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Regio- and stereochemistry of 1,3-dipolar cycloaddition of nitrile oxides to alkenes

R P Litvinovskaya, V A Khripach

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Abstract. The published data on the chemistry of intermolecular 1,3-dipolar cycloaddition of nitrile oxides to different types of alkene derivatives are systematised. Various aspects of stereo- and regiochemistry of this reaction are considered. The bibliography includes 182 references.

I. Introduction

1,3-Dipolar cycloaddition of nitrile oxides to unsaturated systems is commonly used in the synthesis of heterocyclic compounds.[1–5] This is due to at least two reasons. First, nitrile oxides react with a great diversity of dipolarophiles by virtue of their high reactivities [1] and, second, the reaction products, *viz*., isoxazoles and 4,5-dihydroisoxazoles, can be used as starting compounds for various synthetic transformations including synthesis of natural compounds and their analogues.[2,3]

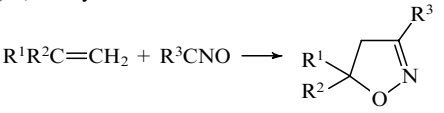
This review summarises the published data on 1,3-dipolar cycloaddition of nitrile oxides to alkenes. Problems of regio- and stereochemistry of intermolecular cycloaddition (as a rule, to non-cyclic dipolarophiles) are considered in more detail.

Nitrile oxides are usually generated by treating hydroximoyl chlorides with triethylamine, by dehydrating primary nitro derivatives with isocyanates or by oxidising aldoximes with *N*-chlorosuccinimide.[6–8] New effective approaches to the generation of nitrile oxides have been developed in recent years, *e.g*., from aldoximes under the action of sodium hypochlorite,[9] from hydroximoyl chlorides in the presence of silver(I) acetate [10] or from conjugated nitroalkenes under the action of titanium(IV) chloride.[11] The latter approach allows preparation of α-functionalised nitrile oxides.

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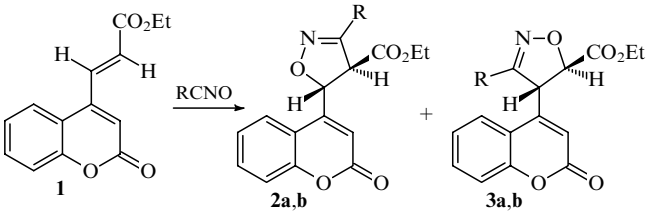
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Usually, it is only regiochemistry that is the matter of discussion in the cycloaddition of nitrile oxides to terminal alkenes, *viz*., the formation of a single regioisomer, *i.e*., 3,5-disubstituted ($R^1 = H$) or 3,5,5-trisubstituted (R^1 = Alk, Ar, *etc*.) 4,5-dihydroisoxazole.[12–17]



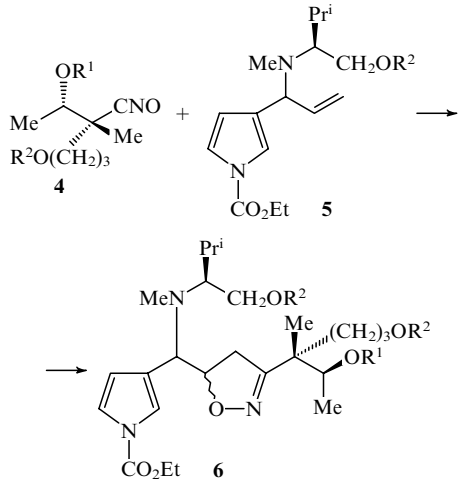
The analysis of stereochemical aspects of these reactions points to their low stereoselectivities [18,19] unless carried out under special conditions (see below).

Non-symmetrical 1,2-disubstituted alkenes usually give two regioisomers.[20–24] However, reactions of certain compounds manifest high regioselectivities with nitrile oxides. Thus the addition of acetonitrile oxide to the coumarin derivative **1** gave the regioisomeric dihydroisoxazoles **2a** and **3a** in a 75 : 3 ratio, whereas 4-methoxybenzonitrile oxide afforded exclusively the regioisomer **3b**.[25]



R = Me (**a**), 4-$MeOC_6H_4$ (**b**).

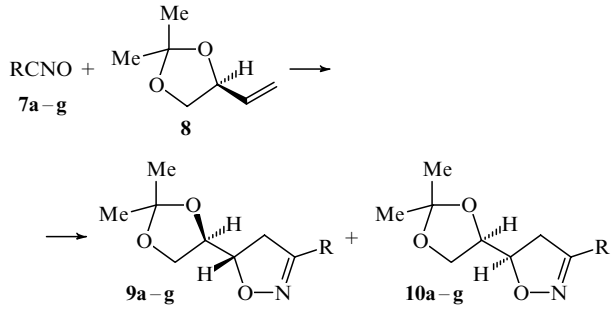
Attempts at performing asymmetric 1,3-dipolar cycloaddition using chiral alkenes or nitrile oxides have been undertaken, however, stereoselective introduction of a new asymmetric centre using chiral nitrile oxides was only partly successful.[26–29] Thus the reaction of the optically active nitrile oxide **4** with the alkene **5** afforded a mixture of diastereomers **6** in a 2.5 : 1 ratio.[30] Reactions with other nitrile oxides yield nearly equimolar mixtures of diastereomers.



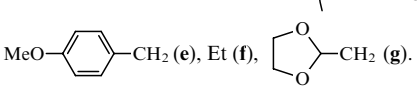
$R^1 = CH_2OMe$; $R^2 = Bu^tMe_2Si$.

II. Cycloaddition of nitrile oxides to allylic and homoallylic alcohols and their derivatives

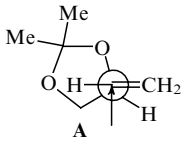
Allylic alcohols and their esters with a chiral centre in the α-position are often used as dipolarophiles; however, the diastereoselectivity of these reactions is not always high. As a rule, reactions of nitrile oxides with allylic alcohols give predominantly *syn*-isomers.[31,32] Cycloaddition of alkenes containing protected hydroxy groups in the α-position to the double bond increases the stereoselectivity.[33–36] The reaction of the nitrile oxide **7a** with (*S*)-(+)-*O*-isopropylidenebut-3-ene-1,2-diol (**8**) is among the first examples of regioselective cycloaddition of nitrile oxides to allylic alcohols; this resulted in the *anti*-adduct **9a** (**9a** : **10a** = 4 : 1) as the main product.[35] In this case, the stereochemistry of the cycloaddition reaction is governed by the oxygen-containing substituent in the allylic position.



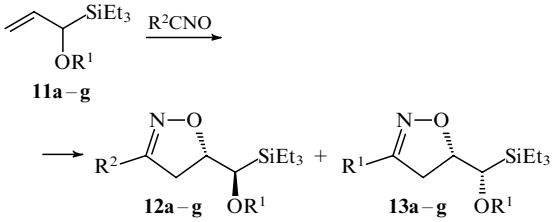
R = EtO_2C (**a**), Me (**b**), $THPOCH_2$ (**c**) (THP = ), Ph (**d**),



Nitrile oxides **7b–g** also react with compound **8** with high diastereoselectivities with the predominant formation of *anti*-addition products (80%–94%); the selectivity of this reaction is only weakly dependent on the structure of the nitrile oxide.[34] But-3-ene-1,2-diol containing unprotected hydroxy groups manifests low diastereoselectivity in reactions with nitrile oxides, this is somewhat higher with dioxolanes analogous to compound **8**.[33] The highest diastereoselectivity is achieved with spiroketals of vicinal diols.[36] It is assumed[34] that the cycloaddition proceeds predominantly *via* the transition state corresponding to the conformer **A** (the Kozikovsky model). Nitrile oxide attacks the C=C bond on the side opposite to the C–O bond (indicated by an arrow). Thus, the allylic oxygen atom displays an *anti*-directing (the so-called antiperiplanar) effect. According to the calculations made by Houk *et al.*,[37] this is due to minimisation of secondary interactions of the non-bonding orbitals.



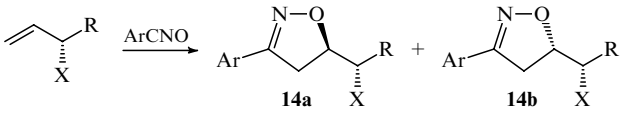
The cycloadditions of pivalo- and benzonitrile oxides to α-hydroxyallylsilane (**11a**) and its *O*-derivatives **11b–g** have been studied.[31,38] Compound **11a** yields a mixture of *syn*- and *anti*-adducts with a small excess of the *syn*-isomer **13a**; with different acylated derivatives, the stereoselectivity of this reaction is weakly affected, whereas silyl ether **11b** gives predominantly the *anti*-addition products **12b** (yield 94%).



R^1 = H (**a**), $SiMe_2Bu^t$ (**b**), COMe (**c**), CO_2Me (**d**), 4-$MeOC_6H_4CO$ (**e**), COPh (**f**), 4-$NO_2C_6H_4CO$ (**g**); R^2 = Bu^t, Ph.

It was shown[31] that the *syn*-selectivity of cycloaddition of nitrile oxides, which is characteristic of the majority of allylic alcohols studied so far, decreases with the increase in the proton-accepting capacity of the solvent used.

The stereochemistry of cycloaddition of benzonitrile oxides to allylic alcohols and their ethers, allylic chlorides and 3,3-diphenylprop-1-ene has been studied in detail.[39,40]



R = Me, Ph, Et, Bu^t; X = OH, OMe, OBn, OTHP, $OSiMe_2Bu^t$, Cl, Ph, Me; Ar = Ph, 4-$NO_2C_6H_4$.

In this case, too, allylic ethers react with nitrile oxides in a stereoselective manner to give the *anti*-addition products **14a** (up to 95% for X = OMe, $OSiMe_2Bu^t$); the selectivity of this reaction increases with the increase in the size of the substituent R. Alcohols yield predominantly the *syn*-addition products **14b**, albeit with low selectivity. The replacement of the ether allylic substituent by Cl, Ph or Me results in a complete or partial loss of stereoselectivity. It is of note that the ratio of the diastereomers strongly depends on the nature of the substituent in the nitrile oxide. Such a behaviour of allylic halides has been described by other authors.[41,42]

Based on the experimental data[37,43,44] and the calculations of transition state models of 1,3-dipolar cycloaddition of nitrile oxides to alkenes, it was suggested that the majority of transition states are structurally close to that shown in Fig. 1*a*. In this case, the substituents in the allyl position can be localised outside, inside or in the *anti*-position with respect to the C–O bond formed.

The main product is formed from the transition state **A** where the largest substituent (L) is in the *anti*-position, whereas the medium substituent (M) is located inside (Fig. 1*b*). The transition state **B** (Fig. 1*c*) yields the minor isomer. The outside position is more sensitive to steric factors due to the interaction of nitrile oxide with the oxygen atom. The electronic characteristics of substituents play a prominent role. Since cycloaddition of nitrile oxides is related to weakly electrophilic reactions, the donor substituent in the allylic position of the transition state is preferably in the *anti*-position, while the acceptor substituents are

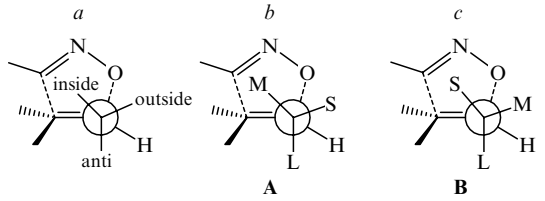


Figure 1. The transition state models in the reaction of 1,3-dipolar addition of nitrile oxides to alkenes.[43,44]
Designations for substituents: L is large, M is medium, S is small.

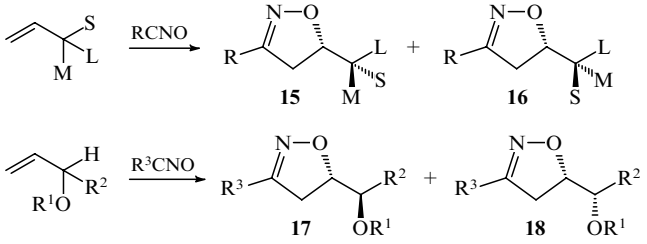
localised either inside or outside (in order to minimise electronic interactions).[39]

This transition state model commonly referred to as the Houk model provides a rationale for the effects of substituents on the stereochemistry of 1,3-dipolar cycloaddition.

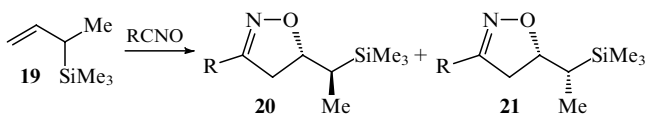
The formation of a hydrogen bond between the oxygen atom of the nitrile oxide and the hydroxy groups of cyclic allylic alcohols results in stabilisation of the *threo*-transition state **A** (Fig. 1*b*). The relatively low stereoselectivities in the case of acyclic allylic alcohols can be assigned to the fact that conformations **A** and **B** compete with one another in the transition state.[43,44]

It is of note that the increase in stereoselectivity with the increase in the size of the substituent R in the allylic alcohol fits well the Houk model, but cannot be explained in terms of the Kozikovsky transition state model.[34]

Thus the cycloaddition of nitrile oxides to terminal alkenes with different sizes of substituents in the allylic positions gives predominantly the diastereomers **15**. The stereoselectivity depends on the relative sizes of the medium (M) and large (L) groups and varies from very low (M = Me, L = Et, **15**:**16** = 1:1) to moderate (M = Me, L = Bu^t, **15**:**16** = 4:1). The same tendency is observed where M = AlkO group, although the stereoselectivity is somewhat higher in this case. The *anti*-diastereomer **17** usually predominates over the *syn*-diastereomer **18** (~3:1). For R^2 = Bu^i, it is the *anti*-isomer that is predominantly formed. The ratios of *syn*- to *anti*-products in these reactions change little with the change in steric and electronic factors in both the nitrile oxide substituent R^3 and the oxygen atom substituent R^1.[39]



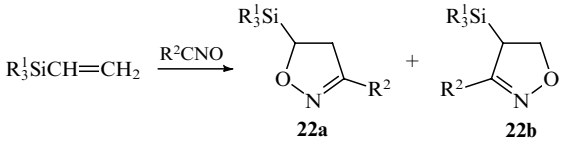
Assuming that the steric and electronic effects of the trimethylsilyl group[43] in the allylic position favour the formation of *anti*-cycloadducts, the behaviour of silanes of the type **19** has been studied in the reaction with nitrile oxides.[45]



R = Ph, Bu^t.

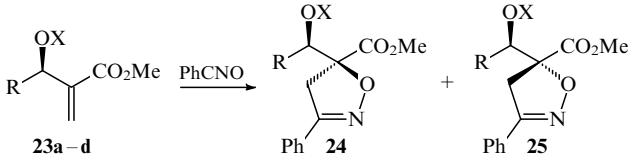
However, the diastereoselectivity of this reaction was low, although the main product **20** (60% – 65%) was formed in accord with the Houk model. Thus, high diastereoselectivity is difficult to achieve in the absence of an oxygen-containing substituent in the allylic position,.

Recent studies have shown[46] that the ratio of 5- and 4-silyl-substituted adducts **22a** and **22b** obtained by cycloaddition of nitrile oxides to trialkoxy(vinyl)silanes depends on the nature of substituents at the silicon atom and the method used to generate nitrile oxides. This reaction is especially selective for R^1 = Me$_3$SiO and R^2 = Me (**22a**:**22b** = 10:1).



R^1 = MeO, EtO, Me$_3$SiO, $\overline{\text{NCH}_2\text{CH}_2\text{O}}$; R^2 = Me, Et, Ph.

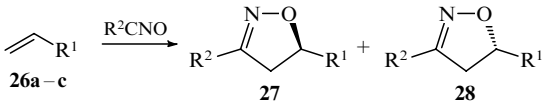
It was shown[47] that cycloaddition of nitrile oxides to 1,1-disubstituted alkenes **23** containing a hydroxy- or an alkoxy group in the allylic position (the so-called Baylis – Hillman adducts) gives predominantly the *syn*-isomers **24**, the stereoselectivity of the reaction being dependent on the substituent R.

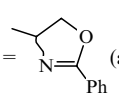
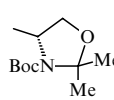
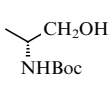


Compound **23**	R	X	Ratio **24**:**25**	Compound **23**	R	X	Ratio **24**:**25**
a	Me	H	3:1	**c**	Pr^i	H	32:1
		Bu^{t}Me$_2$Si	6:1			Bu^{t}Me$_2$Si	7:1
		Ac	1:1			Ac	9:1
b	Pr^n	H	12:1	**d**	Ph	H	2:1
		Bu^{t}Me$_2$Si	7:1			Bu^{t}Me$_2$Si	4:1
		Ac	3:1			Ac	1:1

III. Cycloaddition of nitrile oxides to unsaturated amines, amides and related compounds

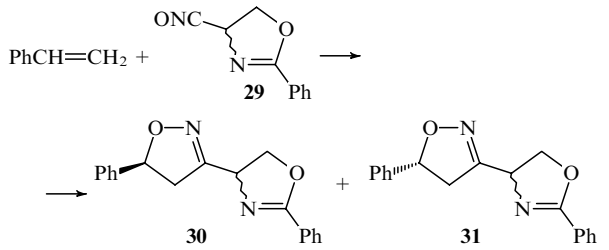
The directing effect of the nitrogen atom in the allylic position has been studied in less detail than that of the oxygen atom. Cycloadditions of nitrile oxides to vinylglycine and 2-aminobut-3-en-1-ol have been described;[48–50] the selectivities of these reactions were low. Reactions of nitrile oxides with (*R*,*S*)-4-vinyl-2-phenyl-4,5-dihydrooxazole (**26a**), *N*-benzyloxycarbonyl-(4*R*)-vinyl-2,2-dimethyloxazolidine (**26b**) and (2*R*)-(*N*-benzyloxycarbonyl)but-3-enol (**26c**) have been studied.[51] It was found that the selectivities of the reactions of the cyclic compounds **26a**,**b** are higher than that of the acyclic analogue **26c**; the *erythro*-isomers of the 4,5-dihydroisoxazoles **27** are the main products. The reaction of alkene **26a** with EtO$_2$CCNO oxide occurs with the highest selectivity (the **27**:**28** ratio is 82:18).



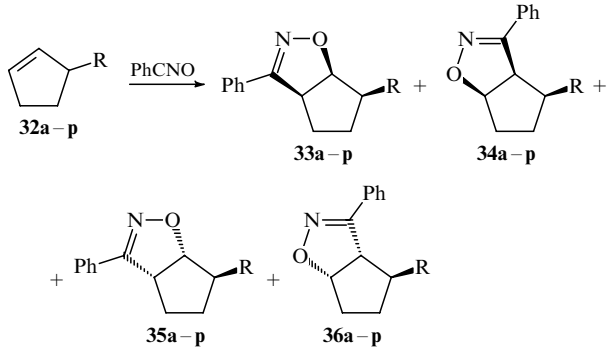
R^1 =  (**a**),  (**b**),  (**c**);

R^2 = Ph, EtO$_2$C, Br.

The effect of introduction of an asymmetric centre into the nitrile oxide component has been studied.[52] Cycloaddition of, *e.g.*, 4,5-dihydrooxazole-4-carbonitrile oxide **29**, to styrene yields a 1:1 mixture of 5-phenyl-4,5-dihydroisoxazoles **30** and **31**. This phenomenon is attributed to the large distance between the asymmetric centre of the molecule and the newly formed centre.

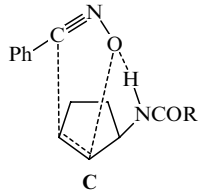


A series of 3-substituted cyclopentenes **32a–p** including amides **32f–p** have been studied as dipolarophiles;[53] variation of the amide acyl group made it possible to change the acidity of the proton in the amide substituent



R = Me (**a**), NMe_2 (**b**), OMe (**c**), OAc (**d**), OH (**e**), NHCOPh (**f**), NMeCOPh (**g**), NHCOMe (**h**), $NHCOCF_3$ (**i**), $NHCOC_4F_9$ (**j**), NHCSMe (**k**), $NHCOC_6H_4OMe$-4 (**l**), $NHCOC_6H_4CF_3$-3 (**m**), $NHCOC_6H_4NO_2$-4 (**n**), $NHSO_2Me$ (**o**), $NHSO_2CF_3$ (**p**).

The content of cycloadducts formed as a result of the nitrile oxide attack on the alkene on the *anti*-side with respect to the substituent *R* exceeded 92% for compounds containing a methyl (**32a**), a dimethylamino (**32b**), a methoxy (**32c**) or an acetoxy (**32d**) group in the allylic position. The reaction of compound **32e** containing an allylic hydroxy group in diethyl ether afforded the adduct **33e** in 30% yield. This adduct was formed due to the formation of a hydrogen bond in the transition state of the reaction. If the reaction is carried out in benzene, which binds a proton more weakly than ether, the yield of the product **33e** increases to 50%. It is assumed that the hydroxy derivative **32e** forms a hydrogen bond with the solvent in ether and with nitrile oxide in benzene. The cycloaddition of the allylic benzamide **32f** yielded the adducts **33f** and **36f** (9 : 1), which can also be ascribed to the formation of a hydrogen bond in the transition state **C** of the cycloaddition.



C

The model proposed sheds more light on the effects of solvents and amide substituents on the reaction rate. The product **33f** is predominantly formed in accordance with the model **C**, since the energy of its transition state decreases due to the formation of a hydrogen bond, while the energies of the transition states leading to the other three products are not changed. Therefore, the alkene **32f** should be more reactive than compounds unable to form hydrogen bonds with the nitrile oxide. Indeed, experiments on competitive reactions of compounds **32f**,**g** with pivalonitrile oxide yielded three products all of which were formed by cycloaddition of nitrile oxide to the alkene **32f** and the yield of the adduct of the type **33** reached 85%.

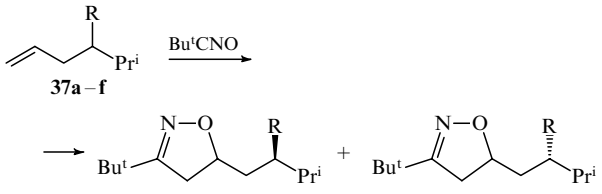
Competitive cycloadditions in benzene, 1,2-dimethoxyethane, dimethylformamide and hexamethylphosphoramide (HMPA) have been studied in order to establish the role of the solvent in this reaction.[54] It was found that the tertiary amide **32g** is much less reactive than the amide **32f**. In the case of the amide **32g**, the nature of the solvent influences neither the degree of conversion of the starting compounds, nor the ratios of the reaction products. Contrariwise, in the case of the amide **32f** the concentration of the reaction product **33f** increases significantly with the increase in the proton-donor capacity of the solvent; while the degree of conversion of the starting compounds changes only slightly. When the reaction was carried out in HMPA, the distribution of the reaction products was similar for both amides, which can be explained within the framework of the model **C**. Substitution of nitrile oxide for the solvent as a hydrogen-bonding acceptor decreases the rate of formation of the adduct **33f**, but the rates of formation of other reaction products change little, as a result of which the total degree of conversion decreases.

The model **C** suggests also that the yields of cycloadducts of the type **33** depend on the ability of the amide to form a hydrogen bond. Thus studies of amides **32h–p** revealed a marked tendency of an increase in the reaction selectivity with increase in the acidity of the amide proton. It is of interest that the sulfonamide group for which the acidity of the proton is the highest in this series, does not manifest high selectivity. In all probability, the bulky sulfonyl group prevents the formation of the transition state **C**. The effects of other factors should not be ruled out either.

These data show that the introduction of a disubstituted amide substituent into the allyl position of alkenes can change both the regio- and stereoselectivity of cycloaddition of nitrile oxides. The formation of hydrogen bonds in the transition state also plays a significant role in this effect.

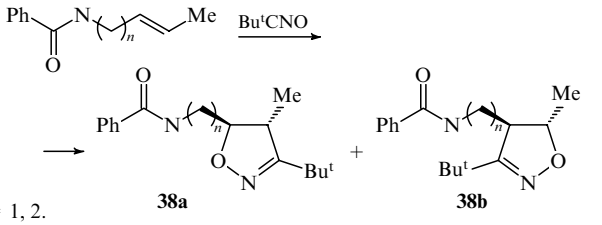
It is of note that the selectivities of cycloaddition reactions with acyclic allylic amides studied earlier [55–58] are low. However, it was shown [59] that amide substituents influence the selectivity of cycloaddition stronger than the allylic hydroxy groups, this effect being especially well-pronounced in the case of cyclic amides.

The stereoselectivity of cycloaddition of the homoallylic amides **37a–d** to nitrile oxides is low in all cases, being comparable to that of the homoallylic alcohol **37e** and amine **37f**.



R = NHCOMe (**a**), $NHCOCF_3$ (**b**), $NHSO_2Me$ (**c**), $NHSO_2CF_3$ (**d**), OH (**e**), NH_2 (**f**).

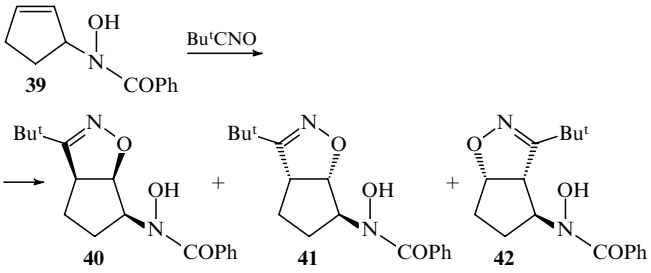
The regioselectivity of cycloaddition of pivalonitrile oxide to allylic and homoallylic acyclic amides containing a disubstituted double bond is also low, *e.g.*, the regioisomers **38a** and **38b** are formed in a ~2 : 1 ratio.[59]



n = 1, 2.

At 20 °C, the cycloaddition occurs slowly; after 5 days, 70% of the original alkene remains unconsumed. At 80 °C, the yield is higher, but the regioselectivity is still very low. It was concluded [59] that the formation of a hydrogen bond in the transition state of acyclic systems is not critical, otherwise the amount of the regioisomer **38a** would have been much higher.

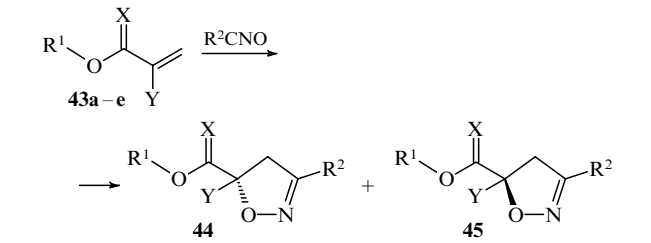
The hydroxy group plays the role of a proton donor when hydroxamic acid **39** is used as a dipolarophile. This reaction gave three isomers (**40** : **41** : **42** = 11 : 2 : 4). This suggests that the hydroxy group of hydroxamic acid is a better directing group than the hydroxy groups of alcohols and produces an effect comparable to that of the NH groups.[59]

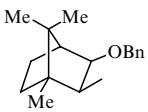
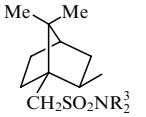


IV. Cycloaddition of nitrile oxides to acrylates, crotonates and acrylamides

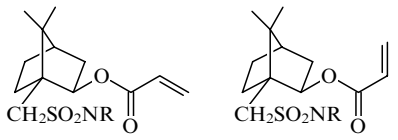
An efficient approach to optically active dihydroisoxazoles might become both an alternative to the well-known aldol-type reactions and a new method for the synthesis of enantiomerically pure primary amines. Two approaches to asymmetric induction in the cycloaddition of nitrile oxides were used, *viz*., the introduction of an allylic asymmetric centre into a dipolarophile [34, 35] or the use of a chiral nitrile oxide.[27] The attempts at developing efficient procedures for diastereoselective 1,3-dipolar cycloaddition of nitrile oxides using menthyl ethers of allylic alcohols [60] were unsuccessful.

Thus 1,3-dipolar cycloaddition of 4-nitrobenzonitrile oxide with optically active acrylate **43a** and allylic ether **43b** yielded a mixture of the diastereomers **44** and **45**, the diastereomeric excess in favour of the latter was only 4%. The selectivity of the reaction of 4-nitrobenzonitrile oxide with the bornyl ester **43c** was somewhat higher. Pronounced stereoselectivity was observed only in the reaction of the sulfonamide derivatives **43d**,**e** with isobutyronitrile oxide and cyclohexanonitrile oxide. The diastereomers **44** having *S*-configurations of the newly formed chiral centres were the main isomers in these reactions.[61]



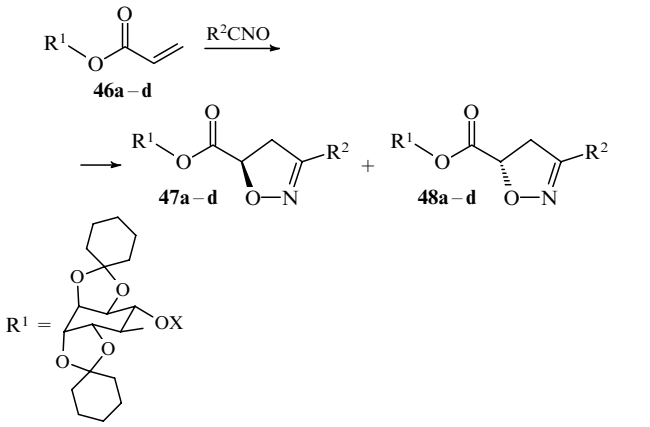
R^1	X	Y	Compound **43**	R^2	Ratio **44** : **45**
	O	H	**a**	4-$NO_2C_6H_4$	1 : 1
	CH_2	H	**b**	4-$NO_2C_6H_4$	1 : 1
	O	H	**c**	4-$NO_2C_6H_4$	1 : 1
	O	H	**d**	Bu^t	1 : 3
	O	H	**d**	Ph	1 : 4
	O	Me	**e**	4-$NO_2C_6H_4$	1 : 2
	O	Me	**e**	Bu^t	1 : 1
R^3 = Pr^i, C_6H_{11}	O	Me	**e**	Ph	1 : 1

It is assumed [61] that the major diastereomers **44** result from the cycloaddition of the nitrile oxide to *s-cis*-confomers **A** of acrylates **43d**,**e**, whereas minor diastereomers are formed by addition to the *s-trans*-conformers **B**.



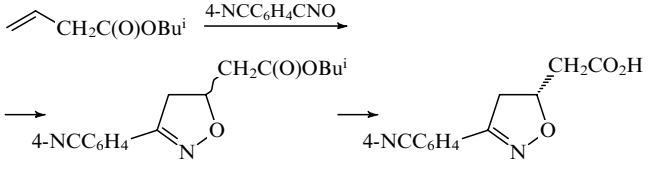
Later it was demonstrated [5] that the acrylates **43d**,**e** containing sulfonamide groups enter into other cycloaddition reactions predominantly in the *s-cis*-conformations.

Optically active 4,5-dihydroisoxazoles were synthesised by Akiyama *et al*.[62, 63] who added nitrile oxides to chiral acrylates where cyclitols played the role of auxiliary chiral substituents. The acrylates **46a**–**d** gave mixtures of dihydroisoxazoles **47** and **48** in the reactions with benzonitrile oxide (R^2 = Ph). The diastereoselectivities in the case of esters containing methoxymethyl (**46a**) and benzyl (**46b**) substituents were low, whereas the presence of bulky *tert*-butyldimethyl- and *tert*-butyldiphenylsilyl substituents in esters **46c**,**d** provided high π-facial selectivity. This stereochemical result is due to the fact that the major isomer **47** is formed from the *s-cis*-conformer of the acrylate. The bulky *tert*-butyldiphenylsilyl group effectively blocks the attack from the opposite side of the double bond. The maximum diastereoselectivity was achieved when the reaction was carried out in benzene.

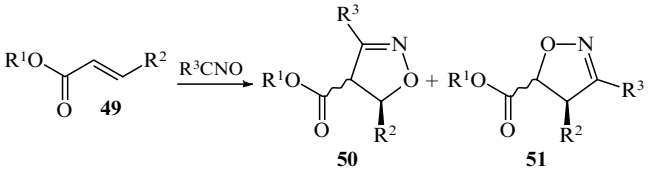


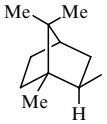
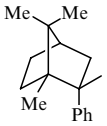
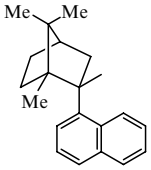
Compound **46**	X	R^2	Ratio **47** : **48**	Compound **46**	X	R^2	Ratio **47** : **48**
a	CH_2OMe	Ph	1 : 2	**d**	Bu^tPh_2Si	Me	10 : 1
b	Bn	Ph	1 : 1	**d**	Bu^tPh_2Si	Et	9 : 1
c	Bu^tMe_2Si	Ph	5 : 1	**d**	Bu^tPh_2Si	$n\text{-}C_5H_{11}$	9 : 1
d	Bu^tPh_2Si	Ph	19 : 1	**d**	Bu^tPh_2Si	Bu^t	10 : 1
				d	Bu^tPh_2Si	4-ClC_6H_4	9 : 1

The cycloaddition of 4-cyanobenzonitrile oxide to isobutyl vinylacetate affords a racemic mixture of dihydroisoxazoles.[64] It was found that the hydrolysis of this mixture using the lipase PS30 gave optically pure [4,5-dihydro-3-(4-cyanophenyl)isoxazol-5-yl]acetic acid with the *R*-configuration of the chiral centre.



The addition of nitrile oxides to bornyl crotonates **49** (R^2 = Me) gave two regioisomeric cycloadducts **50** and **51**, each representing a mixture of diastereomers.[65]

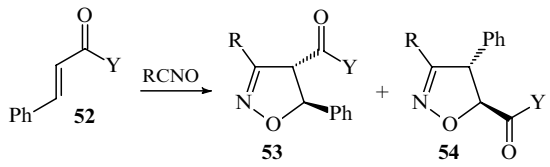


R^1	R^2	R^3	Yield of adducts (%)	
			50	**51**
	Me	Ph	65	22
	Me	Me	75	25
	Me	Ph	56	26
	Me	Me	46	25
	H	Me	–	79
	Me	Ph	63	28
	Me	Me	76	24
	H	Me	–	94

The diastereoselectivity of this reaction is > 80%. The diastereomers were separated and enantiomerically pure 4,5-dihydroisoxazoles were obtained after the cleavage of the ester bond. The regioselectivity of this reaction does not depend on either the substituent in the bornyl residue or the nature of nitrile oxide.

The addition of nitrile oxides to acrylates **49** (R^2 = H) results in an almost overriding formation of the sterically preferrable products **51**. The diastereoselectivity of this reaction is comparable to that of crotonates, which points to the similarity of the transition states generated by the attack of the dipole at the least shielded side of the alkene having an *s-cis*-conformation.[66]

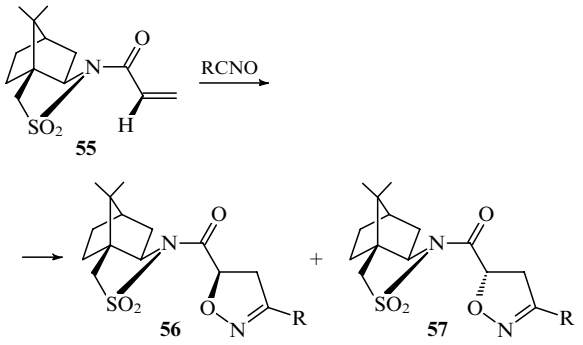
The reaction of methyl cinnamate **52a** with nitrile oxides affords a mixture of regioisomeric dihydroisoxazoles **53a** and **54a** (4 : 1).[67] Quite unexpectedly, the use of other cinnamic acid derivatives, *e.g.*, the tertiary amides **52b–f**, changed the regioselectivity of this reaction, whereas in the case of primary and secondary amines the regioselectivity was the same as with esters. It is also surprising that the substituent at the nitrogen atom virtually did not affect the regiochemistry of the reaction. Hence, its regioselectivity can be varied using different cinnamic acid derivatives and different nitrile oxides.

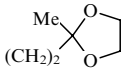


Compound **52**	Y	Ratio **53** : **54**
a	OMe	4 : 1
b	NEt_2	1 : 3
c	$N(Me)CH_2CO_2Me$	1 : 2
d	$N(Ph)CH_2CO_2Me$	1 : 2
e	L-proline methyl ester	see [a]
f	$N(CH_2CO_2Et)_2$	1 : 3

[a] Compound **54** is the main reaction product.

The use of chiral acrylamides as dipolarophiles has been reported;[68–73] acrylamides can have two low-energy rotamers due to rotation around the C–N bond. Cycloaddition of nitrile oxides to the optically active acryloylsultam **55** gives a mixture of diastereomers **56** and **57**; however, the diastereoselectivity of this reaction is rather high, especially in non-polar solvents.[68]



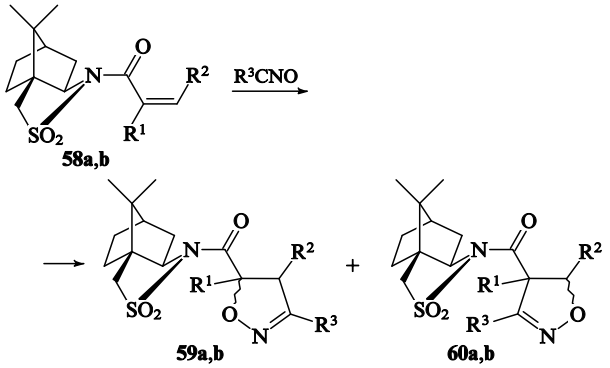
R	Solvent	Ratio **56** : **57**
Bu^t	C_6H_{14}	19 : 1
Bu^t	PhMe	9 : 1
Bu^t	CH_2Cl_2	4 : 1
Ph	C_6H_{14}	19 : 1
Me	C_6H_{14}	9 : 1
Et	C_6H_{14}	9 : 1
	PhH	7 : 1

These results prompted a transition state model the existence of which was confirmed by X-ray diffraction analysis of compound **55**.[68]

According to calculations,[74] the dipole–dipole interaction of the C=O and S=O groups and, as a consequence, steric destabilisation, are absent only in the *s-trans*-conformer. However, this model cannot be applied to reactions promoted by Lewis acids, since the predominant conformation changes upon chelation.[74]

The results of quantum-mechanical calculations of the energy and geometrical parameters of various transition states suggest [75] that Coulomb interactions are the main factor which determines diastereofacial differentiation. The Coulomb interactions of the oxygen atom of the nitrile oxide with the sultam oxygen *endo*-atom and, to a lesser degree, with the sulfur atom determine the energy predominance of the transition states during the approach of nitrile oxide to the double bond above the sultam ring which affords compounds of the type **56** (although the approach of the nitrile oxide to the double bond under the sultam ring is sterically more favourable and results in the formation of isomers **57**).

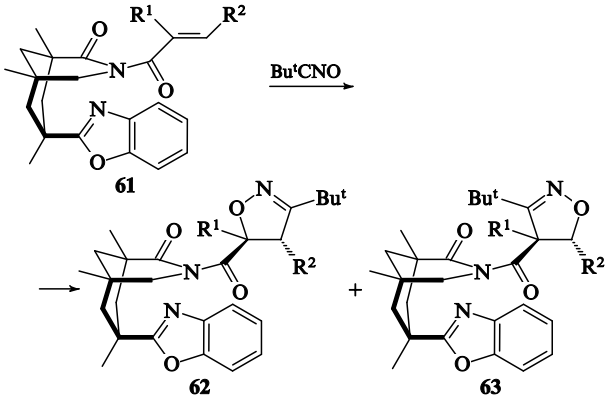
It was shown [21,76] that methacryloylsultam **58a** is inactive in the reaction with nitrile oxides and provides low asymmetric induction, whereas this reaction is completely regiospecific (the ratio of diastereomers **59a** is ~2 : 1; the stereochemistry of the major reaction product was not determined).



R^1 = Me, R^2 = H (a); R^1 = H, R^2 = Me (b); R^3 = Et, Bu^t, Ph.

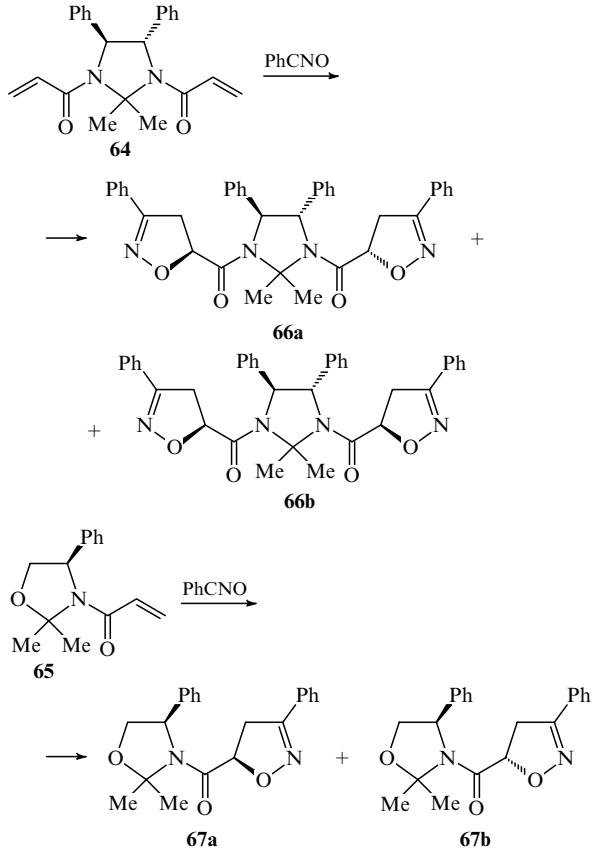
Crotonoylsultam **58b** ensures high diastereoselectivity (the diastereomer ratio is 9 : 1); however, the regioselectivity of this reaction is rather low and four products are formed. The regioisomers **59b** and **60b** are formed in nearly equal amounts.

High selectivity is also reached with the Rebek benzooxazolimides **61**,[77] which manifest a unique ability to control the selectivity of the reaction owing to the U-shape of the molecule. The ratio of the regioisomers **62** : **63** reaches 99 : 1.



R^1 = H, Me; R^2 = H, Me, Ph, CO_2Et.

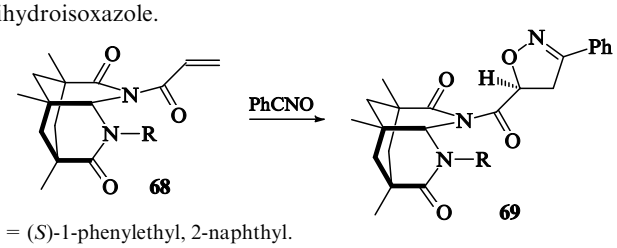
The addition of nitrile oxides to acrylamides[69] and α,β-unsaturated esters[78] containing a symmetrical chiral imidazolidine substituent in the β-position is characterised by extremely high diastereoselectivity. However, the former are difficult to obtain, while the latter manifest low regioselectivities. The reactions of 2,2-dimethyl-(4*S*,5*S*)-diphenyl-*N*,*N*′-diacryloylimidazolidine (**64**) and 2,2-dimethyl (4*R*)-phenyl-*N*-acryloylisoxazolidine (**65**) with benzonitrile oxide are highly diastereoselective.[79] Compound **64** yielded a mixture of the diastereomeric cycloadducts **66a** and **66b** in a ~ 5 : 1 ratio, whereas the reaction with compound **65** afforded a mixture of dihydroisoxazoles **67a** and **67b** (~ 4.5 : 1).



In both cases, hydrolysis of the reaction products leads to the corresponding dihydroisoxazoles possessing high optical purity. Based on the structure of the products **66a**,**b** and **67a**,**b**, it may be concluded that acrylamides **64** and **65** have an *s-cis*-conformation in the transition state, and benzonitrile oxide attacks the double bond from the side opposite to the phenyl substituent.

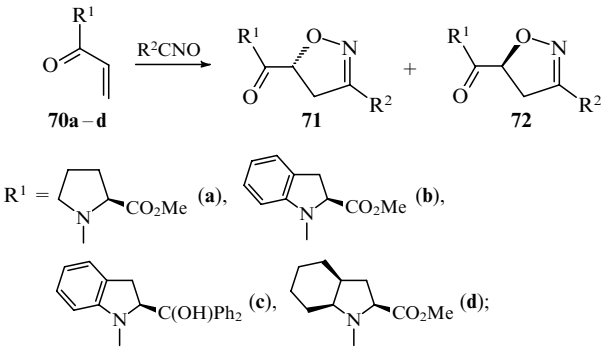
Studies of reactions of unsaturated compounds with benzonitrile oxide by the method of competing reactions[21] made it possible to construct an approximate scale of alkene reactivities, *viz*., activated monosubstituted > activated 1,1-disubstituted > non-activated 1,1-disubstituted = activated *trans*-1,2-disubstituted.

A high level of diastereoselectivity was achieved using compounds **68** which represent Kemp's triacid derivatives with chiral centres at one of the nitrogen atoms as dipolarophiles.[69,76] The adducts **69** with the *R*-configuration of the newly formed chiral centre are formed in more than 98% diastereomeric excess. It was noted that the pseudoenantiomeric alkene gives a C(5′)-isomeric dihydroisoxazole.



R = (*S*)-1-phenylethyl, 2-naphthyl.

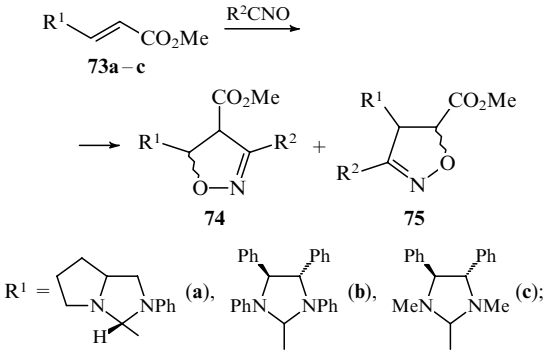
1,3-Dipolar cycloaddition of nitrile oxides to the chiral acrylamides **70a**–**d** derived from (*S*)-proline and (*S*)-indoline-2-carboxylic acid yields chiral 4,5-dihydroisoxazoles **71** and **72**.[80] The stereoselectivity of this reaction is largely determined by the structure of the dipolarophile and is practically independent of the solvent used but varies depending on the nitrile oxide structure. The dipolarophiles **70a**–**d** differ in their steric characteristics. The largest steric factor is inherent in compound **70c** due to the presence of two phenyl rings, whereas the steric factor in the rigid molecule of alkene **70d** is determined by the effect of the cyclohexane ring. In the latter case, the stereoselectivity is the highest (up to 95% of the isomer **71d** is formed).



R^2 = Me, Et, Ph, 3,5-$Cl_2C_6H_3$, 4-MeC_6H_4.

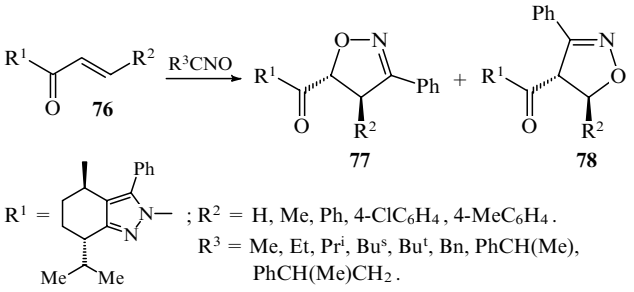
The asymmetric cycloaddition to α,β-unsaturated esters **73a**–**c** containing chiral imidazolidine substituents in the β-position has been studied.[78] With methyl acrylate **73a**, the regio- and stereoselectivity of the reaction is low, *viz*., the *trans*-isomers **74** are formed in small excess. The addition of the unsaturated esters **73b**,**c** containing a symmetrically substituted imidazolidine unit was regio- or diastereoselective depending on the nature of the substituent at the nitrogen atom of the heterocycle. Thus the reaction of the acrylate **73b** was regiospecific and afforded different regioisomers depending on the nature of the nitrile oxide. However, in all cases studied the products represented mixtures of diastereomers [~(3–2) : 1]. With compound **73c**, this reaction occurred with low regioselectivity [the ratio of the regioisomers

74 : **75** was (3 – 2) : 1]; however, each regioisomer in this mixture represented an individual (4*S*,5*S*)-diastereomer.



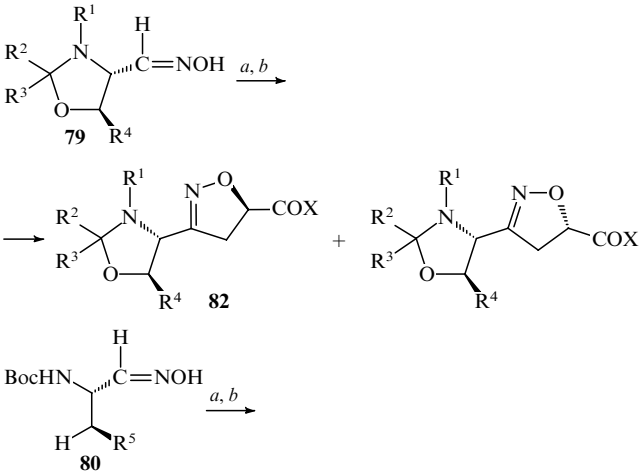
R^2 = Ph, 4-MeOC$_6$H$_4$.

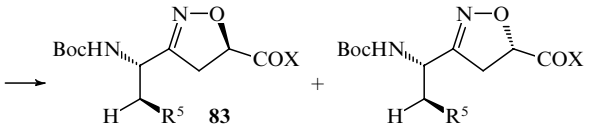
The reactions of acrylates **76** with a (4*R*,7*S*)-7-isopropyl-4-methyl-4,5,6,7-tetrahydro-2*H*-indazol-3-yl fragment as an auxiliary chiral substituent have been studied.[81] Mixtures of two regioisomers **77** and **78** were obtained, the regioselectivity decreased if the reaction was carried out in more polar solvents. The nature of the substituent R^2 in the dipolarophile weakly affected the yield and the regioselectivity.[82] The acrylate **76** (R^2 = H) gives predominantly the cycloadduct **77** with benzonitrile oxide, whereas the corresponding cinnamate (**76**, R^2 = Ph) yields a mixture of the regioisomers **77** and **78**.



R^1 = ; R^2 = H, Me, Ph, 4-ClC$_6$H$_4$, 4-MeC$_6$H$_4$.
R^3 = Me, Et, Pr^i, Bu^s, Bu^t, Bn, PhCH(Me), PhCH(Me)CH$_2$.

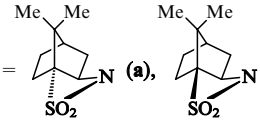
Reactions of nitrile oxides prepared from oximes **79** or **80** with *N*-acryloyl-(2*R*)- or -(2*S*)-bornane-10,2-sultams **81a**,**b** have been successfully used in the synthesis of pseudodipeptides.[83] (5*R*)-Diastereomers of dihydroisoxazoles **82** or **83** containing a chiral fragment XCO in position 5 were formed predominantly from 89% to 100%.





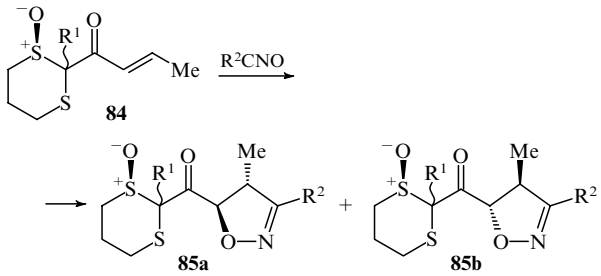
R^1 = Boc, OCOBn; R^2 = H, R^3 = Bu^t; R^2 = R^3 = Me; R^4 = H, Me; R^5 = OSiBu^{t}Me$_2$, CHMe$_2$, Ph;

(*a*) *N*-bromosuccinimide;

(*b*) XCOCH = CH$_2$ (**81a**,**b**), where X =  **(a)**, **(b)**.

As can be seen from the data presented, in the majority of cases the addition of nitrile oxides to substituted alkenes results in the adducts containing substituents in position 5. However, there are exceptions to this rule. Thus 1,3-dipolar cycloaddition of 4-*tert*-butylbenzonitrile oxide to 6^A-acrylamido-6^A-deoxy-β-cyclodextrin gives predominantly 4-substituted dihydroisoxazole[84] (the regioisomeric ratio is 4 : 1). This effect is due to the formation of an intermediate 'host – guest' complex between the cyclodextrin fragment and nitrile oxide.

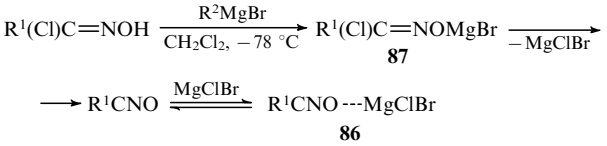
An efficient method for regio- and stereocontrol over the addition of nitrile oxides to the double bond of α,β-unsaturated diketones which makes use of chiral *S*-oxides of their cyclic dithioketals, *viz*., the diastereomeric 2-R-2-crotonoyl-1,3-dithiane *s*-oxides **84**, has been proposed.[85] The reaction with nitrile oxides is regioselective for both *syn*-**84** and *anti*-**84**; the former reacts with benzonitrile oxide to give products **85a** and **85b** in a 5 : 1 ratio, whereas for the latter the ratio is 1 : 3.



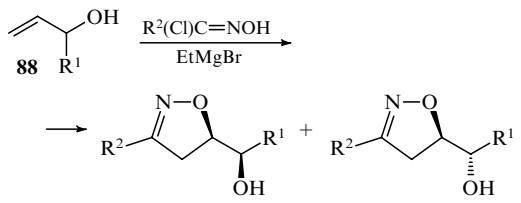
R^1 = Me, Et; R^2 = Me, Bu^i, Ph, Mes.

V. Cycloaddition of nitrile oxides to alkenes in the presence of Lewis acids

Lewis acids catalyse cycloaddition reactions of nitrile oxides to alkenes.[86–89] Thus the reaction of hydroximoyl chlorides with Grignard reagents yields the nitrile oxide complexes **86**. The first step includes *O*-metallation to give the intermediate **87** which undergoes 1,3-elimination of metal halide to give the nitrile oxide which further reacts with metal halide to give the complex **86**.



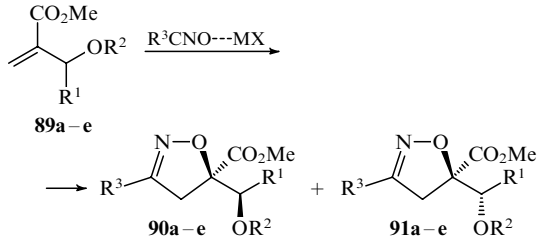
In the presence of ethylmagnesium bromide[86] the reaction rate of hydroximoyl chlorides with allylic alcohols **88** increases; no side products, *e.g*., nitrile oxide dimers, are hereby formed. Cycloaddition occurs in a *syn*-selective manner (up to 95%). Free nitrile oxides generated under the action of triethylamine manifested only weak *syn*-selectivities.



R^1 = Me, Et; R^2 = Ph, 4-$MeOC_6H_4$.

The nitrile oxide complexes of the type **86** can be generated under the action of other organometallic compounds (*e.g.*, Bu^nLi, Et_2Zn, Et_3Al); however, stereoselectivities of reactions are much lower in these cases. The complexes formed in the reaction with Et_2AlCl and $EtAlCl_2$ did not react with allylic alcohols **88** at all.[86]

The cycloaddition of nitrile oxides coordinated to Lewis acids to 1,1-disubstituted alkenes **89a–e** has been studied.[89] The formation of 4,5-dihydroisoxazoles always proceeds with high yields. The cycloaddition of acrylates **89a–d** with hydroxy groups in their chiral centres to free nitrile oxides is accompanied by the formation of a mixture of the diastereomers **90a–d** and **91a–d**, the *anti*-addition products **91a–d** being the main isomers. The proportion of the *anti*-adducts **91** decreases if nitrile oxides are used as complexes with LiCl, whereas magnesium and zinc complexes yield predominantly the cycloadducts **90a–d**. The highest *syn*-selectivity (98%) is observed in the presence of a twofold excess of magnesium alkoxide.

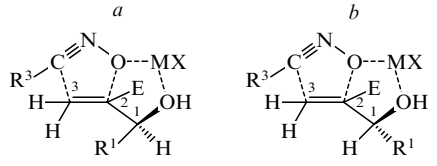


MX = $MgBr_2$, $ZnEt_2$, LiCl, $Mg(OAlk)_2$.

Compound **89**	R^1	R^2	R^3
a	Me	H	Ph
b	Me	H	4-$MeOC_6H_4$
c	Me	H	Bu^t
d	Et	H	Ph
e	Me	$SiMe_3$	Ph

A transition state model which accounts for the formation of *syn*- and *anti*-cyloaddition products has been proposed (Fig. 2).[89]

According to this model, the metal atom in the nitrile oxide–Lewis acid complex is coordinated to the hydroxy group of the dipolarophile. The transition state represents a system of condensed five-membered rings bent along the C(2)–O bond. Localisation of the substituent R^1 at the chiral centre inside the bent condensed system (Fig. 2 *a*) produces significant steric hindrances. Therefore, this reaction occurs *via* a sterically less hindered *syn*-transition state (Fig. 2 *b*). This model explains the effect of the coordinative capacity of the metal atom on the stereoselectivity of this reaction. Lithium and zinc form no stable complexes. In the presence of magnesium salts, dipolarophiles undergo ionisation to produce stronger complexes with metals, as a result of which their *syn*-selectivities increase.



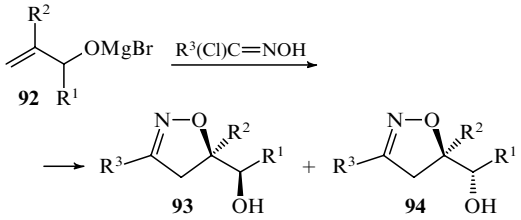
E = CO_2Me.

Figure 2. The transition states of the reaction of cycloaddition of nitrile oxides to chiral homoallylic alcohols **89a–d**.[89]
(*a*) *anti*-transition state, (*b*) *syn*-transition state; E = CO_2Me.

If the hydroxy group is protected by a bulky trimethylsilyl substituent (compound **89e**), the formation of a chelate complex in the transition state is less favourable; therefore, the alkene **89e** yields the *anti*-isomers **91** with moderate stereoselectivities (73%–79%) irrespective of the method used for the generation of nitrile oxides.

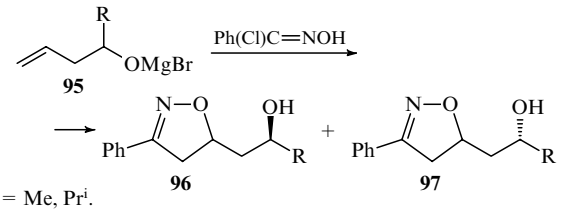
An alternative approach to increase in the stereoselectivity of nitrile oxide addition to alkenes is the use of magnesium alkoxides obtained by the reaction of allylic alcohols [86] or α,β-unsaturated ketones [90] with organomagnesium compounds. This reaction occurs in a *syn*-stereoselective manner. The maximum selectivity is reached with 2 equivalents of the alkoxide and decreases when the reaction is carried out in THF.

In the case of magnesium alkoxides **92** prepared from the corresponding allylic alcohols, the cycloaddition is regioselective and affords the cycloadducts **93** and **94**; with 2 equivalents of alkoxides **92** the *syn*-addition products **93** are predominantly formed.[86]



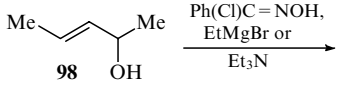
R^1	R^2	R^3	Ratio **93** : **94**
Me	H	Ph	96 : 4
Et	H	Ph	99 : 1
Et	H	4-$MeOC_6H_4$	89 : 11
Pr^i	H	Ph	97 : 3
Bu^n	Me	Ph	96 : 4

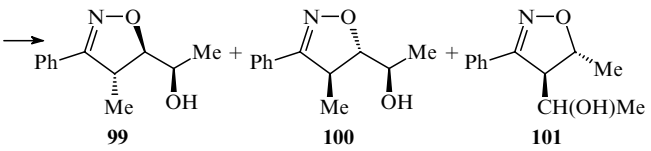
The application of this methodology to alkoxides of homoallylic alcohols resulted in the exclusive formation of the regioisomers **96** and **97** from terminal alkenes with no or very small diastereoselectivity.[86]



R = Me, Pr^i.

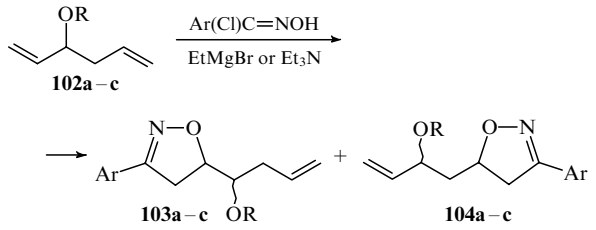
It should be noted that the control over the selectivity of 1,3-dipolar cycloaddition by coordination to metals proved to be efficient in those cases where internal alkenes were used as dipolarophiles. The cycloaddition of nitrile oxides to allylic alcohols **98** in the presence of ethylmagnesium bromide is regiospecific with the predominant formation of the *syn*-adduct **99** (94%), whereas the nitrile oxide generated under the action of triethylamine gave a mixture of compounds **99** and **100** in a 55 : 12 ratio and up to 18% of diastereomers of 4,5-dihydroisoxazole **101**, the total yield of the reaction products being much lower.





99 **100** **101**

The cycloaddition of nitrile oxides to dienes which contain a hydroxy group in both the allylic and homoallylic positions has been studied.[91] Thus the reaction of hexa-1,5-dien-3-ol (**102a**) with benzonitrile oxide generated under the action of Et_3N gives a mixture of the cycloadducts **103a** and **104a** (the diastereomeric ratios were 2 : 1 and 3 : 2, respectively), *i.e.*, under these conditions, the double bond of the allylic fragment was only a little more reactive than that of the homoallylic fragment.



102a–c **103a–c** **104a–c**

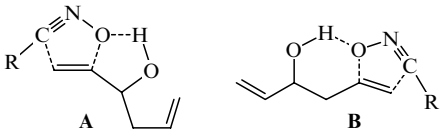
R = H (**a**), Ac (**b**), $SiMe_2Bu^t$ (**c**); Ar = Ph, 2,6-$Cl_2C_6H_3$.

When EtMgBr is used to generate nitrile oxide, the reaction is chemoselective with respect to the allylic fragment, the *syn* : *anti*-diastereomeric ratio in compound **103** being 99 : 1. Thus the magnesium alkoxide methodology proved to be more efficient for allylic alcohols than for homoallylic alcohols.

The influence of hydrogen bond formation on the cycloaddition of 2,6-dichlorobenzonitrile oxide to compounds **102a–c** has been studied.

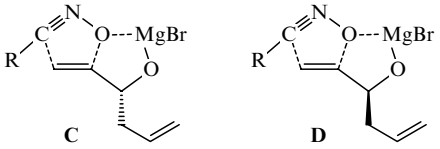
In weakly polar solvents, such as benzene or dichloromethane, nitrile oxide forms a hydrogen bond with the hydroxy group of the alcohol **102a** and coordinates to the double bond of the allylic fragment (the transition state **A** is more favourable than **B**), compound **103a** being the main product. The use of polar solvents, *e.g.*, DMF, prevents the formation of the hydrogen bond, and thus the product **104a** becomes predominant.

In the case of a protected hydroxy group (compounds **102b**,**c**), no hydrogen bond can be formed; therefore, acetate **102b** gives predominantly the adduct **104b** irrespective of the polarity of the solvent used. In addition, the homoallylic double bond in the acetoxy derivative **102b** becomes more reactive as a dipolarophile due to steric repulsion between the acetoxy group and nitrile oxide. For compound **102c**, the yield of dihydroisoxazole **104c** increases even more due to significant steric hindrances.



A **B**

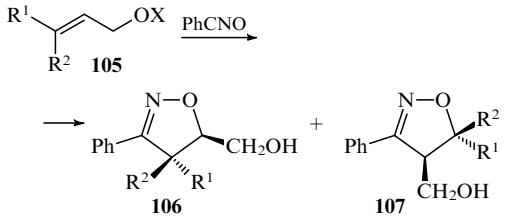
High *syn*-selectivity in the addition to the double bond of the allylic fragment of magnesium alkoxide prepared from the alcohol **102a** can be explained in terms of the reaction mechanism. Magnesium alkoxide forms five-membered intermediates **C** or **D**, the latter being much less stable due to steric hindrances created by the propenyl substituent.



C **D**

Thus the allylic double bond is relatively more reactive in the reaction of 1,3-dipolar cycloaddition of nitrile oxides to hexa-1,5-dien-3-ols than the homoallylic bond due to the formation of a hydrogen bond. In acetyl or silyl derivatives of the alcohol **102a**, it is the isolated homoallylic bond that is more reactive. Chelation with magnesium derivatives results in high regio- and diastereoselectivity. It should be noted that the products of simultaneous addition at two bonds were also isolated.

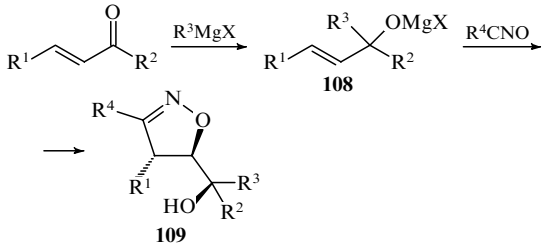
Reactions of 1,3-dipolar cycloaddition of benzonitrile oxide with 3,3-disubstituted allylic alcohols **105** proceed with very low regioselectivity; the nature of the substituent practically does not influence the ratio of the cycloadducts **106** and **107**.[92] In the case of magnesium alkoxides (X = MgBr), the reaction rate increases considerably and so does the regioselectivity,[93,94] this effect being observed exclusively with more than 1 equivalent of magnesium alkoxide. Similar results were obtained for mesitylenecarbonitrile oxide.[94]



105 **106** **107**

R^1 = H, Me, Pr^i, Ph; R^2 = H, Me, Pr^n; X = H, MgBr.

The cycloaddition of 2,6-dichlorobenzonitrile oxide to magnesium alkoxides **108** obtained by treatment of α,β-unsaturated aldehydes and ketones with Grignard reagents has been studied.[90] This reaction is regio- and diastereoselective and results in the *syn*-adducts **109**.



108 **109**

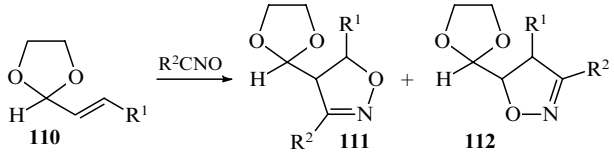
R^1 = H, Me; R^2 = H, R^1-R^2 = CH_2CH_2; R^3 = Me, Et; R^4 = 2,6-$Cl_2C_6H_3$.

Encouraging results were also obtained with cyclopentenone; however, the attempts to carry out an analogous reaction with cyclohexenone were without success.

VI. Cycloaddition of nitrile oxides to unsaturated aldehyde derivatives

Cycloaddition to cinnamaldehyde is one of few examples of cycloaddition of aceto- and benzonitrile oxides to α,β-unsaturated aldehydes.[95] In addition to the expected products, *e.g.*, 4-formyl-5-phenyl-3-R-4,5-dihydrooxazoles, bis-adducts were isolated due to the cycloaddition of nitrile oxide to the carbonyl group of the primary cycloadducts. Therefore, in subsequent experiments the carbonyl groups of α,β-unsaturated aldehydes were protected prior to their cycloaddition to nitrile oxides.

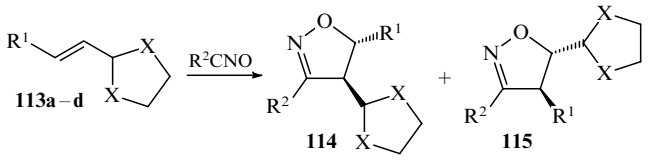
The reactions of cyclic acetals **110** with nitrile oxides[96] gave predominantly the adducts **111**. The desired regioselectivity can be attained by varying the nitrile oxide structure. For example, for R^1 = CO_2Et and R^2 = Ph the **111** : **112** ratio is 99 : 1.



110 **111** **112**

R^1 = Ph, CO_2Et, Et; R^2 = Ph, Me, Pr^i.

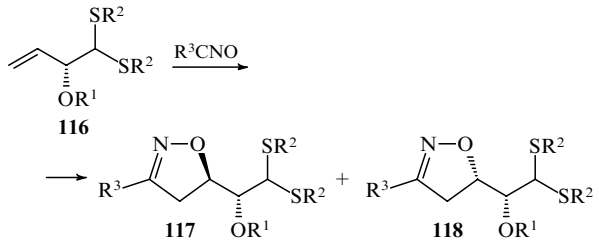
The compositions of cycloaddition products in the case of β-substituted α,β-unsaturated aldehyde derivatives depend on the nature of the protective groups.[97] The cycloaddition to cyclic acetals **113a**,**b** yields predominantly the regioisomers with an acetal substituent in position 4, whereas for dithioacetals **113c**,**d** the regioselectivity is opposite. Calculations led to a conclusion that the orientation in this case of the dithioacetal group is determined by the steric factor, whereas that in the case of the acetal group is determined by the interaction of the frontal orbitals.



Compound **113**	R^1	X	R^2	Ratio **114** : **115**
a	Ph	O	Ph	91 : 9
	Ph	O	4-$MeOC_6H_4$	17 : 1
b	Me	O	$PhCH_2$	9 : 1
c	Ph	S	Ph	17 : 83
	Ph	S	4-$MeOC_6H_4$	27 : 73
d	Me	S	$PhCH_2$	3 : 7

Thus, by varying the protecting group in the α,β-unsaturated aldehyde, one can change the regioselectivity of the reaction resulting in substituted 4,5-dihydroisoxazoles with the formyl substituent in different positions.

High stereoselectivity is achieved in the addition of nitrile oxides to 2-hydroxybut-3-enal dithioacetal derivatives.[98] Thus the diastereoselectivity of the cycloaddition of nitrile oxides to 2-silyloxybut-3-enal dithioacetals **116** virtually does not depend on either the size of the protective group at the oxygen or the sulfur atoms or the nature of the substituent. The *anti*-isomers **117** are formed as the main products and the maximum diastereoselectivity (96%) is achieved with the bulky dithioacetal group ($R^2 = Bu^t$). However, the yield of this reaction depends, to some extent, on the nature of the nitrile oxide; the total yield of the cycloadducts **117** and **118** is low (25%–26%) with $R^1 = SiMe_2Bu^t$, $R^2 = Bu^t$ and $R^3 = CO_2Et$ or CH_2OBn.



R^1 = Bn, $SiMe_2Bu^t$; R^2 = Ph, $(CH_2)_3$, Bu^t; R^3 = Me, Ph, 4-$MeOC_6H_4$,



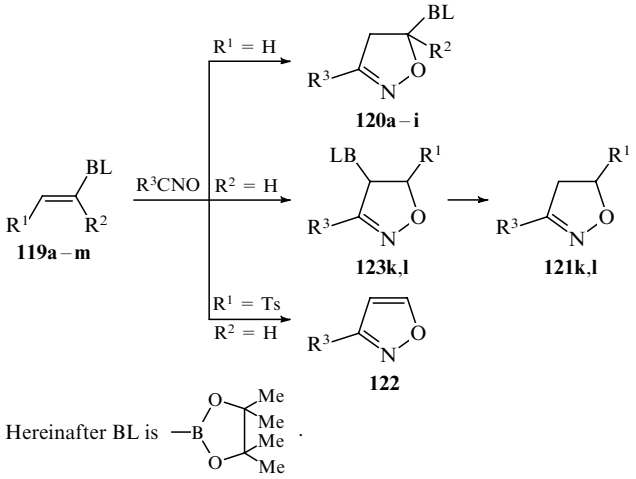
, CO_2Et, CH_2OBn.

Deprotection of the aldehyde group occurs with high yields and without epimerisation of the chiral centres, which apparently makes this method especially attractive from the synthetic point of view.[98]

VII. Alkenylboronates in cycloaddition reactions with nitrile oxides

Organoboron derivatives, particularly alkenylboronate derivatives are readily available and are often used in synthetic practice as convenient building blocks.[99] The possibility of the use of alkenylboronates as dipolarophiles in cycloaddition with nitrile oxides has been studied.[100–102] It is of note that an attempt at enhancing the reactivity of the double bond in alkenylboranes by introducing stronger electron-withdrawing groups, such as borabicyclononyl, catecholboryl or $BHal_2$ groups, has not led to the desired effect.[103]

It was found that the vinylboronates **119a**–**g** react with nitrile oxides in a regiospecific manner to give 4,5-dihydroisoxazoles **120a**–**g**, their yields being only little dependent on the changes in the nitrile oxide structure. α-Substituted alkenylboronates **119h**,**i** gave also 4,5-dihydroisoxazoles **120h**,**i** containing a boronate residue in position 5 as the reaction products, while the trisubstituted compound **119j** gave no cycloadducts. β-Substituted alkenylboronates **119k**–**m** do not afford products similar to compounds **120**; this reaction gave 4,5-dihydroisoxazoles **121k**,**l** or isoxazole **122** containing no boronate substituent.

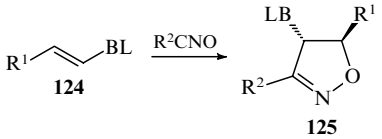


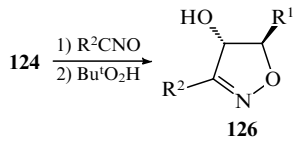
Hereinafter BL is .

Substrate **119**	R^1	R^2	R^3	Reaction product
a	H	H	4-ClC_6H_4	**120a**
b	H	H	Me	**120b**
c	H	H	Bu^t	**120c**
d	H	H	CO_2Et	**120d**
e	H	H	COMe	**120e**
f	H	H	$(CH_2)_3CO_2Me$	**120f**
g	H	H	$CH_2CH(OMe)_2$	**120g**
h	H	Me	4-ClC_6H_4	**120h**
i	H	Ph	4-ClC_6H_4	**120i**
j	$(CH_2)_4$		4-ClC_6H_4	–
k	Bu	H	4-ClC_6H_4	**121k**
l	MeOCO	H	4-ClC_6H_4	**121l**
m	Ts	H	4-ClC_6H_4	**122**

A mechanism of cycloaddition has been proposed [101] based on the results of the reaction of vinylboronates with diazo compounds.[104] According to this mechanism, nitrile oxide is added regioselectively to *cis*-alkenylboronates **119k**–**l** to give 4,5-dihydroisoxazoles **123** with a boronate residue in position 4. Similar compounds were isolated and characterised in previous studies.[105] Spontaneous 1,3-migration of the boronate residue and subsequent hydrolysis give 4,5-dihydroisoxazoles **121**. Elimination of TsOH in the case where R^1 = Ts results in isoxazole **122** (R^3 = 4-ClC_6H_4).[106]

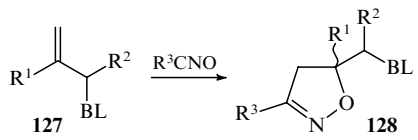
An effective procedure for the synthesis of 4-hydroxy-4,5-dihydroisoxazoles using vinylboronates has been proposed.[105] Thus 1,3-dipolar cycloaddition of nitrile oxides to 2-substituted *trans*-alkenylboronates **124** gives 4,5-dihydroisoxazoles **125** with a boronate substituent in position 4 as the main regioisomers. Treatment of the reaction mixture with Bu^tO_2H gives *trans*-hydroxy-4,5-dihydro-4-isoxazoles **126** in high yields (75%–88%).





R^1 = Pr^n, CH_2OAc, Ph, Bu^n, CO_2Me, $(CH_2)_3Cl$; R^2 = Ph, 4-$MeOC_6H_4$.

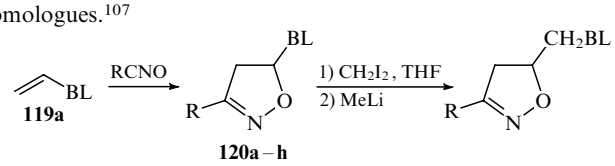
The cycloaddition of nitrile oxides to allylboranes **127** has been studied.[101] As in the case of alkenylboranes, one regioisomer **128** is formed. Allylboranes containing a chiral centre in the α-position yield a nearly equimolar mixture of diastereomers with nitrile oxides; their stereochemistry has not been established.



R^1 = H, Me; R^2 = H, Cl, C_6H_{13}, C_5H_9; R^3 = Bu^t, 4-ClC_6H_4.

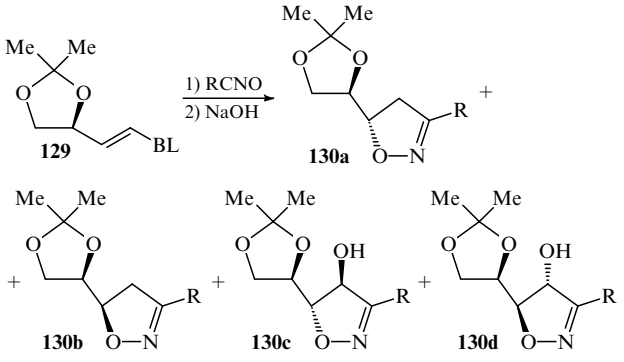
Thus, 1,3-dipolar cycloaddition of nitrile oxides to alkenyl- or allylboronates and subsequent oxidative deborylation of the adducts formed is a direct route to 4-hydroxy- or 5-hydroxyalkyl-4,5-dihydroisoxazoles.

The reaction of [3-R-4,5-dihydroisoxazol-2-yl]boranes **120a**–**h** with diiodomethane in the presence of MeLi yields their homologues.[107]



R = 4-ClC_6H_4 (**a**), Me (**b**), Bu^t (**c**), CO_2Et (**d**), COMe (**e**), Ph (**f**), $(CH_2)_2CO_2Me$ (**g**), CMe_2OSiMe_3 (**h**).

Cycloaddition of nitrile oxides to the optically active alkenylboronate **129** gives four products; the total yield of 4,5-dihydroisoxazoles **130a**,**b** is ~50%, whereas that of (4*S*,5*S*)- and (4*R*,5*R*)-4-hydroxy-4,5-dihydroisoxazoles **130c**,**d** is ~45%, *erythro*-isomers being predominant in both cases.[108] Thus, this reaction occurs in a regiospecific manner but with moderate stereoselectivity. Compounds **130a**,**b** are formed as a result of deborylation of the primary 4,5-dihydroisoxazoles which contain a boronate substituent in position 4 (like compounds **123a**,**b**).

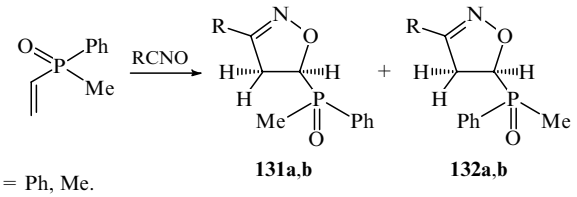


R = Ph, 4-ClC_6H_4.

Compounds **130c**,**d** were the only reaction products (**130c** : **130d** ≈ 4 : 1) when *tert*-butyl peroxide was used for the generation of nitrile oxide.

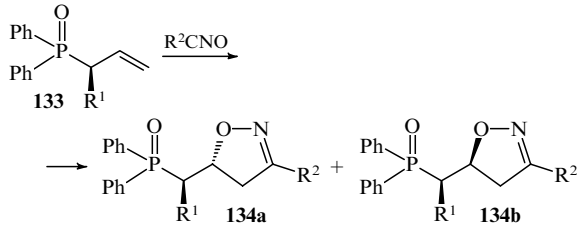
VIII. Vinyl- and allylphosphine oxides in cycloaddition reactions with nitrile oxides

1,3-Dipolar cycloaddition of nitrile oxides to racemic methylphenylvinylphosphine oxide results in phosphorus-containing 4,5-dihydroisoxazoles **131a**,**b** and **132a**,**b** in good yields.[109] The isomers **131a**,**b** with a phosphine oxide substituent in position 5 either predominate or are the only reaction products. The cycloaddition occurs with a significant (~40%) diastereofacial selectivity. According to X-ray diffraction data, compound **131a**, which exists in an *erythro*-configuration, has a conformation in which the C–O and P=O bonds are in the *anti*-position.



R = Ph, Me.

1-R-Propenyldiphenylphosphine oxides **133** were studied in the reaction of 1,3-dipolar cycloaddition.[110]



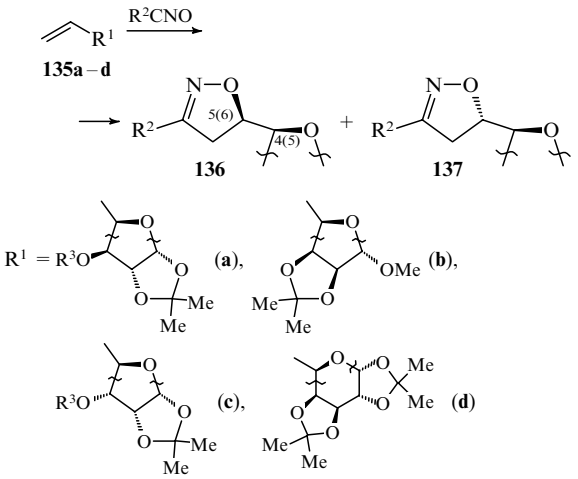
R^1 = Me, Et, Pr, C_6H_{11}, $C_{11}H_{23}$, CO_2Et, $(CH_2)_nCO_2Me$;
R^2 = H, Me, Et, Pr, Bu^i.

Cycloadducts are not formed, if nitrile oxides contain a bulky substituent R^2. In other cases, the reaction proceeds at a very slow rate. The *anti*-addition products **134a** are predominant in all cases. This is one of the few examples of cycloaddition reactions where the substituent in the nitrile oxide has a stronger influence than the substituent R^1 in the allylic position. It was suggested [110] that the extremely bulky phosphorus-containing substituent in the Houk transition state occupies a position opposite to that of the ring which is formed, whereas the R^1 group and the allylic hydrogen atom are localised inside and outside, respectively. Branched substituents R^2, *e.g.*, Pr^i, are too bulky for these positions; therefore, alkenes **133** do not form cycloadducts with such nitrile oxides.

IX. The nitrile oxide method in carbohydrate chemistry

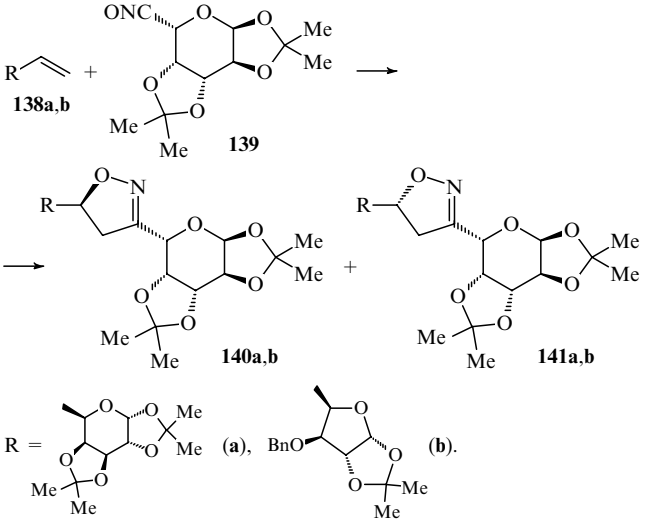
Cycloaddition of nitrile oxides to alkenes is used in the synthesis of various sugar derivatives. The nitrile oxide method proved to be a convenient procedure for the elongation of a carbon chain in the synthesis of higher sugars. The 1,3-dipolar cycloaddition of the simplest nitrile oxides to the double bonds of the sugar derivatives **135a**–**d** has been studied.[111–116] The reaction of compounds **135a**,**b**,**d** with nitrile oxides is regioselective and gives 4,5-dihydroisoxazoles **136** and **137** which contain the sugar moiety in position 5 (74 : 26 and 97 : 3, respectively). The major diastereomers of the adducts **136** have the *R*-configurations of the newly formed chiral centres. Quite a different result is obtained for the corresponding D-ribose derivative **135c**,[113,115] which represents an epimer of compound **135a** as regards the homoallylic C(3) atom. In this case, the *syn*- and *anti*-adducts **136** and **137** are formed in approximately equal amounts. This reaction is the first

example of the dependence of the composition of nitrile oxide cycloaddition products on the configuration of the chiral centre in the homoallylic position.

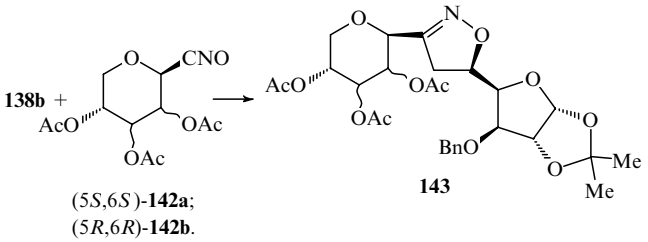


R^2 = Ph, CO_2Et; R^3 = H, OH, OMe, OBn, Ac, Ar.

The 1,3-dipolar addition of ω-unsaturated heptoses and hexoses **138a**,**b** to the nitrile oxide **139** was used in the synthesis of 7-deoxytrideca- and 6-deoxydodecadialdoses.[117] It should be noted that this reaction is one of the few examples of asymmetric induction by a chiral nitrile oxide. Both alkenes react regiospecifically and with high diastereoselectivity to give predominantly the *anti*-adducts **141a**,**b** (**141** : **140** = 4 : 1 and 14 : 3, respectively).

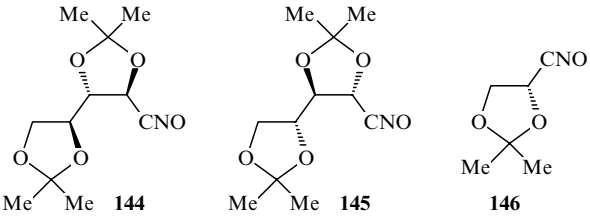


The stereo-controlled cycloaddition of the alkene **138b** to nitrile oxides derived from D-xylose (**142a**) or D-arabinose (**142b**) has been carried out. In both cases, the reaction is regiospecific and diastereoselective with the predominance (up to 80%) of the diastereomers **143** having *R*-configurations of the newly formed chiral centres.[118]

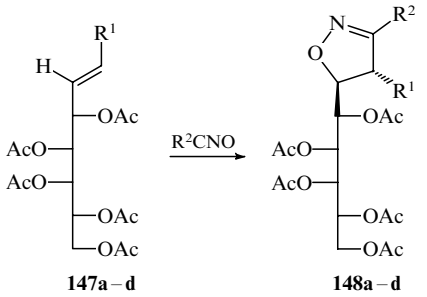


(5*S*,6*S*)-**142a**;
(5*R*,6*R*)-**142b**.

Similar results were obtained with L- or D-arabinonitrile (**145**),[119] oxide derivatives **144** and glyceronitrile oxide (**146**).[115]

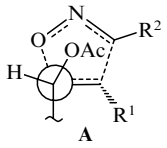


The 1,3-dipolar cycloaddition of nitrile oxides to nitroalkenes and α,β-unsaturated carbonyl compounds **147a**–**d** containing a sugar moiety has been studied. For alkenes **147b**–**d**, this reaction is regio- and stereoselective and yields exclusively the diastereomers **148** with the *trans*-configuration of substituents at the C(4) and C(5) atoms.[120]

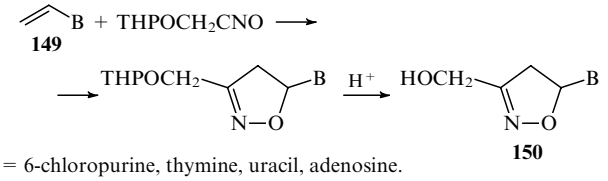


R^1 = NO_2 (**a**), Ac (**b**), CO_2Me (**c**), CO_2Et (**d**); R^2 = Me, Ph, Mes, Br.

Based on molecular-mechanical models and the structure of the reaction products, it was suggested [120] that in this case it is the stable transition state **A** that is realised. This conclusion is in good agreement with the anti-periplanar effect of the acetoxy group in the allylic position.



The regioselective cycloaddition of tetrahydropyranyloxyacetonitrile oxide to the nitrogen bases **149** containing vinyl groups results in the nucleoside aza analogues **150** possessing antiviral activities.[121, 122]

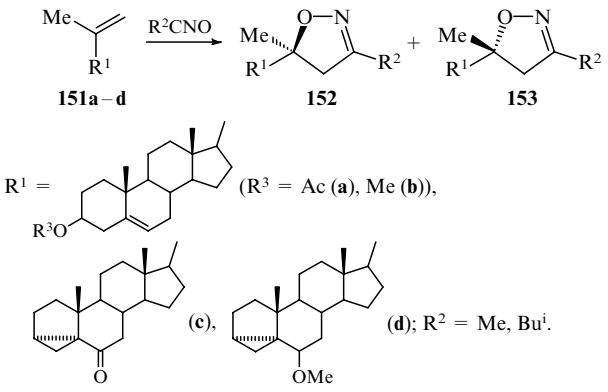


B = 6-chloropurine, thymine, uracil, adenosine.

X. Steroid alkenes as dipolarophiles in cycloaddition reactions with nitrile oxides

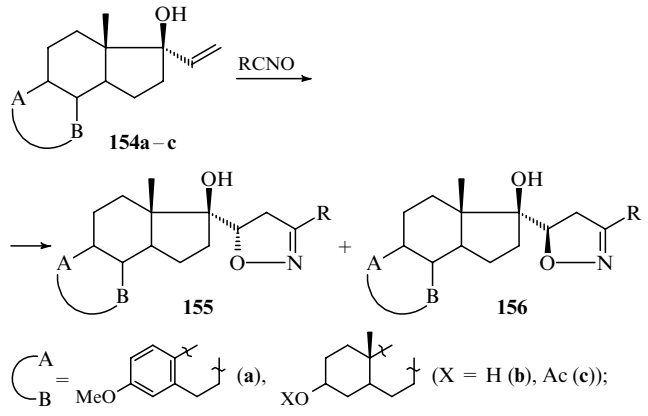
1,3-Dipolar cycloaddition of nitrile oxides to steroid alkenes has been studied using compounds with a double bond in both the cyclic part of the molecule (*e.g.*, $\Delta^{5(6),16(17)}$-steroids) and the side chain.

The addition of nitrile oxides to the disubstituted double bond of the steroids **151a**–**d** occurs at a slow rate and sometimes requires a large excess of nitrile oxide; its result does not change upon modification of the steroid skeleton but strongly depends on the nature of the substituent R^2 of the nitrile oxide.[123] No cycloaddition products were found for R^2 = Pr^i.

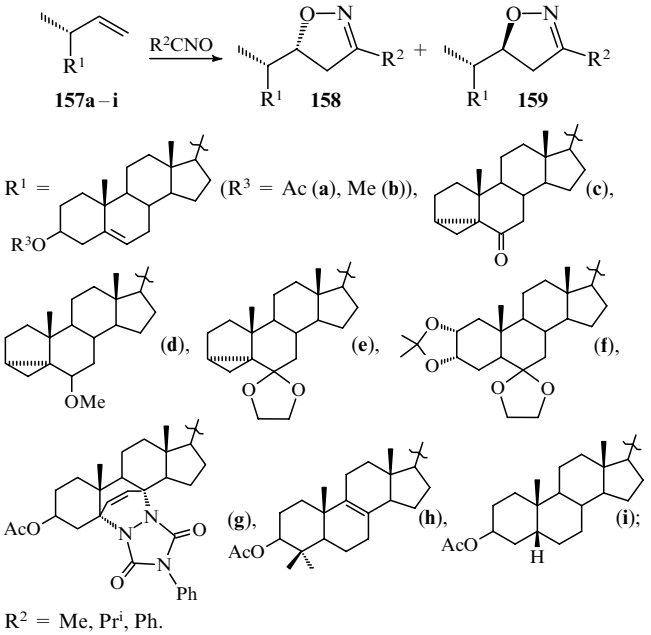


This addition is regiospecific leading exclusively to the formation of 4,5-dihydroisoxazol-5-yl derivatives and stereoselective (**152** : **153** = 3 : 1). The main epimer is formed as a result of an attack of the nitrile oxide at the double bond from the sterically less hindered side (the α-region of the steroid).

1,3-Dipolar cycloaddition of nitrile oxides to the 17β-hydroxy-17α-vinyl estrone derivative **154a** proceeds in a regiospecific and stereoselective manner [**155** : **156** = (10 – 15) : 1]. The stereoselectivity of the reaction decreases on going to the steroids of the androstane series **154b,c** (**155:156** = 1:1) for R^2 = Me and 3 : 1 for R^2 = Pr^i.[124, 125]

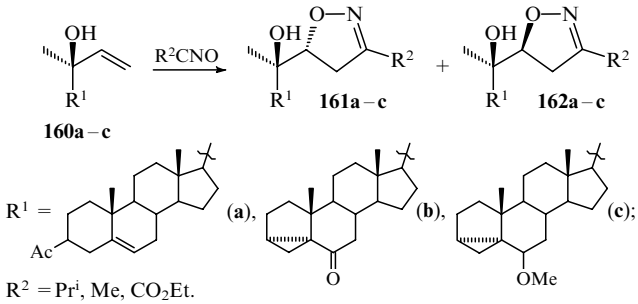


The steroid derivatives **157a** – **i** containing a but-2-enyl substituent in the ring *D* have been studied in the reaction of 1,3-dipolar cycloaddition to nitrile oxides.[126–132] In all cases, this

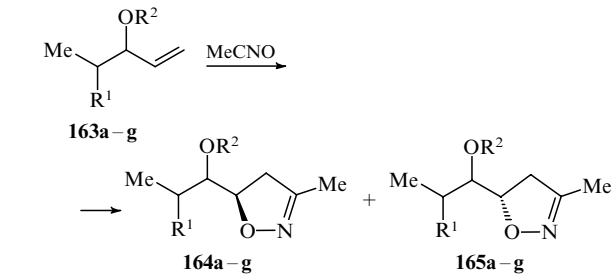


reaction gave a mixture of the 5′-epimeric 4,5-dihydroisoxazol-5-yl steroids **158** and **159**. The ratio of the epimers (5′*R*)-**158** and (5′*S*)-**158** depends on the structures of both the nitrile oxide and the steroid. In some cases, the reaction possessed pronounced stereoselectivity, *e.g.*, the **158** : **159** ratio in the reaction of compound **157h** with benzonitrile oxide is 4.5 : 1, whereas the reaction of the alkene **157f** with isobutyronitrile oxide is not selective. The reaction of compound **157g** with nitrile oxides is a special case, for it gives only one reaction product **158** (R^2 = Me, Pr^i).

1,3-Dipolar cycloaddition of nitrile oxides to steroidal allylic alcohols **160a** – **c** [126, 132, 133] affords the adducts **161** and **162**; the *threo*-isomers **161** are formed with high stereoselectivities. The cycloaddition of EtO_2CCNO to compound **160b** gave only one diasteromer, *viz.*, 4,5-dihydroisoxazole **161b** (R^2 = CO_2Et), albeit in a low yield.



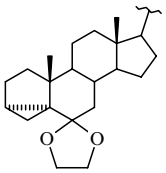
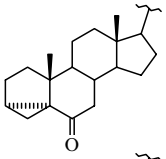
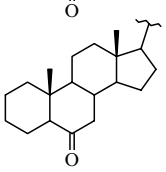
The stereochemistry and the ratio of the reaction products in the cycloaddition of nitrile oxides to the Δ^{23}-steroids **163** is determined by the nature of the oxygen-containing substituents in the α- and β-positions to the double bond and the configuration of the C(20) and C(22) centres in the starting dipolarophile (Table 1).[134–138]



The cycloaddition of acetonitrile oxide to the steroid **163a** containing a (22*S*)-hydroxy group occurs in a regio- and stereoselective manner with the predominant formation of the *threo*-isomers **164a**. The ratio of the epimers formed in the reaction with (22*S*)-acetoxy derivative **163b** was 1 : 1 (with a concomitant decrease in the degree of conversion). The use of the (20*S*,22*R*)-hydroxy derivative **163c** also resulted in the predominant formation of the *threo*-isomer **165c**, whereas in the case of the (22*R*)-acetoxy derivative **165d** the epimers were formed in a 1 : 1 ratio and the degree of conversion was also decreased. This reaction becomes stereospecific upon protection of the hydroxy group by a bulky *tert*-butyldimethylsilyl substituent (compound **163e**), however, the (22*R*,5′*S*)-diastereomer **165e** is formed in a low yield. The (22*S*,5′*S*)-diastereomer **165f** was predominant upon cycloaddition of the (20*R*,22*R*)-22-hydroxy derivative **163f**, but the stereoselectivity of this reaction was not very high. When the (20*R*,22*R*)-22-acetoxy derivative **163g** is used as a dipolarophile, the *syn*-cycloaddition product **165g** is formed in a large excess which is in contrast to the reactions with the acetoxy derivatives **163b** and **163d**.

These reaction patterns differ basically from those for non-steroid compounds and suggest the possible formation of a transition state (an intermediate complex) including nitrile oxide and the allylic hydroxy group of the steroid molecule.[2] The structure of the transition state depends on the nature of the

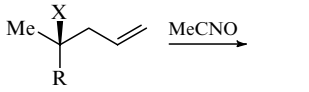
Table 1. The stereochemistry and ratios of reaction products in the reaction of acetonitrile oxide with the steroids **163**.

R^1	R^2	Compound **163**	Configuration of the C(20) and C(22) centres	Total yield	Ratio of adducts **164** and **165**
	H	**a**	(20*S*,22*S*)	88	4 : 1
	Ac	**b**	(20*S*,22*S*)	81 [a]	1 : 1
	H	**c**	(20*S*,22*R*)	88	1 : 4
	Ac	**d**	(20*S*,22*R*)	90 [b]	1 : 1
	$SiMe_2Bu^t$	**e**	(20*S*,22*S*)	16 [c] 25 [e]	see [d]
	H	**f**	(20*R*,22*R*)	70	1 : 2
	Ac	**g**	(20*R*,22*S*)	78 [f]	1 : 4

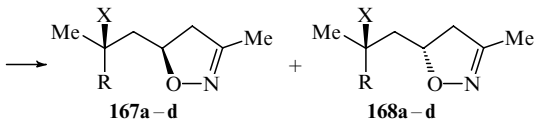
[a] The conversion is 41%. [b] The conversion is 38%. [c] 20 °C. [d] Only the adduct **165** is formed. [e] 60 °C. [f] The conversion is 40%.

steroid fragment and the configuration of the allylic and homoallylic centres.

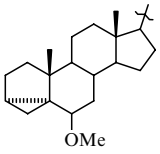
The reaction of acetonitrile oxide with the 20-hydroxy-20-propenyl steroids **166b**,**d** containing the homoallylic hydroxy groups occurs without any noticeable stereoselectivity to afford approximately equal amounts of the epimeric 4,5-dihydroisoxazoles **167b**,**d** and **168b**,**d**.[139]

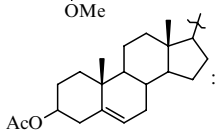


166a–d



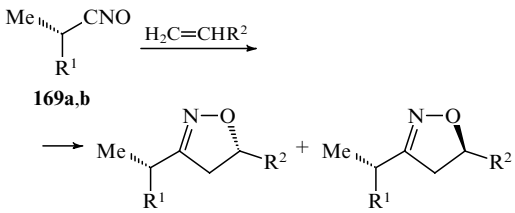
167a–d **168a–d**

R =  : X = H (**a**), OH (**b**);

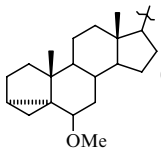
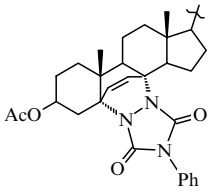
R =  : X = H (**c**), OH (**d**).

This reaction is also non-stereoselective with the steroid alkenes **166a**,**c** devoid of hydroxy groups.[140]

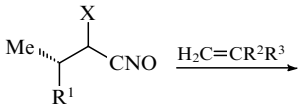
The first attempts to use steroidal nitrile oxides **169a**,**b** and **170a–d** [141–144] as dipoles in reactions with alkenes revealed that the cycloaddition which occurs in a regioselective manner yields one regioisomer in the form of epimeric pairs of 4,5-dihydroisoxazol-3-yl steroids. However, this reaction is non-stereoselective for both C(22)- (**169a**,**b**) and C(23)-nitrile oxides (**170a–d**).



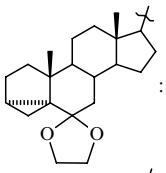
169a,**b**

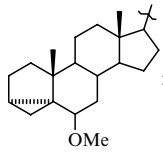
R^1 =  (**a**),  (**b**);

R^2 = CH_2OH, CH_2OAc, CMe_2OH, Ac, CH_2Br, Pr^i.



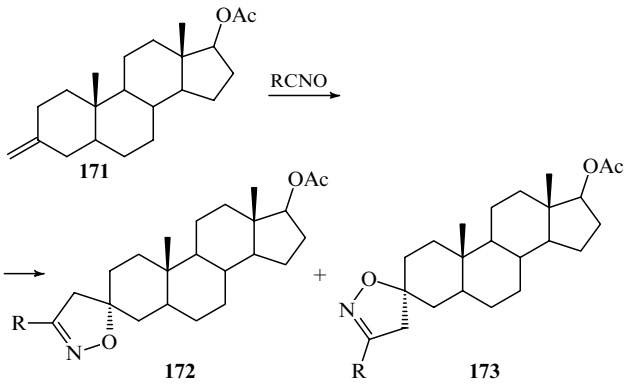
170a–d

R^1 =  : X = H (**a**), OAc (**b**);

R^1 =  : X = H (**c**), OAc (**d**);

R^2 = H, R^3 = Me; R^2 = Me, R^3 = Pr^i.

The reactions of 3-methylidene-17-acetoxyandrostane (**171**) with aceto- and benzonitrile oxides gave mixtures of 3α- and 3β-isomers of the spiro derivatives **172** and **173** with the predominance of the former isomers (2.5–3) : 1.[145,146] The reactions of the steroid **171** with nitrile oxides RCNO, where R = $EtCO_2$, 2,4,6-$Me_3C_6H_2$, always give the only cycloaddition products, *viz*., the 3α-isomers **172** (yields 60% and 25%, respectively). The addition of triphenylacetonitrile oxide to alkene **171** yields a 1 : 1 mixture of two epimeric 4,5-dihydroisoxazoles in a total yield of 87%.[147]



171 **172** **173**

R = Me, Ph, Mes, CO_2Et, Ph_3C.

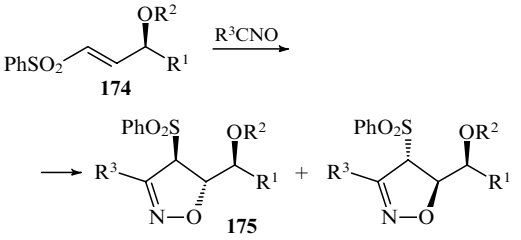
It was reported [145] that 1,3-dipolar cycloaddition of nitrile oxides to 17-methylidene steroids gives regioisomeric 4,5-dihydroisoxazoles *spiro*-conjugated to the steroid fragment in position 17. However, the configuration of the C(17) centre of the steroid has not been established (yield 60% – 70%).[145]

The stereochemistry of 1,3-dipolar cycloaddition of nitrile oxides to steroidal compounds with an endocyclic double bond is usually determined by the attack of the nitrile oxide from the less protected α-region of the steroid. Thus cycloaddition of arenecarbonitrile oxides to the spirost-5-ene derivatives [148] is regio- and stereoselective and results in 3′-substituted [5α,6α-*d*]-4,5-dihydroisoxazoles.

The published data concerning the addition of nitrile oxides to the Δ^{16}-bond of steroids are controversial.[149–155] In some cases, only [17α,16α-*d*]-4,5-dihydroisoxazoles or [16α,17α-*d*]-4,5-dihydroisoxazoles are exclusively formed, but the formation of two regioisomers was also reported. The composition of reaction products depends on the structure of the 1,3-dipole and the method used for its generation. It is of note that sometimes the Δ^5-bond and the cross-conjugated (3-oxo-1,4-diene) system are not involved in this reaction.

XI. Other examples of cycloaddition of nitrile oxides to acyclic alkenes

It was noted [105, 156, 157] that 1,3-dipolar cycloaddition of some achiral vinyl sulfones to nitrile oxides studied previously proceeds without any noticeable regioselectivity.

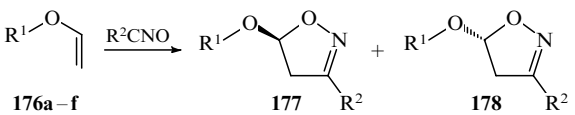


174 **175**

R^1 = Et, Pr^i; R^2 = Ac, MOM, Bu^tMe_2Si; R^3 = Me, Ph.

The reaction of the chiral vinyl sulfones **174** with nitrile oxides does not go to completion even in the presence of a large excess of the 1,3-dipole (the conversion is 36% – 68%).[158] In this case, only the regioisomers with the phenylsulfonyl group at C(4) are formed. The stereoselectivity of this reaction depends on the nature of substituents in both the alkene and nitrile oxide, however, the *anti*-adducts **175** are always predominant and in the case of the bulky substituents R^1 and R^2 they are virtually the only isolated products,[158] which is in agreement with the Houk model.

The first attempts at cycloaddition of nitrile oxides to the homochiral vinyl ethers **176a–f** [159] resulted in reaction products in low yields and with low diastereoselectivities.[160]

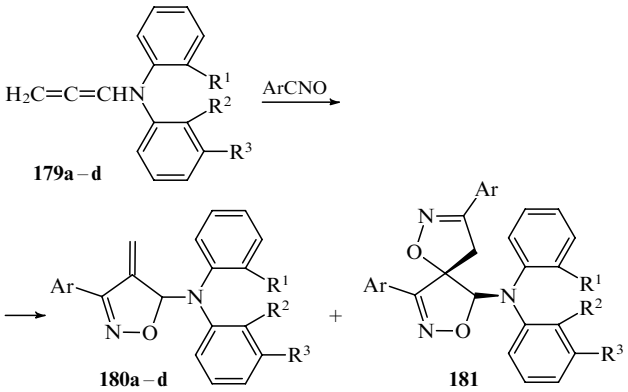


176a–f **177** **178**

R^1 = (–)-menthyl (**a**), 8-phenylmenthyl (**b**), (1*S*)-*endo*-bornyl (**c**), (*R*)-PhCH(CO_2Me) (**d**), (*S*)-1-(2-naphthyl)ethyl (**e**), (*S*)-1-phenylbutyl (**f**);
R^2 = Me, Et, Pr^n, Bu^t, Ph, $Ph(CH_2)_2$, 4-$NO_2C_6H_4$.

The best results were obtained for the vinyl ether **176e**,[161] *viz*., the ratio of the isomers **177** : **178** is (3–4) : 1 in reactions with almost all nitrile oxides. X-Ray diffraction data suggest that compounds **177** with the *R*-configurations of the newly formed chiral centres at the C(5) atoms are the predominant isomers.

1,3-Dipolar cycloaddition of nitrile oxides to allenes yields several reaction products.[162] The reaction of *N*,*N*-diarylamino allenes **179** with 1 equiv. of 3,5-dichloro-2,4,6-trimethylbenzonitrile oxide gives the adduct **180** with the involvement of the α,β-double bond and a small amount of the spirobisadduct **181**.[163]

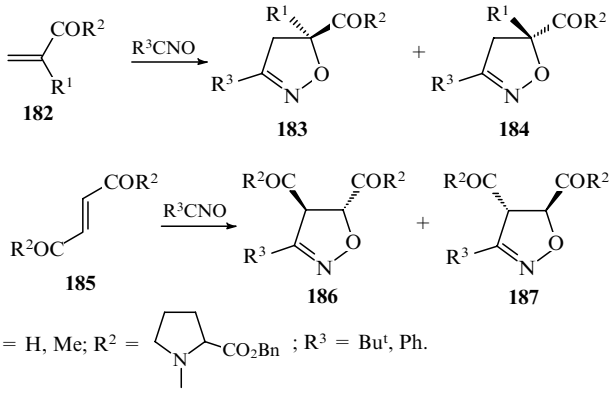


179a–d **180a–d** **181**

R^1 = R^2 = R^3 = H (**a**); R^1 – R^2 = $(CH_2)_2$, R^3 = H (**b**);
R^1 – R^2 = CH = CH, R^3 = H (**c**); R^1 = R^2 = H, R^3 = Me (**d**);
Ar = 3,5-Cl_2-2,4,6-Me_3C_6.

The reaction of the allenes **179** with 2 equivs. of the nitrile oxide gives only spiro compounds **181**. The α,β-double bond in the allenes **179** is more reactive due to the activating and polarisation effects of the nitrogen-containing substituent, which also controls the regio- and stereoselectivity of this reaction.

It was shown [164] that the fragment of proline benzyl ester plays the role of an effective chiral auxiliary group in the asymmetric addition of nitrile oxides to the alkenes **182**. This gives a mixture of the isomers **183** and **184** with the predominance of the former isomer. The regioselectivity does not depend on the reaction temperature and the nature of the substituent R^1. The reaction of the alkene **185** with benzo- and pivalonitrile oxides yields the adducts **186** and **187** in 10 : 1 and 9 : 1 ratios, respectively.[164]

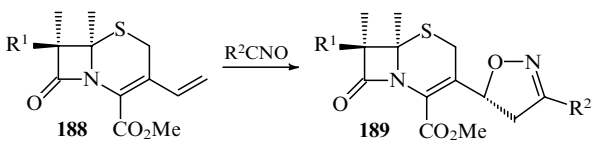


182 **183** **184**

185 **186** **187**

R^1 = H, Me; R^2 = ; R^3 = Bu^t, Ph.

3-Vinylcephalosporins **188** were used in the synthesis of novel 3-substituted cephalosporins **189**.[165] It was found that compounds **188** do not react with nitrile oxides generated from nitroalkanes under the action of phenyl isocyanate in the presence of triethylamine or *N*,*N*,*N*′,*N*′-tetramethylurea.

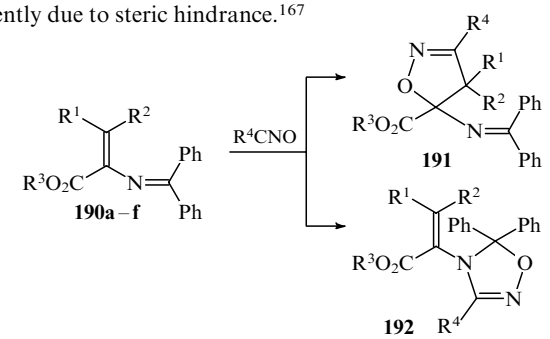


188 **189**

R^1 = BnCONH, $PhOCH_2CONH$; R^2 = Me, Et.

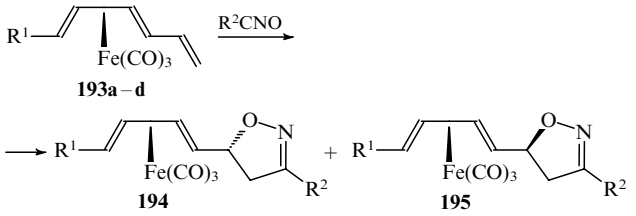
4,5-Dihydroxyisoxazoles **189** could be synthesised by the reaction of alkenes **188** with silyl nitronates as synthetic equivalents of nitrile oxides. These reactions result in *N*-silyloxyisoxazolidines which undergo spontaneous elimination of the trimethylsilanol group to yield 4,5-dihydroisoxazoles **189**; this reaction is regio- and stereoselective.

The simultaneous presence of C=C and C=N bonds in the molecule poses the problem of chemoselectivity.[166] Thus benzonitrile oxide and pivalonitrile oxide react with the heterodienes **190a**,**b** containing a terminal C=C bond to give the substituted 4,5-dihydroisoxazoles **191** in good yields. The cycloaddition of benzonitrile oxide to the β-substituted substrates **190c**–**e** involves exclusively the C = N bond resulting in 4,5-dihydro-1,2,4-oxadiazoles **192**. In this case, *E*-isomers react faster than *Z*-isomers. Compounds **190c**–**f** do not react with pivalonitrile oxide, apparently due to steric hindrance.[167]



$R^1 = R^2 = H$: R^3 = Me (**a**), Et (**b**); R^1 = Me, $R^2 = H$, R^3 = Me (**c**); $R^1 = H$, $R^2 = R^3$ = Me (**d**); R^1 = Ph, $R^2 = H$, R^3 = Me (**e**); $R^1 = H$, R^2 = Ph, R^3 = Me (**f**); R^4 = Ph, Bu^t.

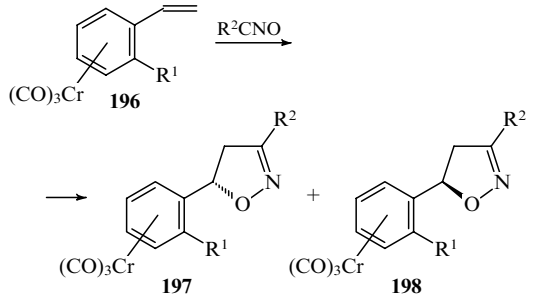
The irontricarbonyl complexes **193a**–**d** can be used to prepare 4,5-dihydroisoxazoles with a high degree of stereoselectivity.[168] This reaction results in the predominant formation of the epimers **194** [**194** : **195** = (7–9) : 1]. It is noteworthy that the formation of the isomers **195** is explained [168] by the presence of *cis*-rotamers in the original complexes **193**.



R^1 = Me (**a**), Et (**b**), Bu^t (**c**), Ph (**d**); R^2 = Me, CO_2Me, $CH_2OSiPh_2Bu^t$.

The chiral synthesis of (+)-(*S*)-[6]-gingerol was performed using the complex **193a**.[169]

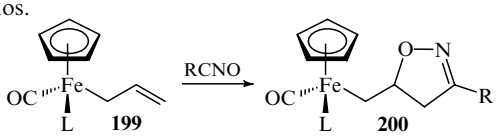
It was shown that the use of the chromiumtricarbonyl complexes of the styrene derivatives **196** in the reaction with 3,5-dichloro-2,4,6-trimethyl-benzonitrile oxide results in the stereoselective synthesis of the adducts **197** with the *S*-configurations of the newly formed chiral centres at the C(5) atoms.[170] It is of note that the reaction of nitrile oxides with styrene proceeds in a non-stereoselective manner.

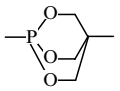


R^1 = OMe, Me, Cl; R^2 = 3,5-Cl_2-2,4,6-Me_3C_6.

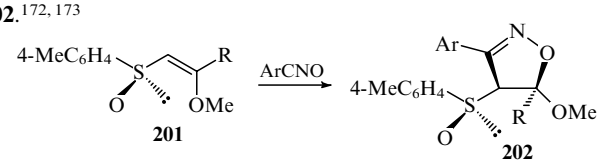
R^1	Ratio **197** : **198**
OMe	80 : 20
Me	98 : 2
Cl	96 : 4

The cycloaddition of nitrile oxides to the η^1-allyliron complexes **199** [171] yields mixtures of 4,5-dihydroisoxazoles **200**. In the case of the chiral complexes **199b**,**c**, mixtures of diastereomeric 4,5-dihydroisoxazoles **200b**,**c**,**e**,**f** are formed in (59–93) : (41–7) ratios.



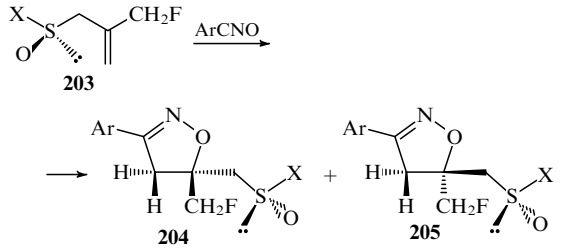
R = Ph: L = CO (**a**),  (**b**), PPh_3 (**c**); R = Mes: L = CO (**d**);  (**e**), PPh_3 (**f**).

The 1,3-dipolar addition of arenecarbonitrile oxides to the chiral vinyl sulfoxides **201** occurs with high regio- and stereoselectivity and results in (4*S*,5*R*,R_S)-4,5-dihydroisoxazoles **202**.[172, 173]



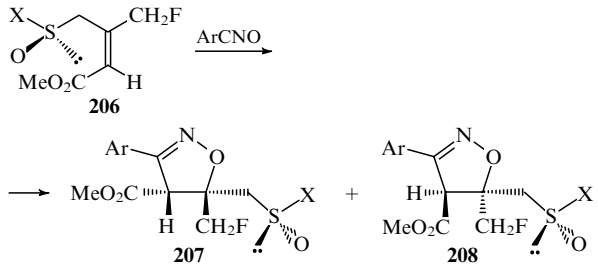
R = CH_2F, CHF_2, CF_3, C_2F_5;
Ar = Ph, 2,6-$Cl_2C_6H_3$, 3,5-Cl_2-2,4,6-Me_3C_6.

The effect of the sulfinyl group is much less pronounced if the latter is in the β-position relative to the double bond.[174] This reaction is characterised by full regioselectivity but moderate stereoselectivity and results in the formation of chiral 4,5-dihydroisoxazoles. Thus, the addition of 3,5-dichloro-2,4,6-trimethylbenzonitrile oxide to the allylic sulfoxide **203** results in the diastereomers **204** and **205** in a 1.4 : 1 ratio.[174]



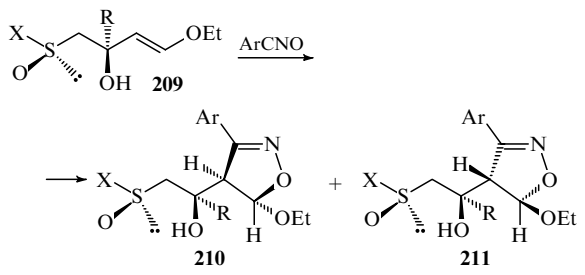
X = 4-MeC_6H_4; Ar = 3,5-Cl_2-2,4,6-Me_3C_6.

A mixture of the diastereomers **207** and **208** (2 : 1) is formed in the reaction of (*Z*)-allylic sulfoxide **206** with 3,5-dichloro-2,4,6-dimethylbenzonitrile oxide.



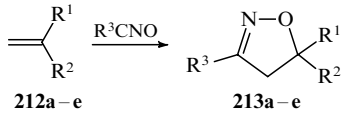
X = 4-MeC_6H_4; Ar = 3,5-Cl_2-2,4,6-Me_3C_6.

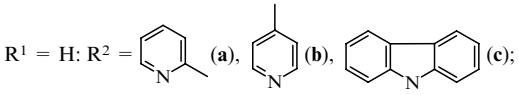
The dipolarophiles **209** have two chiral centres, *viz*., the sulfinyl group and the oxygen-containing substituent in the allylic position. Both functional groups influence the stereochemistry of the 1,3-dipolar cycloaddition.[175] The reactions of compounds (3*S*,R_S)-**209** with arenecarbonitrile oxides give mixtures of 4,5-dihydroisoxazoles **210** and **211**. In all cases studied, the epimers **210** were predominant (up to 67%).



X = 4-MeC_6H_4; R = CF_3, CF_2Cl;
Ar = 3,5-Cl_2-2,4,6-Me_3C_6, 2,6-$Cl_2C_6H_3$.

It was found [176, 177] that baker's yeast *Saccharomyces cerevisiae* are effective chiral catalysts in reactions of asymmetric cycloaddition of nitrile oxides. Thus the addition of nitrile oxides to alkenes **212a–c** in the presence of baker's yeast and cyclodextrin gives 4,5-dihydroisoxazoles **213a–c** with high stereoselectivity.





R^1 = H: R^2 = (**a**), (**b**), (**c**);

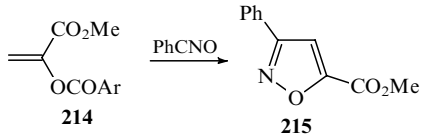
R^1 = Me: R^2 = CN (**d**), CO_2Me (**e**);

R^3 = Mes, 2,6-$Cl_2C_6H_3$, 2,4,6-$(MeO)_3C_6H_2$;

The electron-deficient dipolarophiles **212d,e** also gave optically active 4,5-dihydroisoxazoles **213d,e**.[178]

However, some authors [179] argue against this conclusion assuming that the isolation of only one enantiomer is due to the loss of the second enantiomer in the recrystallisation.

It was noted that cycloaddition of nitrile oxides to captodative alkenes **214** occurs in a regioselective manner and results in the isoxazoles **215**.[180] Here, alkenes **214** behave as acetylene equivalents.



* * *

Thus, 1,3-dipolar cycloaddition of nitrile oxides to the double bond can be applied to various classes of compounds. In the majority of cases, this occurs with good yields and high regio- and, sometimes, stereoselectivity which allows its use for the solution of complex problems of organic synthesis. The reaction products, *viz*., 4,5-dihydroisoxazoles, present interest from the standpoint of their biological activities.[181, 182] In our opinion, further investigations into the cycloaddition of nitrile oxides to alkenes will be associated with the search for novel catalysts and chiral substituents for regio- and stereo-controlled addition.

References

1. C Grundmann, P Grunanger *The Nitrile Oxides* (New York: Springer, 1971)
2. A P Kozikowski *Acc. Chem. Res.* **17** 410 (1984)
3. P G Baraldi, A Barco, S Benetti, G P Pollini, D Simoni *Synthesis* 857 (1987)
4. F A Lakhvich, E V Koroleva, A A Akhrem *Khim. Geterotsikl. Soedin.* 435 (1989) [a]
5. D P Curran *Adv. Cycloadd.* **1** 129 (1988)
6. A A Akhrem, V A Khripach, F A Lakhvich, M I Zavadskaya, O A Drachenova, I A Zorinayu *Zh. Org. Khim.* **25** 2120 (1989) [b]
7. T Mukaijama, T Hoshino *J. Am. Chem. Soc.* **82** 5339 (1960)
8. K E Larsen, K B G Torssell *Tetrahedron* **40** 2985 (1984)
9. E Malamidou-Xenikaki, X N Stampelos, E Coutouli-Argyropoulou *J. Heterocycl. Chem.* **33** 563 (1996)
10. Yu Tokunaga, M Ihara, K Fukumoto *Heterocycles* **43** 1771 (1996)
11. G Kumaran, G H Kulkarni *J. Org. Chem.* **62** 1516 (1997)
12. O Moriya, H Takenaka, Y Urata, T Endo *J. Chem. Soc., Chem. Commun.* 1671 (1991)
13. A Baranski, E Cholewka *Pol. J. Chem.* **65** 319 (1991)
14. M H D Postema *Tetrahedron* **48** 8545 (1992)
15. J I Levin, P S Chan, J Couplet, T K Bailey, G Vice, L Thibauet, F Lai, A M Venkatesan, A Cobuzzi *Bioorg. Med. Chem. Lett.* **4** 1703 (1994)
16. C W Holzapfel, K Bischofberger, J Olivier *Synth. Commun.* **24** 3197 (1994)
17. A Studer, D P Curran *Tetrahedron* **53** 6681 (1997)
18. K Halling, K B G Torssell, R G Hazell *Acta Chem. Scand.* **45** 736 (1991)
19. G Burton, G J Clarke, J D Douglas, A J Eglington, C H Frydrych, J D Hinks, N W Hird, E Hunt, S F Moss, A Naylor, N H Nicholson, M J Pearson *J. Antibiot.* **49** 1266 (1996)
20. R Alguacil, F Farina, M V Martin *Tetrahedron* **52** 3457 (1996)
21. D P Curran, T A Heffner *J. Org. Chem.* **55** 4585 (1990)
22. K Bast, M Christl, R Huisgen, W Mack, R Sustman *Chem. Ber.* **106** 3258 (1973)
23. K Bast, M Christl, R Huisgen, W Mack *Chem. Ber.* **106** 3312 (1973)
24. J Mann, B Pietrzak *Tetrahedron* **45** 1549 (1989)
25. D N Nicolaides, K C Fylaktakidou, K E Litinas *J. Heterocycl. Chem.* **33** 967 (1996)
26. T-J Lu, L-J Sheu *J. Chin. Chem. Soc. (Taipei)* **42** 877 (1995)
27. A P Kozikowski, Y Kitagawa, J P Springer *J. Chem. Soc., Chem. Commun.* 1460 (1983)
28. R H Jones, G C Robinson, E J Thomas *Tetrahedron* **40** 177 (1984)
29. D A Barr, M J Dorrity, R Grigg, J F Malone, J Montgomeri, S Rajviroonigit, P Stevenson *Tetrahedron Lett.* **31** 6569 (1990)
30. A P Kozikowski, A P Cheng *Tetrahedron Lett.* **28** 3189 (1987)
31. D P Curran, S A Gothe *Tetrahedron* **44** 3945 (1988)
32. V Jiger, I Muller, R Schohe, M Frey, R Ehrler, B Hafele, D Schroter *Lect. Heterocycl. Chem.* **8** 79 (1985)
33. V Jiger, R Schohe, E F Paulus *Tetrahedron Lett.* **24** 5501 (1983)
34. A P Kozikowski, A K Ghosh *J. Org. Chem.* **49** 2762 (1984)
35. A P Kozikowski, A K Ghosh *J. Am. Chem. Soc.* **104** 5788 (1982)
36. M B Gravestock, R M Paton, C J Todd *Tetrahedron Asymmetry* **6** 2723 (1995)
37. P Caramella, N G Rondan, M N Paddon-Row, K N Houk *J. Am. Chem. Soc.* **103** 2438 (1981)
38. A Kamimura *J. Synth. Org. Chem. Jpn.* **50** 808 (1992)
39. K N Houk, S R Moses, Y-D Wu, N G Rondan, V Jiger, R Schohe, R Fronczek *J. Am. Chem. Soc.* **106** 3880 (1984)
40. K N Houk, H-Y Duh, Y-D Wu, S R Moses *J. Am. Chem. Soc.* **108** 2754 (1986)
41. J Chanet-Ray, M O Charmier-Januario, S Chou, R Vessiere *J. Chem. Res. (S)* 382 (1994)
42. V Jäger, R Müller, T Leibold, M Hein, M Schwarz, M Fengler, L Jaroskova, M Paetzel, P LeRoy *Bull. Soc. Chim. Belg.* **103** 491 (1994)
43. N G Rondan, M N Paddon-Row, P Caramella, J Mareda, P H Muller, K N Houk *J. Am. Chem. Soc.* **104** 4974 (1982)
44. R Annunziata, M Benaglia, M Cinquini, L Raimondi *Tetrahedron* **49** 8629 (1993)
45. D P Curran, B H Kim *Synthesis* 312 (1986)
46. E Lukevics, V Dirnens, A Kemme, J Popelis *J. Organomet. Chem.* **521** 235 (1996)
47. R Annunziata, M Benaglia, M Cinquini, F Cozzi, L Raimondi *J. Org. Chem.* **60** 4697 (1995)
48. G Keum, Y J Chung, B H Kim *Bull. Korean Chem. Soc.* **13** 343 (1992)
49. T Moriwake, S Hamano, S Saito, S Torii *Chem. Lett.* 2085 (1987)
50. S Fushiya, H Chiba, A Otsubo, S Nozoe *Chem. Lett.* 2229 (1987)
51. E C Boyd, R M Paton *Tetrahedron Lett.* **34** 3169 (1993)

52. A J Blake, E C Boyd, R O Gould, R M Paton *J. Chem. Soc., Perkin Trans. 1* 2841 (1994)
53. D P Curran, S-M Choi, S A Gothe, F-t Lin *J. Org. Chem.* **55** 3710 (1990)
54. T Nishi, Y Morisawa *Heterocycles* **29** 1835 (1989)
55. A A Hagedorn III, B J Miller, J O Nagy *Tetrahedron Lett.* **21** 229 (1980)
56. P A Wade, S M Singh, M K Pillay *Tetrahedron* **40** 601 (1984)
57. A P Kozikowski, X M Cheng *Tetrahedron Lett.* **26** 4047 (1985)
58. D M Vyas, Y Chiang, T W Doyle *Tetrahedron Lett.* **25** 487 (1984)
59. D P Curran, S A Gothe, S M Choi *Heterocycles* **35** 1371 (1993)
60. W Oppolzer, G Poli, C Starkemann, G Bernardinelli *Tetrahedron Lett.* **29** 3559 (1988)
61. D P Surran, B H Kim, H P Piyasena, R J Loncharich, K N Houk *J. Org. Chem.* **52** 2137 (1987)
62. T Akiyama, H Nishimoto, K Ishikawa, S Ozaki *Chem. Lett.* 447 (1992)
63. T Akiyama, K Okada, S Ozaki *Tetrahedron Lett.* **33** 5763 (1992)
64. L Zhang, J C Chung, T D Costello, I Valvis, P Ma, S Kauffman, R Ward *J. Org. Chem.* **62** 2466 (1997)
65. T Olsson, K Stern, G Westman, S Sundell *Tetrahedron* **46** 2473 (1990)
66. T Olsson, K Stern, S Sundell *J. Org. Chem.* **53** 2468 (1988)
67. M A Weidner-Wells, S A Fraga, J P Demers *Tetrahedron Lett.* **35** 6473 (1994)
68. D P Surran, B H Kim, J Daugherty, T A Heffner *Tetrahedron Lett.* **29** 3555 (1988)
69. D P Curran, K Jeong, T A Heffner, J Rebek *J. Am. Chem. Soc.* **111** 9238 (1989)
70. S Kanemasa, K Onimura *Tetrahedron* **48** 8645 (1992)
71. B H Kim, J Y Lee *Tetrahedron Asymmetry* **2** 1359 (1991)
72. B H Kim, D P Curran *Tetrahedron* **49** 293 (1993)
73. S Kanemasa, K Onimura *Tetrahedron* **48** 8631 (1992)
74. W Oppolzer *Tetrahedron* **43** 1969 (1987)
75. K S Kim, B H Kim, W M Park, S J Cho, B J Mhin *J. Am. Chem. Soc.* **115** 7472 (1993)
76. J A Stack, T A Heffner, S J Geib, D P Curran *Tetrahedron* **49** 995 (1993)
77. D P Curran, M-H Yoon *Tetrahedron* **53** 1971 (1997)
78. S Kanemasa, T Hayashi, H Yamamoto, E Wada, T Sakurai *Bull. Chem. Soc. Jpn.* **64** 3274 (1991)
79. S Kanemasa, K Onimura, E Wada, J Tanaka *Tetrahedron Asymmetry* **2** 1185 (1991)
80. Y H Kim, S H Kim, D H Park *Tetrahedron Lett.* **34** 6063 (1993)
81. C Kashima, I Fukuchi, K Takahashi, A Hosomi *Tetrahedron Lett.* **34** 8305 (1993)
82. C Kashima, K Takahashi, I Fukuchi, K Fukusaka *Heterocycles* **44** 289 (1997)
83. B H Kim, Y J Chung, G Keum, J Kim, K Kim *Tetrahedron Lett.* **33** 6811 (1992)
84. A G Meyer, C J Easton, S F Lincoln, G W Simpson *Chem. Commun.* 1517 (1997)
85. P C B Page, M Purdie, D Lathbury *Tetrahedron* **53** 1061 (1997)
86. S Kanemasa, M Nishiuchi, A Kamimura, K Hori *J. Am. Chem. Soc.* **116** 2324 (1994)
87. S Kanemasa, S Kabayashi, M Nishiuchi, H Yamamoto, E Wada *Tetrahedron Lett.* **32** 6367 (1991)
88. S Kanemasa, M Nishiuchi *Tetrahedron Lett.* **34** 4011 (1993)
89. S Kanemasa, S Kobayashi *Bull. Chem. Soc. Jpn.* **66** 2685 (1993)
90. H R Kim, J H Song, S Y Rhie, E K Ryu *Synth. Commun.* **25** 1801 (1995)
91. J N Kim, H R Kim, E K Ryu *Synth. Commun.* **23** 1673 (1993)
92. G Bianchi, C De Micheli, R Gandolfi, P Grunanger, P V Finzi, O V de Pava *J. Chem. Soc., Perkin Trans. 1* 1148 (1973)
93. S Kanemasa, M Nichiuchi, E Wada *Tetrahedron Lett.* **33** 1357 (1992)
94. S Kanemasa, K Okuda, H Yamamoto, S Kaga *Tetrahedron Lett.* **38** 4095 (1997)
95. F De Sarlo, A Guarna, A J Brandi *J. Heterocycl. Chem.* **20** 1505 (1983)
96. T-Y Lu, J-F Yang, L-J Sheu *J. Org. Chem.* **60** 7701 (1995)
97. A Kamimura, K Hori *Tetrahedron* **50** 7969 (1994)
98. R Annunziata, M Cinquini, F Cozzi, L Raimondi *Tetrahedron* **44** 4645 (1988)
99. A Pelter, K Smith, H C Brown *Borane Reagents* (London: Academic Press, 1988)
100. M Jazouli, B Carboni, R Carrie, M Soufiaoui, L Toupet *J. Heteroatom. Chem.* **5** 513 (1994)
101. M Jazouli, S Baba, B Carboni, R Carrie, M Soufiaoui *J. Organomet. Chem.* **498** 229 (1995)
102. J D Bonk, M D Avery *Tetrahedron Asymmetry* **8** 1149 (1997)
103. D A Singleton, J P Martinez, G M Ndip *J. Org. Chem.* **57** 5768 (1992)
104. D S Matteson *J. Org. Chem.* **27** 4293 (1962)
105. R H Wallace, J Liu *Tetrahedron Lett.* **35** 7493 (1994)
106. M Barzaghi, P L Beltrame, P D Croce, P D Buttero, E Licandro, S Maiorana, G Zecchi *J. Org. Chem.* **48** 3807 (1983)
107. R H Wallace, K K Zong *Tetrahedron Lett.* **33** 6941 (1992)
108. A Zhang, Y Kan, G Zhao, B Jiang *Tetrahedron* **56** 965 (2000)
109. A Brandi, P Cannavo, K M Pietrusiewicz, M Zablocka, M Wieczorek *J. Org. Chem.* **54** 3073 (1989)
110. S K Armstrong, E W Collington, J G Kight, A Naylor *J. Chem. Soc., Perkin Trans. 1* 1433 (1993)
111. R M Paton, A A Young *J. Chem. Soc., Chem. Commun.* 132 (1991)
112. R M Paton, A A Young *J. Chem. Soc., Perkin Trans. 1* 629 (1997)
113. A J Blake, R O Gould, K E McGhie, R M Paton, D Reed, I H Sadler, A A Young *Carbohydr. Res.* **216** 461 (1991)
114. M De Amici, C De Micheli, A Ortisi, G Gatti, R Gandolfi, L Toma *J. Org. Chem.* **54** 793 (1989)
115. A J Blake, G Kirkpatrick, K E McGhie, R M Paton, K J Penman *J. Carbohydr. Chem.* **13** 409 (1994)
116. A J Blake, R O Gould, R M Paton, A A Young *J. Chem. Res. (S)* 482 (1993)
117. R M Paton, A A Young *J. Chem. Soc., Chem.Commun.* 993 (1994)
118. R M Paton, K J Penman *Tetrahedron Lett.* **35** 3163 (1994)
119. K E McGhie, R M Paton *Tetrahedron Lett.* **34** 2831 (1993)
120. M Mancera, I Roffe, J A Galbis *Tetrahedron* **51** 6349 (1995)
121. H -J Gi, Y Xiang, K Zhao *J. Org. Chem.* **62** 88 (1997)
122. Y Xiang, J Chen, R F Schinazi, K Zhao *Bioorg. Med. Chem. Lett.* **6** 1051 (1996)
123. A V Baranovskii, R P Litvinovskaya, V A Khripach *Zh. Org. Khim.* **26** 1274 (1990) [b]
124. R P Litvinovskaya, S V Drach, Yu I Lapchinskaya, V A Khripach *Zh. Org. Khim.* **37** 57 (2001) [b]
125. R P Litvinovskaya, A S Lyakhov, S V Drach, V A Khripach, A A Govorova *Zh. Obshch. Khim.* **70** 1571 (2000) [c]
126. H G Cutler, T Yokota, G Adam (Eds) *Brassinosteroids: Chemistry, Bioactivity and Applications* (Washington, DC: American Chemical Society 1991)
127. R K Tkhaper, I G Reshetova, A V Kamernitskii, R P Litvinovskaya *Izv. Akad. Nauk SSSR, Ser. Khim.* 969 (1991) [d]
128. USSR P. 1 747 455; *Byull. Izobret.* (26) 80 (1992)
129. Russ. P. 1 786 807; *Byull. Izobret.* (3) 321 (1996)
130. V A Khripach, R P Litvinovskaya, S V Drach *Zh. Org. Khim.* **29** 717 (1993) [b]
131. R P Litvinovskaya, N V Koval', V A Khripach *Khim. Geterotsikl. Soedin.* 267 (1998) [a]
132. A I Verenich, A A Govorova, N M Galitskii, A V Baranovskii, R P Litvinovskaya, V A Khripach *Zh. Strukt. Khim.* 552 (1992) [e]
133. A A Akhrem, V A Khripach, R P Litvinovskaya, A V Baranovskii, M I Zavadskaya, A N Kharitonovich, E V Borisov, F A Lakhvich *Zh. Org. Khim.* **25** 1901 (1989) [b]
134. R P Litvinovskaya, S V Drach, V A Khripach *Mendeleev Commun.* 215 (1995)
135. R P Litvinovskaya, V A Tereshko, S V Drach, V A Khripach *Zh. Obshch. Khim.* **66** 859 (1996) [c]
136. R P Litvinovskaya, A S Lyakhov, A A Govorova, S V Drach, V A Khripach *Bioorg. Khim.* **23** 147 (1997) [f]
137. R P Litvinovskaya, S V Drach, V A Khripach *Zh. Org. Khim.* **35** 1653 (1999) [b]
138. R P Litvinovskaya, S V Drach, V A Khripach *Zh. Org. Khim.* **36** 1838 (2000) [b]
139. R P Litvinovskaya, S V Drach, E A Ermolenko, V A Khripach *Zh. Org. Khim.* **34** 1037 (1998) [b]
140. V A Khripach, V N Zhabinskii, N D Pavlovskii *Zh. Org. Khim.* **35** 390 (1999) [b]
141. V A Khripach, V N Zhabinskii, A I Kotyatkina *Zh. Org. Khim.* **29**1569 (1993) [b]

142. R P Litvinovskaya, Doctoral Thesis in Chemical Sciences, Institute of Bioorganic Chemistry, National Academy of Sciences of Belarus, Minsk, 1998
143. R P Litvinovskaya, S V Drach, V A Khripach *Zh. Org. Khim.* **33** 201 (1997) [b]
144. V A Khripach, V N Zhabinskii, N D Pavlovskii *Zh. Org. Khim.* **34** 59 (1998) [b]
145. C Parini, S Colombi, A Ius, R Longhi, G Vecchio *Gazz. Chim. Ital.* **107** 559 (1977)
146. J Kalvoda, H Kaufmann *J. Chem. Soc., Chem. Commun.* 209 (1976)
147. H Kaufmann, J Kalvoda *J. Chem. Soc., Chem. Commun.* 210 (1976)
148. A U Siddiqui, A H Siddiqui, T S Ramaiah *J. Indian Chem. Soc.* **69** 282 (1992)
149. W Fritsch, G Seidl, H Ruschig *Liebigs Ann. Chem.* **677** 139 (1964)
150. U Stache, W Fritsch, H Ruschig *Liebigs Ann. Chem.* **685** 228 (1965)
151. G W Moersch, E L Wittle, W A Neuklis *J. Org. Chem.* **43** 1272 (1965)
152. T Kwon, A S Heiman, E T Oriaku, K Yoon, H J Lee *J. Med. Chem.* **38** 1048 (1995)
153. M Khalil, M F Maponya, D H Ko, Z You, E I Oriaku, H J Lee *Med. Chem. Res.* 52 (1996)
154. A Ius, C Parini, G Sportoletti, G Vecchio, G Ferrara *J. Org. Chem.* **36** 3470 (1971)
155. T Kametani, H Furuyuma, T Honda *Heterocycles* **19** 357 (1982)
156. P Saramella, E Albini, T Bandiera, A C Coda, P Grunanger, F M Albini *Tetrahedron* **39** 689 (1983)
157. A Bened, R Durand, D Pioch, P Geneste *J. Org. Chem.* **47** 2461 (1982)
158. J De Blas, J C Carretero, E Dominguez *Tetrahedron Asymmetry* **6** 1035 (1995)
159. T V Rajan Babu, G S Reddy *J. Org. Chem.* **51** 5458 (1986)
160. A N Boa, S E Booth, D A Dawkins, P R Jenkins, J Fawcett, D R Russell *J. Chem. Soc., Perkin Trans. 1* 1277 (1993)
161. A N Boa, D A Dawkins, A R Hergueta, P R Jenkins *J. Chem. Soc., Perkin Trans. 1* 953 (1994)
162. G Broggini, G Zecchi *Gazz. Chim. Ital.* **126** 479 (1996)
163. G Broggini, G Molteni, G Zecchi *J. Chem. Res. (S)* 203 (1993)
164. H Waldmann *Liebigs Ann. Chem.* 1013 (1990)
165. J Pitlik *Synth. Commun.* **24** 243 (1994)
166. C Balzamini, G Spadoni, A Bedini, M Lanfranchi, M Pellinghelli *J. Heterocycl. Chem.* **29** 1593 (1992)
167. G Spadoni, C Balsamini, A Bedini, E Duranti, Tontini *J. Heterocycl. Chem.* **29** 305 (1992)
168. T LeGall, J-P Lellouche, L Toupet, J-P Beaucourt *Tetrahedron Lett.* **30** 6517 (1989)
169. T LeGall, J-P Lellouche, J-P Beaucourt *Tetrahedron Lett.* **30** 6521 (1989)
170. C Baldoli, P Buttero, S Maiorana, G Zecchi *Tetrahedron Lett.* **34** 2529 (1993)
171. W Malisch, J Zöller, M Schwarz, V Jäger, A M Arif *Chem. Ber.* **127** 1243 (1994)
172. P Bravo, L Bruche, A Merli, G Fronza *Gazz. Chim. Ital.* **124** 275 (1994)
173. P Bravo, L Bruche, M Crucianelli, A Farina, S V Meille, A Merli, P Seresini *J. Chem. Res. (S)* 348 (1996)
174. P Bravo, L Bruche, P Seresini, M Zanda, A Arnone *J. Heterocycl. Chem.* **34** 489 (1997)
175. A Arnone, P Bravo, L Bruche, P Seresini *J. Chem. Res. (S)* 198 (1996)
176. K R Rao, N Bhanumathi, P B Sattur *Tetrahedron Lett.* **31** 3201 (1990)
177. K R Rao, Y V D Nageswar, H M Sampathkumar *J. Chem. Soc., Perkin Trans. 1* 3199 (1990)
178. R K Rao, Y V D Nageswar, N Bhanumathi, T N Srinivasan *Indian J. Chem.* **B33** 171 (1994)
179. C J Easton, C M Hughes, E R Tiekink *Tetrahedron Lett.* **36** 629 (1995)
180. R Jimenez, L Perez, J Tamariz, H Salgado *Heterocycles* **35** 591 (1993)
181. Ch Samoutsis, S Nikolaropoulos *J. Heterocycl. Chem.* **35** 731 (1998)
182. S V Drach, R P Litvinovskaya, V A Khripach *Khim. Geterotsikl. Soedin.* 291 (2000) [a]

[a] — *Chem. Heterocycl. Compd. (Engl. Transl.)*
[b] — *Russ. J. Org. Chem. (Engl. Transl.)*
[c] — *Russ. J. Gen. Chem. (Engl. Transl.)*
[d] — *Russ. Chem. Bull. (Engl. Transl.)*
[e] — *J. Struct. Chem. (Engl. Transl.)*
[f] — *Russ. J. Bioorg. Chem. (Engl. Transl.)*