines was found to be highly dependent on the nature of the reducing agent. This was put to good use for the enantioselective synthesis of two natural alkaloids: (−)-desoxoprosopinine (**58**) and (+)-pseudoconhydrine (**59**).[33,37] In this event, the acyloxazolidine **53** was reduced with sodium borohydride to give the alcohol **54** (90 % *de*) through a Felkin−Anh transition state. In contrast, addition of CeCl$_3$ to the reaction medium reversed the stereoselectivity and gave diastereoisomer **55** through a Cram-like chelated transition state, albeit with a lower (70 %) diastereoselectivity. For the two target compounds, the piperidine core was next constructed by an intramolecular reductive amination step, after removal of the Boc group, to give **56** or **57**. Finally, stereoselective addition of vinylmagnesium bromide to a transient iminium ion generated from the amino ether moiety in **56** gave rise to the third stereocenter in **58**, whereas reduction of **57** followed by *N*- and *O*-debenzylation gave **59** (Scheme 11).



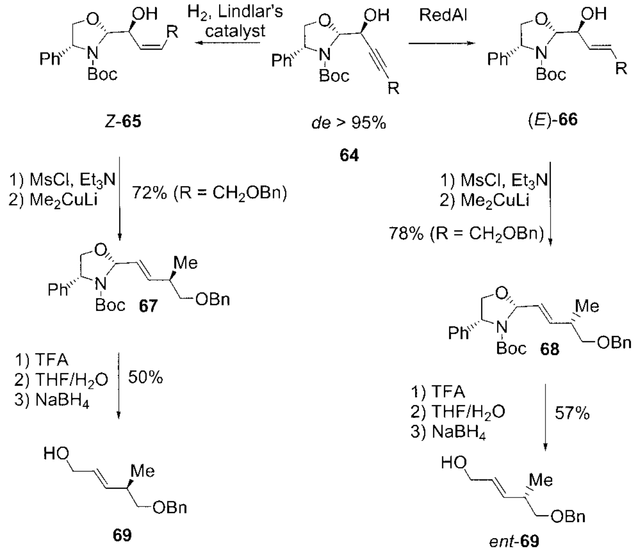
Scheme 11

The hydroxyoxazolidine **54** recently served as a starting material for the synthesis of more complex target compounds:[38] such as quinolizidine heterocycles **60**. These molecules were designed with the aim of improving the cytotoxic activity of an alkaloid **61** named clavepictine A, isolated from a tunicate. From a biological viewpoint, this work allowed the first structure-activity relationship (SAR) studies of these clavepictine analogues as anticancer drugs, and one of these synthetic molecules was found to be as potent as etoposide and irinothecan, two clinically used anticancer drugs. In this synthesis, the piperidine core was constructed through intramolecular aminocyanation after conventional removal of the *N*-Boc group to give **63** in high yield. Interestingly, the TBDPS protecting group on the hydroxy moiety, chosen for orthogonal deprotection at the end of the synthesis and its stereodirecting effect, survived the acidic medium of this *N*-Boc cleavage (Scheme 12).

This methodology is also well suited for the stereoselective synthesis of the allylic alcohols (*Z*)-**65** or (*E*)-**66**, prepared by Lindlar-catalyzed hydrogenation or RedAl reduction, respectively, of carbinols of general structure **64** (vide supra). Efficient 1,3-transfers of chirality could be performed on these substrates. For example, their methanesulfonyloxy derivatives reacted with organocuprate reagents[39] to give the alkenyloxazolidines **67** or **68** stereoselectively through an *anti* S$_N$2′ alkylation process. The masked enantiomeric enals were then recovered as described previously and reduced to give allylic alcohols **69** and *ent*-**69** (Scheme 13).



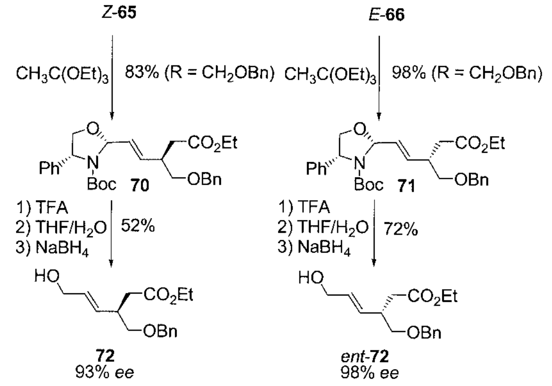
Scheme 12



Scheme 13

Claisen rearrangements involving these allylic alcohols were also stereospecific.[40] This allowed the synthesis of, for instance, enantiomeric functionalized allylic alcohols **72** and *ent*-**72** from (*Z*)-**65** or (*E*)-**66**, respectively (Scheme 14). This methodology could also be applied to the starting alkynol **64**, thus providing stereodefined allenes.

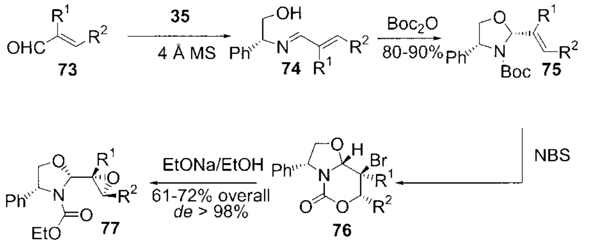
The Boc group in this acyloxazolidine methodology plays a conventional part as a protecting group: easily introduced and removed, it protects the oxazolidine ring against hydrolysis. Furthermore, this protecting group also contributes to the diastereoselectivity of the process, because of its bulkiness (selective protection of the less crowded *cis* isomer in Scheme 9) or chelating properties (chelated model in Scheme 8). The next section illustrates a more active role for the Boc group, through the diastereoselective functionalization of 2-alkenyloxazolidines.



Scheme 14

Epoxidation of *N*-Boc-2-alkenyloxazolidines

In 1995[41] we reported a convenient synthesis of *N*-Boc-2-alkenyloxazolidines, and their diastereoselective epoxidation. Condensation of the enals **73** with (*R*)-phenylglycinol gives the α,β-unsaturated imino alcohol **74**, and treatment of this with Boc_2O produces an acyliminium ion that irreversibly cyclizes to give *cis* 2-alkenyloxazolidines **75** with high stereoselectivity. Unlike the method of Scolastico (vide supra), which was based on acid-catalyzed transacetalisation and can be to some extent placed under thermodynamic control, this reaction occurs in neutral medium and its stereoselectivity is the result of kinetic control. Treatment of these alkenes with NBS then produces bicyclic oxazolidinones **76**, which can further react with an alkoxide to give diastereoisomerically pure α,β-epoxyoxazolidines **77** (Scheme 15).



Scheme 15

This reaction is general and can be conveniently scaled up: intermediate urethanes **76** are usually crystalline solids that can be easily purified by simple trituration in an apolar solvent. The key step of this synthetic sequence is the regio- and stereoselective bromocarbamation of the adjacent alkene: in this reaction, the Boc group acts as an internal nucleophile and directly contributes to the functionalization of the alkene. The high stereoselectivity of this reaction was explained by the intervention of a *pseudo* chair transition state for the cyclization, as depicted in Figure 2. This methodology was later applied to other kinds of internal nucleophiles.[42]

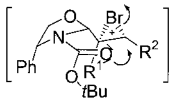
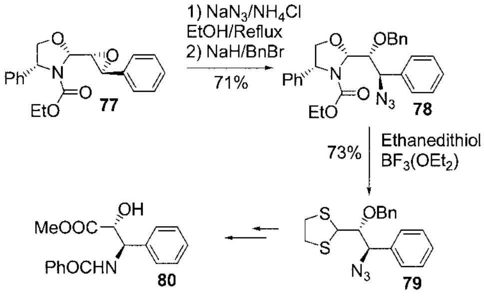


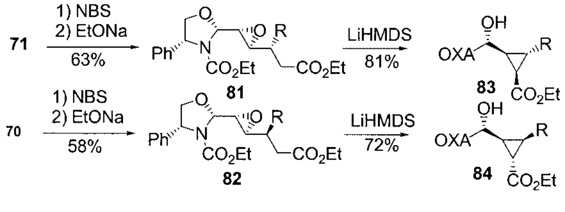
Figure 2. Bromocarbamation of *N*-Boc-2-alkenyloxazolidines through a *pseudo* chair transition state

Enantiopure masked α,β-epoxy aldehydes **77** were shown to react regioselectively with different nucleophiles. When the nucleophile was an azide ion, this was applied to the enantioselective synthesis of the *anti* isomer of the taxol side chain **80** (Scheme 16), or to a building block for an HIV-protease inhibitor.[43] When the nucleophile was a cuprate reagent, this allowed the synthesis of pheromones.[44]



Scheme 16

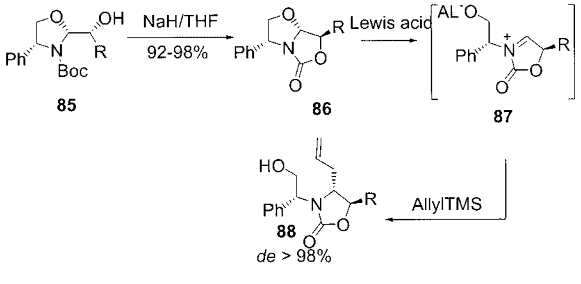
Alkenyloxazolidines resulting from a 1,3-transfer of chirality (vide supra) could also be epoxidized, and it was demonstrated that the stereocenter introduced by the rearrangement did not influence the stereochemical outcome of the bromocarbamation step. This was applied to the stereoselective synthesis of trisubstituted cyclopropanes **83** and **84** as depicted in Scheme 17.[40] Intramolecular alkylation of diastereoisomeric esters **81** and **82** produced the corresponding cyclopropanes. This example illustrates the link between the chemistry of *N*-Boc-2-acyl and 2-alkenyloxazolidines: combination of these two methodologies through 1,3-transfers of chirality allowed control over three contiguous stereocenters in the oxazolidine side chain.



Scheme 17

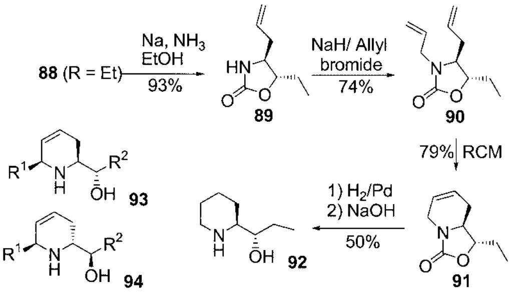
Chiral Oxazolidinones from 2-(Hydroxyalkyl)-oxazolidines

The 2-(hydroxyalkyl)oxazolidines **85** can also be transformed in high yields into the corresponding bicyclic oxazolidinones **86**. In this transformation, the Boc group now acts as an electrophile with regard to the alkoxide. Compound **86** is the precursor of an acyliminium ion **87** through the opening of the bicyclic amido-ether system under the action of a Lewis acid, and additions of allylsilanes or enoxysilanes to this intermediate were found to occur with high stereocontrol, to give the *trans*-oxazolidinones **88**[45] (Scheme 18).



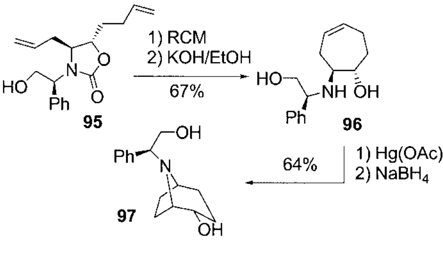
Scheme 18

This methodology, combined with RCM, was well suited for the stereoselective synthesis of piperidine heterocycles, as demonstrated in Scheme 19 for the synthesis of (−)-β-conhydrine **92**.[46] It was then extended to the synthesis of piperidines of general structure **93** and **94**.[47]



Scheme 19

Starting from diolefinic oxazolidinones **95**, a convenient route to tropane derivative **97** could also be devised,[48] the key step involved here was an intramolecular aminomercuration of the alkene, in the intermediate cyclic amino alcohol **96** (see Scheme 20).



Scheme 20

Conclusion

As outlined in this review article, the use of *N*-Boc-oxazolidines in asymmetric synthesis is very flexible and can provide numerous enantiomerically pure building blocks or stereodefined alkaloids with different frameworks, such as piperidines, quinolizidines, and tropanes. The diversity of targets that can be prepared is indisputably connected to the different roles that the Boc group can play in these transformations: of a conventional protecting group, of a bulky moiety that can induce stereodifferentiation, of a chelating function, or of an active electrophile or nucleophile. This ubiquitous protecting group, usually considered to be inert, in fact shows an underrated reactivity[49] that could be efficiently exploited in these transformations to allow the independent control over up to four contiguous stereocenters.

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