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Isoxazolidine

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Introduction

Heterocyclic compounds are the main class of cyclic organic compounds characterized by containing at least one heteroatom, the most common heteroatoms being nitrogen, oxygen and sulfur although other heterocyclic rings containing different heteroatoms are also known

The saturated five-membered isoxazolidine, containing adjacent nitrogen and oxygen atoms, part of several natural products, has shown increasing interest in the past decade. This heterocycle can be obtained through the well-known 1,3-dipolar cyclo-addition, providing access to a large diversity of compounds.

other efficient strategies have been proposed to enlarge the variety of isoxazolidines that could not be obtained by this classical method. Since this moiety is rarely found in natural products, it represents an important synthetic intermediate, especially due to the labile nature of the N−O bond.

Accordingly, several groups of investigators have developed mild conditions to improve the synthesis of a large variety of isoxazolidine derivatives and their use for the total syntheses of natural compounds. Alternately, isoxazolidines are important scaffolds in drug discovery mimicking a wide range of natural building blocks and being found to exhibit interesting diverse

biological activities.

Introduction

Heterocyclic compounds are the main class of cyclic organic compounds characterized by containing at least one heteroatom, the most common heteroatoms being nitrogen, oxygen and sulfur although other heterocyclic rings containing different heteroatoms are also known Isoxazolidines are 1,2-N,O-pentatomic heterocycles which play a very important role in organic chemistry as constituents of biologically interesting compounds or as valuable intermediates in many synthetic routes . In particular, this ring system is characterized by a labile N-O bond, which can be easily cleaved under mild reducing conditions to afford 1,3-aminoalcohols , and it is useful for the synthesis of many important biologically active compounds. Furthermore, the isoxazolidine system itself can be considered as a mimetic of the ribose unit and has been exploited for the synthesis of nucleoside analogues endowed with anticancer and/or antiviral activities .

The most used strategy for the synthesis of the isoxazolidine skeleton is the classical 1,3-dipolar cycloaddition reaction of nitrones with alkenes, that allows up to three new stereogenic centers to be assembled in a stereospecific manner, in a single step .

The [4s + 2s] pericyclic reaction is a stereoconservative (su-prafacial) process (Fig. 1). The regio- and stereoselectivity of the concerted cycloaddition process can be rationalized according to the frontier molecular orbital theory.

In particular, the regioselectivity is controlled by the orbital coefficients of the reacting atoms and by the energy of the frontier orbitals of the nitrone or the dipolarophile, while the stereoselectivity depends on the geometry of the nitrone (E/Z configuration) and from the modes of interaction with the dipolarophile (exo or endo).

The transition state of the process can involve either a LUMOdipole/HOMO-dipolarophyle or a LUMO-dipolarophile/HOMOdipole interaction. In some cases, a combination of both modes of interaction can occur. The presence of a metal, such as a Lewis acid, can alter both the orbital coefficients of the reacting atoms and the energy of the frontier orbitals of the dipole or the dipolarophile, thus influencing the regio-, diastereo- and enantioselectivity of the process .

Over the past two decades, a growing interest has been addressed to the development and applications of this methodology towards the synthesis of enantiomerically pure compounds. The enantioselectivity of the process can be assured by the use of chiral 1,3-dipoles, chiral dipolarophiles, or chiral catalysts. The latter methodology probably offers the greatest potential. In particular, the enantioselective version, promoted by chiral Lewis acid complexes, and by chiral secondary amines, as organocatalysts, has further enhanced the potentiality of the cycloadditions.

Isoxazolidine derivatives have also been prepared starting from aryl halides and O-homoallyl hydroxylamine using palladium catalyzed cascade reactions (Fig. 2).

More recently, unsaturated isoxazolidines have been prepared starting from N-protected hydroxyl amino allylic-acetate or alcohol by the iron-catalyzed cycloaddition: this methodology further expands the possibility to obtain this heterocycle in good yield and in a more ecofriendly, inexpensive and low-polluting chemical process (Fig. 3).

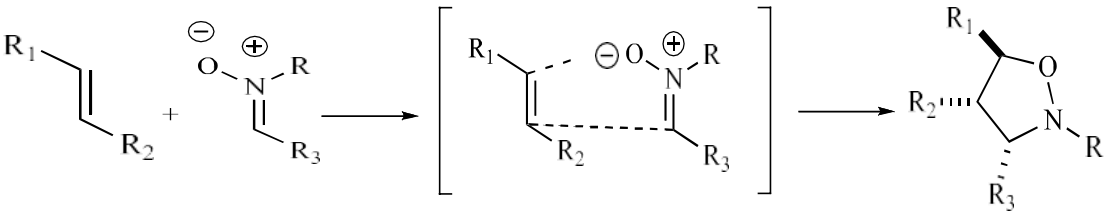


Fig 1. The 1,3 dipolar cycloaddition of nitrones.

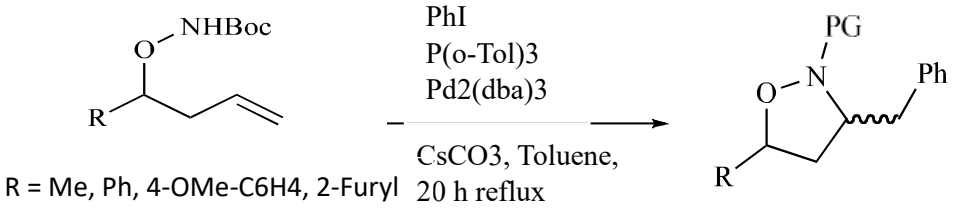


Fig 2. Synthesis of isoxazolidines from aryl halides and O-homoallyl hydroxylamine

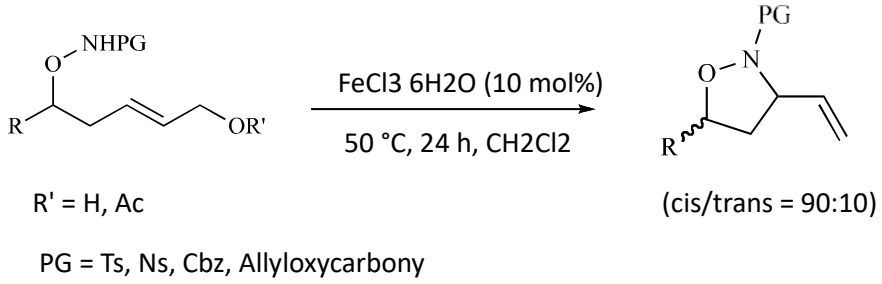


Fig 3. Synthesis of isoxazolidines from N-protected hydroxyl amino allylic-acetate or alcohol.

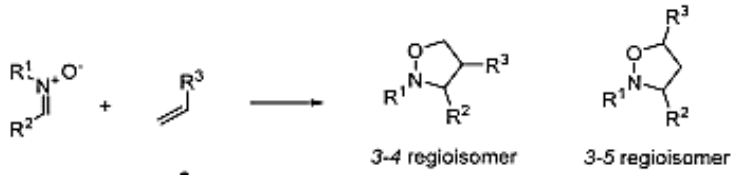
Synthetic Strategies to Prepare the Isoxazolidine Ring

1,3-Dipolar Cycloaddition

According to the literature, the principal synthetic route to access to isoxazolidines is the 1,3-dipolar cycloaddition of nitrones and ethylenic dipolarophiles, which was proposed by Morita et al. in 1967.37 This versatile pericyclic reaction, which can involve a range of electron-poor, neutral, and electron-rich dipolarophiles, offers the possibility of generating isoxazolidines with up to three new contiguous stereocenters. Such 1,3-DC reactions and relevant (3 + 2) processes have been reviewed in a general manner29,38 or more focused on some specific cycloreactants, such as heterosubstituted dienophiles.34,35

The isoxazolidine synthesis through 1,3-DC involves a nitrone 1 as a 1,3-dipolar molecule and an alkene 2 as a dipolarophile by analogy with the dienophile of the Diels− Alder cycloaddition. Sterically demanding cycloreactants are well tolerated in a number of 1,3-DC reactions. From monosubstituted dipolarophiles, both regioisomers 3 and 4 (3−4 and 3−5) could be obtained, in which the regioselectivity principally depends on the R3 group (Scheme 6).

Scheme 6. Formation of 3−4 and 3−5 Isoxazolidines through 1,3-DC

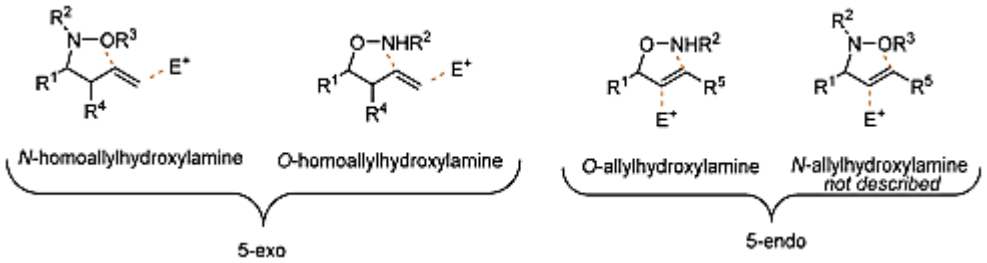


Cyclizations of Unsaturated Hydroxylamines

Unsaturated hydroxylamines, through intramolecular cyclization, offer an alternative method to efficiently form the 2,3- bond and the 1,5-bond, affording original isoxazolidine derivatives. This strategy allowed access to novel isoxazolidines that could not be obtained by 1,3-DC. Depending on the intramolecular cyclization conditions that are applied, the reaction mechanism is different. Thus, we decided to divide this section in four subparts: (i) electrophilic cyclizations, (ii) palladium-catalyzed cyclizations, (iii) radical cyclizations, and (iv) Michael additions.

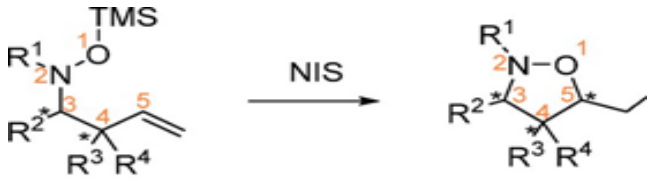
Electrophilic Cyclizations. Among the cyclization of unsaturated hydroxylamines, an interesting route to access the isoxazolidine skeleton concerned electrophilic cyclization. Initially described to build other heterocyclic ring systems such as oxazolines or pyrrolidines,this chemical strategy requires alkenes bearing N- or O-nucleophilic functionality. Such starting compounds are suitable for intramolecular cyclization by means of different electrophilic sources, halides or phenylselenides. Since all reported substrates were unsaturated hydroxylamine derivatives, various combinations for the intramolecular cyclization have been designed depending on the nucleophilic species involved and on the double bond position. Various synthetic strategies involving 5-exo cyclizations were reported leading to 5-halomethyl-, 3-halomethyl-, or 3-phenylselenyl-isoxazolidines, while synthetic strategies involving 5-endo cyclizations were described leading to 4-haloisoxazolidines and 4-phenylselenyl-isoxazolidine derivatives. (Scheme 11)

Scheme 11. Possible Combinations for the Electrophilic Cyclization



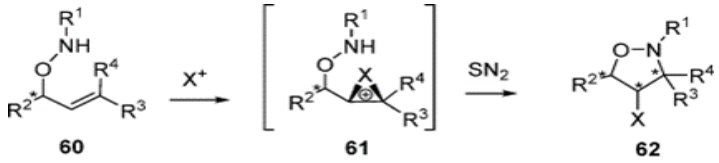
Electrophilic 5-Exo Cyclizations. Starting from Nhomoallyl-hydroxylamine derivatives 49, electrophilic 5-exo cyclization to reach 5-iodomethyl isoxazolidines 50 has been investigated by Trombini et al.129,130 (Scheme 12).

Scheme 12. 5-Exo Iodocyclization with Substituted Hydroxylamines



Electrophilic 5-Endo Cyclizations. To the best of our knowledge, 5-endo cyclizations could only be realized from O-allyl-hydroxylamines. Seleno cyclizations were reported by Tiecco et al.33,141,142 as well as Li et al.,143 whereas Egart et al.144 tested various halogeno cyclizations. As for the 5-exo cyclization of O-homoallyl-hydroxylamines, the 5-endo cyclization required use of N-protected hydroxylamines 60. However, contrary to 5-exo cyclization, the 5-endo cyclization leads preferentially or exclusively to a 3−4-trans selectivity, which was explained through a SN2 pathway (Scheme 18).

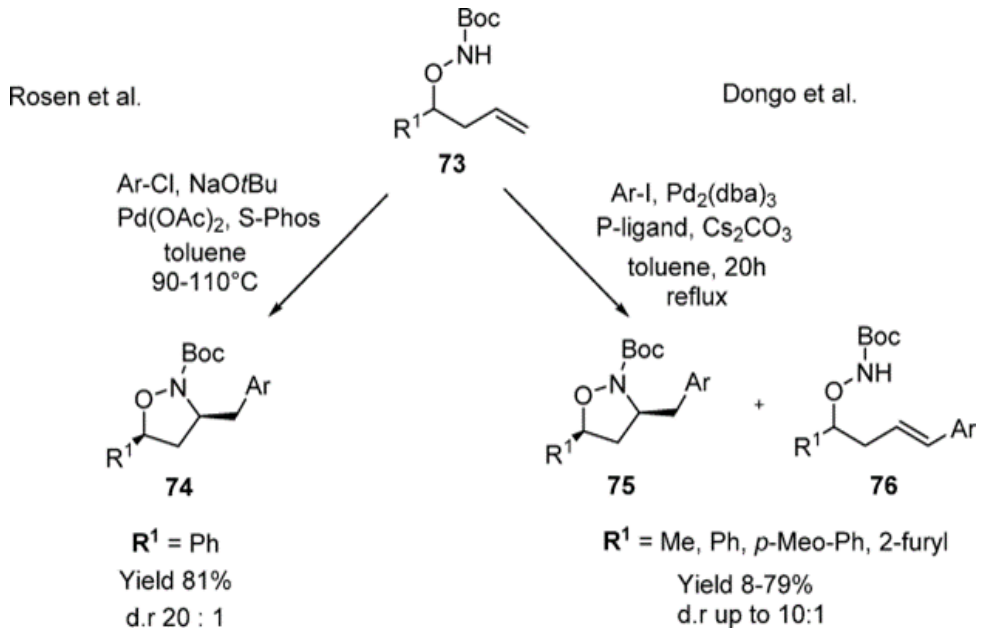
Scheme 18. 5-Endo Electrophilic Cyclization of O-Homoallyl-hydroxylamines.



$\mathbf{R^1}$ = COMe, COPh, *i*-Pr, Bn, Et.

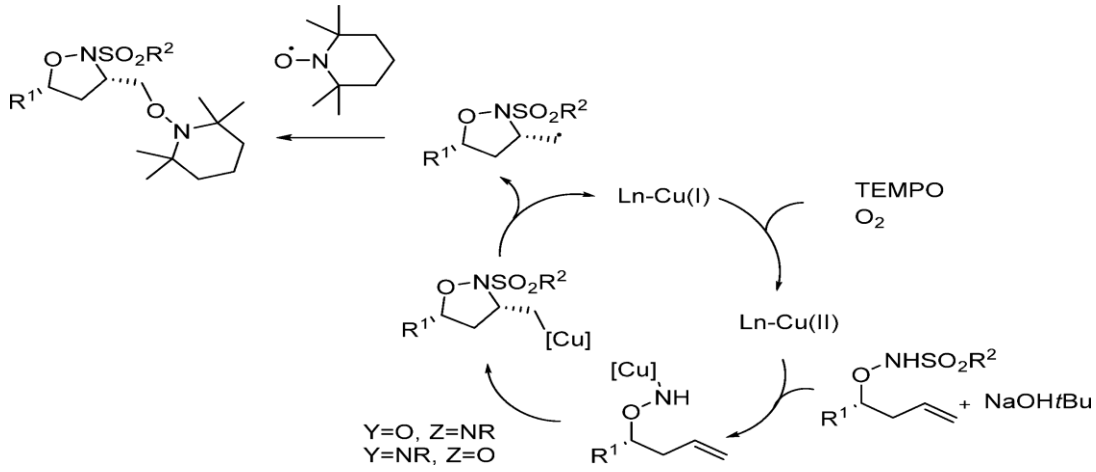
Palladium-Mediated Cyclizations. Palladium catalyzed diastereoselective cascade reaction is a suitable method for the synthesis of heterocyclic compounds. Accordingly, several groups have naturally extended this method for carbo-etherification of unsaturated hydroxylamine substrates, providing a new stereoselective method for the construction of substituted isoxazolidines. In many cases the stereochemical outcome of these transformations is complementary to that of nitrone cycloadditions. The power of this cyclization was deeply studied to get suitable N-protected isoxazolidines. Thus, Dongol et al.145 synthesized isoxazolidine derivatives 75 from N-Boc-O-homoallyl-hydroxylamine 73 with a ratio cis/trans of up to 10:1. However, moderate to good yields were obtained, due to the isolation of a Heck coupling adduct 76. Changing either the catalyst loading or the ligand did not result in any improvement. This methodology was improved by Rosen et al.,146,147 who performed the efficient cyclization of the same hydroxylamine derivatives 73 using different experimental conditions, affording only the expected ring 74 in excellent yield and dr (Scheme 22).

Scheme 22. Palladium-Catalyzed Cyclization of N-Boc-O-homoallyl-hydroxylamine

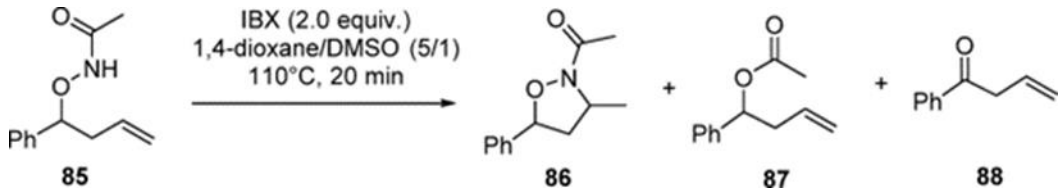


Radical Cyclizations. Among the cyclization of unsaturated hydroxylamines, there are only a few reports about radical cyclization. The first study was described by Janza and Studer153 in 2005. They described the generation of the alkoxy−amidyl radical under oxidative conditions using oiodoxybenzoic acid (IBX). By this method they mainly obtained the desired cycle 86 (54−71%) in a cis:trans 6:1 mixture with concomitant formation of two byproducts 87 and 88 (Scheme 27). Using either no or other N-protecting groups (N-PGs) such as Boc or sulfonyl, the reaction did not proceed, while using N-p-methoxybenzamide PG, the ester 87 was the major product formed (40%). Using copper complexes and (2,2,6,6-tetramethylpiperidin-1- yl)oxyl radical (TEMPO) as mild oxidant on N-sulfonyl-hydroxylamines, Karyakarte et al.154 observed the selective formation of 3−5-cis-isoxazolidines with excellent yields and dr (up to 20:1), except with the β-phenyl substrate, which yielded the 3,4-trans product. They proposed a mechanism, which is described in Figure 11.

Figure 11. Catalytic cycle with copper complexes.

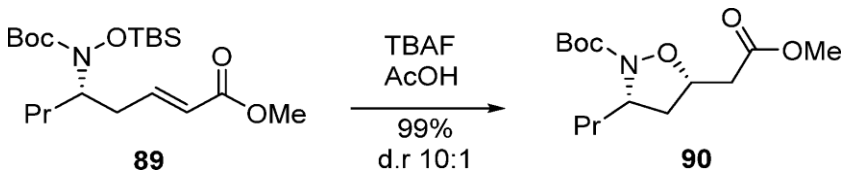


Scheme 27. Radical Cyclization of O-Homoallyl-hydroxylamines Using IBX



Michael Additions. The hetero-Michael addition reaction emerged as a powerful synthetic strategy to create C− N or C−O bonds. By means of bis-nucleophiles such as hydroxylamines, this method provided novel access to Nprotected isoxazolidines. After the first reports in 1978155 and then in the 1990s,156,157 the reaction was deeply developed in 2006 by Chen et al.158 After removal of the silyl group from NBoc-unsaturated hydroxylamines 89, an intramolecular oxyMichael addition was observed, leading to Boc-isoxazolidines 90 in excellent yields (99%) and dr (10:1) (Scheme 28).

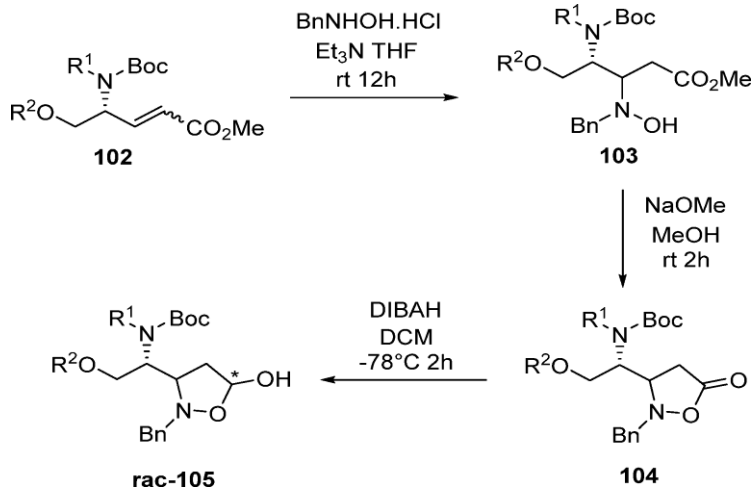
Scheme 28. Synthesis of N-Boc Isoxazolidine via an Intramolecular Oxy-Michael Addition



Other Synthetic Strategies

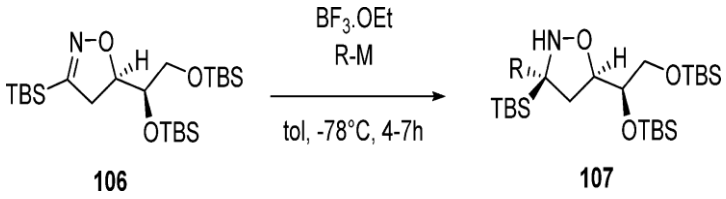
From Isoxazolidinones. Also synthesized via an aza-Michael addition followed by a cyclization step, isoxazolidine-3- ones 104 have been efficiently converted into the corresponding 5-hydroxyisoxazolidines 105 in the presence of DIBAH thanks to a chemoselective reduction (Scheme 33).166

Scheme 33. Synthesis of Isoxazolidines by Reduction of Isoxazolidin-3-one in the Presence of DIBAH



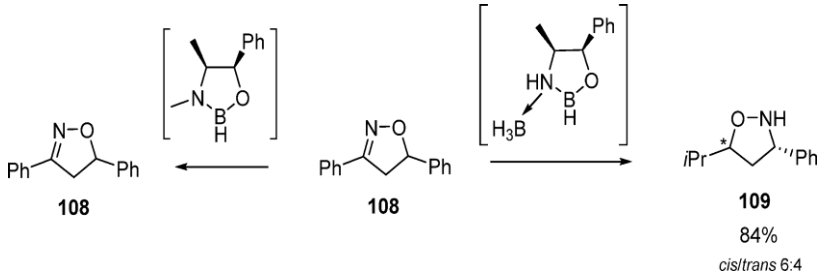
From Isoxazolines. Isoxazoline is an unsaturated five-member ring, which can be prepared by 1,3-DC of nitrile oxides and olefins. This substrate is easily transformed into the corresponding saturated cycle through various methods. For example, using different organometallics in the presence of etherate borane, Buhrlage et al.167 performed a nucleophilic addition on isoxazolines 106 to obtain original isoxazolidines 107 in 73−80% yield with a dr between 7:1 and 20:1 (Scheme 34, R = Bn, Ph, allyl, Me, thienyl, 2-methylallyl). Thus, they proposed an efficient method to prepare suitable N-unprotected isoxazolidines.

Scheme 34. Synthesis of Isoxazolidines by Nucleophilic Addition on Isoxazolines



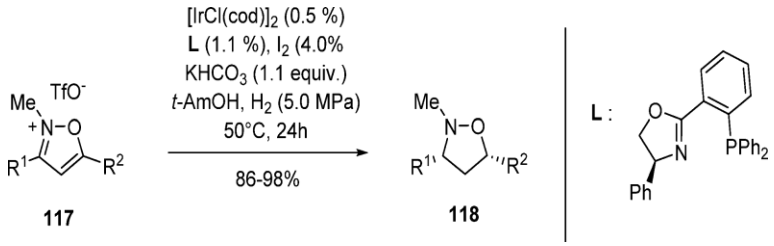
use of borane/1,2-amino alcohol complex as chiral source, a racemic mixture of isoxazolines could be efficiently reduced into diastereomerically pure isoxazolidines. By changing the chiral source and the substrate, Tokizane et al.168 succeeded to orientate the reaction to the privileged formation of one product. Using (−)-norephedrine as the chiral source and 2,4-diphenyl-isoxazoline as the substrate, only isoxazolidines 109 in 84% with a 6:4 cis/trans ratio were obtained. In contrast, using (−)-ephedrine as the chiral source, only the starting isoxazoline 108 was recovered (Scheme 35).

Scheme 35. Synthesis of Isoxazolidines by Reduction of Isoxazolines with Borane/1,2-Amino Alcohol Complexes



From Isoxazolinium Salts. Hydrogenation of isoxazolinium salts 117 in the presence of iridium catalyst lead to a fully saturated cis-isoxazolidine 118 in excellent yield and er (up to 89:11), Scheme 38. 171 Interestingly, when the reaction was performed in the presence of a double amount of catalysts in THF at 70 °C for 4 h, a mixture of saturated and unsaturated rings 120, 121, and 122 was obtained, Scheme 39.

Scheme 38. Synthesis of Isoxazolidines by Reduction of Isoxazolinium Salts



Scheme 39. Synthesis of Isoxazolidines and Isoxazolines by Isoxazolinium Salts Reduction