

# Oxazolidin-2-one Ring, a Popular Framework in Synthetic Organic Chemistry: Part 1. The Construction of the Oxazolidin-2-one Ring

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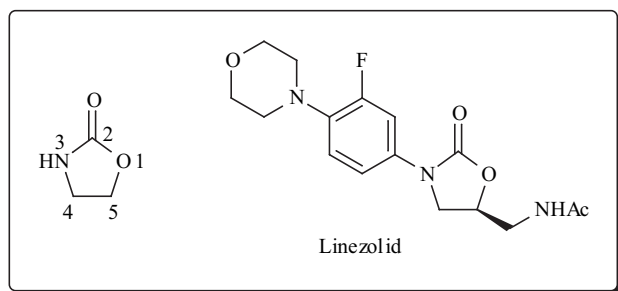
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**Abstract:** The 1,3-oxazolidin-2-one nucleus is a popular heterocycle framework in synthetic organic chemistry, as well as in medicinal chemistry. This paper deals with the huge number of synthetic approaches addressed to the construction of this five-member ring, with a particular care for the mechanistic and stereochemical outcome.

**Keywords:** 1,3-Oxazolidin-2-one, cyclocarbamation reactions, 1,2-aminoalcohol, epoxides and aziridines, amino-acids, Curtius- rearrangement.

## 1. INTRODUCTION

The 2-oxo-1,3-oxazolidine ring is a cyclic carbamate skeleton quite rare in natural product chemistry but very popular in the Synthetic Organic Chemistry since the Evans' report [1] in 1981 on the use of enantiomerically pure 4-substituted oxazolidin-2-ones as chiral auxiliaries in asymmetric synthesis. Oxazolidinones have also a large application as protective groups for the 1,2-aminoalcohol system. Finally, the introduction in the pharmaceutical market of Linezolid [2], an oxazolidin-2-one-based antibacterial drug, attracted the interest of the scientists and resulted in the production of several publications.



A review on the oxazolidin-2-ones chemistry has been published by Dyen and Swern [3a] in 1967, whilst Ager *et al.* [3b] have reviewed only the use of oxazolidin-2-ones as chiral auxiliaries. The aim of this article is to make the reader not only up-to-date about the recent papers in the field, but also aware of the endless possibilities concerning the preparation and the utilization of this small molecule.

Owing to the huge amount of literature reports we have divided the reviewed material in two parts. Part I will cover the synthetic approaches to the construction of the five-membered ring since Swern's review, while the utilization of

oxazolidin-2-ones as chiral auxiliaries, protecting group, building blocks for the preparation of foldamers etc. will be discussed in Part II.

Considerable efforts have been addressed by the synthetic organic chemists to the construction of the oxazolidinone frame. A lot of pathways have been reported for the building of this cottage-like molecule. In the approach starting from 1,2-aminoalcohol, the future carbons C-4 and C-5 are the basement, the oxygen and nitrogen atoms are supported by the walls, and the carbonyl group closes the building as a roof. In other approaches the five elements are already present and the ring closure is promoted by different catalysts. The opening of smaller (three membered) heterocyclic rings, such as those of epoxides and aziridines, represents another building choice and may occur by intervention of isocyanate for the first ones, and CO<sub>2</sub> or its surrogates in the second case.

Many other interesting pathways to the oxazolidin-2-one framework will be presented, type by type, with a particular care for the stereochemical outcome.

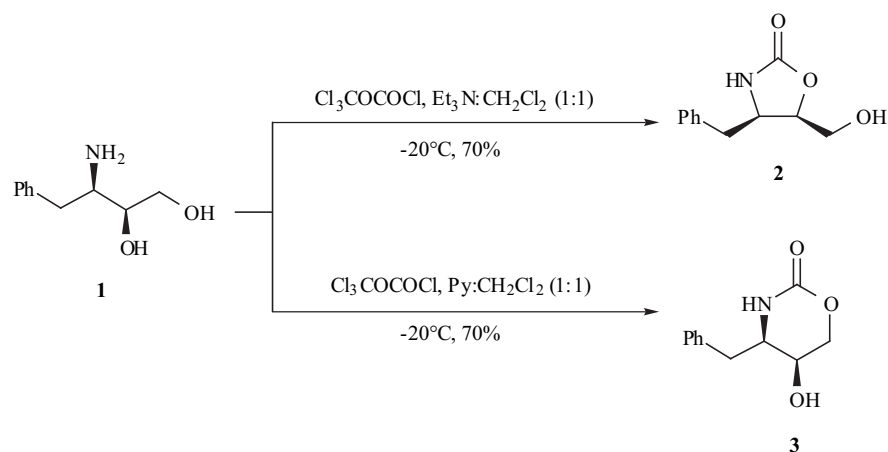
## 2. SUBSTRATES AND REACTIONS

By far, 1,2-aminoalcohols and  $\alpha$ -amino acids are the most used substrate for the preparation of oxazolidin-2-ones. Several other substrates have been, however, employed to build this simple five-membered ring and a huge number of reactions have been applied to it. The literature production will be reviewed according to the type of both substrate and reaction.

### 2.1. Carbonyl Ring Closure

The origin of the carbonyl roof-closing may come from an outside reactant or can be present inside the starting molecule, *e.g.* in *N*-Boc derivatives or in isocyanate intermediate.

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Scheme 1.

### 2.1.1. 1,2-Aminoalcohols

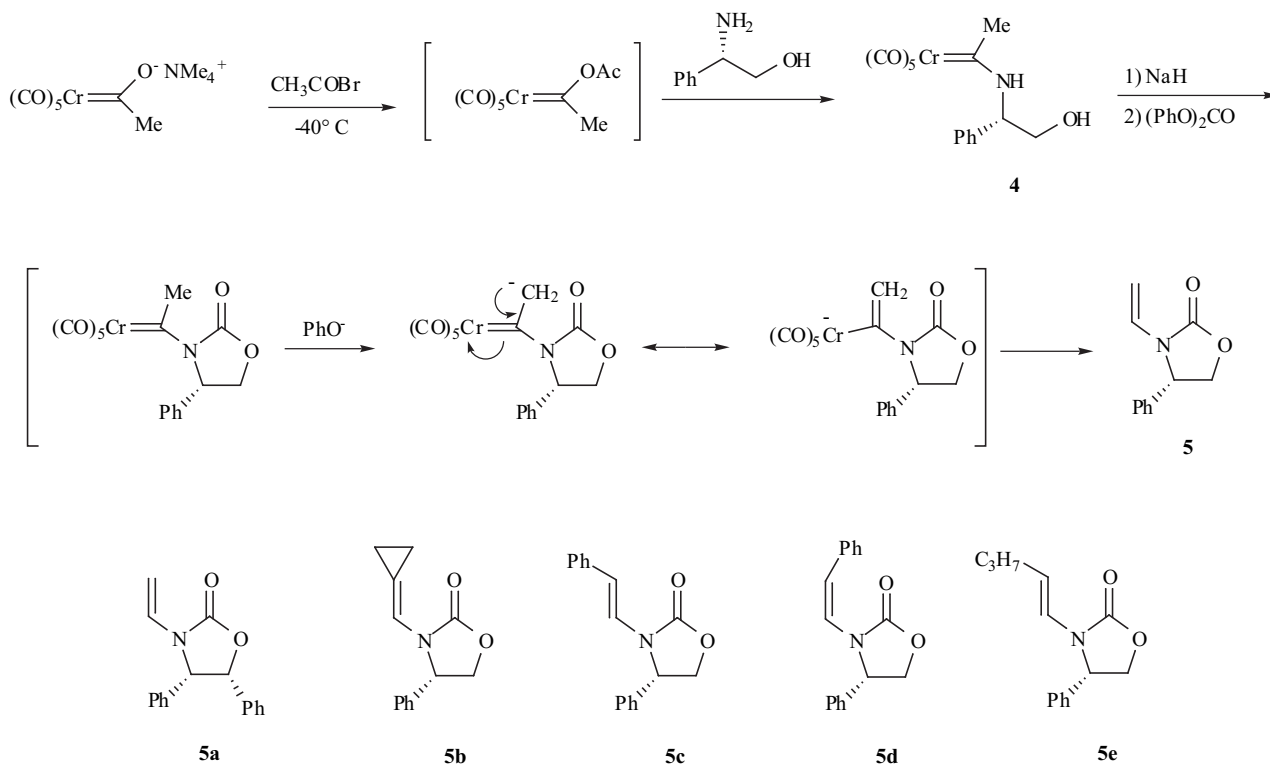
1,2-Aminoalcohols are readily available by reduction of the corresponding  $\alpha$ -amino acids [4] and can be converted into cyclic carbamates using phosgene [5] or safer synthetic equivalent reactants, such as diphosgene [6], triphosgene [7], and urea [8]. For instance, Depezay reported on the reaction with diphosgene of the aminodiol **1**, leading to the base-dependent formation of different products (Scheme 1) [9].

The 1,3-oxazolidin-2-one **2** and the isomeric oxazin-2-one **3** were actually obtained in the presence of  $\text{Et}_3\text{N}$  and pyridine (Py), respectively. The access to compound **3** from **2** by reaction with  $\text{Py}/\text{CH}_2\text{Cl}_2$ , suggested that the first one is formed under kinetic controlled conditions, whereas the second one is the thermodynamic product. Diethyl carbonate

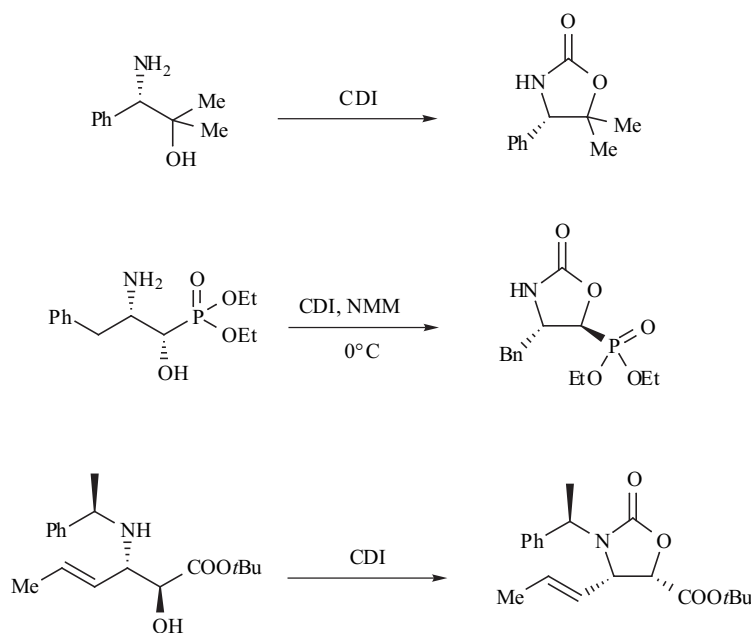
[10] and diphenylcarbonate [11] have been used to ameliorate the conversion of 1,2-aminoalcohols into oxazolidin-2-ones. In particular, Hegedus *et al.* described a simple procedure for the preparation of ene carbamates, such as **5** (65% overall yield), by treatment of the amino chromium-carbene complex **4** with NaH (2 eq), followed by the addition of diphenylcarbonate (Scheme 2) [11].

By this pathway, a variety of optically active aminoalcohol carbenes were converted to ene carbamates (**5a-e**) in fair yield. Tungsten-carbene complexes undergo analogous transformations in comparable yields.

1,3-Oxazolidin-2-ones were also synthesized in good yields from  $\beta$ -aminoalcohols by treatment with 1,1'-carbodiimidazole (CDI) [12].



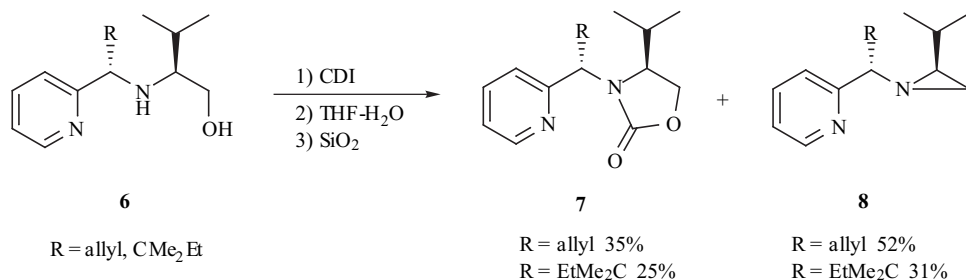
Scheme 2.



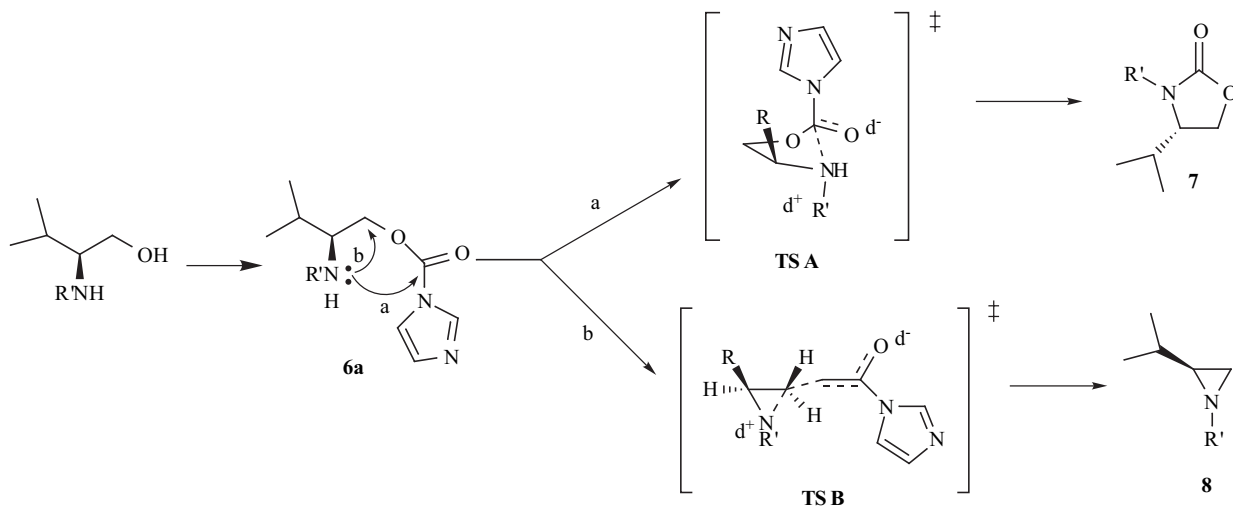
Scheme 3.

Savoia *et al.* investigated [13] the influence of the nitrogen-substituent in the reaction with CDI of *N*-substituted  $\beta$ -aminoalcohols (**6**): cyclic carbamates **7** are formed exclusively and in high yields from substrates bearing small *N*-substituents, such as Me or Et, whereas the competitive formation of the aziridines **8** is favoured by large *N*-substituent, as shown in Scheme 4a.

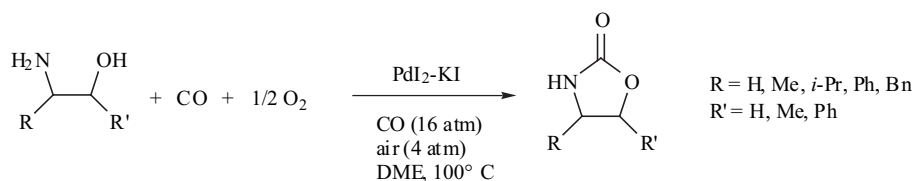
The proposed reaction pathway, leading to both the cyclic carbamates **7** and aziridines **8** (Scheme 4b), involves the following steps: i) first are formed the *O*-imidazole-carbonyl derivatives **6a**; ii) the intramolecular attack of the amine function at the carbonyl group of the carbamate moiety of **6a**, *via* the transition state A (TS A), leads to compound **7**; iii) aziridines are formed otherwise from



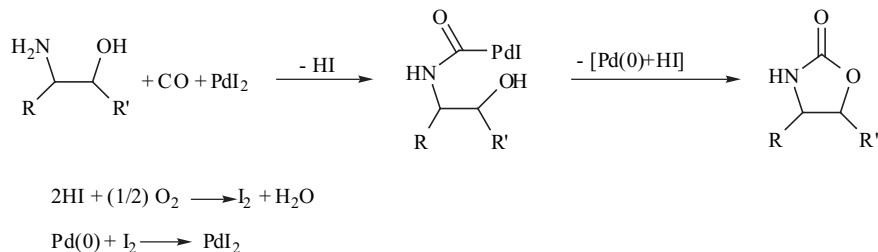
Scheme 4a.



Scheme 4b.



Scheme 5a.



Scheme 5b.

conformers of the same intermediate, *via* the transition state **B** (TS **B**), by intramolecular  $\text{S}_{\text{N}}2$  reaction of the nitrogen to the carbon atom bearing the *O*-imidazolecarbonyl leaving group. The observation that the formation of aziridines is favoured, in terms of rate reaction and regioselectivity, by an aqueous medium, which stabilizes the TS **B** by solvation, further supports the mechanism.

$\beta$ -Aminoalcohols can be converted to 1,3-oxazolidin-2-ones also by palladium-catalyzed oxidative carbonylation [14]. In particular, Gabriele and co-workers used  $\text{PdI}_2\text{-KI}$  as a catalytic system under 20 atm of a CO/air 4:1 mixture (*i.e.* CO, 16 atm, and  $\text{O}_2$ , *ca.* 1 atm), as resumed in Scheme 5a [14a,c].

The group, improving a previously reported procedure, in which MeOH and a KI- $\text{PdI}_2$  molar ratio of 100 had been used [14c], attained excellent yields (90-100%) and high catalytic efficiencies (1000-2000 moles of product per mole of palladium) using 1,2-dimethoxyethane (DME) and a molar ratio of 10 for KI/ $\text{PdI}_2$  catalytic system. The new milder conditions depend on the ability of the solvent (DME) to increase the solubility of the catalytic system and to lower the basicity of the substrate: as a result, a higher concentration of free HI, required for the re-oxidation of Pd(0) is achieved (Scheme 5b).

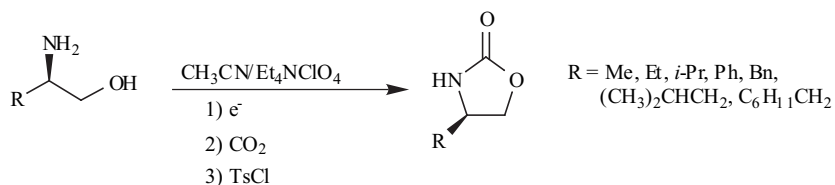
Oxidative carbonylation of 1,2-aminoalcohols using a  $\text{Pd}(\text{OAc})_2$  as a catalyst has been carried out also under atmospheric pressure of CO at room temperature, by electrochemical re-oxidation of palladium, but with lower efficiency (10 moles/mol of catalyst) [15].

A number of procedures for the electrochemical synthesis of enantiopure 1,3-oxazolidin-2-ones from both protected and free  $\alpha$ -aminoalcohols have been investigated by Inesi and coworkers [16]. The last reported protocol is based on the electrolysis of  $\beta$ -aminoalcohols in  $\text{CH}_3\text{CN}$ -TEAP solutions, followed by bubbling of  $\text{CO}_2$  and addition of TsCl (Scheme 6) [16a].

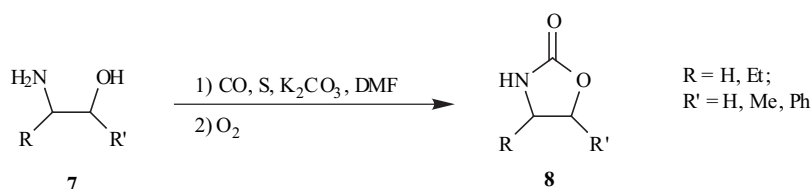
The mechanism of the reaction involves very likely the initial carboxylation and deprotonation of the amino group, prior to the TsCl-mediated ring closure.

Oxazolidin-2-ones **8** were also prepared in good to excellent yields (80-94 %) from  $\beta$ -aminoalcohols **7** by a two-step process involving thiocarboxylation with CO, promoted by elemental S, and oxidative cyclization with molecular oxygen (1 atm), as resumed in Scheme 7 [17].

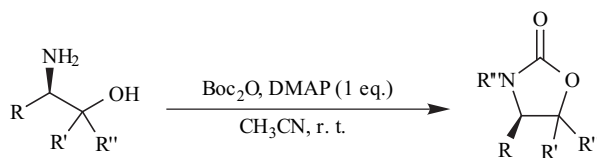
Knölker and Braxmeier [18] reported a convenient preparation of carbamates by dimethyl-aminopyridine (DMAP)-catalysed reaction of amines with  $\text{Boc}_2\text{O}$  (1.1 eq.), to generate *in situ* isocyanate intermediates, and following



Scheme 6.



Scheme 7.

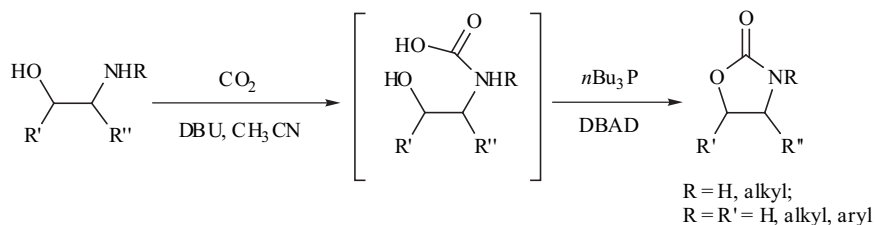


R = (*S*)-Me, (*S*)-*i*-Pr, (*S*)-*t*-Bu, (*R*)-Ph, (*R*)-Bn  
 R' = H, (*R*)-, (*S*)-Ph  
 R'' = H, Ph  
 R''' = H, Boc

Scheme 8.

addition of alcohols. The intramolecular version [19] of this reaction provides a safe and general method for the preparation of 4,5-trisubstituted 1,3-oxazolidin-2-ones in high yields (70-95%) from the suitable  $\beta$ -aminoalcohols; the use of 2.1 eq. of  $\text{Boc}_2\text{O}$  produced the corresponding *N*-Boc derivatives (Scheme 8).

Recently, researchers of the Merck Labs extended to several substrates [20] a mild method for the synthesis of enantiopure oxazolidin-2-ones from  $\beta$ -aminoalcohols, previously reported by Kodaka [21]. The procedure (Scheme 9a) involves initial carboxylation with carbon dioxide, followed by an intramolecular Mitsunobu reaction [22].

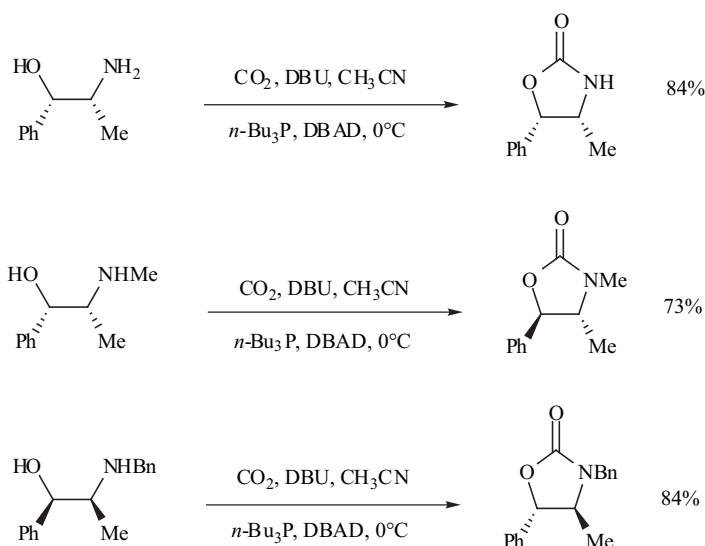


Scheme 9a.

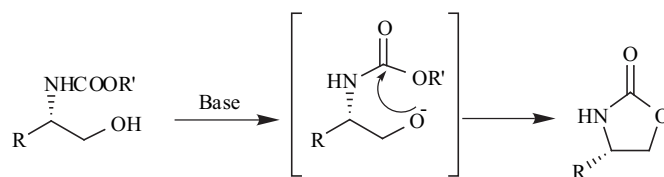
The stereochemical course of the reaction is dependent on the *N*-substitution: primary amines produce thus the corresponding 5-substituted oxazolidin-2-ones with retention of configuration at the oxygen bearing the stereogenic centre, whereas substrates containing secondary amine functions

net inversion of configuration at the stereogenic centre bearing the hydroxyl group.

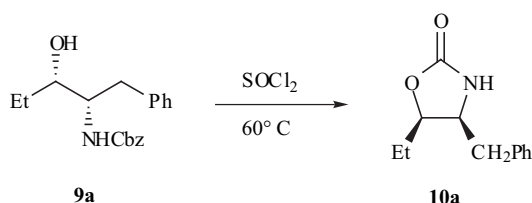
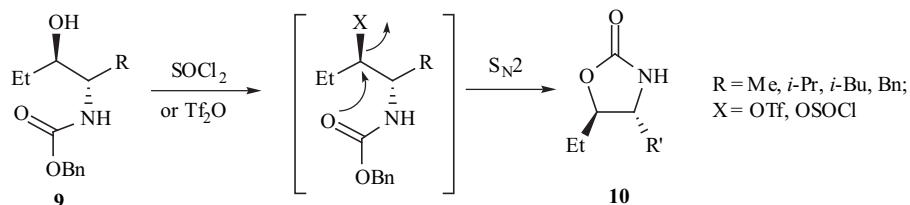
The direct conversion of *N*-alkoxycarbonyl protected  $\beta$ -aminoalcohols was described first by Kano [23], who used  $\text{TiF}_2\text{O}$  at  $-78^\circ\text{C}$  or  $\text{SOCl}_2$  at  $60^\circ\text{C}$  to promote the formation



Scheme 9b.



Scheme 10.



Scheme 11.

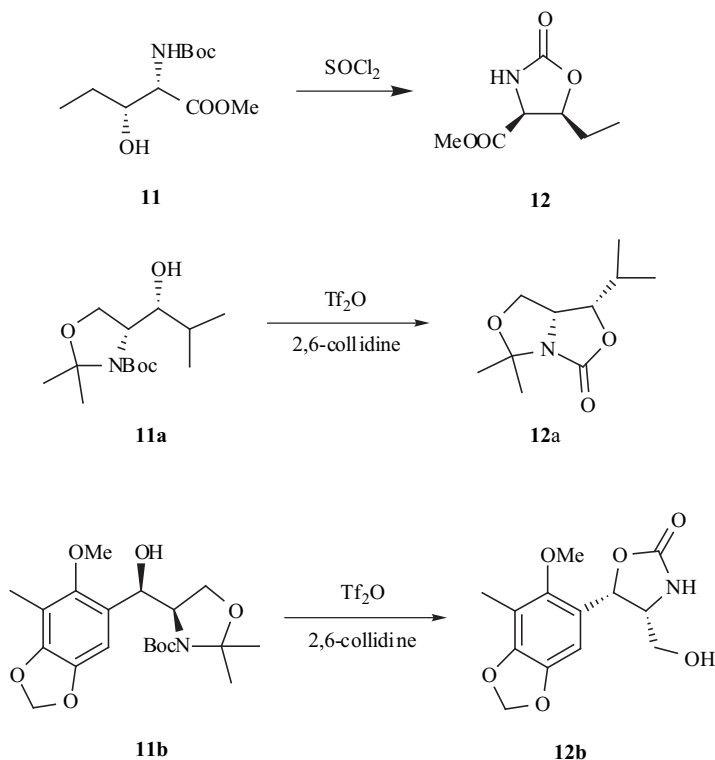
of *trans*-**10** and *cis*-**10a** from **9** (*threo*) and **9a** (*erythro*), respectively (Scheme 11).

The reaction takes place with inversion of configuration, but with moderate yields for both reagents.

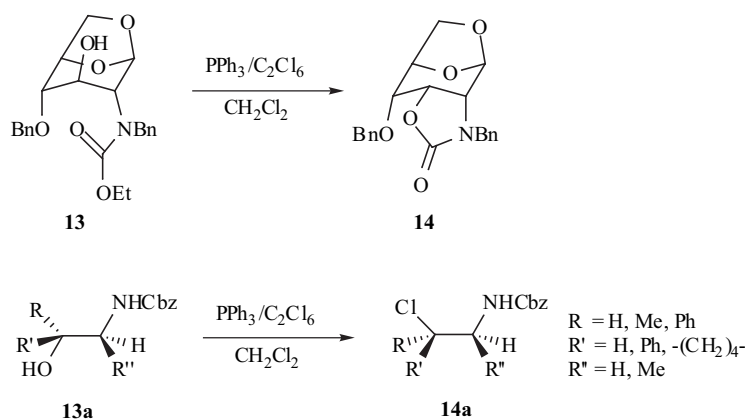
Usually, *N*-Boc  $\beta$ -aminoalcohols require milder conditions to react with both the same systems. For instance, the compound **11** afforded the oxazolidin-2-one **12**

by treatment with  $\text{SOCl}_2$  at room temp. [24], whereas the protected  $\beta$ -aminoalcohols **11a**/**11b** gave **12a** and **12b** with  $\text{Tf}_2\text{O}/2,6$ -lutidine at room temperature (Scheme 12) [25].

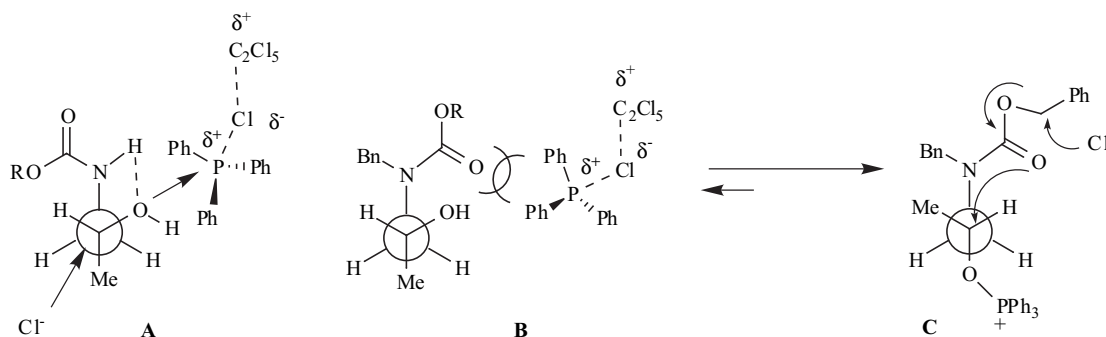
Several other reagent-systems, such as  $\text{Ph}_3\text{P}:\text{Cl}_2$  [24a],  $\text{MsCl}$  [26] and  $\text{Ph}_3\text{P}/\text{CCl}_4/\text{Et}_3\text{N}$  [27], have been used to promote the cyclisation of *N*-alkoxycarbonyl- $\beta$ -aminoalcohols.



Scheme 12.



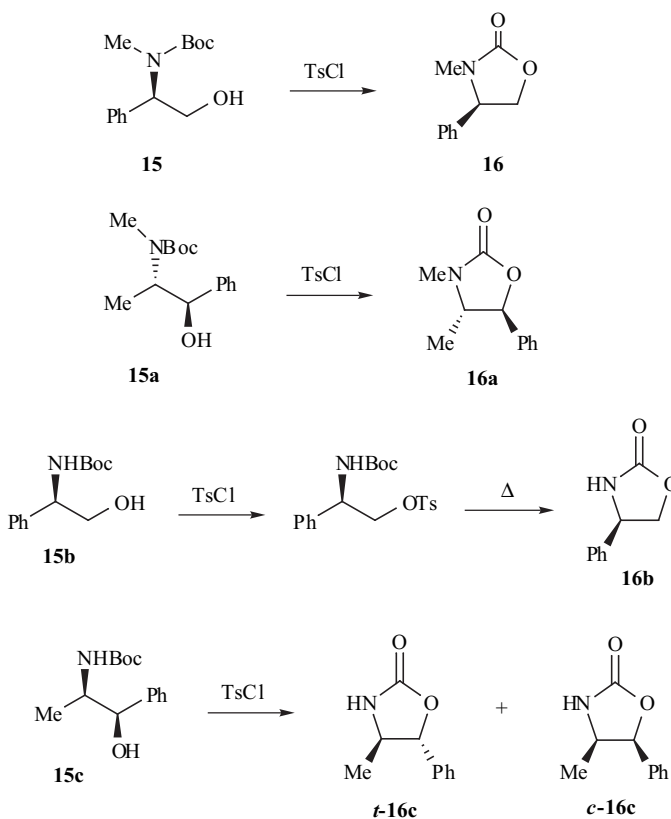
Scheme 13a.



Scheme 13b.

An interesting finding was disclosed by van Boom, who showed that *N*-benzyl protected *N*-alkoxy carbonyl  $\beta$ -aminoalcohols **13** can be converted into *N*-benzyloxazolidin-2-ones **14** by treatment with  $\text{PPh}_3$ /hexachloroethane ( $\text{C}_2\text{Cl}_6$ )

[28], whereas the mono-substituted *N*-Cbz  $\beta$ -aminoalcohols **13a** afford the corresponding chloride derivatives **14a** in moderate to good yields (46-91%) (Scheme **13a**) [29].



Scheme 14.

The different outcomes have been rationalised by the authors as shown in Scheme 13b for *N*-Cbz-(*R*)-1-aminopropan-2-ol: the C2-hydroxyl group may adopt in the ground state two different hydrogen bonded gauche orientations (**A** and **B**) with the carbamate group. In case of **A** conformation, according to a Mitsunobu-like reaction [22] mechanism, the attack of the hydroxyl group to the positively charged complex  $\text{Ph}_3\text{P}/\text{C}_2\text{Cl}_6$  is followed by the rearside attack of  $\text{Cl}^-$  (originated from  $\text{C}_2\text{Cl}_6$ ), to generate the corresponding chlorides.

By contrast in the **B** case, the larger steric interactions of  $\text{PPh}_3$  with the carbamate group may induce a rotation of  $120^\circ$  around the C1-C2 bond leading to the conformer **C**. As a consequence, the intramolecular attack of the carbonyl oxygen to the developing cationic centre at C2 is followed by the elimination of  $\text{Ph}_3\text{PO}$  and the formation of benzyl chloride, to finally afford oxazolidin-2-ones.

Moreover, the intramolecular attack is facilitated by the presence of the alkyl *N*-substituent which enhances the nucleophilicity of the carbonyl oxygen.

Agami *et al.* [30a,b] obtained oxazolidin-2-ones **16** and **16a** by treatment with  $\text{TsCl}/\text{Pyr}$  at  $0^\circ\text{C}$  of *N*-Boc-*N*-methyl-(*R*)-aminoalcohol **15** (Scheme 14) or substrates, such as **15a**, derivatives of the *N*-methylephedrine family. The reaction is an  $\text{S}_{\text{N}}2$  process involving a nucleophilic attack of the carbonyl oxygen of the carbamate group to the benzylic carbon centre. By contrast, starting from *N*-Boc-(*R*)-phenylglycinol **15b** under the same reaction conditions, the intermediate tosylate was isolated and closed to oxazolidin-

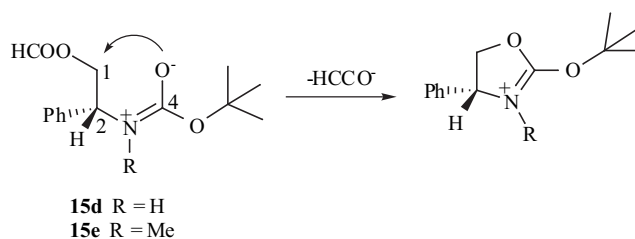
2-one **16c** only by heating. Moreover, in the cases of *N*-Boc derivative of nor-pseudoephedrine **15c**, the reaction gave a *trans/cis*-mixture (80:20) of the oxazolidin-2-ones **t-16c** and **c-16c**.

The phenomenon, *i.e.* the great influence of the *N*-methyl substituents on the reactivity, was related to the well documented “Thorpe-Ingold” effect [31], which has been invoked in several cases to explain how cyclization is favoured by a gem-dialkyl substitution of an involved carbon atom.

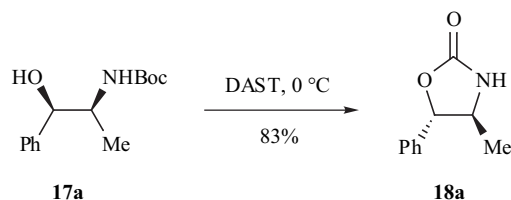
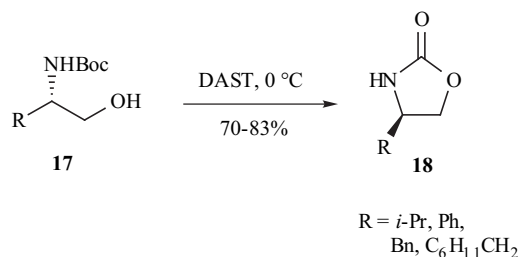
Quantistic semiempirical calculations on model compounds, such as **15d** and **15e**, revealed that the *E*-conformer is always predominant on the *Z*-conformer (Scheme 15); in particular, in accord with the Thorpe-Ingold” effect the *N*-methyl substituents induce a compression of the C2-N=C4 valence angle, going from  $122.6^\circ$  (**15d**) to  $120.6^\circ$  (**15e**).

A direct cyclization [32a] took place (Scheme 16a) also when *N*-Boc derivatives of  $\beta$ -aminoalcohols **17** and **17a** were treated at  $0^\circ\text{C}$  with a stoichiometric amount of *N,N*-diethylaminosulfur trifluoride (DAST), a well known fluorinating agent [32c].

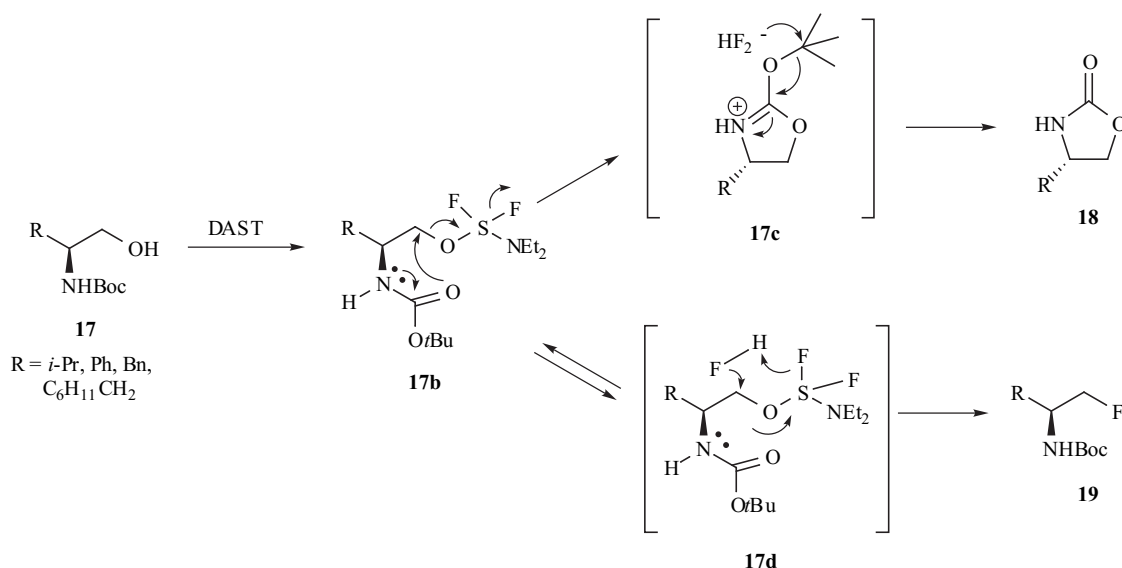
The formation of **18/18a** has been rationalised by the initial activation of the hydroxyl group as in **17b**, followed by an intramolecular  $\text{S}_{\text{N}}2$  nucleophilic attack, giving the cationic intermediate **17c**, where the loss of the *tert*-butyl group drives to the formation of oxazolidin-2-ones (Scheme 16b). This pathway is preferred over the classical fluorination mechanism, for the minor stability of the



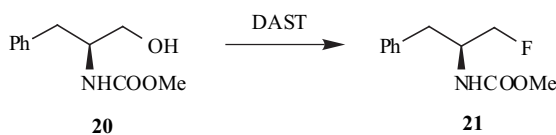
Scheme 15.



Scheme 16a.



Scheme 16b.



Scheme 17.

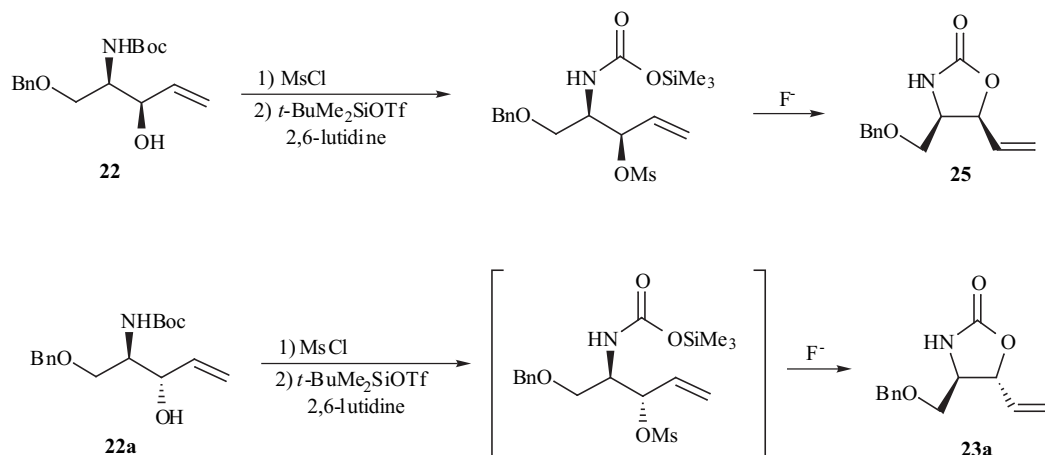
intermediate **17d**, which has to receive a fluorine by an intermolecular reaction to give **19**.

Conversely, when the *N*-carboxymethyl  $\beta$ -aminoalcohol **20** was treated under the same conditions, only the fluorinated product **21** was formed in 48% yield.

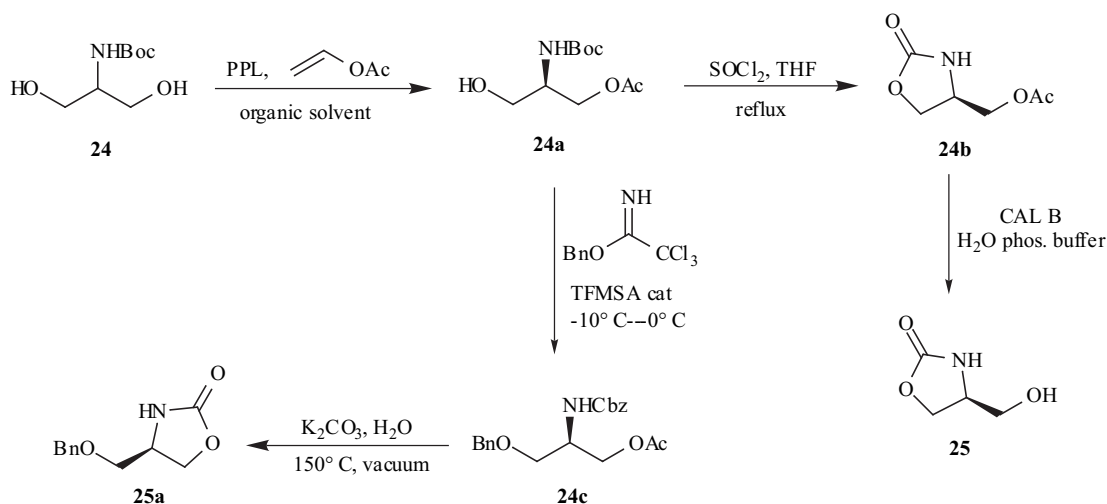
A multi steps fluoride-mediated formation of oxazolidin-2-ones from *threo*- and *erythro*-*N*-Boc- $\beta$ -aminoalcohols **22** and **22a** was documented by Ohfuné and coworkers [33]. The three-step approach includes *i*) initial *O*-mesylation, *ii*) interconversion of *N*-Boc into *N*-silylcarbamate group by *t*-BuMe<sub>2</sub>SiOTf/2,6-lutidine, and *iii*) final treatment with a fluoride ion. The last step generates an *N*-carboxylate ion, which is quite nucleophilic to provide the cyclic carbamate with inversion of the original stereochemistry of the leaving group. Good to excellent yields (51-93%) have been

obtained from 1,2-*syn* and 1,2-*anti*  $\beta$ -aminoalcohols (Scheme 18).

Enantiomerically enriched oxazolidin-2-ones were obtained starting from the enzymatic desymmetrisation of *N*-Boc-protected serinol **24** with PPL (porcine pancreatic lipase) and vinyl acetate in organic solvent: the monoacetyl derivative **24a** was obtained in 69% yield and >99% *ee* and cyclized to the (*S*)-oxazolidin-2-one **24b** (72% yield and >98% *ee*) by reaction with SOCl<sub>2</sub> in THF under reflux. Finally, treatment of **24b** with CAL B gave the (*S*)-4-hydroxymethyl oxazolidin-2-one **25** (77% yield and >98% *ee*). The (*R*)-4-benzyloxymethyl-2-oxazolidinone **25a** was obtained by simple manipulations of the intermediate **24a** (Scheme 19) [34].



Scheme 18.



Scheme 19.

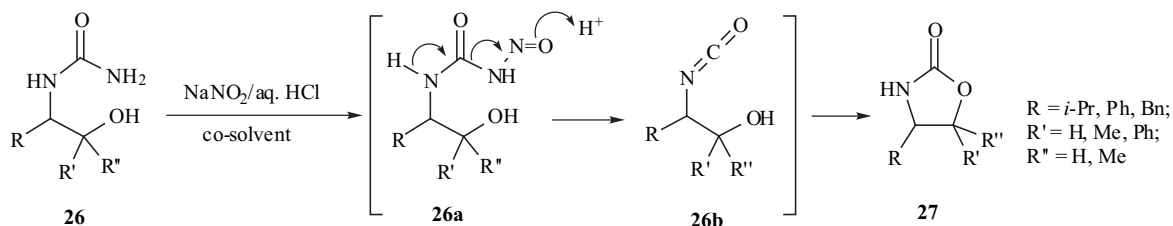
Finally, oxazolidin-2-ones could also be obtained in good yields (>75%) by nitrosation ( $\text{NaNO}_2/\text{HCl}$ ) of *N*-carbamoylaminoalcohols **26**. The reaction requires a biphasic system, *i.e.* a co-solvent [ $\text{AcOEt}$  or  $(i\text{-Pr})_2\text{O}$ ] to dissolve the starting material [35]. The *N*-nitroso intermediates **26a** cyclise to carbamates **27**, presumably *via* the  $\beta$ -hydroxy isocyanate **26b**, as in the Scheme 20.

The last comments of this section are dedicated to  $\beta$ -iodo amines, substrates very similar to  $\beta$ -hydroxy amines. The spontaneous formation of 1,3-oxazolidin-2-ones by pyrolysis of *N*-alkoxycarbo- $\beta$ -iodo amines (Scheme 21), was observed for the first time by Heathcock and Hassner [36] and later

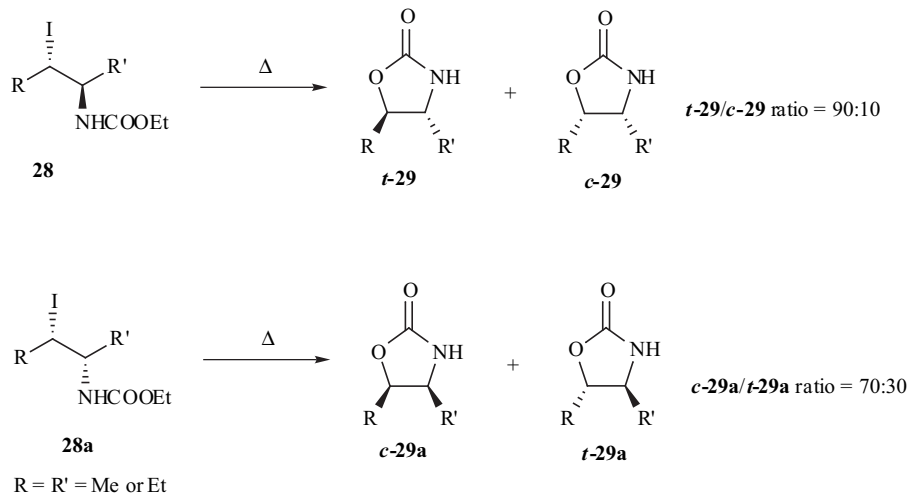
investigated in details by Foglia and Swern [37]. The last authors studied the cyclization of *erythro*-**28** and *threo*- $\beta$ -iodo carbamates **28a** respectively, which proceeded with a moderate stereoselectivity depending on the relative configuration of the starting  $\beta$ -iodocarbamates.

The lack of stereospecificity in the case of the *threo*-series has been explained by an iodide ion-mediated equilibrium between the *threo* and *erythro*-diastereomeric substrates.

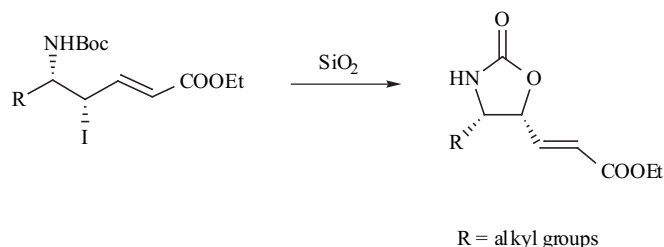
A high yields (>95%) silica-gel-mediated cyclisation of iodo-*N*-Boc- $\beta$ -aminoalcohol derivatives (Scheme 22) has been also reported [38].



Scheme 20.



Scheme 21.



Scheme 22.

2.1.2.  $\alpha$ -Aminoacids

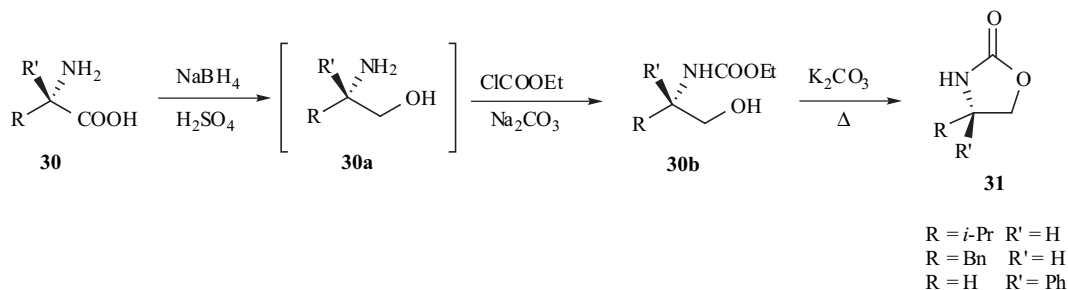
The approach to build the oxazolidin-2-one ring from  $\alpha$ -aminoacids involves: a) reduction of the carboxylic function, b) conversion of the free amino group into carbamate and c) base promoted cyclization. In the low-cost, high yield synthesis (Scheme 23) of Wu and Shen [39] the  $\alpha$ -amino acid **30** is reduced, *via* the procedure of Abiko and Masamune [40], to the corresponding  $\beta$ -aminoalcohol **30a** with  $\text{NaBH}_4/\text{H}_2\text{SO}_4$ , and immediately treated with  $\text{EtO}_2\text{CCl}$ . The crude alkoxy carbonylated carbamate **30b** is heated with catalytic  $\text{K}_2\text{CO}_3$  at 100-130 °C, to give enantiomerically pure oxazolidin-2-ones (**31**, 82-95%), which are suitable to be used as chiral auxiliaries without any further purification.

In another approach [41], the carboxylic group of  $\alpha$ -amino acids such as **30c** was first esterified and the amino group was protected to give the *N*-benzyloxy carbamate **30d**

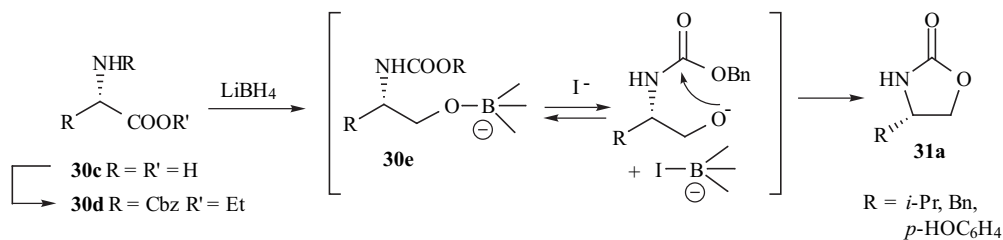
in quantitative yields (Scheme 24). Reduction of intermediates **30d** with lithium borohydride afforded the 1,3-oxazolidin-2-ones **31a** in high yields (88-100%).

The formation of the ring is promoted by the exchange between iodide ion and alkoxy group in the intermediate alkoxyborohydride **30e**.

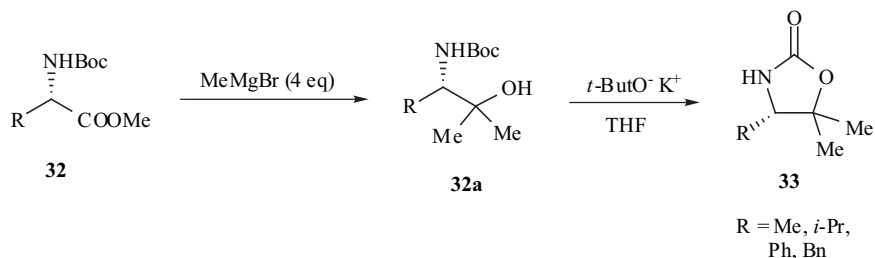
$\alpha$ -Aminoacids were also the starting material for a multigram synthesis of Davies' SuperQuat chiral auxiliaries. The reaction of **32**, *N*-Boc protected  $\alpha$ -amino acid methyl esters, with  $\text{MeMgBr}$  in excess gave the corresponding tertiary alcohols **32a**, which were in turn cyclized with potassium *t*-butoxide in THF (Scheme 25) to afford the homochiral (*ee* > 99%) SuperQuat auxiliaries **33**. The two-step procedure does not need any purification and the final oxazolidin-2-ones can be isolated in moderate (40%) to good (81%) yields from the crude reaction mixture by simple recrystallization [42].



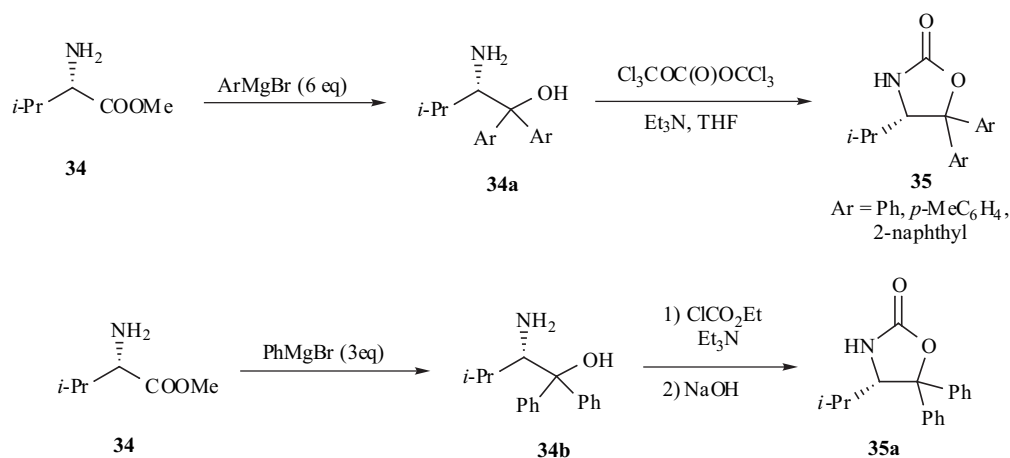
Scheme 23.



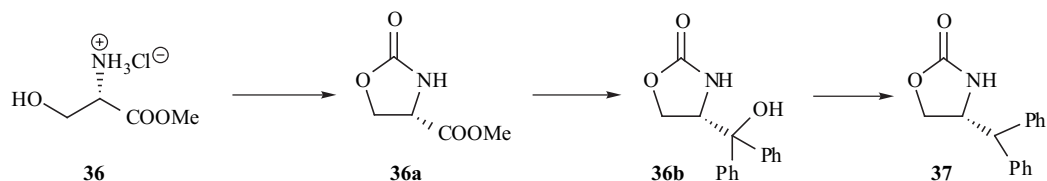
Scheme 24.



Scheme 25.



Scheme 26a.



Scheme 26b.

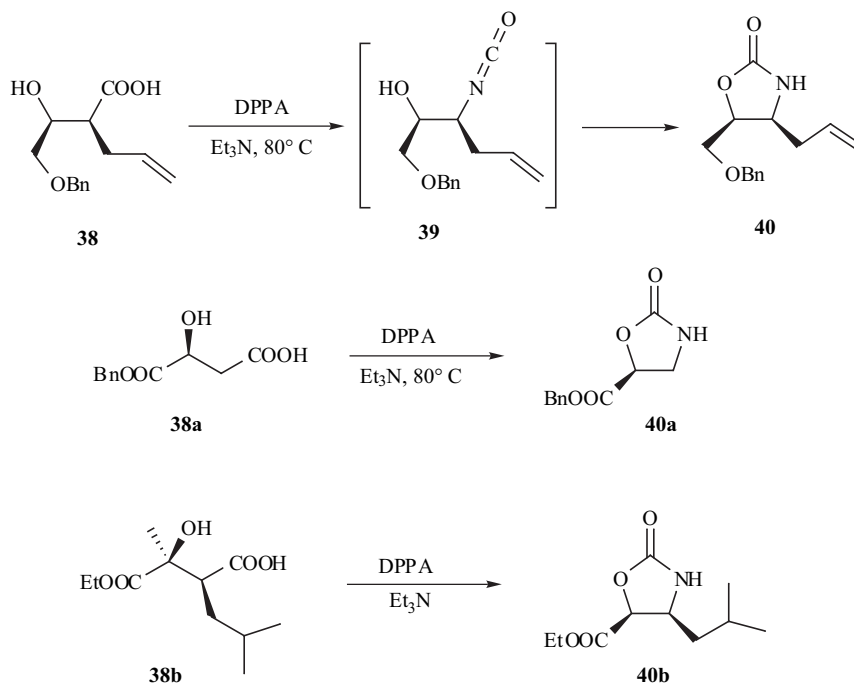
Gibson and Seebach have reported, independently, [43] similar results in the preparation of 5,5-diaryl oxazolidin-2-ones. Treatment of amino acid ester **34** with excess  $\text{ArMgBr}$  and ring closure by triphosgene under basic conditions of the 2-amino-1,1-diaryl alcohols **34a** gave the oxazolidin-2-one derivatives **35** [43a]. The same starting material was converted into **34b** with  $\text{PhMgBr}$ , to give **35a** by a two-step procedure [43b] (Scheme 26a).

Conversely, treatment of L-serine methyl ester hydrochloride **36** with triphosgene/ $\text{Et}_3\text{N}$  afforded directly 4-

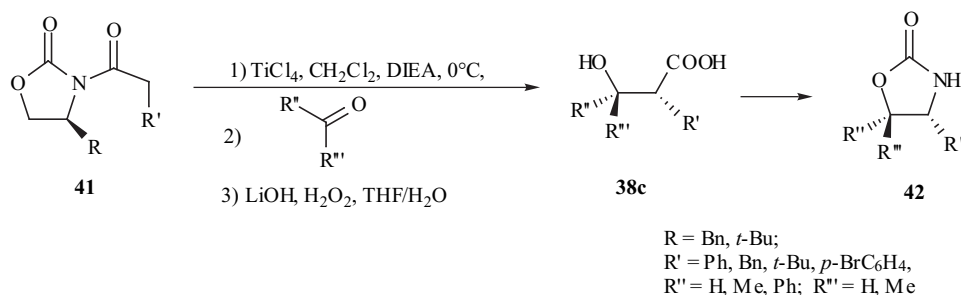
carboxymethyl oxazolidin-2-one **36a**, that is the starting material for the preparation of the Sibi's chiral auxiliary, (*R*)-4-diphenylmethyl-oxazolidin-2-one **37** [44]. The introduction of the two phenyl groups was accomplished by treatment of **36a** with a solution of Grignard reagent to give the tertiary alcohol **36b**, which was in turn dehydroxylated with  $\text{Na}/\text{NH}_3$  (Scheme 26b).

### 2.1.3. $\beta$ -Hydroxy Acids and Amides

The intramolecular Curtius degradation-cyclization reaction [45] of  $\beta$ -hydroxy acids is used to obtain



Scheme 27.



Scheme 28.

oxazolidin-2-ones mono- or disubstituted at C4 and C5. For instance, treatment of  $\beta$ -hydroxy acid **38** with diphenylphosphoryl azide (DPPA) and Et<sub>3</sub>N at 80 °C afforded the  $\beta$ -hydroxyisocyanate **39**, which directly cyclized into carbamate **40** in 92% yield (Scheme 27) [46].

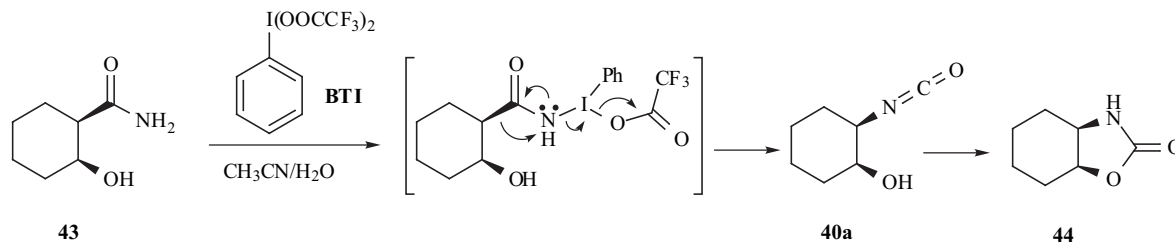
Similarly from **38a** and **38b** the oxazolidin-2-ones **40a** and **40b** were obtained, respectively. High yields (> 80%) are usually obtained for this reaction [47], which moreover takes place with net retention of configuration at the migrating stereogenic center, as expected [45].

Another elegant synthesis of 4-substituted and 4,5-disubstituted oxazolidin-2-ones, such as **42** has been

The conversion of *anti*- $\beta$ -hydroxyazides **45** into oxazolidin-2-ones **46**, via the  $\beta$ -hydroxy isocyanate **40b**, by treatment with Me<sub>3</sub>P/Boc<sub>2</sub>O/DMAP (50%-72% yields) or Me<sub>3</sub>P/CO<sub>2</sub> under basic conditions (Scheme 30, > 90% yield) must be finally mentioned [51].

## 2.2. Carbonyl Ring Enlargement

The cycloaddition of substituted three-membered rings, oxiranes and aziridines, with heterocumulenes is another important method for the construction of the oxazolidin-2-one nucleus.



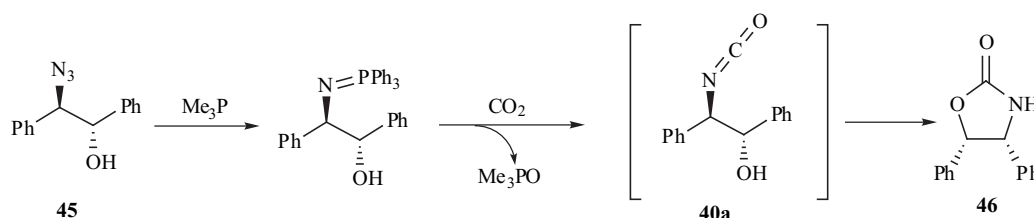
Scheme 29.

reported by Takacs *et al.* [48]. The steps of this route, outlined in Scheme 28, were a) the condensation of a chiral *N*-acyl oxazolidin-2-one (**41**) as titanium enolate with an aldehyde or ketone, b) hydrolysis to the corresponding  $\beta$ -hydroxy acid **38c** and c) final Curtius degradation-cyclization.

Hoffman-rearrangement [49] of  $\beta$ -hydroxy amides, such as **43**, generates an isocyanate intermediate **40a** as above, which evolves into the carbamate **44** (Scheme 29). A mild and efficient protocol, using *bis*(trifluoroacetoxy)iodobenzene (BTI) in acetonitrile at room temperature, allows performing the reaction in high yield (> 95%) [50a]. Other methods, based on NaClO/OH<sup>-</sup> [50b], AgOAc/NBS [50c] or iodosobenzene acetate [50d], did not ameliorate either yields or efficiency.

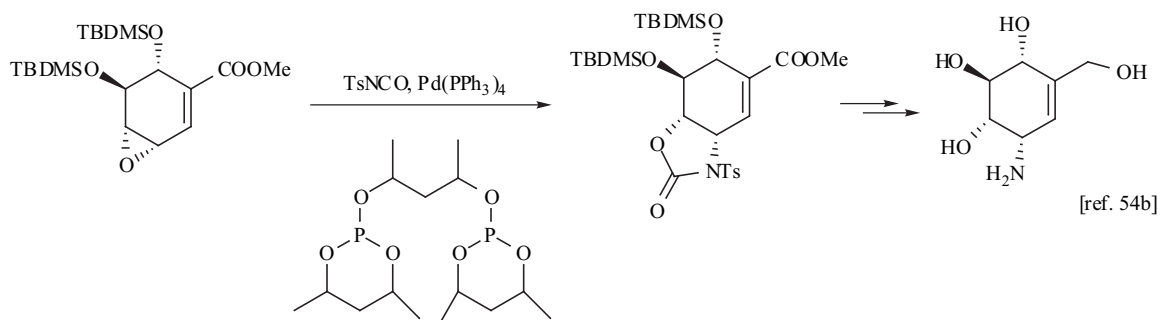
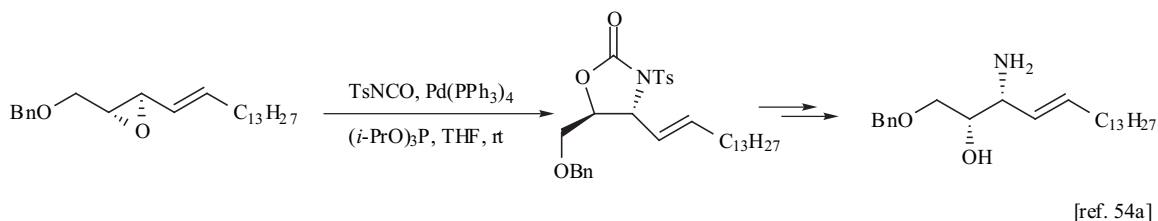
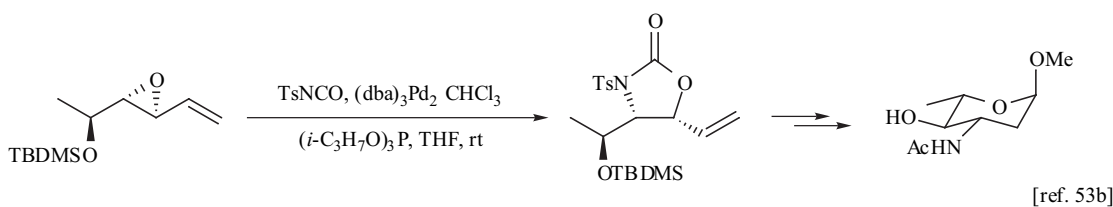
### 2.2.1 Epoxides

In the case of epoxides, the reaction usually requires severe conditions (*e.g.* temperatures  $\geq 150$  °C) and results in low chemical yields and, for unsymmetrical oxiranes, low regioselectivity. Moreover, polymerization and trimerization of isocyanate may occur as side reactions during the cycloaddition, even with lithium halides [52a,b], quaternary ammonium salts [52c], Lewis bases [52d] or Lewis acids [52e] as a catalyst. Better results, in terms of yields and regioselectivity, are obtained under mild (40° C) and neutral conditions, by the use of complexes such as organostibonium- [52f,g] and organotin-halide/Lewis base [52h] (Scheme 31).



Scheme 30.



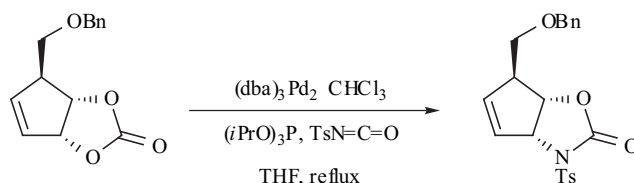


### Scheme 32c.

A cyclic carbonate was also used in the same reaction (Scheme 33) as a surrogate of the epoxide [55].

Recently, a direct synthesis of enantiopure 5-substituted oxazolidin-2-ones **50** from racemic epoxides has been reported by Bartoli *et al.* the method consists in the kinetic resolution of terminal epoxides **49** with urethane, catalyzed by the *in situ* generated Jacobsen's (*R,R*)-(salen)-Co<sup>III</sup> complex, followed by addition of NaH to achieve the oxazolidin-2-one **50** from the *N*-protected aminoalcohols **49a** (Scheme 34, upper part) [56].

However, the kinetic resolution of **49** afforded actually the  $\beta$ -aminoalcohol **49a** along with the "mismatched" epoxide (*R*)-**49b** (50% conversion). The enantioconvergent strategy, elaborated to convert both products into the corresponding enantiopure 5-substituted oxazolidin-2-ones, is described in Scheme 34 (lower part).

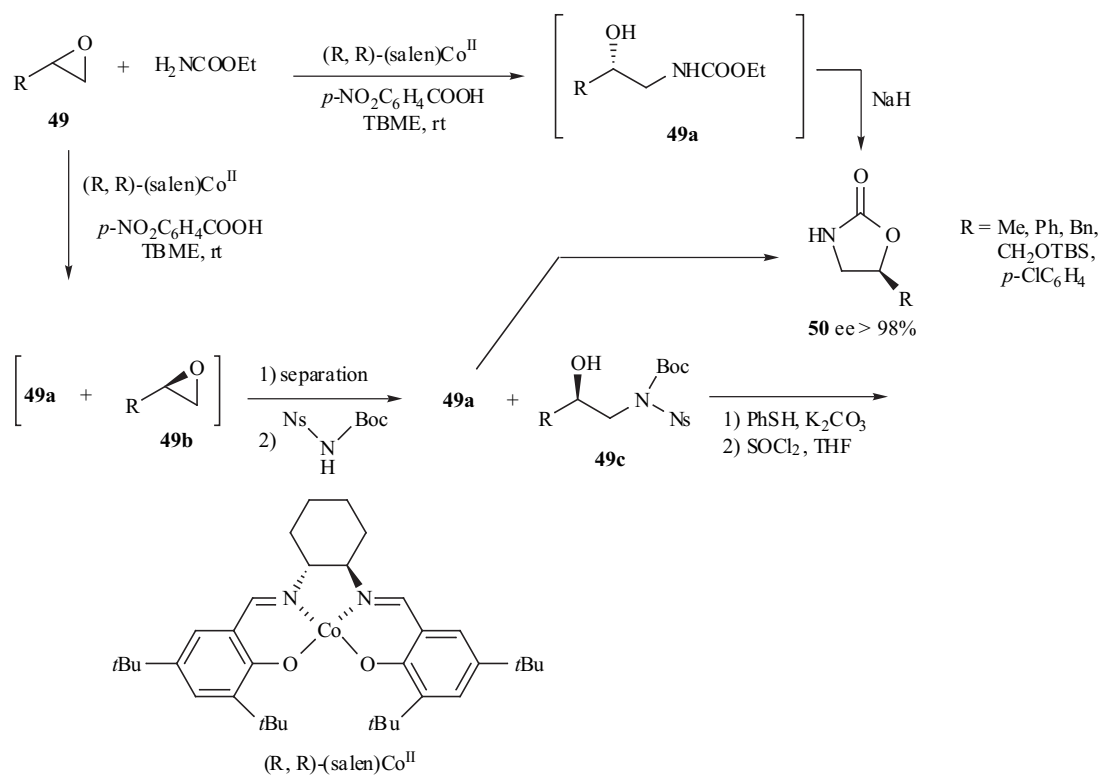


### Scheme 33.

### 2.2.2. Aziridines

By analogy with the preparation of cyclic carbonates from epoxides by chemical fixation of CO<sub>2</sub>, the reaction of aziridines **51** with CO<sub>2</sub> was expected to lead to the corresponding oxazolidin-2-ones.

The main problem for this conversion was the low reactivity of CO<sub>2</sub>, a shortcoming which was overcome by high pressure conditions, by electrochemical processes in the presence of nickel complex as a catalyst [57] or by flash vacuum pyrolysis in the presence of ethyl chlorocarbonate [58]. Recently, the reaction was performed under milder conditions by different research groups. For instance, Kawanami converted the 2-phenyl aziridine **51a** into 5-phenyl oxazolidinone **52** (75% yield) under supercritical conditions (*sc*CO<sub>2</sub>) in the presence of catalytic iodine [59]. By contrast, the reaction with propylene imine **51b** afforded



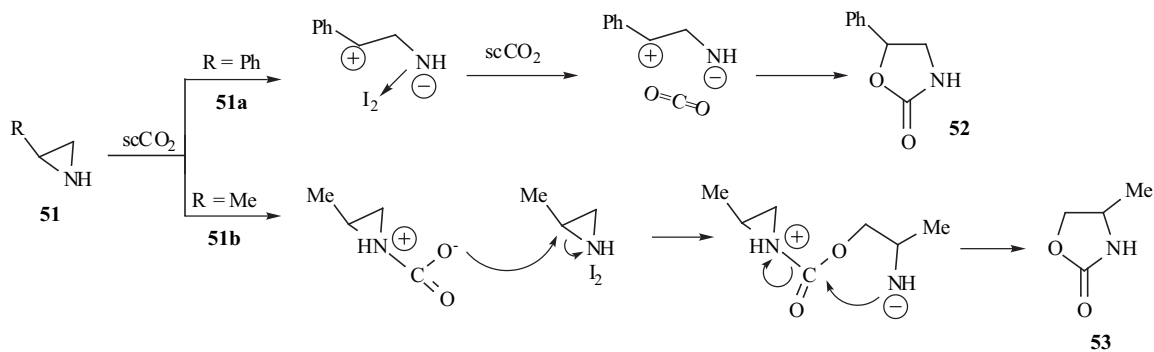
Scheme 34.

only 4-methyl oxazolidinone **53**. A plausible mechanism is shown in Scheme 35a.

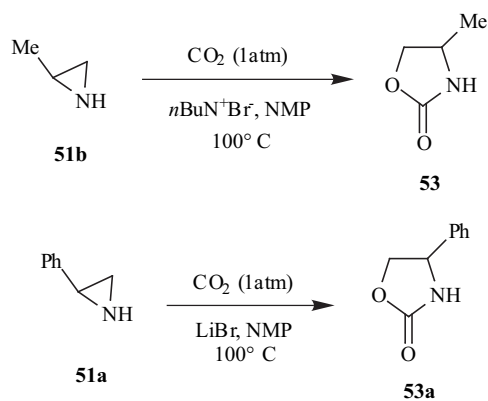
Cycloaddition of CO<sub>2</sub> to 2-methyl aziridine **51b** at room temperature and atmospheric pressure in the presence of

tetrabutyl ammonium bromide gave directly the 4-methyl oxazolidin-2-one **53** in 95% yield (Scheme 35b) [60].

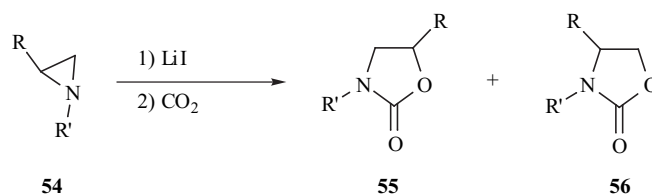
The conversion of 2-phenyl aziridine **51a** to 4-phenyl oxazolidinone **53a** (Scheme 35b) required more drastic



Scheme 35a.

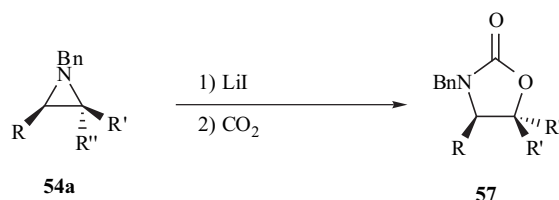


Scheme 35b.



R = Ph, Bn, pentyl;  
R' = Me, Bn

Scheme 36a.



R = R' = Me    R'' = H  
R = R'' = Me    R' = H  
R, R' = -(CH<sub>2</sub>)<sub>4</sub>-    R'' = H

Scheme 36b.

conditions, as 20% LiBr as a catalyst and a temperature of 100° C. Notably, the reaction product **53a** was the regioisomer of **52**, obtained under *sc*CO<sub>2</sub> conditions.

Moreover, the *N*-benzyl 5-phenyl isomer **55** was prepared by treatment of 2-phenyl-*N*-benzyl aziridine **54** with LiI under reflux, followed by CO<sub>2</sub> bubbling at room temperature [61] (Scheme 36). When R and R' in **54** were alkyl groups a mixture of 5- and 4-substituted oxazolidin-2-ones (**55** and **56**) was obtained (Scheme 36a), whereas the use of hexamethylphosphoramide (HMPA, 1 eq.) as co-solvent addressed the cyclization to 4-substituted oxazolidin-2-ones **56** as the sole products.

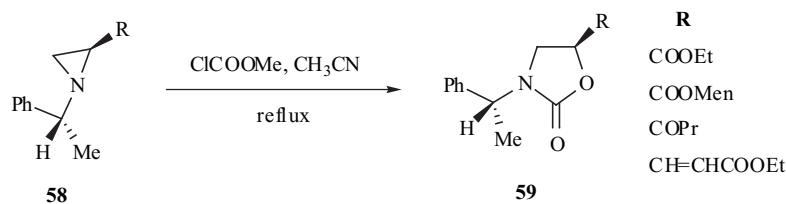
Finally, with *cis*- and *trans*-trisubstituted aziridines **54a** as a starting material, the reaction occurred with net retention of configuration at the stereogenic centers, as a consequence

of a double inversion, affording *cis*- and *trans*-oxazolidin-2-ones **57**, respectively (Scheme 36b).

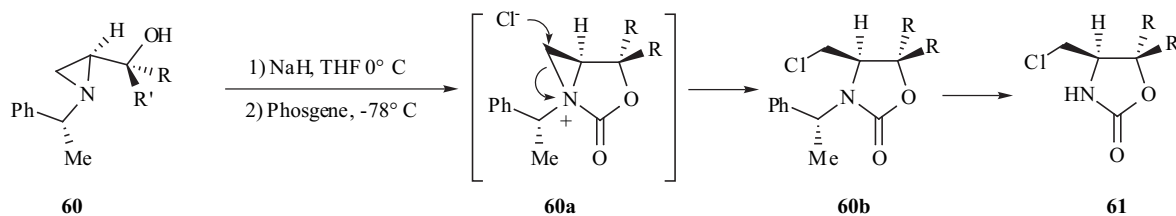
On the other hand, enantiomerically pure 5-functionalized oxazolidin-2-ones **59** were obtained in high yields (85-97%) by treatment of the chiral aziridines **58**, bearing an electron withdrawing group at C-2, with methylchloroformate in CH<sub>3</sub>CN at reflux (Scheme 37) [62].

(*R*)-*N*-α-Methylbenzylaziridine-2(*R*)-carbinols **60** have been converted into the corresponding enantiomerically pure 4-(*R*)-chloromethyloxazolidin-2-ones **61** (80-92% yields) by treatment with sodium hydride and intermolecular cyclization with phosgene, through the intermediate **60a** (Scheme 38) [63].

Removal of the α-methylbenzyl substituent from the chloro-oxazolidin-2-one **60b**, by anisole and CH<sub>3</sub>SO<sub>3</sub>H in

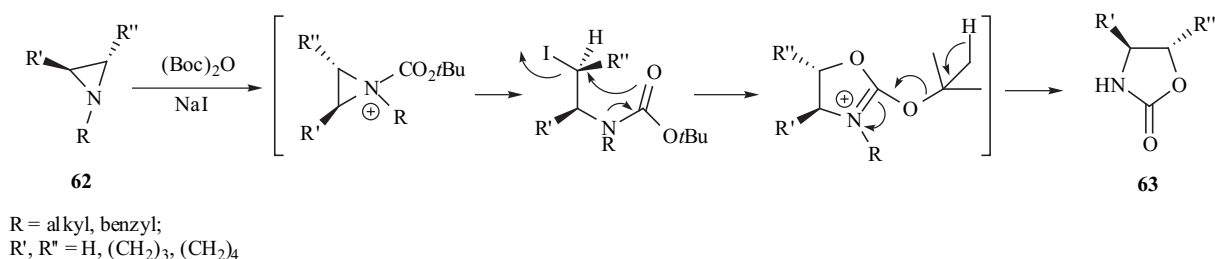


Scheme 37.

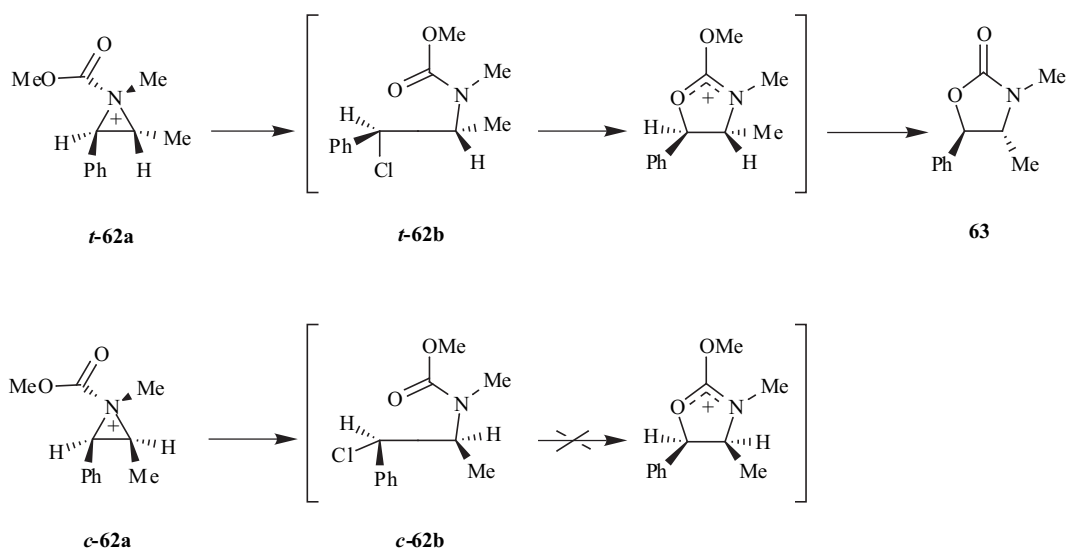


R = H, Me, Ph, vinyl  
R' = H, Me, Ph, *n*-Bu, *t*-Bu

Scheme 38.



Scheme 39a.



Scheme 39b.

hexane at reflux [63b], provided the free 4-chloromethyl-oxazolidin-2-ones **61** in almost quantitative yields.

The one-pot ring rearrangement of *N*-alkyl aziridines **62** into *N*-alkyl-4,5-disubstituted 1,3-oxazolidin-2-ones **63** (Scheme 39a) by reaction with Boc<sub>2</sub>O/NaI in acetone has been extensively studied by Sepúlveda-Arqués and co-workers [64].

The reaction occurs at room temperature in high yield (> 85%), according to the mechanism shown in Scheme 39a. The formation of the oxazolidin-2-one skeleton is explained by the initial *N*-acylation by (Boc)<sub>2</sub>O, followed by ring opening by NaI, to give a *t*-butyl-*N*-alkyl-β-iodocarbamate, which finally rearranges spontaneously to oxazolidin-2-one.

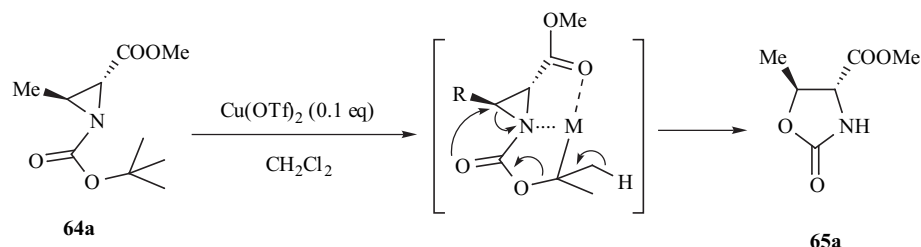
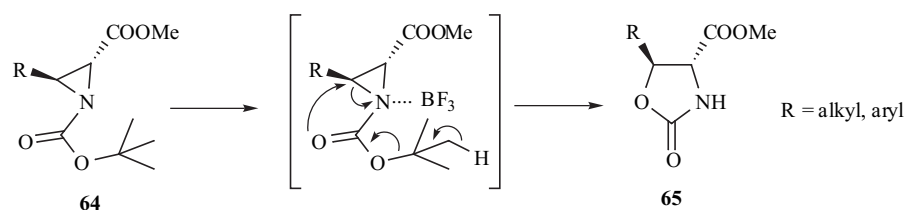
Further work by the same authors on this topic has pointed out that a C2-C3 *trans* 1,2,3-trisubstituted aziridines **t-62a** can be converted into *trans*-oxazolidin-2-ones **63** in good yield, whereas a C2-C3 *cis* configuration in 1,2,3-trisubstituted aziridines **c-62a** is a limiting factor for the conversion into cyclic carbamates. Indeed, *ab initio* calculations showed that while the initial iodine-assisted ring opening of both isomers was regioselective and took place with net inversion at the carbon atom involved in the nucleophilic attack, the subsequent ring-closure was responsible for the retention of the configuration in the final *trans*-product. On the other hand, the sterical hindrance between the substituents at the C3 and C2 positions in the

intermediate **c-62b** prevented the final *cis* ring-closure (Scheme 39b).

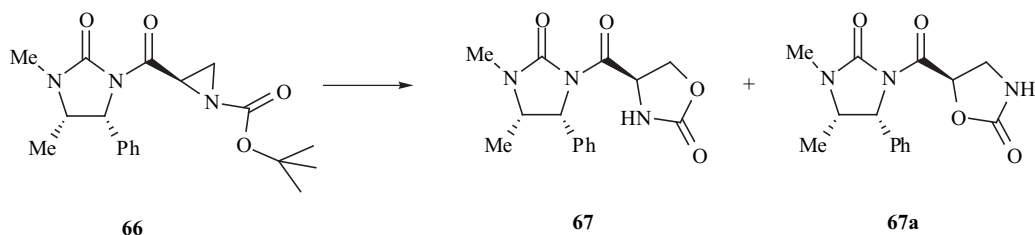
The Lewis acid-catalysed ring expansion of chiral aziridines into oxazolidin-2-ones has been also explored by Tomasini *et al.* [65]: 4-carboxymethyl-5-aryloxazolidin-2-ones **65** were thus formed in 98% yield by BF<sub>3</sub>-catalysed rearrangement of *N*-Boc-aziridines **64**. The reaction occurs with total regioselectivity, affording exclusively 4-carboxymethyl oxazolidin-2-ones, and with whole stereo selectivity, giving *cis* and *trans*-oxazolidin-2-ones from *cis* and *trans* disubstituted *N*-Boc aziridines, respectively (Scheme 40).

The reaction takes place with excellent yield (98%) when R is an aryl, whereas lower yields were obtained when R was an alkyl groups. However, for both 4-aryl/alkyl substituted aziridines, good results can be achieved with a catalytic amount of chelating Lewis acids such as Cu(OTf)<sub>2</sub>, Zn(OTf)<sub>2</sub>, Sn(OTf)<sub>2</sub>. The best yields (98%) and stereoselectivity were obtained with Cu(OTf)<sub>2</sub> (0.1 eq.) in CH<sub>2</sub>Cl<sub>2</sub>. Microwave-assisted ring expansion [66] of *N*-Boc-aziridine-2-imides **66** in the presence of Cu(OTf)<sub>2</sub> (1 eq.) afforded a mixture of isomeric oxazolidin-2-ones **67** and **67a** (Scheme 41), but the former was exclusively obtained (99% yield) when Zn(OTf)<sub>2</sub> or BF<sub>3</sub>/Et<sub>2</sub>O (0.028M) were used.

On the other hand, clean ring expansion of the *N*-Bocaziridine-2-carboxylate into the corresponding 4-



Scheme 40.



Scheme 41.

substituted oxazolidin-2-one occurred under the same conditions in presence of 1 eq. of  $\text{Cu}(\text{OTf})_2$ , whereas a complex mixture of products had been obtained with other Lewis acids. In summary these results reveal a role of the aziridine substituent in the selection of the Lewis acid to be used in the expansion reaction.

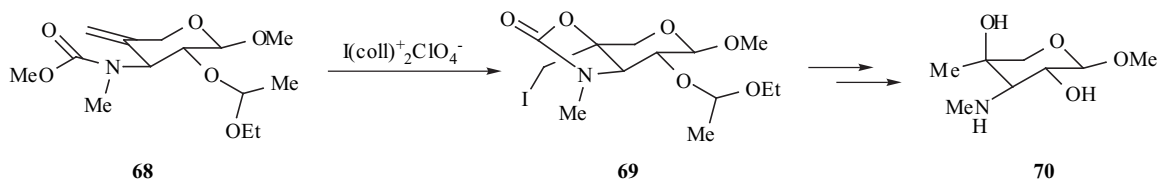
## 2.3 Cyclocarbamation

### 2.3.1. Iodocyclization

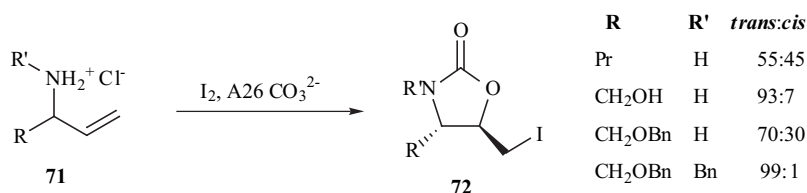
An interesting approach to obtain oxazolidin-2-ones is the halo-cyclofunctionalization of allyl-carbamates, a reaction resulting very often in high regio- and stereocontrol. The

first report in this field came from Fraiser-Reid [67], concerning a step of the synthesis of methyl  $\alpha$ -L-gargosaminide **70** (Scheme 42), a key component of a number of amino cyclitol antibiotics, such as the gentamycins, sisomycin, etc. Treatment of carbamate **68** with a stoichiometric amount of iodonium bis-sym collidine perchlorate [ $\text{I}(\text{coll})_2^+\text{ClO}_4^-$ ] gave the *cis* oxazolidin-2-one **69** in 80% yield (Scheme 42b).

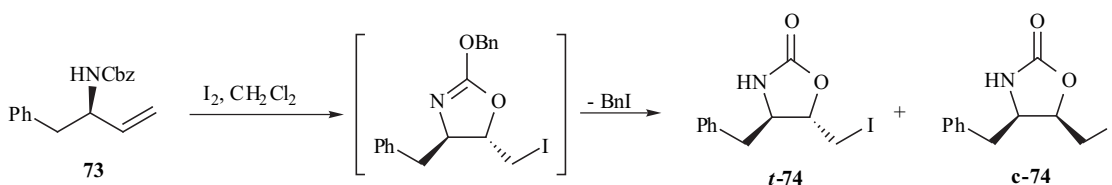
Oxazolidinones **72** have been also obtained from alicyclic allyl amines hydrochlorides **71**, upon treatment with a polymeric reagent, prepared by adsorbing  $\text{I}_2$  on resin Amberlist A26 ( $\text{CO}_3^{2-}$  form) (Scheme 43) [68].



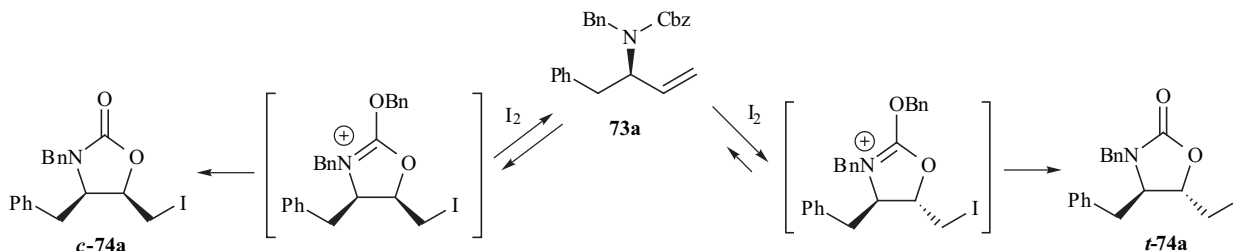
Scheme 42.



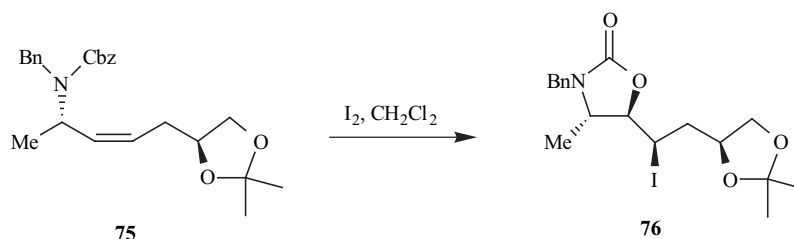
Scheme 43.



Scheme 44a.



Scheme 44b.



Scheme 44c.

The *cis/trans* ratio is strongly dependent on the nature of the substituents R and R', better results being obtained when R was a hydroxymethyl group; moreover, the presence of an *N*-benzyl substituent in the urethane moiety increases the *trans/cis* ratio from 70:30 to 99:1 (Scheme 43).

The key role played by the *N*-substituent in the stereochemical outcome of the cyclization reaction was evidenced by Ohno *et al.* in the synthesis of (-)-bestatin [69]. The reaction of chiral allylic amine **73** with  $I_2$  in  $CH_2Cl_2$  at room temp., afforded a mixture of oxazolidin-2-ones *t*-**74** and *c*-**74** with a low *trans/cis* (1.5:1) selectivity (Scheme 44a), which was associated to the irreversible formation of the cyclic imino acetal intermediate.

However, by reaction of *N*-benzylated **73a** under the same conditions, the *trans/cis* ratio of the iodocyclization products increased to 6.7:1, due to the equilibration process through the iminium intermediates, which favoured the thermodynamically more stable *trans*-product (Scheme 44b).

Exclusive formation of the *trans*-oxazolidin-2-one **76** was obtained (Scheme 44c) when the chiral *Z*-allyl amine **75**

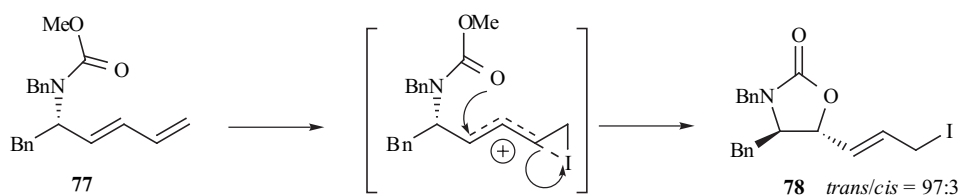
was processed under the same conditions [70], whereas lower stereoselectivity was observed for the *E*-isomer.

Similarly, iodocyclocarbamation of **77** afforded the *trans*-oxazolidin-2-one **78**, bearing a 3-iodo-(1'*E*)-propenyl group at C5 position (Scheme 45) [71].

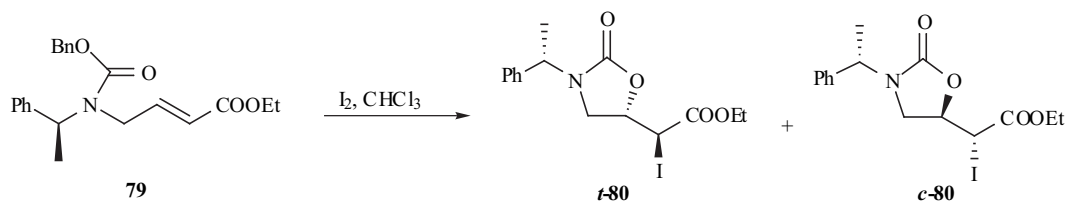
Our group investigated the iodocyclocarbamation of electron-poor allylic carbamates, as a powerful method to obtain highly functionalised and entirely protected chiral intermediates.

In a previous report by Cardillo *et al.* [72] the cyclisation of **79** with iodine in  $CHCl_3$  had been shown to provide a 1:1 mixture of two oxazolidin-2-ones *t*-**80** and *c*-**80** (Scheme 46).

We achieved a significant improvement using as substrates chiral allylic carbamates, as *E*- and *Z*-**81**, derived from the corresponding  $\alpha$ -aminoacids. Iodocyclocarbamation ( $I_2$  3 eq. in  $CH_3CN$ ) of the *E*-isomers gave mainly a mixture of *trans*- and *cis*- oxazolidin-2-ones *t*-**82** and *c*-**82**, but *Z*-isomers afforded almost exclusively *trans*-derivatives *t*-**83a** and *t*-**83b** (Scheme 47a) [73].



Scheme 45.



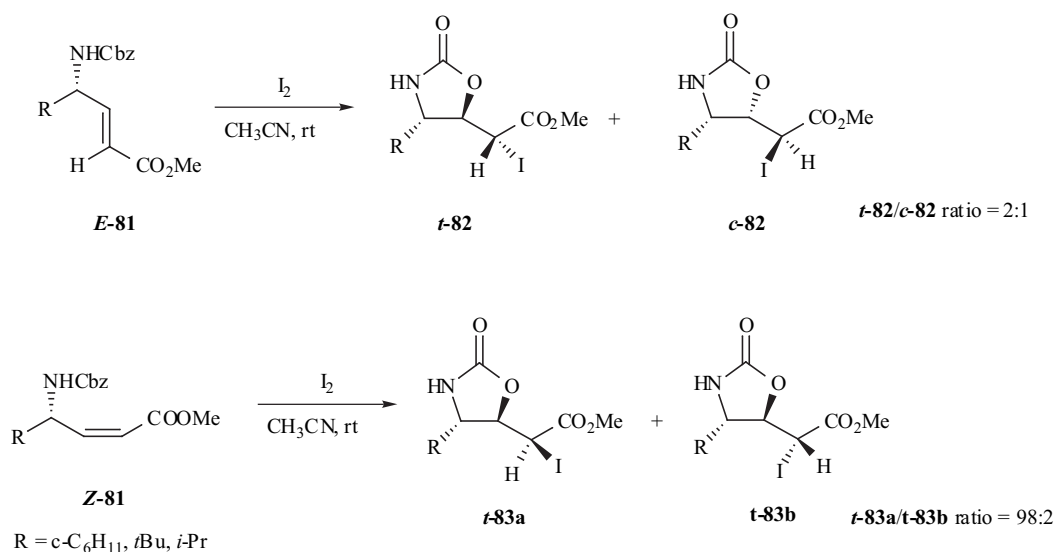
Scheme 46.

Notably, the use of different carbamates, *e.g.* *N*-Boc derivatives, produced only products with unprotected amine function, while the use of different solvents strongly reduced the reaction time.

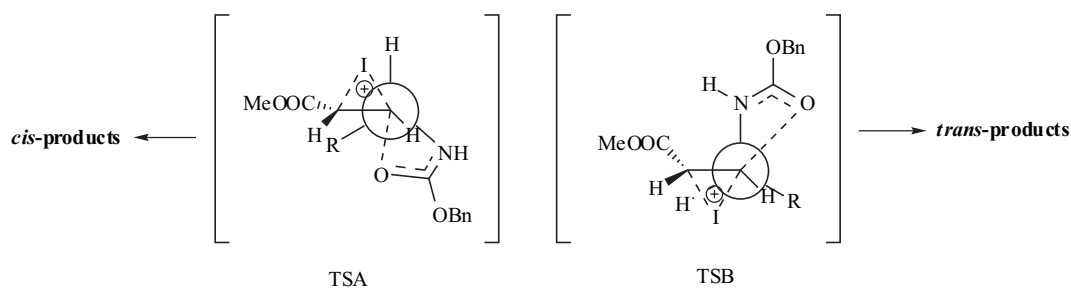
To explain qualitatively the stereochemical outcome of the reaction, we invoked the 1,3-allylic strain,  $A^{1,3}$ , as the driving force [74]. The *trans*-derivative is formed by the reaction of the *Z*-olefins through a transition state in which the allylic 1,3-strain is minimized (Scheme 47b). The

transition state A (TSA) suffers from the interaction between the residue R and the ester groups, whereas TSB is essentially strain free.

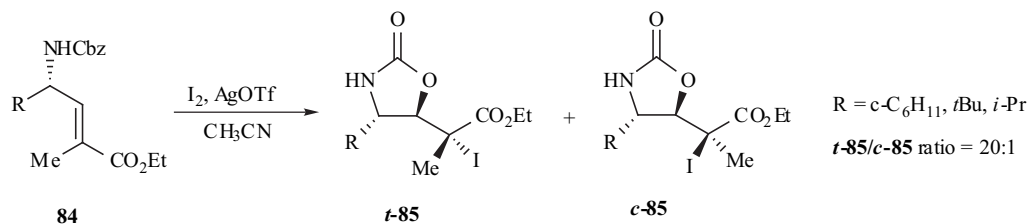
As reported by Guindon *et al.* [75], high levels of diastereoselection are obtained in the iodocyclocarbamation with chiral *E*-allylic carbamates bearing a 2-substituent, such as in **84**; moreover, the reaction time decreases to 3 h by addition of a stoichiometric amount of silver trifluoromethanesulfonate (Scheme 48).



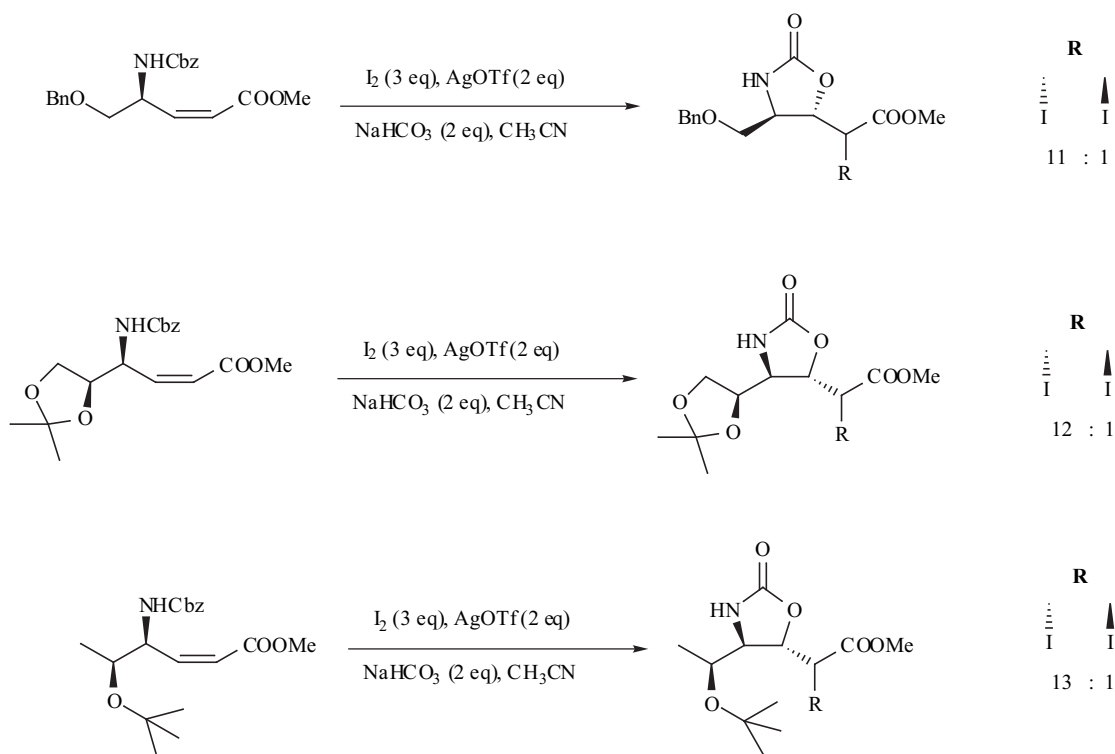
Scheme 47a.



Scheme 47b.



Scheme 48.

**Scheme 49.**

A proper choice of the reaction conditions allows carrying out the cyclization even in the presence of other potential nucleophiles or labile protecting groups, as in the examples of Scheme 49 [76].

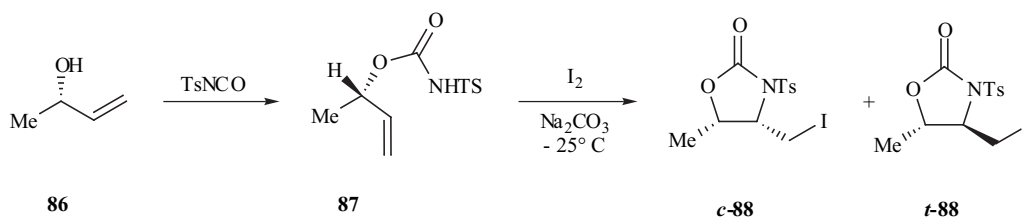
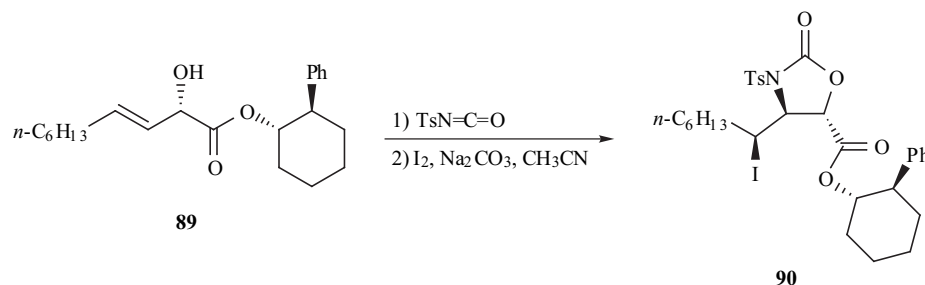
The iodine mediated cyclization of allyl carbamates has been also studied by Hirama *et al.* [77].

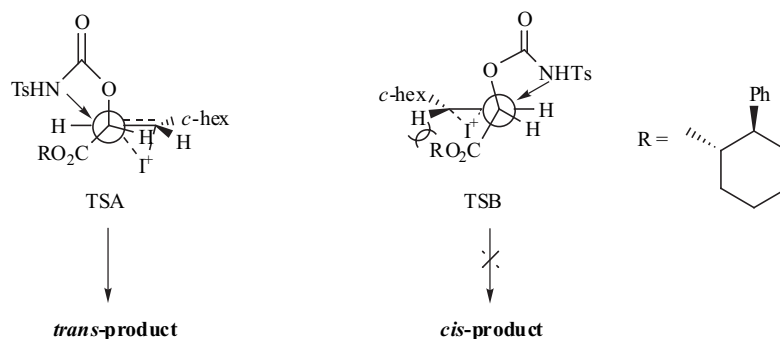
Thus reaction of the *N*-sulphonylated allylic carbamate **87**, with I<sub>2</sub> and potassium carbonate in ether under kinetically controlled conditions affords a diastereomeric

mixture of oxazolidin-2-ones *c*-**88** and *t*-**88** (3.4:1) in high yields (78%) (Scheme 50).

Sugimura *et al.* [78] have reported the iodocyclization with Na<sub>2</sub>CO<sub>3</sub> in CH<sub>3</sub>CN of **89**, which gave almost exclusively *trans*-4,5-disubstituted cyclic carbamate **90** in 73% yield (Scheme 51a).

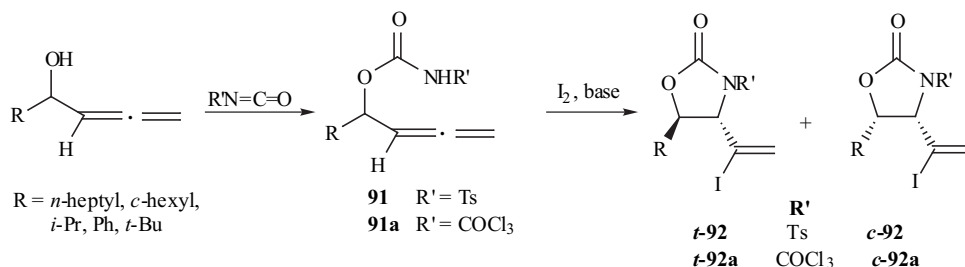
The preferential formation of the *trans*-product is in agreement with a transition state (TSA in Scheme 51b), where the steric interaction between the ester moiety and the alkenyl side chain is minimized.

**Scheme 50.****Scheme 51a.**



Scheme 51b.

The electrophilic mediated amino-cyclization of allenyl *N*-tosyl carbamate has been explored by several research groups. Friesen [79] has reported (Scheme 52a) the cyclization of allenyl *N*-tosyl **91** and *N*-trichloroacetyl carbamates **91a** by reaction with  $\text{I}_2$  (2 eq.) in the presence of a base ( $\text{Na}_2\text{CO}_3$ ,  $\text{K}_2\text{CO}_3$ ,  $\text{NaHCO}_3$ ). The procedure affords the corresponding *trans*-5-alkyl-4-(1-iodoethylene)-oxazolidin-2-ones **t-92** and **t-92a** as the major diastereoisomers in a ratio 6:1 and 99:1, respectively.

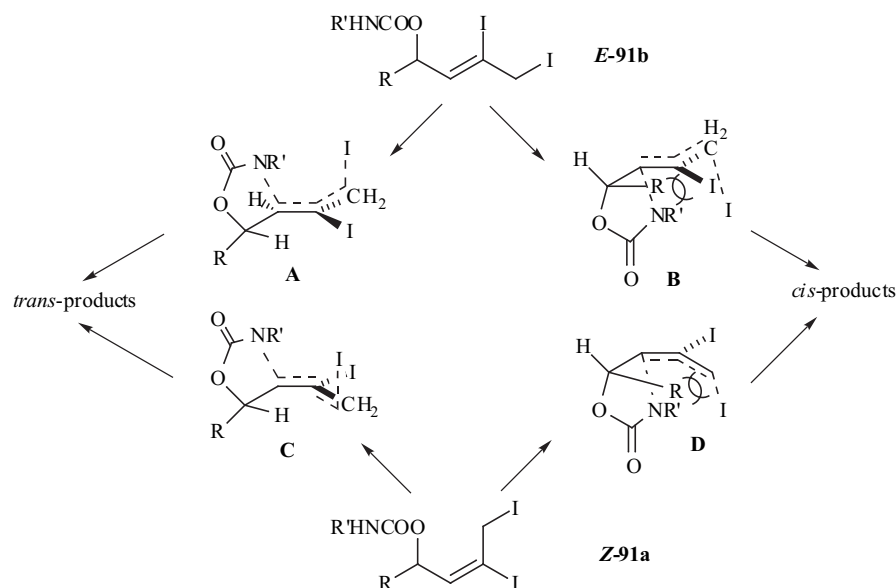


Scheme 52a.

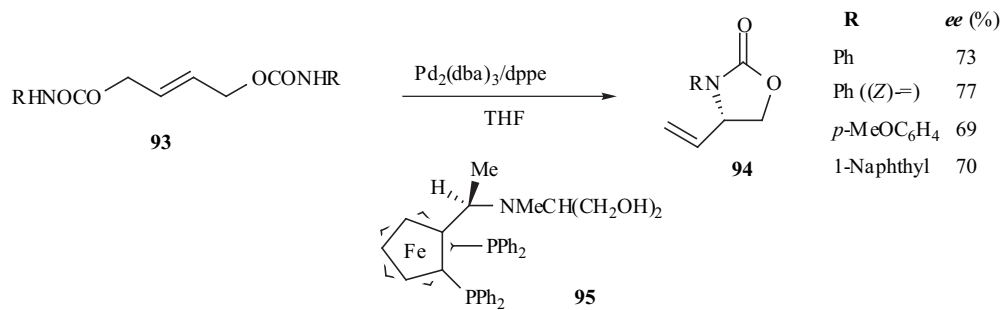
The proposed mechanism involves the initial addition of  $\text{I}_2$  to the terminal double bond of the allenyl moiety, to afford a mixture of *E*-**91b** and *Z*-**91a** diiodides, followed by a kinetically controlled intramolecular  $\text{S}_{\text{N}}2'$  type displacement of the halogen (Scheme 52b). Accordingly, the formation of the *cis*-products are highly penalized by the

presence of a chiral (hydroxyalkyl)-ferrocenylphosphine ligand (**95**), gave optically active vinyloxazolidin-2-ones **94** with *ee* up to 77% (Scheme 53a).

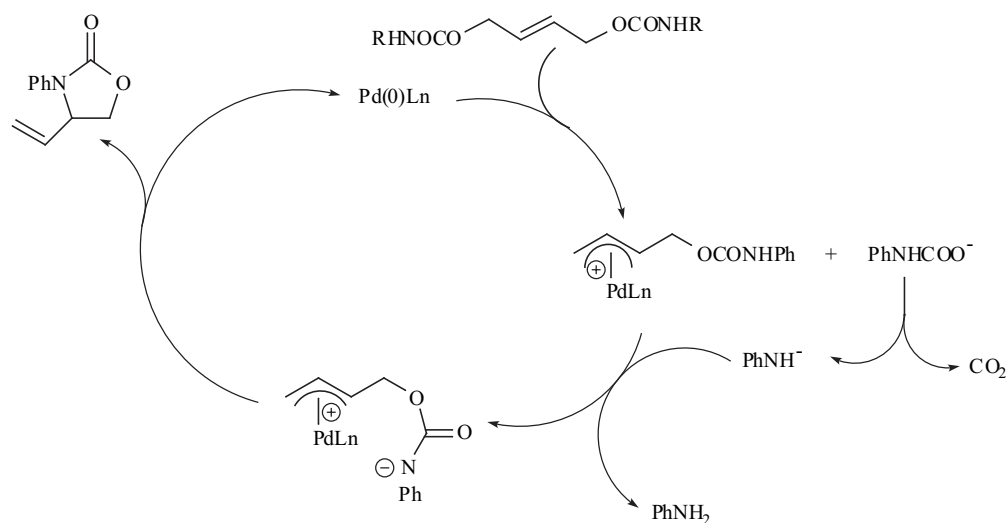
The catalytic cycle, which proceeds by the way of a  $\pi$ -allyl palladium intermediate, is depicted in Scheme 53b.



Scheme 52b.



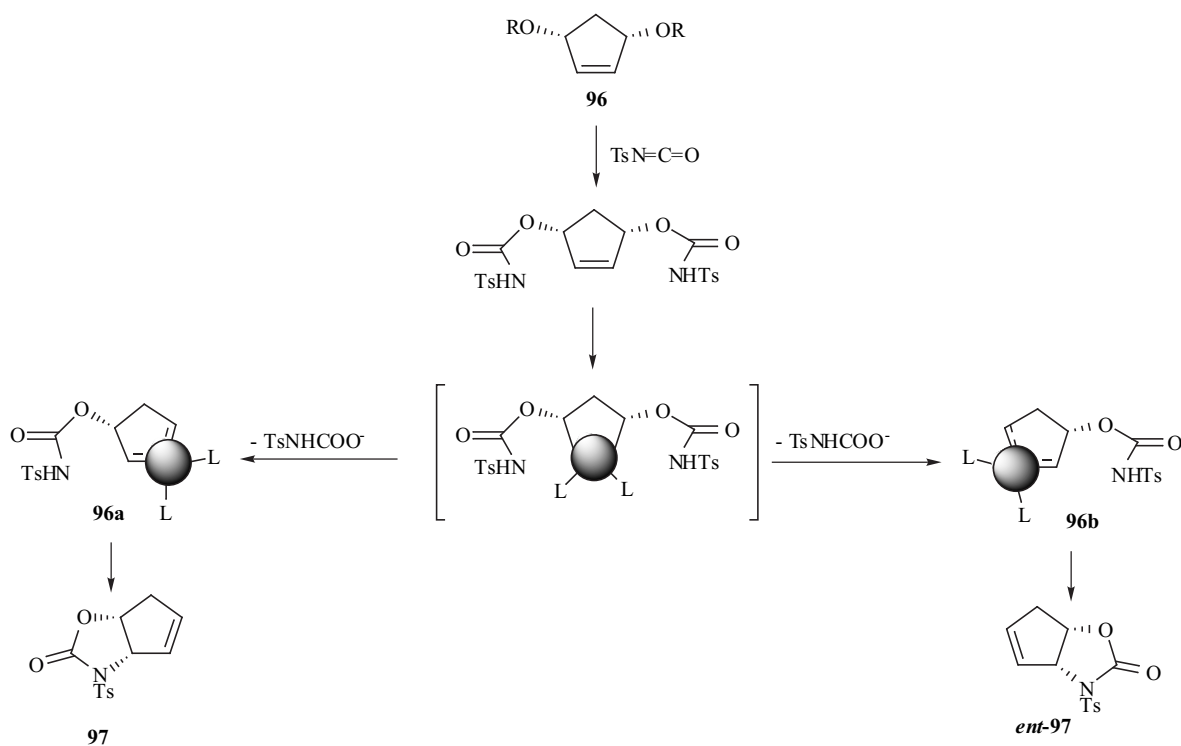
Scheme 53a.



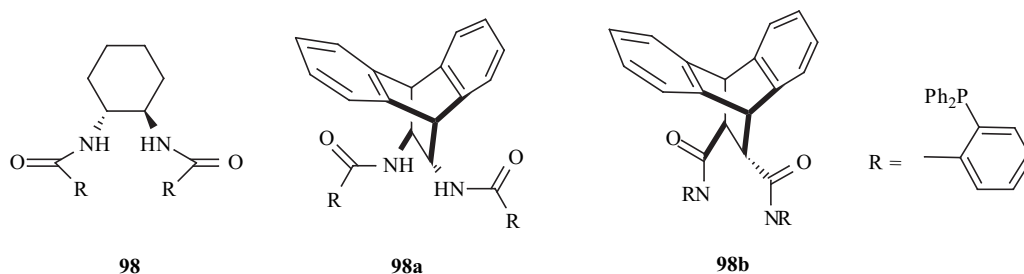
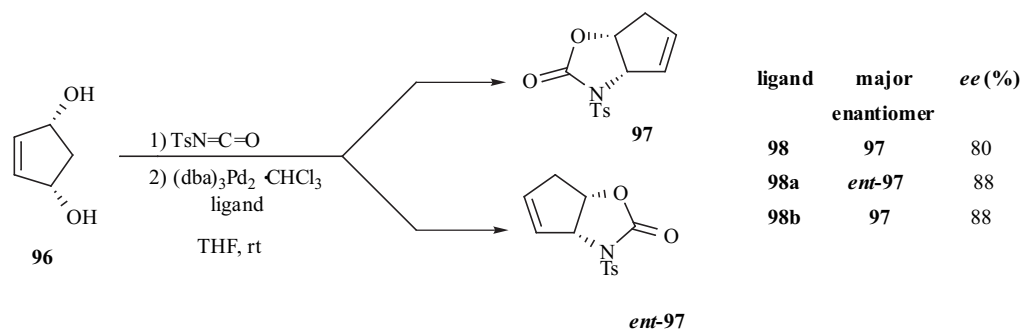
Scheme 53b.

Remarkable results have been obtained by Trost *et al.* [81] in the palladium-catalysed desymmetrization of cyclic *meso*-2-ene-1,4-diol biscarbamates, such as **96**, to give the

corresponding 5-vinyl oxazolidin-2-one derivatives **97** or *ent*-**97**. In this reaction (Scheme **54a**), the asymmetric induction takes place during the formation of the allylic



Scheme 54a.



Scheme 54b.

complex when one of the two enantiotopic carbamates is lost to form the intermediate palladium complex (**96a** vs. **96b**). The subsequent attack of the internal nucleophile gives rise to the product. Since the key step is the ionization of the prochiral leaving groups, great efforts have addressed to design ligands suitable for driving the enantioselectivity of the reaction.

A series of ligands, based mainly upon 2-(diphenylphosphino)benzoic acid (DPPBA) frame, with chiral diol or 1,2-diamino groups and a  $C_2$  symmetry, have been prepared and tested [81e] in the intramolecular allylic substitution reaction, giving rise to products with *ee* up to 88%.

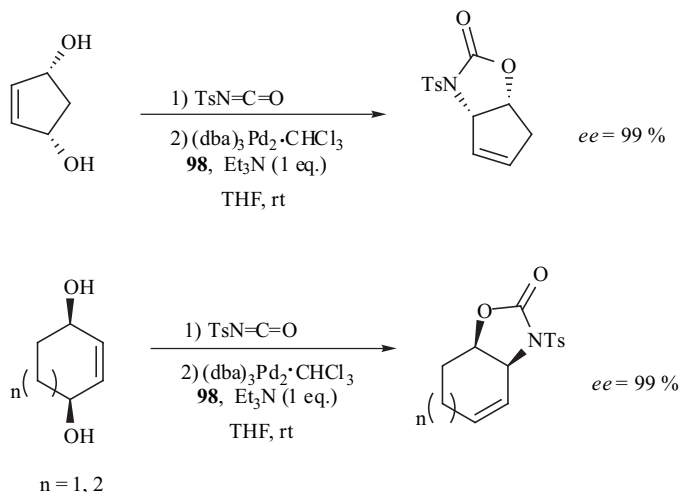
In particular, the use of ligands **98** and **98a** afforded the best results (Scheme 54b).

Notably, the use of the “invertomer” ligand **98b** gave a product possessing the same *ee* but opposite sense of chirality from that obtained with the ligand **98a**. Impressive

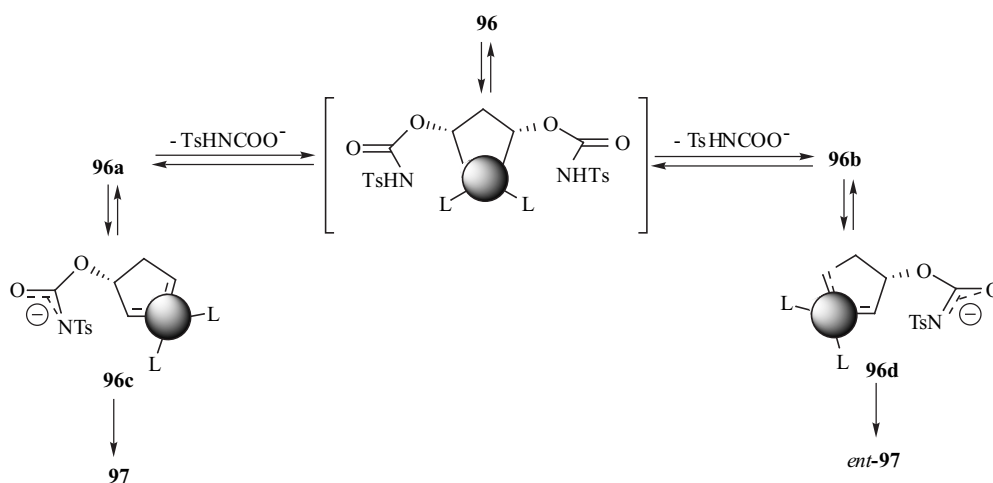
increase of the enantioselectivity was observed, more recently [81c], when the reaction was performed in the presence of 1 equiv of triethylamine (Scheme 54c).

These results reveal that ionization is not the rate-determining step, the  $\pi$ -allyl palladium intermediate **96a** and **96b** being produced in the absence of a base, whereas the cyclization requires actually the formation of the zwitterions **96c** and **96d**. Since the ionization step produces carboxylate, a weak base and at a very low concentration, significant return to the starting material may compete with the cyclization, leading to erosion of the *ee*. The use of a base, which suppresses this competition, allows the intrinsic enantiodiscrimination step to be maintained (Scheme 54d).

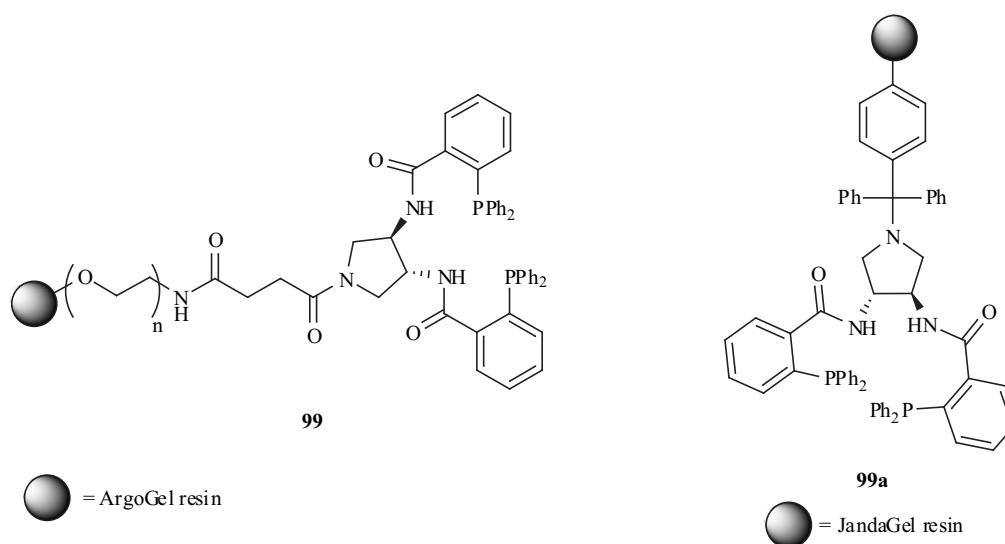
These results were applied to the synthesis of biologically relevant natural compounds, such as mannostatin A and allosamizoline [55] and swainsonine [82]. Other  $C_2$ -symmetric bisphosphine ligands have been used to perform this reaction, but lower enantioselectivity



Scheme 54c.



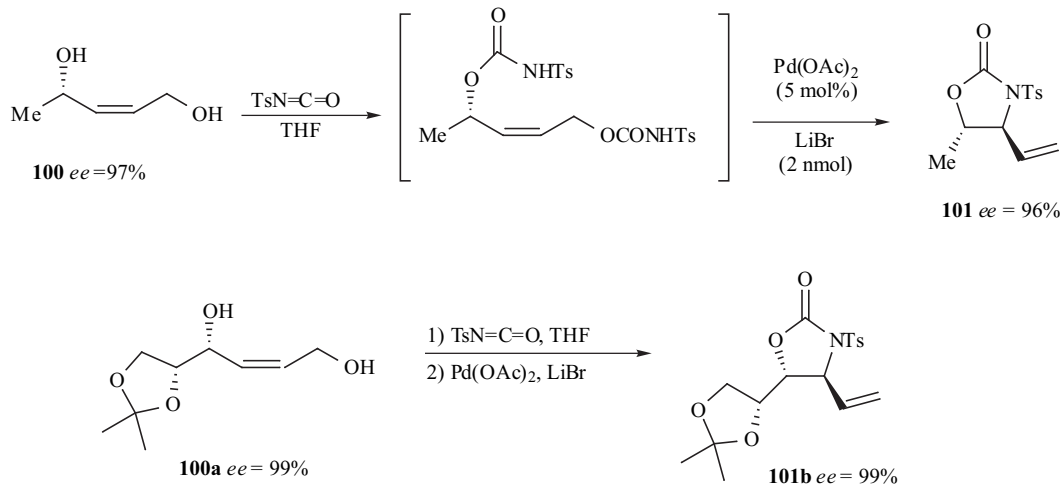
Scheme 54d.



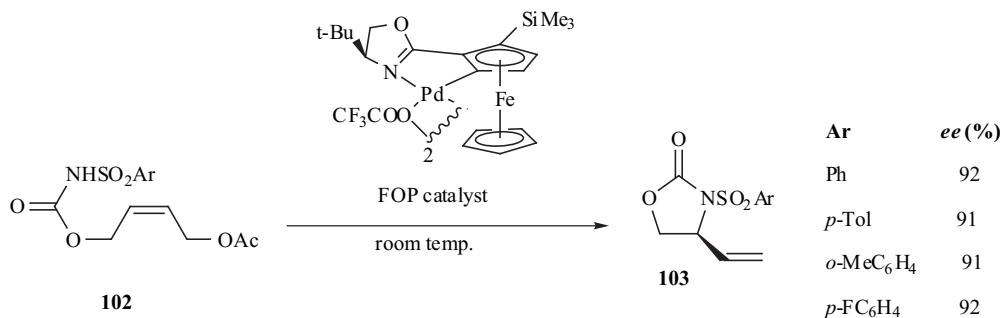
Scheme 54e.

was always observed [83]. By contrast, polymer-bound ligands, such as **99** and **99a**, have been reported [84] to promote efficiently the Pd-catalyzed desymmetrization of **96** (Scheme 54e).

The Pd(II)-catalyzed cyclization of biscarbamates, derived from homochiral butenylene alcohols **100-100a**, with catalytic Pd(OAc)<sub>2</sub> (5 mol%) and LiBr gave the corresponding *trans*-5-vinylloxazolidin-2-ones **101-101b** in



Scheme 55.



Scheme 56.

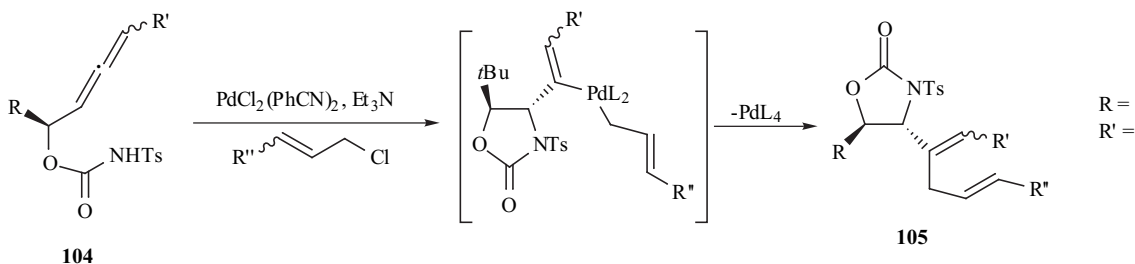
high yields (> 84%) and excellent diastereoselectivity [85] (Scheme 55).

Conversely, Overmann [86] documented the use of ferrocenyloxazoline palladacycle (FOP catalyst) as a catalyst in the enantioselective synthesis of vinyl-substituted oxazolidin-2-ones **103** from the carbamates **102** (Scheme 56). The reaction requires 0.5-5 mol % catalyst and occurs at room temp. in good yields (>91%) and high levels of enantioselectivity (*ee* > 89%).

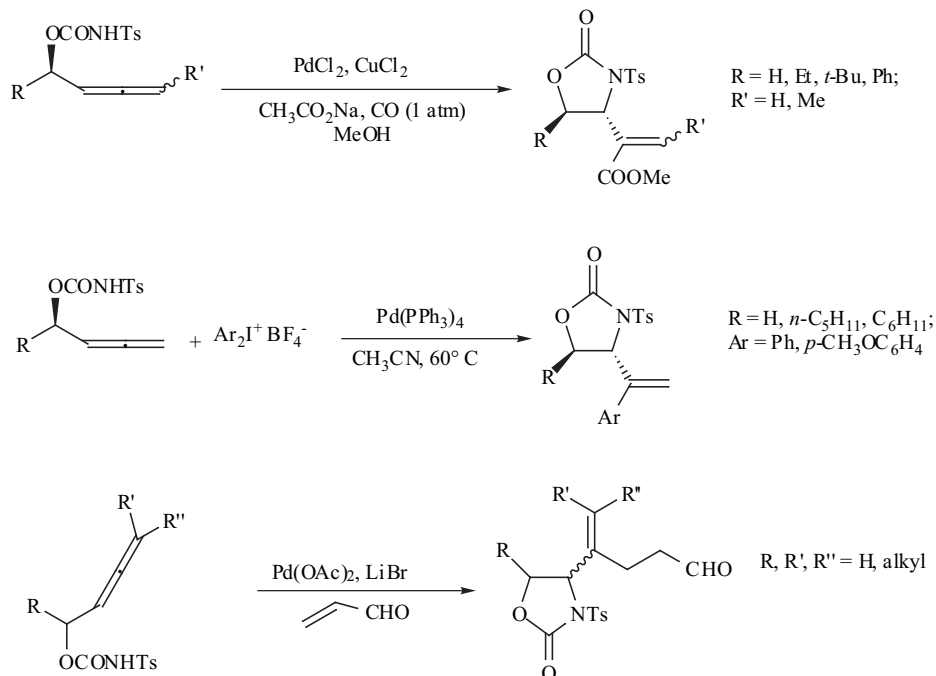
Tamaru has used both PdCl<sub>2</sub>(PhCN)<sub>2</sub> and Pd<sub>2</sub>(dba)<sub>3</sub> in the palladium-mediated allylamino cyclization of 2,3-

butadienyl tosylcarbamates **104** with allylic chlorides, that provides selectively polifunctionalized *trans*-4,5-disubstituted oxazolidin-2-ones **105** in good yields (51-80%) (Scheme 57a) [87a,b].

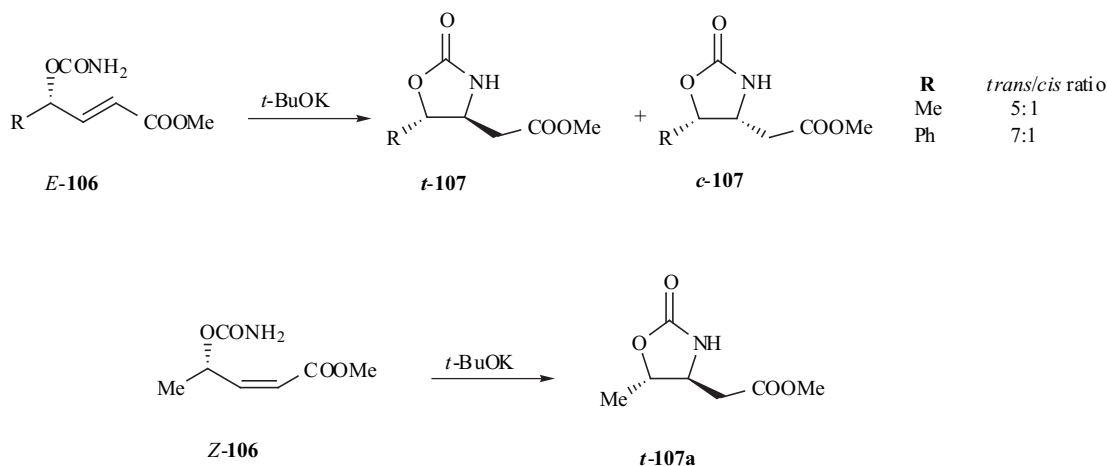
Otherwise, when the reaction was performed in the presence of Pd(Ph<sub>3</sub>)<sub>4</sub>, the *N*-allyl derivatives were the main products. On the basis of the above procedure, several Pd(II)-catalyzed cyclization-coupling of allenyl *N*-tosyl carbamates with different electrophiles, such as CO [87c], ArI<sup>+</sup> [87d], and acroleine [87e] have been obtained successfully (Scheme 57b).



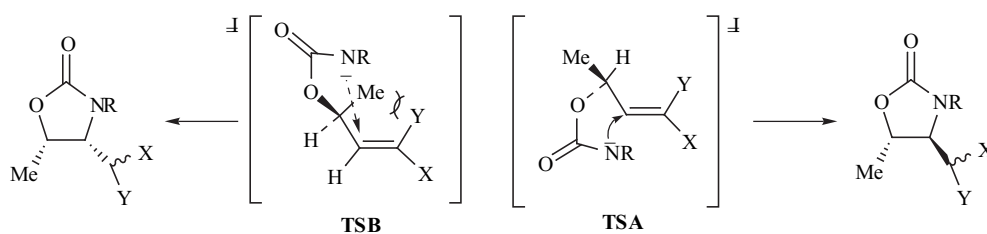
Scheme 57a.



Scheme 57b.



Scheme 58a.



Scheme 58b.

### 2.3.3. Base- or Acid-Promoted Cyclization

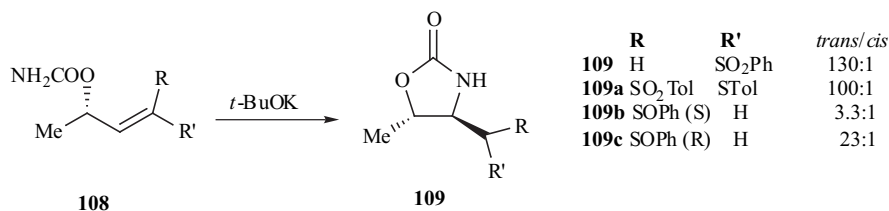
The base-promoted ( $t\text{-BuOK}$ ) intramolecular Michael-type cyclization (Scheme 58a) of electron-poor allylic *O*-carbamates, such as substrates **E-106** and **Z-106**, was studied mainly by Hirama *et al.* [88]. For simply *E*- $\alpha,\beta$ -unsaturated esters (**E-106**, R=Me) the *trans/cis* ratio of the cyclization products **t-107** and **c-107** was modest, but increased when R was a sterically demanding group. Very high 1,2-asymmetric induction was observed for the *Z*-isomer (**Z-106**) and the *trans*-oxazolidin-2-one **t-107a** was the only product.

The high 1,2-asymmetric induction in the cyclization of the *Z*-isomers, can be rationalized in terms of  $A^{1,3}$  strain [74]

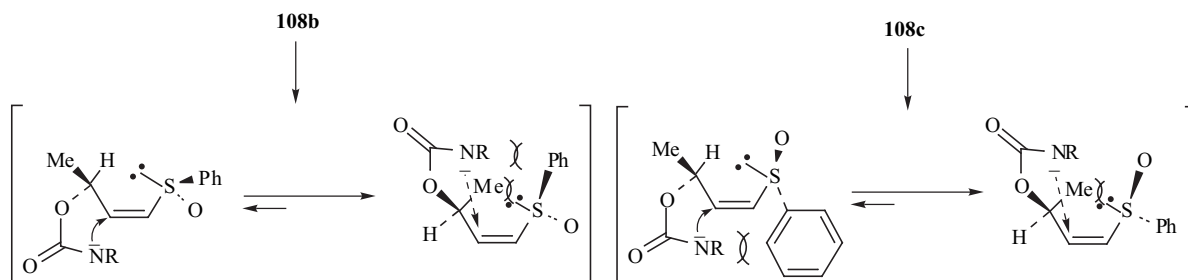
in the transition state B (TS B in Scheme 58b) leading to the *cis* product, whereas the TS A is essentially free of sterical interactions.

Similar results (Scheme 59a) have been observed by another group dealing with vinyl sulfoxides and vinyl sulphones [89].

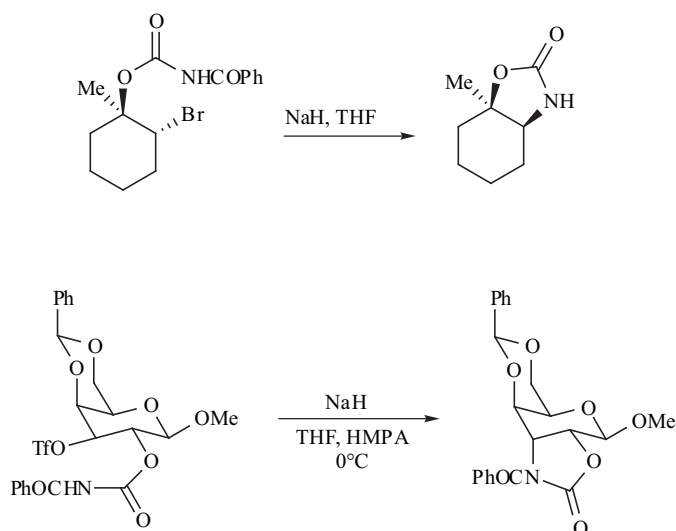
Notably, in the cases of vinyl sulfoxides **108b** and **108c**, the diastereomeric ratio between the corresponding oxazolidinones **109b** and **109c** was a consequence of an "intramolecular double asymmetric induction", generated by the two stereogenic centers. In fact, while the carbon center induces 1,2-asymmetric induction, by the  $A^{1,3}$  strain [74] in



Scheme 59a.



Scheme 59b.



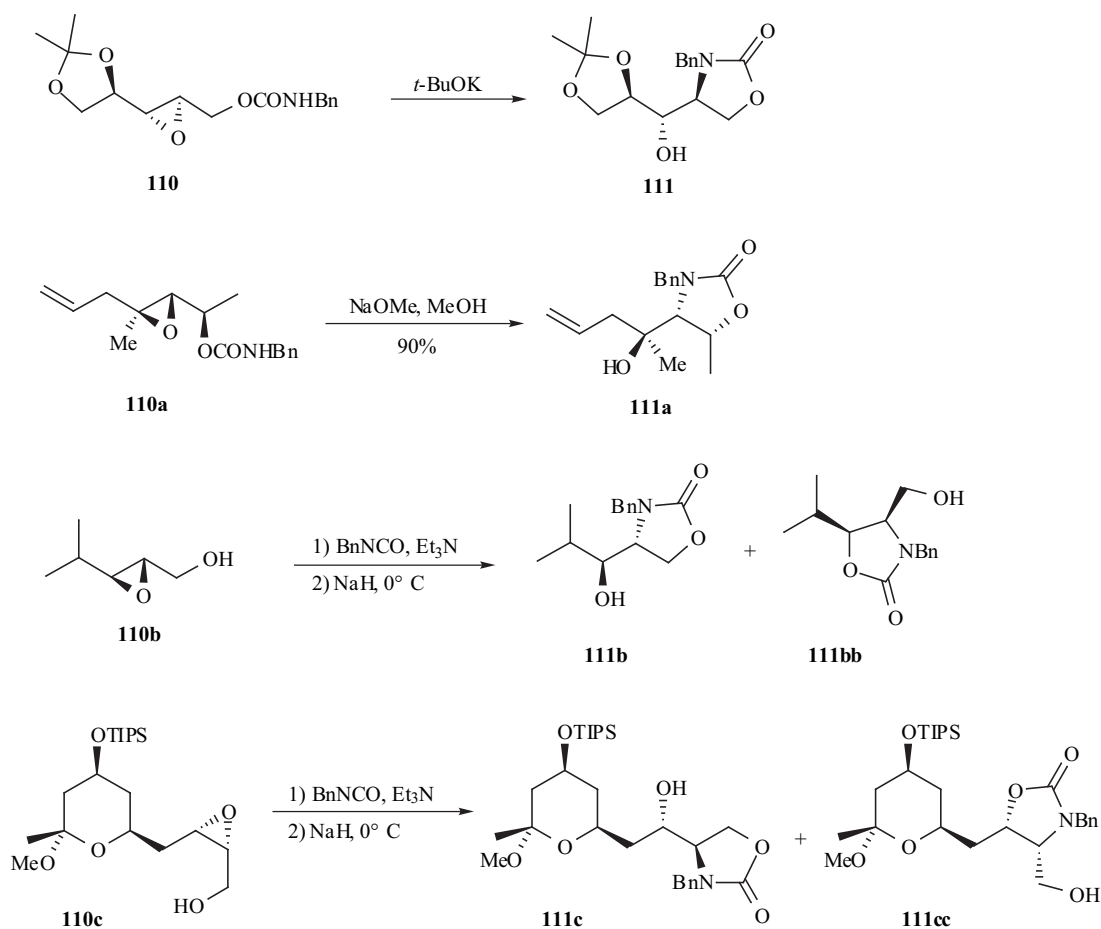
Scheme 60.

the transition state, the additional sulphoxide chirality effects 1,3-asymmetric induction by steric interaction between the incoming nucleophile and the phenyl group on the sulphur or by electronic interaction between the nucleophile and the lone pair (Scheme 59b).

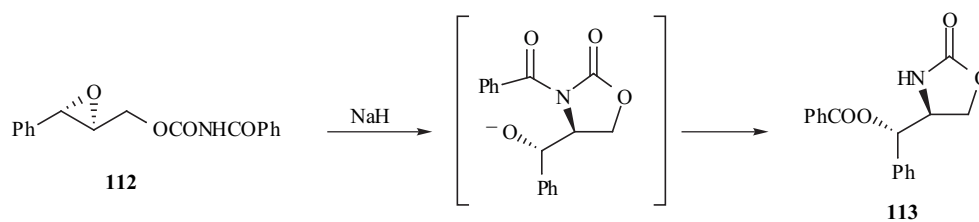
The base-promoted intramolecular nitrogen delivery from an urethane to a vicinal electrophilic center, bearing a leaving

group (Br, OTf, 2,3-epoxy, etc.) is a general method (Scheme 60), to prepare the oxazolidin-2-one nucleus [90].

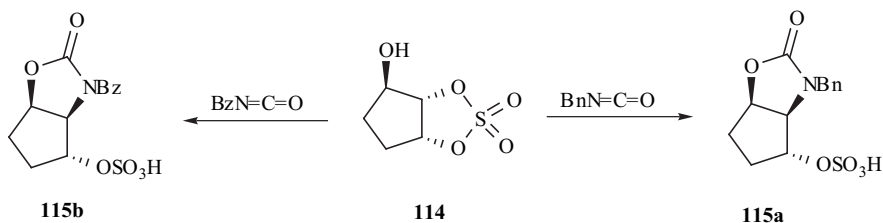
By a similar approach, epoxyurethanes, such as **110-110c**, prepared from the corresponding epoxy alcohols, cyclize to oxazolidin-2-one derivatives **111-111c** in high yields (80-90%) by treatment with *t*-BuOK, NaH or NaOMe (Scheme 61a) [91].



Scheme 61a.



Scheme 61b.



Scheme 62.

The reaction proceeds with a good regioselectivity through an intramolecular addition of the urethane nitrogen to the epoxide  $\alpha$ -position; however, a small amount of the regioisomer oxazolidin-2-one can be formed at times by acyl migration.

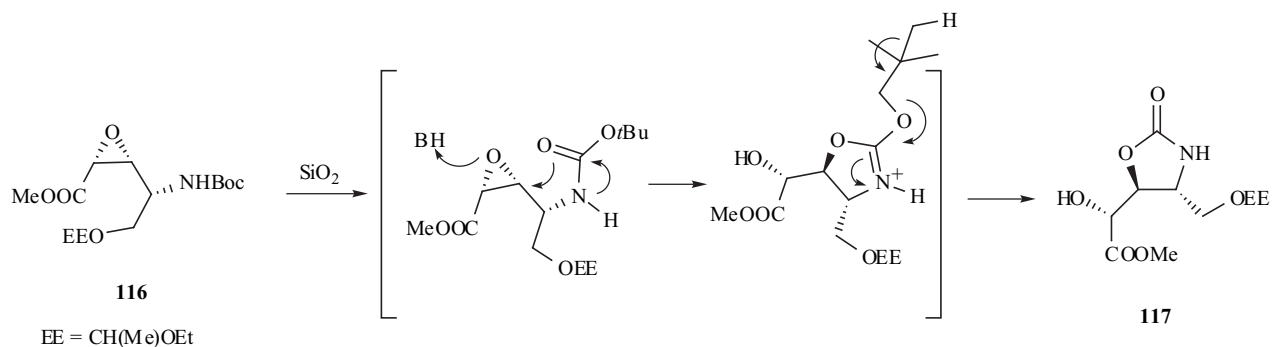
On the other hand, the intramolecular base-promoted cyclisation of *N*-benzoyl epoxycarbamates, such as **112**, occurs on the proximal epoxide carbon (Scheme 61b) and is followed by *N*-*O*-benzoyl migration, which affords the final product **113** [92].

By a similar approach, Imperiali [93] has reported the reaction of the hydroxyl sulphate **114** with benzylisocyanate and benzoylisocyanate to give the corresponding oxazolidin-2-ones **115a** and **115b** (Scheme 62).

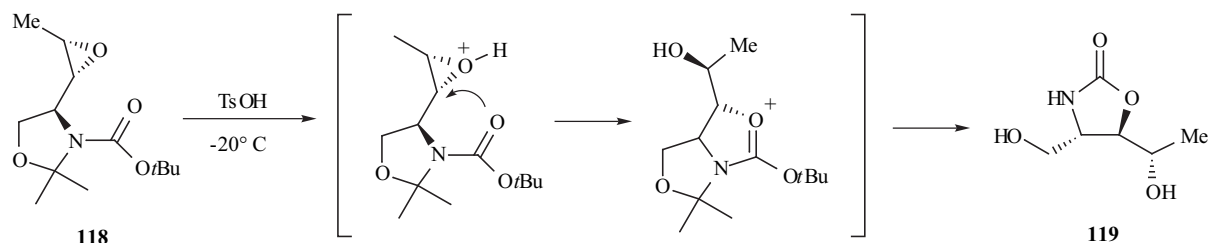
By contrast, *N*-Boc aminoepoxy derivatives **116** undergo an acid-catalysed regio- and stereo-selective intramolecular epoxide-opening reaction, with the assistance of the *N*-Boc neighboring groups (Scheme 63), to provide the corresponding 4,5-*trans*-disubstituted oxazolidin-2-ones **117** in a 5-*exo-tet* mode [94].

Analogous results have been reported (Scheme 64), starting from *trans*-*N*-alkoxycarbonylamino epoxide **118**, containing an oxazolidine moiety [95].

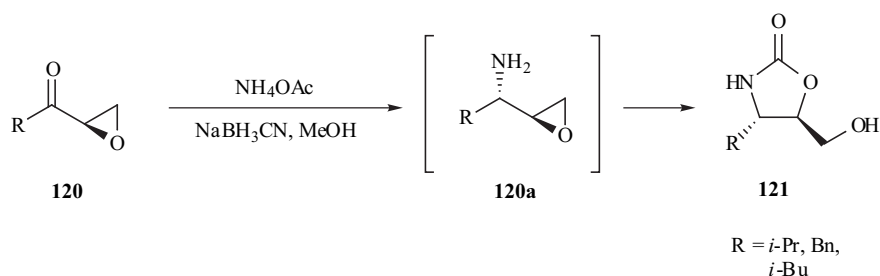
*trans*-5-Hydroxymethyloxazolidin-2-ones **121** can be also obtained from epoxyamines **120a**, by treatment with carbonated Amberlist A26 resin (Scheme 65) [96]. The amines are easily prepared by reduction of the corresponding epoxyketones **120** with sodium cyanoborohydride in the presence of  $\text{NH}_4\text{OAc}$ .



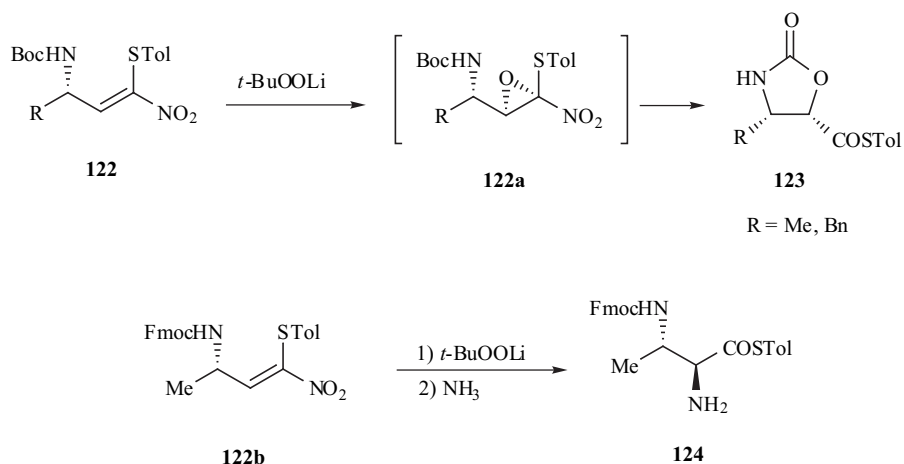
Scheme 63.



Scheme 64.



Scheme 65.



Scheme 66.

*cis*-Oxazolidin-2-ones such as **123** have been obtained [97] by epoxidation with *t*-BOOLi of some *N*-Boc-allylic amines **122**, as a consequence of the intramolecular trapping of the intermediate epoxides **122a** by the carbamate group (Scheme 66).

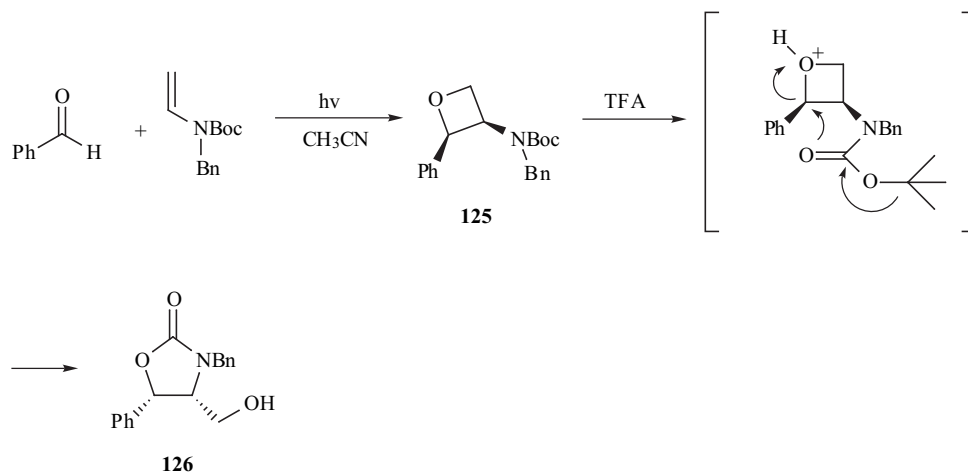
On the other hand, epoxidation of the corresponding *N*-Cbz or *N*-Fmoc derivatives **122b** afforded the corresponding *syn*-epoxides, which are unstable and were immediately treated with ammonia to give the *anti*  $\alpha,\beta$ -diamino derivatives **124**.

Similarly, *N*-Boc protected *cis*-2-aryl-3-amino oxetanes **125** gave *cis*-4-hydroxymethyl-5-phenyl *trans*-oxazolidin-2-ones **126** with inversion of configuration, by TFA-catalyzed

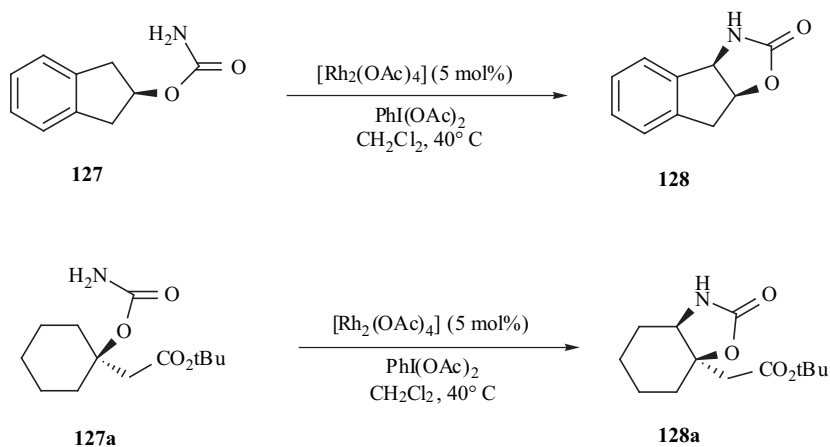
intramolecular nucleophilic substitution at the C2 carbon atom of the oxetane. The oxetanes **125** were prepared with excellent diastereoselectivity by a Paterno-Buchi reaction of aromatic aldehydes with enecarbamates (Scheme 67) [98].

### 2.3.4. Intramolecular C-H Amidation

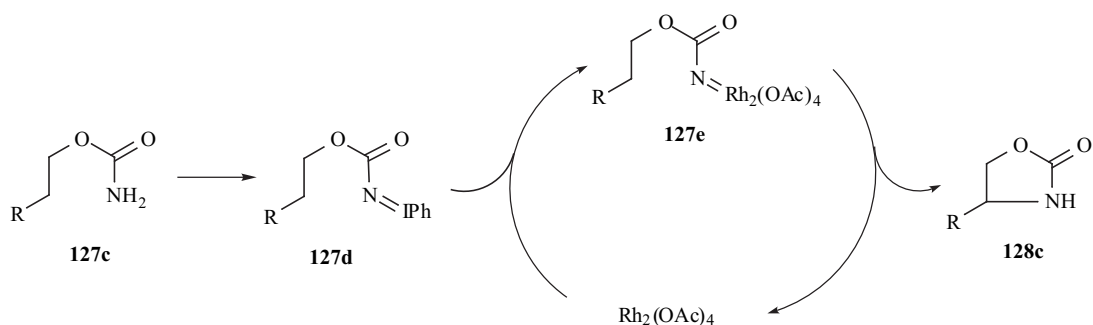
The intramolecular amidation of C-H bonds of carbamates **127-127a**, by dirhodium(II)tetracarboxylate ( $\text{Rh}_2(\text{OAc})_4$ ) as a catalyst and  $\text{PhI}(\text{OAc})_2$  as an oxidant, was also used to form the oxazolidin-2-one ring **128-128a** (Scheme 68a) [99]. The intramolecular reaction occurs with high levels of regio- and stereoselectivity; *syn*-oxazolidin-2-ones are formed with retention of stereochemistry at the insertion carbon.



Scheme 67.



Scheme 68a.



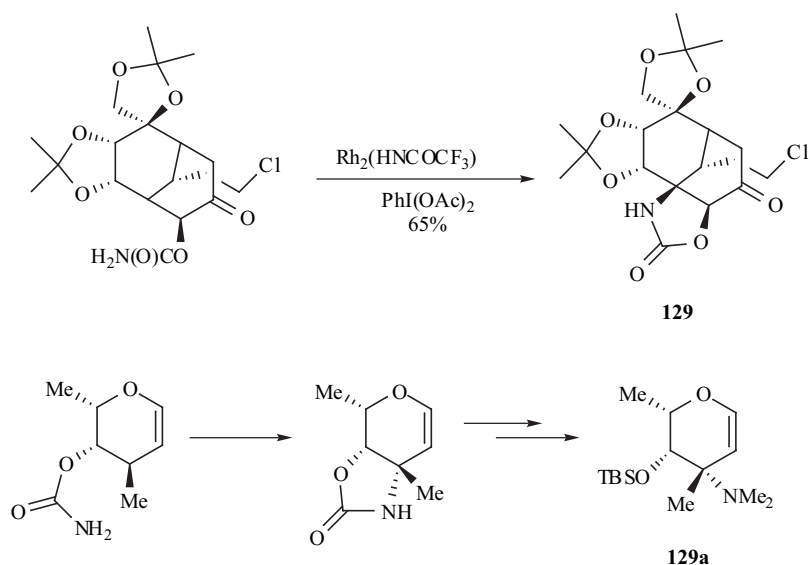
Scheme 68b.

The formation of the products (Scheme 68b), arises very likely from an initial oxidation of the carbamate moiety in **127c** to the iodoimine **127d**, which in turn generates the reactive metallonitrene **127e** in the presence of the dirhodium complex. Final C-H insertion affords the oxazolidin-2-ones **128c** and the rhodium complex to continue the catalytic cycle.

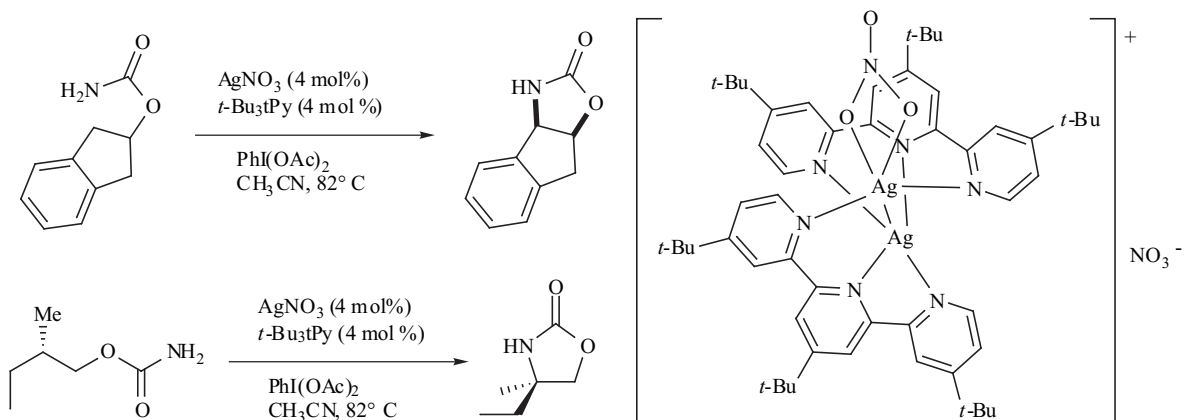
Notably, the reaction can be successfully applied to complex substrates, such as compound **129**, a key intermediate in the total synthesis of (-)-tetrodotoxin [100a],

as well as in the preparation of the *N,N*-dimethyl-vancosamine glycal **129a**, an intermediate for the synthesis of pluramycin antibiotics [100b] (Scheme 68c).

More recently a disilver(I) catalyst (Scheme 69), generated in situ from commercially available  $\text{AgNO}_3$  and *t*- $\text{Bu}_3\text{P}$ -Py, has been reported to promote the same reaction in good yields (> 70%). The reaction with combinations of other ligands and silver (I) salts occurs with lower yields [101].



Scheme 68c.



Scheme 69.

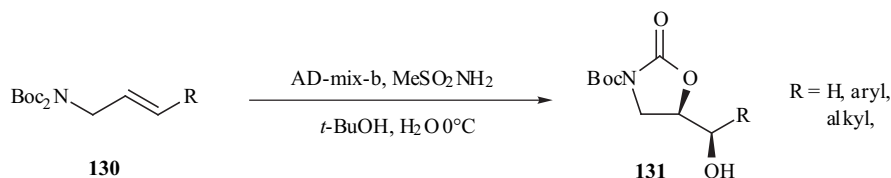
## 2.4. Addition to Double Bond

### 2.4.1. Asymmetric Aminohydroxylation

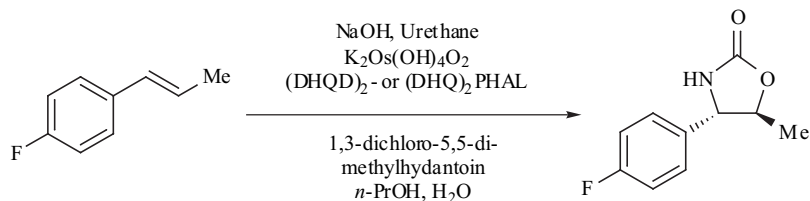
The asymmetric dihydroxylation (AD) of *N*-diBoc allylic amines **130** (Scheme 70), to give directly 5-substituted oxazolidin-2-ones **131**, was first reported by Sharpless *et al.* [102]. Typically, the yields of the reaction were good (73–93%), while the enantioselectivity was dependent on the substitution pattern of the olefin and ranged from 34 to 98%. Lower enantiomeric excess (75%) were obtained with monoacetylated allylic amines.

Sharpless' asymmetric aminohydroxylation (AA) of  $\beta$ -substituted styrene derivatives coupled with a base-mediated (NaOH, CsCO<sub>3</sub>) ring closure was explored in Merck laboratories: as a result, a modified procedure, in which *tert*-butyl hypochlorite was replaced by 1,3-dichloro-5,5-dimethyl hydantoin, became a practical one-pot preparation of 4-aryl-5-substituted oxazolidin-2-ones in good yields and high regio- and enantio-selectivity (Scheme 71) [103].

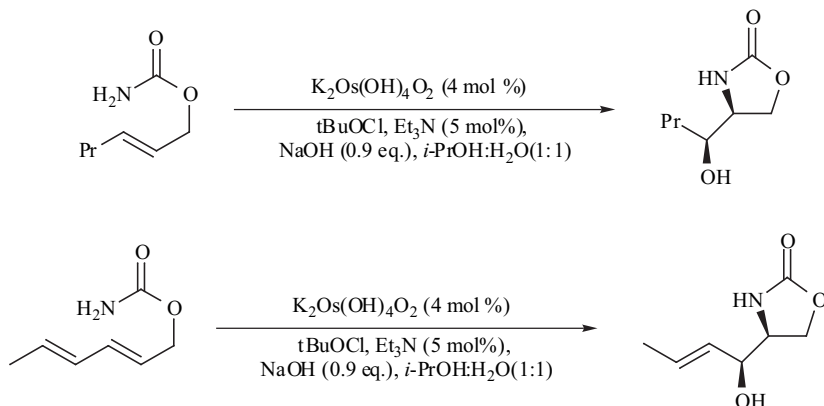
However, the control of the regioselectivity in the Sharpless AA reaction is a problem, when some unsymmetrical olefins are to be oxidized. To overcome these



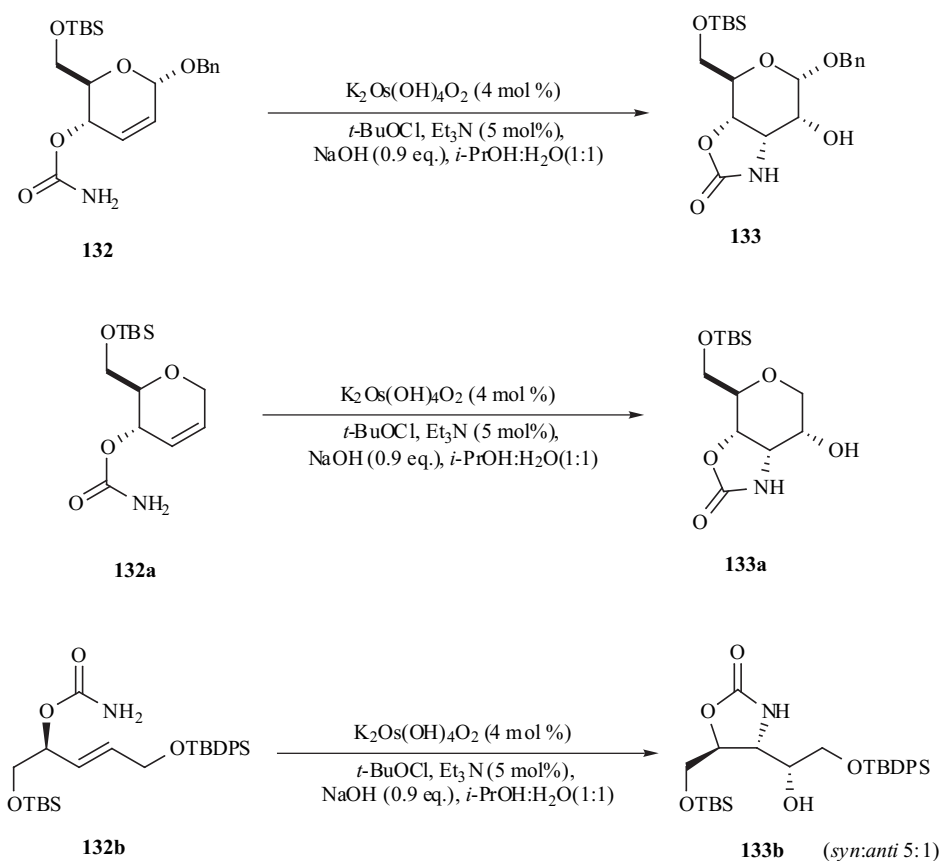
Scheme 70.



Scheme 71.



Scheme 72a.



Scheme 72b.

shortcomings, Donohoe studied the aminohydroxylation of allylic carbamates, the tethered AA (Scheme 72a) [104].

The reaction makes use of 4% of  $\text{K}_2\text{Os(OH)}_4\text{O}_2$  in the presence of NaOH (1 eq) and  $t\text{-BuOCl}$  (1 eq) in  $i\text{-Pr}/\text{H}_2\text{O}$ . Together with the cyclization products (40-60%), the starting material is recovered in variable yields. The addition of a base, such as  $i\text{-Pr}_2\text{NEt}$  or  $(\text{DHQ})_2\text{PHAL}$  increases yields and rates of the reaction, but a racemic mixture of hydroxyloxazolidin-2-ones was obtained in all investigated cases.

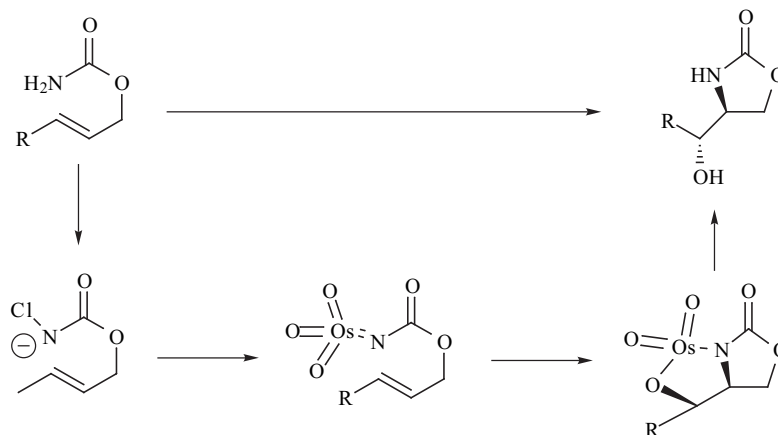
Extension of this procedure to chiral cyclic substrates [105a], such as **132** and **132a**, and more recently [105b] to

chiral acyclic substrates, such as **132b**, allowed to prepare the target products (**135-135b**) under regio- and stereo-selectivity control (Scheme 72b).

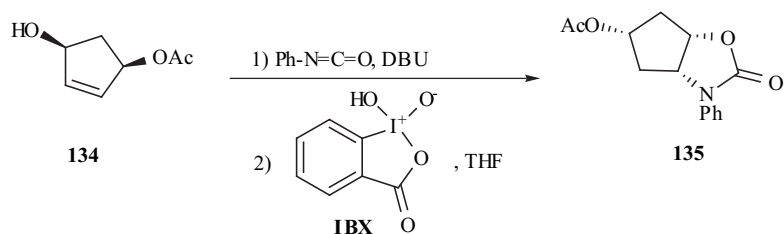
The proposed mechanism is depicted in Scheme 72c.

#### 2.4.2. IBX-mediated Cyclization

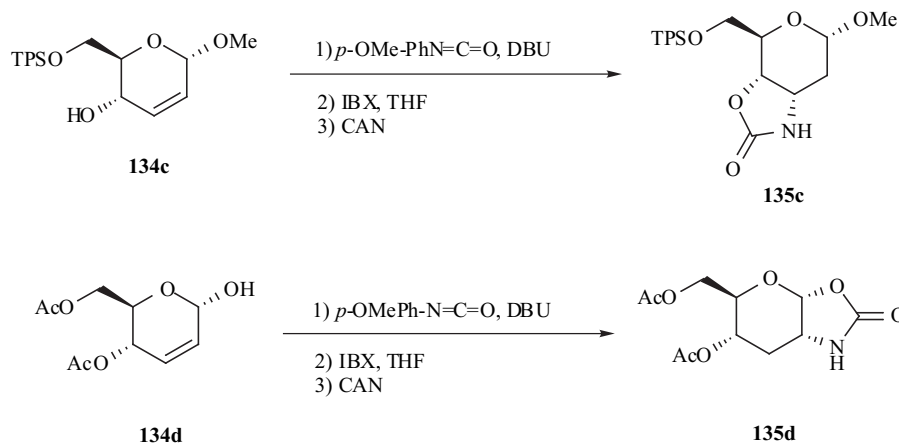
Nicolaou has reported a simple, high yield (72-95%) procedure to convert different substrates bearing an allylic alcohol moiety, such as **134**, into variously substituted *N*-phenyloxazolidin-2-ones **135** (Scheme 73a). The two-step procedure involves a reaction with phenyl isocyanate to give the corresponding carbamate and *o*-iodoxybenzoic acid (IBX)-mediated cyclisation [106a].



Scheme 72c.



Scheme 73a.

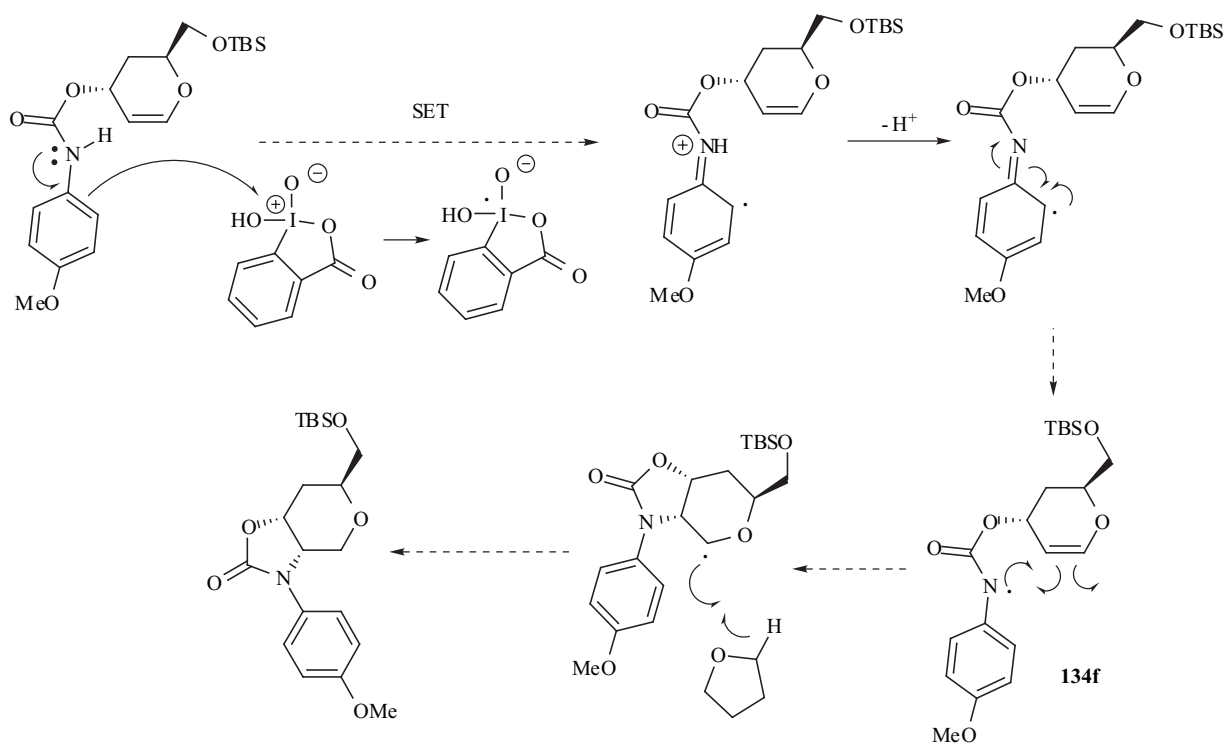


Scheme 73b.

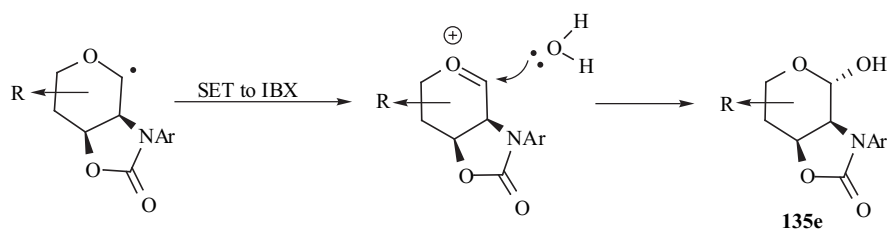
In a more advanced strategy [106b], phenyl isocyanate was replaced by *p*-methoxyphenylisocyanate and the final removal of the aryl group, with cerium ammonium nitrate (CAN), allowed obtaining the corresponding *cis*-*N*-unsubstituted oxazolidin-2-ones (Scheme 73b).

The authors have postulated that the IBX selectively activates the nitrogen atom of anilides to react with a nearby

olefin; thus, the formation of the products have been rationalized (Scheme 73c) in the following steps: a) formation of a nitrogen-centered reactive intermediate **134f**, formed from the carbamate by a single electron transfer (SET) mechanism, loss of a proton and rearomatization; b) reaction with the olefin moiety in a 5-*exo-trig* mode; c) final hydrogen abstraction from the solvent.



Scheme 73c.

**Scheme 73d.**

Notably when the reaction was conducted in presence of water, the amino sugar **135e** was formed as the main product, presumably through an oxonium species (Scheme **73d**).

### 2.4.3. Acilnitrene Insertion

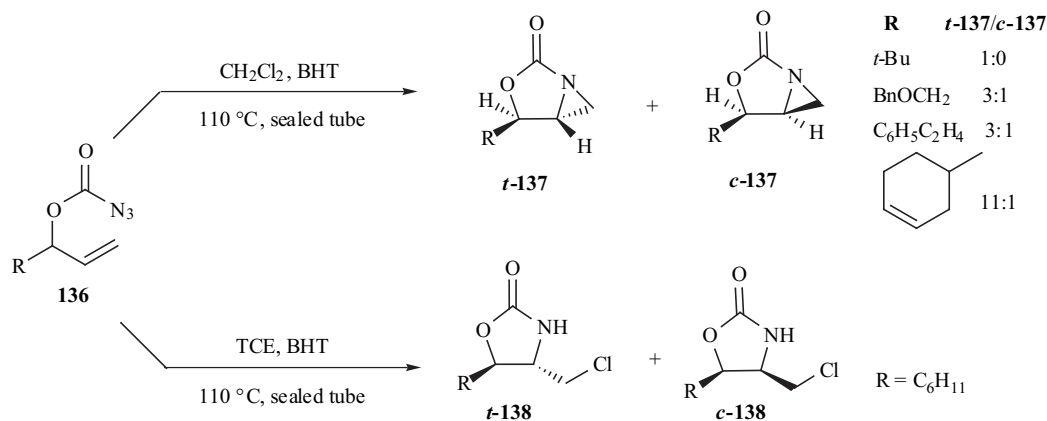
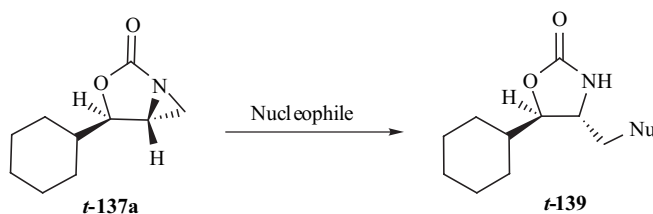
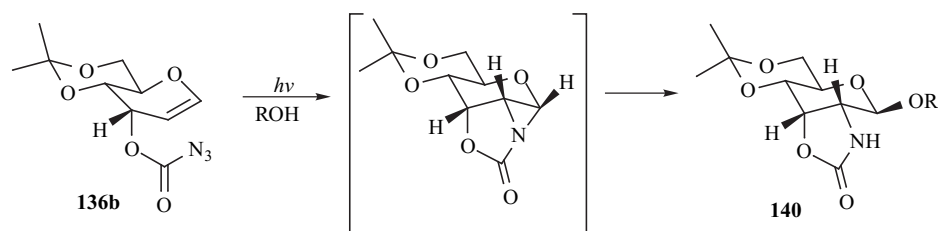
The thermal intramolecular acylnitrene insertion into C=C unit, to give the bicyclic oxazolidin-2-one/aziridine system has been reported by Bergmeier [107], who obtained a diastereomeric mixture of *trans*- and *cis*-bicyclo derivatives, **t-137** and **c-137**, by heating at 109° C in a sealed tube a CH<sub>2</sub>Cl<sub>2</sub> solution of allyl azidoformates **136** in the presence of 10% of 2,6-di-*tert*-4-methylphenol (BHT) (Scheme **74a**).

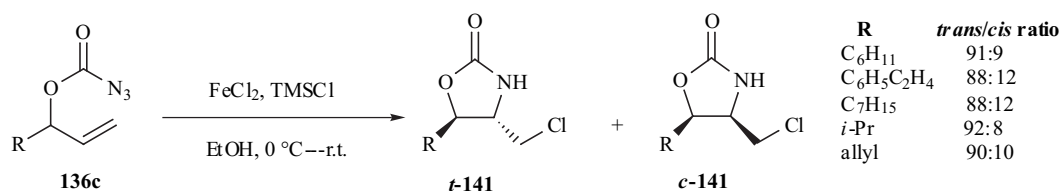
The role of solvent was shown to be critical: when the reaction was performed in tetrachloroethane (TCE), a mixture

(6.7:1) of *trans* and *cis* chlorides, **t-138** and **c-138**, was obtained (Scheme **74b**). The chlorides may derive from the opening of the aziridine ring by HCl or a Cl radical produced in the mixture reaction by the heating in TCE. Owing to facile opening of the three membered ring in the bicyclic compound **t-137a**, different nucleophiles (H<sub>2</sub>O, MeOH, AcOH, TMSN<sub>3</sub>, TMSCl, Ph/CuI, *n*-Bu<sub>2</sub>CuLi, RMgX/CuCN) were investigated for the obtainment of varying 4-substituted oxazolidin-2-ones **t-139** (Scheme **74b**).

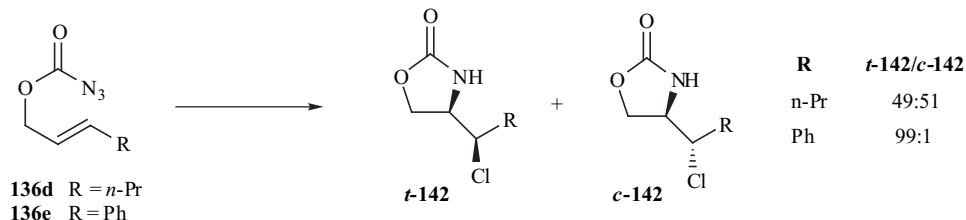
The photochemical version of this reaction has been reported by Rojas *et al.* [108].

Photolysis of a solution of the allyl C-3 azidoformate **136b** in the presence of an alcohol (5 eq), resulted in the isolation of the corresponding β-2-amido allopopyranosides **140** (Scheme **75**) in reasonable yields (35-40%).

**Scheme 74a.****Scheme 74b.****Scheme 75.**



Scheme 76a.

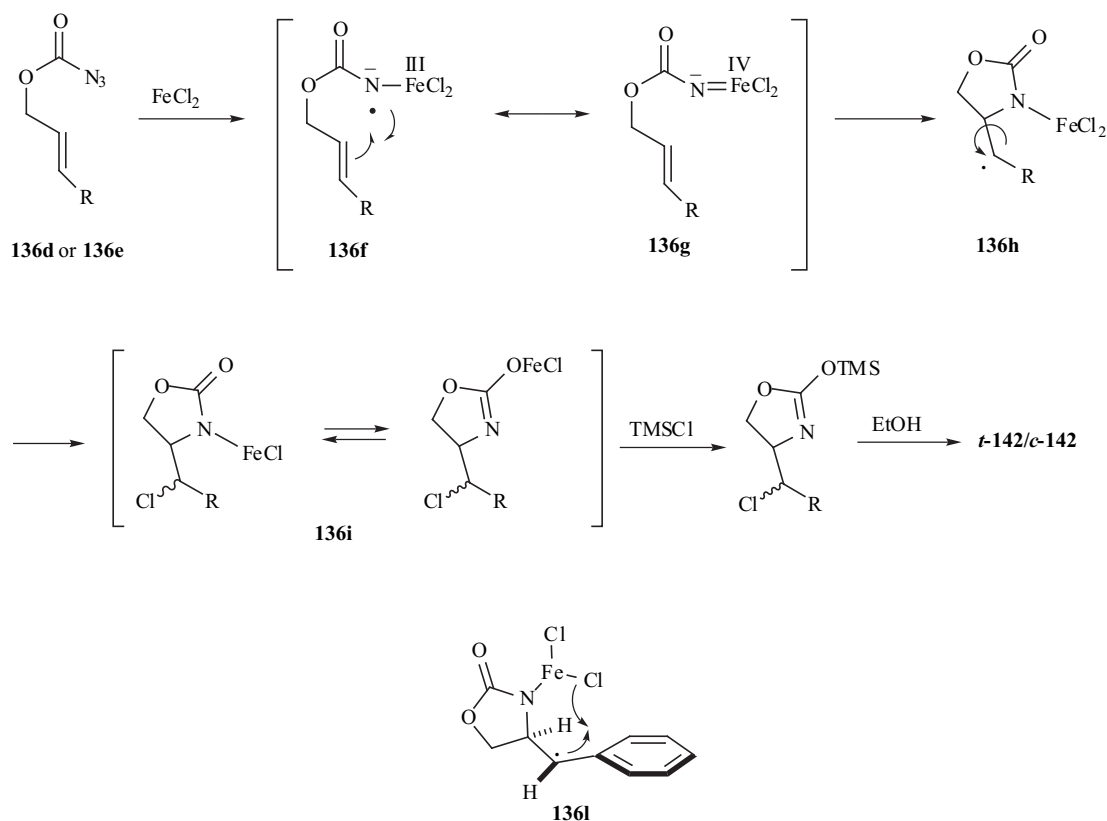


Scheme 76b.

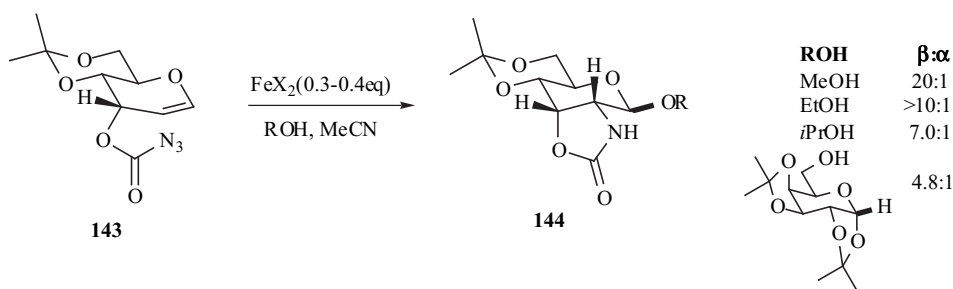
The intramolecular metal-catalyzed reaction of unsaturated alkoxy carbonyl azides has been studied by Bach [109] and Padwa [110]. The first one found that iron(II) promotes the intramolecular reaction of 2-alkenyl oxycarbonyl azides **136c** to give a diastereomeric mixture of 4-chloromethyl-oxazolidin-2-ones **t-141** and **c-141** (*trans/cis* 9:1) (Scheme 76a).

Notably, the diastereomeric ratio was on a par for trend and size with the selectivity observed for the aforementioned thermal reaction. Significant differences in the stereochemical outcome were, however, observed when azido formates **136d** and **136e** were used as a substrate (Scheme 76b).

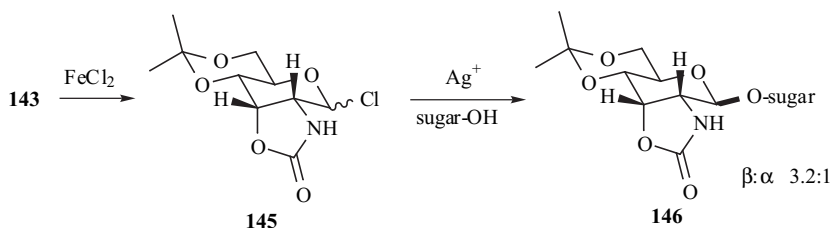
A non-stereospecific reaction occurred with compound **136d**, which gave *ca* 1:1 mixture of **t-142** and **c-142**, whereas exclusive formation of the *threo*-product **t-142** was achieved with substrate **136e**. On the basis of these results, the proposed mechanism (Scheme 76c) involves an initial electron transfer from FeCl<sub>2</sub> to the carbonyl group, leading to an  $\alpha$ -cleavage of the N-N<sub>2</sub> bond to generate a radical-like Fe<sup>III</sup> species **136f** or a Fe<sup>IV</sup>-nitrene complex **136g**. The following radical addition to the olefinic double bond generates the intermediate **136h**, where an intramolecular transfer of chlorine atom gives the Fe<sup>II</sup>-intermediate **136i**, which finally affords the two oxazolidin-2-ones losing FeCl<sub>2</sub> by reaction with TMSCl or by direct cleavage with HCl.



Scheme 76c.



Scheme 77a.



Scheme 77b.

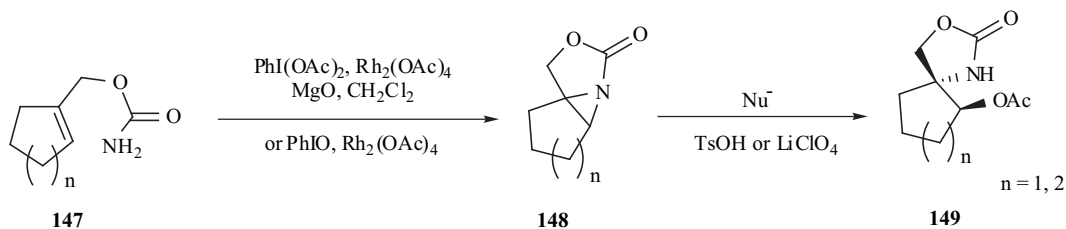
The intermediate **136h** is a reasonable intermediate to explain the different stereochemical results for the chloroamination of the substrates **136d** and **136e**; the high *threo*-selectivity for the azide **136e** is due to a restricted rotation around the C-C single bond in the intermediate **136h**, with a clear preference for the conformation **136l** from which the chlorine transfer can occur intramolecularly.

The intramolecular alkene amidation of some all *C*<sub>3</sub>-azido formate **143** (Scheme 77a), promoted by FeX<sub>2</sub> (X = Cl, I), has been reported by Rojas [111]. Performing the reaction in the presence of a large excess of alcohols (MeOH, EtOH, *i*-PrOH),  $\beta$ -glycosylation occurred ( $\beta:\alpha > 10:1$ ) in appreciable yields (50%).

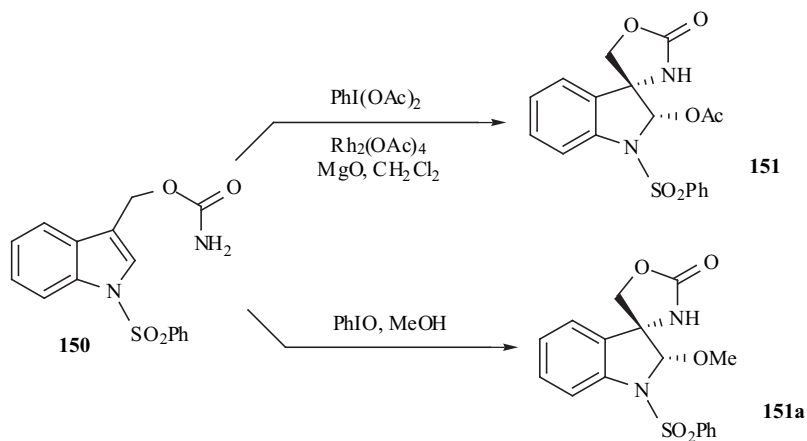
On the other hand, in the absence of the alcohol, **143** afforded an anomeric mixture of glycosyl chlorides **145**, which were used as donors in silver ion-promoted glycosylations (Scheme 77b).

The intramolecular Rh(II)-catalysed aziridination of cycloalkenyl derivatives **147** to generate the tricyclic products **148** (Scheme 78a) has been reported by Padwa [110].

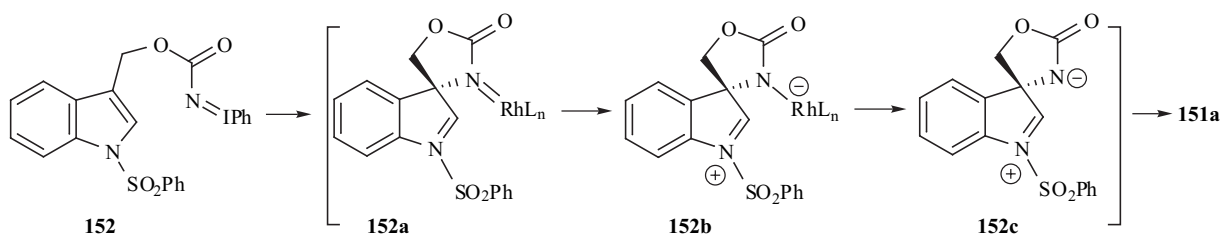
Thus, reaction of the carbamates **147** under the Du Bois conditions [99] gave exclusively the tricyclic aziridines **148** in good yields (> 70%); identical results were obtained using iodosobenzene (PhI=O) as the oxidant in the presence of an excess of alcohol with or without Rh(II) catalyst.



Scheme 78a.



Scheme 78b.



Scheme 78c.

Ring opening of the three member ring can occur with various nucleophiles (1-5 eq) in the presence of either TsOH or  $\text{LiClO}_4$ . Notably, only the *trans*-isomers **149** were formed in about 85% yield as expected from a backside attack of the nucleophiles on the aziridine ring. By contrast, the reaction of the protected 3-indolyl-carbamate **150** under Du Bois' conditions, provided the oxazolidin-2-one **151** (85% yield) as a single diastereoisomer (Scheme 78b).

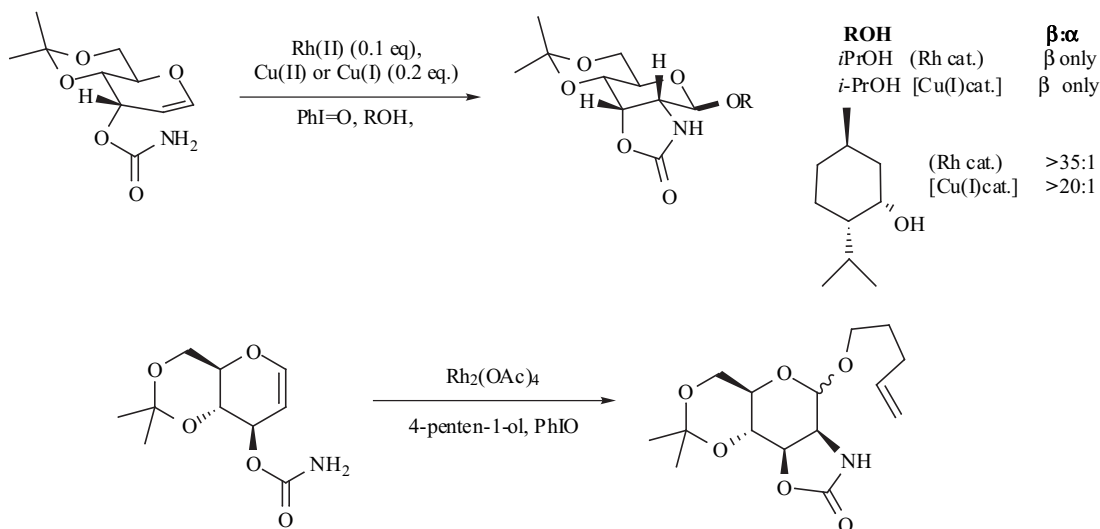
The stereochemical outcome, not consistent with a classical  $\text{S}_{\text{N}}2$  opening of the transient aziridine intermediate, was the same obtained by reaction of **150** with PhIO in the presence of excess (5 eq) of alcohol.

The proposed mechanism (Scheme 78c) for the different behavior of the substrates **147** and **150** involves the formation of a common iminoiodinane intermediate **152**,

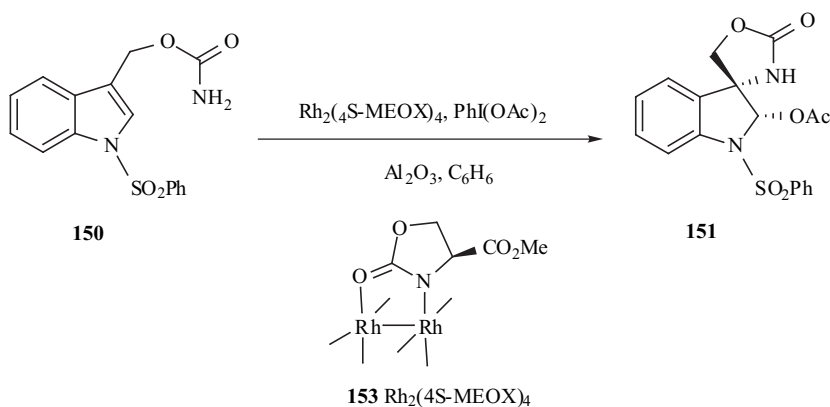
which readily reacts with the electron-rich  $\pi$ -bond in the cycloalkene derivatives. In the case of the indole system, the formation of the intermediate **152** is followed by the Rh(II)-mediated loss of PhIO to afford the metalnitrene **152a**, which evolves into the metal-free zwitterionic intermediate **152c**, likely *via* compound **152b**. The final attack of the nucleophile occurs on the side of the amide anion.

The different behavior of **147** and **150** can be explained by a faster addition of the iminoiodinane to the electron-rich  $\pi$ -bond of the cycloalkene system, than to the  $\pi$ -bond of the indole system, as a result of the heteroaromatic character of the latter.

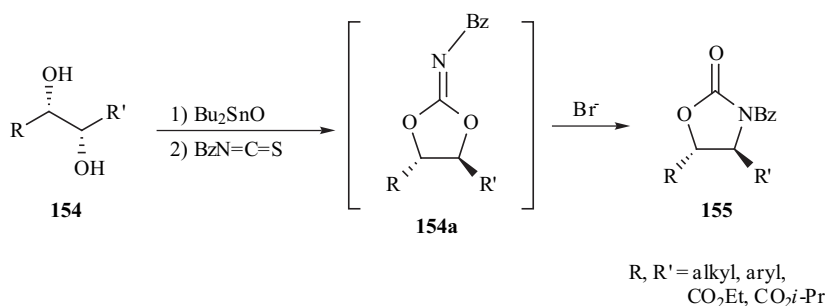
Similarly, Rojas *et al.* [112] have reported the rhodium  $[\text{Rh}_2(\text{OAc})_4]$  or copper  $[\text{Cu}(\text{CH}_3\text{CN})_4\text{PF}_6]$  or  $\text{Cu}(\text{acac})_2$ -catalyzed amidoglycosylation of allal C3-carbamates



Scheme 79.



Scheme 80.



Scheme 81.

(Scheme 79). Highly  $\beta$ -stereoselective glycosylation reactions occurred in all cases examined, whereas an anomeric mixture was obtained in the case of glucal C3-carbamates [112b].

The asymmetric intramolecular aziridination of indole carbamate **150** (Scheme 80) takes place in the presence of 10% mol of [Rh<sub>2</sub>(4S-MeOX)<sub>4</sub>] **153**, 1 equiv. of PhI(OAc)<sub>2</sub> and Al<sub>2</sub>O<sub>3</sub> [113]. Intramolecular aziridination and nucleophilic ring-opening *co-occur* to give, according to the above results [110], the oxazolidin-2-one **151** in 74% yield and 53% *ee*.

## 2.5. Miscellaneous Preparations

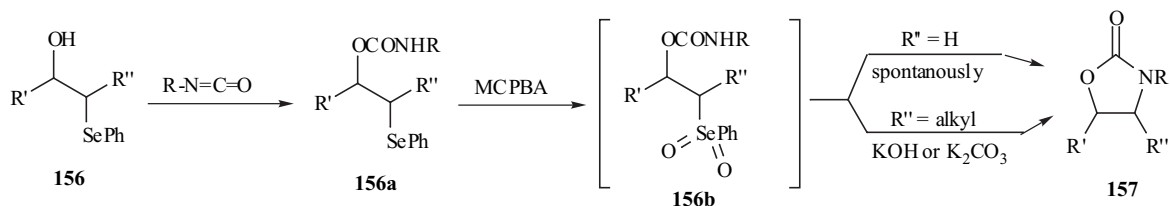
The conversion of *syn*-diols into *trans*-4,5-disubstituted oxazolidin-2-ones, reported by Ko and coworkers [114], comprehends a three-step sequence: i) activation of the starting diols **154** *via* tin ketal, ii) treatment with benzoyl isothiocyanate to form the *N*-benzoyl imonocarbonate **154a**, and iii) reaction with Bu<sub>4</sub>N<sup>+</sup> Br<sup>-</sup> at reflux to give the *N*-benzoyloxazolidin-2-ones **155** (Scheme 81).

The rearrangement occurs in a regioselective manner and the nitrogen functionality is incorporated at the  $\alpha$  position

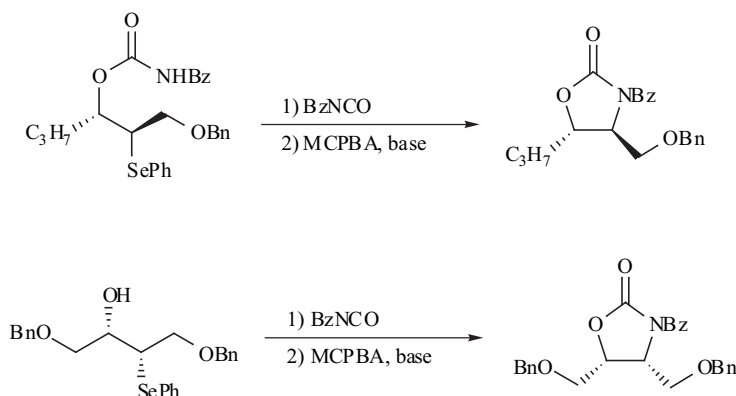
of both carbonyl and benzyl groups. Tiecco and co-workers [115] have developed a new and convenient method for the preparation of 4- and 4,5-disubstituted oxazolidin-2-ones from  $\beta$ -hydroxyalkylphenylselenides. The approach involves the initial conversion of the  $\beta$ -hydroxy-selenide **156** in the carbamate **156a**, followed by treatment with *m*-chloroperoxybenzoic acid to afford the corresponding selenone **156b** (Scheme 82a). The subsequent ring-closure to **157** occurred spontaneously or required the use of a base depending on the substrates.

The reactions occurred in good yields (60-90%) and enantiopure oxazolidin-2-ones (> 98% *ee*) are obtained from optically pure  $\beta$ -hydroxyalkylphenylselenides, with the intramolecular substitution of the phenylselenonyl group by the nitrogen atom that occurred in a stereospecific fashion with inversion of configuration at the carbon bearing the selenonyl group (Scheme 82b).

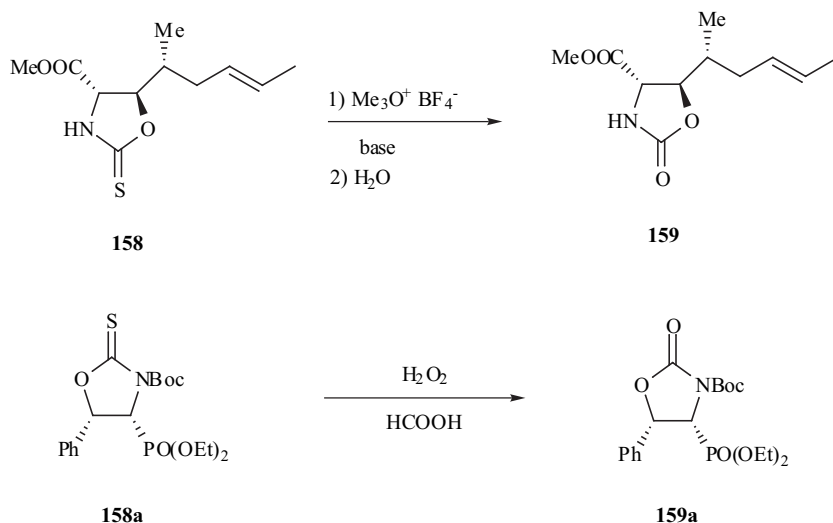
The direct conversion of thioxazolidin-2-ones, such as **158** and **158a**, into oxazolidin-2-ones has been reported using different reagent systems, such as trimethyloxonium tetrafluoroborate/base [116a], MCPBA [116b], nitronium tetrafluoroborate [116c], H<sub>2</sub>O<sub>2</sub>/HCOOH [116d,e] and Hg(OAc)<sub>2</sub> [116f] (Scheme 83).



Scheme 82a.



Scheme 82b.



Scheme 83.

### 3. SOLID-PHASE PREPARATION OF OXAZOLIDIN-2-ONES

In the last years solid phase chemistry gained rising interest within the synthetic community, as a powerful tool for the preparation of combinatorial libraries of small organic molecules [117].

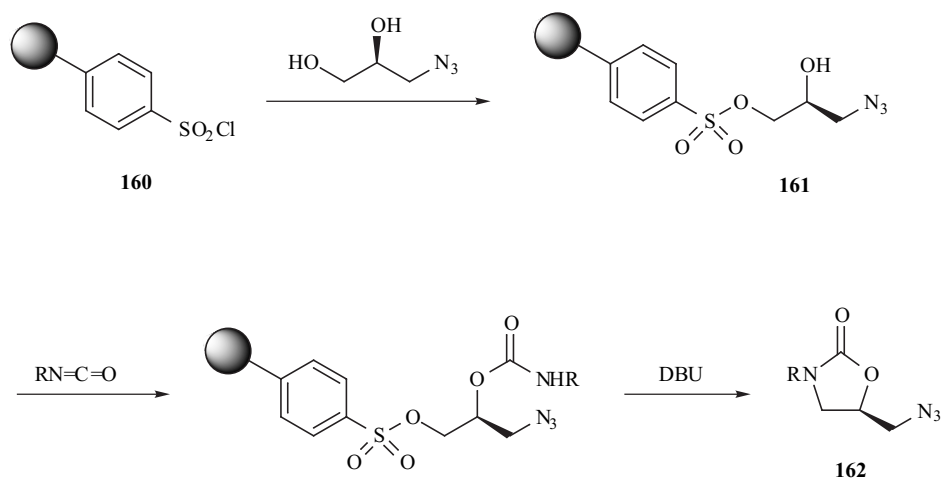
The solid-phase organic synthesis (SOPS) of substituted 1,3-oxazolidin-2-ones was investigated by different research groups. Moreover, a number of homochiral polymer bound 1,3-oxazolidin-2-ones has been prepared for the asymmetric synthesis of libraries of chiral compounds. In an elegant solid-phase synthesis of 3,5-disubstituted oxazolidin-2-ones, reported by Zwanenburg *et al.* (Scheme 84) [118], treatment of 1,2-diols with a polymer-supported sulphonyl chloride **160** gave the hydroxysulphonate **161** by selective activation of the primary alcohol function.

The reaction of **161** with the proper isocyanate and the subsequent base-promoted cycloelimination afforded enantiomerically pure N-substituted 1,3-oxazolidin-2-ones **162** in 39-43% overall yields.

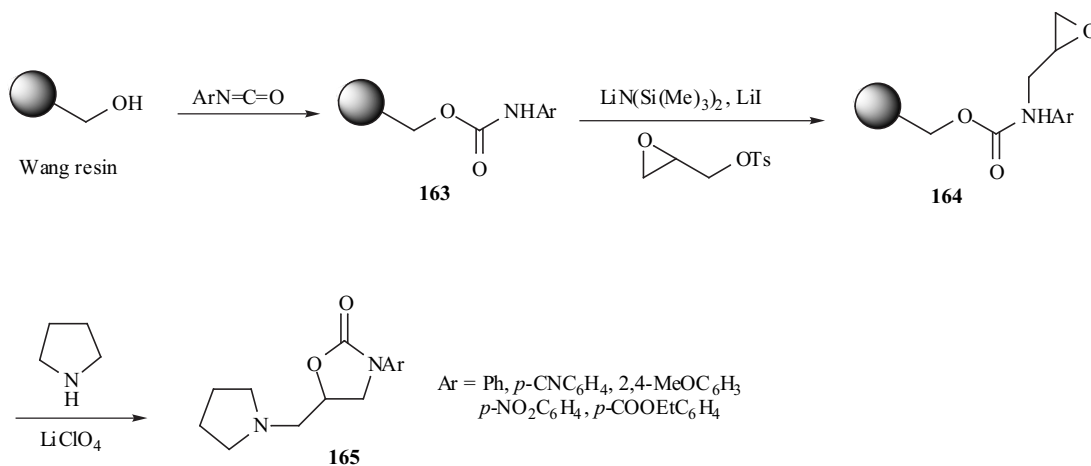
A different SOPS of oxazolidin-2-ones was based on a cyclisation/cleavage reaction (Scheme 85a) [119]: the resin-bound carbamates **163**, prepared by the reaction of Wang resin with different isocyanates, were deprotonated with  $(\text{LiN}(\text{Si}(\text{CH}_3)_3)_2)$  and alkylated with glycidyltosylate to give the epoxy-carbamates **164**.

Reaction of **164** with pyrrolidine, in the presence of  $\text{LiClO}_4$  caused the epoxyde ring-opening, the cyclisation of the amino-alcohol intermediate, and the release of the cyclic carbamates **165** from the resin. The same author recently presented a more versatile approach, which involves a lithium bromide/ $\text{Bu}_3\text{PO}$ -catalysed cycloaddition of aryl isocyanates to the resin-bound epoxides **164**, to afford the resin-bound carbamates **166** (Scheme 85b). After acidic cleavage, N-arylamino-1,3-oxazolidin-2-ones **167** were obtained in high yields and excellent purity [120].

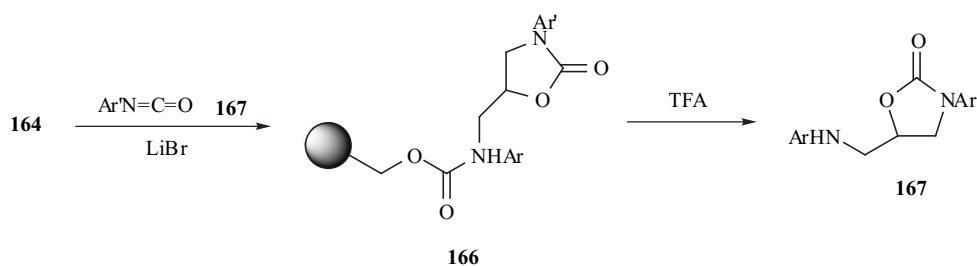
In a different approach, the alkylation of a resin-bound phenolic group **168** with racemic epichloridine was followed by conversion of the epoxide ring into azido alcohol **168a**, (Scheme 86a).



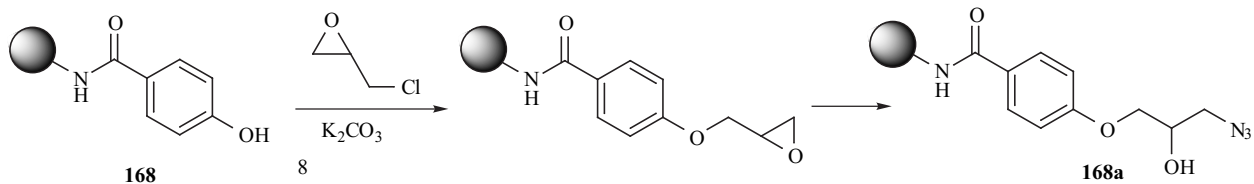
Scheme 84.



Scheme 85a.



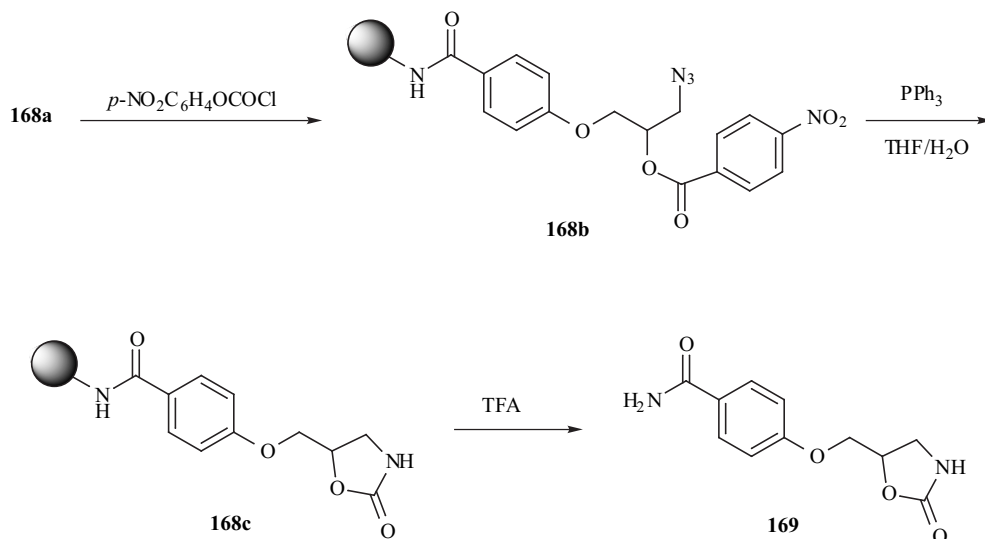
Scheme 85b.



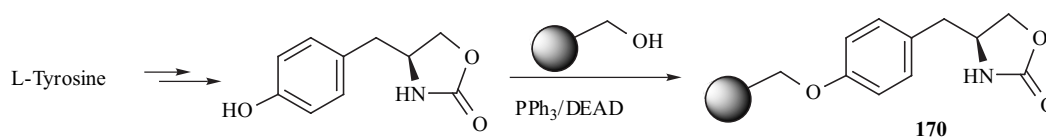
Scheme 86a.

The polymer-bound 1-azido-3-aryloxypropan-2-ol was then treated with *p*-nitrophenylchloroformate/DIPEA/DMAP, to form the azido carbonate **168b** (Scheme **86b**), which yielded directly the polymer-bound oxazolidin-2-one

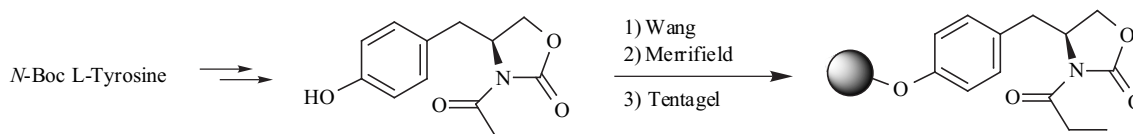
**168c** under Staudinger's conditions (PPh<sub>3</sub>, THF/H<sub>2</sub>O, 50 °C). Free oxazolidin-2-one **169** (R = H) was obtained by treatment with TFA [121].



Scheme 86b.



Scheme 87a.



Scheme 87b.

Polymer supported chiral auxiliaries based on oxazolidin-2-one framework have been prepared by several research groups. Oxazolidin-2-ones derived from L-tyrosine and L-serine have been studied as suitable chiral linkers by the side-chain hydroxyl function. Polymer-bound tyrosine-based oxazolidin-2-ones **170** have been prepared from commercial L-tyrosine following the general procedure described below in Scheme **87a**. The chiral linker was attached to Wang resin by a Mitsunobu reaction or to a chlorobenzyl Merrifield resin by a nucleophilic substitution reaction using the phenolate of the chiral auxiliary [122].

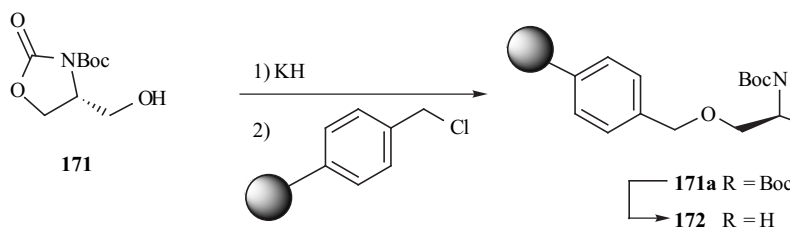
In a slightly modified procedure, Burgess *et al.* [123] reported the direct attachment of *N*-acylated tyrosine-based oxazolidin-2-one using the Mitsunobu coupling for Wang or Tentagel resins, and the nucleophilic displacement for the Merrifield's resin (Scheme **87b**).

A polymer-bound L-serine-derived oxazolidin-2-one was described for the first time by Allin and Shuttleworth [124].

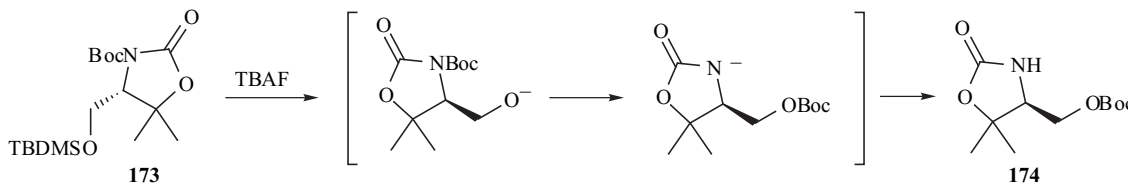
The chiral linker *N*-Boc-4-hydroxymethyl oxazolidin-2-one **171** was attached onto the polymer *via* a substitution reaction (Scheme **88a**) between the corresponding potassium alkoxide and the Merrifield's resin; the final Boc cleavage afforded **172**.

These claims have been however revised by Davies and co-workers [125] during studies addressed to the preparation of polymer-bound SuperQuats. The authors established that an N—O carbonyl exocyclic rearrangement to **174** may occur during the treatment of **173** with a solution of TBAF in THF (Scheme **88b**).

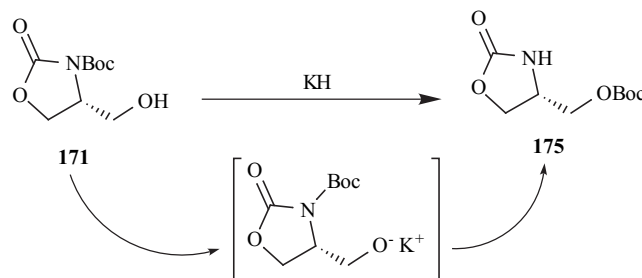
The product **174** is formed in consequence of the migration of Boc protecting group from the oxazolidin-2-one nitrogen to the side-chain oxygen. This finding was further supported when **171** gave **175** under basic conditions intended to promote the attachment of the chiral linker to the polymer (Scheme **88c**).



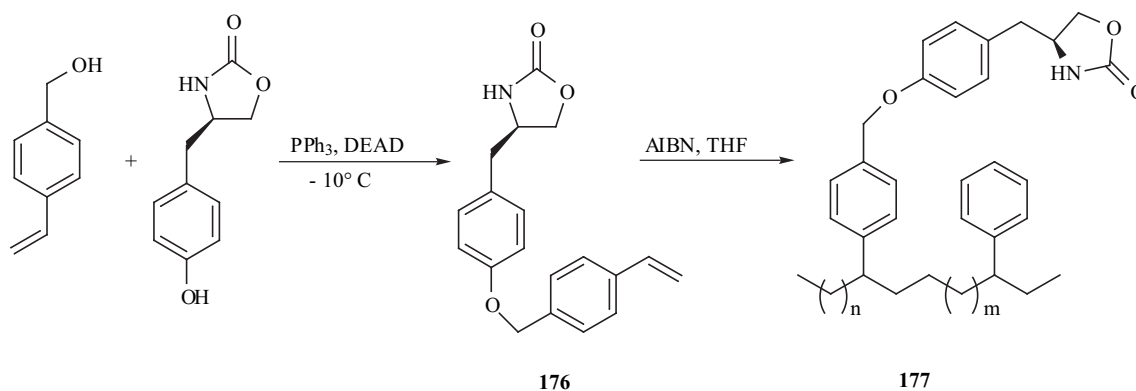
Scheme 88a.



Scheme 88b.



Scheme 88c.

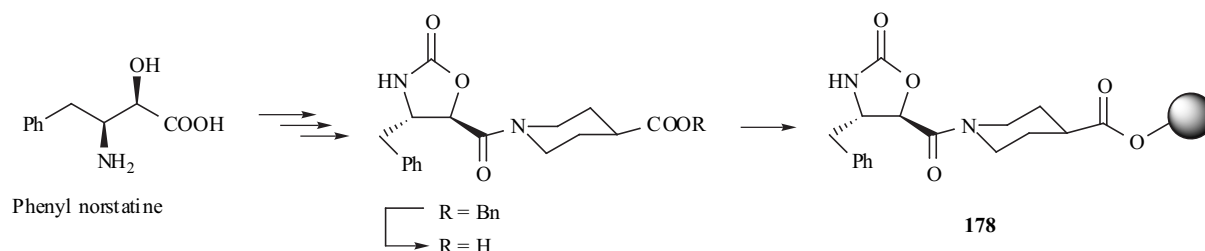


Scheme 89.

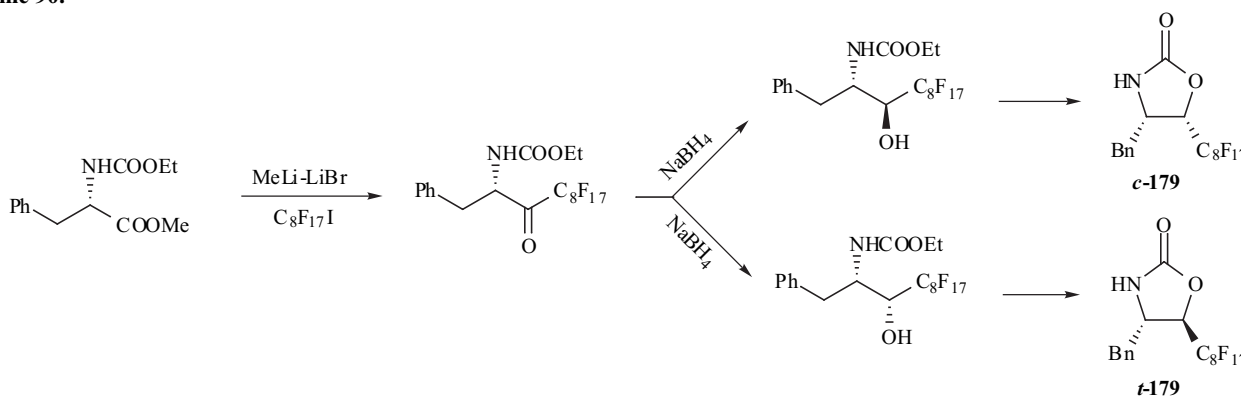
From these results Davies and co-workers concluded that, in contrast to the report of Allin and Shuttleworth [124], the oxazolidin-2-one **171** was attached to the polymer by the ring nitrogen rather than the side-chain oxygen. The only soluble polymer-bound chiral oxazolidin-2-one **177** derived from L-tyrosine, described up to now [126], was prepared by copolymerization of **176** with styrene using AIBN as a radical initiator (Scheme 89).

Polymers, incorporating 30 and 50% of monomer were prepared in good yields (>80%).

The strategy proposed by Kiso [127] to link a chiral oxazolidin-2-one unit to a solid support, differs from the tyrosine-based approach for having the chiral discriminating unit, the benzyl group, not involved in the anchoring to the resin. The new polymer-supported oxazolidin-2-one **178** (Scheme 90) was prepared from (2*R*, 3*S*)-3-amino-2-hydroxy-4-phenylbutanoic acid (phenyl norstatine), and was attached to the resin by a piperidine-4-carboxylic acid linker. Wang resin was selected as the solid-support, because the ester bond between linker and resin can be easily cleaved, allowing a facile monitoring of the reaction.



Scheme 90.



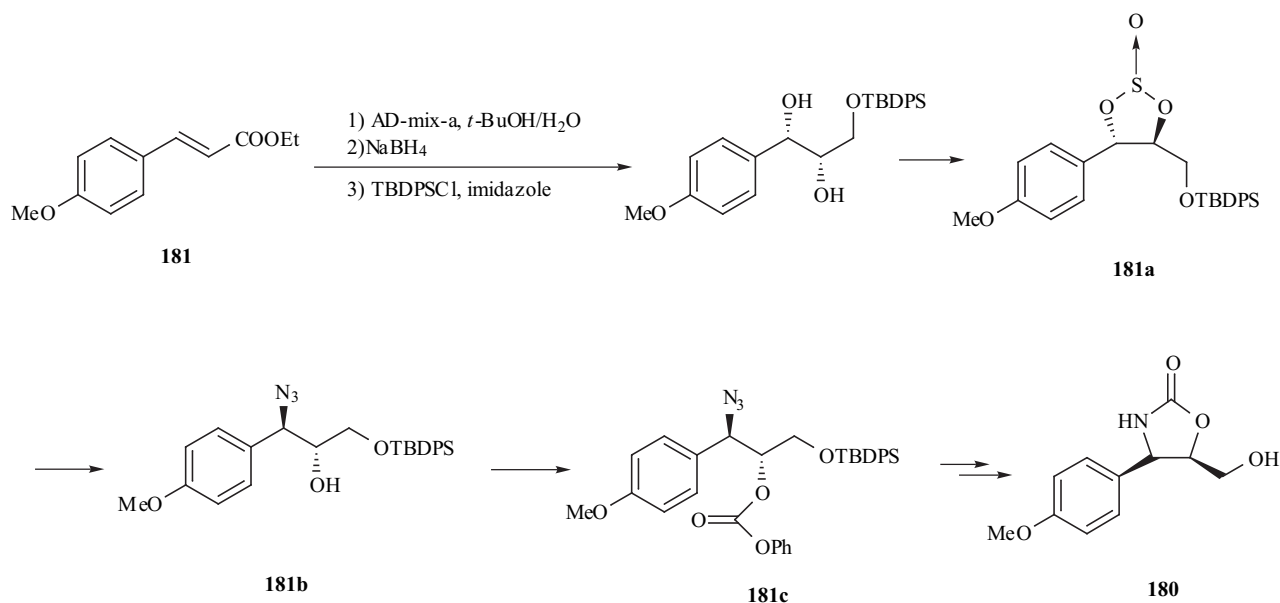
Scheme 91.

A report from Hein and Hultin [128] has disclosed the preparation and the use in asymmetric aldol reactions of the first fluorinated version of oxazolidin-2-one chiral auxiliaries. The oxazolidin-2-ones *c*-**179** and *t*-**179** were prepared from (*S*)-phenylalanine according to Scheme 91.

## 4. SYNTHESIS OF NATURAL OXAZOLIDIN-2-ONES

### 4.1 (-)-Cytoxazone

Natural products bearing an oxazolidin-2-one moiety are quite rare in the literature. One of them, (-)-cytoxazone, (4*R*,5*R*)-5-(hydroxymethyl)-4-(4-methoxyphenyl)-2-oxazolidinone (**180**), a microbial metabolite isolated from a soil sample of *Streptomyces sp.*, was shown to have cytokine-modulating activity by inhibiting selectively the signaling pathway of Th2 (but not Th1) cells [129]. The first total syntheses of **180** were reported simultaneously in 1999 by Nakata [130] and Mori [131] groups.



Scheme 92.

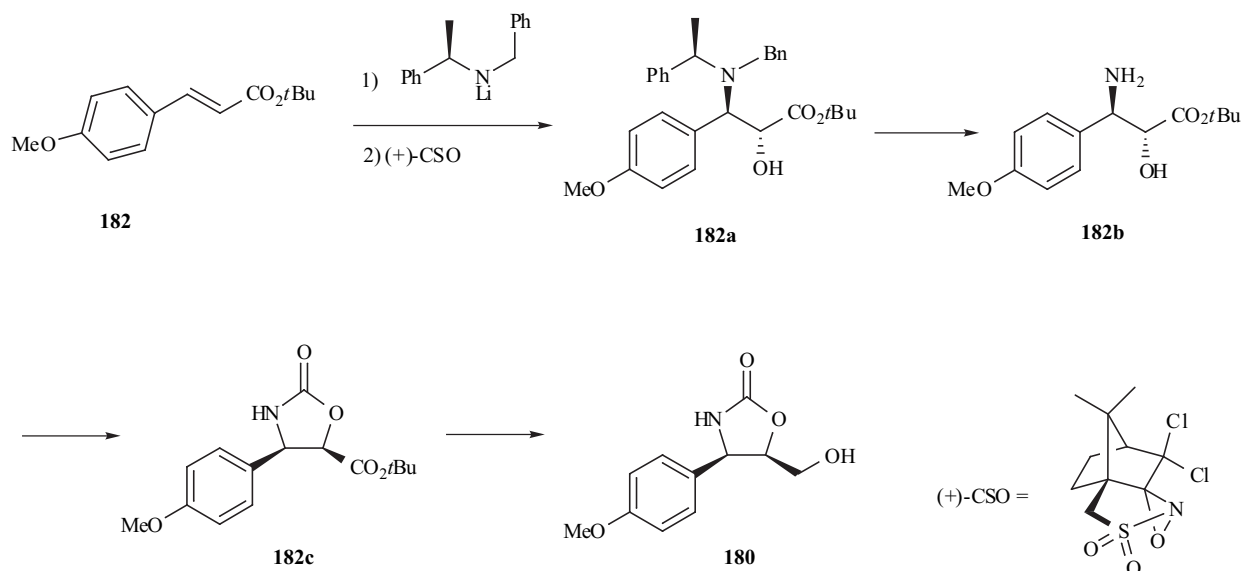
Both Nakata and Mori groups followed a similar approach starting from 4-methoxycinnamate **181**, to give the cyclic sulphite **181a**, which in turn was treated with LiN<sub>3</sub> to give the azido-alcohol **181b** in high yields. Nakata thus prepared (-)-cytoxazone **180** through *i*) conversion of **181b** into the corresponding phenyl carbonate **181c** and *ii*) treatment of the latter with Ph<sub>3</sub>P in THF/H<sub>2</sub>O, whereas Mori performed the synthesis by *ii*) conversion of **181b** into the corresponding aminoalcohol and *iii*) subsequent cyclization (Scheme 92).

Cytosazone maintained a high level of interest as it is testified by the number of syntheses [132] published during the last years. Among the several syntheses of **180** and of its stereoisomers, few more will be now cited.

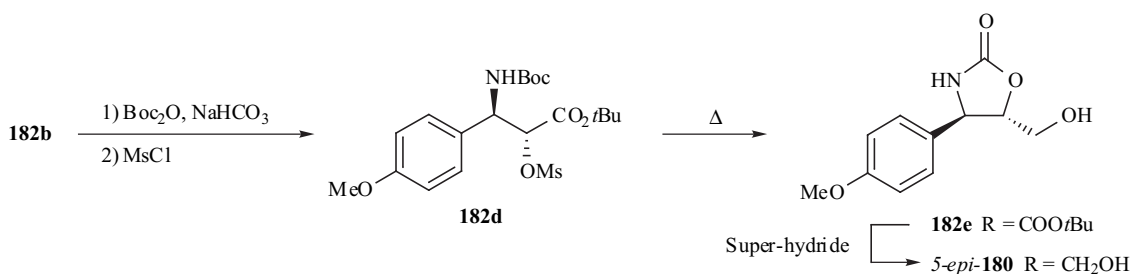
Davies [132b] reported a four steps preparation of **180** in 61% overall yield and with *ee* > 98% (Scheme 93a). The

approach was based on the conjugate addition of (*R*)-lithium *N*-benzyl-*N*- $\alpha$ -methylbenzylamide to the cinnamate **182** and *in situ* diastereoselective enolate oxidation with (+)-(camphorsulfonyl)oxaziridine, (+)-CSO, to give the (2*R*, 3*R*,  $\alpha$ *R*)- $\alpha$ -hydroxy- $\beta$ -amino ester **182a** in 79% and 98% *ee*. The subsequent hydrogenolysis (H<sub>2</sub>, 5atm) with Perlmann catalyst afforded the partially protected (2*R*,3*R*)- $\alpha$ -hydroxy- $\beta$ -amino ester **182b**, which was converted into the oxazolidin-2-one **182c** with diphosgene. The final reduction of the ester function into the hydroxymethylene group was achieved in 92% yield by the Chamberland procedure [133].

Conversely, (4*R*, 5*S*)-5-*epi*-cytoxazone (5-*epi*-**180**) was prepared by heating a DMF solution of the *O*-Ms *N*-Boc **182d**, to give in 77% yield the *trans*-oxazolidin-2-one **182e**, and by reducing the ester group with lithium triethylborohydride (Scheme 93b).



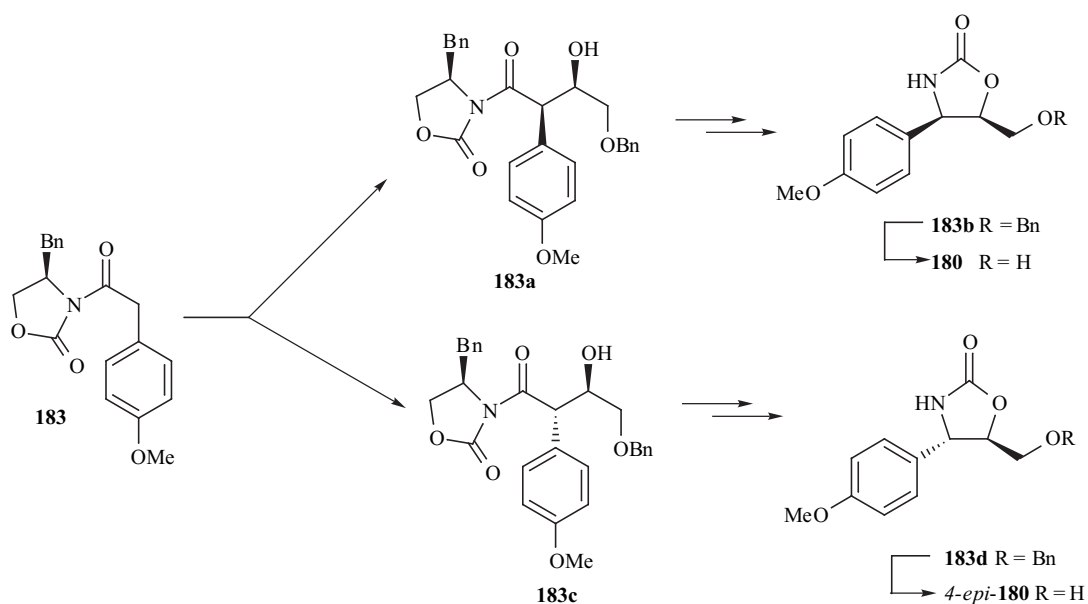
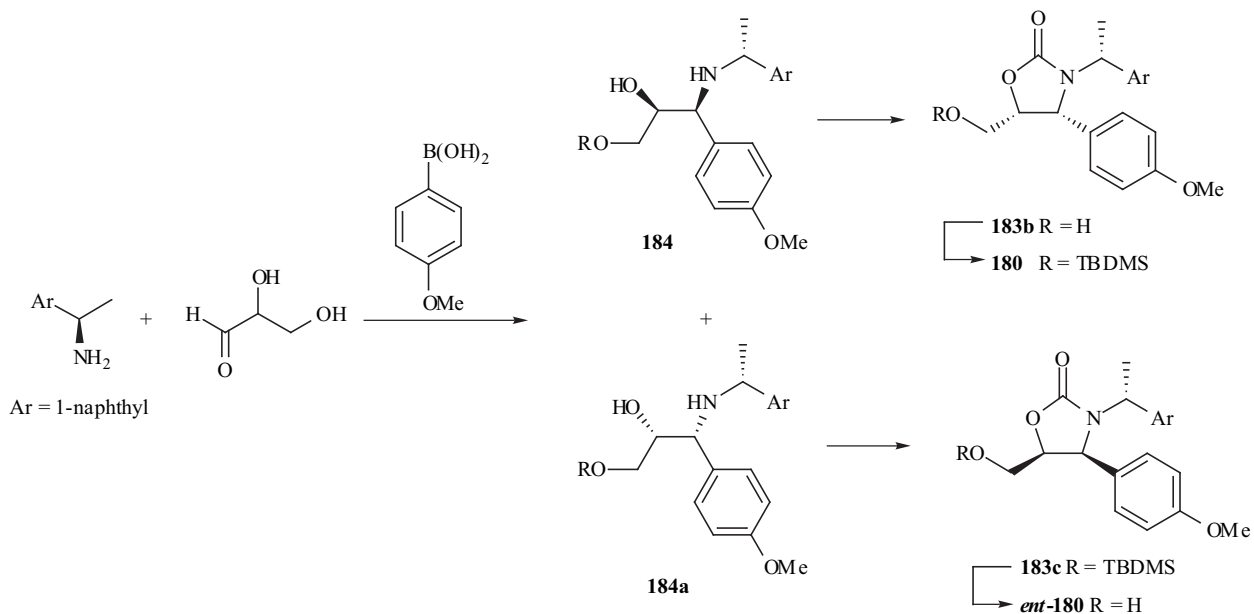
Scheme 93a.

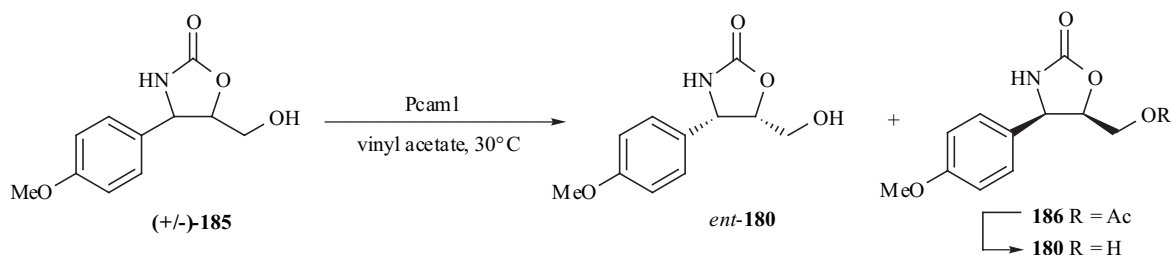
**Scheme 93b.**

The stereoselective synthesis of Carter *et al.* [132g] utilized an aldol/Curtius sequence of reactions: i) the chiral imide **183** provided with benzyloxyacetaldehyde the aldol **183a** with good (> 95:5) *syn*-diastereoselectivity; ii) removal of the chiral auxiliary from **183a** gave a hydroxy acid, which was converted into the oxazolidin-2-one **183b** by a Curtius

rearrangement; iii) final debenzoylation of **183b** with  $\text{Pd}(\text{OH})_2$ ,  $\text{H}_2$  (1 atm) afforded enantiomerically pure (-)-cytoxazone **180** (Scheme 94).

4-*epi*-cytoxazone, 4-*epi*-**180**, was prepared from the reaction of **183** with benzyloxyacetaldehyde, following the

**Scheme 94.****Scheme 95.**



Scheme 96.

Heathcock procedure, which gave the *anti*-adduct **183c** in 75:25 ratio. Pure **183c** was finally transformed into 4-*epi*-**180** by standard methods (Scheme 94).

The Petasis three-component coupling reaction [132e] was utilized to prepare both enantiomers of cytoxazone (Scheme 95). By holding DL-glyceraldehyde, boronic acid and (*R*)-1-(1-naphthyl)ethylamine in EtOH at reflux, a 1:1 mixture of the two stereoisomers **184** and **184a** was obtained in 54% yield; the two amino-diols were separated and converted in one-pot reaction into the corresponding oxazolidin-2-ones after removal of the 1-(1-naphthyl)ethyl group.

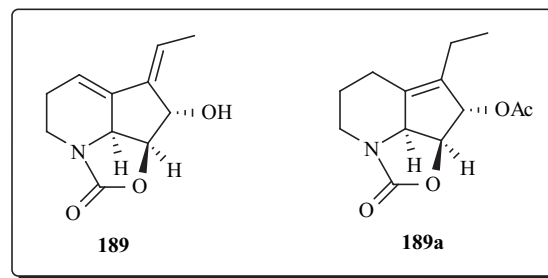
A chemoenzymatic synthesis (Scheme 96) of the (-)-cytoxazone and its (+)-isomer was also achieved by kinetic resolution of **(+/-)-185** with *Penicillium camambertii* (PcamI): for a 50.6% conversion, the *ee* of the alcohol **ent-180** was 89.3%, whereas the *ee* of the acetate **(-)-186** was 88.2%. Crystallization increased to 95.2% the *ee* of **ent-180**, while the natural isomer **180** was obtained also with a 95.2% *ee* after acetate hydrolysis and crystallization [132j].

The Naito's group studied the imino 1,2-Wittig rearrangement of hydroximates as a base for an original synthesis of cytoxazone [132d]. Upon treatment of the *Z*-hydroximate **187** with LDA, a stereoselective rearrangement took place to afford the *Z*-2-hydroximate ether **187a** in 82% yield (Scheme 97). Two different reaction pathways have been proposed by the authors, an ionic addition-elimination

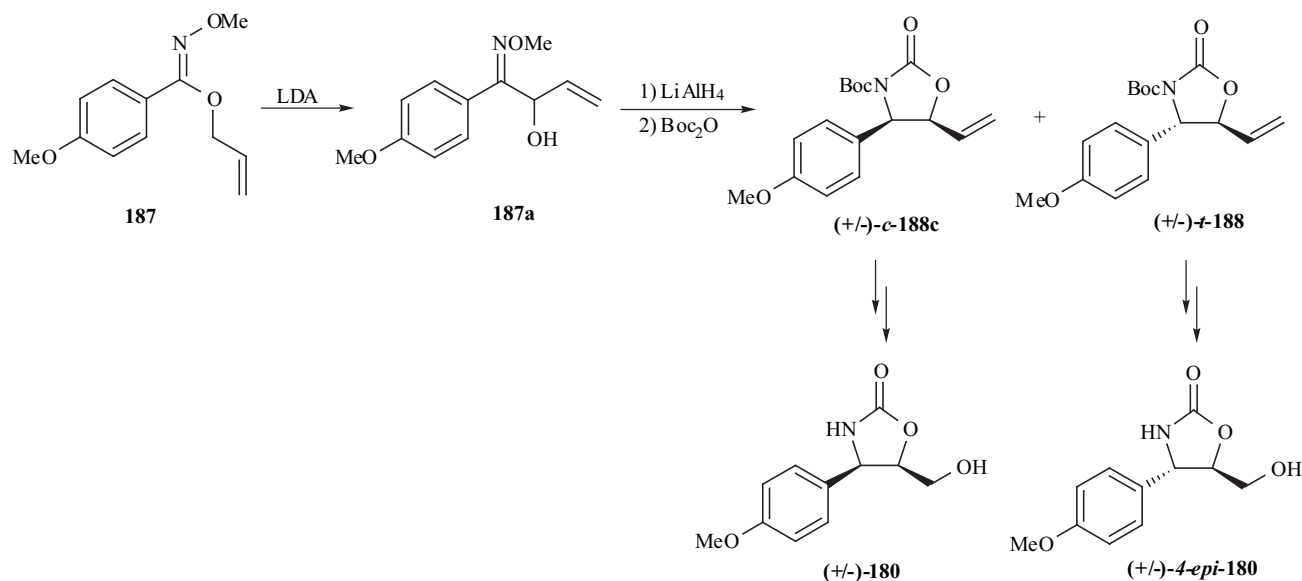
process or a radical dissociation-recombination mechanism; however no definitive results have been reported. The synthesis of cytoxazone was instead accomplished by LiAlH<sub>4</sub> mediated reduction of the hydroxyoxime **187b** to give a crude amino-alcohol which was acylated with (Boc)<sub>2</sub>O to give a 2:1 mixture of *cis* and *trans*-oxazolidin-2-ones **c-188c** and **t-188c**, as a major product. The two compounds were converted after separation into the **(+/-)**-cytoxazone and the **(+/-)**-4-*epi* isomer **172**. The racemic mixtures were optically resolved by standard methods.

#### 4.2. (+)-Streptazolin

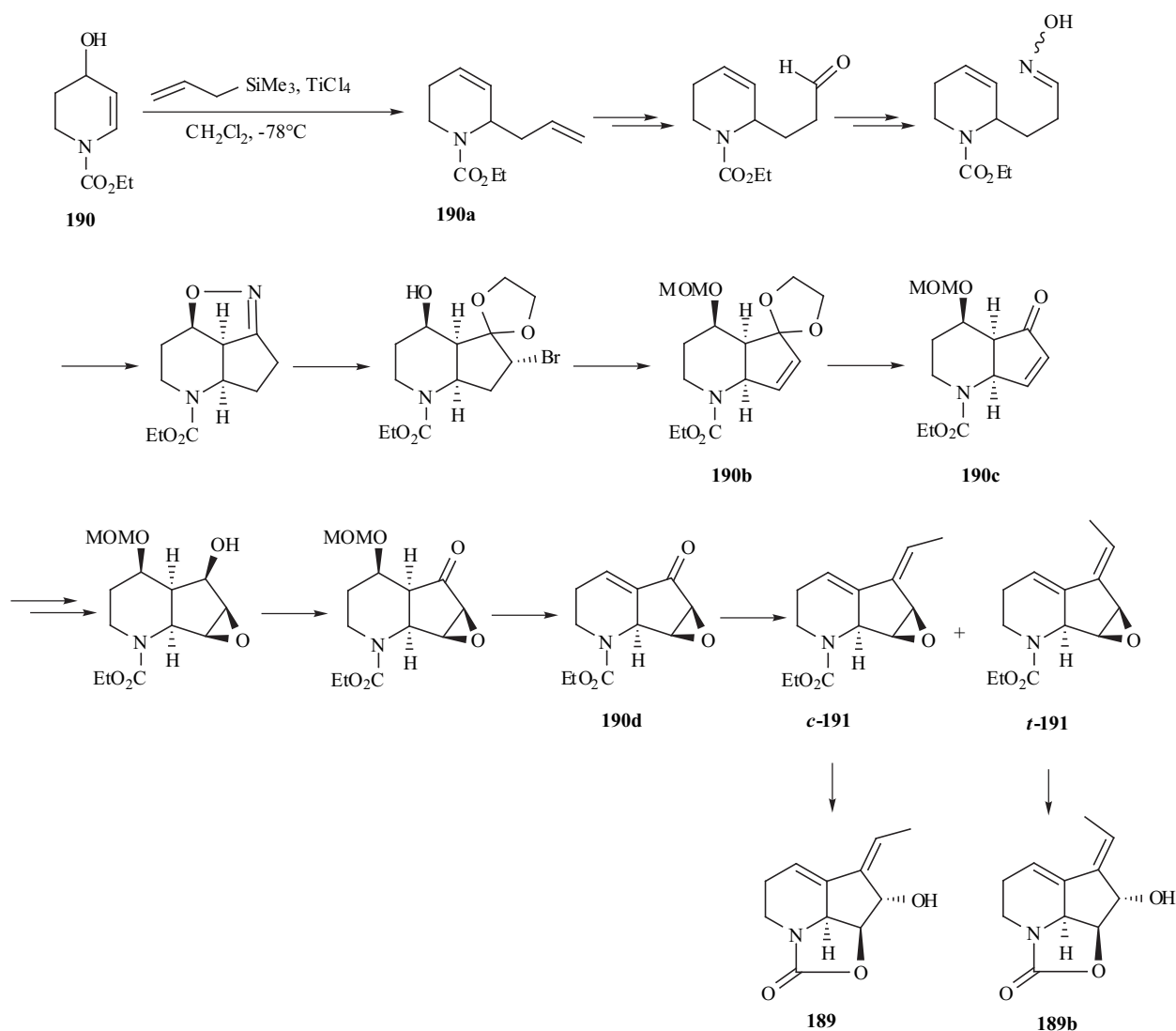
(+)-Streptazolin **189**, a lipophilic neutral tricyclic compound, was first isolated by Drautz *et al.* in 1981 from a culture of *Streptomyces viridochromogenes* [134].



The more stable *O*-acetyl dihydrostreptazolin **189a**, obtained by catalytic hydrogenation and acetylation was used



Scheme 97.

**Scheme 98.**

for the structural investigation, based on NMR spectral data, chemical degradation and X-ray analysis. In spite of the low antimicrobial activity exhibited by streptazolin, some Diels-Alder adducts of the compound with naphthoquinones have been reported to possess antitumor activity comparable to that of adriamycin on leukemia L1210 cells [135].

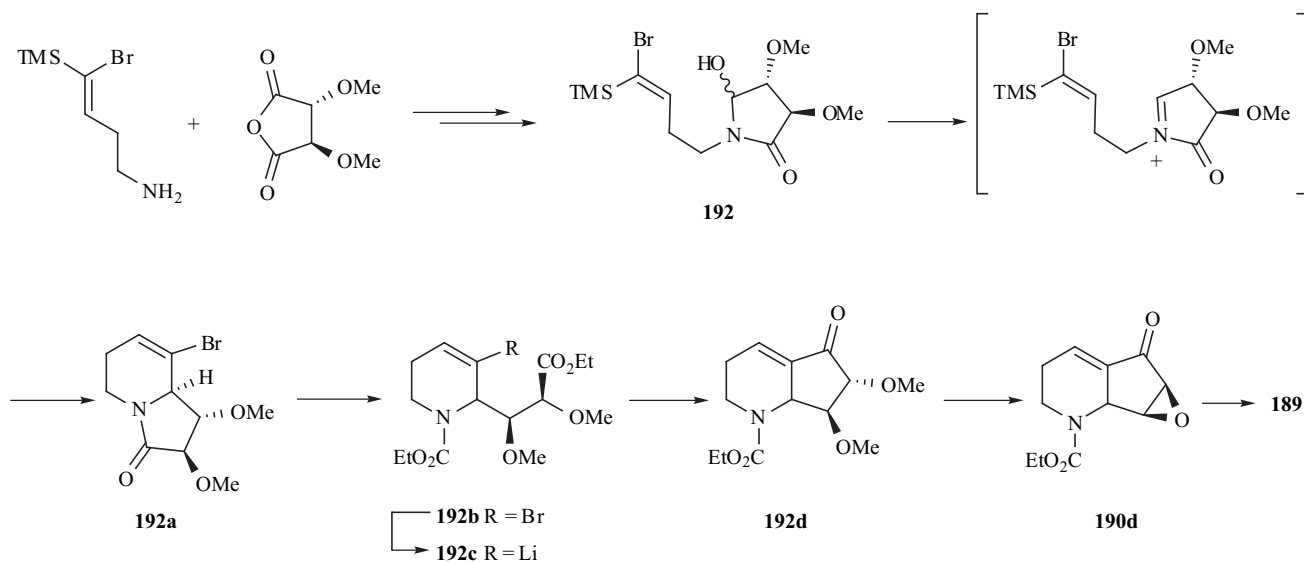
The first total synthesis of streptazolin in racemic form has been reported by Kozikowski and Park [136]. The synthetic approach (Scheme 98) was based essentially on the following steps:

i) Ferrier rearrangement of  $\Delta^2$ -piperidinol **190** with allyl trimethylsilane to prepare the intermediate **190a**; ii) intermolecular nitride (INOC) [2+3]-cycloaddition for the construction of the azabicyclo[4.3.0]-framework; iii) opening of the oxazolidinone ring and introduction of the C7-C8 double bond to give the fully protected azabicyclo derivative **190b**; iv) conversion of **190b** into the enantiomerically pure allylic alcohol **190c**; v) epoxidation of **190c** with 3,5-dinitroperbenzoic acid followed by conversion into the  $\alpha,\beta$ -unsaturated ketone **190d**; vi) Wittig condensation, to produce a separable diastereomeric mixture of *E/Z* olefins; vii) epoxide ring opening with  $\text{NaOAc}/\text{AcOH}$

and formation of the oxazolidin-2-ones **c-191** and **t-191** with the inclusion of the urethane carbonyl group; viii) final hydrolysis ( $\text{MeONa}/\text{MeOH}$ ) to give streptazolin **189** and its isomer **189b**.

The total synthesis (7% overall yield) confirmed the structure assignment of streptazolin, and, in particular, the stereochemistry of the exocyclic olefin, a feature that had not been rigorously assigned in the analytical work.

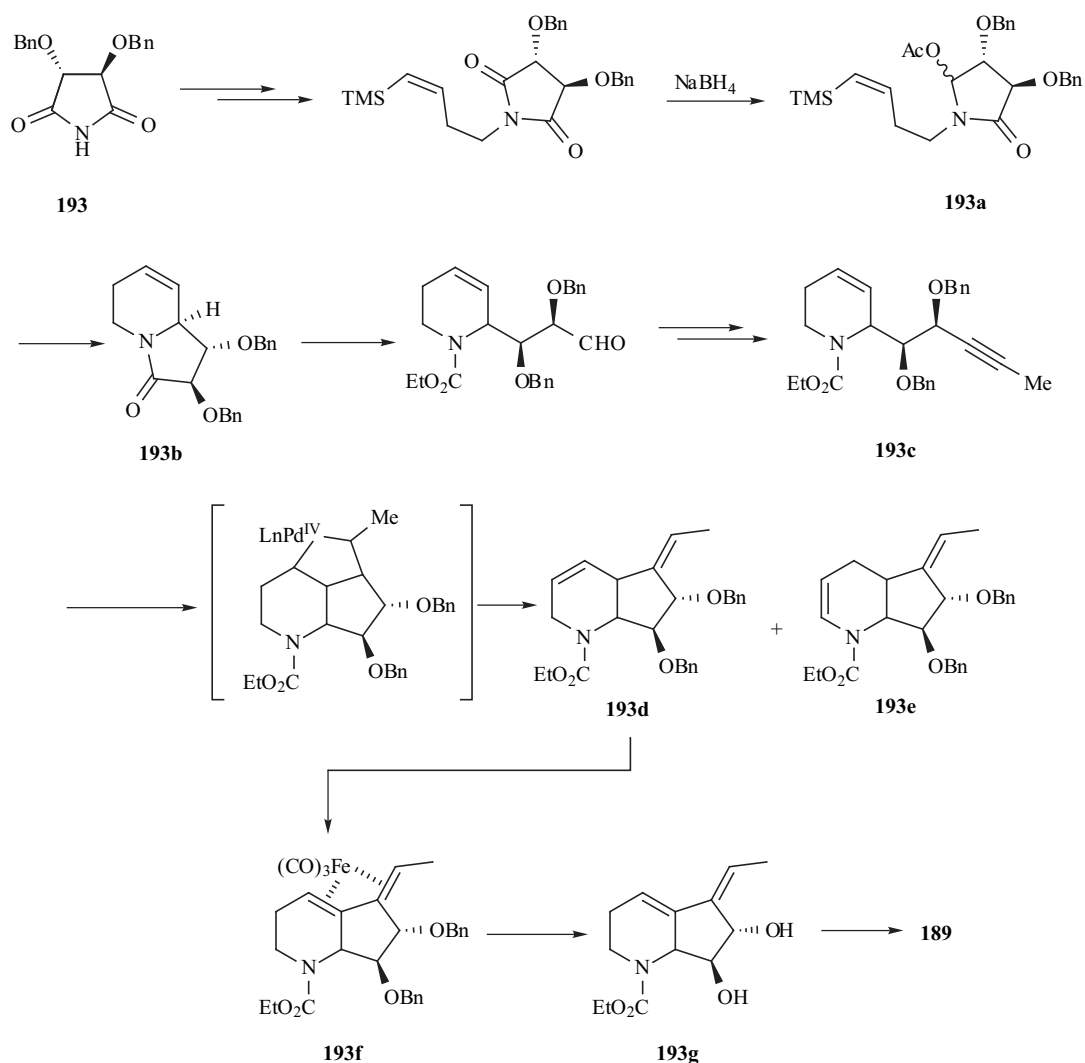
The enantioselective synthesis, performed by Overmann and Flann [137] and starting from L-tartaric acid, is characterized by a ring-closure reaction of the imide **192** at reflux in trifluoroacetic acid to afford the bicyclo-derivative **192a** as a single product. The intermediate **183a** was then converted by standard transformations into the crystalline carbamate **192b**, which, by treatment with *sec*-butyl lithium at  $-78^\circ\text{C}$ , provided *via* a vinyllithium derivative **192c** the bicyclic enone **192d** in 60-70% yields (Scheme 99). The treatment of **192d** with  $\text{BBR}_3$  at  $0^\circ\text{C}$  afforded, in enantiomerically pure form, the epoxy-ketone **190d** which was finally converted to (+)-streptazolin by the three steps sequence developed by Kozikowski and Park [136].



Scheme 99.

The enantioselective synthesis of Kibayashi and co-workers [138], resting on a palladium-catalyzed enyne

bicyclization, starts from the chiral succinimide derivative 193 (Scheme 100).



Scheme 100.

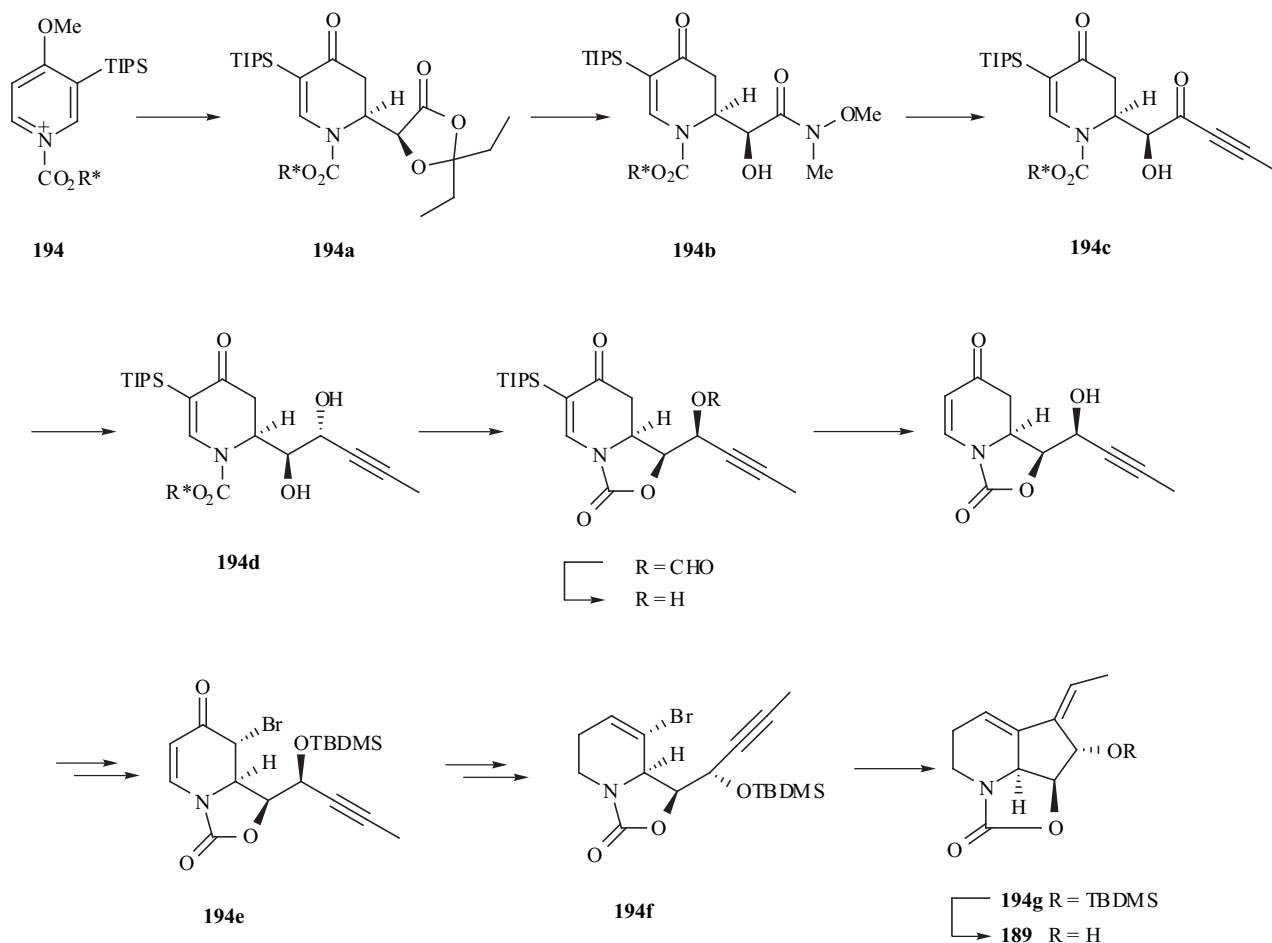
The enyne **193c** was prepared from **193a**, through the *N*-acyliminium ion cyclization of the acetoxy lactam **193b**, followed by partial reduction of the amide function, conversion into the dibromo olefin and final treatment with *n*-BuLi and then iodomethane. The bicyclization of **193c** was carried out with 30% Pd(OAc)<sub>2</sub> and *N,N'*-bis(benzylidene)-ethylenediamine (BBEDA) as the ligand at reflux in benzene, to give in 84% yield a 93:7 mixture of the 1,2,4 $\alpha$ ,7 $\alpha$ ,6,7-hexahydro-5H-1-pyridine (*Z*)-**193d** together with the isomerized product (*Z*)-**193e**. The isomerization of the 1,4-diene of **193d** to the 1,3-diene system was obtained by treatment with 2 equiv of triiron dodecacarbonyl to yield the stable complex **193f**. Exposure to BBr<sub>3</sub> caused the removal of both the Fe(CO)<sub>3</sub> fragment and the benzyl protecting groups, to give the diol **193g**, which was finally converted to (+)-streptazolin **189** (4.3% overall yield) under basic conditions.

The chiral pyridinium salt **194** was the starting material for the asymmetric synthesis of **181** described by Comins [139] (Scheme 101). The reaction of **194** with the zinc enolate derived from 2,2-diethyl-1,3-dioxolan-2-one afforded in 76% yield the enantiomerically pure *N*-acyldihydropyridone **194a**, which was converted to the Weinreb's amide **194b** [140] by standard transformations. Addition of propynyllithium afforded the hydroxy-ketone **194c**, which was reduced to the *anti* diol **194d**, according to the Luche procedure [141].

Notably, the last three steps occurred without side reactions at the enone functionality, probably for the presence of the bulk TIPS group. A basic-promoted cyclization introduced the oxazolidin-2-one moiety, while the inversion of configuration at the stereogenic center of the free hydroxyl group was achieved under Mitsunobu conditions. Standard reactions yielded the vinyl bromide **194e**, as a base for further elaboration to the tricyclic framework (in **194f**) via a palladium promoted Grigg's cyclization. Final cleavage of the silyl protecting group from **194g** provided (+)-streptazolin **189**.

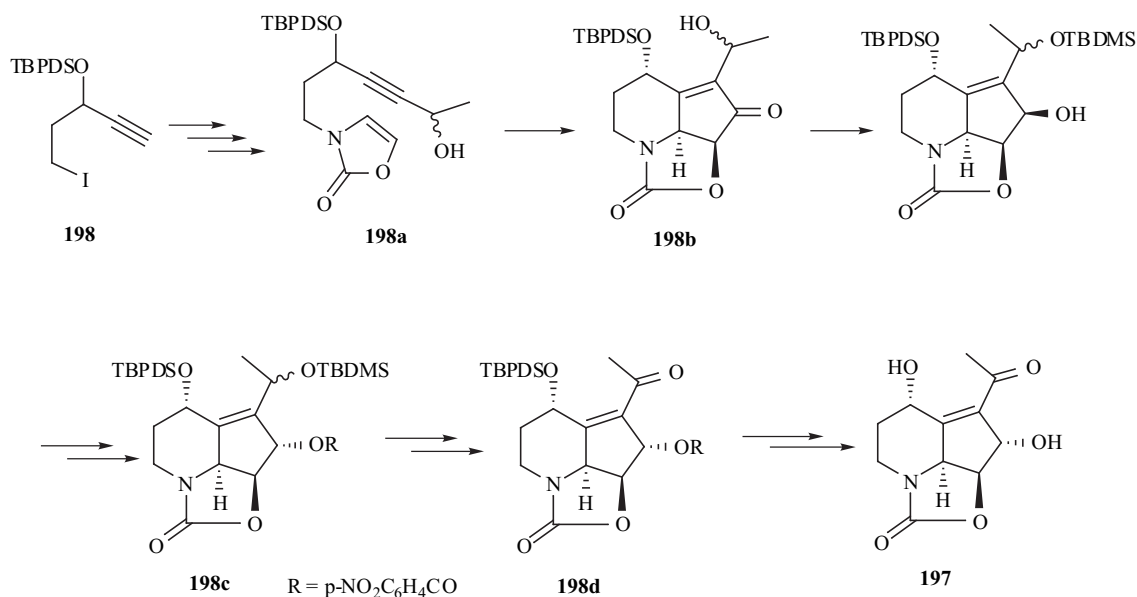
An efficient, atom-economical [142] preparation of (+)-streptazolin, based on a palladium-catalyzed reductive diyne cyclization as the key step, has been reported by Trost [143] (Scheme 102).

A classical procedure, starting from the commercially available D-mannitol diacetonide **195**, afforded the 4,5-disubstituted oxazolidin-2-one **195a**. The primary alcohol of **195a** was oxidized (Swern) to the corresponding aldehyde and the reaction mixture was treated with an excess amount of propynyl magnesium bromide in the presence of zinc chloride at -78°C to afford the diastereomeric secondary alcohols **195b**, as a 6:1 mixture in favor of the desired chelation-oriented product (Scheme 102). The diene **195c** was obtained in 61% yield, by treatment of **195b** with a catalytic amount (2.5%) of Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub>, HCOOH, Et<sub>3</sub>SiH, according to the "ligandless" reductive cyclization



Scheme 101.





Scheme 104.

The intermediate **198b** was converted to the target molecule by the following steps: a) protection of the secondary alcohol with the TBDMS group; b) stereoselective reduction of the carbonyl group; c) inversion of the C7-hydroxyl group under Mitsunobu conditions; d) removal of the TBDMS group and oxidation of the free secondary alcohol under Dess-Martin conditions and e) final hydrolysis of the *p*-nitrobenzoate **198c** and desilylation of **198d** to afford **197**.

## REFERENCES

- [1] For earlier reviews see: Evans, D.A.; Takacs, J. M.; McGee, L. R.; Ennis, M. D.; Mathre, D. J.; Bartroli, J. *Pure Appl. Chem.* **1981**, *53*, 1109; Evans, D. A. C. *Aldrichim. Acta* **1982**, *15*, 23.
- [2] For a review on Linezolid see: Barbachyn, M.R.; Ford, C.W. *Angew. Chem. Int. Ed.* **2003**, *42*, 2010.
- [3] a) Dyen, M. A.; Swern, D., *Chem. Rev.* **1967**, *67*, 197; b) Ager, D. J.; Prakash, I.; Schaad, D. R. *Aldrichim. Acta* **1997**, *30*, 3; Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835.
- [4] For a recent review: Bergmeier, S.C. *Tetrahedron* **2000**, *56*, 2561.
- [5] a) Makoto, S.; Tetsuya, S. *Chem. Lett.* **2002**, 808; b) Seki, M.; Shimizu, T.; Matsumoto, K. *J. Org. Chem.* **2000**, *65*, 1298; c) Sibi, M.P.; Renhowe, P.A. *Tetrahedron Lett.* **1990**, *31*, 7407; d) Sibi, M.P.; Deshapande, P.K.; Ji, J. *Tetrahedron Lett.* **1995**, *36*, 8965.
- [6] a) Bunnage, M.E.; Burke, A.J.; Davies, S.G.; Millican, N.L.; Nicholson, R.L.; Roberts, P.M.; Smith, A.D. *Org. Biomol. Chem.* **2003**, *1*, 3708. b) Ma, S.; Zhao, S. *J. Am. Chem. Soc.* **2001**, *123*, 5578; c) Matsunaga, S.; Kumagai, N.; Harada, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 4712; d) f) O'Hagan, D.; Tavasli, M. *Tetrahedron: Asymmetry* **1999**, *10*, 1189; e) Tamura, O.; Hashimoto, M.; Kobayashi, Y.; Katoh, T.; Nakatani, K.; Kamada, M.; Hayakawa, I.; Akiba, T.; Terashima, S. *Tetrahedron Lett.* **1992**, *33*, 3497; f) Pridgen, L.N.; Prol, J., Jr.; Alexander, B.; Gillyard, L. *J. Org. Chem.* **1989**, *54*, 3231.
- [7] a) O'Hagan, D.; Royer, F.; Tavasli, M. *Tetrahedron: Asymmetry* **2000**, *11*, 2033; b) Pojarliev, P.; Biller, W.T.; Martin, H.J.; List, B. *Synlett* **2003**, 12, 1903; c) Petrini, M.; Profeta, R.; Righi, P. *J. Org. Chem.* **2002**, *67*, 4530; d) Lindsay, K.B.; Pyne, S.G. *J. Org. Chem.* **2002**, *67*, 7774; e) Delle Monache, G.; Misiti, D.; Salvatore, P.; Zappia, G. *Chirality* **2000**, *12*, 143; f) Sibi, M.P.; Rutherford, D.; Renhowe, P.A.; Li, B. *J. Am. Chem. Soc.* **1999**, *121*, 7509; g) Gibson, C.L.; Gillon, K.; Cook, S. *Tetrahedron Lett.* **1998**, *39*, 6733.
- [8] Huebner, C. F.; Donoghue, E. M.; Novak, C. J.; Dorfman, L.; Wenkert E. *J. Org. Chem.* **1970**, *35*, 1149.
- [9] Mellon, D.; Gravier-Pelletier, C.; Le Merrer, Y.; Depezay, J.C. *Bull. Soc. Chim. Fr.* **1992**, *129*, 585.
- [10] a) Nicolas, E.; Russell, K.C.; Hruby, V.J. *J. Org. Chem.* **1993**, *58*, 766; b) Guerlavais, V. Carroll, P.J., Jollie, M.M. *Tetrahedron: Asymmetry* **2002**, *13*, 675; c) Green, R.; Taylor, P.J.; Bull, S.D.; James, T.D.; Mahon, M.F.; Merritt, A.T. *Tetrahedron: Asymmetry* **2003**, *14*, 2619.
- [11] Montgomery, J.; Wieber, G.M.; Hegedus, L.S. *J. Am. Chem. Soc.* **1990**, *112*, 6255.
- [12] a) Lohray, B.B.; Baskaran, S.; Rao, B.S.; Reddy, Y.; Rao, N. *Tetrahedron Lett.* **1999**, *40*, 4855; b) Barco A.; Benetti S.; Bergamini P.; De Risi C.; Marchetti P.; Pollini G. P.; Zanirato V. *Tetrahedron Lett.* **1999**, *40*, 7705; c) Carda, M.; Murga, J.; Rodriguez, S.; González, F.; Castillo, E.; Marco, J.A. *Tetrahedron: Asymmetry* **1998**, *9*, 1703; d) Davies, S.G., Fenwick, D.R.; Ichihara, O. *Tetrahedron: Asymmetry* **1997**, *8*, 3387.
- [13] Cutugno, S.; Martelli, G.; Negro, L.; Savoia, D. *Eur. J. Org. Chem.* **2001**, 517.
- [14] a) Gabriele, B.; Mancuso, R.; Salerno, G.; Costa, M. *J. Org. Chem.* **2003**, *68*, 601; b) Gabriele, B.; Salerno, G.; Costa, M.; Chiusoli, G. P. *J. Organomet. Chem.* **2003**, *687*, 219; c) Gabriele, B.; Salerno, G.; Brindisi, D.; Costa, M.; Chiusoli, G. P. *Org. Lett.* **2000**, *2*, 625; d) Tam, W. *J. Org. Chem.* **1986**, *51*, 2977; e) Imada, Y.; Mitsue, Y.; Ike, K.; Washizuka, K.-I.; Murahashi, S.-I. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 2079.
- [15] Chiarotto, I.; Feroci, M. *Tetrahedron Lett.* **2001**, *42*, 3451.
- [16] a) Feroci, M.; Gennaro, A.; Inesi, A.; Orsini, M.; Palombi, L. *Tetrahedron Lett.* **2002**, *43*, 5863; b) Casadei, M. A.; Feroci, M.; Inesi, A.; Rossi, L.; Sotgiu, G. *J. Org. Chem.* **2000**, *65*, 4759; c) Feroci, M.; Inesi, A.; Mucciantante, V.; Rossi, L. *Tetrahedron Letters* **1999**, *40*, 6059; d) Inesi A.; Mucciantante, V.; Rossi, L. *J. Org. Chem.* **1998**, *63*, 4759; e) Casadei, M. A.; Micheletti, F.; Inesi, A.; Zappia, G.; Rossi, L. *J. Org. Chem.* **1997**, *62*, 6754.
- [17] Mizuno, T.; Takahashi, J.; Ogawa, A. *Tetrahedron* **2002**, *58*, 7805.
- [18] Knölker, H.-J.; Braxmeier, T. *Tetrahedron Lett.* **1996**, *37*, 5861.
- [19] Knölker, H.-J.; Braxmeier, T.; Schlechtingen, G. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2497.
- [20] Dinsmore, C.J.; Mercer, S. *Org. Lett.* **2004**, *6*, 2885.
- [21] Kodaka, M.; Tohomiro, T.; Okuno, H. *J. Chem. Soc. Chem. Commun.* **1993**, 81.
- [22] a) Mitsunobu, O. *Synthesis* **1981**, 1; b) Hughes, D.L. *Org. Prep. Proceed. Int.* **1996**, *28*, 127.
- [23] Kano, S.; Yokomatsu, T.; Iwasawa, H.; Shibuya, S. *Tetrahedron Lett.* **1987**, *28*, 6331.
- [24] a) Delle Monache, G.; Di Giovanni, M.C.; Misiti, D.; Zappia, G. *Tetrahedron: Asymmetry* **1997**, *8*, 231; b) Ghosh, A. K.; Shin, D.; Mathivanan, P. *Chem. Commun.* **1999**, 1025; c) Benedetti, F.; Berti F.; Norbedo, S. *J. Org. Chem.* **2002**, *67*, 8635.

- [25] a) Williams, L.; Zhang, Z.; Shao, F.; Carroll, P. J.; Joullé, M. *Tetrahedron* **1996**, *52*, 11673; b) De Paolis M.; Blankenstein J.; Bois-Choussy, M.; Zhu, J. *Org. Lett.* **2002**, *4*, 1235.
- [26] a) Benedetti, F.; Norbedo, S. *Tetrahedron Lett.* **2000**, *41*, 10071; b) Tossi, A.; Benedetti, F.; Norbedo, S.; Skrbec, D.; Berti, F.; Romeo, D. *Biorg. Med. Chem.* **2003**, *11*, 4719.
- [27] Madhusudhan, G.; Reddy, G. O.; Ramanathan, J.; Dubey, P. K. *Tetrahedron Lett.* **2003**, *44*, 6323.
- [28] Bringmann, G.; Schneider, S. *Synthesis* **1983**, 139.
- [29] van Delft, F.L.; Timmers, C.M.; van der Marel, G.A.; van Boom, J.H. *Synthesis* **1997**, 450.
- [30] a) Agami, C.; Couty, F.; Hamon, L.; Venier, O. *Bull. Soc. Chim. Fr.* **1995**, 132, 808; b) Agami, C.; Couty, F. *Tetrahedron* **2002**, *58*, 2701; see also: c) Couty, F.; Hamon, L.; Venier, O. *Tetrahedron Lett.* **1993**, *34*, 4509; d) Curran, T.; Pollastri, M.P.; Abelleira, S.M.; Messier, R.J.; McCollum, T.A.; Rowe, C.G. *Tetrahedron Lett.* **1994**, *35*, 5409.
- [31] a) Beesly, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc.* **1915**, 1080; b) Ingold, C. K. *J. Chem. Soc.* **1921**, 305; c) Ingold, C. K.; Sako, S.; Thorpe, J. F. *J. Chem. Soc.* **1922**, 1117; d) Hammond, G. in *Steric Effects in Organic Chemistry*, ed. Newman, M. S., Wiley, New York, **1956**, pp. 462-470; e) Kirby, A. J. *Adv. Phys. Org. Chem.* **1980**, *17*, 183; f) Jung, M. E.; Gervay, J. *J. Am. Chem. Soc.* **1991**, *113*, 224, and reference therein.
- [32] a) Zhao, H.; Thurkauf, A. *Synlett* **1999**, 8, 1280; b) De Jonghe, S.; Van Overmeire, I.; Van Calenbergh, S.; Hendrix, C.; Busson, R.; De Keukeleire, D.; Herdewijn, P. *Eur. J. Org. Chem.* **2000**, 3177; c) Fauq, A.L. *N,N-Diethylammosulfur trifluoride*. In: *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L.A.; Burke, S.D.; Coates, R.M.; Danheiser, R.L.; Denmark, S.E.; Hart, D. J.; Liebeskind, L. S.; Liotta D.C.; Pearson, A.J.; Reich, H. J.; Rigby, J.H.; Roush, W.R.; Eds; John Wiley & Sons Ltd: New York. **1995**, Vol 3, pp. 1787.
- [33] a) Hori, K.; Ohfuné, Y. *J. Org. Chem.* **1988**, *53*, 3886; b) Sakaitani, M.; Ohfuné, Y. *J. Am. Chem. Soc.* **1990**, *112*, 1150.
- [34] a) Neri, C.; Williams, J.M.J. *Adv. Synth. Catal.* **2003**, *345*, 835; b) Neri, C.; Williams, J.M. *J. Tetrahedron: Asymmetry* **2002**, *13*, 2197.
- [35] Suzuki, M.; Yamazaki, T.; Ohta, H.; Schima, K.; Ohi, K.; Nishiyama S.; Sugai, T. *Synlett* **2000**, 189.
- [36] Heathcock, C.; Hassner, A. *Angew. Chem. Int. Ed.* **1963**, *2*, 213.
- [37] Foglia, T.A.; Swern, D. *J. Org. Chem.* **1969**, *34*, 1680.
- [38] Righi, G.; Potini, C.; Bovicelli, P. *Tetrahedron Lett.* **2002**, *43*, 5867.
- [39] Wu, Y.; Shen, X. *Tetrahedron: Asymmetry* **2000**, *11*, 4359.
- [40] Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1992**, *33*, 5517.
- [41] Sudharshan, M.; Hultin, P. G. *Synlett* **1997**, 171.
- [42] Bull, S. D.; Davies, S. G.; Jones, S.; Polywka, M. E.C.; Prasad, R. S.; Sanganee, H. *Synlett* **1998**, 519; Bull, S. D.; Davies, S. G.; Jones, S.; Sanganee, H. *J. Chem. Soc., Perkin Trans. 1* **1999**, 387.
- [43] a) Alexander, K.; Cook, S.; Gibson, C. L.; Kennedy, A. R. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1538; b) Hintermann, T.; Seebach, D. *Helv. Chim. Acta* **1998**, *81*, 2093.
- [44] Sibi, M.P.; Deshpande, P.K.; La Loggia, A.J.; Christensen, J.W. *Tetrahedron Lett.* **1995**, *36*, 8961.
- [45] For a review on organic azides: Brase, S.; Gil, C.; Knepper, K.; Zimmermann, V. *Angew. Chem. Int. Ed.* **2005**, *44*, 5188; pp. 5221.
- [46] a) Ghosh, A.K.; Bischoff, A.; Cappiello, J. *Org. Lett.* **2001**, *3*, 2677; b) Misiti, D.; Zappia, G.; Delle Monache, G. *Synthetic Commun.* **1995**, 2285; c) Roers, R.; Verdine, G. L. *Tetrahedron Lett.* **2001**, *42*, 3562.
- [47] a) Andruszkiewicz, R.; Wyszogrodzka, M. *Synlett* **2002**, 2101; b) Coelho, F.; Rossi, R.C.; *Tetrahedron Lett.* **2002**, *43*, 2797; c) Bertau, M.; Burli, M.; Hungerbuhler, E.; Wagner, P.; *Tetrahedron: Asymmetry* **2001**, *12*, 2103; d) Pais, G. C. G.; Maier M. E. *J. Org. Chem.* **1999**, *64*, 4551; e) Oetting, J.; Holzkamp, J.; Meyer, H.H.; Pahl, A.; *Tetrahedron: Asymmetry* **1997**, *8*, 477; f) Ghosh, A.K.; Hussain K.A.; Fidanze, S. *J. Org. Chem.* **1997**, *62*, 6080; g) Ghosh, A.K.; Liu, W. *J. Org. Chem.* **1996**, *61*, 6175; h) Grunewald, G.L.; Ye, Q. *J. Org. Chem.* **1988**, *53*, 4021; i) Norman, B. H.; Morris, M. L. *Tetrahedron Lett.* **1992**, *33*, 6803.
- [48] Takacs, J. M.; Jaber, M. R.; Vellekoop, A. S. *J. Org. Chem.* **1998**, *63*, 2742.
- [49] Hofmann, A. W. *Ber.* **1881**, *14*, 2725; Wallis, E. S.; Lane, J. *Org. React.* **1946**, *3*, 267.
- [50] a) Yu, C.; Jiang, Y.; Liu, B.; Hu, L. *Tetrahedron Lett.* **2001**, *42*, 1449; b) Wang, G.; Hollingworth, R. I. *Tetrahedron: Asymmetry* **2001**, *11*, 4429; c) Hakogi, T.; Monden, Y.; Taichi, M.; Iwama, S.; Fujii, S.; Ikeda, K.; Katsumura, S. *J. Org. Chem.* **2002**, *67*, 4839; d) Garcia-Urdiales, E.; Rebollo, F.; Gotor, V. *Tetrahedron: Asymmetry* **1999**, *10*, 721.
- [51] Ariza, X.; Pineda, O.; Urpi, F.; Vilarrasa, J. *Tetrahedron Lett.* **2001**, *42*, 4995.
- [52] a) Herweh, J. E.; Foglia, T. A.; Swern, D. *J. Org. Chem.* **1968**, *33*, 4029; b) Herweh, J. E.; Kauffman, W. J. *Tetrahedron Lett.* **1971**, 809; c) Speranza, G. P.; Peppel W. J. *J. Org. Chem.* **1958**, *23*, 1922; d) Weiner, M. L. *J. Org. Chem.* **1961**, *26*, 951; e) Braun, D.; Weinert, J. *Liebigs Ann. Chem.* **1979**, *200*; f) Baba, A.; Fujiwara, M.; Matsuda, H. *Tetrahedron Lett.* **1986**, *27*, 77; g) Fujiwara, M.; Baba, A.; Matsuda, H. *J. Heterocyclic Chem.* **1988**, *25*, 1351; h) Shibata, I.; Baba, A.; Iwasaki, H.; Matsuda H. *J. Org. Chem.* **1986**, *51*, 2177.
- [53] a) Trost, B. M.; Sudhakar, A. R. *J. Am. Chem. Soc.* **1987**, *109*, 3792; b) Trost, B. M.; Sudhakar, A. R. *J. Am. Chem. Soc.* **1988**, *110*, 7933.
- [54] a) Rama Rao, A. V.; Gurjar, M. V.; Rama Devi, T.; Kumar, R. K. *Tetrahedron Lett.* **1993**, *34*, 1653; b) Olofsson B.; Somfai, P. *J. Org. Chem.* **2002**, *67*, 8574; c) Olofsson, B.; Somfai, P. *J. Org. Chem.* **2003**, *68*, 2514; d) Trost, B. M.; Chupak, L. S.; Lubbers, T. *J. Am. Chem. Soc.* **1998**, *120*, 1732.
- [55] Trost B. M.; Van Vranken, D. L. *J. Am. Chem. Soc.* **1993**, *115*, 444.
- [56] Bartoli, G.; Bosco, M.; Carloni, A.; Locatelli, M.; Melchiorre, P.; Sambri, L. *Org. Lett.* **2005**, *7*, 1983.
- [57] Tascetta, P.; Dunach, E. *Chem. Commun.* **2000**, 449.
- [58] Banks, M. R.; Cadogan, J. I. G.; Gosney, I.; Hodgson, K. G.; Thomson, D. E. *J. Chem. Soc. Perkin Trans. 1* **1991**, 961.
- [59] Kawanami, H.; Ikushima, Y. *Tetrahedron Lett.* **2002**, *43*, 3841.
- [60] Sudo, A.; Morioka, Y.; Koizumi, E.; Sanda, F.; Endo, T. *Tetrahedron Lett.* **2003**, *44*, 7889.
- [61] Hancock, M. T.; Pinhas, A. R. *Tetrahedron Lett.* **2003**, *44*, 5457.
- [62] a) Sim, T. B.; Kang, S. H.; Lee, K. S.; Lee, W. K.; Yun, H.; Dong, Y.; Ha H.-J. *J. Org. Chem.* **2003**, *68*, 104. For a recent review on the chemistry of enantiopure aziridine-2-carboxylates see: b) Lee, W. K.; Ha, H.-J. *Aldrichimica Acta* **2003**, *2*, 57.
- [63] a) Park, C. S.; Kim, M. S.; Sim, T. B.; Pyun, D. K.; Lee, C. H.; Choi, D.; Lee, W. K.; Chang, J.-W.; Ha, H.-J. *J. Org. Chem.* **2003**, *68*, 43. b) Sugiyama, S.; Morishita, K.; Ishii, K. *Heyterocycles*, **2001**, *55*, 353.
- [64] a) Sepúlveda-Arquéc, J.; Armero-Alarte, T.; Acero-Alarcón, A.; Zaballos-García, E.; Yruretagoyena, S. B.; Ezquerro-Carrera, J. *Tetrahedron* **1996**, *52*, 2097; b) Testa, M. L.; Hajji, C.; Zaballos-García, E.; García-Segovia, A.B.; Sepúlveda-Arquéc, J. *Tetrahedron: Asymmetry* **2001**, *12*, 1369; c) Testa, M. L.; Akssira, M.; Zaballos-García, E.; Arroyo, P.; Domingo, L.R.; Sepúlveda-Arquéc, J. *Tetrahedron* **2003**, *59*, 677.
- [65] a) Tomasini, C.; Vecchione, A. *Org. Lett.* **1999**, *1*, 2153; b) Luppi, G.; Tomasini, C. *Synlett* **2003**, 797. See also ref. 54b.
- [66] a) Cardillo, G.; Gentilucci, L.; Gianotti, M.; Tolomelli, A. *Synlett.* **2000**, *9*, 1309. For a recent review on the chemistry of aziridines see: b) Cardillo, G.; Gentilucci, L.; Tolomelli, A. *Aldrichim. Acta* **2003**, *2*, 39.
- [67] a) Pauls H. W.; Fraiser-Reid, B. *J. Am. Chem. Soc.* **1980**, *102*, 3956. For stereoselective cyclofunctionalizations of double bonds see: b) Harding, K. E.; Tiner, T. H. in "Comprehensive Organic Synthesis", Eds. Trost, B. M., Fleming, I. Pergamon Press: Oxford, **1991**, vol. 4, pp. 363; c) Cardillo, G.; Orena, M. *Tetrahedron* **1990**, *46*, 3321.
- [68] Cardillo, G.; Orena, M.; Sandri, S. *J. Org. Chem.* **1986**, *51*, 713.
- [69] Kobayashi, S.; Isobe, T.; Ohno, M. *Tetrahedron Lett.* **1984**, *25*, 5079.
- [70] Kamiyama, K.; Urano, Y.; Kobayashi, S.; Ohno, M. *Tetrahedron Lett.* **1987**, *28*, 3123.
- [71] Takemoto, Y.; Takeuchi, J.; Iwata, C. *Synlett* **1995**, 737.
- [72] Bongini, A.; Cardillo, G.; Orena, M.; Porzi, G.; Sandri, S. *Tetrahedron* **1987**, *43*, 4377.
- [73] a) Misiti, D.; Zappia, G. *Tetrahedron Lett.* **1990**, *31*, 7359; b) Delle Monache, G.; Dell'Uomo, N.; Misiti, D.; Zappia, G. *Liebigs Ann. Chem.* **1994**, 641; c) Di Giovanni, M. C.; Misiti, D.; Zappia, G.; Delle Monache, G. *Gazz. Chim. Ital.* **1997**, *127*, 475.
- [74] a) Hoffmann, R.W. *Chem. Rev.* **1989**, *89*, 1841; b) Johnson, F. *ibid.* **1968**, *68*, 375.
- [75] Guindon, Y.; Slassi, A.; Ghire, E.; Banale, G.; Yung, G. *Tetrahedron Lett.* **1992**, *33*, 4257.

- [76] a) Di Giovanni, M. C.; Misiti, D.; Zappia, G.; Delle Monache, G. *Tetrahedron* **1993**, *49*, 11321; b) Di Giovanni, M. C.; Misiti, D.; Di Giovanni, M. C.; Misiti, D.; Zappia, G.; Villani, C.; Zappia, G. *Tetrahedron: Asymmetry* **1996**, *7*, 2277; c) Delle Monache, G.; Misiti, D.; Zappia, G. *Tetrahedron: Asymmetry* **1999**, *10*, 2961.
- [77] Hiramama, M.; Iwashita, M.; Yamazaki, Y.; Ito, S. *Tetrahedron Lett.* **1984**, *25*, 4963.
- [78] Sugimura, H.; Miura, M.; Yamada N. *Tetrahedron: Asymmetry* **1997**, *8*, 4089.
- [79] a) Friesen, R. W.; Kolaczewska, A. E. *J. Org. Chem.* **1991**, *56*, 4888; b) Friesen, R. W. *Tetrahedron Lett.* **1990**, *31*, 4249.
- [80] a) Hayashi, T.; Yamamoto, A.; Ito, Y. *Tetrahedron Lett.* **1987**, *28*, 4837; b) Hayashi, T.; Yamamoto, A.; Ito, Y. *Tetrahedron Lett.* **1988**, *29*, 99.
- [81] For an excellent review in asymmetric allylic alkylation: a) Trost, B.M. *J. Org. Chem.* **2004**, *69*, 5813; b) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395; c) Trost, B. M.; Patterson, D. E. *J. Org. Chem.* **1998**, *63*, 1339; d) Trost, B. M.; van Vranken, D. L. *J. Am. Chem. Soc.* **1990**, *112*, 1261; e) Trost, B. M.; van Vranken, D. L.; Bingel, C. *J. Am. Chem. Soc.* **1992**, *114*, 9327; f) Trost, B. M.; van Vranken, D. L. *Angew. Chem. Int., Ed. Engl.* **1992**, *31*, 228; see also ref. 55.
- [82] Trost, B. M.; Patterson, D. E. *Chem. Eur. J.* **1999**, *5*, 3279.
- [83] a) Zhao, D.; Wang, Z.; Ding, K. *Synlett.* **2005**, *13*, 2067; b) Berkowitz, D. B.; Maiati, G. *Org. Lett.* **2004**, *6*, 2661; c) Agarkov, A.; Uffman, E. N.; Gilbertson, S. R. *Org. Lett.* **2003**, *5*, 2091; d) Tanimori, S.; Inaba, U.; Kato, Y.; Kirihata, M. *Tetrahedron* **2003**, *59*, 3745; e) Lee, S.-g.; Lim, C. W. *Tetrahedron* **2000**, *56*, 5131; f) Lee, S.-G.; Lim, C. W.; Song, C. E.; Kim, K. M.; Jun, C. H. *J. Org. Chem.* **1999**, *64*, 4445.
- [84] Trost, B. M.; Pau, Z.; Zambrano, J.; Kujat, C. *Angew. Chem. Int. Ed. Engl.* **2002**, *41*, 4691; Song, C. E.; Yang, J. W.; Roh, E. J.; Lee, S.-G.; Ahn, I. H.; Han, H. *Angew. Chem. Int. Ed. Engl.* **2002**, *41*, 3852.
- [85] a) Lei, A.; Liu, G.; Lu, X. *J. Org. Chem.* **2002**, *67*, 974; b) Amador, M.; Ariza, X.; García, J.; Sevilla, S. *Org. Lett.* **2002**, *4*, 4511.
- [86] Overmann, L. E.; Remarchuk, T. P. *J. Am. Chem. Soc.* **2002**, *124*, 12.
- [87] a) Kimura, M.; Tanaka, S.; Tamaru, Y. *J. Org. Chem.* **1995**, *60*, 3764; b) Rimura, M.; Tanaka, S.; Fugami, K.; Tamaru, Y. *ibid.* **1992**, *57*, 6377; c) Kimura, M.; Saeki, N.; Uccida, S.; Harayama, H.; Tanaka, S.; Fugami, K.; Tamaru, Y. *Tetrahedron Lett.* **1993**, *34*, 7611; d) Kang, S.-K.; Baik, T.-G.; Hur, Y. *Tetrahedron* **1999**, *55*, 6863; e) Liu, G.; Lu, X. *Org. Lett.* **2001**, *3*, 3879.
- [88] a) Hiramama, M.; Shigemoto, T.; Yamazaki, Y.; Ito, S. *J. Am. Chem. Soc.* **1985**, *107*, 1797; b) Hiramama, M.; Shigemoto, T.; Ito, S. *J. Org. Chem.* **1987**, *52*, 3342; d) Hiramama, M.; Hioki, H.Y.; Ito, S.; Kabuto, C. *Tetrahedron Lett.* **1988**, *29*, 3121; e) Hiramama, M.; Hioki, H.Y.; Ito, S. *Tetrahedron Lett.* **1988**, *29*, 3125.
- [89] a) de Blas, J.; Carretero, J. C.; Domínguez, E. *Tetrahedron Lett.* **1994**, *35*, 4603; b) Bueno, A. E.; Carreño, M. C.; García Ruano, J. L.; Arrayás, R. G.; Zarzuelo, M. M. *J. Org. Chem.* **1997**, *62*, 2139.
- [90] a) Knapp, S.; Kukkola, P. J.; Sharma, S.; Murali Dhar, T. G.; Naughton, A. B. *J. Org. Chem.* **1990**, *55*, 5700; b) Larsen, R. D.; Davis, E. G.; Corley, P. J.; Reider, T. R.; Grabowski, E.J. *J. Org. Chem.* **1990**, *55*, 299; c) Nugent, W. A. *J. Am. Chem. Soc.* **1998**, *120*, 7139; d) Knapp, S. *Chem. Soc. Rev.* **1999**, *28*, 61.
- [91] a) Minami, N.; Ko, S. S.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 1109; b) Roush, W. R.; Adam, M. A. *J. Org. Chem.* **1985**, *50*, 3752; c) Toshiaki, S.; Tohru, N.; Haruo, T.; Satoshi, O.; Sprengeler, P.; Smith III, A. B. *Tetrahedron Lett.* **1993**, *34*, 4447; d) Wipf, P.; Lim, S. *J. Am. Chem. Soc.* **1995**, *117*, 558.
- [92] a) McCombie, S. W.; Nagabhushan, T. L. *Tetrahedron Lett.* **1987**, *28*, 5395; b) Knapp, S.; Kukkola, P. J.; Sharma, S.; Pietranico, S. *Tetrahedron Lett.* **1987**, *28*, 5399; c) Masaki, H.; Maeyama, J.; Kamada, K.; Esumi, T.; Iwabuchi, Y.; Hatakeyama, S. *J. Am. Chem. Soc.* **2000**, *122*, 5216; see also ref. 91a and 91b.
- [93] Tai, V.W.-F.; Imperiali, B. *Tetrahedron Lett.* **1998**, *39*, 7215.
- [94] Langlois, N.; Moro, A. *Eur. J. Org. Chem.* **1999**, 3483.
- [95] Casado-Bellever, F. J.; González-Rosende, M. E.; Asensio, A.; Jordá-Gregori, J. M.; Alvarez-Sorolla, A.; Sepúlveda-Arqués J.; Orena, M.; Galeazzi, R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1650.
- [96] Pégrier, L.; Haddad, M.; Larchevêque, M. *Synlett* **1996**, 585.
- [97] Ambroise, L.; Dumez, E.; Szeki, A.; Jackson, R. F. *J. Synthesis* **2002**, 2296.
- [98] a) Bach, T.; Schroder, J. *J. Org. Chem.* **1999**, *64*, 1265; b) *Tetrahedron Lett.* **1997**, *38*, 3707.
- [99] a) Espino, C. G.; Du Bois, J. *Angew. Chem. Int. Ed.* **2001**, *40*, 598; for a recent review on catalytic intramolecular C-H aminations see: b) Davies, H. M. L.; Long, M. S. *Angew. Chem., Int. Ed.* **2005**, *44*, 3518.
- [100] a) Hinman, A.; Du Bois, J. *J. Am. Chem. Soc.* **2003**, *125*, 11510; b) Parker, K. A.; Chang, W. *Org. Lett.* **2003**, *5*, 3891.
- [101] Cui, Y.; He, C. *Angew. Chem. Int. Ed.* **2004**, *43*, 4210.
- [102] Walsh, P. J.; Bennani, Y. L.; Sharpless, K. B. *Tetrahedron Lett.* **1993**, *34*, 5545.
- [103] Barta, N. S.; Sidler, D. R.; Somerville, K. B.; Wessmann, S. A.; Larsen, R. D.; Reider, P. J. *Org. Lett.* **2000**, *2*, 2821.
- [104] Donohoe, T. J.; Johnson, P. D.; Helliwell, M.; Keenan, M. *Chem. Commun.* **2001**, 2078.
- [105] a) Donohoe, T. J.; Johnson, P.D.; Cowley, A.; Keenan, M. *J. Am. Chem. Soc.* **2002**, *124*, 12934; b) Donohoe, T. J.; Johnson, P. D.; Pye, R. J.; Keenan, M. *Org. Lett.* **2004**, *6*, 2583.
- [106] a) Nicolaou, K. C.; Zhong, Y.-L.; Baran, P. S. *Angew. Chem., Int. Ed.* **2000**, *39*, 625; b) Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L.; Vega J. A. *Angew. Chem. Int. Ed.* **2000**, *39*, 2525.
- [107] a) Bergmeier, S. C.; Stanchina, D. M. *J. Org. Chem.* **1997**, *62*, 4449; b) Bergmeier, S. C.; Stanchina, D. M. *J. Org. Chem.* **1999**, *64*, 2852; c) Bergmeier, S. C.; Katz, S. J. *J. Comb. Chem.* **2002**, *4*, 162.
- [108] Kan, C.; Long, C. M.; Paul, M.; Ring, C. M.; Tully, S. E.; Rojas, C. M. *Org. Lett.* **2001**, *3*, 381.
- [109] Bach, T.; Schlummer, B.; Harms, K. *Chem. Eur. J.* **2001**, *7*, 2581, and ref. cited therein.
- [110] a) Padwa, A.; Stengel, T. *Org. Lett.* **2002**, *4*, 2137; b) Padwa, A.; Flick, A. C.; Leverett, C.A.; Stengel, T. *J. Org. Chem.* **2004**, *69*, 6377.
- [111] Churchill, D. G.; Rojas, C. M. *Tetrahedron Lett.* **2002**, *43*, 7225.
- [112] a) Levites-Agababa, E.; Menhaji, E.; Perlson, L. N.; Rojas, C. M. *Org. Lett.* **2002**, *4*, 863; b) Bodner, R.; Marcellino, B. K.; Severino, A.; Smenton, A. L.; Rojas, C. M. *J. Org. Chem.* **2005**, *70*, 3988.
- [113] Liang, J.-L.; Yuan, S.-X.; Hong Chan, P.W.; Che, C.-M. *Tetrahedron Lett.* **2003**, *44*, 5917.
- [114] a) Cho, G. Y.; Ko, S. Y. *J. Org. Chem.* **1999**, *64*, 8745; b) Kwon, S. J.; Ko, S. Y. *J. Org. Chem.* **2001**, *66*, 6833.
- [115] a) Tiecco, M.; Testaferri, L.; Temperini, A.; Marini, F.; Santi, C. *Chem. Eur. J.* **2004**, *10*, 1752; b) Tiecco, M.; Testaferri, L.; Temperini, A.; Terlizzi, R.; Bagnoli, L.; Marini, F.; Santi, C. *Synthesis* **2005**, 579.
- [116] a) Evans, D. E.; Weber, A. E. *J. Am. Chem. Soc.* **1986**, *108*, 6757; b) Kochlar, K. S.; Cottrell, D. A.; Pinnick, H. W. *Tetrahedron Lett.* **1983**, *24*, 1323; c) Olah, G. A.; Arvanaghi, M.; Ohannesian, L.; Prakash, G. K. S. *Synthesis* **1984**, 785; d) Blazewska, K.; Sikora Gajda, T. *Tetrahedron Lett.* **2003**, *44*, 4747; e) Schmidt, U.; Leitnberger, V.; Griesser, H.; Schmidt, J.; Meyer, R. *Synthesis* **1992**, 1248; f) Herbert, B.; Kim, I. H.; Kirk, K. J. *J. Org. Chem.* **2001**, *66*, 4892.
- [117] a) Zaragoza Dorwald, F. "Organic Synthesis on Solid Phase", Wiley-VCH, 2000; b) Sammelson, R. E.; Kurth, M. *J. Chem. Rev.* **2001**, *101*, 137; c) Franzen, R.-G. *J. Comb. Chem.* **2000**, *2*, 195.
- [118] ten Holte, P.; van Esseveldt, B. C. J.; Thjis, L.; Zwanenburg, B. *Eur. J. Org. Chem.* **2001**, 965; ten Holte, P.; Thjis, L.; Zwanenburg, B. *Org. Lett.* **2001**, *3*, 1093; ten Holte, P.; Thjis, L.; Zwanenburg, B. *Tetrahedron Lett.* **1998**, *39*, 7407.
- [119] Buchstaller, H.-P. *Tetrahedron* **1998**, *54*, 3465.
- [120] Buchstaller, H.-P. *J. Comb. Chem.* **2003**, *5*, 789.
- [121] Rastogi, S. K.; Srivastava, G. K.; Singh, S. K.; Grover, R. K.; Roy, R.; Kundu, B. *Tetrahedron Lett.* **2002**, *43*, 8327.
- [122] Phoon, C. W.; Abell, C. *Tetrahedron Lett.* **1998**, *39*, 2655; Purandare, A. V.; Natarajan, S. *Tetrahedron Lett.* **1997**, *38*, 8777.
- [123] Burgess, K.; Lim, D. *Chem. Commun.* **1997**, 785.
- [124] Allin S. M.; Shuttleworth, S. J. *Tetrahedron Lett.* **1996**, *37*, 8023.
- [125] a) Bew, S. P.; Bull, S. D.; Davies, S. G.; Savory, E. D.; Watkin, D. J. *Tetrahedron* **2002**, *58*, 9387; b) Bew, S. P.; Bull, S. D.; Davies, S. G. *Tetrahedron Lett.* **2000**, *41*, 7577.
- [126] Desimoni, G.; Faita, G.; Galbiati, A.; Pasini, D.; Quadrelli, P.; Rancati, F. *Tetrahedron: Asymmetry* **2002**, *13*, 333.
- [127] a) Kotake, T.; Hayashi, Y.; Rajesh, S.; Mukai, Y.; Takiguchi, Y.; Kimura, T.; Kiso, Y. *Tetrahedron* **2005**, *61*, 3819; b) Kotake, T.;

- Rajesh, S.; Hayashi, Y.; Mukai, Y.; Ueda, M.; Kimura, T.; Kiso, Y. *Tetrahedron Lett.* **2004**, *45*, 3651.
- [128] a) Hein, J. E.; Hultin, P. G. *Synlett* **2003**, 635; b) Hein, J. E.; Geary, L. M.; Jaworski, A. A.; Hultin, P. G. *J. Org. Chem.* **2005**, *70*, 9940
- [129] a) Kakeya, H.; Morishita, M.; Kobinata, K.; Osono, M.; Ishizuka, M.; Osada, H. *J. Antibiot.* **1998**, *51*, 1126; b) Kakeya, H.; Morishita, M.; Koshino, H.; Morita, T.; Kobayashi, K.; Osada, H. *J. Org. Chem.* **1999**, *64*, 1052.
- [130] Sakamoto, Y.; Shiraishi, A.; Seonhee, J.; Nakata, T. *Tetrahedron Lett.* **1999**, *40*, 4203.
- [131] Seki, M.; Mori, K. *Eur. J. Org. Chem.* **1999**, 2965.
- [132] a) Boruwa, J.; Borah, J.C.; Kalita, B.; Barua, N.C. *Tetrahedron Lett.* **2004**, *45*, 7355; b) Davies, S. G.; Hughes, D.; Nicholson, R. L.; Smith, A. D.; Wright, A. *Org. Biomol. Chem.* **2004**, 1549; c) Milicavic, S.; Matovic, R.; Saicic, R. *Tetrahedron Lett.* **2004**, *45*, 955; d) Miyata, O.; Koizumi, T.; Asai, H.; Iba, R.; Naito, T. *Tetrahedron* **2004**, *60*, 3893; e) Sugiyama, S.; Arai, S.; Ishii, K. *Tetrahedron: Asymmetry* **2004**, *15*, 3149; f) Swamy, N. R.; Krishnaiah, P.; Reddy, N. S.; Venkateswarlu, Y. *J. Carbohydrate Chem.* **2004**, *23*, 217; g) Carter, P. H.; LaPorte, J. R.; Scherle, P. A.; Decicco, C. P. *Biorg. Med. Chem. Lett.* **2003**, *13*, 1237; h) Kumar, A. R.; Bhaskar, G.; Madhan, A.; Rao, B. V. *Synthetic Commun.* **2003**, *33*, 2907; i) Carda, M.; González, F.; Sánchez, R.; Marco, J.A. *Tetrahedron: Asymmetry* **2002**, *13*, 1005; j) Hamersak, Z.; Ljubovic, E.; Mercep, M.; Mesic, M.; Sunjic, V. *Synthesis* **2001**, 1989; k) Madhan, A.; Kumar, A.; Rao, B. V. *Tetrahedron: Asymmetry* **2001**, *12*, 2009; l) Park, J. N.; Ko, S. Y.; Koh, H. Y. *Tetrahedron Lett.* **2000**, *41*, 5553.
- [133] Boojamra, C. G.; Lemoine, R. C.; Lee, J. C.; Leger, R.; Stein, K. A.; Vernier, N. G.; Magon, A.; Lomovskaya, O.; Martin, P. K.; Chamberland, S.; Lee, M. D.; Hecker, S. J.; Lee, V. J. *J. Am. Chem. Soc.* **2001**, *123*, 870.
- [134] Drautz, H.; Zahner, H.; Kupfer, E.; Keller-Schierlein, W. *Helv. Chim. Acta* **1981**, *64*, 1752.
- [135] Grabley, S.; Kluge, H.; Hoppe, H.-U. *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 664.
- [136] a) Kozikowski, A. P.; Park, P. *J. Am. Chem. Soc.* **1985**, *107*, 1763; b) Kozikowski, A. P.; Park, P. *J. Org. Chem.* **1990**, *55*, 4668.
- [137] Flann, C. J.; Overmann, L. E. *J. Am. Chem. Soc.* **1987**, *109*, 6115.
- [138] Yamada, H.; Aoyagi, S.; Kibayashi, C. *J. Am. Chem. Soc.* **1996**, *118*, 1054.
- [139] Huang, S.; Comins, D. L. *Chem. Commun.* **2000**, 569.
- [140] Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.
- [141] Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226.
- [142] Trost, B. M. *Science* **1991**, *254*, 1471.
- [143] Trost, B. M.; Chung, C. K.; Pinkerton, A. B. *Angew. Chem. Int. Ed.* **2004**, *43*, 4327.
- [144] Trost, B. M.; Lee, D. C. *J. Am. Chem. Soc.* **1988**, *110*, 7255; Trost, B. M.; Fleitz, F. J.; Watkins, W. J. *J. Am. Chem. Soc.* **1996**, *118*, 5146.
- [145] Li, F.; Warshakoon, N. C.; Miller, M. J. *J. Org. Chem.* **2004**, *69*, 8836.
- [146] Tang, Y.-Q.; Wunderlich, D.; Sattler, I.; Grabley, S.; Feng, X.-Z. In Abstract of Division of Organic Chemistry, 223rd ACS National Meeting, Apr. 7-12, Orlando; American Chemical Society: Washington, DC, **2002**, pp. 341.
- [147] a) Nomura, I.; Mukai, C. *Org. Lett.* **2002**, *4*, 4301; b) Nomura, I.; Mukai, C. *J. Org. Chem.* **2004**, *69*, 1803.
- [148] Magnus, P.; Fielding, M. R.; Wells, C.; Lynch, V. *Tetrahedron Lett.* **2002**, *43*, 947; Dominguez, G.; Casarrubios, L.; Rodriguez-Noriega, J.; Perez-Castells, J. *Helv. Chim. Acta* **2002**, *85*, 2856.

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