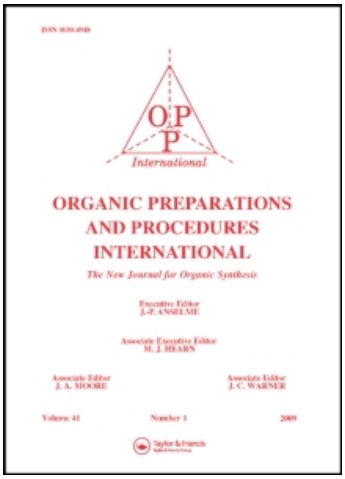

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Introduction

Cycloaddition reactions occupy a special place in organic synthesis because of the simultaneous creation of several bonds and generation of new stereogenic centers in often highly stereocontrolled manners. The ability to fulfill all the conditions of the atom economy principle is partly responsible for the great interest for these reactions among which [4+2] reactions were probably the most developed. Although 1,3-dipolar cycloaddition (1,3-DC) was discovered in 1893 by Büchner[1,2] (*i. e.* about thirty-five years before the Diels-Alder reaction), it fell into relative obscurity until Huisgen's systematic studies in the 1960s.[3] Interest for 1,3-DC has grown over the past twenty years and in particular 1,3-dipolar cycloaddition reactions of nitrones with alkenes and alkynes have found general applications in organic synthesis.[4,5] The corresponding adducts (isoxazolidines) are versatile intermediates for the synthesis of a multitude of natural products. In particular, they have been used to elaborate various amino alcohols and β-amino acid derivatives by reductive cleavage of the N—O bond.

One of the main features of 1,3-DC reactions of nitrones is their ability to create up to three contiguous stereogenic centers with a stereochemical control. Providing that the regioselectivity of the reaction is totally controlled, the most recent asymmetric developments using chiral Lewis acids have proved that almost exclusively one stereoisomer can be obtained, from the four possible formed.

It is therefore unsurprising that most of the reviews on [3+2] cycloadditions published over the past fifteen years were devoted to its asymmetric version.[4,6–8] Among the large amount of studies published on 1,3-DC of nitrones, several reviews were dedicated to intramolecular versions[9] or to the cycloaddition of carbohydrate derived nitrones.[10] This

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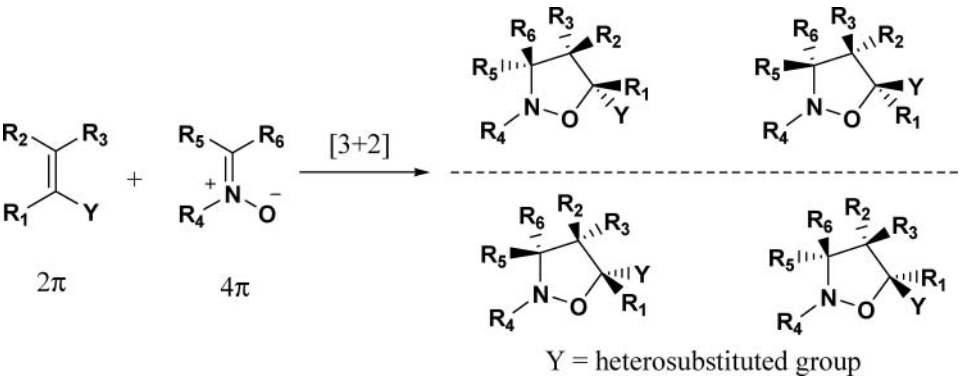


Scheme 1

review will concern the 1,3-DC reactions involving nitrones as dipoles and hetero-substituted alkenes as dipolarophiles (*Scheme 1*). Part I will describe the 1,3-DC of *O* and *N*-substituted dipolarophiles. Part II will present the reactions involving other classes of hetero-substituted alkenes. In both parts, stereochemical aspects will be emphasized. Because of the formation of complex mixtures when an aminoaldehyde or an aminoketone is generated from the isoxazolidine adduct in reductive conditions, alternative transformations have been developed. The ring-opening reactions will be presented at the end of each part of this review.

The 1,3-DC reaction of a nitrone with an alkene/alkyne involves 4 π electrons from the nitrone and 2 π electrons from the alkene and is thermally allowed, according to the Woodward-Hoffmann rules.[11] The three p_z orbitals from the dipole and the two p_z orbitals from the dipolarophile combine suprafacially. The reaction mechanism (concerted or not) was subjected to a great deal of debate.[12] Huisgen[3] proved, that in some cases, 1,3-DC reactions can proceed with a stepwise mechanism involving open intermediates. However, besides what could be expected from the representation of the nitrone and the strong polarization of the alkene due to the heterosubstituent(s), the course of the reaction is in most cases concerted as confirmed by the recent Magnuson and Pranata's ab initio studies.[13] Furthermore, the formation of the C—C bond and the C—O bond is only very slightly asynchronous. For example, in the case of vinyl amine the bond length of the forming C—O bond is 2.30 Å and 2.17 Å for the C—C bond. This is surprising considering the strongly polarized double bond of such an alkene on the one hand, and the soft and hard feature, respectively, of carbon atom and oxygen atom of the nitrone on the other hand.

The specific feature of this type of $[4\pi+2\pi]$ cycloaddition reaction probably relies on the recovery of the nitrogen lone pair, leading to the progressive recovering of the pyramidal nitrogen atom during the course of the reaction. As a result, different conformers of the resulting isoxazolidine formed can exist, thus hardening, in some cases, the interpretation of NOE measurements.

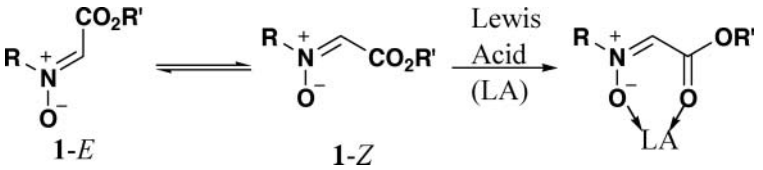
The prediction of both regioselectivity and reactivity of 1,3-DC, and later the diastereoselectivity of these reactions, has attracted much attention from the beginning. These questions are pivotal for application in total synthesis. The regioselectivity of 1,3-DC reactions has been the subject of various theories and rules first based on empirical data. In the

present case, due to the strong partial negative charge on the terminal oxygen atom (hard site),[14,15] a high regioselectivity is generally observed. It is admitted that nitrones react with alkenes bearing one strong electron-withdrawing group to give the C-4 substituted isoxazolidine, while the C-5 regioisomer is preferred when electron donating and moderate electron-withdrawing substituted olefins are added.[16–24] Nevertheless, if the addition of 1,2-disubstituted olefins have proved to respect the same selectivity, some cases exist where the prediction fails.[25–28] The frontier molecular orbital (FMO) model introduced by Fukui[29–31] has generally been used to explain the regioselectivity and the reactivity of such cycloaddition reactions in a quite successful agreement with the experimental results.[16,32–35] Indeed, the prediction of monosubstituted olefins with electron-withdrawing or electron-donating effect matches well with the FMO theory.[29–31] However, a significant number of cases where predictions are unreliable exists in the case of [4+2] cycloadditions,[36] as well as for 1,3-DC when disubstituted olefins are involved in the reaction as dipolarophiles.[26–28] Recently, a novel theoretical model based on the density functional theory (DFT) and the hard and soft acid and base principle (HSAB) was developed and proved to be in good agreement with experimental results.[37,38] This model using DFT descriptors such as local hardness or softness was successfully applied to the cycloaddition of nitrones with captodative dipolarophiles by Herrera *et al*.[25] In a recent study based on the comparison of FMO and DFT/HSAB models to describe the cycloaddition of nitrones, Mekelleche *et al*.[39] also observed the limitations of the FMO model and the potency of DFT descriptors.

I. Reactions with Oxa-substituted Alkenes

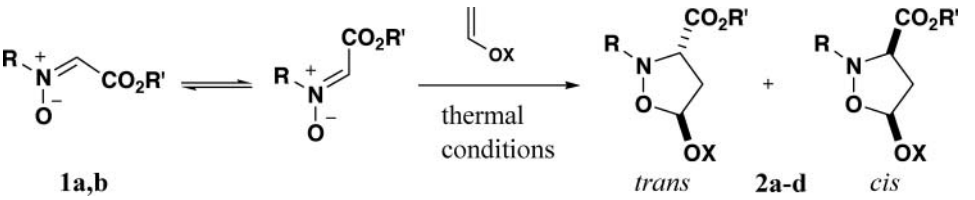
1. Nitrones Activated by Electron-withdrawing Groups

Alkoxycarbonyl-substituted nitrones **1** are interesting dipoles. These activated nitrones are thermally stable and are glycine-type electrophilic synthons. However, a difficulty related to their use lies in their configurational unstability. Indeed, although exhibiting a pure *Z* configuration in solid state, such nitrones undergo a rapid *Z*/*E* equilibrium in toluene or chloroform solution, even at room temperature. The *Z*/*E ratio* is dependent on the solvent (dielectric constant), temperature, and steric hindrance of the *N*-substituent and of the ester. Interestingly, this equilibrium can shift from *E* to *Z* geometry in the presence of a chelating Lewis acid (*Scheme 2*).



Scheme 2

Table 1
Cycloaddition Reactions between Nitrones **1a**,**b** and Vinyl Ethers or Esters



1a,b **2a-d**

Nitrone	R	R′	X	Conditions	Yield (%)	Adduct (*trans*:*cis*)	Ref
1a	Bn	Et	Et	CH_2Cl_2, 50°C (sealed tube), 66 h	58[a]	**2a** (78:22)	40
1a	Bn	Et	Et	CH_3CN, 50°C, 23 h	45[a]	**2a** (65:35)	40
1a	Bn	Et	Et	toluene, 50°C, 23 h	76[a]	**2a** (88:12)	40
1a	Bn	Et	Ac	$AcOCH{=}CH_2$ (10 eq.), 70°C, 24 h	87	**2b** (75:25)	41
1b	Ph_2CH	Me	Et	$EtOCH{=}CH_2$ (20 eq.), rt, 36 h	89	**2c** (72:28)	42
1a	Ph_2CH	Me	*n*-Bu	*n*-$BuOCH{=}CH_2$ (20 eq.), rt, 36 h	73	**2d** (75:25)	42

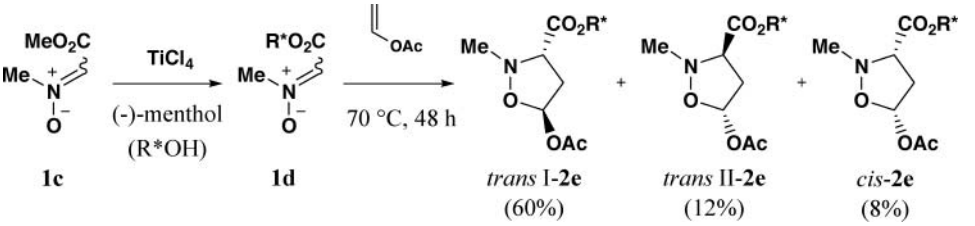
a) Yield determined by ^{1}H NMR spectroscopy.

a) Thermal Conditions

i. Acyclic Nitrones

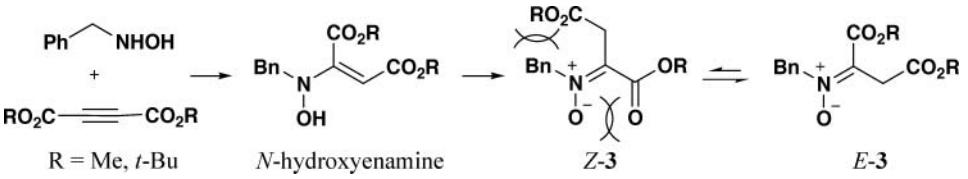
In the absence of a Lewis acid, dipolar cycloadditions of acyclic activated nitrones **1** with vinyl ethers or vinyl acetate proceed with moderate conversions under mild conditions (20–70°C, 23–66 h). A moderate to good *trans* stereocontrol is homogeneously observed, even with nitrones bearing a bulky *N*-substituent (**1b**, R = Ph_2CH, *Table 1*). A favored *exo* approach involving the more reactive *E* nitrone is commonly assumed to explain this (partial) *trans* stereoselectivity.

Interestingly, by reaction of a menthyl ester-derived chiral nitrone with vinyl acetate, Chiacchio *et al*. observed under the same mild thermal conditions an enhanced *trans*



1c **1d**

Scheme 3



Scheme 4

stereoselectivity (9:1) together with a fair facial diastereoselectivity (*trans* I : *trans* II = 5:1) (*Scheme 3*).[43]

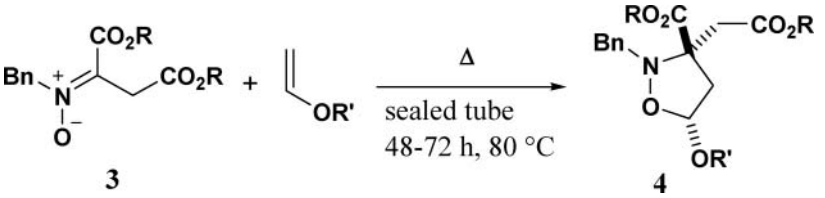
Very recently, a significant progress in the research of stereocontrol in the thermal 1,3-DC of acyclic activated nitrones with vinyl ethers was disclosed with the use of aspartic nitrones **3** (*Scheme 4*). This new type of dipole, quantitatively prepared in one step from a *N*-protected hydroxylamine and an dialkyl acetylenedicarboxylate, was found to display a single *E* configuration of the substituted C=N bond in solution in contrast to monosubstituted ones, together with a fair reactivity towards a wide range of dipolarophiles.[44,45]

The thermal 1,3-DC of **3** with simple vinyl ethers afford adducts **4** in high yields and with a remarkable *trans* selectivity, up to 98: 2 with the bulky *t*-butyl vinyl ether (*Table 2*).[44]

This *trans*-stereocontrolled 1,3-DC access to isoxazolidines containing a quaternary-center proves equally efficient with nitrones bearing two different functions, such as **5** (Table 3).[45]

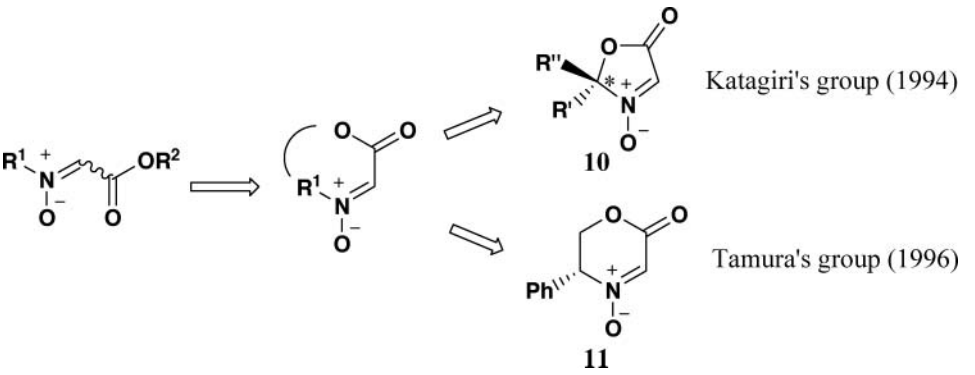
Asymmetric extension with either chiral vinyl ethers or chiral aspartic nitrones **7** was studied and afforded, in the latter case, diastereomerically and enantiomerically pure adducts in acceptable yields. These unprecedent isoxazolidines **8** were conveniently converted into enantioenriched new α,α-disubstituted α-amino acids **9** (*Table 4*).[44]

Table 2
Thermal Cycloaddition of Disubstituted Nitrones **3** with Vinyl Ethers

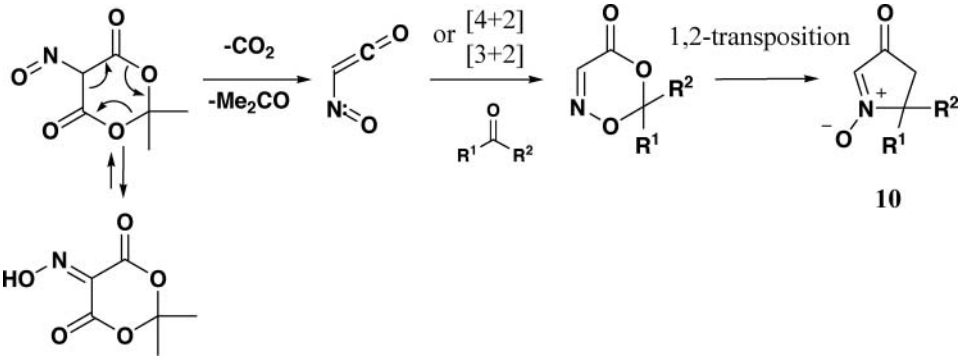


3 **4**

Nitrone	R	R′	Adduct	Yield (%)	*trans*:*cis*
3a	Me	Ac	**4a**	89	80:20
3a	Me	Et	**4b**	95	92:8
3b	*t*-Bu	Et	**4c**	99	95:5
3a	Me	*t*-Bu	**4d**	92	>98:2
3b	*t*-Bu	*t*-Bu	**4e**	99	>98:2

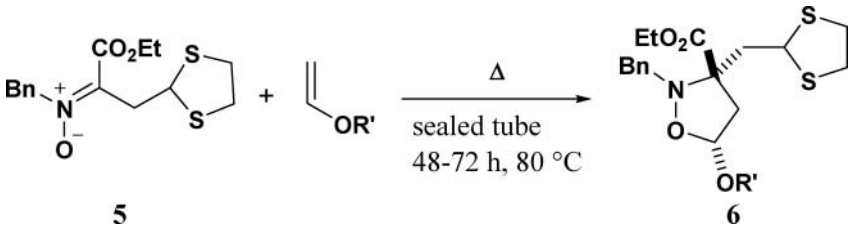


Scheme 5



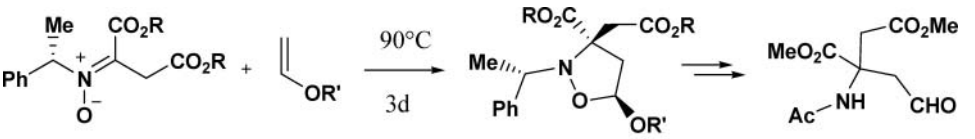
Scheme 6

Table 3
Thermal Cycloaddition of Nitrone **5** with Vinyl Ethers and Vinyl Acetate



R′	Adduct	Yield (%)	*trans*:*cis*
Ac	**6a**	90	80:20
Et	**6b**	91	92:8
t-Bu	**6c**	89	>98:2

Table 4
Cycloaddition Reactions involving (*S*)-α-Methylbenzylnitrone **7**



7 8 9

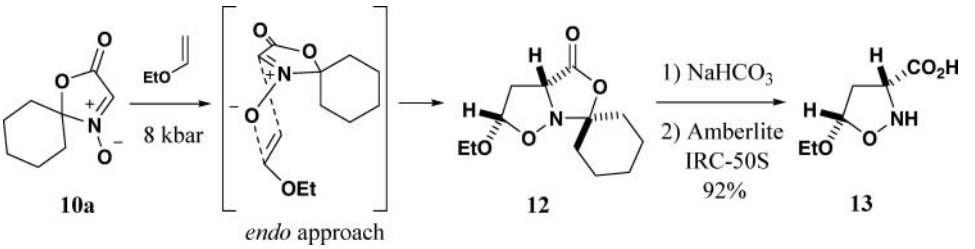
Nitrone	R	R′	Adduct	Yield (%)	*trans* I:*trans* II *cis* I :*cis* II
7a	Me	Et	**8a**	99	69:31:0:0
7a	Me	*t*-Bu	**8b**	95	72:28:0:0 (major isomer isolable, 50% yield)
7b	*t*-Bu	Et	**8c**	99	67:33:0:0
7b	*t*-Bu	*t*-Bu	**8d**	97	72:28:0:0

ii. Cyclic Nitrones

An obvious way to ensure a pure *E* geometry for the nitrone is to create a 5 or 6 membered lactonic ring between the ester function and the *N*-substituent.

The first synthesis of such cyclic activated nitrones **10** was reported by Katagiri's group in 1994 (*Scheme 5*).[46] The nitrosoketene intermediate, generated by thermolysis of hydroxyimino Meldrum's acid, was found to react with various ketones to afford the 5-membered ring nitrones **10** after 1,2-rearrangement of the transient imino-lactone (*Scheme 5*).

The cycloaddition of cyclic nitrones **10** with ethyl vinyl ether required appropriate conditions.[47] Indeed, with spiro-nitrone **10a**, 1,3-DC was unsuccessful under classical thermal conditions, but proceeded under solvent-free and hyperbaric conditions (8 kbar) with high yields and a total *cis* stereoselectivity, resulting from an *endo* approach (*Scheme 7*). Adduct **12** was easily transformed into the corresponding acid **13**.

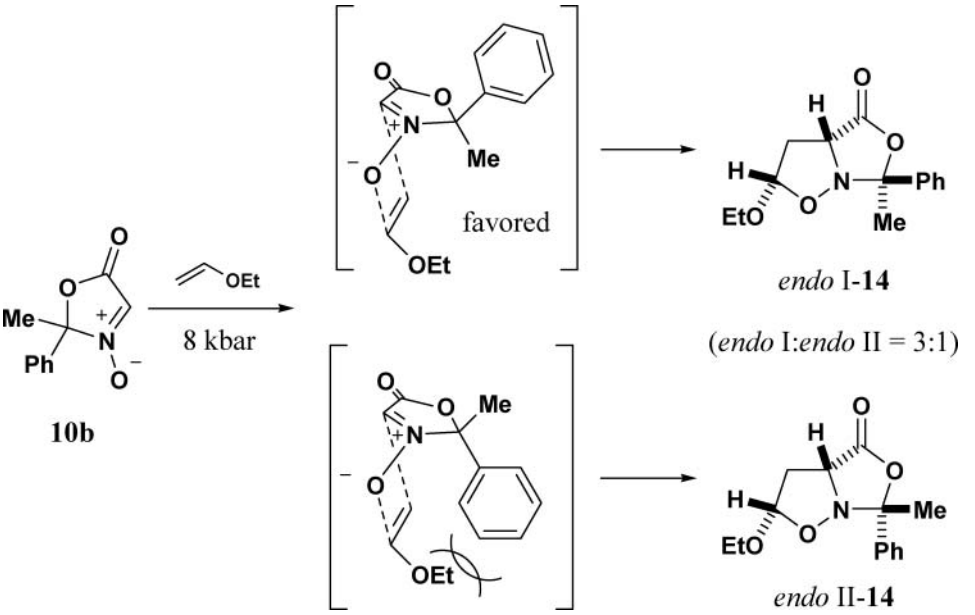


10a *endo* approach 12 13

Scheme 7

Under the same conditions, 1,3-DC of ethyl vinyl ether with the nitrone **10b** deriving from acetophenone proceeded again with a total *endo* stereoselectivity, and a 3:1 diastereofacial selectivity (*Scheme 8*).

The chiral 6-membered ring nitrone **11**, deriving from (*R*)-phenylglycinol **15** was reported by Tamura's group in 1996.[48] Prepared by a five-step sequence in an enantiopure

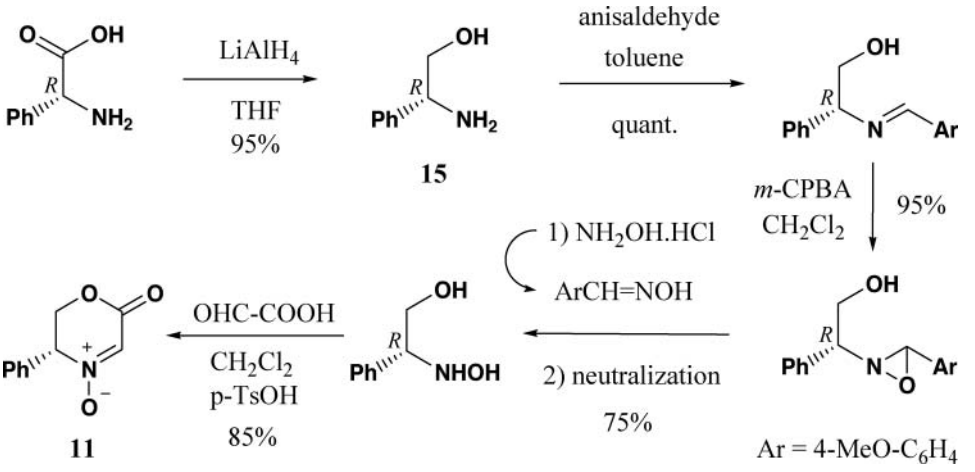


Scheme 8

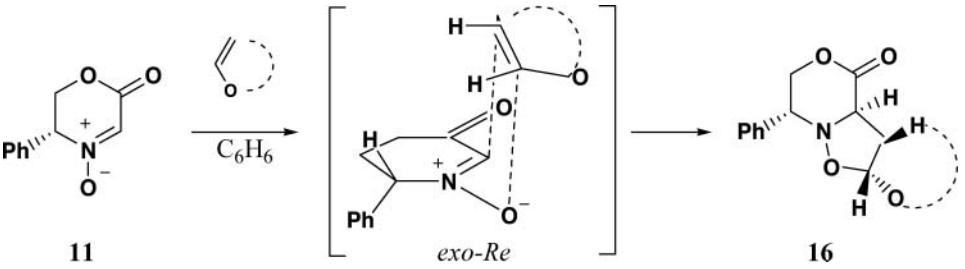
form (*Scheme 9*),[49] this promising nitrone displayed a high reactivity towards a range of dipolarophiles.

With ethyl vinyl ether and dihydrofuran, cycloadducts **16** are produced under mild thermal conditions, with excellent yields and with high *trans* and facial diastereoselectivities. The 1,3-DC results from a highly controlled *exo* approach of the dipolarophile to the *Re* face of the nitrone (*Scheme 10*).

In contrast to the hyperbar conditions required for the 1,3 DC of Katagiri's nitrones, 1,3-DC of Tamura's nitrone proceeds under standard conditions. This gap of reactivity was

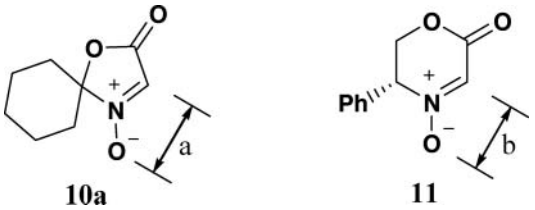


Scheme 9



Scheme 10

attributed to geometric factors.[49] In the case of the 6-membered ring nitrone **11**, the (b) length between the two reactive sites of the dipole is lower than (a) in the 5-membered ring nitrones **10**, thus favoring the orbital overlap between the LUMO of the nitrone and the HOMO of the vinyl ether (*Scheme 11*).



Scheme 11

b) Brønsted Acid-catalyzed Conditions

One of the first attempts to fix the configuration of an acyclic nitrone was reported by Fukumoto's group[47] with the use of carboxylic derivatives (*Table 5*).

In the absence of a base, nitrone **1e** displays exclusively a *Z* geometry, stabilized by the internal hydrogen bond. 1,3-DC of this nitrone with ethyl vinyl ether or vinyl acetate led to *cis* adducts with a good to high stereoselectivity (*Table 5, Entries* 1 and 2). With triethylamine, the Z geometry is destabilized due to the proximity of the two negatively charged oxygen atoms. As a consequence, the 1,3-DC takes place with the opposite *trans* selectivity (*Table 5, Entries* 3 and 4). However, yields are restricted by the unstability of nitrone **1e**, in its acidic or salt form.

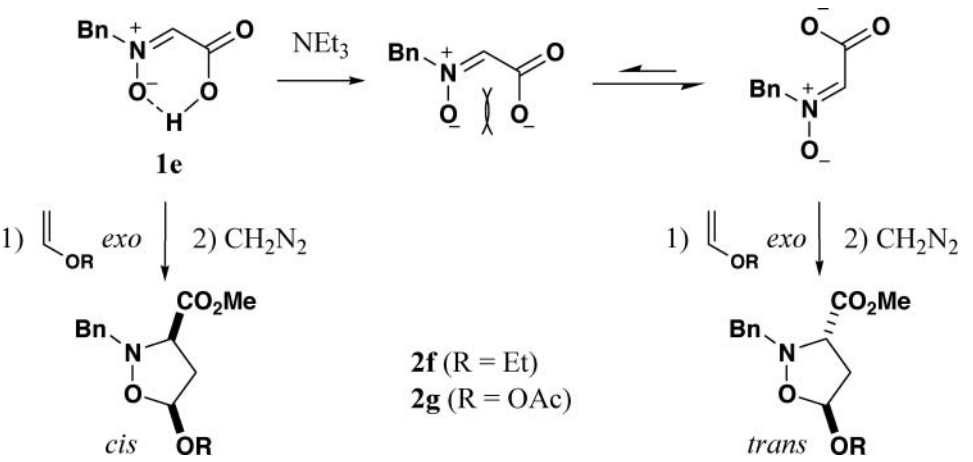
c) Lewis Acid-catalyzed Conditions

i. Europium(III) Catalyst

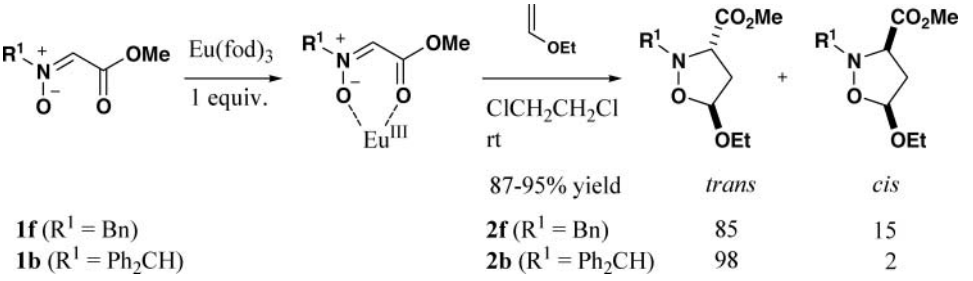
Organosoluble lanthanide salts such as $Eu(fod)_3$ (fod = 6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato) were used by Tamura *et al*. as activating agents,[51] in order to control the stereoselectivity of the 1,3-DC between *N*-alkyl-α-carbonyloxyalkylnitrones **1** and vinyl ethers (*Scheme 12*).

The chelation was expected to lower the LUMO of the nitrone in a *Z* configuration and to improve their reactivity towards electron-rich dipolarophiles such as vinyl ethers. *trans*-Adducts **2** were thus selectively obtained under very mild conditions with high yields,

Table 5
Effect of the Presence of a Brønsted Acid on the Configuration of the Nitrone



Entry	R	Base	Adduct	Yield (%)	*trans*:*cis*
1	Et	none	**2f**	20	26:74
2	OAc	none	**2g**	54	7:93
3	Et	NEt_3	**2f**	68	86:14
4	OAc	NEt_3	**2g**	16	68:32

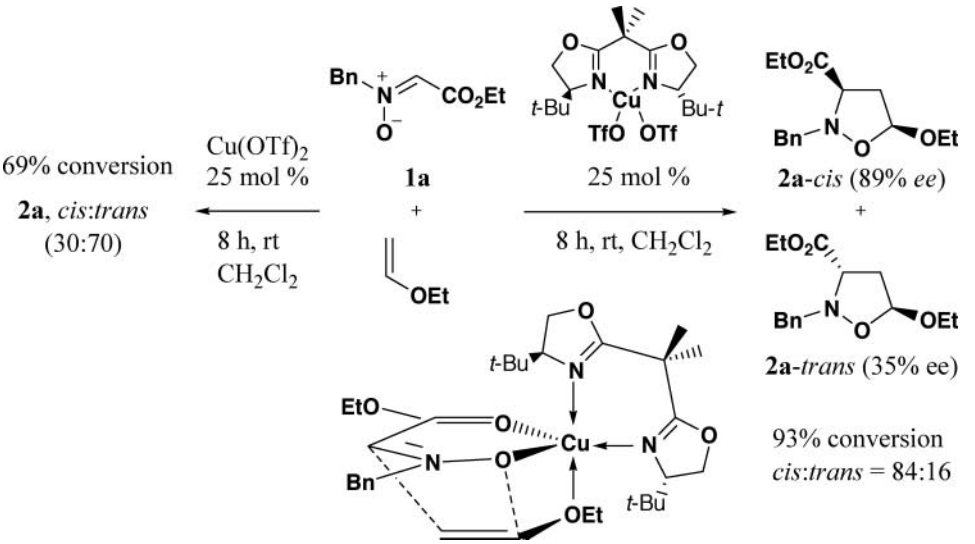


Scheme 12

especially when $Eu(fod)_3$ was used in stoichiometric amounts. *trans*-Selectivity was also found to significantly increase with the size of the *N*-substituent of the nitrone **1**.

ii. Copper(II) and Zinc(II) Catalysts

Copper(II)-catalyzed 1,3-DC of activated nitrones and vinyl ethers was studied by Jørgensen's group in 1999.[40] With copper(II) triflate (25 mol%), the reaction of nitrone **1a** and ethyl vinyl ether was moderately accelerated without significant change of the diastereomeric ratio (*trans*:*cis* = 70:30) compared to the thermal process. However, the adducts **2a** result in this case from an *endo* approach on the *Z* nitrone rather than from an *exo* thermal-like process on the *E* nitrone. Interestingly, the chiral complex $Cu(OTf)_2$-BOX deriving from *t*-leucine proved to be more efficient than $Cu(OTf)_2$ to catalyze this reaction (*Scheme 13*).



Scheme 13

As another major fact, a significant *cis* stereoselectivity is divergently observed (*cis*:*trans* = 84:16) and the major *cis* diastereoisomer is obtained with a good *ee* (89%), whereas enantioselectivity is poor for the minor *trans* isomer. With the same catalyst, changing the solvent from dichloromethane to toluene increased the *ee* of the major *cis* isomer (up to 93%) but decreased the diastereoselectivity (*cis*:*trans* = 70:30).

To explain this stereochemical and asymmetric outcome, an intermediate was postulated, in which the copper(II) atom interacts with both BOX and cycloreactants in a way that minimize steric interactions between *t*-Bu groups and the incoming heteroadduct.

2. *C-Aryl-substituted Nitrones*

a) Thermal Conditions

In contrast to activated acylic nitrones, C-aryl and C-alkyl acyclic nitrones commonly display a stable *Z* configuration avoiding the steric repulsion assumed in the *E* form.

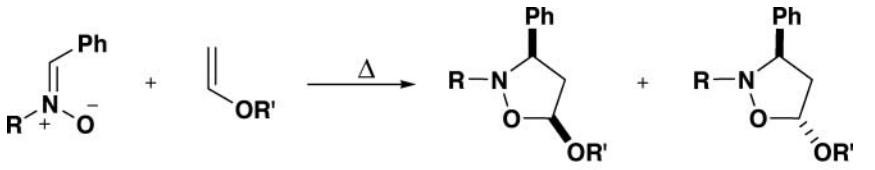
The thermal 1,3-DC of *Z* α-aryl nitrones **17** was reported at 50°C with vinyl ethers[52] and at 80°C with vinyl acetate[53] and is typically *exo*-controlled, leading mainly to *cis* adducts (*Table 6*). This *cis* stereoselectivity is favored with a nitrone displaying a high rotation barrier of its C=N bond (*e. g.* **17a**, R = Ph) towards a bulky dipolarophile (R′ = *t*-Bu), and can reach up to 97:3 when these two factors are cumulated (*Table 6,* Entry 2). However, in this last case, complete conversion at 50°C required an extended time of 14 days.

b) Lewis Acid-catalyzed Conditions

i. TMSOTf-promoted Reactions

Tromboni's group demonstrated in 1992 that TMSOTf was a powerful promotor for the 1,3-DC of α-aryl nitrones **17** and silyl enol ethers.[54,55] When thermal 1,3-DC of silyl enol

Table 6
Thermal Cycloaddition of Nitrones **17** with Vinyl Ethers and Vinyl Acetate



17 *cis*-**18** *trans*-**18**

Entry	Nitrone	R	R′	Conditions	Adduct	Yield (%)	*cis:trans*	Ref
1	**17a**	Ph	Et	50°C, 50 h	**18a**	72	86:14	52
2	**17a**	Ph	*t*-Bu	50°C, 14 d	**18b**	70	97:3	52
3	**17b**	Bn	Et	50°C, 53 h	**18c**	78	67:33	52
4	**17b**	Bn	*t*-Bu	50°C, 5 d	**18d**	74	80:20	52
5	**17c**	Me	Et	80°C, 72 h	**18e**	61	50:50	53
6	**17c**	Me	Ac	80°C, 72 h	**18f**	61	70:30	53

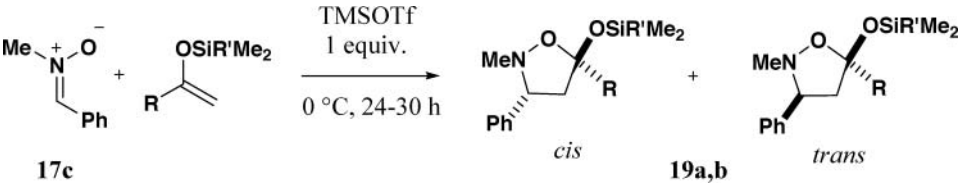
ether required harsh conditions (refluxing *p*-xylene), the use of TMSOTf as stoichiometric promotor allowed the reaction to proceed at –10 to 0°C with a total conversion after 30 h (Table 7) and a moderate *trans* selectivity.

Concerning the role of TMSOTf, it is assumed that the activation energy required for the formation of the new carbon-carbon bond is reduced by prior silylation of the nitrone **17c** to afford *N*-siloxyiminium ion **20**, which then gives *via* a probable non-concerted mechanism the oxonium ion **21**, an immediate precursor of isoxazolidines **19** (*Scheme 14*).

ii. Boron(III) Catalyst

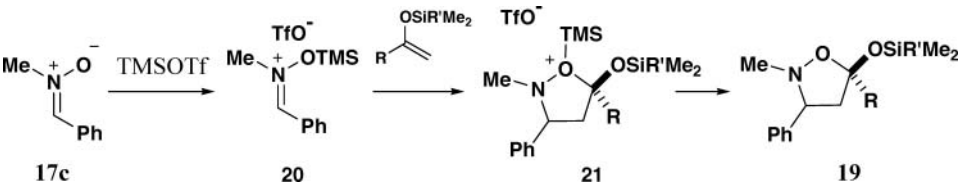
In 1994, the use of chiral oxazaborolidinones **22** deriving from *N*-tosyl-L-α-aminoacids as catalysts for the 1,3-DC between ketene ketals and the *N*,α-diphenylnitrone **17a** was investigated by Scheeren's group.[56] 5,5-Diethoxy-isoxazolidines **23** were thus produced at very low temperature (−78°C) in high yields (80–98%) and with fair enantioselectivity (up

Table 7
Cycloaddition Reactions Promoted by TMSOTf



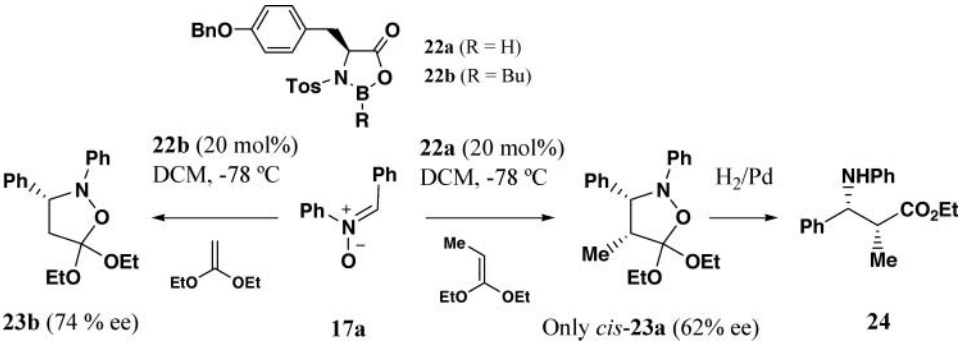
17c **19a,b**

R	R′	Adduct	Yield (%)	*cis:trans*
H	*t*-Bu	19a	87	36:64
Me	Me	19b	77	40:60



Scheme 14

to 74% *ee*) (*Scheme 15*).[57] This enantioselectivity was found to be highly solvent-dependent and to be reversible by changing the nature of the α-side chain substituent of the catalyst, by addition of ligand-like solvents.[57] Hydrogenolysis of the N—O bond under mild conditions led quantitatively to enantiopure β-amino-esters **24**. Extension of this chiral oxaborolidine methodology to vinyl ethers towards the same nitrone allowed the formation of adducts at room temperature, but only with poor (*cis*) stereoselectivities and low *ee* (<34%).[56,59]

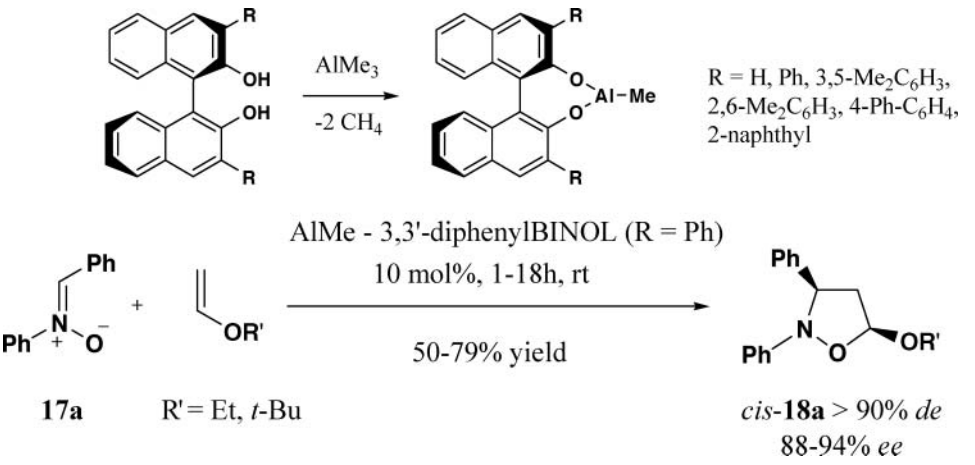


Scheme 15

iii. Aluminium(III) Catalyst

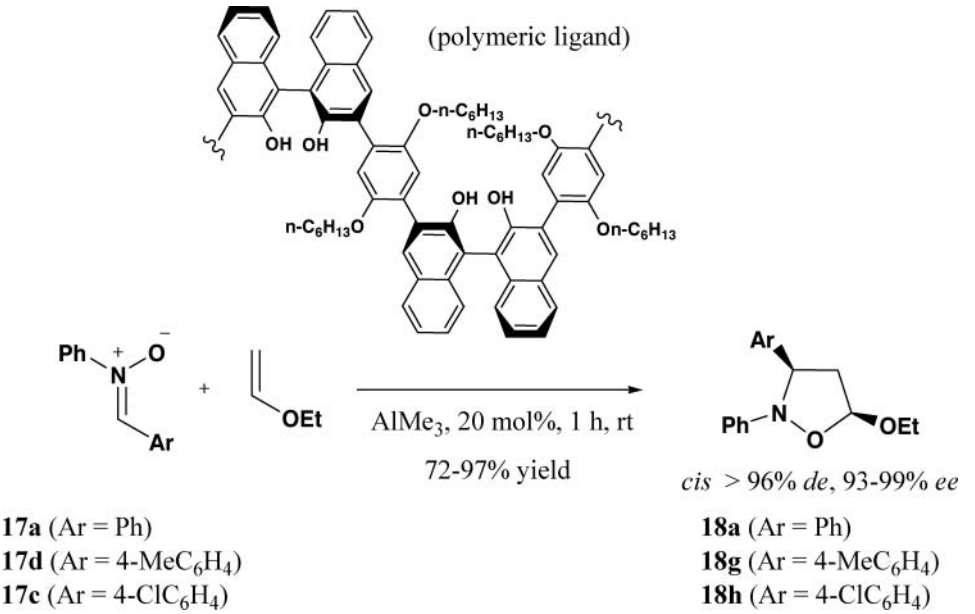
The powerful use of chiral aluminium(III) catalysts was introduced by Jørgensen's group in 1999.[60] The catalysts involved were AlMe-3,3′-diaryl-BINOL complexes obtained by addition of the corresponding ligand to $AlMe_3$ (*Scheme 16*). The 1,3-DC reaction between the *N*,α-diphenylnitrone **17a** and *t*-butyl vinyl ether was studied extensively, leading to the best results with AlMe-3,3′-diphenyl-BINOL complex. In this optimal case, the corresponding *cis* isoxazolidine **18a** was obtained as a sole diastereomer in 84% yield and 89% *ee*. The scope of this powerful enantioselective 1,3-DC was successfully extended to other *C*-aryl *N*-phenyl nitrones (up to 97% *ee* with C-4-chlorophenyl nitrone), but not evaluated to our knowledge in the critical case of *N*-benzyl *C*-aryl nitrones which are subject to the Behrend rearrangement.

In order to make easier the separation and recycling of the ligand, polymeric 3,3′-disubstituted BINOL ligands were investigated by the same group (*Scheme 17*).[61] High yields, *cis* stereoselectivity and enantioselectivity (94–99%) were obtained between *N*-phenyl-α-arylnitrones **17** and ethyl vinyl ether. The polymer ligand was efficiently removed and isolated after final hydrolysis and precipitation in methanol, and was conveniently recycled (without loss of efficiency after 3 cycles).

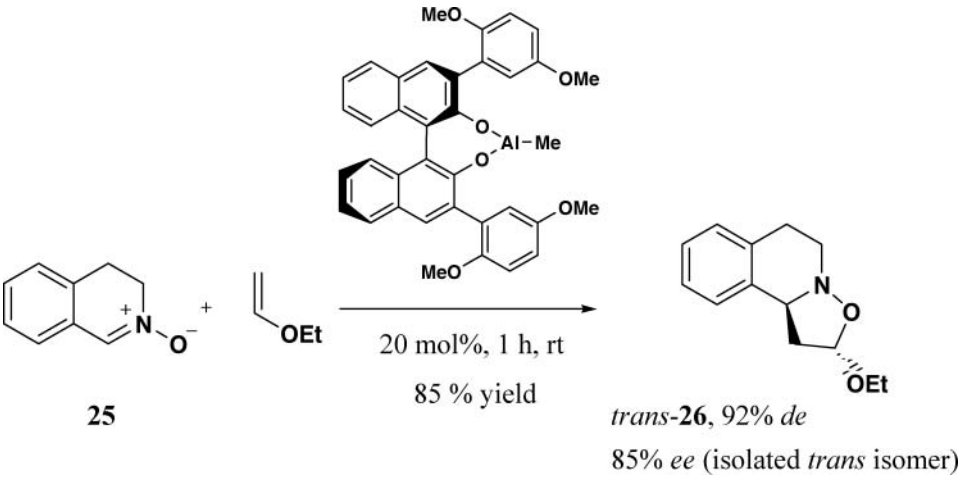


Scheme 16

The use of chiral monocomplexing Lewis acids was also investigated in the case of cyclic *C*-aryl nitrones, featuring a *E*-fixed geometry, with the representative 3,4-dihydroisoquinoline-*N*-oxide **25**. As in acylic series, the best results were reported by Jørgensen's group[62] with Binol derived-aluminium(III) catalysts, affording tricyclic adducts **26** with high *trans* selectivity and good enantioselectivity (up to 85% *ee* with R = 2,5-diMeO-Ph) (*Scheme 18*).



Scheme 17

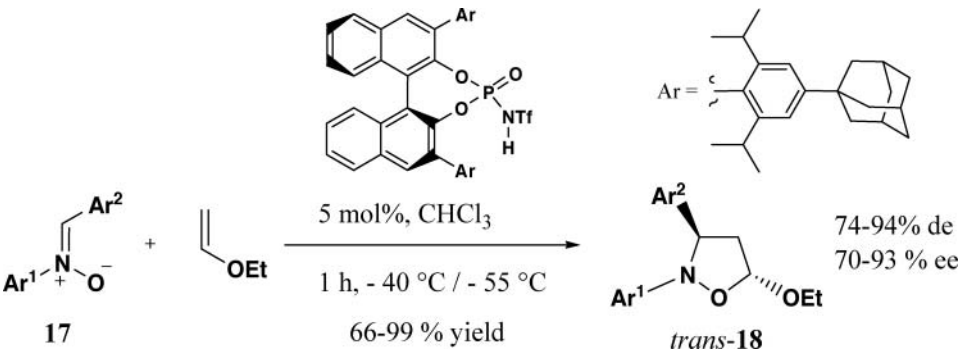


Scheme 18

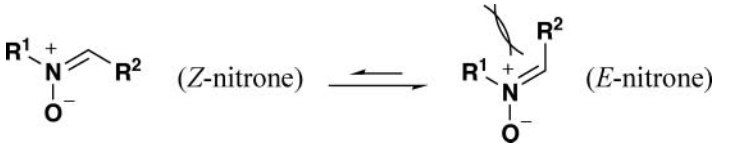
Attempts to promote the stereocontrolled and asymmetric 1,3-DC of 3,4-dihydroisoquinoline-*N*-oxide **25** towards vinyl ethers or ketene acetals with other chiral Lewis acids (titanocenes,[63] oxazaborolidines[57]) gave only weak results.

c) Brønsted Acid-catalyzed Conditions

Binol-*N*-triflyl-phosphoramides were successfully used as chiral Brønsted acids in the 1,3-DC of aryl and heteroaryl nitrones towards ethyl vinyl ether.[64] From the ligand optimization study performed at −55°C in chloroform, Binol-ligand bearing two (4-adamantyl-2,6-diisopropyl)phenyl groups led to the more efficient catalyst for achieving *endo* and enantiocontrol (*cis* : *trans* = 4:96, 84% *ee*). Interestingly, this reaction, that could be extended to a range of *N*,α-diaryl and *N*-aryl-α-heteroaryl nitrones (**17**) in a 6:1 to 32:1 *trans* selectivity and in 70–93% *ee* (*Scheme 19*), proved to be usefully complementary to the *exo* selective Binol-$AlMe_3$ method, previously reported.[60]



Scheme 19



Scheme 20

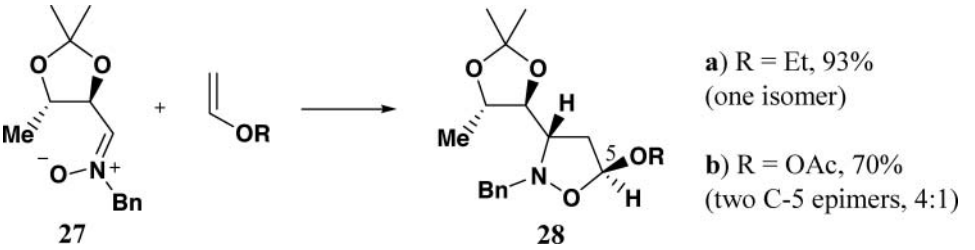
3. Other Nitrones

a) Thermal Conditions

i. Acyclic Nitrones

As the α-substituted *C*-aryl nitrones, the α-substituted *C*-alkyl nitrones generally adopt the more stable *Z*-configuration to avoid the steric repulsion shown by the *E* form (*Scheme 20*).

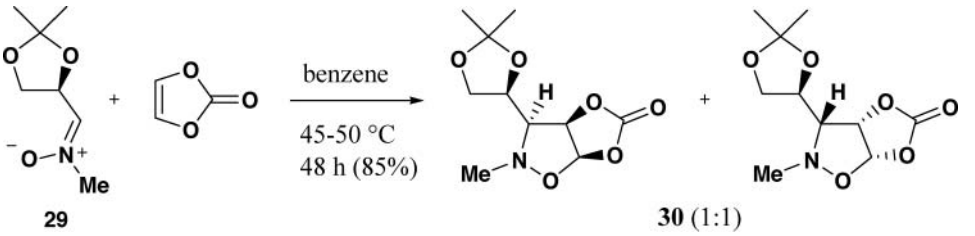
The diastereoselectivity in the cycloaddition with electron-rich dipolarophiles is strongly dependent on the structure of nitrone and dipolarophile. The diastereoselectivity of the cycloaddition of chiral racemic α,β-dialkoxynitrones was first studied by DeShong *et al*. group to access to the amino sugar daunosamine.[22] Cycloaddition of nitrone **27** in the presence of an excess of ethyl vinyl ether or vinyl acetate (*Scheme 21*) proceeded *via* an *endo* transition state and resulted in the formation of the *anti*-isoxazolidine **28** with a high diastereofacial selectivity (100%).



27 28

Scheme 21

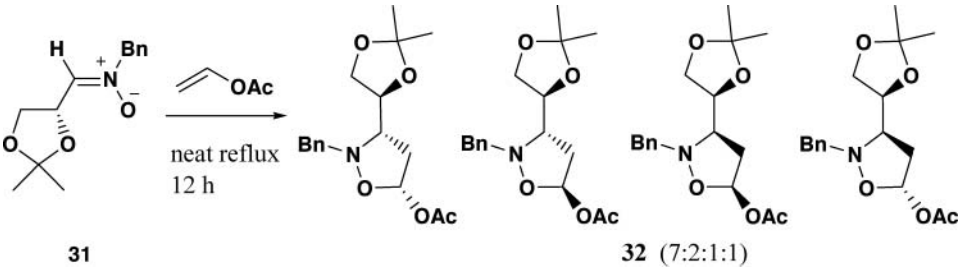
Asymmetric dipolar cycloaddition of a (*R*)-glyceraldehyde acetonide derived nitrone **29** and vinylene carbonate resulted in the formation of a 1:l mixture of adducts **30**, through an *endo* transition state, in 85% yield. In this case, no diastereofacial selectivity was observed (*Scheme 22*).[22]



29 **30** (1:1)

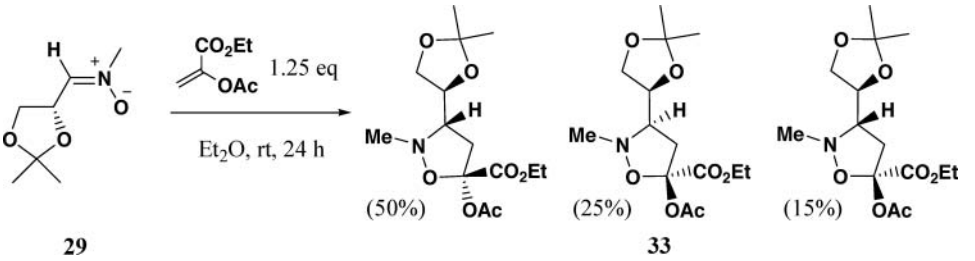
Scheme 22

The cycloaddition of the nitrone **31** with vinyl acetate took place without additional solvent and gave a mixture of the four stereoisomeric isoxazolidines **32** in 94% combined yield (*Scheme 23*). The major stereoisomer of the cycloaddition reaction results from an *exo* transition state and from a reaction on the most sterically accessible *Si* face of the nitrone.[65]



Scheme 23

The asymmetric 1,3-dipolar cycloaddition of the *C*-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-*N*-methyl nitrone **29** with ethyl 2-acetyloxyacrylate in dry ether at room temperature for 24 h, affords a mixture of three isoxazolidines **33** with a 90% global yield (*Scheme 24*). The reaction proceeds with good *cis*/*trans* diastereoselectivity and a moderate diastereofacial selectivity.[66,67]

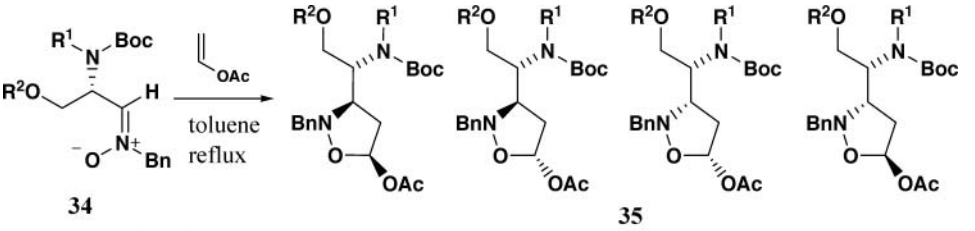


Scheme 24

With the aim to obtain new isoxazolidinyl analogues of deoxypolyoxin C, reaction of L-serine-derived nitrones **34** with vinyl acetate was carried out in refluxing toluene and gave rise to 5-acetoxy isoxazolidines **35** (*Scheme 25*). The diastereofacial selectivity with respect to the *R*-chirality of nitrones was *anti* in both cases and the preference for the *cis* isomers resulted from an *exo* attack.[68]

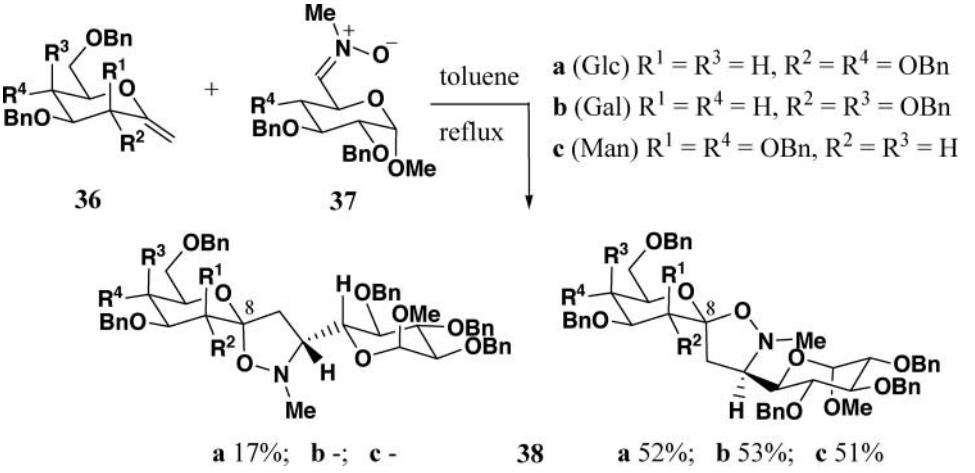
For access to novel amino-C-ketosyl disaccharides, the 1,3-dipolar cycloadditions of *exo*-methylenesugars **36** were performed with sugar nitrone **37** by refluxing in a toluene solution to provide the corresponding ketosyl spiro-isoxazolidines **38**.[69] The cycloaddition of methyleneglucoside derivative **36a** and the nitrone underwent diastereoselectively and afforded only two anomeric isomers possessing *R*-configuration at C-6. Under the same conditions, the cycloadditions of galactose and mannose derivatives **36b,c** with glycosyl nitrone **37** were carried out, but only *O*-β-anomeric isomers were obtained in these two cases (*Scheme 26*).

As exemplified in the synthesis of (−)-tetrodotoxin, the 1,3-dipolar cycloaddition of a ketonitrone **39**, prepared from the known 4-oxo-mannopyranose derivative, is a



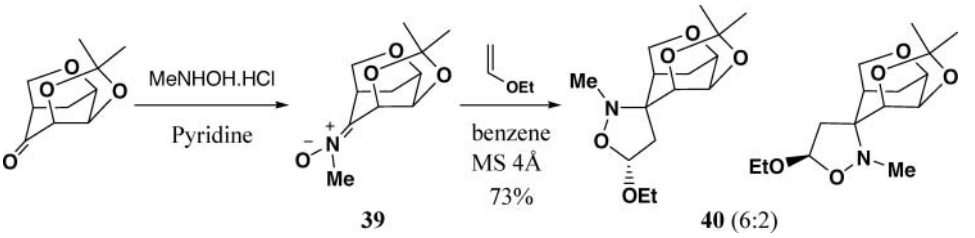
a) R^1, $R^2 = CMe_2$	50	20	21	19
b) $R^1 = H$, $R^2 = TBS$	70	17	13	0

Scheme 25



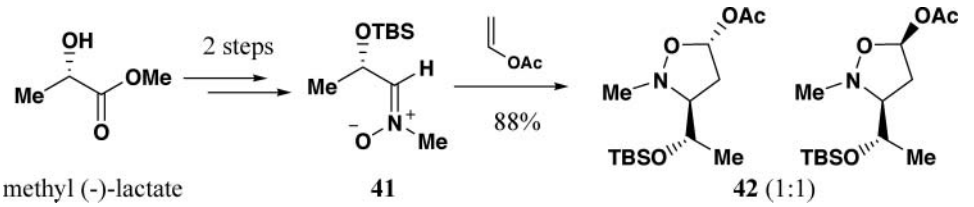
Scheme 26

synthetically useful procedure for the stereocontrolled preparation of nitrogenated quaternary centers in sugar substrates.[70] Reaction of the ketonitrone **39** with ethyl vinyl ether took place regioselectively to give cycloadducts **40** with 73% global yield, and a 6:1 stereoselectivity (*Scheme 27*).



Scheme 27

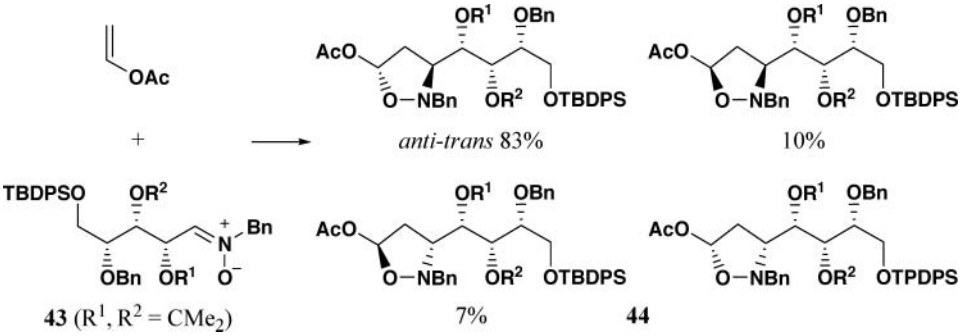
With the aim to prepare isoxazolidinyl nucleosides, silylated nitrone **41** was prepared in a *Z* configuration from (−)-methyl lactate. Its reaction with vinyl acetate gives two epimeric isoxazolidines **42** in good overall yield (88%) (*Scheme 28*).[43]



methyl (-)-lactate **41** **42** (1:1)

Scheme 28

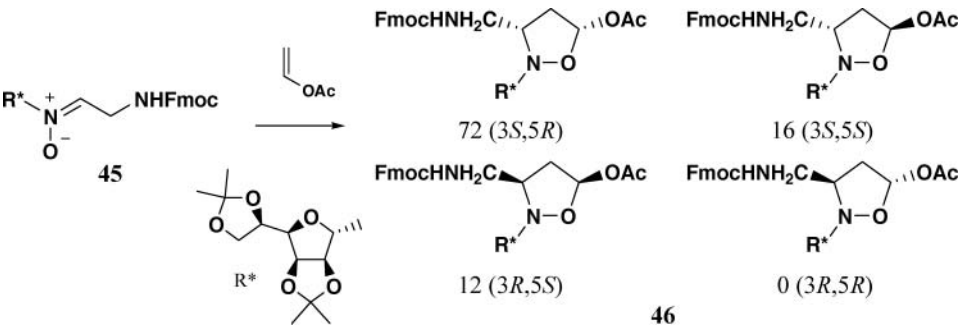
For access to azanucleosides, chiral sugar-derived D-xylosyl nitrone **43** reacted smoothly in vinyl acetate at reflux over 24 h to give an 83:10:7 mixture of diastereoisomeric isoxazolidines **44** in 85% yield.[71,72] The cycloaddition proceeded regioselectively with a very good *anti* diastereoselectivity. *trans*-Isoxazolidine was formed as a result of dipolarophile attack on the less sterically hindered *Si* diastereotopic face of the nitrone (*Scheme 29*).



43 (R^1, $R^2 = CMe_2$) **44**

Scheme 29

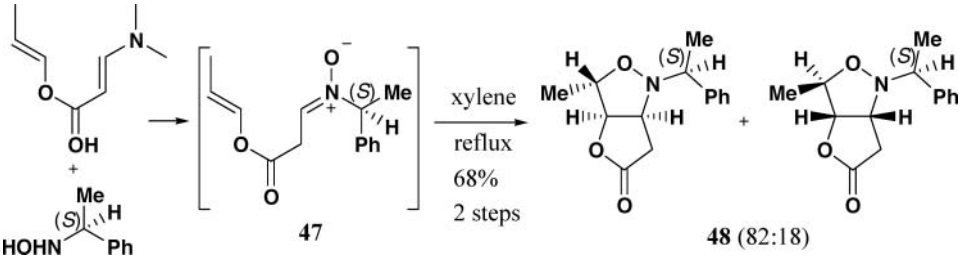
The synthesis of orthogonally protected isoxazolidinylthymine has been achieved through diastereoselective 1,3-dipolar cycloaddition between *N*-glycosyl nitrones and vinyl acetate.[73] The use of D-mannose derived hydroxylamine to form the chiral nitrone **45**, led to the best results affording isoxazolidine **46** with good *exo* (*cis*:*trans* = 84:16) and diastereofacial (*Si*:*Re* = 88:12) selectivities (*Scheme 30*).



45 **46**

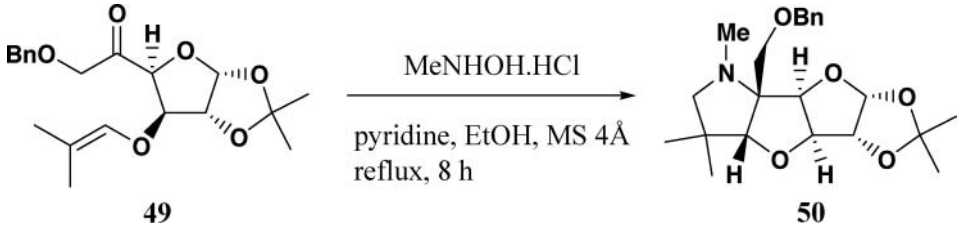
Scheme 30

In order to achieve the synthesis of L-acosamine, the nitrone **47** deriving from *N*-(*S*)-1-phenylethyl)hydroxylamine underwent intramolecular cycloaddition with vinyl acetate in refluxing xylene to give in 68% yield an 82:18 mixture of diastereomers **48** (*Scheme 31*).[74]



Scheme 31

To complete the scope of the 1,3-dipolar cycloaddition of sugar ketonitrones, the intramolecular cycloaddition of derived 1,3–5,6-diisopropylidene-α-D-glucofuranose **49** proceeded exclusively to the fused isoxazolidine-tetrahydrofuran system **50** in 43% yield (*Scheme 32*).[75]

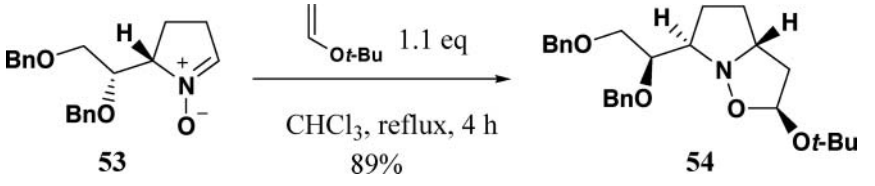


Scheme 32

ii. Cyclic Nitrones

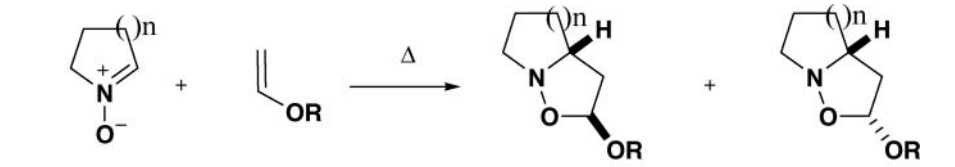
In contrast to most of their acyclic partners, cyclic nitrones are configurationally locked, therefore the *endo-exo* selectivity of their 1,3-dipolar cycloadditions to olefins can be directly deduced from the stereochemistry of the adducts formed. In the case of piperidinic and pyrrolidinic nitrones **51**, the *exo* approach is predominant with major formation of the *trans* adduct **52** (*Table 8*).

The 1,3-dipolar cycloaddition of pyrrolidine *N*-oxide **53**, an enantiopure D-glyceraldehyde derived nitrone, with *tert*-butyl vinyl ether shows complete 1,4-*anti* facial and *exo* selectivity, furnishing the highly functionalized and enantiopure bicyclic isoxazolidine **54** (*Scheme 33*).[78]



Scheme 33

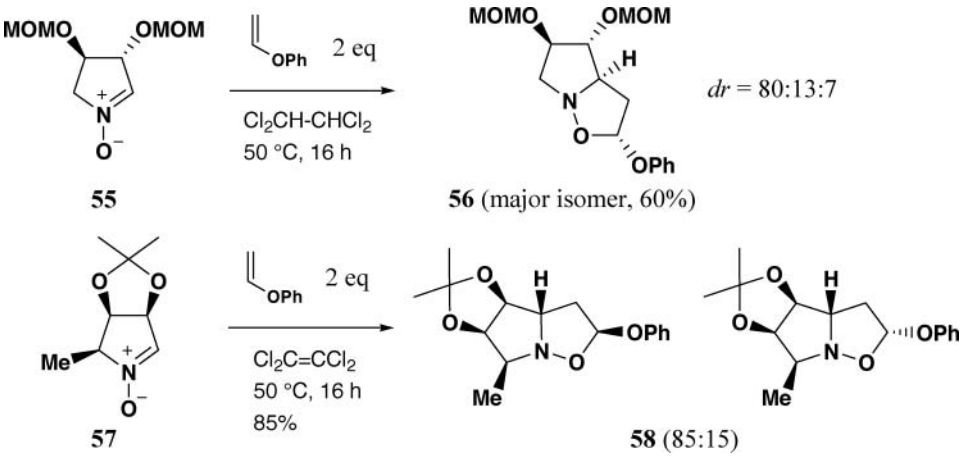
Table 8
Thermal Cycloaddition Reactions between Cyclic Nitrones **51** and Vinyl Ethers



51 (n = 1, 2) *exo / trans* **52** *endo / cis*

Nitrone	n	R	Conditions	Adduct	Yield (%)	*trans*:*cis*	Ref
51a	1	Et	$CHCl_3$, 50 °C, 7 d	**52a**	73	90:10	52
51a	1	Et	CH_2Cl_2, 60 °C, 8 h	**52a**	70	92:8	76
51a	1	Ph	$Cl_2CH\text{-}CHCl_2$, 50 °C, 16 h	**52b**	45	90:10	77
51b	2	Et	EtOH, 40 °C, 12 h	**52c**	67	93:7	76

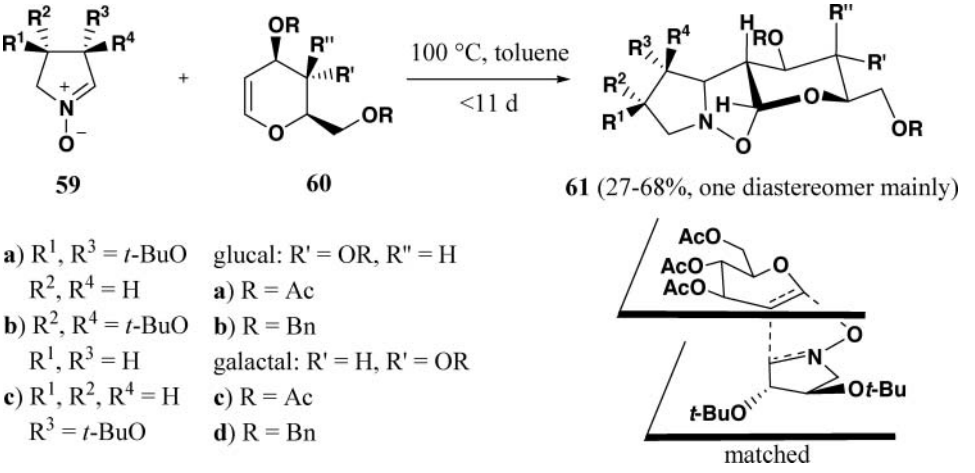
Cycloadditions with other pyrrolidine *N*-oxides, a (*R*,*R*)-tartaric acid derived nitrone **55**[76] and a D-ribose derived nitrone **57** analogue of 5-deoxy-L-lyxose,[79] displayed moderate selectivities (*Scheme 34*).



Scheme 34

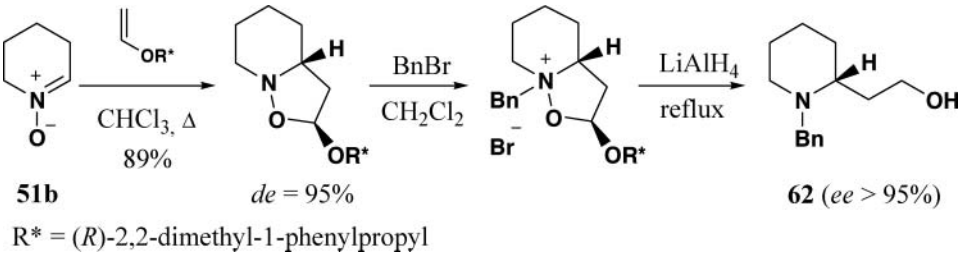
The 1,3-dipolar cycloaddition, of DL-tartaric and L-malic acids derived nitrones **59** with glucose and galatose-derived 1,2-glycals **60**, proceeds with essentially total regio- and stereoselectivity.[80,81] The stereoselectivity is controlled by the pseudoequatorial group at C-3, thus favoring the *exo* approach of the nitrone to the less hindered *bottom* face to lead to the *anti* product. D-Tartaric acid-derived nitrone **59a** gave, with this *bottom-exo-anti* approach, a "matched" interaction with glucal **60a** (*Scheme 35*).

In contrast to the well-documented asymmetric Diels-Alder reaction, asymmetric 1,3-dipolar cycloadditions involving vinyl and enol ethers of chiral alcohols have been less explored. To synthesize piperidine alkaloids, the nitrone cycloaddition of



Scheme 35

tetrahydropyridine-*N*-oxide **51b** with optically active vinyl ethers was considered in order to access a chiral piperidine synthon **62** (*Scheme 36*).[82] The asymmetric control is strongly dependent of the nature of the chiral inducer and large variation of the diastereoisomeric excess is observed (*de* = 0% with R* = 8-phenylmenthyl; *de* > 95% with R* = (*R*)-2,2-dimethyl-1-phenylpropyl).



Scheme 36

b) Lewis Acid-catalyzed Conditions

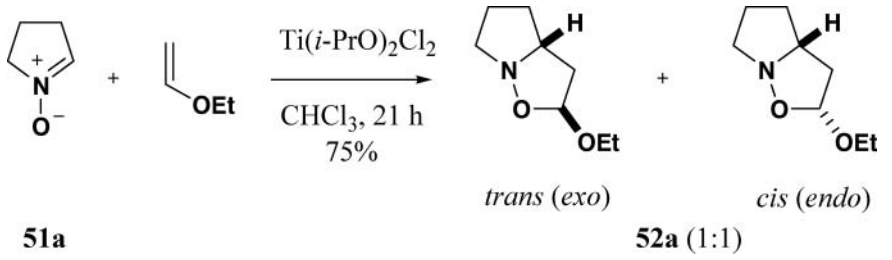
In the field of 1,3-dipolar cycloaddition of α-substituted *C*-alkyl nitrones with alkyl vinyl ethers, the use of Lewis acids as catalysts decreased the reaction time. However, whenever the nitrone or the Lewis acid is chiral, facial selectivity remains weak.

i. Titanium(IV) Catalyst

The 1,3-dipolar cycloaddition of pyrrolidinic nitrone **51a** to vinyl ethers is accelerated by Ti(IV) species. Comparatively to the uncatalyzed reaction (*exo*:*endo* 10:1), the use of $Ti(O\textit{i}\text{-}Pr)_2Cl_2$ increases the formation of *endo* cycloadduct **52a**, presumably *via* a bidentate complex (*Scheme 37*).[52]

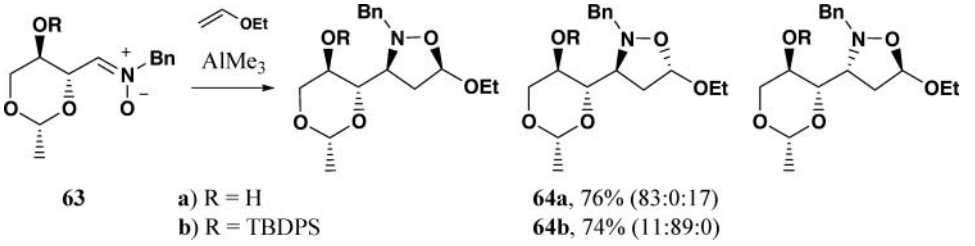
ii. Aluminium(III) Catalyst

The $AlMe_3$-catalyzed 1.3-dipolar cycloaddition of chiral D-erythrose derived nitrone **63a** with ethyl vinyl ether proceeds diastereoselectively. With the nitrone **63b**, the



Scheme 37

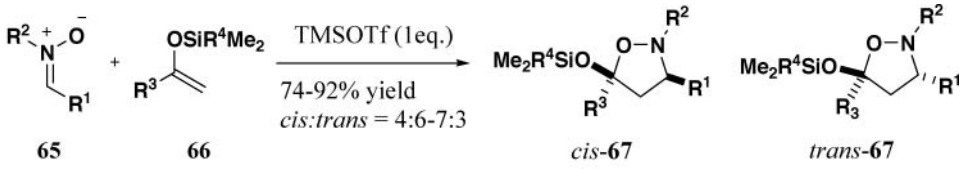
protection of the hydroxyl group with (*tert*-butyl)diphenylsilyl group reverses dramatically the diastereoselectivity of the cycloaddition (*Scheme 38*).[83]



Scheme 38

iii. Trimethylsilyl Trifluoromethanesulfonate

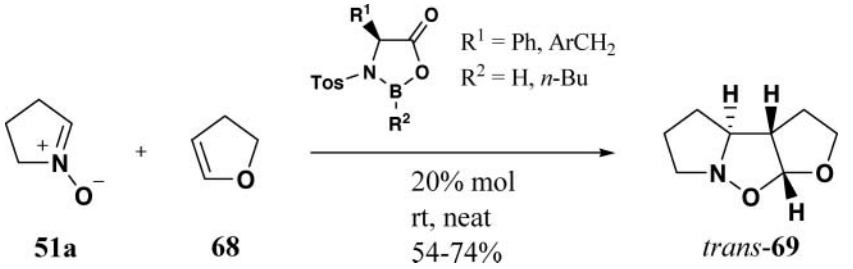
Aldonitrones **65** and trialkylsilyl enol ethers **66** undergo a TMSOTf catalysed cycloaddition reaction under mild conditions affording regioselectively and in excellent yields 5-trialkylsiloxyisoxazolidines **67** (*Scheme 39*), as a mixture of *cis* and *trans* isomers. However, the use of 1 equiv. of TMSOTf at –10/–0°C was necessary to optimize the formation of isoxazolidines **67**.[54]



Scheme 39

iv. Boron Catalyst

The scope of the (chiral) Lewis acid catalyzed *exo*-selective 1,3-dipolar cycloadditions of nitrones with cyclic *Z*-alkyl vinyl ethers was studied with pyrrolidine *N*-oxide **51a**.[57] This reaction catalyzed by the chiral oxazaborolidine (20 mol%) at room temperature and ambient pressure in neat 2,3-dihydrofuran **68** gave exclusively the *trans*-isoxazolidine **69** in good yields (*Scheme 40*).



Scheme 40

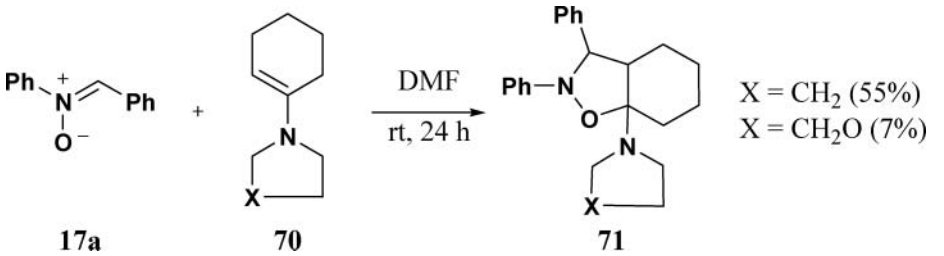
The enantioselectivity was strongly dependant on the structure of the chiral catalyst. The highest but still moderate enantioselectivity (38% *ee*) was obtained with *N*-tosyl-L-phenylglycine derived oxazaborolidine ($R^1 = Ph$, $R^2 = H$).

II. Reaction with Aza-substituted Alkenes

1. Enamines as Dipolarophile

Although the cycloaddition of nitrones with enamines has been studied for more than forty years beginning with the pioneering work of Japanese chemists,[84–86] the *cis-trans* geometry of the obtained adducts was not established and remains unknown until now.

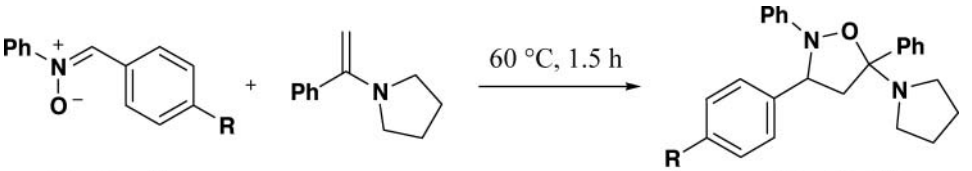
The high reactivity of such dipolarophiles is illustrated in the cycloaddition reaction of *N*,α-diphenylnitrone **17a** with enamines **70** derived from cyclohexanone and pyrrolidine or morpholine which proceeds even at room temperature (*Scheme 41*).[84]



Scheme 41

When 1-phenyl-substituted enamines **72** were employed as dipolarophiles, thermal conditions are necessary to achieve good conversions (*Scheme 42*).[85]

The cycloaddition of nitrones **17e,g** with 1-pyrrolidino-*cis*-3,5-dimethylcyclohexene **74** at room temperature in DMF provided adducts **75** with the inverse regioselectivity (*Scheme 43*).[86] In this case, the regioselectivity is controlled by the 3-methyl group. The transition state leading to the formation of the "normal" regioisomer suffers in this case from severe destabilizing interactions between non-bonded *C*-aryl and methyl group. Moreover, this unfavorable interaction in the corresponding adduct lowers its stability. The formation of reverse-oriented adducts which are free from this type of interaction is kinetically and thermodynamically favored.

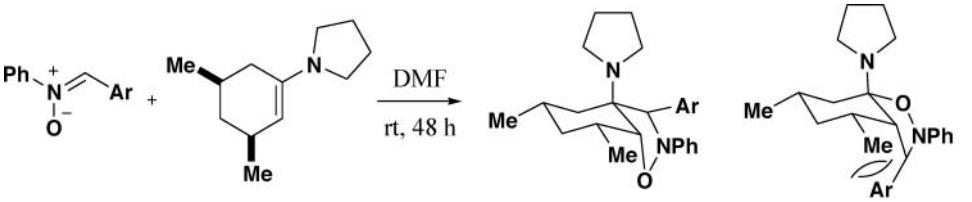


17a, R = H
17e, R = Cl
17f, R = NO_2

72

73 R = H, 48%
R = Cl, 62%
R = NO_2, 49%

Scheme 42



inverse regioisomer normal regioisomer

17e, Ar = *p*-ClC_6H_6
17g, Ar = *m*-$NO_2C_6H_6$ **74**

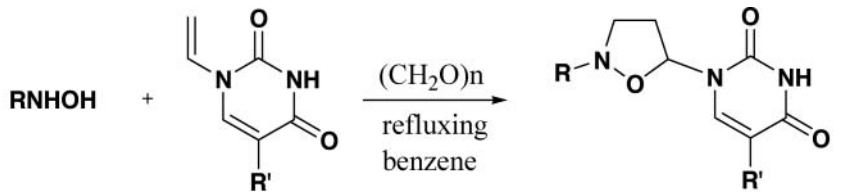
75 Ar = *p*-ClC_6H_6, 27%
Ar = *m*-$NO_2C_6H_6$, 66%

Scheme 43

2. Enamides as Dipolarophiles

*a) **N**-Vinylnucleobases*

Modified nucleoside analogues inhibit viral polymerases by acting as DNA/RNA chain terminators or as competitive inhibitors.[87] In this context, interesting biological results have been observed by using nucleosides analogues in which the carbohydrate moiety is replaced by an isoxazolidine nucleus. The 1,3-dipolar cycloaddition methodology between nitrones and vinyl-nucleobases is therefore important to achieve a straightforward procedure and provide a very useful route to this type of modified nucleosides. As model reaction, the cycloaddition carried out with nitrones (formed *in situ* by the action of hydroxylamines **76** on paraformaldehyde) and vinylthymine **77a** or vinyluracil **77b** (*Scheme 44*) proceeded under mild thermal conditions in good yields.[88,89]



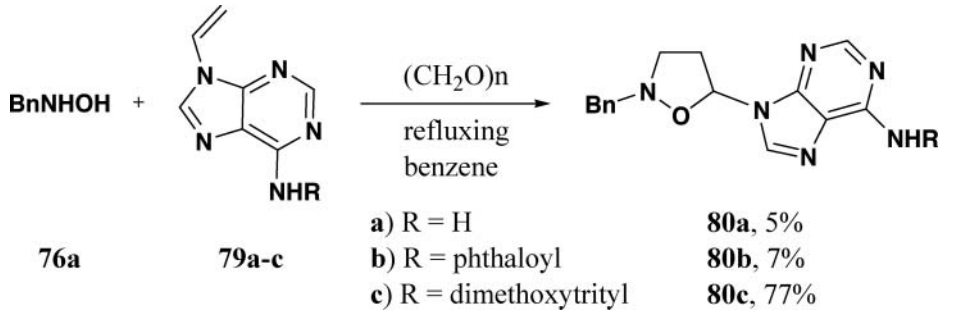
76a, R = Bn
76b, R = THP

77a, R' = Me
77b, R' = H

78a, R = Bn, R' = Me, 63%
78b, R = THP, R' = H, 65%
78c, R = THP, R' = Me, 58%

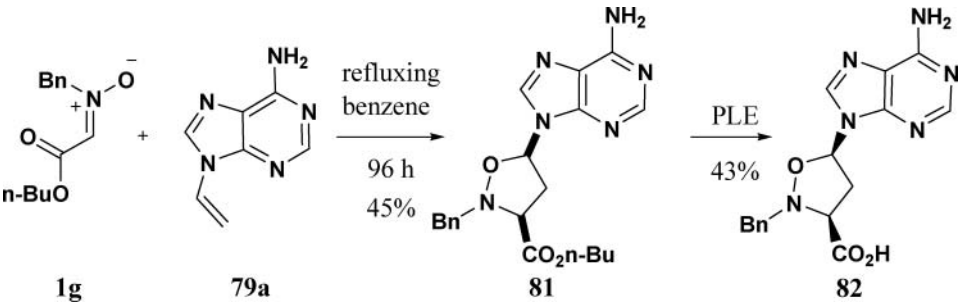
Scheme 44

The same reaction failed with *N*-9 unprotected adenine derivative **79a**, due to the formation of the side product *N*-9-hydroxymethyl as a result of the interaction of purine bases with formaldehyde. Employing a base labile phthaloyl protecting group (**79b**) was shown to be ineffective because of the side reaction between this protection and the hydroxylamine group. In contrast to these protecting groups, *N*-9 dimethoxytrityl (**79c**) was a more robust protection under these conditions and allowed 1,3-DC reaction to be achieved in good yield (*Scheme 45*).[90]



Scheme 45

The cycloaddition of ester nitrone **1g** with *N*-9-vinyladenine **79a** is an efficient method to synthesize 4′-aza-2′,3′-dideoxyadenosine which could exhibit antiviral activities (*Scheme 46*).[90] This reaction in refluxing benzene provided *cis*-adduct **81** arising from an *endo* attack of the dipolarophile on the *E*-nitrone. In this approach, the presence of the purine ring provides a high degree of *endo* selectivity, probably arising from strongly favored secondary orbital overlap between the nitrone phenyl group and purine nucleus. The kinetic resolution of this adduct was achieved by enzymatic hydrolysis of the ester function in the presence of PLE.

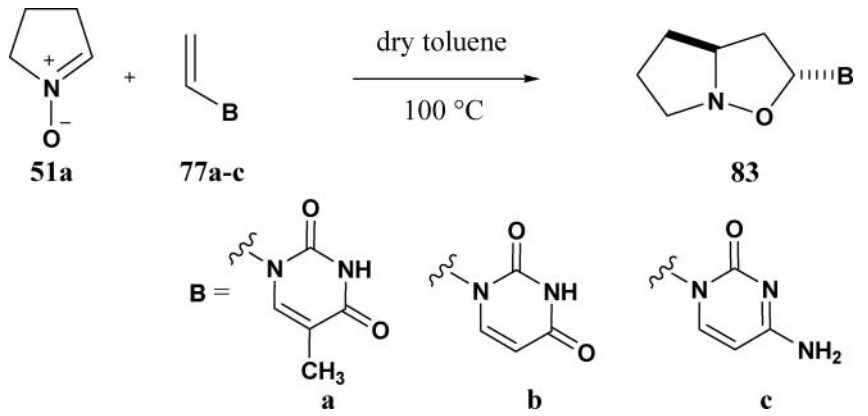


Scheme 46

In order to rigidify the structure of modified nucleosides, the use of a cyclic nitrone such as 3,4-dihydro-2*H*-pyrrole 1-oxide **51a** has been attempted.[91] Its cycloaddition with vinylnucleobases **77a-c** was found to be highly *exo*-selective and afforded the corresponding *trans* adducts **83** in good to excellent yields (*Table 9*).

When the chiral nitrone **84** derived from borneol was used as dipole in cycloaddition towards vinylnucleobases a good degree of asymmetric induction was observed (*Table 10*).[92] Nitrone **84** (as 3:1 *E*:*Z* mixture) reacted with purine and pyrimidine *N*-vinylnucleobases

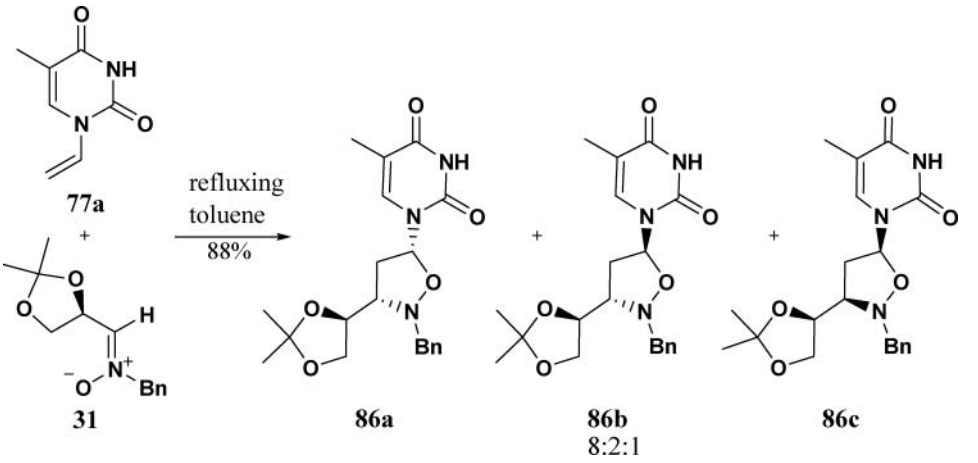
Table 9
Thermal Cycloadditions between Cyclic Nitrone **51a** and Vinylbases **77**



Nucleobase	Reaction time	Adduct	Yield (%)	*trans*:*cis* Ratio
thymine **77a**	6 h	**83a**	95	98:2
uracil **77b**	17 h	**83b**	65	90:10
cytosine **77c**	20 h	**83c**	80	98:2

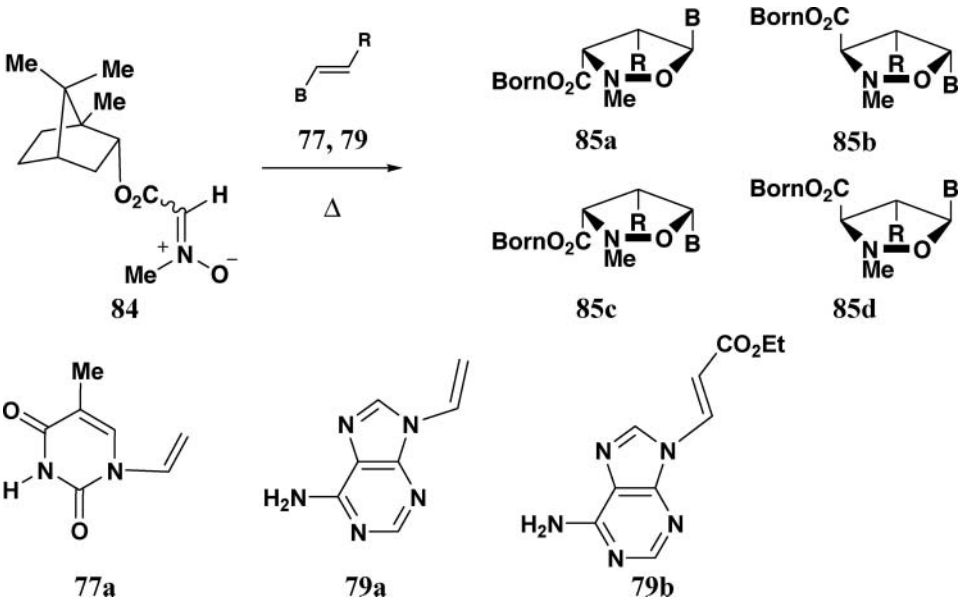
77, 79 to furnish the adducts **85** with *trans* (>72% *de*) and facial (>82% *de*) selectivities. Interestingly, in the case of acrylate **79b**, a single diastereoisomer was obtained in good yield (84%).

The cycloaddition of nitrone **31** derived from 2,3-*O*-isopropylidene-D-glyceraldehyde and vinylthymine **77a** in refluxing toluene gives a separable 8:2:1 mixture of three adducts **86a-c** in 88% combined yield (*Scheme 47*).[65] This method provides an alternative approach to modified nucleosides **86** which can be obtained by a two-step sequence: (a) cycloaddition to vinyl acetate, (b) Vörbruggen nucleosidation using silylated bases.



Scheme 47

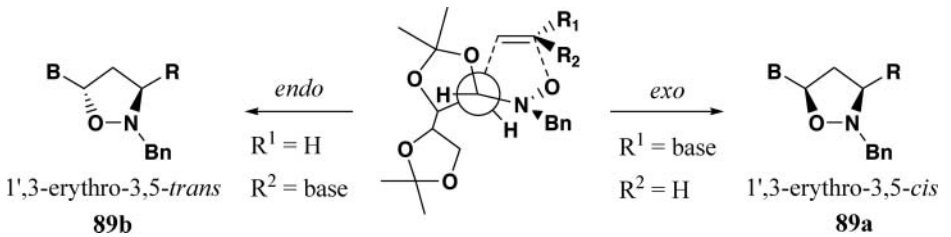
Table 10
Thermal Cycloadditions between Chiral Nitrone **84** and Vinylnucleobases



Nucleobase	**85** a:b:c:d	Global yield (%)
77a	78:8:14:0	90
79a	0:91:0:9	88
79b	100:0:0:0	84

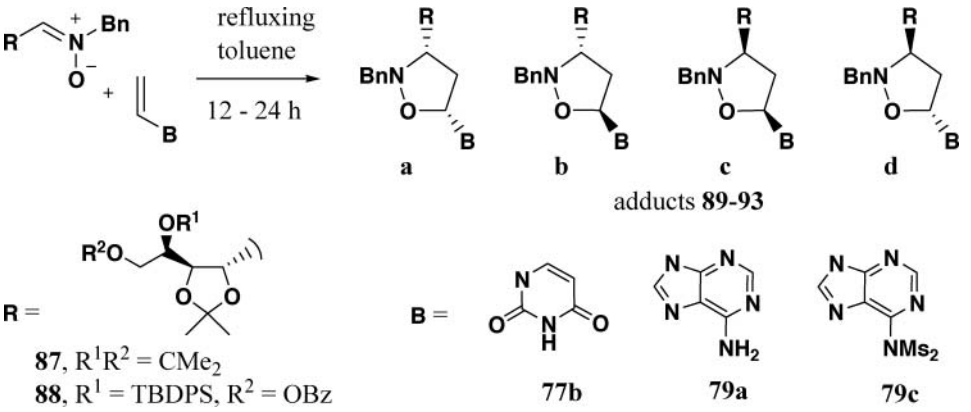
The same strategy applied to two differently protected nitrones **87** and **88** derived from D-xylose resulted in the formation of the four possible adducts with moderate facial (73:27 to 86:14) and *cis*:*trans* (59:41 to 82:18) selectivities (*Table 11*).[93] In the case of adenine nucleobases **79**, these selectivities depend not only on C-3′ and C-4′ protection of the nitrone, but also on *N*-9 protection of the dipolarophile. In the case of the uracil nucleobase **77b**, the two major adducts could arise from an *exo* approach for **89a** and an *endo* approach for **89b** on the less hindered *Si* face of the *Z*-nitrone (*Scheme 48*).

As an effort to avoid drastic thermal cycloaddition conditions, the use of a lanthanide Lewis acid catalyst $Er(OTf)_3$ in an ionic liquid medium (butylmethylimidazolium



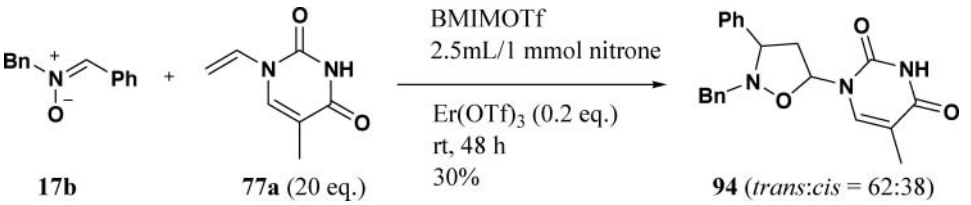
Scheme 48

Table 11
Cycloadditions of Nitrones from D-Xylose with Vinylnucleobases



Entry	Nitrone	Vinyl Base	Total Yield (%)	Adduct	a:b:c:d	*cis*:*trans* Ratio	Facial selectivity
1	**87**	**77b**	75	**89**	63:17:15:5	78:22	80:20
2	**87**	**79a**	86	**90**	39:34:20:7	59:41	73:27
3	**87**	**79c**	83	**91**	73:13:9:5	82:18	86:14
4	**88**	**77b**	77	**92**	59:24:11:6	70:30	83:17
5	**88**	**79a**	95	**93**	45:30:19:6	64:36	75:25

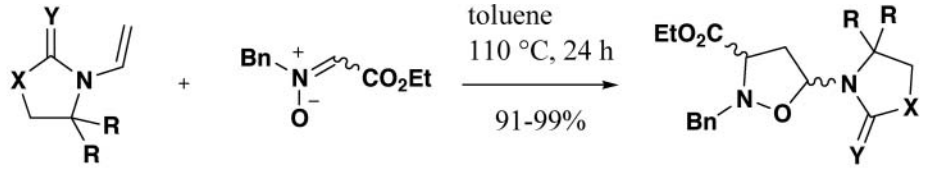
triflate BMIMOTf) proved efficient to promote the reaction, even at room temperature (*Scheme 49*).[94] However, some drawbacks of this method (large amounts of dipolarophile, ionic liquid and catalyst required, low conversion) limit its application.



Scheme 49

b) Simple N-Vinylamides and Hetero Derivatives

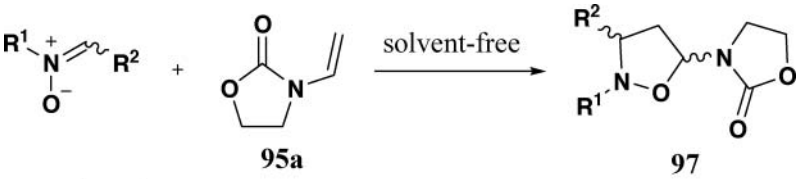
In 2006, the first use of *N*-vinyloxazolidin-2-ones as dipolarophiles in nitrone 1,3-dipolar cycloaddition was disclosed.[95] This type of dipolarophile, readily prepared from the corresponding oxazolidin-2-ones,[96] in one step *via* copper-catalyzed coupling or *via* condensation with aldehydes/ketones,[97,98] exhibits a moderate reactivity under classical conditions compared to alkyl vinyl ethers. Unsuccessful under Lewis-acid catalyzed conditions, the reaction of *N*-vinyloxazolidin-2-one **95a** and analogues with ester nitrone **1a** gave good



Scheme 50

isolated yields of two adducts **96** but with low-to-moderate *cis-trans* selectivity in refluxing toluene (*Scheme 50*).[95]

Under these thermal conditions, the *N*-vinyloxazolidinone **95a** exhibited also a good reactivity and a better *cis*-selectivity towards *N*,α-diphenylnitrone **17a** (*Scheme 51*). However, disappointing results were observed with *N*-benzyl-α-arylnitrones **17h**. In fact, due to low reactivity towards these thermally unstable nitrones, prolonged heating promoted decomposition of the starting materials and adducts **97**.

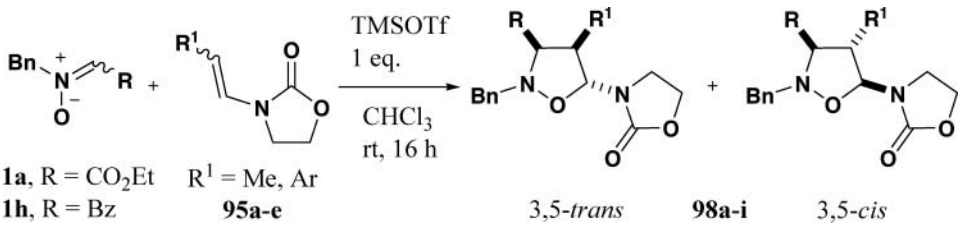


Scheme 51

The lack of reactivity of this type of dipolarophile was solved by using solvent free conditions.[97] Without solvent, the cycloaddition could be achieved in shorter reaction times and furnished the adducts in higher yield and nearly unchanged *cis*:*trans* ratio. The reactivity of *N*-vinyloxazolidin-2-one is significantly reduced by steric hindrance at the β-position of the double bond: β-methyl derivative reacted sluggishly and even under more drastic heating conditions, β,β-disubstituted- or β-aryl-*N*-vinyloxazolidin-2-ones failed to react with ester nitrone **1a**.

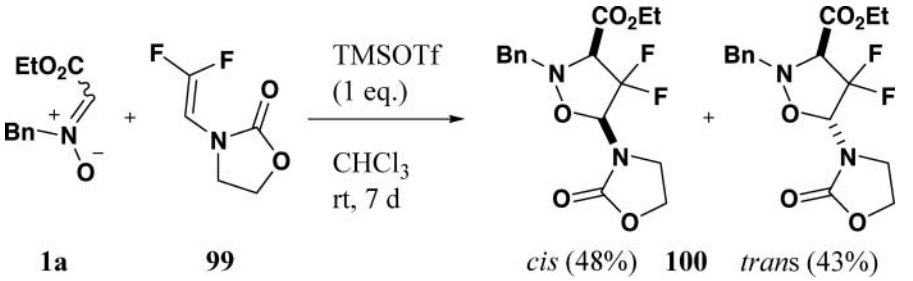
To overcome this drawback, the use of TMSOTf as activating reagent has been proposed.[98] After prior *O*-silylation of the nitrone, which would enhance the electropositivity of the α-carbon, the 1,3-DC reaction is assumed to follow a stepwise Mannich-type mechanism in which the nucleophilic attack of the β-substituted-*N*-vinyloxazolidin-2-one **95** on iminium intermediate would be less sensitive to steric hindrance than in a concerted process. Although the reaction could be carried out with a sub-stoichiometric amount of TMSOTf, using one equivalent of this reagent ensured good conversions and provided desired 4-substituted adducts **98** in high to excellent yields (*Table 12*). This modification could be also applied to thermally unstable α-benzoylnitrone **1h** with success.

Table 12
Cycloaddition Reactions Involving β-Substituted Vinyloxazolidinones



Nitrone	*Enamide*	*R^1*	*Adduct*	trans:cis *Ratio*	*Yield (%)*		
					trans	cis	*Total*
1a	***95b***	*Me*	***98a***	*1.4:1*	*53*	*37*	*90*
1a	**Z-*95c***	*Ph*	***98b***	*1:2.3*	*24*	*69*	*93*
1a	**E-*95c***	*Ph*	***98c***	*2.8:1*	*50*	*25*	*75*
1a	**Z-*95d***	*4-$O_2NC_6H_4$*	***98d***	*1:1.5*	*26*	*66*	*92*
1a	**E-*95d***	*4-$O_2NC_6H_4$*	***98e***	*2.4:1*	*57*	*38*	*95*
1a	**E-*95e***	*4-$MeOC_6H_4$*	***98f***	*1.8:1*	*54*	*35*	*89*
1h	***95a***	*H*	***98g***	*2.5:1*	*63*	*25*	*88*
1h	**E-*95c***	*Ph*	***98h***	*<1:4*	—	*80*	*80*
1h	**Z-*95c***	*Ph*	***98i***	*<1:4*	—	*76*	*76*

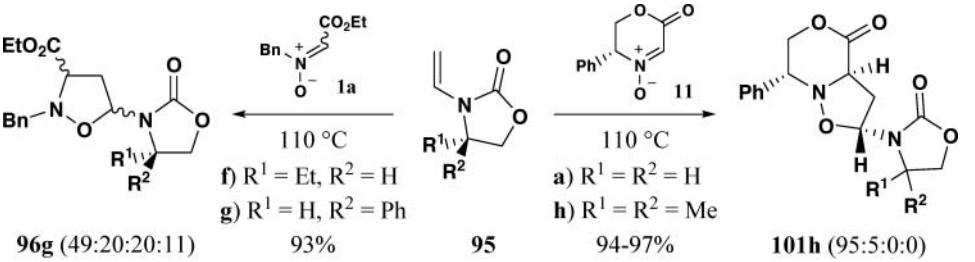
This study was extended to *N*-(β,β-difluorovinyl)oxazolidin-2-one **99**. Despite the low reactivity (reaction in seven days at rt in the presence of TMSOTf) and the low selectivity observed with this new dipolarophile, the cycloadduct **100** was obtained with an excellent global yield (*Scheme 52*).[99]



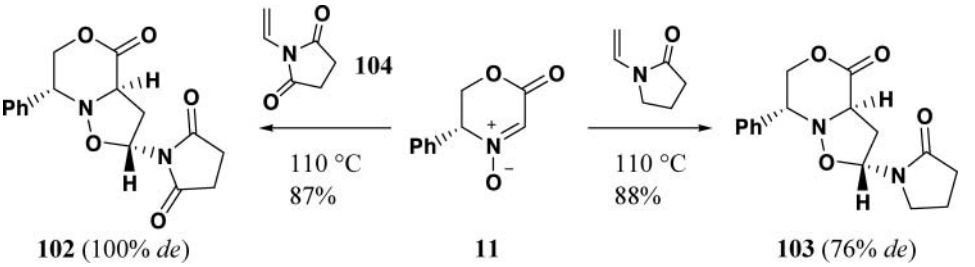
Scheme 52

An asymmetricversion involving *N*-vinyl 4-substituted oxazolidinones **95f,g** as chiral source in the cycloaddition with ester nitrone **1a** was also investigated by the same authors (*Scheme 53*). This reaction resulted in low *trans*:*cis* (~7:3) and facial selectivities (<7:3), possibly due to the variable configuration of the ester nitrone and the flexible conformation of the dipolarophile.[97,100] Similarly, 1,3-DC between β,β-difluorinated analog of **95g** with nitrone **1a** led to poor diastereoselectivity (four diastereomers in a 50/30/20/0 ratio).[99]

Based upon previous results of Tamura,[48] the use of a geometry-fixed nitrone such as **11** with a more rigid skeleton as dipole proved to be crucial for the stereochemical outcome of the reaction (*Scheme 53*).[97] The major adducts **101**–**103** obtained in high yields and selectivities arose from an *exo*-approach on the less hindered β-face of the nitrone, and the stereoselectivity was culminated with *N*-vinyl succinimide **104** used as dipolarophile (*Scheme 54*).



Scheme 53



Scheme 54

III. 5-Heterosubstituted Isoxazolidine Ring Opening Methods

The N—O bond scission of 5-heterosubstituted isoxazolidine can be roughly classified into three categories: reduction, oxidation, and disproportionation methods.

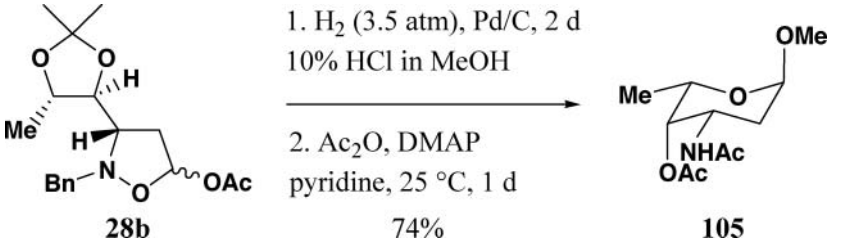
1. 5-Oxa-substituted Isoxazolidines

a) via Reduction

Reduction of the N—O bond of a 5-oxa-isoxazolidine adduct releases in principle a secondary amine function and a masked aldehyde function (hemiacetal) which could react further together in a hardly controllable way. With the exception of some cases in which one of these functions could be trapped by a reagent in the reaction medium or by other functions of the same molecule, this method was rarely applied to such adducts.

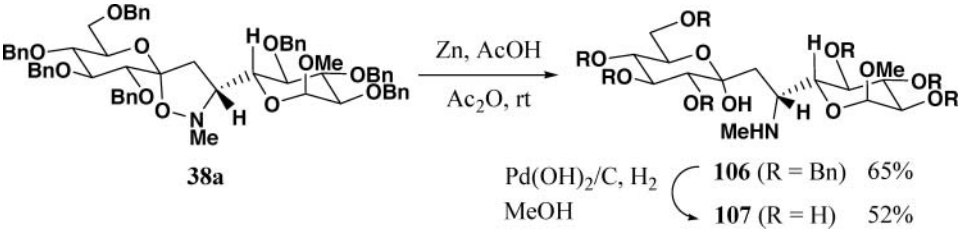
DeShong *et al.* disclosed a concise synthesis of amino sugars *via* dipolar cycloaddition (*Scheme 55*).[22] Adduct **28b** was cleaved by hydrogenolysis in acidic medium. The cyclic product was obtained as a result of the reaction between the hemiacetal function released

by N—O bond scission and the terminal alcohol function resulting from acetonide removal in methanol solution. Peracetylation of this cyclic product afforded amino sugar **105** as an isolable product in high yield.



Scheme 55

Ikegami *et al.* explored the reductive cleavage of the N—O bond of adduct **38a** under different conditions (*Scheme 56*).[69] By exposure to activated zinc powder in AcOH/Ac_2O, **38a** could be converted in the 1,3-aminoalcohol **106** in 65% yield. The reductive ring-opening could be accompanied with debenzylation by catalytic hydrogenolysis conditions. However, the stability of product **107** thus obtained was not mentioned.



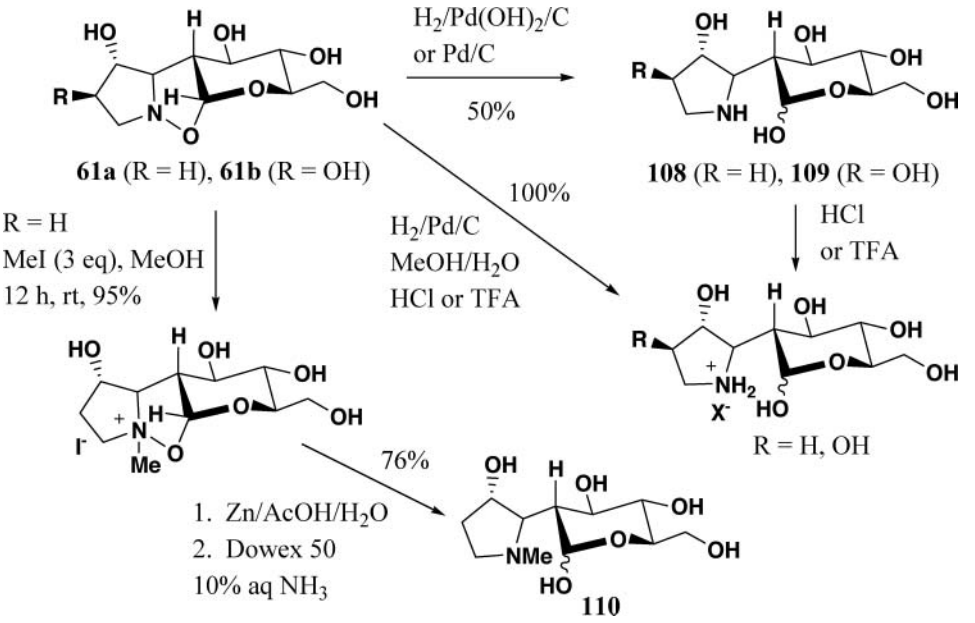
Scheme 56

Brandi *et al.* also reported the direct reductive ring-opening of **61a** and **61b** under palladium catalyzed hydrogenolysis conditions, which produced pseudo azasaccharides **108** and **109** in anomeric mixture and moderate yields (*Scheme 57*).[80,81] This limitation due to the low stability of **108** and **109** was solved by *N*-protonation or by *N*-alkylation before the N—O bond scission. The latter provides a more efficient protection as the *N*-methyl group could not react further with the hemiacetal and the product **110** could be obtained in high overall yield.

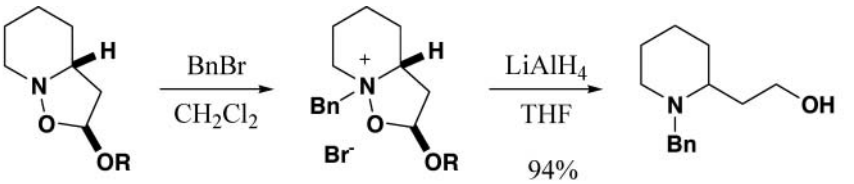
This sequence of alkylation-reduction was also successfully applied to the bicylic adduct **52** by Carruthers[82,101] (*Scheme 58*) by using BnBr as alkylating agent. In this case, the hemiacetal intermediate was *in situ* reduced by $LiAlH_4$ to yield alcohol **111** in excellent yield without debenzylation.

It has been shown by Gallos *et al*. that the reductive scission of N—O bond of **112** could lead to **113** in good yield by utilizing H_2/Ni Raney.[102] N—O bond cleavage was accompanied by methanol elimination to form transiently an aminoketoaldehyde, which spontaneously cyclized to yield *N*,*O*-acetal-*O*′,*O*′-hemiketal **113** (*Scheme 59*).

The same conditions applied to related tricylic adduct **114** afforded a mixture of ketone **115** and alcohol **116** as a result of two over-reductions: reductive amination of the

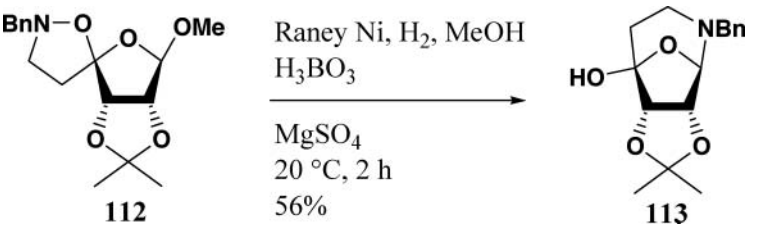


Scheme 57



d) R = *i*-Bu; **e)** R = (-)-menthyl; **f)** R = 8-phenylmenthyl; **g)** R = isopinocamphenyl
h) R = (*S*)-MeCHPh; **i)** R = (S)-*i*-Pr-CHPh; **j)** R = (*R*)-*t*-Bu-CHPh

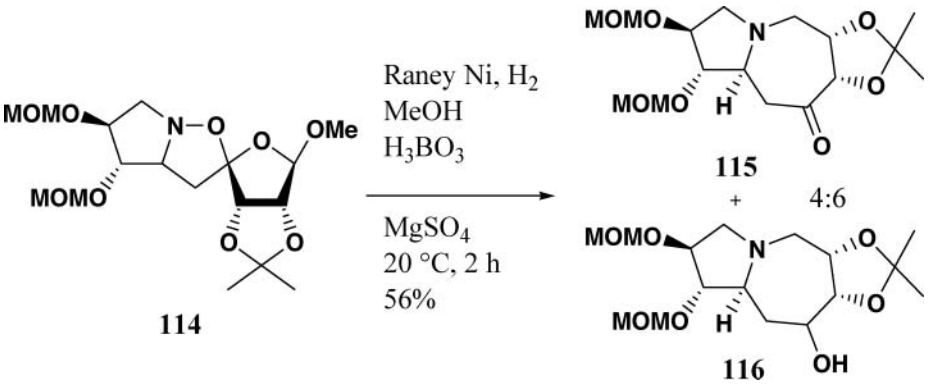
Scheme 58



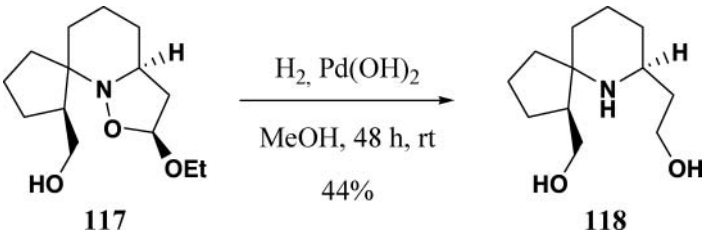
Scheme 59

aldehyde-derived carbon center and partial reduction of the ketone-derived carbon center (*Scheme 60*).

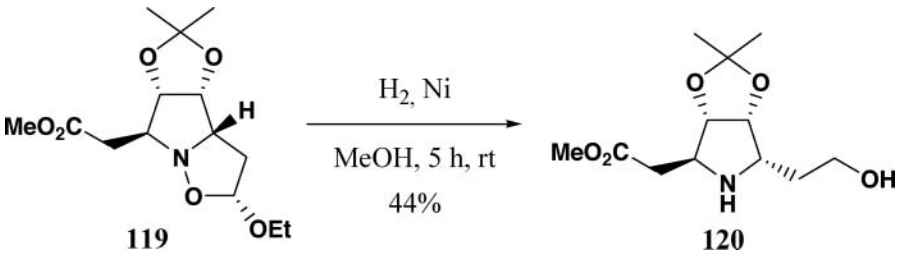
In situ over-reduction of aldehyde-derived carbon center into alcohol has also been used to avoid undesirable interaction between the amino function and the hemiacetal



Scheme 60



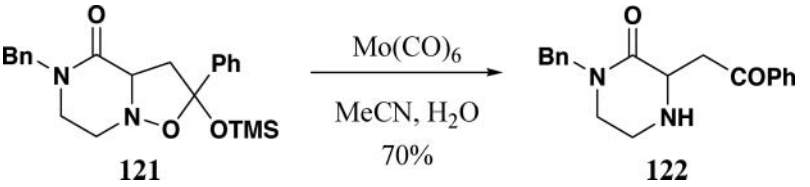
Scheme 61



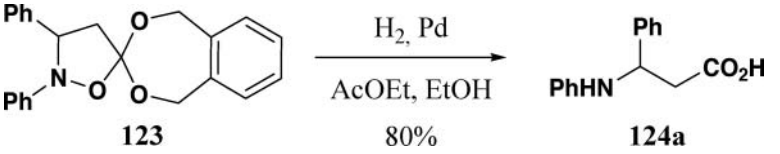
Scheme 62

function as described in the preparation of 1,3-aminoalcohols **118**[103] (*Scheme 61*) and **120**[104] (*Scheme 62*).

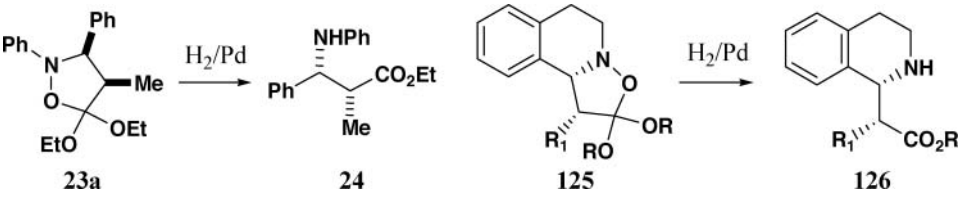
When the masked function of the isoxazolidine is a ketone (5-carba-5-oxa substituted) or an ester/acid (5,5-dioxa substituted), the N—O bond cleavage can readily occur, leading to a stable amino ketone or amino acid. Amino ketone **122**[105] and amino acid derivatives **24**, **124** and **126**[24,56] could thus be obtained in high yields as exemplified (*Scheme 63*, *Scheme 64* and *Scheme 65*). In the former case, the use of $Mo(CO)_6$ in wet acetonitrile is highly efficient as this reagent could selectively reduce the N—O bond under very mild conditions with respect to multifunctionality of molecules.



Scheme 63

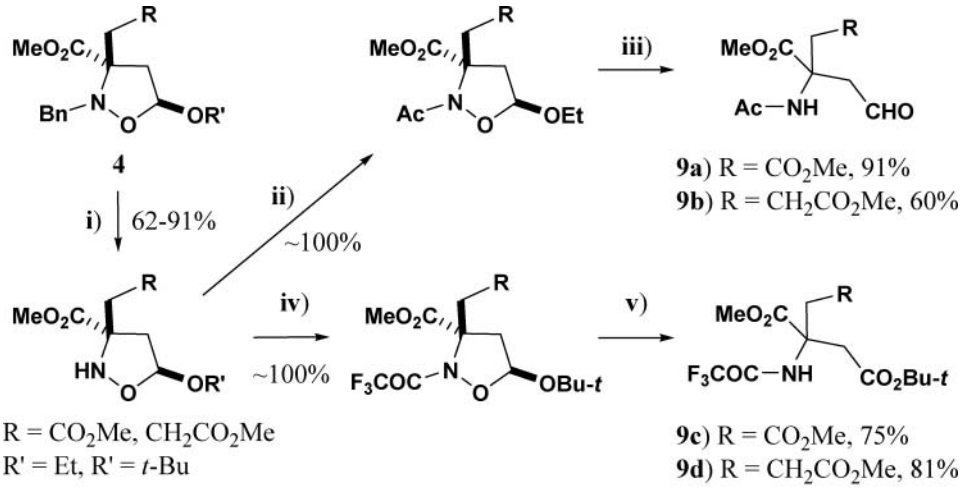


Scheme 64



Scheme 65

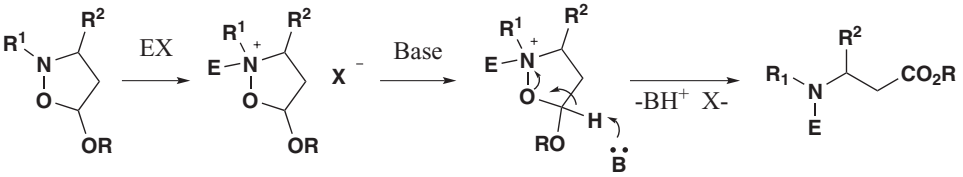
Selective reduction of N—O bond with $Mo(CO)_6$ was used to prepare new aldehydic α,α-disubstituted α-aminoacids *N*-acetyl derivatives **9a**,**b** while SmI_2 in THF was efficient to obtain *N*-trifluoroacetyl triester derivatives **9c**,**d** (*Scheme 66*).[45]



Scheme 66

b) via Disproportionation

Quarternization of 5-oxa-isoxazolidine adducts with strong alkylating agents (E^+) such as alkyl halides followed by the thermal treatment with an appropriate base were first reported by Murahashi *et al.* to give the corresponding β-amino acid esters efficiently.[101] The mechanism of this transformation was outlined in *Scheme 67*. The reaction of isoxazolidines with electrophiles gives ammonium salts **127**. Deprotonation at the C-5 position of **127** would lead to the ring-opening to give β-amino acid esters **124**.



127 **124**

Scheme 67

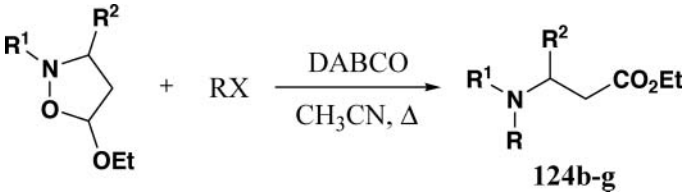
As a base, triethylamine and DABCO (*Table 13*) were shown to be highly efficient, in contrast to sodium ethoxide, potassium *t*-butoxide or sodium hydride which could not afford ring-opening products.

More recently, another version of this method was applied successfully on different substrates without using a base as demonstrated in the modification of Bayón,[52] Defoin,[77,79] Meske[59] (*Table 14* and *Table 15*), Fisera[83] (*Scheme 68*) and Jørgensen [62] (*Scheme 69*).

As an alternative for heat sensitive substrates, using alkyl triflates as alkylating agents could avoid prolonged heating and the quaternarization step could therefore be carried out at low temperature (*Scheme 70*).[107] Subsequent base-induced ring opening of triflate salts furnished the expected β-amino esters **133** in moderate yields.

Table 13

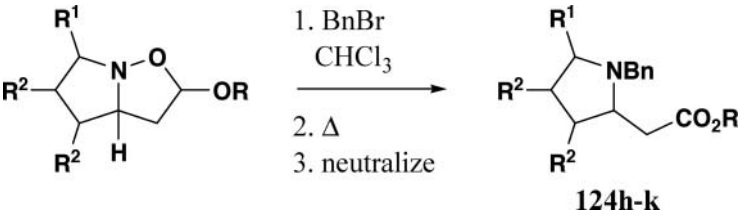
Disproportionation of Isoxazolidines by *N*-Alkylation in the presence of DABCO



124b-g

Adduct	R^1	R^2	RX	Aminoester	Yield (%)
18i	Et	Me	BnBr	**124b**	97
18c	Bn	Ph	MeI	**124c**	69
52a	$(CH_2)_3$		MeI	**124d**	61
52a	$(CH_2)_3$		CH_2=$CHCH_2Br$	**124e**	71
52c	$(CH_2)_4$		BnBr	**124f**	89
52c	$(CH_2)_4$		(*E*)-PhCH=$CHCH_2Br$	**124g**	73

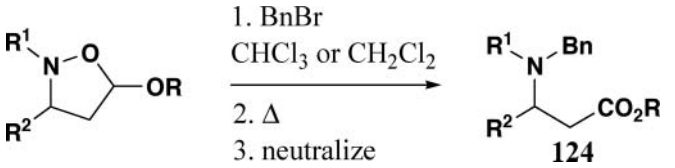
Table 14
Disproportionation of Bicyclic Isoxazolidines by *N*-Alkylation promoted by Benzyl Bromide



124h-k

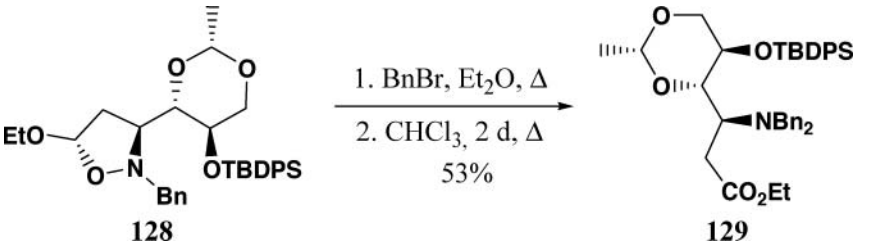
Adduct	R^1	R^2	R	Aminoester	Yield (%)	Ref
52a	H	H	Et	**124h**	57	52
52b	H	H	Ph	**124i**	78	77
56	H	OMOM	Ph	**124j**	quant.	77
58	Me	acetonide	Ph	**124k**	quant.	79

Table 15
Disproportionation of Monocyclic Isoxazolidines to the Corresponding Ester



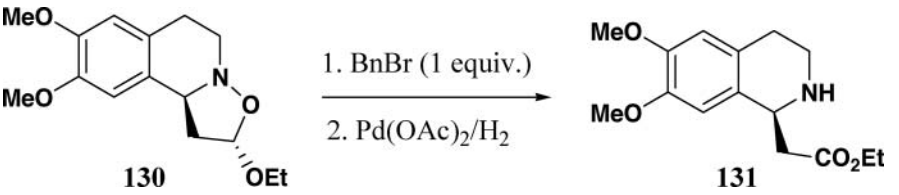
124

Adduct	R^1	R^2	R	Aminoester	Yield (%)	Ref
18j	*n*-Bu	*n*-Pr	Ph	**124l**	73	77
52k	$(CH_2)_4$		Ph	**124m**	65	77
18k	Me	Ph	Et	**124c**	91	59

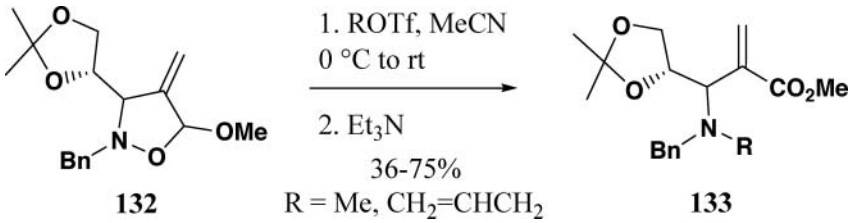


128 **129**

Scheme 68



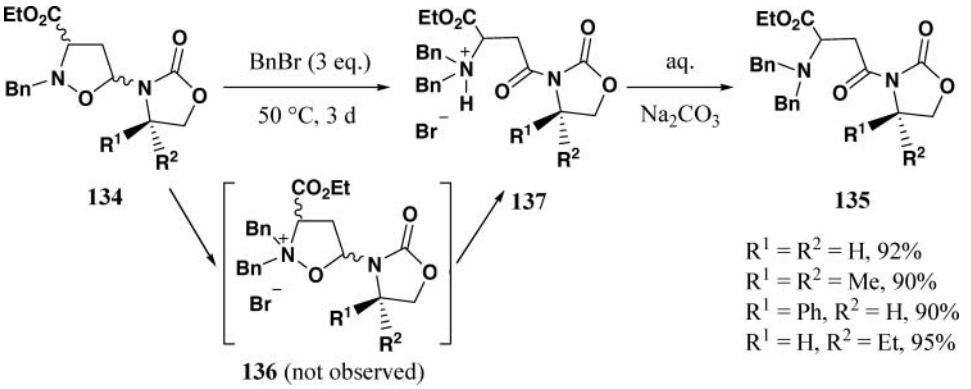
Scheme 69



Scheme 70

2. 5-Aza-substituted Isoxazolidines

Similar limitations encountered with 5-oxa isoxazolidines could be envisioned with 5-aza adducts. The only example to date of such a recently reported transformation, relies on disproportionation pathway (*Scheme 71*).[97] In the presence of benzyl bromide in excess without solvent, 5-oxazolidinyl adducts **134** were converted cleanly into the aspartimides **135** which are valuable precursors for carboxy-differentiated aspartates. The reaction proceeds *via* intermediate quaternary isoxazolidiniums **136** of low thermal stability, which transformed spontaneously into the ring-opened products **137**. Subsequent treatment with a slightly basic aqueous solution provided the desired products **135** in excellent yields.



Scheme 71

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