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MINI-REVIEW: ORGANIC CATALYSTS IN THE 1,3-DIPOLAR CYCLOADDITION REACTIONS OF NITRILE OXIDES

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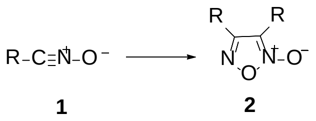
Abstract – In 1961, Huisgen categorized the nitrile oxides (NOs) as a member of a broader class of 1,3-dipoles that were capable of undergoing 1,3-dipolar cycloaddition (DC) reactions. Nevertheless, the cycloaddition (CA) reactions of NOs to alkenes and alkynes are in many cases hampered by the tendency to the dimerization of the NO to the related furoxan (1,2,5-oxadiazole-2-oxide). In addition, although monosubstituted alkenes and alkynes show high regioselectivity in their cycloadditions with NOs, 1,2-disubstituted derivatives often give mixtures of regioisomers. Catalyzed NOs cycloadditions constitute in many cases an appropriate response to these problems and, in particular, the metal catalyzed cycloaddition reactions-have been extensively used. However, the cost, toxicity and removal of trace amounts of the metal residues from desired products is quite costly and challenging, while crucial, especially in the pharmaceutical industry. Obviously, alternative pathways under metal-free conditions to fulfill the metal-catalyzed reactions are highly appealing. The present review is devoted to the consideration of the use of organic molecules as catalysts for 1,3-dipolar cycloaddition reactions of nitrile oxides.

CONTENTS

1. INTRODUCTION AND OBJETIVES

1.1. Nitrile oxides. An overview.

Nitrile oxides (NOs) **1** belong to the class of 1,3-dipoles known as “nitrilium betaines” and are versatile intermediates for the preparation of heterocyclic compounds *via* 1,3-dipolar cycloaddition. Most of NOs are chemically unstable and dimerize readily to form the corresponding furoxans **2** (Scheme 1) *via* a stepwise reaction path involving a quasi diradical dinitrosoalkene intermediate.[1]



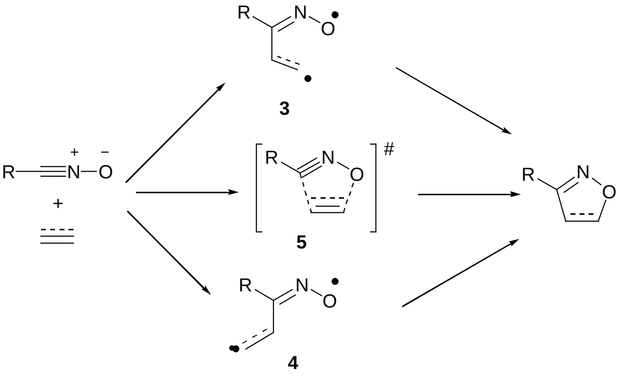
Scheme 1. Dimerisation of NOs

The rate of this dimerisation is exceptionally fast for lower aliphatic NOs, with acetonitrile oxide dimerising in less than one minute, whereas the half-life of most aromatic NOs at room temperature is several hours. Intramolecular bis (nitrile oxide) dimerization has also been reported and synthetically exploited.[2] Stable NOs can be obtained as a result of steric shielding of the nitrile oxide functionality (for instance 2,4,6-trimethylbenzonitrile oxide or 2,4,6-trimethoxybenzonitrile oxide). Donor-acceptor interactions between the atoms of the CNO moiety and adjacent polar substituents and electron delocalization in π-systems also enhance the stability of NOs.

To avoid dimerization, NOs are usually generated *in situ*. There are two frequently utilized methods of generation of NOs.[3] The Mukaiyama method is based on reaction of primary nitroalkanes with phenyl isocyanate and a catalytic amount of triethylamine. The other most frequently used method is base-mediated dehydrohalogenation of hydroximoyl halides obtained by reaction of aldoximes with N-chlorosuccinimide or N-bromosuccinimide, halogens, 1-chlorobenzotriazol, sodium hypochlorite and chloramine-T.

The mechanism of 1,3-DC of NOs to alkenes and alkynes has been object of a vigorous debate. On the basis of kinetic and stereochemical results, Huisgen postulated a concerted but, in some cases, asynchronous, mechanism (**5**, Scheme 2).[4] Dozens of examples of geometrically isomeric dipolarophiles have been tested in the 1,3-DC reactions of NOs and, in all cases, the configuration of the dipolarophile is retained in the cycloadducts. Besides that, additional experimental data such as little influence of solvent polarity on the reaction rate and low enthalpies of activation and large, strongly negative, entropies of activation, seem to confirm that 1,3-DC reactions of NOs proceed *via* a concerted mechanism.

As a mechanistic alternative, Firestone suggested[5] in 1968 a stepwise mechanism involving a *syn*-diradical intermediate **3** (Scheme 2).



Scheme 2. Concerted and stepwise mechanism for the CA of NOs with alkenes and alkynes

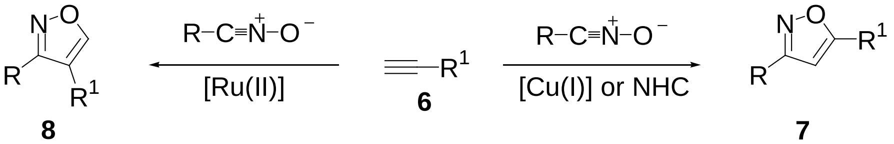
The *syn*-diradical **3** is a short-lived intermediate which undergoes a cyclization before a rotation around the newly formed σ bond. Consequently, retention of the stereochemical information is the expected result if the reaction occurs through this intermediate. Obviously, the stepwise mechanism which proceeds via a long-lived *anti* diradical **4** should be ruled out on the basis of the stereochemical results.[6]

Numerous quantum chemical investigations have been performed to shed light on the mechanism of 1,3-dipolar cycloadditions including NOs cycloadditions and these calculations could solve the Huisgen-Firestone controversy. As a general result it can be indicated that the concerted mechanism is favored for the reactions of the unsubstituted 1,3-dipoles with ethylene and acetylene whereas the stepwise mechanism becomes more favourable when the 1,3-dipoles and dipolarophiles are substituted by radical-stabilizing groups.

1. 2. Catalyzed 1,3-DC of NOs.

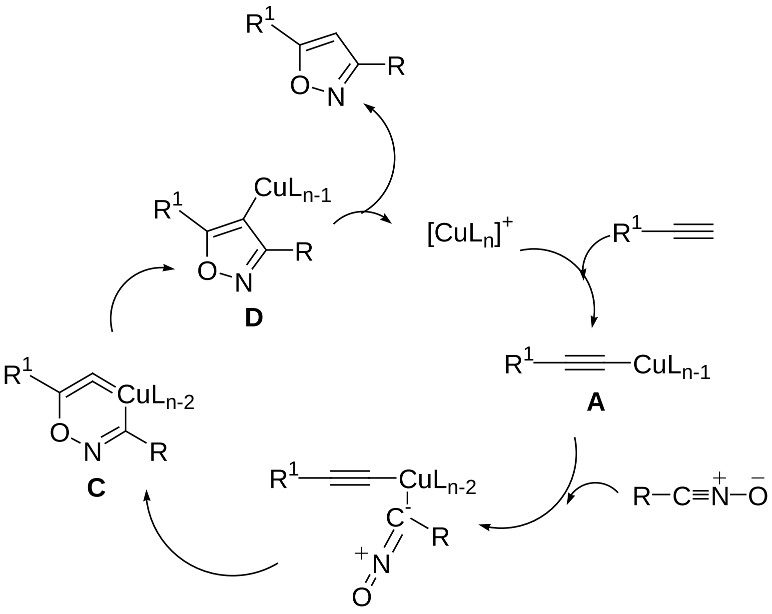
The effects of different catalysts on the rates, regioselectivity and stereoselectivity of cycloaddition reactions have been thoroughly investigated. In general, large rate accelerations and greatly increased regioselectivity and stereoselectivity were observed. In the case of Lewis acids catalysts these phenomena have been rationalized by the application of frontier orbital (FO) theory.[7]

In the case of the cycloadditions between NOs and alkynes regiocomplementary control has been demonstrated in the presence of a copper (I),[8] an *N*-heterocyclic carbene (NCH)[9] or a ruthenium (II) catalysts.[10] Both the copper (I)- and the carbene-mediated reactions promote formation of 3,5-disubstituted isoxazoles **7**, whereas ruthenium (II) catalysis favours 3,4-disubstituted ones **8** (Scheme 3).



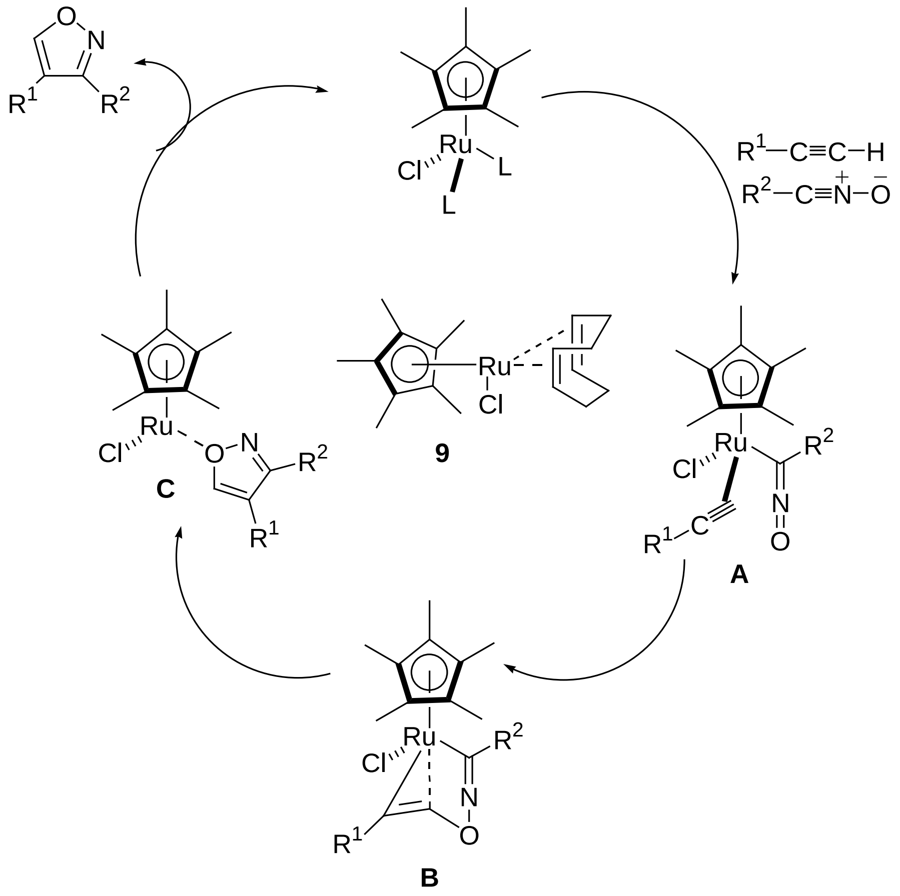
Scheme 3. Catalyst-controlled regioselective cycloaddition reactions between nitrile oxides and terminal alkynes

Regarding the mechanism of the reactions described in the Scheme 3, a few brief descrptions seem appropriate. For the Cu(I) catalyzed reactions, computational studies revealed a stepwise mechanism such as follows: the catalytic sequence begins (Scheme 4) with the coordination of the alkyne to the Cu(I) species $[CuLn]^+$ displacing one of the Ln ligands (intermediate **A**). In the case of acetonitrile ligands this step was calculated to be endothermic by ca. 0.6 kcal/mol. However, with water as a ligand, the displacement process becomes exothermic in 11.7 kcal/mol. This is in good agreement with the experimental observation that the reaction proceeds much faster in aqueous solutions. In the next step, the NO replaces one of the ligands and binds to the copper atom *via* the carbon proximal to nitrogen, forming intermediate **B**. After that, the oxigen of the NO in **B** attacks the C-2 carbon of the acetylide, forming the six-membered copper (III) metallacycle **C**. From **C**, the barrier for ring contraction, which forms the copper derivative **D**, is very low. Proteolysis of **D** releases the isoxazole product, thereby completing the catalytic cycle. Calculations indicate that the barrier in the copper-catalyzed reaction is 13.2 kcal/mol, some 7 kcal/mol lower than for the thermal process. That corresponds to a rate acceleration of 5 orders of magnitude.



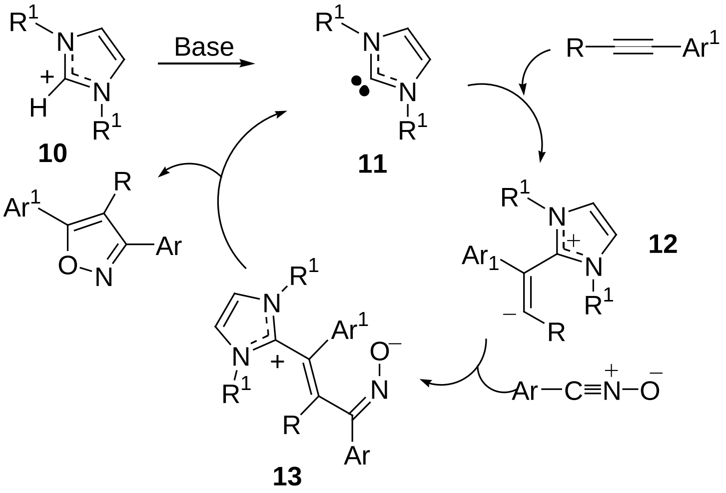
Scheme 4. Proposed mechanism reaction for the Cu(I)-catalyzed 1,3-DC of NOs and alkynes

For the ruthenium(II)-catalyzed reaction using [Cp*RuCl(cod)] **9** as catalyst (Scheme 5), the displacement of a cyclooctadiene ligand from the ruthenium catalyst[11] by an alkyne and NO produces the activated complex **A**, which mediates the oxidative coupling of a NO and alkyne, resulting in ruthenacycle **B**. The oxidative coupling step controls the regioselectivity of the overall process. Interestingly, in this case the carbon-oxygen bond is formed between the more electronegative carbon center of the alkyne and the oxygen atom of the NO. That represents an unexpected mode of activation of NOs because normally their carbon center is electrophilic and readily reacts with nucleophiles.[12] Thus, coordination to the ruthenium atom effectively changes the polarity of the NO. Ruthenacycle **B** undergoes reductive elimination giving **C**, and further release of the isoxazole product completes the catalytic cycle.



Scheme 5. Proposed reaction mechanism for the Ru(II)-catalyzed 1,3-DC of NOs and alkynes

A plausible mechanism has been proposed for the *N*-Heterocyclic Carbene (NHC)-catalyzed 1,3-DC reactions. From the imidazolium salt **10** the NHC catalysts **11** were generated in presence of Et_3N.[13] The formation of isoxazoles could occur in a domino fashion cycloadditions. According to Scheme 6, the organo-NHC catalyst will interact first with the alkyne with formation of a zwitterion **14.**[12] This reactive zwitterionic species will now interact with the NO through nucleophilic attack forming a second zwitterion **13**. Finally **13** undergo C–O heterocyclization to produce regioselectively the corresponding isoxazoles.



Scheme 6. A plausible mechanism for the formation of 3,5-disubstituted isoxazoles catalyzed by *N*-Heterocyclic carbene

Despite the amply recognized efficiency of these catalytic methods, the cost and toxicity of metals, especially for applications in medicinal chemistry, have urged the development of new metal-free reactions. After the excellent review published by Gothelf and Jorgensen concerning the asymmetric 1,3-DC,[15] other review articles on this topic have been published,[16] and in particular, the recent review by Maruoka and Hashimoto should be emphasized.[17] In some of these articles and in others[18] several catalyzed 1,3-DCs of NOs have been described but, to the best of our knowledge, no specific reviews dedicated to the organic catalyzed reactions of these dipoles have been published.

The expression “organic catalyst”[19] has been introduced in order to define an organic compound capable of promoting a given transformation in substoichiometric quantity. In this definition, organic is equivalent to “metal-free” in order to differentiate these catalysts from the metal catalytic species. Some advantages of the organic catalysts include, among others, the possibility of (a) working in wet solvents and under an aerobic atmosphere, (b) dealing with a stable and robust catalyst, and (c) avoiding presence of a metal into the resulting final product.

Currently four types of organocatalysts may be considered: Lewis bases, Lewis acids, Brønsted bases, and Brønsted acids. These catalysts initiate their catalytic cycles by either providing or removing electrons or protons from a substrate or a transition state. Organocatalysis is dominated by Lewis base catalysts such as amines and carbenes, while Lewis acids such as carbonyl compounds are rarely used. The use of chiral organic Brønsted acid catalysts[20] constitutes a new concept that is likely to grow strongly in the next years.

1.3. Objectives.

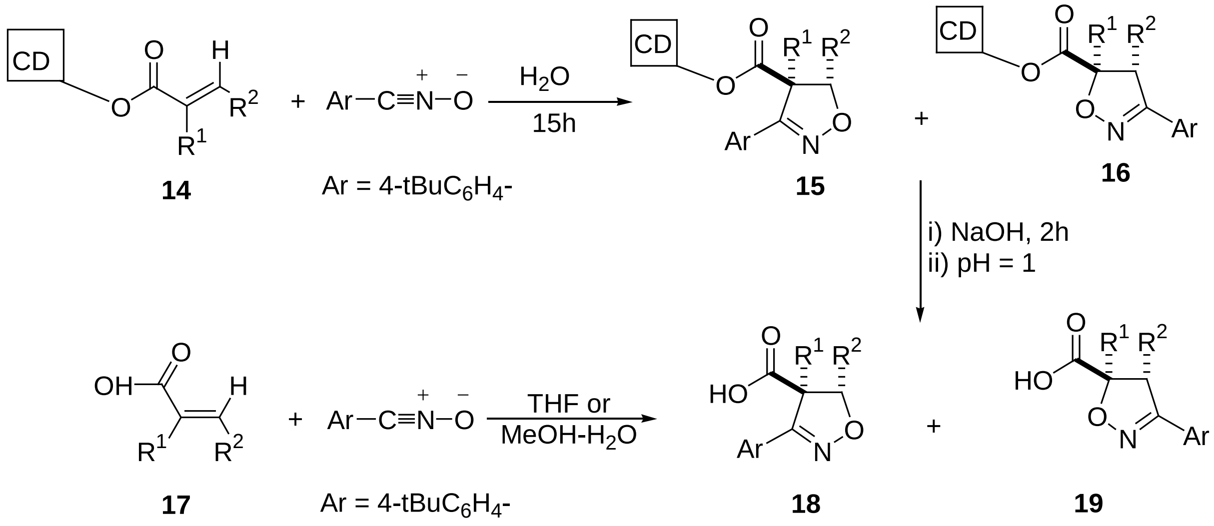
In the next paragraphs an overview on the development of the organic catalyzed 1,3 DC of NOs, mainly in the last decade, will be presented and discussed. The aim of this review is to give coverage on the progress made in the topic until June 2018.

2. ORGANIC COMPOUNDS CATALYZED 1,3-DC OF NITRILE OXIDES.

Metal-catalyzed cycloaddition reactions have made significant progress in the last half century and become one of the most efficient and direct strategies for bond formation. The extensive variations and modifications of metal-catalyzed reactions enabled wide applications in organic synthesis and were regarded as the most reliable, accurate, and powerful tools in chemists' arsenal. Nevertheless, metal-catalyzed reactions are still limited in applications and confront challenges to some extent, owing to the instinctive drawbacks of the catalytic systems. First, most of the metal catalysts are normally very expensive, and the supporting ligands are usually even more expensive and sometimes difficult to prepare. Second, most of the metals are toxic to different extents, and removal of trace amounts of metal residues from desired products is quite costly and challenging, while crucial, especially in the pharmaceutical industry. Third, many metal catalysts are usually sensitive to oxygen and moisture; thus, very strict manipulation is indispensable. Fourth, in many cases, special additives and cocatalysts are also critical to promote the efficiency and selectivity of transformations. Last, the large consumption of metals does not indeed meet the requirement of sustainable development. For these reasons, alternative pathways under metal-free conditions to fulfill the metal-catalyzed cycloadditions are highly appealing. In recent years, attention has been paid to the development of NO cycloaddition reactions catalyzed by organic molecules and significant efforts have been made to promote such chemistry. The results are summarized in following paragraphs.

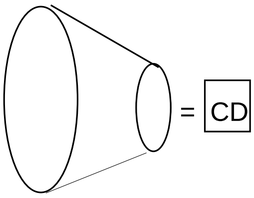
2.1. The transient attachment of the dipolarophiles to Cyclodextrins (CDs).

The use of cyclodextrins (CDs) derivatives incorporating functional groups in order to catalyze different type of transformations has been well documented[21] particularly in Diels-Alder (DA) reactions[22]. In the case of the 1,3-DC of NOs, transient attachment of the dipolarophiles to CDs promoted a reversal of the usual regioselectivity of the reactions[23]. For instance, treatment of esters **9** with 4-tbutylbenzonitrile oxide (H_2O, 25 ºC) took place with a dramatic change of the regioselectivity regarding the reaction achieved under conventional conditions (Scheme 7).[24] On the other hand, cyclodextrin increases the reaction rate of the 1,3-dipole with **9a** in 475 fold regarding the reaction with **12a**.



For compounds **14, 15**, **16 17**, **18** and **19**

a) $R^1 = R^2 = H$
b) $R^1 = Me$, $R^2 = H$
c) $R^1 = H$, $R^2 = Me$
Ar = 4-tBuC_6H_4-



Ratios of formation of the isoxazolines **18a-c** and **19a-c**

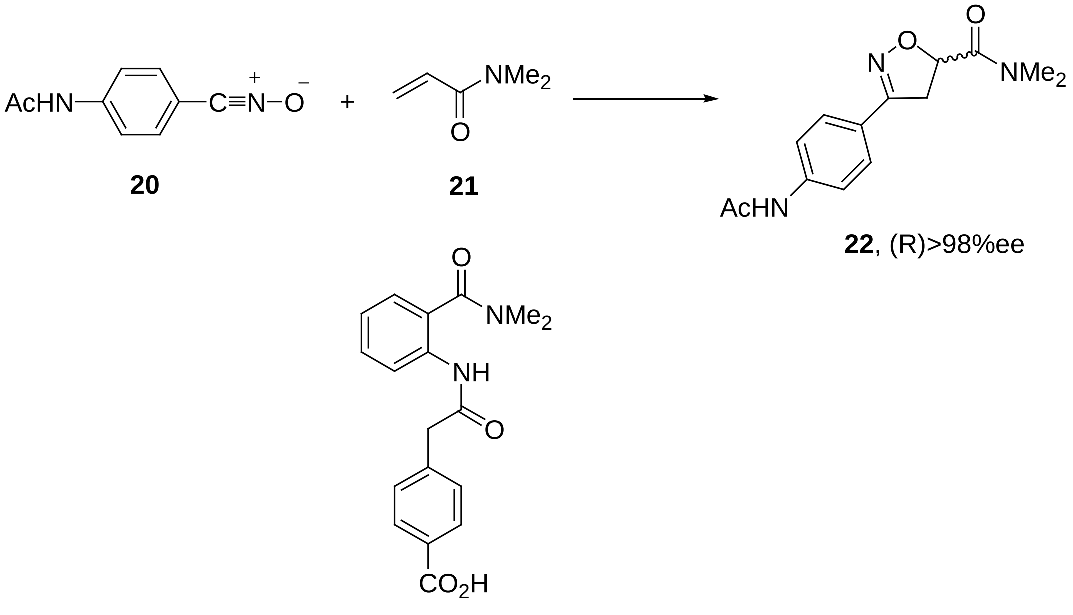
	Dipolarophile	
	14	**17**
18a:19a	20:1	1:20
18b:19b	1:10	<1:100
18c:19c	>100:1	1:1

Scheme 7. Influence of β-cyclodextrin attached to dipolarophile on the regioselectivity of cycloaddition of 4-t butylbenzonitrile oxide

2.2. Antibody catalyzed 1,3-DC of NOs.

An antibody is a large, Y-shaped glycoprotein produced by the plasma cells of the immune system and used in order to neutralize pathogens.[25] They mechanism of action is as follow: antibody recognizes a unique molecule of the pathogen, allowing these two structures to bind together with precision. Using this binding mechanism, an antibody can tag an infected cell for attack by other parts of the immune system. If an antibody is developed to bind to a molecule structurally and electronically similar to the transition state of a given chemical reaction, the developed antibody will bind to the transition state stabilizing it like a natural enzyme, lowering the activation energy of the reaction, and thus catalyzing the reaction.

The first example of an antibody-catalyzed 1,3-DC was reported in 2000 in the case of the 1,3-DC between 4-acetamide-benzonitrile N-oxide **20** and *N*,*N*-dimethylacrylamide **21** to give the 5-acyl-2-isoxazoline **22** (Scheme 8)[26] on the following basis: since the most accepted mechanism for the 1,3-DC reaction involves a planar, asynchronous and concerted transition state with aromatic character,[27] antibodies elicited against the planar aromatic core of hapten[≠] **23** (a mimetic of the transition state of the reaction) which may be capable of constraining the two reactants into a reactive conformation thus reducing the translational entropy of the reaction,[28] that is to say the “price” associated to the loss of translational modes (conversion in vibrational modes) as consequence of the proper orientation of the reactants on their path to the TS$^{\#}$. In this way, it should be emphasized that the 1,3-DC reactions of NOs as other analogous CAs proceeds through an entropically disfavored, highly ordered transition state, with large activation entropies in the range -25 to -40 cal mol^{-1} K^{-1}.[29] In this context, hapten **23** was conceived upon the “entropic trap” concept.[30] After the coupling of *N*-hydroxysuccinylester of hapten **23** to carrier proteins, eighteen monoclonal antibodies specific for hapten **23** were produced. Among them, the antibody, 29G12 catalyzes the formation of the 5-substituted oxazolidine **22** as the only product, with excellent enantioselectivity (98% ee, Scheme 8).



20

21

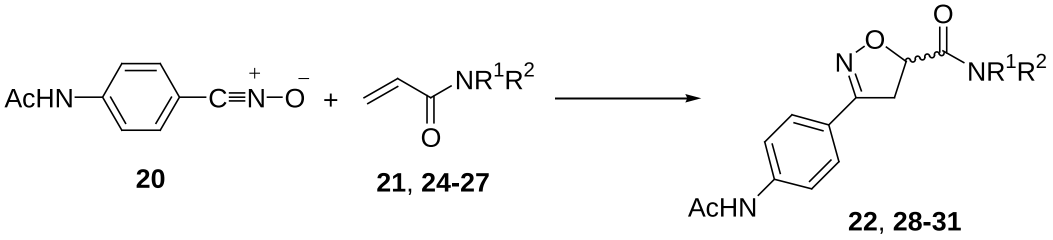
22, (R)>98%ee

23

Scheme 8. Antibody-catalyzed 1,3-DC of NO **20** and amide **21**

[≠] Haptens are small molecules that provoke no immune response by themselves, but once they bind to proteins, the resulting complex or hapten-carrier adduct stimulates the production of antibodies. The hapten then reacts specifically with the antibodies generated against it to produce an immune response.

The scope of this 29G12 antibody catalyzed 1,3-DC of NO **20** and other analogous substrates was later explored. The most significant results are depicted in Scheme 9.[31]

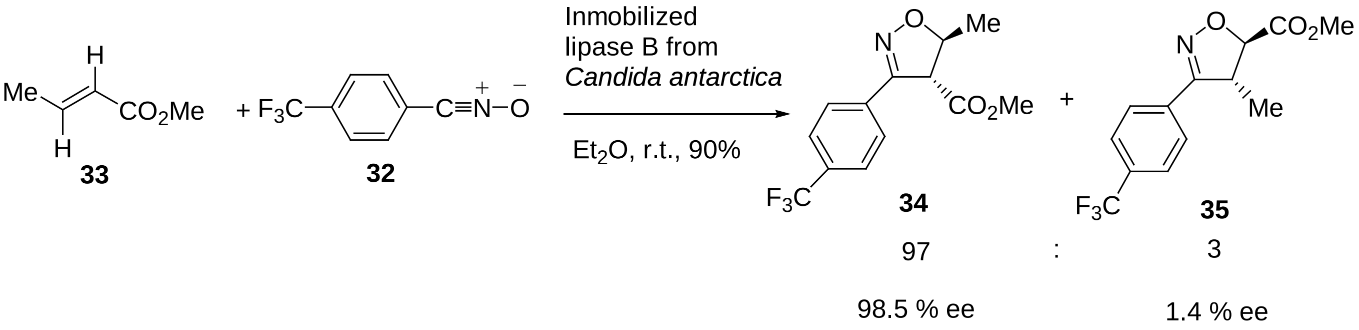


Amide	Isoxazoline	R^1	R^2	%ee	krel
21	**22**	Me	Me	98	1
24	**28**	H	tBu	94	28.7
25	**29**	H	iPr	85	38.2
26	**30**	H	sBu	97	52.7
27	**31**	H	Ph	71	66.9

Scheme 9. 29G12 Antibody-catalyzed 1,3-DC of NO **20** and acrylamide derivatives

2.3. Lipase-catalyzed 1,3-Dipolar Cycloaddition of NOs.

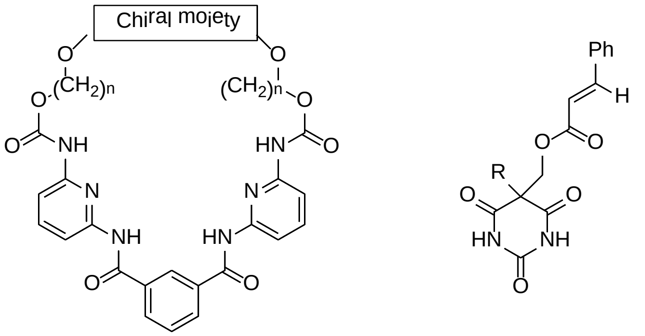
To the best of our knowledge only one example of lipase-catalyzed 1,3-DC of NOs has been reported.[32] Thus, in the presence of immobilized lipase B from *Candida antarctica*, the reaction of 4-trifluoromethylbenzonitrile oxide **32** to crotonate **33** afforded isoxazolines **34** and **35** in very good yield and excellent regio- and enantioselectivities in the major regioisomer **34** (Scheme 10).



Scheme 10. Catalyzed 1,3-dipolar cycloaddition of NOs by *Candida antarctica* lipase

2.4. Chiral macrocyclic systems as catalysts in 1,3-dipolar cycloaddition reactions of NOs.

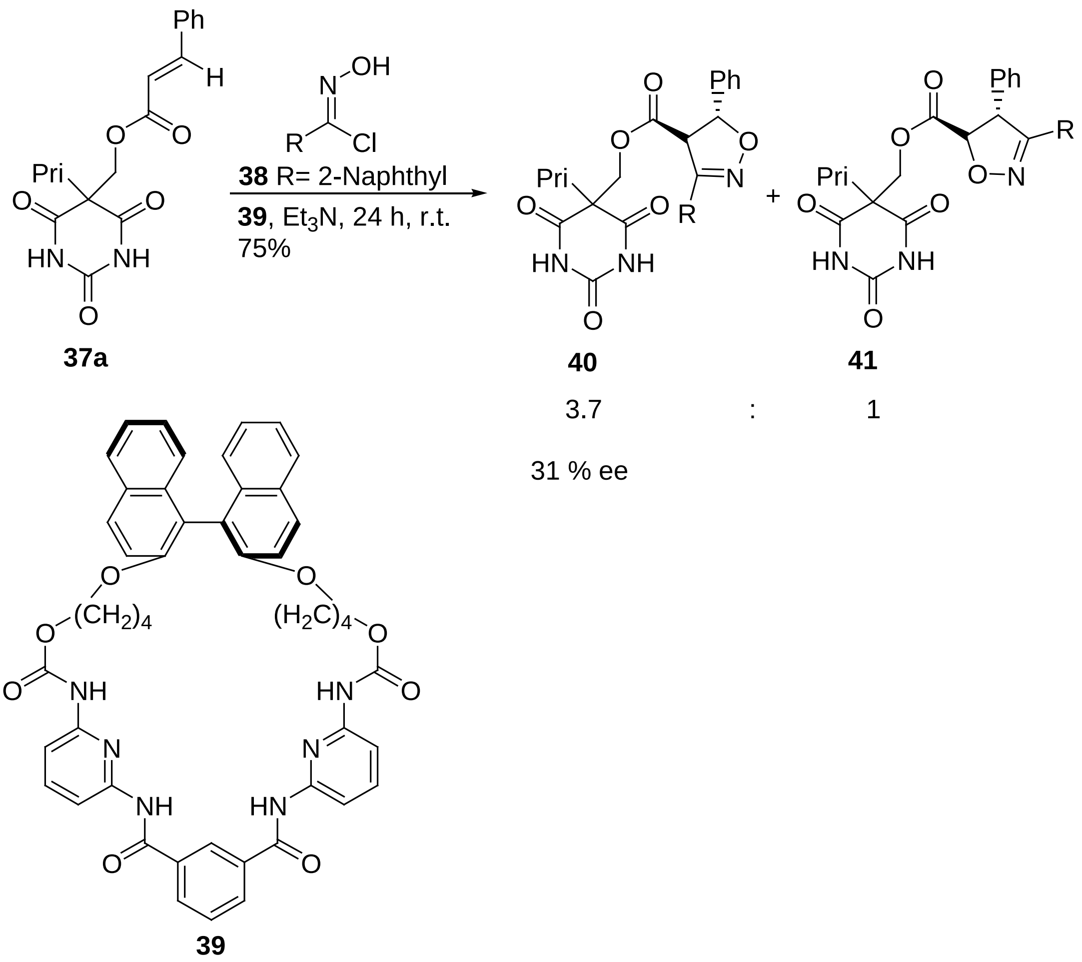
The chiral transfer from a macrocyclic chiral receptor (host) to the appropriate substrate (guest) has been considered in the context of several asymmetric synthetic approaches.[33] In the case of the 1,3-DC of NOs some chiral macrocyclic barbiturate receptors[34] of general structure **36** (Figure 1) have been used as chiral transfer reagents and using as guest substrates the barbiturate cinnamate derivatives **37a-c** (Figure 1).[35]



36 **37a**, R= iPr; **37b**, R=Me; **37c**, R=Ph

Figure 1. Chiral macrocyclic barbiturate receptors and barbiturate-cinnamate derivatives used in asymmetric 1,3-DC of NOs.

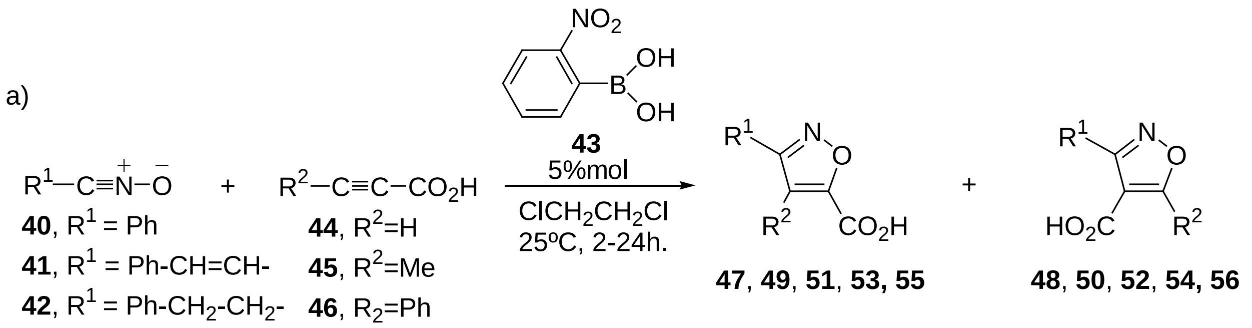
In these cases the expectation was that, upon host-guest binding, the orientation of the barbiturate conjugate in the chiral host will place the cinnamate moiety proximate to the chiral environment so that one face of the C=C double bond remains shielded. The best results, albeit with low ee in the major regioisomer, was obtained in the reaction of **37a** with the NO precursor **38** in the presence of the chiral macrocyclic barbiturate receptor **39** (Scheme 11).



Scheme 11. Barbiturate receptor as catalyst in 1,3-DC of a NO.

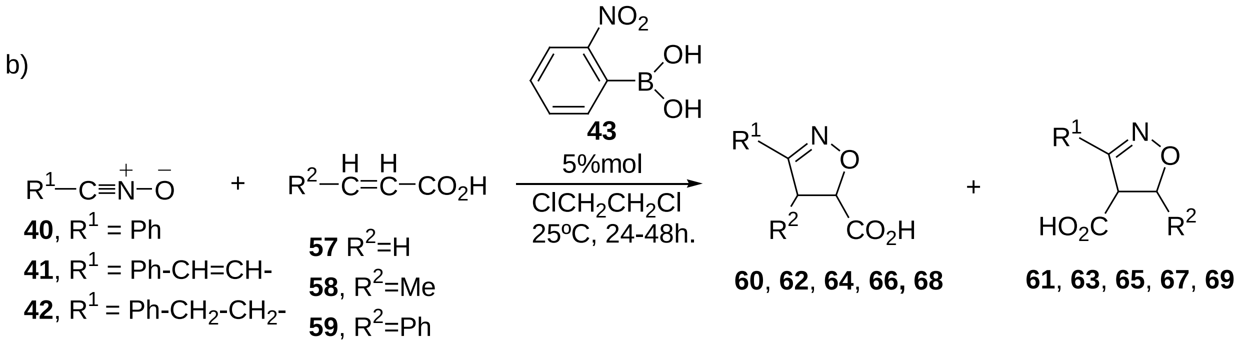
2.5. Boronic acid catalyzed 1,3-dipolar cycloaddition of NOs and α,β-unsaturated carboxylic acids.

Electrophilic activation of unsaturated carboxylic acids (LUMO-lowering) by arylboronic acids constitutes a well established synthetic tool[36] and, for instance, catalysis by boronic acid has been demonstrated in the DA cycloadditions of acrylic acids.[37] In the case of the 1,3-DC of NOs **40**, **41** and **42** with several alkynoic (Scheme 12a) and acrylic acid (Scheme 12b) derivatives, catalysis by o-nitrophenylboronic acid **43** allows for the synthesis of the expected cycloadducts in improved yields and regioselectivity compared with the uncatalyzed reaction (Scheme 12).[38]



47, **48**	R^1 = Ph, R^2 = H
49, 50	R^1 = CH=CH-, R^2 = H
51, 52	R^1 = CH_2CH_2-, R^2 = H
53, 54	R^1 = Ph, R^2 = Me
55, **56**	R^1 = Ph, R^2 = Ph

Startig materials	Reaction time (h.)	Yield	Regioisomeric ratio
40+**44**	2	87 (15)	**47**:**48**>98:2 (9:1)
41+**44**	24	71 (4)	**49:50**>98:2 (6:1)
42+**44**	24	73 (5)	**51**:**52** >98:2 (6:1)
40+**45**	24	78 (10)	**53:54** 1:16 (1:5)
40+**46**	24	69 (5)	**55:56** 1:6 (1:1.2)

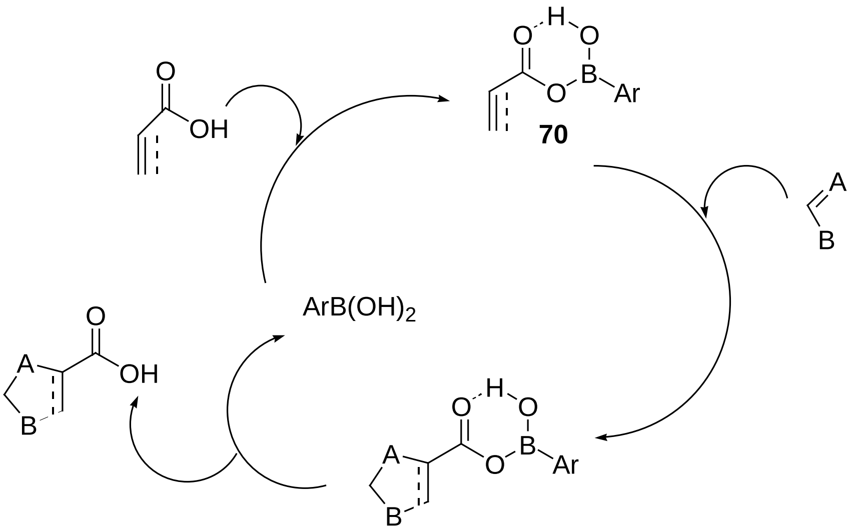


60, 61	R^1=Ph, R^2=H
62, **63**	R^1= CH=CH-, R^2=H
64, 65	R^1= CH_2CH_2-, R^2=H
66, 67	R^1=Ph, R^2=Me
68, 69	R^1=Ph, R^2=Ph

Startig materials	Reaction time (h.)	Yield	Regioisomeric ratio
40+**57**	24	67(7)	**60**:**61**>98:2 (95:5)
41+**57**	48	67 (6)	**62**:**63**>98:2 (10:1)
42+**57**	48	65 (3)	**64:65**>98:2 (5:1)
40+**58**	24	77 (10)	**66:67**<2:98 (<2:98)
40+**59**	24	65 (10)	**68**:**69**<2:98 (<2:98)

Scheme 12. Boronic acid catalyzed 1,3-DC of NOs. The results for non-catalyzed reactions (yields and regioisomeric ratios) are indicated parenthetically

On the basis of ^{13}C NMR experiments combined with the observed retardation effect of water in these catalyzed cycloaddition reactions, it may be concluded that the boronic acid **43** catalyzes the 1,3-DC of NOs and other 1,3-dipoles such as azides and nitrones through a LUMO-lowering activation of the dipolarophile *via* formation of a covalent adduct **70** (a monoacylated hemiboronic ester) with the unsaturated carboxylic acid as depicted in Scheme 12.



Scheme 12. Proposed mechanism for the boronic acid catalyzed 1,3-DC reactions.

3. SUMMARY, CONCLUSIONS AND PERSPECTIVES

The utility of nitrile oxides as dipoles in heterocyclic synthesis *via* 1,3-dipolar cycloadditions has been intensively studied considering that the final cycloadduct products, isoxazoles and their analogues, constitute an important class of heterocyclic compounds which are presents in natural products and drugs, among others, being also important synthetic intermediaries. In general, the uncatalyzed, thermal cycloaddition reactions of nitrile oxides with asymmetrically substituted alkenes or alkynes are neither chemo- nor regioselective, and these reactions are limited to highly activated alkynes such as acetylene dicarboxylate and other electron-deficient alkynes. The use of different catalysts, including metals and organic molecules allow to carry out this type of reactions with good chemo-, regio- and enantioselectivities in some cases and avoids the NO dimerization because the cycloaddition reaction rates are also increased. However, the cost, toxicity and removal of trace amounts of metal residues is crucial, especially in areas such medicinal chemistry. That is why alternative pathways using organic molecules to fulfill the metal-catalyzed reactions are highly appealing.

This article has reviewed the nitrile oxide –alkene or alkyne cycloaddition reactions catalyzed by organic compounds.The synthetic applications of nitrile oxide-alkyne cycloadditions have been studied in recent years in fields such as medicinal chemistry, bioconjugation and radiochemistry. In our opinion, it cannot be doubted that applications of nitrile oxide click cycloadditions will continue to emerge across the broad field of polymer and bioconjugation chemistry. The need for quick, precise and flexible synthetic methodology to carry out modern research in biochemical, biotechnology and materials science has put special atenttion in metal free 1,3-dipolar cycloaddition chemistry. It can be concluded that NOs cycloadditions are interesting reactions in with lots of possibilities and will certainly contribute to future creative advances in chemical biology as well as in materials science.

4. ACKNOWLEDGEMENTS

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