SYNTHESIS OF ISOXAZOLIDINES BY 1,3-DIPOLAR CYCLOADDITION: RECENT ADVANCES

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Loredana Maiuolo and Antonio De Nino

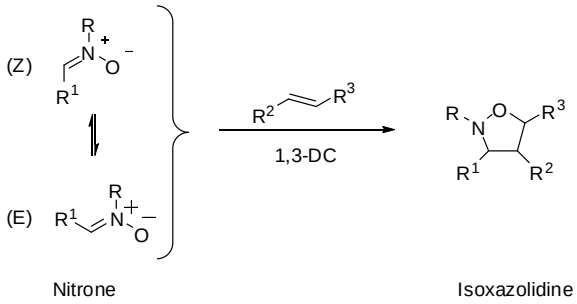
Department of Chemistry and Chemical Technologies, University of Calabria, 87036 Rende (Cosenza), Italy (e-mail: maiuolo@unical.it, denino@unical.it)

Abstract. *This chapter aims to review recent developments in the last five years on the synthesis of isoxazolidine compounds under reaction conditions that include the application of the thermal warming, the microwave irradiation, the metal- or organocatalysis and the use of ionic liquids (ILs). Several examples to construct isoxazolidines by 1,3-dipolar cycloadditions will be discussed in this chapter, which we have decided to divide for reaction conditions. The discussion will be allow to obtain a broader vision of the real effects of applied reaction methods on yields, regio-, diastereo- and enantioselectivity of the reaction.*

Contents

1. Introduction

The reaction of 1,3-dipolar cycloaddition (1,3-DC) is a valid approach to a variety of heterocycles: a highlight of its power in synthesis is its use to construct the five-membered ring such as isoxazolidines. Nitrone cycloaddition to olefins is one of the most versatile protocol for the construction of isoxazolidine where the dipolarophiles are usually alkenes, whereas dipoles are represented by suitable nitrones (Scheme 1).[1]



Scheme 1. Nitrone cycloaddition to olefins.

Three types of selectivity must be considered in 1,3-dipolar cycloadditions: regioselectivity, diastereoselectivity and enantioselectivity. Their prediction is realized through a consideration of steric and electronic factors, but most significantly through the frontier molecular orbital (FMO) theory.[2]

The regioselectivity is controlled by both steric and electronic effects and, generally, in the cycloadditions of electron-rich or electron-neutral alkenes with nitrones, the 5-substituted isomer is obtained respect to 4-sustituted isomer.

In cycloadditions of nitrones with an alkene the nitrone can approach in an *endo* or an *exo* mode giving rise to two different diastereomers. The *endo*/*exo* selectivity in the 1,3-dipolar cycloaddition reaction is primarily controlled by the structure of the substrates or by a catalyst. However, in reaction in which the nitrone can undergo *Z*/*E*-interconversion, the *endo*/*exo* assignment of the products is ambiguous and

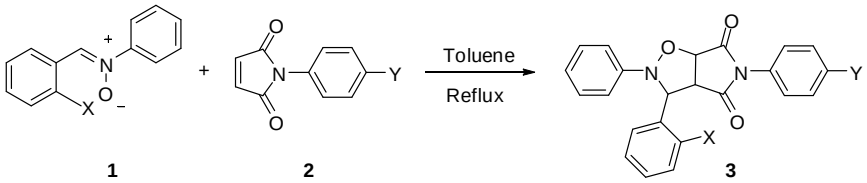
therefore the definition of *cis* or *trans* should be used. Finally, there is the enantioselectivity of the 1,3-dipolar reactions. The only factor present for control of the enantioselectivity is the chiral catalyst.

2. Thermal intermolecular 1,3-dipolar cycloaddition

2.1. Fused isoxazolidines

The presence of a second ring fused to the isoxazolidines moiety induces to substrates a restricted conformational mobility. This peculiarity is reflected in the observation that Reverse Transcriptase is able to discriminate between two conformationally locked nucleoside analogues.[3]

Recent developments in the preparation of fused isoxazolidines have regarded the synthesis of molecules containing a pyrrole portion for theirs biological activities as anti-HIV,[4] anti-bacterial,[5] anti-fungal,[6] anti-diabetic,[7] etc. In 2013, the synthesis of some pirrole-isoxazolidine cycloadducts **3** was carried starting from nitrones **1** and *N*-substituted pyrrole derivatives **2** (Scheme 2), by refluxing in toluene.[8]



X = Cl; OH ; Y = H, CH_3, OCH_3, COOH

Scheme 2. Synthesis of pirrole-isoxazolidine derivatives by substituted diaryl nitrones and maleimides.

The reaction proceeded in regioselective manner with moderate to good yields. NMR studies revealed in all reactions the formation of two diastereomers with preference of *trans*-isomer (ratio *cis*:*trans* 20:80), due to more stability of *exo*-TS. Tests *in vitro* have exhibited significant inhibition against Advanced Glycation End Product (AGEs) formation and the analysis of results has leaded to the conclusion that the activity is widely affected by stereochemistry and substitution of cycloadducts.

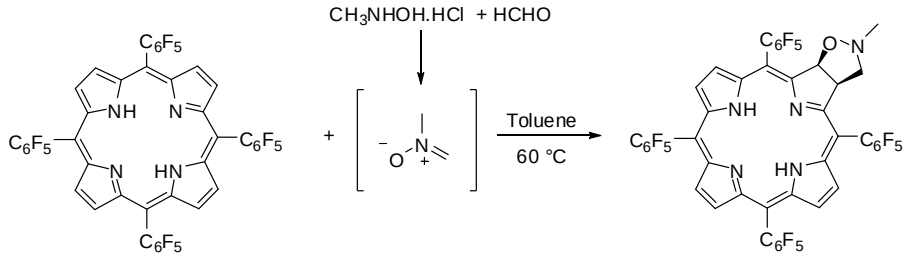
The insertion of a porphyrinic structure fused on isoxazolidines allows the formation of macrocycles that generally maintain the electronic properties of porphyirines adding characteristics of versatility in synthetic transformation or potential biological activity.[9] In 2015, the synthesis of isoxazolidine-fused meso-tetraarylchlorin **6** as unique molecule was realized by a 1,3-dipolar cycloaddition of *meso*-tetrakis (pentafluorophenyl) porphyrin **4** and *N*-methyl nitrone **5** in toluene at 60 °C with 71% yield (Scheme 3).[10]

X-ray diffraction analysis confirmed unequivocally the structure of the compound **6**, revealing that the isoxazolidine ring is arranged nearly perpendicular respect to the porphyrin system with an angle of mean planes of 89.79°.

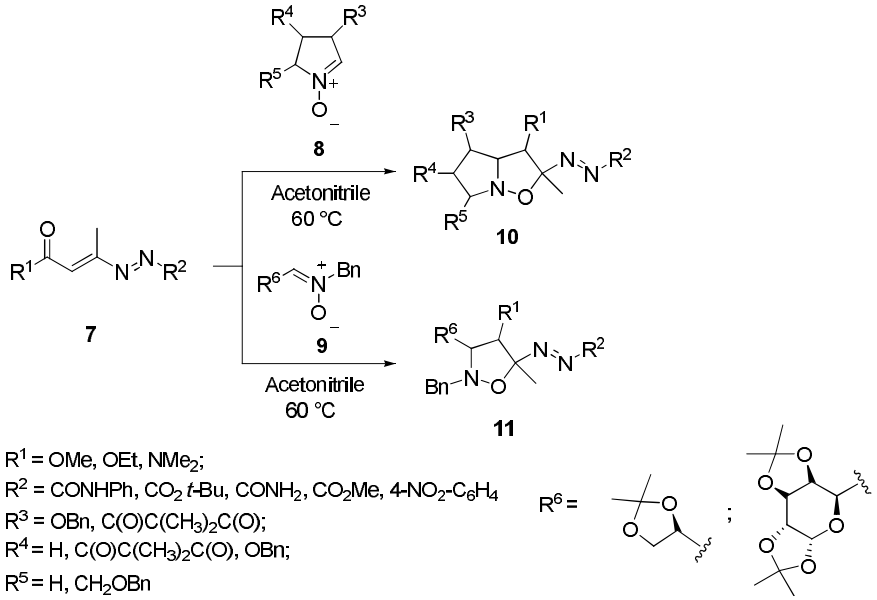
The substrate **6** was primarily important as intermediate for further transformations in a quaternary ammonium salt of isoxazoline moiety or reductive cleavage of *N-O* bond with subsequent rearrangement.

1,2-Diaza-1,3-dienes (DDs) are substrates of great importance in the synthesis of heterocyclic frameworks.[11] Recently, a detailed indications of the synthetic use of DDs **7** as dipolarophiles were provided

to the formation of fused isoxazolidines **10** or **11** by 1,3-dipolar cycloaddition with nitrones **8** or **9**, respectively (Scheme 4).[12]



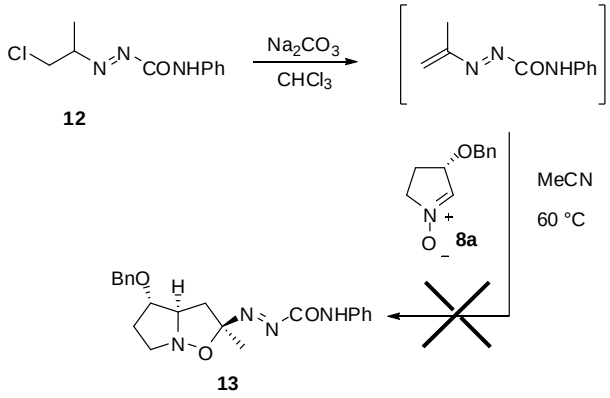
Scheme 3. Synthesis of isoxazolidine-fused *meso*-tetraarylchlorin **6**.



Scheme 4. Cycloaddition between cyclic and acyclic nitrones (**8** or **9**) and DDs **7**.

An initial screening of reaction conditions was conducted on a model thermal cycloaddition between a diazadiene **7** and a cyclic nitrone **8**, varying solvents and heating temperatures and observing a completely regio- and stereoselective reaction in acetonitrile at 60 °C, with a 91% yield and a diastereomeric ratio (*dr*) of 1:0. Therefore, the optimized conditions were extended to a wide range of cyclic nitrones and diazadienes, isolating byciclic isoxazolidines with comparable yields and same diastereoisomeric ratio (*dr*) in all cases. In contrast, use of acyclic nitrones derived from D-glyceraldeide and D-galactose produced isoxazolidines as a mixture of two stereoisomers. NMR and crystallographic studies have allowed assignation of configuration

of stereogenic centres, confirming the hypothesis of a *re*-cycloaddition through an *exo* attack of DD to less hindered *re*-face of nitrone. The application of microwave irradiation or Lewis acid catalysis was compared to employed classical method; in the first case, the MW irradiation showed less reaction time respect to thermal conditions but also minor diastreomeric excess, whereas in the second case, the use of Lewis acids produced a great instability of nitrones. Interestingly, attempts to induce thermal or Mw cycloaddition of DD **12** and nitrone **8a** (Scheme 5) were unsuccessful, deducing the necessary presence of appropriate electron-withdrawing groups on the diazadienes. A depth theoretical study was carried out to predict the regio- and diastereoselectivity of the cycloadditions, obtaining results in quite agreement with the observed experimental data.



Scheme 5. Cycloaddition between nitrone **8a** and diazadiene **12**.

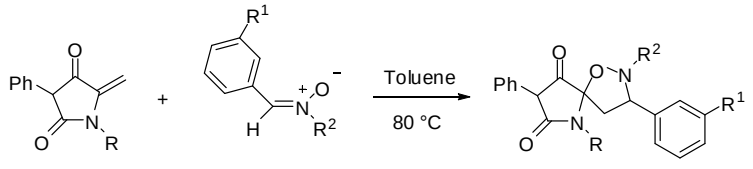
2.2. Spiro-isoxazolidines

Spiro compounds are structurally represented by a cycle fused at a central carbon; they are of current interest due to their conformational and structural features that are relevant for the biological activities. In particular, spioroisoxazolidines are synthesized by 1,3-dipolar cycloaddition between olefins and nitrones, obtained from cyclic ketones.[13]

Spirohydantoin derivatives are an interesting class of spirocycloadducts for their various biological activity such as anticancer,[14] anti-arrhythmic,[15] neurotransmissive,[16] herbicidal,[17] etc.

In 2010, the construction of spirohydantoin isoxazolidines **16** was realized by 1,3-dipolar cycloaddition in classic conditions (toluene, 80°C), starting from variously substituted 5-methylenehydantoins **14** and some nitrones **15** (Scheme 6).[18]

The reactions proceeded with quite long times (6 days) and the resulting adducts were isolated in moderate to good yields (50-74%). The regioselectivity of cycloaddition was oriented towards the exclusively formation of the 5,5-disubstituted regioisomer, obtained from an *endo*-approach of the dipole toward the C=O group of the hydantoin ring. Generally, the formation of only one diasteroisomer was observed, while the use of a chiral hydantoin substrate afforded the formation of two nonracemic diasteroisomers.

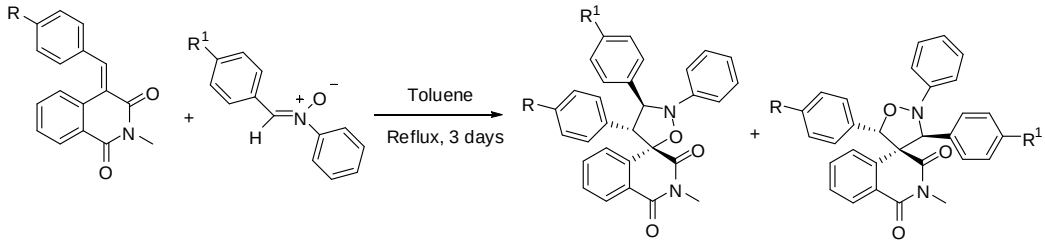


14 **15** **16**

R = Bn, *i*-Bu, *i*-Pr, $CH_2CH(CH_3)Ph$
R^1 = H, OCH_3
R^2 = Ph, *t*-Bu, *i*-Pr

Scheme 6. Reaction of methylenehydantoins **14** with nitrones **15**.

In 2014, a subsequent and more recent report showed the results obtained to achieve isoxazolidines (**19** and **20**) connected to a *N*-substituted homophthalimide group by a spiro carbon (Scheme 7).[19]



17 **18** **19** **20**

R = H, Me, OMe, NO_2

R^1= H, Me, OMe

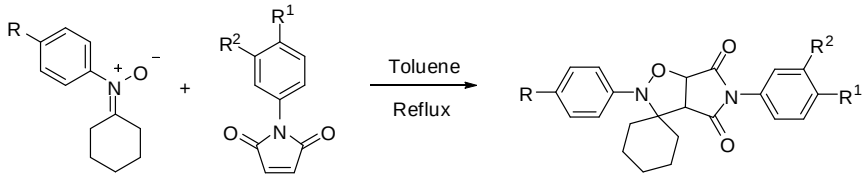
Scheme 7. 1,3-dipolar cycloaddition of *C*-aryl-*N*-phenylnitrones **17** with (*E*)-4-arylidene-(2H,4H)-isoquinoline-1,3-diones **18**.

The reactions were regiospecific (100% 5-spirocycloadduct *versus* 4-spiroderivatives) in the majority of cases and a careful screening of different solvents (benzene, acetonitrile, toluene or chloroform) and temperatures (reflux or room temperature) showed no changes in the regioisomeric ratios of other substrates. The diastereomeric selectivity was the result of an *endo* approach, more favorite than *exo*-approach because of electronic and steric interactions of the reagents, as confirmed by density functional theory (DFT) calculations.

Lately, the choice to use *N*-cyclohexyldiene *N*-aryl nitrones **21** with *N*-arylmaleimides **22** as dipoles and dipolarophiles, respectively, allowed the synthesis of spiroisoxazolidines fused to succinimide moieties (**23**) (Scheme 8).[20]

Several starting substrates were used to synthesize a wide range of spirocycloadducts with decent yields (61-75%), observing the formation of a single diastereoisomer provided through an *endo* transition state (TS 2), more favorite if compared to the *exo* transition state (TS 1) *via* secondary interaction

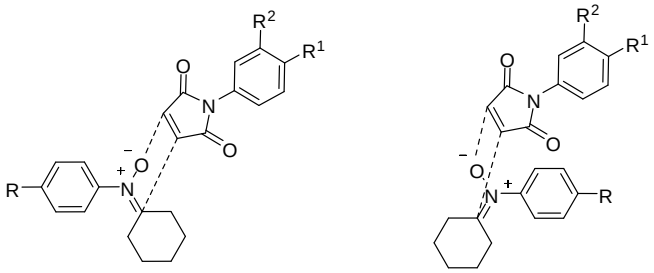
stabilization between one of the carbonyl group of succinimide moiety and the *N*-phenyl group of nitrone (Figure 1).



21 **22** **23**

R = H, Cl, CH_3
R^1 = H, CH_3, OCH_3, Cl
R^2 = H, NO_2

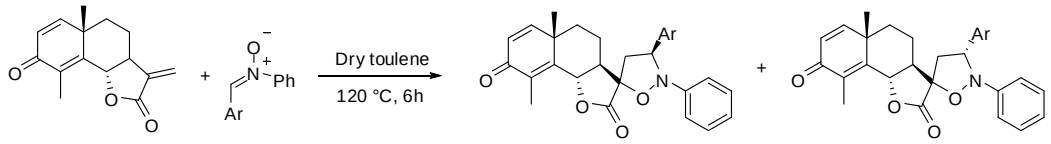
Scheme 8. Synthesis of 3-spiroisoxazolidines **23**.



TS 1 **TS 2**

Figure 1. Transition state (TS) of *exo*- and *endo* approaches.

Throughout the 1990s various studies demonstrated the biological importance of derivatives of α-santonin for their antipyretic, anti-inflammatory and fungicidal activity, although the main interest was toward anti-cancer activity of some compounds resulting from the opening of the lactone ring of α-santonin.[21] In 2013, several spiro-isoxazolidines **26** and **27** were prepared by 1,3-dipolar cycloaddition between nitrones **25** and the exocyclic double bond generated on the α-santonin (**24**) scaffold through appropriate modifications (Scheme 9).[22]



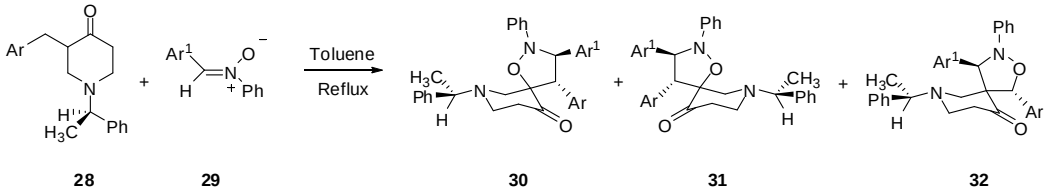
24 **25** **26** **27**

Ar = 4-NO_2-C_6H_4, 4-Br-C_6H_4, 2,5-Cl-C_6H_4, 3-Br-4F-C_6H_4, 3,5-F-C_6H_4, 3-Br-4-OMe-C_6H_4, 3-NO_2-C_6H_4, 1-naphthyl

Scheme 9. Synthesis of spiro-isoxazolidines of α-santonin **26** and **27**.

The reactions proceeded with good yields and an elevated degree of regiocontrol attributed to steric hindrance due to the methyl group present on the six membered ring of dipolarophile. In all cases, two diastereoisomers (**26** and **27)** were observed in a 3:1 ratio. Crystallographic studies of the major stereoisomer determine the configuration of the new chiral centers in *S* and *R* at the C-3 and C-5 positions of the isoxazolidines ring, respectively. All the compounds were tested *in vitro* against some human cancer cell lines with promising antiproliferative results.

In recent times, a synthesis of enantiomerically pure spiroisoxazolidines was realized by adding chiral 3-arylmethylidene piperidones **28** to *C*-aryl-*N*-phenyl nitrones **29** in classic reaction conditions (toluene, reflux) (Scheme 10).[23]



28 **29** **30** **31** **32**

Ar = C_6H_5, 4-Cl-C_6H_4, 4-MeC_6H_4, 2-ClC_6H_4, 2-thienyl, 1-naphtyl

Ar^1 = C_6H_5, 4-MeC_6H_4

Scheme 10. Synthesis of chiral spiroisoxazolidines **30**, **31** and **32**.

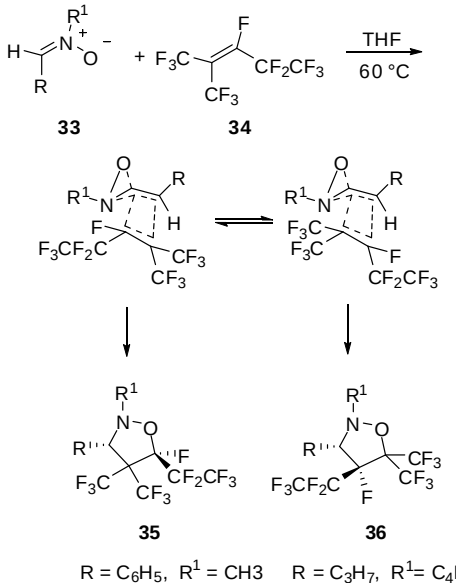
The reaction proceeded with moderate yield and usually in regioselective manner, affording predominantly two diastereisomers (**30** and **31)** that arised from the addition of the oxygen of the nitrone to the carbon in α position of the arylidene group. However, the results pointed out a low diasterestereoselectivity with a slight increased formation of stereoisomer **30** over the **31**, probably due to diminished steric hindrance in the first case than the other. However, in two cycloadditions the formation of spiroisoxazolidines **32** with reversal regiochemistry was also obtained in addition to **30** and **31** adducts. The explanation might be postulate by the reaction of nitrones **29** with two interconvertible diastereomeric conformers of **28**.

2.3. Fluorinated isoxazolidines

The introduction of perfluoroalkyl groups on heterocyclic structures induces a relative metabolic stability and increases the bioavailability of substrate respect to hydrocarbon analogues.[24] Therefore, in 2010, an efficient method was described to synthesize partially-fluorinated isoxazolidines **(35** and **36**, Scheme 11).[25]

The reaction was conducted in THF at 60 °C without using of catalyst between electron-rich nitrones **33** and electron-deficient olefins **34**, obtaining an inseparable mixture of regioisomers **35** and **36** of partially-fluorinated isoxazolidines by a Type I cycloaddition dominated by a $HOMO_{nitrone}$ and $LUMO_{olefin}$ interaction. The aryl or alkyl nature of the substituents of the reagents induced the formation of products with yields from poor to high (40-87%). The moderate regio- and diasteroselectivity of the reaction were

established with the aim of one- and two-dimensional NMR experiments, while the absolute configuration assignment was achieved by X-ray structure.



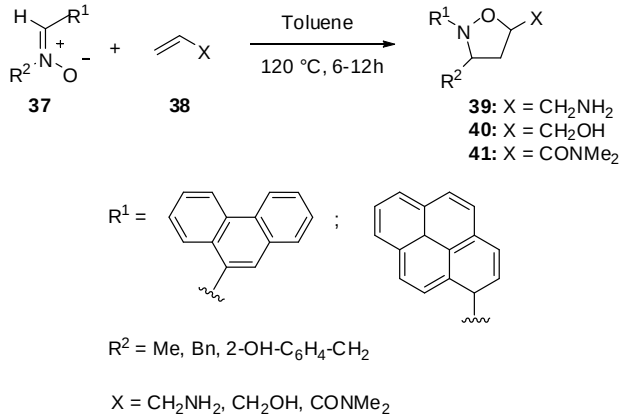
Scheme 11. 1,3-Dipolar cycloaddition of nitrones **33** and perfluoro-2-methyl-2-pentene **34**.

2.4. 3'-Substituted-4'aza-2',3'-dideoxynucleosides

The 4'aza-2',3'-dideoxynucleosides are analogues of the dideoxynucleosides in which a nitrogen atom replaces the 4'-chiral carbon of the dideoxyribose ring of the natural nucleosides, thus providing the system with more conformational degrees of freedom. The 1,3-dipolar cycloaddition between opportune nitrones and alkenes represents the best method to synthesize 3'-substituted-4'aza-2',3'-dideoxynucleosides with a isoxazolidine ring. Structure-activity relationship data reveals that the substitution in C-3' position seems to influence considerably the biological activity of the cycloadducts.

DNA intercalators are molecules that act as antitumoral agents, inserting perpendicularly into DNA base pairs through noncovalet linkages.[26] This feature could be well satisfied by the presence of polycyclic aromatic rings (PAHs); NMR studies on the size and nature of uncharged intercalators indicate that the minimal dimension of aromatic system sufficient to have stacking interactions is represented from three anellated aromatic rings.[27] The presence of a substituent such as hydroxyl or amino group favors generally the formation of possible intermolecular hydrogen bonds, thus increasing the intercalating properties of substrates.[28] Three examples involving the synthesis of isoxazolidinyl polycyclic aromatic hydrocarbons (isoxazolidyl-PAH) with an aminomethyl (**39**)[29] or a hydroymethyl (**40**)[30] or an ammido group (**41**)[31] connected to 5-Carbon of the isoxazolydine moiety are illustrated in Scheme 12. In the first, the reaction components were several nitrones **37** and the opportune allyl compounds **38** that were pleased in a sealed tube, with dry toluene at 120 °C for 6 d. The cycloaddition furnished a mixture of two diastereoisomers in

ca.1,5-2.0:1 ratio, with a yield between 80-92% and the unique 5-substituted regioisomer **39**. The work was supported by molecular docking experiments and biological evaluation against some cancer cellular lines. The insertion of an amino group on the isoxazolidine-PAH scaffold seems increase the intercalating capacity of these compounds through potential hydrogen bonds with the AT nucleobase system. Second, a similar study has been conducted, introducing a hydroxymethyl and 2-hydroxybenzyl groups in position 5 and 2 of isoxazolidine ring (**40**), respectively, to amplify the intercalating power of the substrates through a better interaction with DNA sites. The application of same reaction conditions afforded the only 5-regioisomeric adducts **40** with a *cis*/*trans* ratio of 1.3:1 and yield of 89%. Finally, the insertion of an amido group at C-5 carbon of the isoxazolidine gave substrates **41** with a low level of regio- and *cis*/*trans* selectivity, but with a high intercalating capacity and major biological activity.



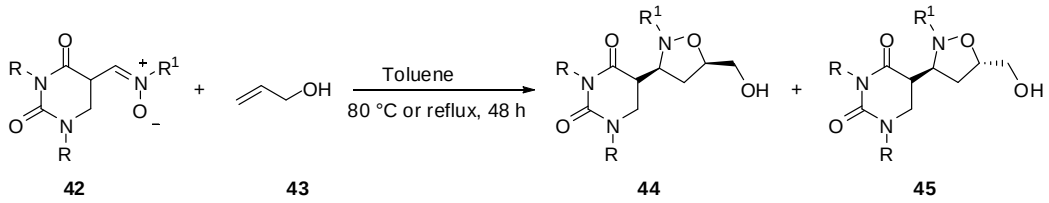
Scheme 12. Synthesis of isoxazolidine-PAHs **39**-**41**.

2.5. *C*-Nucleosides

C-Nucleosides are a class of biologically active nucleosides analogues possessing a nonhydrolyzable C-C rather than the usual N-C glycosyl bond that links base and sugar.[32] In particular, in pseudouridine, which is the most abundant *C*-nucleoside in natural RNA, the C-5 position of uracil is linked to the C-1' position of the sugar, resulting in an increase in hydrogen bonding capacity compared to uracil.[33] The presence of an isoxazolidine ring instead of the sugar unit on the pseudouridine framework may be a versatile way to make potential modified analogues also to use for further transformations to azaheterocycles. The route to construct isoxazolydinyl pseudouridine **44** and **45** was relied on the 1,3-dipolar cycloaddition of suitable nitrones of uracil **42**, prepared from the corresponding aldehydes applying conventional procedures, using allyl alcohol **43** as dipolarophile at reflux for 48 h (Scheme 13).[34]

In almost all reactions moderate diastereofacial selectivity was observed in a ratio 1.5:1, although in one case there was an inseparable mixture of two 5-substituted stereoisomers in a ratio 2:1. The exact configuration of the compounds was assigned by NOE experiments, observing the prevalent formation of *cis* isomer **44**. The experimental observation could find an explanation in the fact that *cis* (**44**) and *trans* cycloadducts (**45**) were formed from an *exo*- and *endo*-approach, respectively, both assuming the *Z*-

configuration of nitrones **42**[35] and considering that hydroxymethyl group not promote secondary orbital interactions that favor the *endo*-TS.



42 **43** **44** **45**

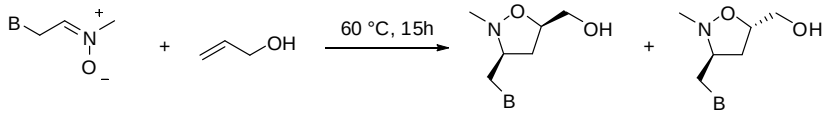
R = CH_3, $CH_3(CH_2)_6CH_2$;

R^1 = H, CH_3, $C_6H_5CH_2$

Scheme 13. Formation of isoxazolydinyl pseudouridine.

2.6. Homonucleosides and homonucleotides

1'-Homo-*C*- and *N*-nucleosides have been designed with the intent to improve the resistance to hydrolytic or enzymatic cleavage as well as to increase the conformational and rotational freedom through the insertion of a methylene group between the nucleobase and the carbohydrate ring.[36] In a recent work, 1'-homo-*N*-nucleosides analogues **48** and **49** bearing an isoxazolidine as a pseudosugar were obtained by a cycloaddition between nitrones of nucleobases (**46**) and allyl alcohol **43**, warming at 60 °C for 15h. (Scheme 14).[37]



46 **43** **48** **49**

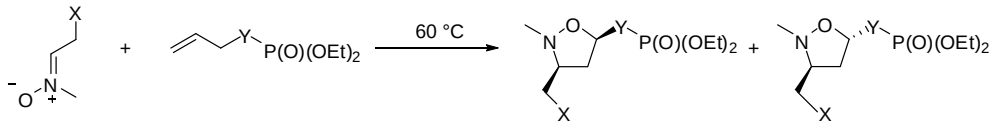
B = Thy, Ura, 5F-Ura, 5Br-Ura, Ade

Scheme 14. Synthesis of homonucleoside analogues **48** and **49**.

This latter reagent allowed to introduce a second hydroxymethyl group on the C-5 position of the isoxazolidine portion, to simulate the $HOCH_2$- group on C-4' residue of the natural nucleosides or to favor further transformations. The cycloadditions proceeded in regioselective manner, favoring the formation of the C-3 regioisomer, while a mixture of *cis*/*trans* diastereoisomers **48** and **49** was observed with a good *cis* selectivity in all reactions. The use of two different conditions reactions (thermal reaction or MW irradiation) showed only a reduction of reaction times in the microwave-assisted synthesis (from 15h to 2.5 h, respectively).

Since the biological activity *in vivo* of 1'-homo-N-nucleosides with a hydroxymethyl moiety in C-5 is generally due to intracellular phosphorylation, the presence of a non-hydrolysable P-C bond (as a phosphonate group) on the scaffold of the homo-derivatives may be really important.[38] Therefore, in 2014, a

more recent development was reported for the preparation of 1'-homo-*N*-nucleotides analogues.[39] The thermal 1,3-dipolar cycloaddition was conducted between allylnucleobases **50** as dipholarofile and phoshonate nitrones **51** as dipole (Scheme 15). By a careful and wide choice of allylsubstrates (substituted purines, pyrimidines, triazines, oxopyrimidines, imidazoles, indoles and morpholines) and solvents (toluene, toluene/ethanol, toluene/chloroform), various 1'-homo-*N*-nucleotides derivatives **52** and **53** were synthesized as a mixture of *trans*/*cis* diastereoisomers with low to moderate *trans*-selectivity. All compounds were screened against a variety of DNA and RNA viruses with promising results for substrates with benzimidazole, indole and benzuracil rings.



50 **51** **52** **53**

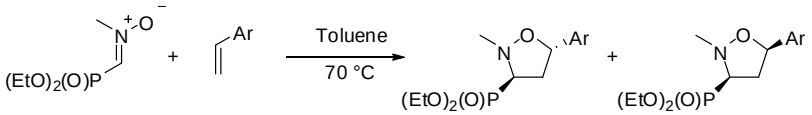
X = nucleobases, purines, pyrimidines, triazines, oxopyrimidines, imidazoles,indoles, morpholines

Y = none, CH_2, CH_2O, CH_2OCH_2

Scheme 15. Synthesis of 1'-homo-*N*-nucleotides analogues **52** and **53**.

2.7. Phosphonated *N,O*-nucleosides

According to the observation that antiviral activity of is related to their conversion to the triphosphate form,[40] phosphonated *N,O*-nucleosides were designed as mimetic of monophosphate nucleosides, bypassing the first step of phosphorylation. Lately, a series of synthesis of isoxazolidine-type phosphonates as analogues of *N,O*-nucleosides was proposed, considering that the nitrogen of isoxazolidine ring could be involved in metal ion coordination, an important step for biological activity.[41] An example was represented by the formation of (3-dialkoxyphosphoryl) isoxazolidines that was achieved starting from *C*-phosphorylated arylnitrones **54** and vinyl aryls **55** by thermal conditions (toluene, 70°C, 24h, Scheme 16).[42]



54 **55** **56** **57**

Ar = 4-MeO-C_6H_4, 3-MeO-C_6H_4, 2-MeO-C_6H_4, 1-naphthyl, 2-naphthyl,

9-anthryl, 9-carbazolyl, imidazolyl, phthalimidyl

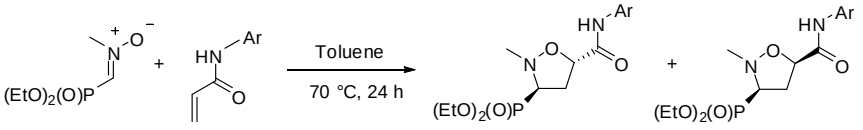
Scheme 16. 1,3-Dipolar cycloaddition between *C*-phosphorylated arylnitrones **54** and vinyl aryls **55**.

In all cases, the major product (**56)** showed a *trans*-configuration in ratios from 85:15 to 97:3 that was determinate through the previous assignment on similar substrates. These compounds were also transformed

in the corresponding phosphonic acids to effect biological evaluation on three cancerous cell lines, noticing very interesting results of activity for two substrates.

To completeness of these results, in 2013, the number of obtained C-3-phosphonated isoxazolidines **56** and **57** was implemented by replacing the functional groups on the aryl moiety of vinyles, confirming the diasterofacial selectivity of the cycloaddition, which, also in this case, favored the *trans* isomer.[43] All phosphonated cycloadducts were screened against some viruses and tumors cells not observing any significant inhibitory activity.

In addition, the insertion of a carbamoyl linkage between the isoxazolidine ring and aromatic group was realized,[44] evaluating that heterocycles with one or more heteroatoms and carbocycles of various size can be considered a valid alternative to the furanose ring.[45] The cycloaddition involved the use of *N*-methyl-*C*-phosphoryl nitrone **54** and several acrylamides **58** as starting materials, warmed in toluene to 70 °C for 24 h (Scheme 17).



54 **58** **59** **60**

Ar = 2-F-C_6H_4, 3-F-C_6H_4, 4-F-C_6H_4, 2,4-diF-C_6H_3, 2-Br-C_6H_4, 3-Br-C_6H_4, 4-Br-C_6H_4, 2-Cl-C_6H_4, 3-Cl-C_6H_4, 4-Cl-C_6H_4, 2-NO_2-C_6H_4, 3-NO_2-C_6H_4, 4-NO_2-C_6H_4, 3-CN-C_6H_4, 4-CN-C_6H_4, 2-CH_3-C(O)C_6H_4, 3-CH_3-C(O)C_6H_4, 4-CH_3-C(O)C_6H_4, 3-CH_3-C_6H_4, 4-CH_3-C_6H_4, 3-CH_3O-C_6H_4, 4-C_2H_5O-C_6H_4, 3,4-di-CH_3O-C_6H_3, 3,5-di-CH_3O-C_6H_3, 3,4,5-tri-CH_3O-C_6H_2, 4,5-di-CH_3O-2-CN-C_6H_2, 4,5-di-CH_3O-2-CH_3C(O)-C_6H_2

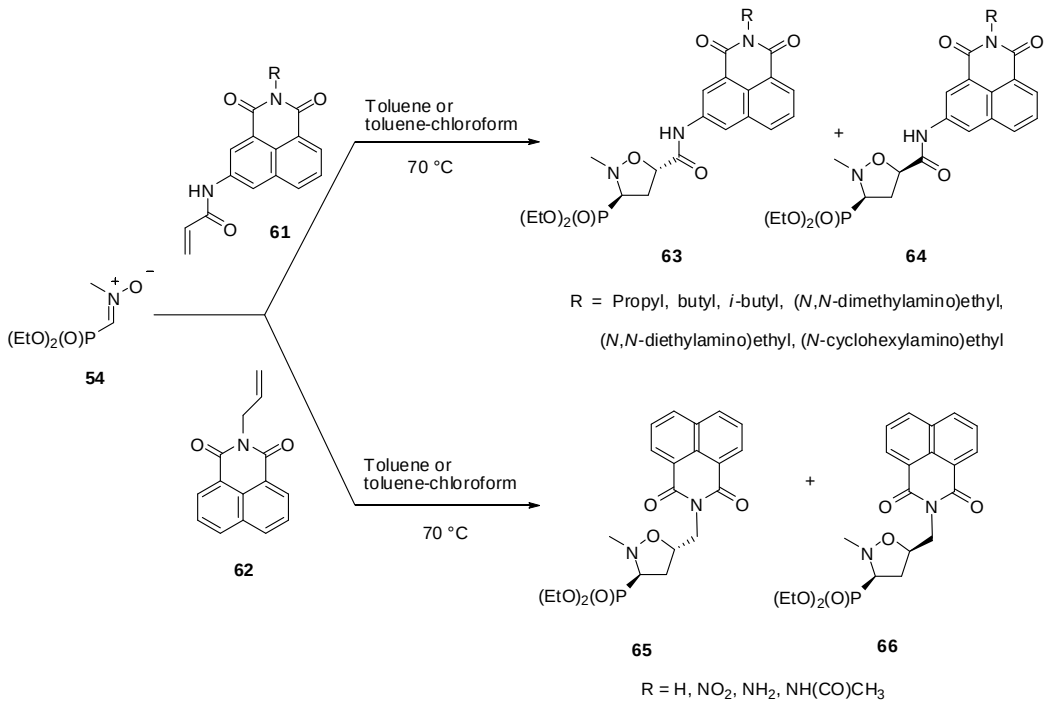
Scheme 17. Synthesis of compounds **59** and **60**.

An enriched diastereoisomeric mixture was obtained for all substrates with a prevailing majority for *trans* isomer **59** (up to 80%), confirmed by NOE experiments and ^{1}H and ^{13}C NMR measurements of PCCH and PCCC vicinal couplings. The antiviral activity of the synthetized phosphonate heterocycles was not significant although some *cis*-configurated isoxazolidines behaved as good anticancer agents.

In 2015, in the wake of the previous works, phosphonated isoxazolidine containing amonafide residues as intercalators were synthesized, exploiting the thermal cycloaddition of *N*-substituted naphthalimide acrylamides (**61**) or *N*-allylated naphthalimides (**62**) with *N*-methyl-*C*-phosphoryl nitrone **54**. The cycloaddition produced a diastereomeric mixture of products, the major product of which was the *trans* isomer **63** with a diastreomeric excess of 56-72% and 72-82%, respectively (Scheme 18).[46]

The chemical scaffold of these substrates could be the responsible of the significant biological activity of both *trans* (**63** and **65**) and *cis* adducts (**64** and **66**) against viruses as varicella-zoster, cytomegalovirus and HSV, if compared to approved drugs such as ganciclovir, acyclovir, ribavirin, etc.

Truncated phosphonated carbocyclic 2'-oxa-3'-aza nucleosides (TPCOANs) represent a class of phosphonated nucleoside analogues in which the phosphonate group is directly linked to the C-4' position of the sugar-mimicking moiety, which may be represented by a isoxazolidine ring.



Scheme 18. Synthesis of phosphonated isoxazolidine containing amonafide residues.

Truncated phosphonated C-1'-branched *N,O*-nucleosides **71** and **72** were achieved by a two-step procedure that involved an initial 1,3-dipolar cycloaddition between *N*-methyl-*C*-(diethoxyphosphoryl) nitrone **54** and ethyl 2-acetyloxyacrylate **67** in THF at reflux for 24 h with good *trans* selectivity (*cis*:*trans* ratio 1:4.5) and high yield (80%).[47] Subsequently, the crude mixture of the obtained isoxazolidines (**69** and **70**) was reacted with opportunely protected nucleobases, according to glycosylation procedure of Vorbrüggen (Scheme 19).[48]

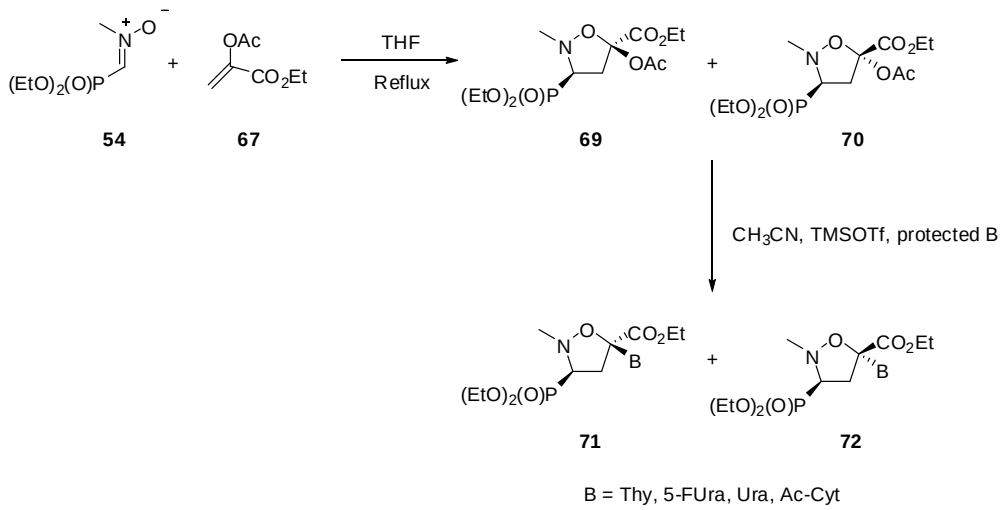
The resulting anomeric distribution of products was dependent on the used nucleobase; in fact, a mixture of the β- and α-anomers in a ratio of 3:2 has been obtained with thymine, uracil and *N*-acetylcytosine, while a better selectivity in favor of the β-anomer has been achieved by using 5-fluorouracil (α:β ratio 1:4).

3. Thermal intramolecular 1,3-dipolar cycloaddition

3.1. Fused isoxazolidines

Intramolecular 1,3-dipolar cycloadditions represent a very important method capable to construct fused ring structures in an higher degree of regio- and diasteoselectivity respect to intermolecular reactions, due to entropy factors and limited conformational mobility in the transition state.[49]

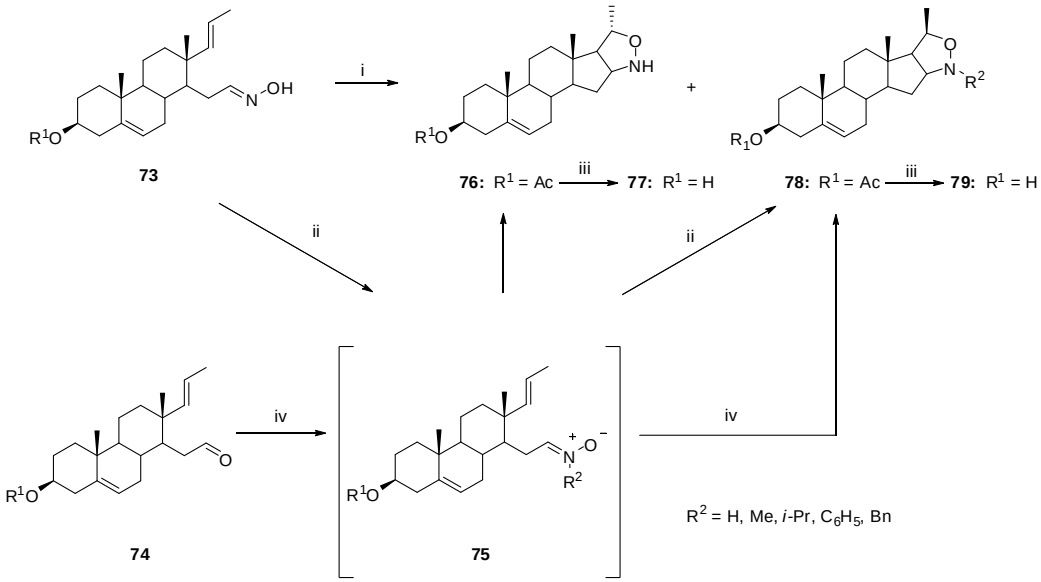
Recently, the synthesis of D-ring-fused steroidal isoxazolidines was developed, considering that steroidal compounds containing heterocyclic moieties may be very interesting bioactive substrates.[50]



54 **67** **69** **70** **71** **72**

Scheme 19. Synthesis of truncated phosphonated C-1'-branched *N,O*-nucleosides.

Initially, exploiting the internal ring closure of alkenyl oximes to form isoxazolidines, olefinic nitrones **75** were prepared *in situ* from D-secopregnene aldoxime **73** in a mixture of *E*- and *Z*-isomers in the ratio of 3:4, respectively, using isopropyl alcohol as solvent (Scheme 20).



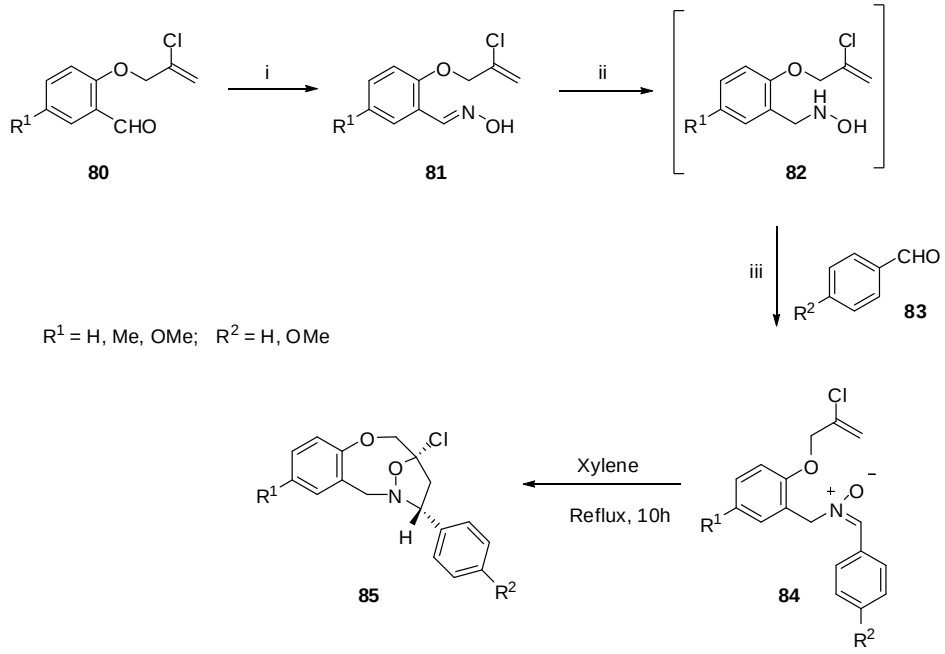
73 **74** **75**

(i) $BF_3{\cdot}OEt_2$, CH_2Cl_2, rt, N_2 atm, 6h; (ii) toluene, 111 °C, 6h; (iii) KOH, MeOH, rt, 2h; (iv) $R_2NHOH.HCl$ (80), NaOAc, MeOH, 65 °C, 2h

Scheme 20. Formation of D-ring-fused steroidal isoxazolidines.

The resulting crude was employed in thermal intramolecular cycloaddition in refluxing toluene, providing a 3:2 mixture of cyclic diastereoisomers **76** and **78** with poor yield (51%). However, the course of reaction may be changed by the addition of $BF_3 \cdot Et_2O$ as Lewis acid-catalyst at room temperature, observing the formation of a single stereoisomer (**76**) and a yield of 85%. Moreover, the direct cycloaddition of secopregnene aldehyde **74** with *N*-substituted hydroxylamines **80** in methanol at reflux furnished the other diastereomer (**78**) with yields highly dependent on the nature of substituents on hydroxylamines. Furthermore, the work was supported by theoretical studies and *in vitro* biological tests of inhibition of C_{17-20}-lyase enzyme.

More recently, the intramolecular synthesis of chlorinated isoxazolidines was realized through a thermal 1,3-dipolar cycloaddition by choosing 2-chloroallyloxy nitrones **84** as starting material (Scheme 21).[51]



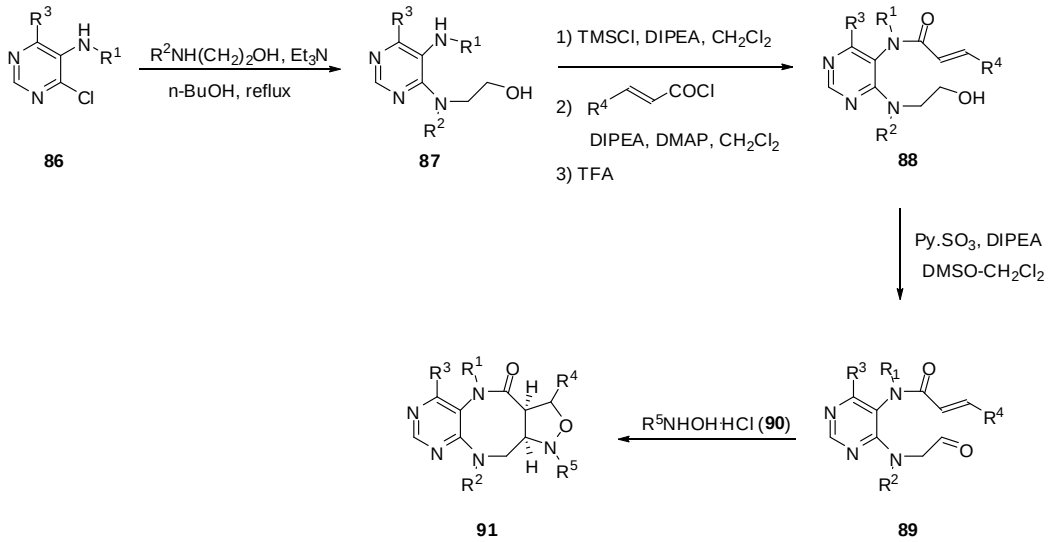
i = $NH_2OH.HCl$, EtOH, reflux, 3h; ii = $Na(CN)BH_3$, MeOH, HCl, 3h; iii = CH_2Cl_2, anhydrous $MgSO_4$, 10-15h

Scheme 21. Dipolar cycloaddition between nitrones **84** and aldehydes **83**.

The preparation of nitrones **84** was performed starting from the initial conversion of 2-chloroallyloxy aldehydes **80** in the corresponding oximes **81** and their subsequent reduction to no-isolable hydroxylamines **82** with $Na(CN)BH_3$ in methanol. Finally, condensation with suitable aldehydes **83** gave stable nitrones with 65-75% yield that refluxed in xylene for 9-12 h, furnished the chlorinated isoxazolidines **85** with excellent yield. The output of the cycloaddition was observed to depend on the solvent applied: although the

dichloromethane reduced considerably the reaction times (1.5 h), the use of xylene allowed the highest yields. The exclusive formation of one diastereoisomer could be explained through the bridged-ring transition state of *Z*/*E* nitrones. In fact, this bridged scaffold may energetically favor the *Z*-nitrone transition state at the expense of the more reactive *E*-nitrone.

In 2015, an approach to the synthesis of isoxazolidine-fused eight-membered heterocycles **91** was developed by intramolecular nitrone-alkene cycloaddition reaction (Scheme 22).[52] The strategy of synthesis of these heterocyclic adducts contemplated an initial production of pyrimidine substituted aminoethanols **88** by a one-pot three-step sequence (orthogonal protection of the hydroxyl- and amino- groups and subsequent deprotection of OH moiety) followed by an oxidation reaction to aldehydes (**89**). Crude aldehydes were used for the cycloaddition reaction with *N*-substituted hydroxylamine hydrochloride **90** without preliminary purification. The resulting *cis*-fused products **91** have been obtained after investigation of optimal reaction conditions through a careful screening of different solvents, temperatures and bases with yields from good to high (53-87%). An accurate dissertation was done on the nature and dimensions of substituent groups that affected the yields of the reaction without changing the diasteroselectivity.



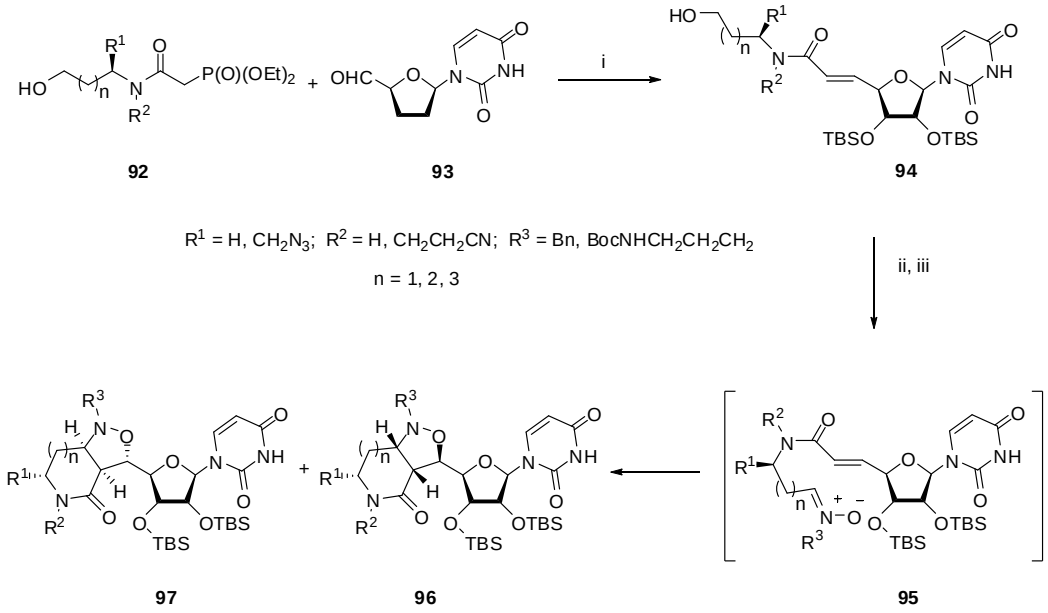
R^1 = Me, allyl, Bn; R^2 = Me, Bn, c-Hex; R^3 = 4-MeOC$_6$H$_4$S, Cl, pyrrolidinyl; R^4 = H, Me, Ph; R^5 = Me, Bn, hexyl, Ph

Scheme 22. Strategy to access isoxazolidines fused eight-membered heterocycles **91**.

Muraymycins[53] and caprazamycins[54] belong to a class of liponucleosides antibiotics characterized by a uridine with a 5'-*O*-aminoribosyl-5'-*C*-glycyne residue and a 5'-*C*-diazepanone moiety, respectively, which can give rise to problems associated to epimerization and β-elimination; moreover, their preparation generally requires complex and length steps of synthesis.

A recent idea was the insertion of a simpler scaffold as lactam-fused isoxazolidines.[55] The choice of this moiety could allow to modulate the three dimensional orientation of the key functional groups simply by

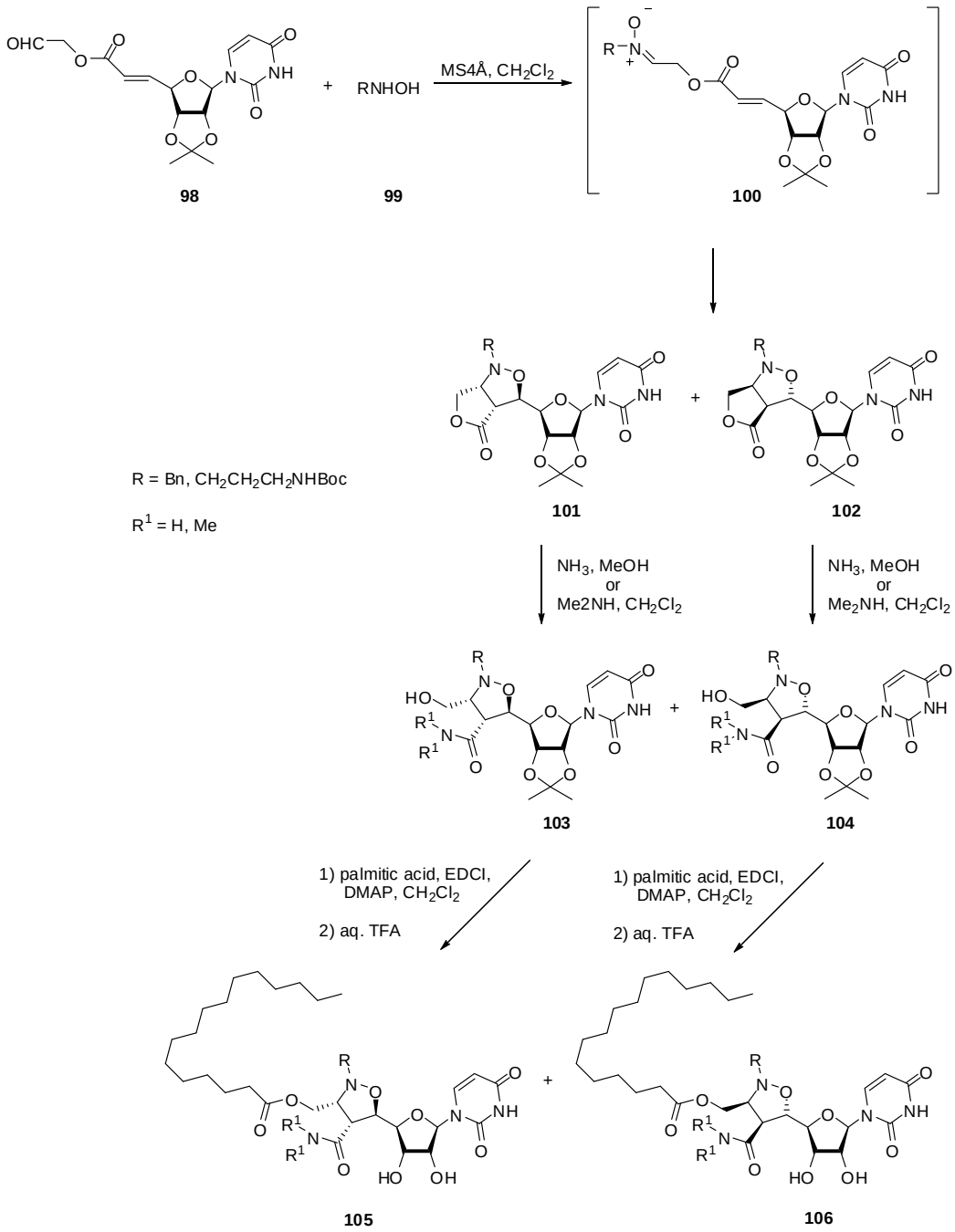
modifying the stereochemistry or the fused-ring size. A series of lactam-fused isoxazolidine core compounds **96** and **97** was synthesized by using a rapid and efficient synthetic route as the intramolecular cycloaddition of alkenyl nitrones (Scheme 23). The initially formed *trans* α-β-unsaturated amides (**94**) was combined with 2-iodoxybenzoic acid to oxidize *in situ* the primary hydroxyl functional group to aldehyde which on intramolecular cycloaddition with hydroxylamines yielded the desired substrates through the intermediate no-isolable nitrone **95**. The reaction yields were strongly dependent from the ring dimensions, decreasing dramatically from 77% of yield for *cis*-bicyclo[4.3.0]-type isoxazolidines to no product for bicyclo[6.3.0]-type isoxazolidines. Therefore, the cyanoethyl group insertion on carboxamide portion has been proposed as a solution to problem, considering that the suggested *N*-protection could induce conformational changes to favor intramolecular reaction; really, this insertion process increased considerably the yields for all substrates (78%-82%). Finally, further transformation by linking a lipophilic side chain and an arginine residue furnished a set of compounds **96** and **97** that were tested as antibacterial agents.



i = $Zn(OTf)_2$,TMEDA, Et_3N, THF; ii = IBX, MeCN/DMSO; iii = R^3NHOH, MeCN

Scheme 23. Synthesis of lactam-fused isoxazolidines **96** and **97**.

In 2015, a variety of isoxazolidine structures analogues of caprazamicina (**105** and **106**) was constructed by intramolecular cycloaddition of alkenyl nitrones **100** followed by a ring-opening of the fused lactone-moiety and subsequent acylation of the resulting primary alcohol to introduce key substituents on the scaffold (Scheme 24).[56] The stereoselective trend of cycloaddition gave a mixture of *anti*-products, while *syn*-adducts were obtained when Lewis acids as $MgBr_2 \cdot OEt_2$, $ZnCl_2$ or $Sc(OTf)_3$ were added to reaction.



Scheme 24. Synthesis of caprazamycin analogues.

Antibacterial evaluation was performed against a range of bacterial pathogens; the results highlighted that isoxazolidine analogues **106** with the same stereochemistry of caprazamicina at the 5'-position exhibited a good antibacterial activity.

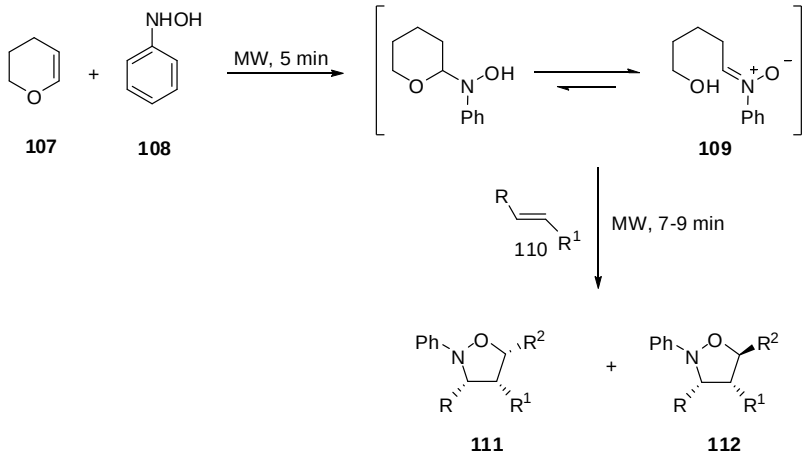
4. Microwave-assisted 1,3-dipolar cycloaddition

The beneficial effects of microwave irradiation are finding an increased role in process chemistry, especially in cases when usual methods require drastic reaction conditions or prolonged times.

This non-conventional energy source is able to reduce chemical reaction time and the formation of by-products, increasing yield.[57] In the last years, microwave reactions has been successfully applied to 1,3-dipolar cycloadditions, observing reactions quite often cleaner and faster than conventional thermal method. Generally, reactions give higher selectivity and yields when microwave heating is used. Moreover, this methodology can be regarded as environmental friendly, mainly because solvent-free reactions are especially suited to microwave conditions.

4.1. Fused isoxazolidines

In 2012, solvent-free microwave technology was used to perform a green synthesis of heterocycloadducts, starting from dihydropyran derived nitrone **109**, prepared *in situ* by treating 2,3-dihydro-4*H*-pyran (**107**) with *N*-phenylhydroxylamine (**108**).[58] A set of cyclic and acyclic alkenes **110** was reacted with non-isolable nitrone **109** in absence of solvents and by MW irradiation, achieving prevalently bicyclic *cis*-isoxazolidines **111** with high yields and moderate diastereofacial control (Scheme 25).



R = CONMeCO, CONPhCO, CONCyCO, $COOCH_2CH_3$, C_6H_5
R^1 = CONMeCO, CONPhCO, CONCyCO, H; $R^2 = (CH_2)_4OH$

Scheme 25. Strategy to synthesize novel isoxazolidine derivatives **111** and **112**.

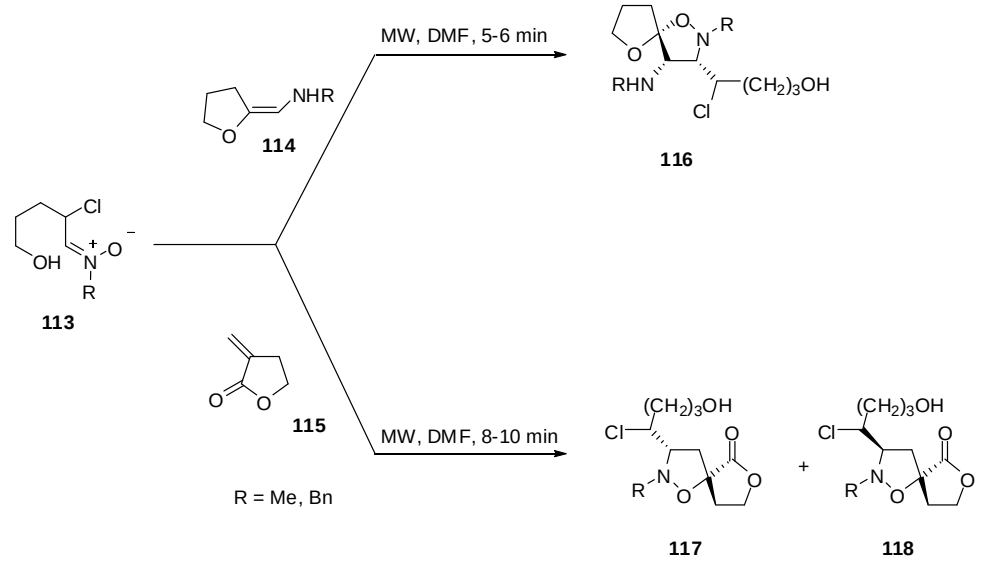
The thesis of an *exo*-approach of *Z*-nitrone for the formation of major product was supported as well as in the transition state, because of the 4,5-fused pyrrolidindione, the isoxazolidine ring adopts an envelope

conformation with nitrogen atom directed out of the envelope (minor conformation) or inside (major configuration). In all diastereomers the configuration of H-3, H-4 and H-5 are *cis* as well as in the case of the two examples of cycloaddition with acyclic nitrones. Moreover, a useful application of the obtained isoxazolidines **111** and **112** was represented by their subsequent conversion to 1,3-aminoalcohols by Zn powder in acetic acid under microwave irradiation.

4.2. Spiro-isoxazolidines

In 2012, the formation of 5-spiro isoxazolidines **117** and **118** was performed using α-chloronitrones (**113**) as dipole and α-*N*-methyl/phenyl furan derivatives (**114**) or α-methylene-γ-butyrolactone (**115**) as dipolarophiles under irradiation of domestic microwave oven for a specific time (5-10 minutes) (Scheme 26).[59]

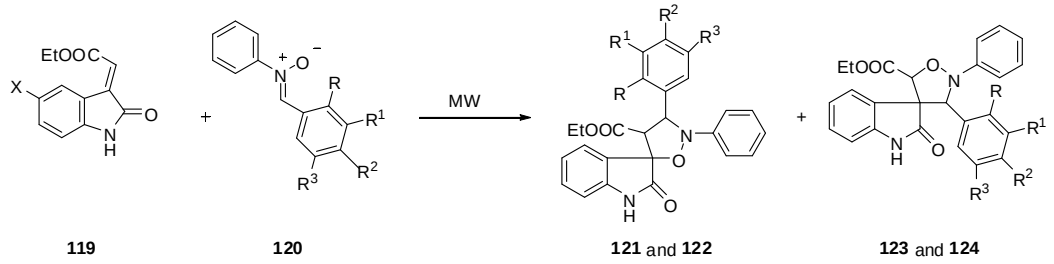
Excellent regio- and diastereoselectivity towards 5-isomer *via* an *exo*-approach of *Z*-nitrone were observed in reaction with *C*-*N*-methyl/phenyl furan derivatives, while good diastereofacial selectivity was obtained in reaction with α-methylene-δ-butyrolactone, in which a mixture of diastereisomers was evidenced in the ratio approximatively 75:25 in favor of *exo*-cycloadducts. In subsequent year, the work was extended to the synthesis of various 5-spiro isoxazolidines deriving from α-chloronitrones and α-*N*-substituted furan derivatives by varying substituent groups of starting materials, with the further purpose of transforming them into corresponding 1,3-aminoalcohols.[60]



Scheme 26. Microwave-assisted synthesis of novel spiro-isoxazolidines.

The biological importance of compounds containing spiro carbon at C-3 position of indoline or oxindole skeleton has been emphasized in the literature.[61] More recently, the regioselective synthesis of spiro-indoline-isoxazolidines was achieved by the microwave-assisted cycloaddition between ethyl (5-

fluoro-2-oxo-1,2-dihydro-3(*H*)-indol-3-ylidene)-acetate/ethyl(2-oxo-1,2-dihydro-3(*H*)-indol-3-ylidene)-acetate (**119**) and substituted *C*,*N*-diphenylnitrones (**120**) (Scheme 27).[62] An initial multi-step approach was conducted to synthesize the precursors **119**, which were reacted with α,*N*-diphenylnitrones **120** under microwave irradiation (850 W) and solvent-free conditions, isolating two series of spiro-indoline-isoxazolidines (**121-122** and **123-124**). The regioselectivity of reaction was totally reversed for substrates with a fluorine atom in C-5 position of isatine ring, because of a probable exocyclic double bond shifting in (5-fluoro-2-oxo-1,2-dihydro-3(H)-indol-3-ylidene)-acetate/ethyl(2-oxo-1,2-dihydro-3(H)-indol-3-ylidene)-acetate (**119**) in two different mode. It is possible that the high electronegativity of fluorine atom decreases the electronic density of aromatic ring, favoring the conjugation of nitrogen lone pair toward aromatic group. In this way, the α-electrons polarize towards C-3 respect to C-10; differently the polarizability of the α-electrons favors C-10 position when a less electronegative hydrogen atom replaces fluorine atom in C-5. NMR studies allowed the assignment of the absolute configuration of the three newly formed stereocenters in (*R*) C-3', (*R*) C-5' and (*S*) C-4' for **121** and **122** while (*R*) C-3', (*R*) C-5' and (*R*) C-4' for **123** and **124**. All substrates were checked as anti-inflammatory against human umbilical vein endothelial cells (HUVECs), observing significant inhibitory activity.



119 **120** **121** and **122** **123** and **124**

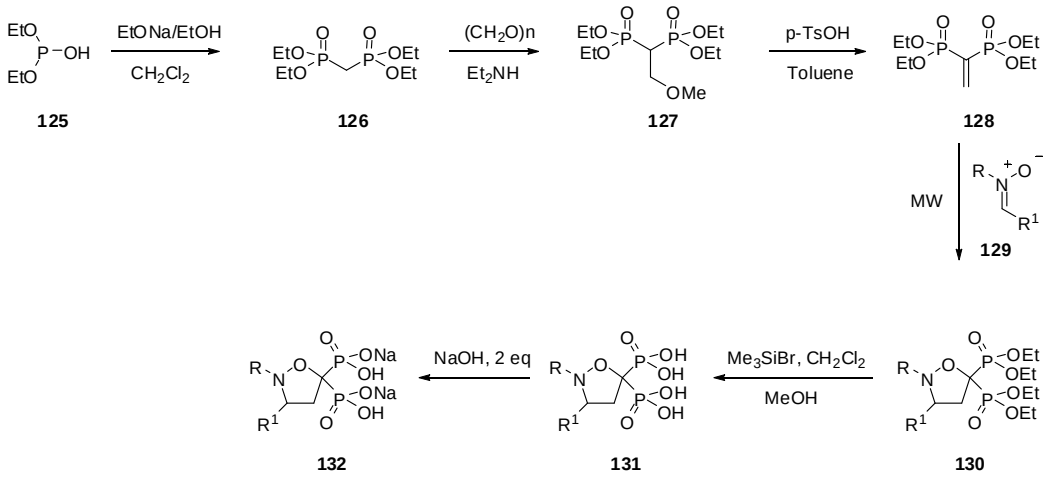
X = F, H; R = H, OMe; R^1 = H, Me, OMe, F, Cl, Br, NO_2; R^2 = H, Me, CN, CF_3, OMe, OEt, F, Cl, Br, NMe_2, NO_2; R^3 = H, OMe

Scheme 27. Synthesis of spiro-indoline-isoxazolidines.

4.3. Bisphosphonated isoxazolidines

Geminal bisphosphonates (BPs) are structural and stable analogues of naturally occurring pyrophosphates and constitute an important class of pharmacologically active molecules used in the treatment of bone diseases as osteoporosis, Paget's disease, and tumor bone diseases.[63] The studies on the inhibitory potency of nitrogen cycles containing bisphosphonates indicate that the presence of two geminal phosphonate groups is determinant for interaction with the molecular target. In addition, a basic nitrogen in the heterocyclic side chain affects potency. Therefore, a recent proposal considered the synthesis of a new class of bisphosphonates having in *gem* position an isoxazolidine ring that simultaneously holds the required basic nitrogen and an oxygen atom in place of the hydroxyl group, acting as third hook.[64]

The key step in the synthesis involved the formation of dipolarophile tetraethylvinylidene-1,1-bisphosphonate **128** that was prepared in high yields with a three step-reaction, starting from diethyl posphite (**125**) and sodium ethoxide (Scheme 28).

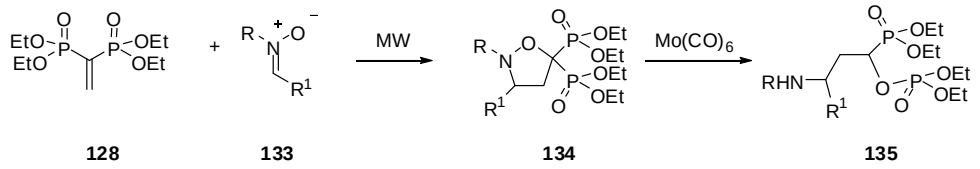


R = Me, Bn; R^1 = Ph, *o*-Cl-C6H4, 3-Pyridyl, 2-Furyl, *p*-OH-C_6H_4, *o*-F-C_6H_4

Scheme 28. Synthetic process to obtain bisphosphonate isoxazolidines **130** and their sodium salts **132**.

The final cycloaddition reaction of nitrones **129** with bisphosphonate vinyl derivative (**128**) came as result of several attempts to optimize the reaction protocol that preferred free-solvent condition and MW irradiation to conventional conditions (toluene or dichloromethane at reflux) or presence of Lewis acids as catalyst. A low MW power (200W), a short reaction time (10-20 min) and a slight excess of nitrone were required to complete the cycloaddition, isolating bisphosphonate isoxazolidines **130** in high yields. The regiochemistry of the reaction, detected by decoupling ^{1}H NMR experiments, followed the usual pattern with exclusive formation of the 5-bisphosphonated isomer over the 4-derivative. Accordingly, the cycloaddition takes place between the *Z*-nitrone and the vinylidene bisphosphonate, with attack of the *N*-oxygen atom on the germinal carbon of the vinylidene group. Considering that bisphosphonates are calcium-regulating agents used in the form of the sodium salt, the synthetized bisphosphonate esters (**130**) were hydrolyzed and the resulting acids **131** were transformed into the corresponding disodium salts **132** by reaction with two equivalent of aqueous NaOH, to exalt their biological activity.

In 2014, an application of isoxazolidine-substituted bisphosphonates was proposed through their transformation into molecules containing *gem*-phosphonate-phosphate group (Scheme 29).[65]



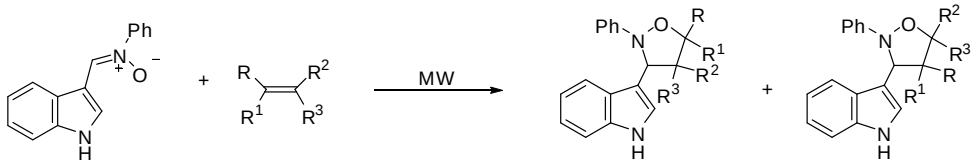
R = Me, Bn; R^1 = Ph, 2-Cl-C_6H_4, 4-Cl-C_6H_4,Naphthyl, 2-F-C_6H_4

Scheme 29. Synthesis and ring opening of bisphosphonate isoxazolidines **134**.

The literature reports that *gem*-phosphonate-phosphate derivatives shows an interesting biological activity in the treatment of sclerosis and of diseases associated to the poor production of apoliprotein E.[66] Therefore, a set of bisphosphonates bearing a substituted isoxazoldine ring in germinal position (**134**) were prepared by eco-friendly regioselective cycloaddition (solvent-free condition, MW irradiation). Successively, the isoxazolidine ring was opened through cleavage of the *N-O* bond, producing *gem*-phosphonate-phosphate substrates **135**.

4.4. 3'-Substituted-4'-aza-2',3'-dideoxynucleosides

Pyridinyl isoxazolidines are substrates with a pyridyl group in the C-3 position of isoxazolidine ring, which have exhibited good anticancer activities.[67] Recently, a substitution of pyridyl group with an indole ring was proposed and 3-indolyl-isoxazolidines (**138** and **139)** were synthesized under solvent-free microwave irradiation conditions in stereoselective manner with high yields. The cycloadditions were performed between *C*-(3-indolyl)-*N*-phenylnitrone **136** and mono-substituted, disubstituted and cyclic dipolarophiles **137** at 150 W and 100°C in a short time (Scheme 30).[68] All isoxazolidine analogues **138** and **139** were obtained in high yield and good stereoselection towards **138** isomer and, successively, were evaluated against various human cancer cell lines.



136 **137** **138** **139**

R = H, Me, C(O)-N(Ph)-C(O); R^1 = H; R^2 = H, Me, C(O)-N(Ph)-C(O)

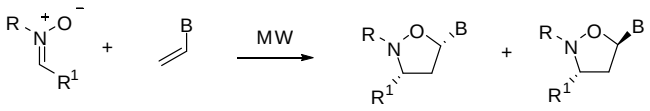
R_3 = Ph, CO_2CH_3, pyridyl, CN, $CONH_2$, $COCH_3$

Scheme 30. Synthesis of substituted 3-indolyl-isoxazolines.

N-vinylnucleobases may represent important starting materials for the synthesis of *N,O*-nucleoside derivatives.[69] Therefore, exploiting the protocol for the direct vinylation of nucleobases through the reaction between transient protected nucleobases and vinyl acetate,[70] the generation of a class of 3'-substituted-4'aza-2',3'-dideoxynucleosides **142** and **143** was obtained by reacting unprotected vinylnucleobases **141** and suitable nitrones **140** in the absence of solvent and /or catalyst using MW irradiation (Scheme 31).[71]

The cycloadducts are formed in good yield and with a remarkable *cis-trans* selectivity, in some cases higher than 99:1 (de 98%). The stereoselectivity of the reaction may be predicted taking into account the possible geometries of approach of the two reacting species. The obtainment of the *cis* adduct **142** is explained by invoking either an *exo*-approach of the alkene to the (*Z*) nitrone isomer or an *endo* approach to the (*E*) nitrone isomer. The corresponding opposite parallel may be done in the case of *trans*-cycloadducts **143**. Considering that *N*-tert-butyl or *N*-aryl nitrones exist almost exclusively as (*Z*)-isomers, the approach

for this cycloaddition was predominantly of (*Z*)-*exo* type. In contrast, with *N*-methyl, *N*-phenyl, and *N*-benzyl nitrones it was possible the formation under microwave conditions of small quantities of (*E*) isomers by possible *E*/*Z* interconversion, giving account for the formation of minor amounts of *trans*-cycloadducts.



140 **141** **142** **143**

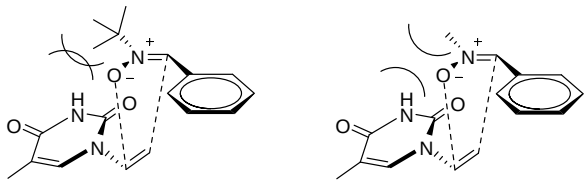
B = Thy, Ura, Cyt, 5-F Ura, Ade

R = Me, Bn, Ph, *t*-butyl

R^1 = Ph, 2-furyl, 2-Cl-C_6H_4, 2-OH-C_6H_4, 4-OH-C_6H_4, 4-NO_2-C_6H_4

Scheme 31. Synthesis of *N*, *O*-nucleosides via cycloaddition of nitrones **140** and vinylnucleobases **141**.

Variable-temperature NMR spectra showed the presence of the sole (*Z*)-isomer of nitrone, even after heating at 80 °C for 24 h or after MW-irradiation for 10 min, thus excluding an *E*/*Z* isomerisation. Consequently, the formation of minor amounts of *trans*-cycloadduct may be explained by the occurrence of a second reaction pathway for the diene-dienophile approach, that is, the (*Z*)-*endo*. This latter reaction channel is not active in the case of bulky *N*-substituents due to a disfavored transition state (TS 1) if compared with the approach of smaller *N*-alkyl nitrone derivatives to the dienophile (TS 2) (Figure 2).



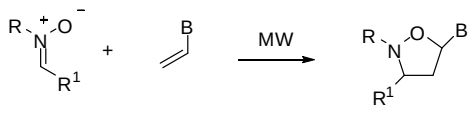
TS 1 **TS 2**

Figure 2. Model transition states for the diene-dienophile approach.

Most of the *N*,*O*-nucleoside derivatives prepared according to this procedure were evaluated by *in vitro* assays for their antiproliferative activity against human lymphoblastoid cell lines (LCL), Ji-Joye cells, an EBV-positive Burkitt cell line and Jurkat cells, a human T-cell lymphoblast-like cell line with good capacity to inhibit the cancer cell growth at a relatively low concentration.

Successively, in 2014, a small library of 3'-substituted-4'aza-2',3'-dideoxynucleosides **146** were synthesized through same reaction conditions by investigation of variations in the four canonical quadrants according to specific absorption rate (SAR) tests[72] designed to prove the minimal structural requirements for antiproliferative activity in the NCI 60 panel of human cancers (Scheme 32).[73]

SE quadrant was varied with thymine or fluorouracil as nucleobases, while NW and SW quadrants were modified with various R and R^1 substituents, respectively (Figure 3).



144 **145** **146**

B = Thy, 5-FUra

R = Me , *t*-butyl, Bn

R^1 = Ph, 2-Cl-C_6H_4, 2-F-C_6H_4, 4-Cl-C_6H_4, 3-pyridyl, 1-naphthyl

Scheme 32. Synthesis of *N*, *O*-nucleosides by microwave-induced 1,3-dipolar cycloaddition.

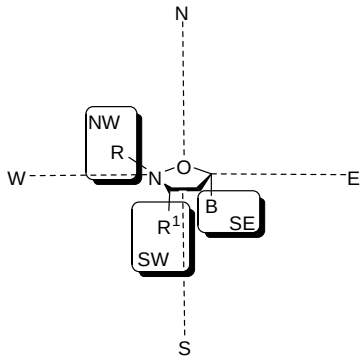


Figure 3. Representation of isoxazolidines in quadrants for changes of B, R and R^1.

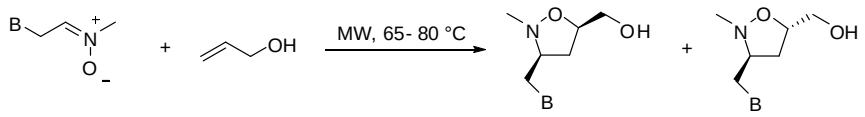
The structural changes planned by SAR tests were crossed with physicochemical data related to solubility and permeability.[74] The combination of these data with *in vitro* test of all isolated substrates confirmed that thymine, *N*-benzyl substituents and aromatic rings were the optimal combine for biological activity against different lines of ovarian and colon carcinoma.

4.5. Homonucleosides

Based on the idea of replacing a furanose ring with a isoxazolidine moiety and introducing a methylene bond between the sugar mimetic ring and the nucleobase, MW-induced 1,3-dipolar cycloadditions between allyl alcohols **43** and nitrones of nucleobases **46**, were conducted to afford homonucleosides analogs **48** and **49** (Scheme 33).[37] The same cycloadditions were conducted in parallel by thermal conditions and have already been described in Scheme 14. Excellent regioselectivity towards the 5-substituted isoxazolidines was observed, while moderate to good diastereofacial selectivity in favor of the *cis* isomer **48** was obtained, as confirmed by 2D NMR spectral data. The comparison of the results with those obtained by thermal condition highlighted the remarkable reduction of reaction time (from 15h to 2.5h).

Moreover, under same reaction conditions, uracil-derived nitrone **147** was reacted with vinyl-, allyl-, vinyloxymethyl- and allyloxymethylphosphonates **51** to form a mixture of two diastereoisomers of 5-phosphonated homonucleosides **148** and **149** at greater abundance to *cis* isomer (**148**) than *trans* isomer

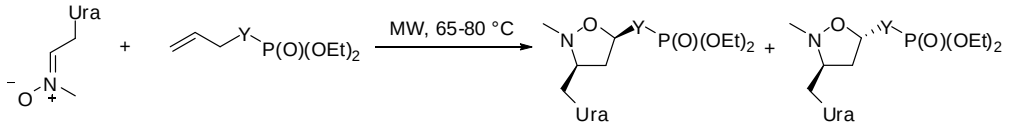
(**149**) (Scheme 34). The *cis* and *trans* configuration of the all diastereoisomers were assigned through ^{1}H and ^{13}C NMR spectra.



46 **43** **48** **49**

B = Thy, Ura, 5F-Ura, 5Br-Ura, Ade

Scheme 33. Synthesis of homonucleosides **48** and **49** by microwave irradiation.



147 **51** **148** **149**

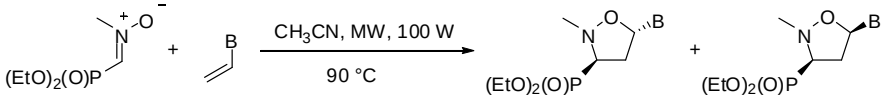
Y = none, CH_2, CH_2O, CH_2OCH_2

Scheme 34. Formation of 5-phosphonated homonucleosides **148** and **149**.

4.6. Phosphonated *N,O*-nucleosides

Truncated phosphonated carbocyclic 2'-oxa-3'-aza nucleosides (TPCOANs), are a class of *N,O*-nucleosides characterized by a phosphonate group directly linked to the *C*4'-position of the isoxazolidine moiety, which mime the first monophosphate group of natural nucleosides.

Recently, a one-step procedure was suggested for the formation of TPCOANs.[75] Vinylnucleobases **145** as dipolarophile and phosphonate nitrones **54** as dipole were employed in 1,3-dipolar cycloaddition (Scheme 35) and, by careful choice of solvent and reaction conditions (CH_3CN, MW, 100W, 90 °C) it was possible to isolate final phosphonated cycloadducts **150** and**151** with good yields and high distereomeric selectivity towards *trans*-isomer (**150**), as confirmed by 2D NOE NMR experiments.



54 **145** **150** **151**

B = Thy, 5F-Ura

Scheme 35. Synthesis of truncated phosphonated carbocyclic 2'-oxa-3'-aza nucleosides.

5. Catalyzed 1,3-dipolar cycloaddition

In the 1,3-dipolar cycloaddition with nitrones as dipole, the catalysis plays a fundamental role in the regiochemistry and stereochemistry of synthesis. In fact, the catalyst role is not only limited to lower the

energy of HOMO-LUMO molecular orbital interaction but also to control the regioselectvity, diastero- and enantioselectivity (in the case of chiral catalyst) of the reaction.

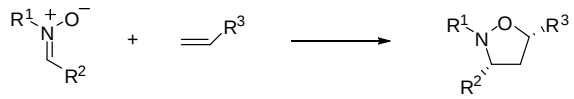
In addition, the choice of the employed catalyst determines which substrate (dipole or dipolarophiles) is activated to a normal or inverse electron demand reaction. The normal electron-demand reaction is a HOMOdiene-LUMOdienophile-controlled cycloaddition, which predominantly occurs between electron-rich dienes and electron-deficient dienophiles. The inverse electron-demand cycloaddition reaction is primarily controlled by a LUMOdiene-HOMOdienophile interaction, which can be found for alkenes with electron-donating groups.[2] Recent developments in catalysis have emphasized the value of asymmetric 1,3-dipolar cycloadditions as fast and clean reactions towards functionalized and diastereo- and enantiopure *N,O*-cycloadducts.[76]

5.1. Metal-catalyzed reactions

Metal-catalysis is the most widely used method to make asymmetric induction. In particular, the main strategy for catalytic enantioselective cycloaddition reactions is the use of a chiral Lewis acid catalyst. This approach is probably the most efficient and cheap way to effect a selective reaction, because it allows the direct formation of chiral compounds from achiral substrates under mild conditions and generally requires a sub-stoichiometric amount of chiral material.[77]

5.1.1. Chromium

In 2013, stereoselective Cr-promoted-1,3-dipolar cycloaddition between *trans*-C-(η^6-phenyl chromium tricarbonyl)-*N*-methyl nitrone **152**[78] and styrene **153** or η^6-(styrene) chromium tricarbonyl **154** were carried out in sealed glass tubes at 80-90 °C *in vacuo* for 6-40 h (Scheme 36).[79]



152 **153:** R^3 = Ph; **154:** R^3 = Ph[Cr(CO)$_3$] **155**

R^1 = Me, Ph, *t*-Bu; R^2 = Ph[Cr(CO)$_3$], Ph

Scheme 36. Chromium-catalyzed 1,3-dipolar cycloaddition.

The reactions proceeded with very high regio- and stereoselectivity to form exclusively *cis*-2,3,5-trisubstituted isoxazolidines **155**. Although the mechanism is not very clear, this selectivity might be explained through both frontier orbital theory and charge distribution in the reacting molecules theory.[80] However, it is correct to invoke presumable stacking interactions to stabilize the transition states. In fact, as reported in Figure 4, the transition states A and C are more preferable than that B and D because of possible π-π interaction of the dipolarophile benzene ring with the coordinate aromatic ring of the nitrone.

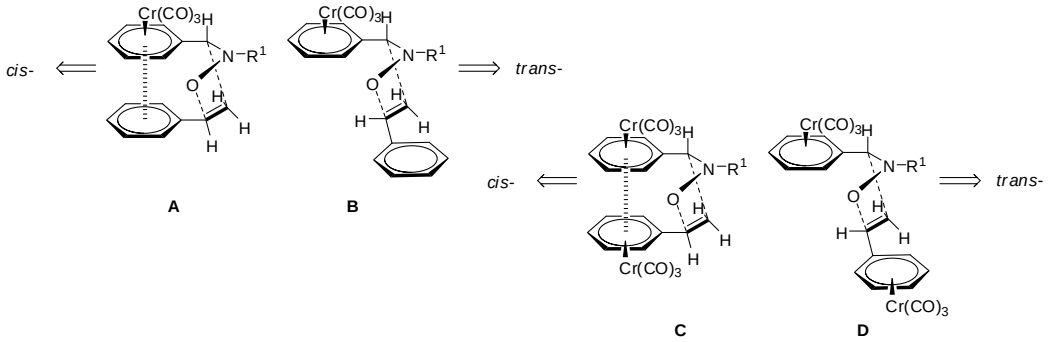
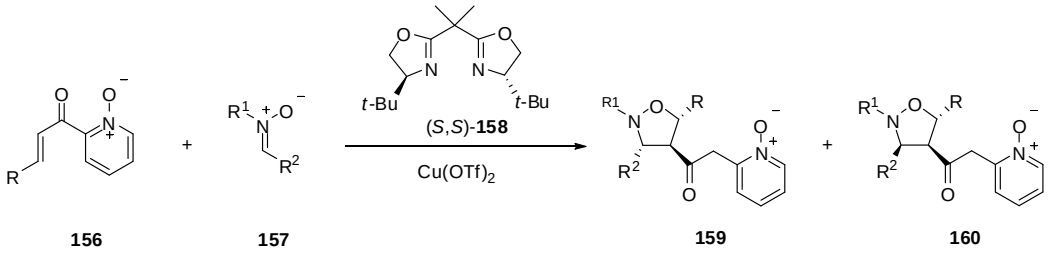


Figure 4. Proposed transition states favoring *cis*-isomer.

5.1.2. Copper

In the literature only a limited number of cases of copper-catalyzed nitrone cycloadditions with electron-deficient alkenes are described because of numerous unsuccessful outcomes of goals.[81] In 2011, the choice of alkenoylpyridine *N*-oxides **156** as bidentate dipolarophile allowed to perform copper catalyzed-cycloaddition using chiral *t*-Bu-bisoxazoline (BOX) ligands **158** (Scheme 37).[82]



156 **157** **159** **160**

R = Ph, 4-MeOC$_6$H$_4$, 4-BrC$_6$H$_4$, 4-NO$_2$C$_6$H$_4$, 2-furyl, 2-thienyl, (*E*)-PhCH=CH-, *t*-Bu
R^1 = Me, Ph, Bn
R^2 = Ph, 4-MeOC$_6$H$_4$, 4-BrC$_6$H$_4$, 4-NO$_2$C$_6$H$_4$, cyclohexyl

Scheme 37. Nitrone 1,3-dipolar cycloaddition to alkenoyl pyridine *N*-oxides **156**.

The addition of molecular sieves as additives was extremely important for the yield and the stereoselectivity of cycloaddition, observing that 4 Å MS gave better diasteroselectivity than 3 and 5 Å MS, while 3 Å MS showed a slightly better enantioselectivity. However, the best compromise between diastereo- and enantioselectivity was found, observing a *de* and an *ee* ratio up to 98 and 96%, respectively. The workers suggested a possible distorted square-planar complex formed between bidentate dipolarophile, ligand and metal, which favors an approach of the nitrone to the *re*-fase of the double bond (Figure 5).

In a recent work, the ability of 3-aryl-$_L$-alanine amides to complex Cu(II) was utilized in asymmetric 1,3-dipolar cycloaddition between *C*-aryl-*N*-benzylnitrones **161** and acryloylpyrazoles **162** (Scheme 38)**.** The reaction promoted by complex **163** in dichloromethane and 4 Å MS, produced prevalently the corresponding *endo*-cycloadduct **164** with high enantioselectivity (83-94%).[83]

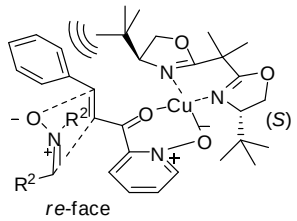
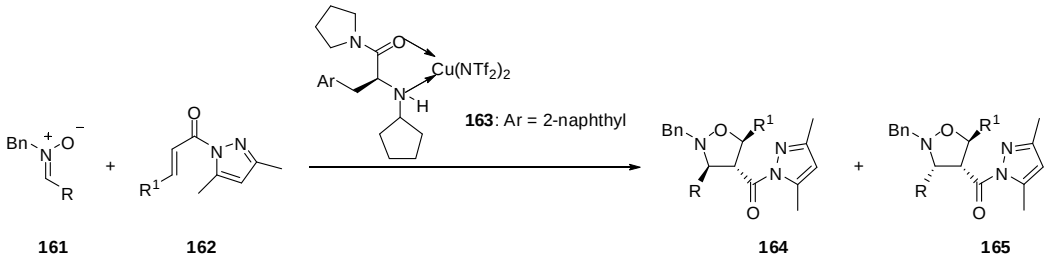


Figure 5. Proposed stereochemical model for the synthesis of cycloadducts **159** and **160**.



R = Ph, 2-naphthyl, 3-methylfuryl; R^1 = Me, H, COOEt

Scheme 38. Copper-catalysis in 1,3-DC.

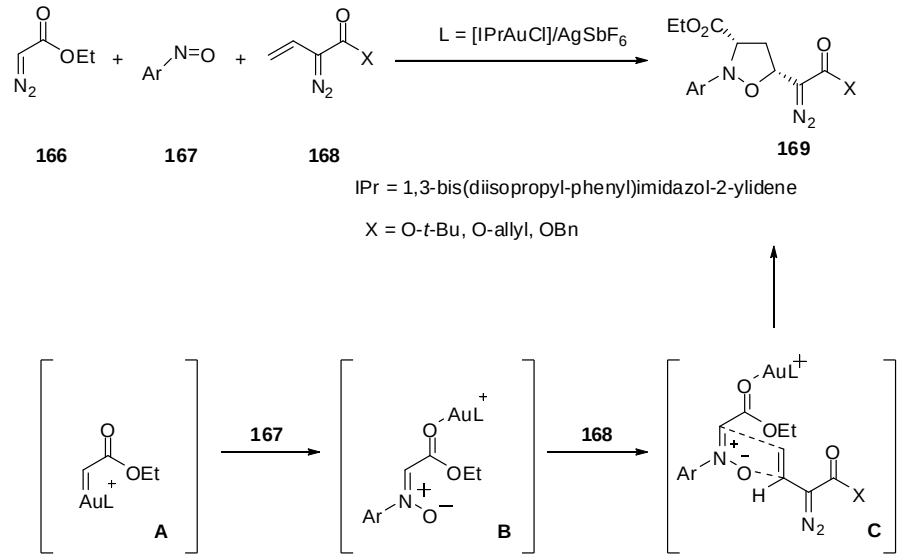
Steric repulsions were invoked to justify a major preference for the *endo*-transition state (TS) respect to *exo*-TS, due to a *trans*-chelation of acryloylpyrazoles **162** with the complex **163**, which implies both the shielding of carbonyl re-face from the aryl group and the steric hindrance between the *N*-cyclopentyl group of **163** and the aryl group of nitrone in *exo*-TS. Therefore, the nitrone would approach the *Si* face *via* the *endo*-TS.

5.1.3. Gold

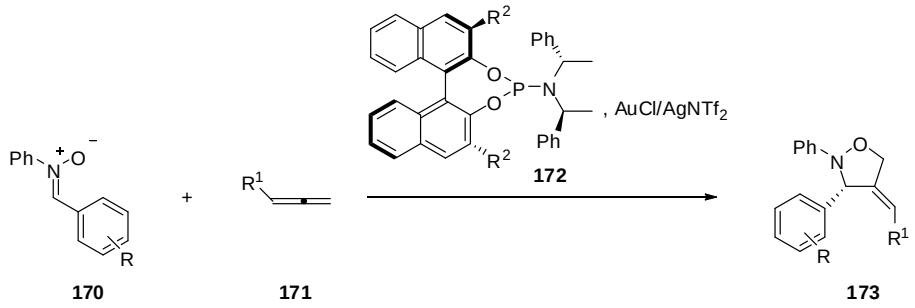
A catalytic normal electron demand 1,3-dipolar cycloaddition of nitrones using α,β-unsaturated carbonyl compounds as dipolarophile was recently investigated,[84] describing a gold-catalyzed cycloadditions of ethyl diazoacetate **166**, nitrosoarenes **167** and vinyldiazocarbonyl compounds **168** to yield stereoselectively isoxazolidine derivatives **169**. The reaction delivered the isoxazolidine derivatives as a single *exo*-product, deriving from stereoselective reaction of nitrone intermediate **B** with vinyldiazocarbonyl substrates **168** (**C** in Scheme 39). The cycloaddition worked well with various nitrosoarenes bearing both electron-deficient and electron-rich substituents including 4-chloro, 4-bromo, and 4-methyl groups, providing the desired products in 71-79% yield.

In 2013, a gold catalyzed enantioselective [3+2] dipolar cycloaddition of nitrones **170** with *N*-allenyl amides **171** was developed, employing phosphoroamidate ligands **172** (Scheme 40).[85] The reaction provides chiral 4-alkylidenyl isoxazolidine derivatives **173** in high yields and excellent enantioselectivities (92-98% *ee*), utilizing some BINOL derived chiral phosphoramidate Au(I) catalysts (**172**), in dichloromethane as

solvent and -20 °C. One probable explanation could be linked to the coordination of the cationic gold catalyst to the internal allenyl double bond, so activating the terminal alkene moiety.



Scheme 39. Stereoselective 1,3-dipolar cycloaddition of nitrones with vinyldiazocarbonyl substrates.



Scheme 40. Nitrone cycloaddition with *N*-allenyl amides.

5.1.4. Iridium

Chiral chelated phosphano-oxazolines (PN*) **174** and diphosphanes (PP) **175** (Figure 6) were employed in a preparative route of octahedral iridium(III) aqua complexes of general formula $[IrH(H_2O)(PN^*)(PP)][SbF_6]_2$ (**178**, Scheme 41), which were applied to asymmetric 1,3-dipolar cycloadditions of *N*-benzylidenephenylamine *N*-oxide **176** to methacrolein **177** (Scheme 41).[86]

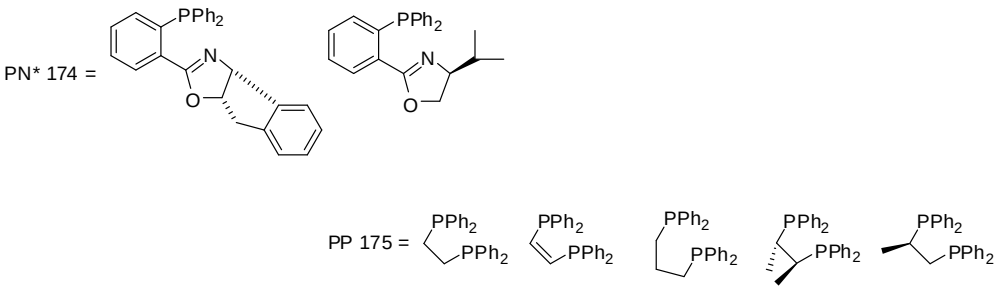
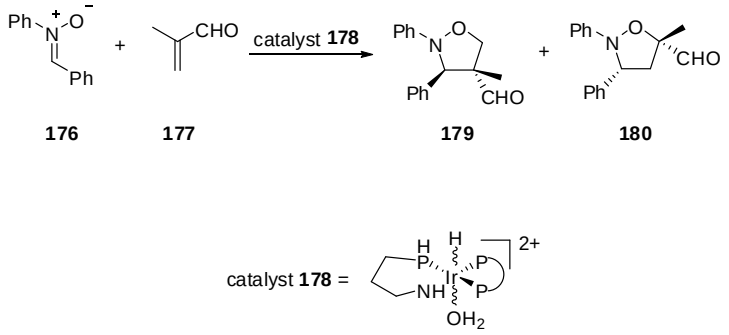


Figure 6. Chiral chelated phosphano-oxazolines (PN*) and diphosphanes (PP).



Scheme 41. Application of $[IrH(H_2O)(PN^*)(PP)][SbF_6]_2$ catalyst in 1,3-DC.

Accurate X-ray diffraction studies allowed the molecular structure determination of the complexes **178** that favored an *endo* approach. The synthesis were also conducted at lower temperature without observing modified diasteroselectivity of the cycloadditions, but improving the enantioselective trend of the reactions.

5.1.5. Nickel

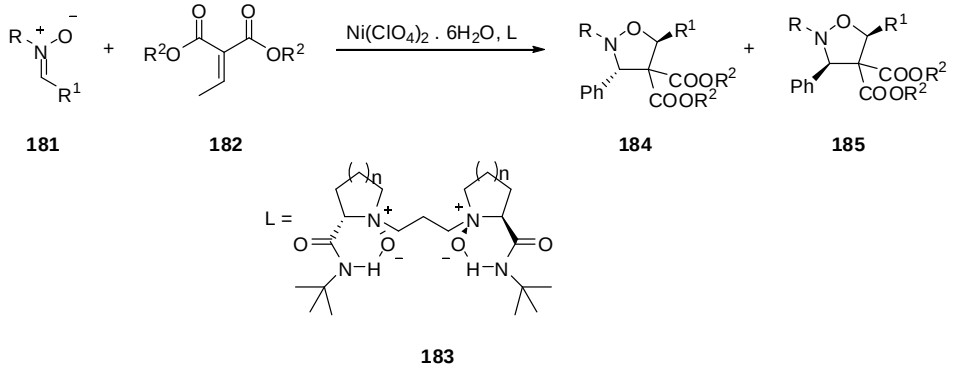
In 2011, an highly diastereo- and enantioselective synthesis of cycloadducts **184** and **185** was performed between nitrones **181** and alkylidene malonates **182** in presence of chiral *N*,*N*'-dioxide-$Ni(ClO_4)_2{\cdot}6H_2O$ complex **183** as catalyst (Scheme 42).[87]

A careful screening of the nickel salt (as precatalyst) and the ligand indicated that $Ni(ClO_4)_2{\cdot}6H_2O$ and *N*,*N*-dioxide **183** represented the best combination as source of chirality with excellent diastereoisomeric ratio and enantiomeric excess values (up to 99%, respectively). The workers proposed that the reaction might take place *via* the formation of a complex with octahedral geometry which favored the attack of nitrone at the *Si* face because of steric hindrance at the *Re* face.

5.1.6. Rhodium

In general, dirhodium(II) carboxamidates are weak promoters of dipolar cycloadditions because of their poor attitude to coordinate carbonyl compounds, but a recent discovery showed that chiral dirhodium(II,III) carboxamidate catalyst $[Rh_2(5S,R\text{-}MenPy)_4]SbF_6$ exhibited preferential binding to

aldehydes rather than nitrones.[88] Therefore, the selective formation of cycloadducts **190** and **191** was realized through the reaction of *C*-aryl-*N*-substitued nitrones **186** with acrolein (**187**), methacrolein (**177**) and *trans*-crotonaldehyde (**188**) in presence of $[Rh_2(5S,R\text{-MenPy})_4]SbF_6$ (**189**) as chiral catalyst (Scheme 43).[89]



181 **182** **184** **185**

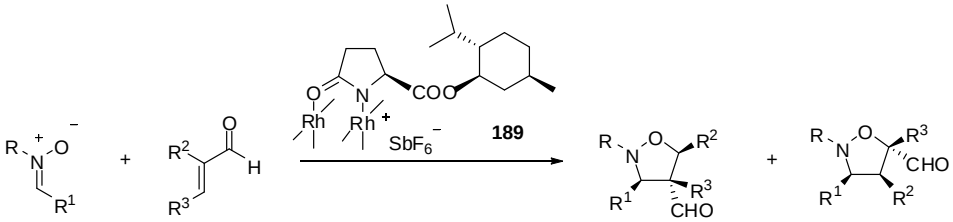
183

R = Me, Ph, Bn

R^1 = Ph, 2-NO_2-C_6H_4, 4-Br-C_6H_4, 4-F-C_6H_4, 4-MeO-C_6H_4, 4-Me-C_6H_4, 2-naphthyl

R^2 = Me, Et, *i*-Pr, *t*-Bu, Bn

Scheme 42. Asymmetric cycloaddition between nitrones **181** and alkylidene malonates **182**.



186 **187:** $R^2 = R^3 = H$ **190** **191**
177: R^2 = Me; R^3 = H
188: R^2 = H; R^3 = Me

R = Ph, Bn; R^1 = Ph, 4-MeO-C_6H_4, 4-Me-C_6H_4, 4-Cl-C_6H_4, 4-CF_3-C_6H_4, 2-furyl, 2-naphthyl

Scheme 43. $[Rh_2(5S,R\text{-MenPy})_4]SbF_6$ as chiral catalyst in 1,3-dipolar cycloadditions.

The reaction solvent influenced dramatically the reactivity and selectivity of cycloaddition; in fact, the using of halogenated solvents as dichloromethane or chloroform increased slightly the regio- and stereocontrol of the reaction, reducing considerably the conversion, while aromatic solvents (especially toluene) promoted elevated yields, highly regioselectivity to 4-isomer (**190**), excellent diastereoisomeric ratio (99:1 *endo*:*exo*) and notable enatiomeric excess (98%).

DFT calculations were used to explain the contributing factors of the solvent to selectivity and Figure 7 illustrates an example of the possible geometries of the catalytic system acrolein-Rh_2(5*S*,*R*-MenPy)$_4$]SbF_6 in dichloromethane and in toluene.

In case **A** the acrolein adopts a dihedral angles respect to ligands of 32.7° in dichloromethane, while in toluene (case **B**) the same angle decreases to 6.6°. Considering the selective shielding of the top and bottom face of the acrolein due to esters groups of the pyrrolidinone ligands (E), in toluene it is possible to observe greatest steric hindrance from one side of the dipolarophile, resulting in higher control of the reaction.

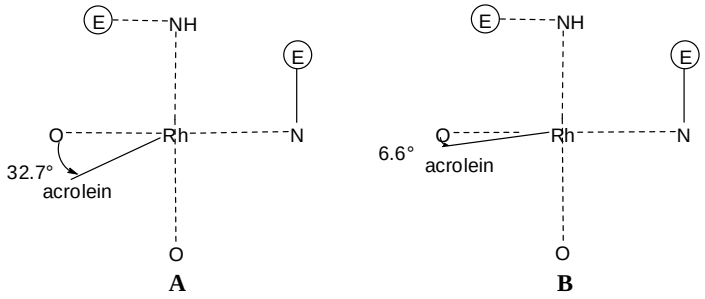


Figure 7. Proposed geometries of the system acrolein-Rh_2(5*S*,*R*-MenPy)$_4$]SbF_6 in solvents.

5.1.7. Ruthenium

The difficulties to using enals as dipolarophiles in 1,3-dipolar cycloadditions were highlight in 2002 when Kundig's group proposed the chiral ruthenium Lewis acid catalyst Ru(*R*,*R*-BIPHOP-F)(Cp)]SbF_6 **192** to promote highly enantioselective cycloadditions of nitrones ans enals (Figure 8).[90]

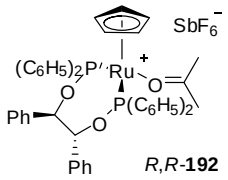
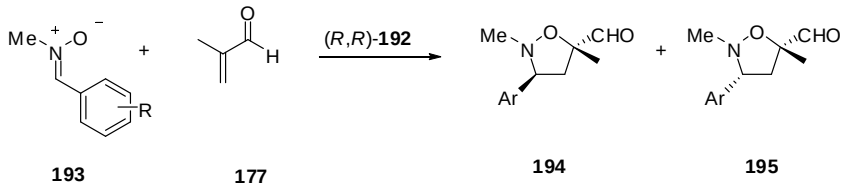


Figure 8. Kundig's Ru-catalyst.

More recently, the chiral Ru-complex **192** was the optimal catalyst to give *endo*-cycloadducts of methacrolein **177** and *N*-methyl-*C*-arylnitrones **193** with moderate to good yields and elevated diastereo- and enantiocontrol (Scheme 44).[91] Reactions involving electron-rich and electron-poor substituted nitrones were found to proceed with very different reactivity, revealing the limited reactivity of the catalytic system in the case of substrates with electron-donating groups.

Successively, an ampliation of the previous results was made, varying the substituents both on the aryl group of the nitrone (Ar) and on the nitrogen of the nitrone (R) (Scheme 45). In the first case, no products were achieved with electron-donating nitrones, whereas electron-poor dipoles gave 3,5-disubstituted cycloadducts in good diastereo- and enantioselective manner. In the second case, *N*-*i*-Pr and *N*-*t*-Bu

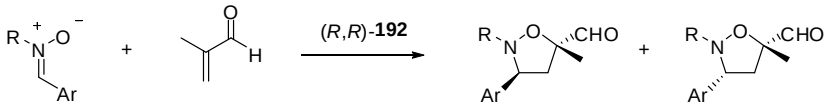
substituents greatly extended the reaction times, whereas *N*-Bn and *N*-PMB groups favored the regio-, diastereo- and enantioselectivity of the cycloaddition.



193 **177** **194** **195**

R = H, 2-F, 4-F, 4-Cl, 4-Br, 4-CF_3, pentafluoro, 4-NO_2, 4-CN, 4-Me, 4-OMe, 4-NMe_2

Scheme 44. Ru-complex **192** as catalyst in asymmetric cycloadditions.



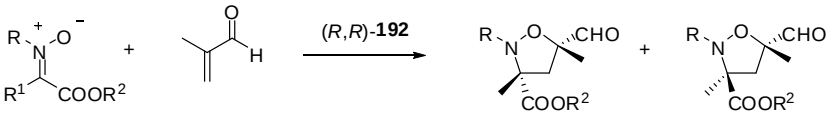
196 **177** **197** **198**

R = Me, *i*-Pr, *t*-Bu, Bn, PMB, DPM

Ar = H, 2-F-C_6H_4, 4-F-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4, 4-CF_3-C_6H_4, C_6F_5, 4-NO_2-C_6H_4, 4-CN-C_6H_4, 4-Me-C_6H_4, 4-OMe-C_6H_4, 4-NMe_2-C_6H_4, η-C_6H_4-$Cr(CO)_3$, 2-Py

Scheme 45. Screening of several nitrones for the catalytic 1,3 dipolar cycloadditions.

In 2014, the Kundig's Ru-catalyst was successfully applied to cycling reaction of *C*-carboalkoxy ketonitrones **199** as dipole and methacrolein **177** as monodentate dipolarophile (Scheme 46).[92]



199 **177** **200** **201**

R = Me, Bn; R^1 = Me, Et, *n*-Pr; R^2 = Et, Me, *t*-Bu

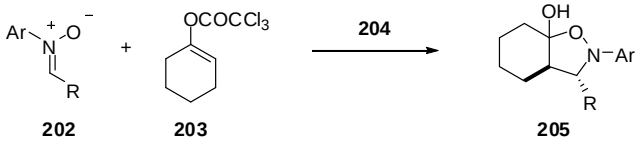
Scheme 46. Kundig's catalyst in cycloaddition of *C*-carboalkoxy ketonitrones **199** and methacrolein **177**.

Diastereo- and enatioselective formation of 3,5-tetrasubstitued isoxazolidines **200** and **201** was noticed although with reaction time of nearly one week. Properties and coordinating activity of the solvents was found to have a great influence on the *endo*/*exo*-selectivity. In fact, weakly polar and noncoordinating

solvent as toluene favored the *exo*-isomer, while solvents as tetrahydrofuran (THF) or *t*-butyl methyl ether (MTBE) produced prevalently *endo*-isomers. DFT calculations explained the solvent effect as a possible competition between the counterion of the catalyst and the solvent.

5.1.8. Tin

Alkenyl trichloroacetates (**203**) as electron-rich dipolarophile were recently used in chiral tin-catalyzed asymmetric 1,3-dipolar cycloaddition of alkenyl- and arylnitrones **202**, isolating bicyclic adducts **205** in reasonable enantiomerical excess and high diastereoselectivity (Scheme 47).[93]

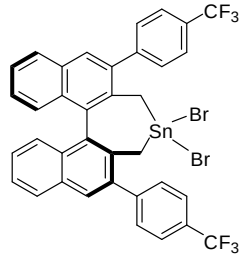


202 **203** **205**

R = Ph, 2-Me-C_6H_4, 2-MeO-C_6H_4, 4-MeO-C_6H_4, 4-Br-C_6H_4, 4-CF_3-C_6H_4, 1-naphthyl, 2-naphthyl, (*E*)-Ph-CH=CH, *i*-Pr, *c*-C_6H_{11}, N-benzylpiperidine

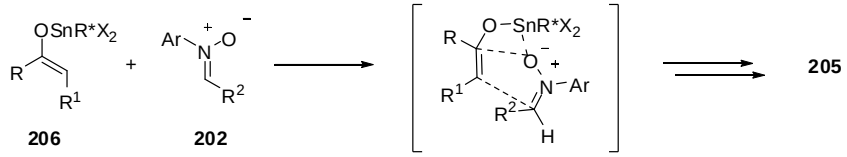
Ar = Ph, 3-Me-C_6H_4, 4-F-C_6H_4, 4-Me-C_6H_4, 3,5-Me-C_6H_3,4-MeO_2C-C_6H_4

204:



Scheme 47. Tin-catalyzed synthesis of bicyclic adducts **205**.

The proposed mechanism proceeded with high probability *via* the formation of tin enolates **206** that reacted with the nitrones **202** in concerted manner for a stereoselective production of bicyclic isoxazolidines **205** (Scheme 48).



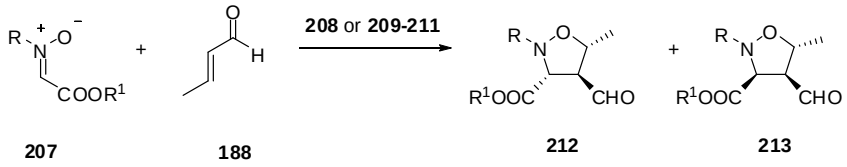
206 **202**

Scheme 48. Proposed mechanism of formation of isoxazolidines **205**.

5.2. Organocatalyzed reactions

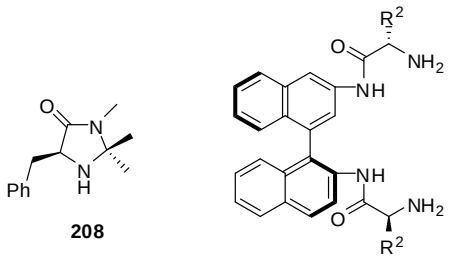
The use of organocatalysts in asymmetric synthesis has received increased attention in recent years.[94] In particular, the use of chiral secondary amines as organocatalysts for reaction with α,β-unsaturated aldehydes is one of the most promising synthetic method to have emerged recently.[95] Among them, MacMillan's imidazolidinone catalyst revealed the ability to promote highly enantioselective 1,3-dipolar cycloadditions.[96]

In 2011, MacMillan's catalyst **208** and three hybrid diamines catalysts (**209**-**211**) were tested in 1,3-dipolar cycloaddition between glyoxylate-derived nitrones **207** and *trans*-crotonaldehyde (**188**) (Scheme 49).[97]



207 **188** **212** **213**

R = Me, Bn, *i*-Pr; R_1 = Me, Et, *i*-Pr, *n*-Bu, *t*-Bu, Cy, PMB, 4-NO_2-Bn, Bn



208

209: R^2 = Bn
210: R^2 = Me
211: R^2 = *i*-Bu

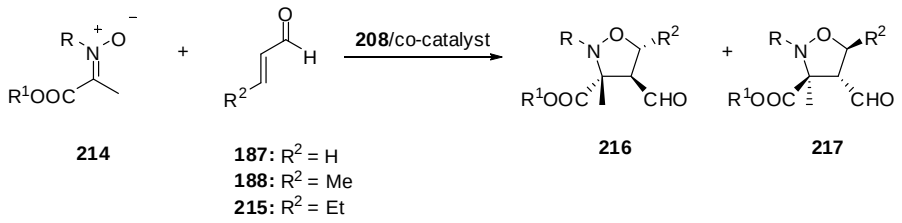
Scheme 49. Catalyzed-cycloadditions of glyoxylate-derived nitrones **207** with *trans*-crotonaldehyde **188**.

Variations in structure of nitrones were evaluated by their effect on diastereo- and enantioselection to arrive at an asymmetric induction; therefore, it was possible to observe that the ester moiety of the nitrone affected largely the diastereocontrol of the reaction without modifying considerably yields and enantioselection (Scheme 50).

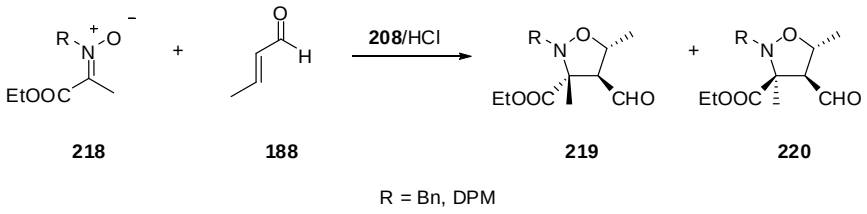
Successively, cycloadducts with a tetrasubstituted carbon center were synthesized by using of MacMillan's imidazolidinone catalyst **208** in reaction between pyruvate-derived nitrones **214** and α,β-unsaturated aldehydes **187**, **188** and **215**.[98]

A careful screening of salt of catalyst highlighted that catalyst **208**/HCl system promoted high level of asymmetric induction (up to 92%) although with poor yields.

The catalyst **208**/HCl was also used as stereoinductor in similar cycloadditions of ketonitrones **218** and *trans*-crotonaldehyde **188** with excellent results of stereocontrol (Scheme 51).[99]



Scheme 50. Asymmetric formation of adducts **216** and **217**.



Scheme 51. Use of the catalytic system **208**/HCl in synthesis of **219** and **220**.

A reasonable explanation for the diastereo- and enantioselection might be given by high *Si*-facial selectivity due both to the preferred configuration *E* of the iminium intermediate and both the shielding of the *Re*-face of the catalyst benzyl group (Figure 9).

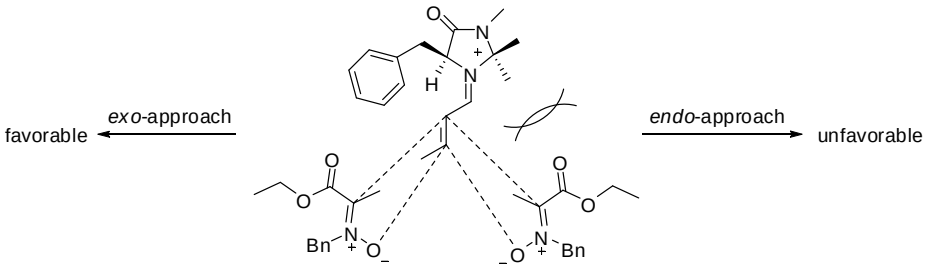
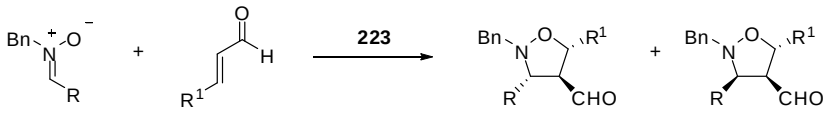


Figure 9. The possible transition state.

In 2014, a tetraarylphosphonium supported imidazolidinone catalyst **223** was developed to promoted asymmetric 1,3-dipolar cycloadditions of nitrones **221** and unsaturated aldehydes (**187**, **188** and **222**) in good yields with excellent diastereo-and enantioselectivities (Scheme 52).[100] The choice of solvent was found to have a significant impact on the trend of the reaction, not only in terms of yield, but also in the diastereo- and enantioselectivity (best result was 82% yield, 94/6 *endo*/*exo* and *endo* 88% *ee*). Most importantly, the

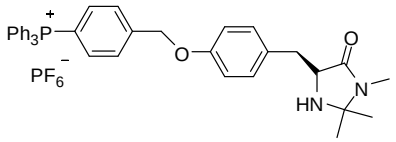
catalyst **223** was readily recovered and recycled at least four cycles without observing significant decrease in yield and stereoselectivity.



221 **187:** R^1 = H; **188:** R^1 = Me; **222:** R^1 = *n*-Pr **224** **225**

R = Ph, 4-Cl-C_6H_4, 4-OMe-C_6H_4, 2-naphthyl

223:



Scheme 52. Asymmetric synthesis of cycloadducts **224** and **225**.

6. Ionic liquids in 1,3-dipolar cycloadditions

In recent years, ionic liquids (ILS) have received a good deal of attention, since classical organic reactions can be performed in these solvents with great advantages of yield and selectivity if compared with conventional conditions. Ionic liquids are defined as salts, which have a normal melting point below 100 °C. Common ionic liquids include those containing imidazolium, pyridinium, pyrrolidinium, ammonium and phosphonium cations.

The use of ionic liquids as support for organic synthesis, especially in cycloaddition reactions, has been reported in some recent publications.[101] Ionic liquid have many advantages over common organic solvents, such as nonvolatility, easy recycling and tunable miscibility/immiscibility with other reaction components, although hydrogen bonding specific interactions seem play a crucial role to improve yield, selectivity, including enantioselectivity, and reaction time.[102]

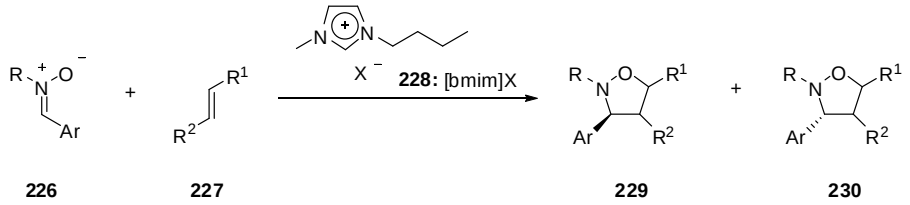
6.1. Substituted isoxazolidines

In 2013 and 2014, some similar applications of ionic liquids as recyclable solvents were proposed in 1,3-dipolar cycloaddition of alkenes and various substituted nitrones (Scheme 53).[103]

Several butylmethylimidazolium based ILS [bmim]X (**228**) with variable anions (X=PF_6^-, Br^-, BF_4^-) were screened and [bmim]BF_4 gave the best results in terms of regio-, diastereo- and enantioselectivity compared also to the conventional conditions. Moreover, the recovered ionic liquid might be reused at least five times without loss of catalytic activity and selectivity.

In recent times, ionic liquid-supported imidazolidinone catalyst **232** gave good to excellent *endo*-enantioselective 1,3-dipolar cycloadditions between *N*-benzylnitrones (**231**) and α,β-unsaturated aldehydes

(**187**, **188**, **215** and **222**), with recovering and recycling of the catalyst for at least five runs without observing any relevant decrease in its activity (Scheme 54).[104]

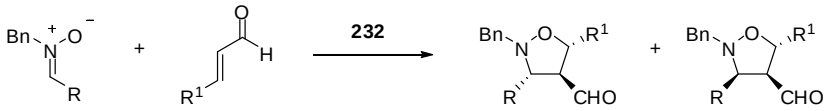


Ar = 2,6-F-C_6H_3, ,2-F-C_6H_4, 4-F-C_6H_4, 3,4-F-C_6H_3

R = Me, Ph, Bn; R^1 = CHO, -CON(Ph)CO-, -CON(Me)CO-, -CON(Cy)CO-;

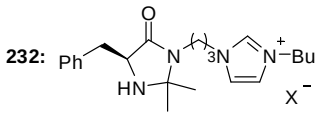
R^2 = H, CON(Ph)CO-, -CON(Me)CO-, -CON(Cy)CO-

Scheme 53. Application of catalyst **228** to 1,3-dipolar cycloaddition.



187: R^1 = H
188: R^1 = Me
215: R^1 = Et
222: R^1 = *n*-Pr

R = Ph, 4-Br-C_6H_4, 4-Cl-C_6H_4, 4-Me-C_6H_4, 4-OMe-C_6H_4, 2-naphthyl



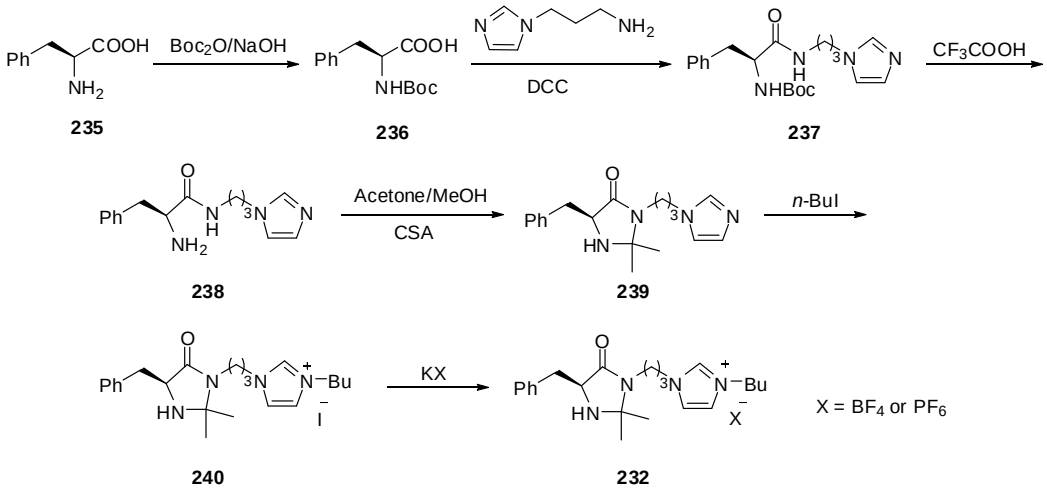
Scheme 54. 1,3-Dipolar cycloaddition of *N*-benzylnitrones with α,β-unsaturated aldehydes in IL.

An efficient synthetic strategy was proposed to support the imidazolidinone catalyst on the ionic liquids **232**, starting from protection of L-phenylalanine (**235**), followed by condensation of intermediate **238** with acetone and final anion exchange of I^- with BF_4^- or PF_6^- anions (Scheme 55). Six types of protic acids were employed as the reaction co-catalysts, selecting HBF_4 as the most efficient for high yields, good diastereoisomeric ratio and excellent *endo*-enantiomeric excess.

6.2. Fused isoxazolidines

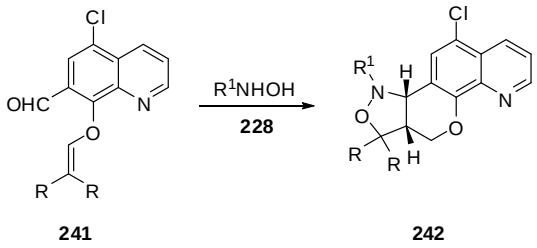
Ionic liquid [bmim]PF_6 **228** promoted recently the intramolecular dipolar cycloaddition of quinoline-derived olefins (**241**) with nitrones generated *in situ*, affording tetracyclic isoxazolidine fused pirano [3,2-*h*]

quinolines (**242**) (Scheme 56).[105] Various reaction media were screened for the optimization of the reaction, but the best results was performed in ionic liquid (80% of yield). The reaction was largely stereoselective performing exclusively the c*is*-fused substrates, as confirmed by NMR studies and single-crystal X-ray crystallography.



235 **236** **237** **238** **239** **240** **232**

Scheme 55. Synthetic route to ionic liquid-supported imidazolidinone catalyst.



241 **228** **242**

R = H, Me; R^1 = Me Ph, Bn

Scheme 56. Synthesis of intramolecular dipolar cycloaddition for fused tetracyclic quinolines.

7. Conclusions

The driving force for all recent reported developments in the isoxazolidine synthesis has been high diastereo- and enantioselectivity in 1,3-dipolar cycloaddition reactions.

This has been accomplished through a better understanding of reactivity of the dipole and the dipolarophile and the advent of new catalysts in parallel with increased ease of access and handling of isoxazolidine compounds. The impact of new chiral catalysts and non-conventional solvents have facilitated the use of this chemistry. Chemists are now better equipped to target much more elaborate molecules in total synthesis using 1,3-dipolar cycloadditions in selective manner.

In conclusion, 1,3-dipolar cycloadditions are highly attractive reactions for the synthesis of heterocycles and other heteroatom-containing molecules. Of course, we are hopeful that our contribution will facilitate future synthetic chemistry research and will provide many challenges for future work.

Acknowledgements

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