



Metal-Catalyzed 1,3-Dipolar Cycloaddition Reactions of Nitrile Oxides.

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In the present review advances on the metal-catalyzed 1,3-dipolar cycloaddition reactions of nitrile oxides, mainly in the last decade, will be presented and discussed. An overview on the structure, preparation, dimerization and related reactions as well as relevant aspects on the cycloaddition chemistry of nitrile oxide (including mechanistic aspects) have also been considered.

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1. Introduction and objectives

Several milestones marked out the history of the nitrile oxides (NOs). After the discovery of fulminic acid (Howard, 1800), the cycloadditions (CAs) of NOs to olefins were first reported in 1927 (Weygand) and later developed in 1950 (Quilico). In 1961, Huisgen categorized the NOs as a member of a broader class of 1,3-dipoles that were capable of undergoing 1,3-dipolar cycloaddition (DC) reactions. In the 1960s and 1970s the factors governing the reactivity and selectivity of NOs cycloadditions were brilliantly described and systemized by Huisgen and coworkers.

Nevertheless, the cycloaddition reactions of NOs¹ 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, see below).

In addition, although monosubstituted alkenes and alkynes show high regioselectivity in their cycloadditions with NOs, 1,2-disubstituted derivatives often give mixtures of regioisomers. In this context, it should be pointed out that the ensuing cycloadducts, isoxazoles and their analogues, constitute an important class of heterocyclic compounds.² For instance, 2-isoxazolines are valuable intermediates in synthetic organic chemistry because their capacity to mask other functionalities including α,β -unsaturated ketones, β -hydroxycarbonyl compounds and 1,3-aminoalcohols. Most of these can be accessed from 2-isoxazolines by reductive cleavage of the heterocycle³. In particular the β -hydroxy ketone functionality is a typical example, making the NO-alkene cycloaddition reactions a

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synthetically equivalent methodology of aldol reactions⁴. Efficient syntheses of chiral compounds using such methodologies require the development of catalytic asymmetric cycloaddition reactions. In this context, the use of Lewis acids (LA) catalyzed NOs CAs may be a convenient solution. The effects of Lewis acids (LA) and other catalysts on the rates, regioselectivity and stereoselectivity of Diels-Alder (DA) reactions have been thoroughly investigated. In general, large rate accelerations and greatly increased regioselectivity and stereoselectivity were observed.⁵ These phenomena have been rationalized by the application of frontier orbital (FO) theory. In principle, the same theoretical considerations can be applied to the 1,3-DC reactions and, in particular, to the NOs cycloadditions. The rate enhancement of the 1,3-DC of NOs by a LA can be readily explained on the basis that the complexation of the NO is expected that will occur preferentially with the oxygen because of its rather large negative charge. Thus, as the NO orbital energies are lowered upon complexation, the LUMO dipole-HOMO dipolarophile interaction will be strengthened, and the reaction rate will increase. The catalyzed reaction becomes LUMO dipole controlled.⁶

Relatively few LA catalyzed 1,3-DC reactions of NOs have been studied. In fact, the development of LA-catalyzed 1,3-DC of NOs is a challenging task because NOs coordinate strongly to LA, dimerize easily, and facilitate background reaction. In addition, the incompatibility of LA catalysis with the base required for (in many cases) the generation of NOs from hydroximoyl chlorides is problematic. Regarding the synthesis of isoxazoles, in general the uncatalyzed, thermal CAs of NOs with alkynes are neither chemo- nor regioselective. However, the copper (I) and Ru(II) CAs ("click" chemistry conditions) not only accelerate the reaction but also allowed for a convenient and complementary control of the regioselectivity of the process. Thus, whereas copper(I) catalyzed CAs generate 3,5-disubstituted isoxazoles, the regiocomplementary 3,4-disubstituted isomers may be easily obtained using Ru(II) derived catalyst. In addition, thermal reactions of NOs with internal alkynes are limited to highly activated alkynes such as acetylene dicarboxylate and other electron-deficient alkynes. The use of Cu(I) and, particularly, Ru(II) derived catalyst allowed to carry out efficiently these reactions. The present review is devoted to the consideration of both types of metal-catalyzed NOs cycloadditions giving coverage on the more significant

progress made in the last ten years and until March 2018. The following subjects have been considered: (a) an overview on the structure, physical properties, synthesis and stability of NOs, including mechanistic aspects of their 1,3-dipolar cycloadditions. In our opinion this is important for a suitable interpretation of some results described later; (b) the use of different LA catalyst in NOs cycloadditions with special attention on the asymmetric version of these reactions; (c) the applications of the click chemistry conditions to the 1,3-DC reactions of NOs and alkynes

2. Nitrile Oxides. An Overview.

2.1. Structure and Some Physical Properties of Nitrile Oxides.

Nitrile oxides belong to the class of 1,3-dipoles known as “nitrilium betaines”. These compounds are described by the resonance structures **1a-g** exemplified for the case of the parent compound, fulminic acid (Figure 1).

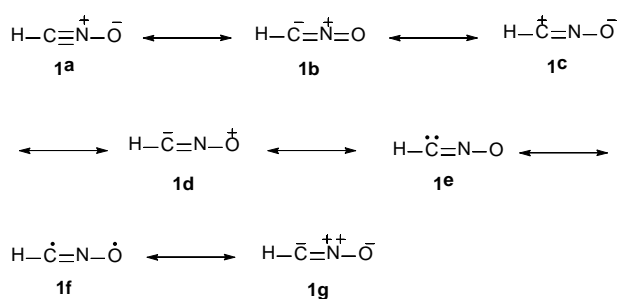


Figure 1. Resonance hybrids of fulminic acid **1**.

Mesomeric structures **1a** and **1b** (octet structures) are respectively heteropropargyl and heteroallenyl anions. Sextet structures **1c** and **1d** are classical 1,3-dipolar formulas. A more realistic representation of 1,3-dipoles involves only three Lewis structures, two zwitterionic ones (**1a** and **1b**) and a diradical one (**1f**). The computation of the weights of the individual Lewis structures has been carried out⁷ by means of the “breathing-orbital valence bond” (BOVB) method, a reliably *ab initio* valence bond method.⁸ The weights of VB structures for fulminic acid were determined as **1a**: 0.580, **1b**: 0.206 and **1f**: 0.213. Obviously as long as structure **1a** dominates, the ground-state geometry of NOs should remain almost linear whereas participation of the cumulated structure **1b** increases the bending tendency. Computational studies at different levels indicate that fulminic acid have an almost linear geometry. Geometries of unstable nitrile oxides such as acetonitrile oxide,⁹ fluorofulminate,¹⁰ chlorofulminate,¹¹ cyanogen *N*-oxide¹² and trifluoroacetonitrile *N*-oxide¹³ have been theoretically calculated or experimentally (gas phase) evaluated also suggesting a possible quasi-linear geometry. Some stable nitrile oxides have also been investigated using X-ray methods, displaying a similar structure.¹⁴ Cumulated structure **1b** place the negative charge on

the nitrile carbon and compensate the electronic distribution toward the oxygen atom as implied in **1a**. This is reflected, for example, in the values of the dipole moments of some nitrile oxides¹⁵ smaller than those that would be expected compared with the carbonitrile analogs (Table 1).

R	R ⁻ CNO	RCN
H	3.099	2.965
Me	4.49	3.40
Ph	4.00	3.37

Table 1. Dipole moments of some nitrile oxides and nitriles (in Debye units).

The various temperature ¹³C NMR (¹³C-VT-NMR) study of the ¹³C-labeled stable (¹³CNO) 2,6-dimethoxybenzonitrile oxide has been carried out.¹⁶ At high temperature the signal of CNO appears as a triplet which gradually fused into a singlet peak as the solution was cooled to a low temperature. When the temperature increased to room temperature, the peak returned to the original triplet signal, indicating a reversible change of CNO on an NMR time scale. It might be attributed to the change from a bended conformation to a coplanar conformation with the benzene ring, as shown in Figure 2.

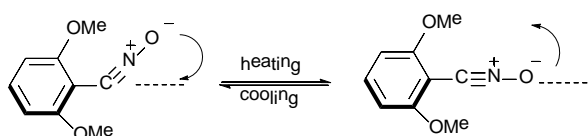


Figure 2. Possible dynamic structural change of CNO moiety in 2,6-dimethoxy benzonitrile oxide in solution.

The experimentally available (photoelectron spectroscopy) or estimated ionization potential and the estimated electron affinity have been determined for several NOs.¹⁷ These values represent the energies of the HOMOs and LUMOs respectively for these dipoles. Regards to the family of nitrilium betaines, comparison of the parents formonitrile oxide and formonitrile imine (Table 2) lets conclude that the increase of the electronegativity of the terminal atoms lowers the HOMO energy significantly but changes the LUMO less. Consequently, the HOMO-LUMO gap increases from formonitrile oxide to formonitrile imine. Since the HOMO-LUMO gaps of triple bonded species are greater than those of double bond species, the former has less diradical character than the latter (see Table 2).

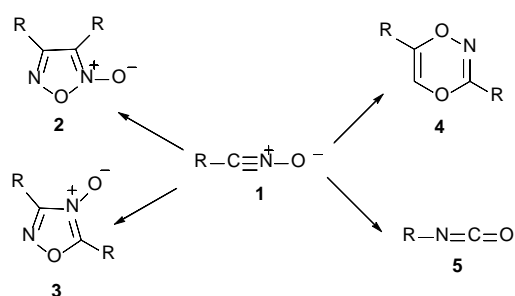
Compound	E _{HOMO} (eV)	E _{LUMO} (eV)	
HCNH	-9.2 ^a	0.1 ^a	a) Estimated
HCNO	-10.8 ^b	-0.5 ^a	b) Determined by PES

	Weights of VB Structures		
	H-C≡N ⁺ -X ⁻	H-C=N ⁺ -X ⁻	H-C ⁺ =N-X ⁻
HCNH	0.379	0.356	0.365
HCNO	0.580	0.206	0.213

Table 2. Frontier orbital energy (E_{HOMO} and E_{LUMO}) and weights of valence bond (VB) structures of formonitrile imine and formonitrile oxide.

2.2. Stability of NOs. The dimerization and isomerization reactions.

Most of NOs, like the other classes of nitrilium betaine 1,3-dipoles, are chemically unstable and readily undergo dimerisation to form the corresponding furoxan **2** (Scheme 1) *via* a stepwise reaction path involving a quasi diradical dinitrosoalkene intermediate.¹⁸



Scheme 1. Dimerizations and isomerization 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 nitrile oxides at room temperature is several hours. Intramolecular bis (nitrile oxide) dimerization has also been reported and synthetically exploited.¹⁹ Stable NOs can be obtained as a result of steric shielding of the nitrile oxide functionality (for instance 2,4,6-trimethylbenzonitrile 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 nitrile oxides.

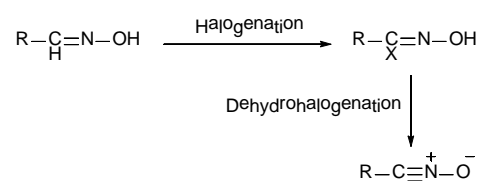
Dimerizations of NOs to 1,2,4-oxadiazole 4-oxides **3** under acidic or basic conditions²⁰ and to 1,4,2,5-dioxadiazines **4** in the presence of BF_3 or pyridine are of lesser importance. Isomerization of NOs to isocyanates **5**, proceeds at elevated temperature and is practically the only reaction of sterically stabilized nitrile oxides.²¹

2.3. Preparation of NOs.

A comprehensive review on the synthetic methods (stable NOs) or generation procedures (unstable NOs) of NOs have been compiled in reference 1a and publications cited therein. Here we will include a summary of these procedures and those more relevant ones published since 2007.

2.3.1. From aldoximes.

The transformation of aldoximes to NOs is conceptually a dehydrogenation process. It should be indicated that the process constitutes in practice a halogenation-dehydrohalogenation sequence. The intermediate hydroximoyl halide is frequently not isolated (Scheme 2). The reaction is convenient for both the generation of unstable NOs (in the presence of a dipolarophile) and the preparation of stable NOs.



Scheme 2. Formation of nitrile oxides by halogenation-dehydrohalogenation of aldoximes.

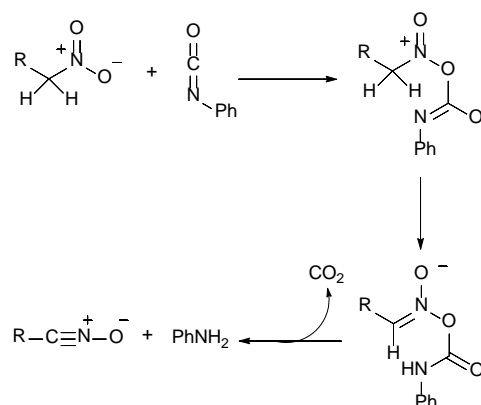
Hydroximoyl halides can be readily prepared by halogenation of oximes using various reagents such as halogen, hydrogen chloride/N,N-dimethylformamide/oxone, KCl/oxone/water²² and hydrogen chloride/silica gel/oxone under solvent-free conditions,²³ NaOCl, N-bromo- and N-chlorosuccinimides,²⁴ chloramine-T, trichloroisocyanuric acid and N-(*t*-butyl)-N-chlorocyanamide among others related procedures.²⁵ Dehydrochlorination of hydroxamic acid chlorides can be performed using a tertiary base, usually Et₃N, DABCO-Et₃N,²⁶ aqueous sodium carbonate, silver salts, organotin compounds, KF-Al₂O₃ solid support,²⁷ polymeric base catalysts²⁸ and by thermal dehydrochlorination using a stream of N₂ to displace the HCl formed. The water-assisted generation of NOs from oxime halides under mild acidic conditions (pH 4–5) has been reported.²⁹ Comparison of aryl nitrile oxide cycloadditions, using the dehydrohalogenation of hydroximoyl chlorides route, under conventional conditions, microwave-assisted, and under continuous flow has been carried out.³⁰ Direct oxidation of oximes have been applied for the generation of NOs. Mercury(II) acetate,

dimethyldioxirane, ceric ammonium nitrate, hypervalent iodine compounds,³¹ Mn (IV) oxide,³² and electroorganic methods³³ have been described. In the presence of calcium carbide, aryl aldoximes afforded 3-aryl-substituted isoxazoles. In this reaction calcium carbide acts as a source of acetylene and as a source of Ca(OH)₂ which enables the generation of the corresponding NO.³⁴

Recently it has been reported that the visible-light photoredox catalysis of hydroxyimino acids generates NOs by two sequential oxidative single electron transfer processes.³⁵

2.3.2. Dehydration of Nitro Compounds.

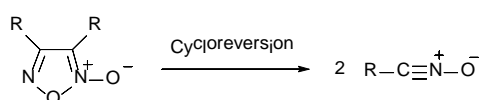
Generation of NOs by dehydration of primary nitroalkanes (Mukaiyama reaction) is of high importance in NO chemistry. The reaction is usually achieved by treatment with phenyl isocyanate under basic conditions (see Scheme 3 for a proposed mechanism).



Scheme 3. Generation of NOs from primary nitroalkanes.³⁶ A plethora of other reagents have been used. Primary nitro compounds bearing an electron withdrawing group geminal to the nitro group usually undergo dehydration reaction with acids, under acylation conditions, on thermolysis or on treatment with thionyl chloride and tertiary diamines such as DABCO (1,4-diazabicyclo[2.2.2]octane) or TMEDA (tetramethylethylenediamine). NOs can be generated not only from primary but also from some functionalized secondary nitroalkanes using the AcOH·Ac₂O mixture in the presence of a catalytic amount of H₂SO₄, at room temperature. Highly efficient modifications of Mukaiyama's procedure, convenient for combinatorial syntheses, were also reported.

2.3.3. Cycloreversion of Furoxans and Related Heterocycles.

The thermal fragmentation of furoxans (1,2,5-oxadiazole N-oxides), involving cleavage at O(1)–N(2) and C(3)–C(4) bonds, has proved to be an effective method for the generation of NOs (Scheme 4).³⁷



Scheme 4. Cycloreversion of furoxans.

This method is particularly useful for bis(nitrile oxides) for which alternative approaches are often less

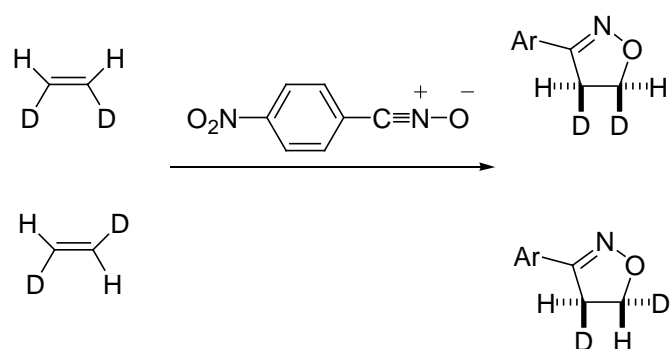
successful.³⁸ Cycloreversion with NO formation is known not only in furoxans but also in isoxazolines, 1,2,4-oxadiazoles, furazans, and some other five-membered heterocycles.³⁹

2.4. A brief survey on the 1,3-Dipolar Cycloadditions of Nitrile Oxides.

Several comprehensive reviews on the 1,3-dipolar cycloadditions of NOs and both double and triple carbon-carbon bonds⁴⁰ including allenes⁴¹ and enolates,⁴² carbonyl, imino and thiocarbonyl compounds, carbonitrile derivatives,⁴³ aromatic and related compounds, heterocyclic compounds and fullerenes⁴⁴ have been published in the last years.

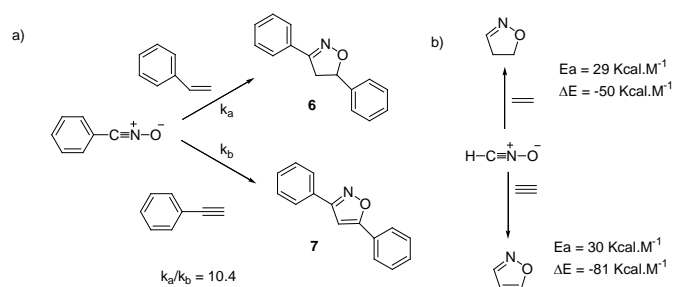
2.4.1. Mechanistic considerations.⁴⁵

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.⁴⁶ 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. One significant example is the reaction of *para*-nitrobenzoxonitrile oxide to *cis*- and *trans*-1,2-dideuterioethylene (Scheme 5).⁴⁷



Scheme 5. Reaction of *cis*- and *trans*-1,2-dideuterioethylene with *p*-nitrobenzonitrile oxide.

The reactivity of alkynes is lower than the corresponding alkenes. The second-order rate of BNO to identically substituted alkenes and alkynes show a lower reaction rate for the formation of aromatic isoxazoles (for instance, **7**) regarding the non-aromatic isoxazolines (for instance, **6**, Scheme 6a).⁴⁸

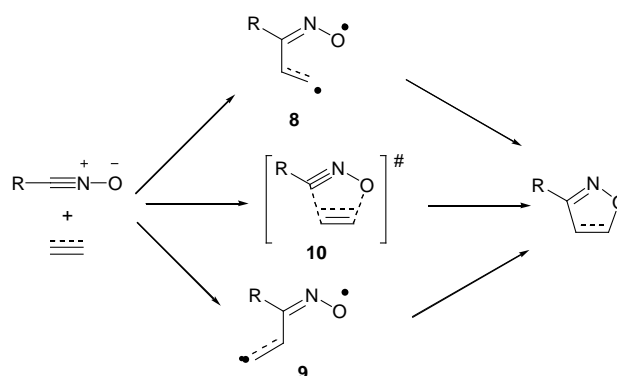


Scheme 6. Kinetic, activation energy and thermochemical data for the formation of isoxazoles and isoxazolines by 1,3-dipolar cycloaddition of NOs.

That has been used as a criterion for an early TS in the concerted 1,3-DC in the following way: calculated heat of reaction for the formation of isoxazole by reaction of

fulminic acid with acetylene (-81 Kcal.M^{-1}) account for the aromatic resonance energy of isoxazole compared with the same magnitude in the isoxazoline obtained for reaction of fulminic acid with ethylene (-50 Kcal.M^{-1}) (Scheme 6b).⁴⁹ Calculated activation energy differs only in 1 Kcal. On the other hand more accurate theoretical thermochemical determinations show values ΔH° (gas phase, 0°C) -39.3 and $-74.0 \text{ Kcal.M}^{-1}$ for the formation of isoxazolidine and isoxazolone respectively.⁵⁰ On the basis of 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, the current doctrine is that 1,3-DC reactions of NOs proceed via a concerted mechanism.⁵¹

As a mechanistic alternative, Firestone suggested⁵² in 1968 a stepwise mechanism involving a *syn*-diradical intermediate **8** (Scheme 7).



Scheme 7. Concerted and stepwise mechanism for the CA of NOs with alkenes and alkynes.

The *syn*-diradical **8** 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 **9** should be ruled out on the basis of the stereochemical results.⁵³

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.

Other mechanistic questions concerning the driving force of the cyclization and the electronic factors that determine the barrier height remain still opened. Currently, three different rate-determining factors are discussed in the literature: (a) the distortion energy of

dipole and dipolarophile as defined by Houk *et al.*,⁵⁴ (b) the reaction acceleration by an excitation of the bending vibrations of the 1,3-dipole⁵⁵ and (c) the biradical character of the 1,3-dipole molecule.

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

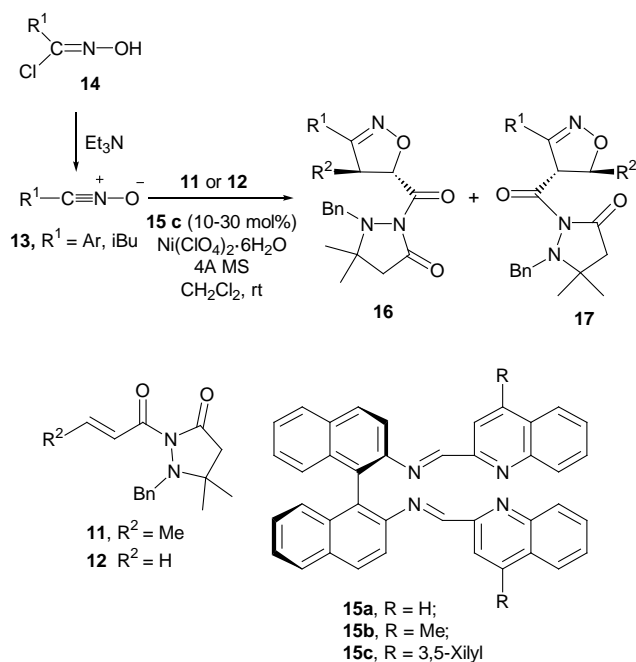
In connection with catalyzed 1,3-DC reactions and after the excellent review published by Gothelf and Jorgensen concerning asymmetric 1,3-DC⁵⁶, other review articles on this topic have been published.⁵⁷ In some of these articles, several catalyzed 1,3-DCs of NOs have been described but, to the best of our knowledge, no specific reviews dedicated to the catalyzed reactions of these dipoles have been published. In the next paragraphs an overview on the development of the LA- and other metal-catalyzed (click chemistry) 1,3 DC of NOs mainly in the last decade, will be presented.

3.1. Lewis Acid Catalyzed 1,3-DC Reactions of NOs.

3.1.1. Ni(II) catalyzed 1,3-DC of NOs.

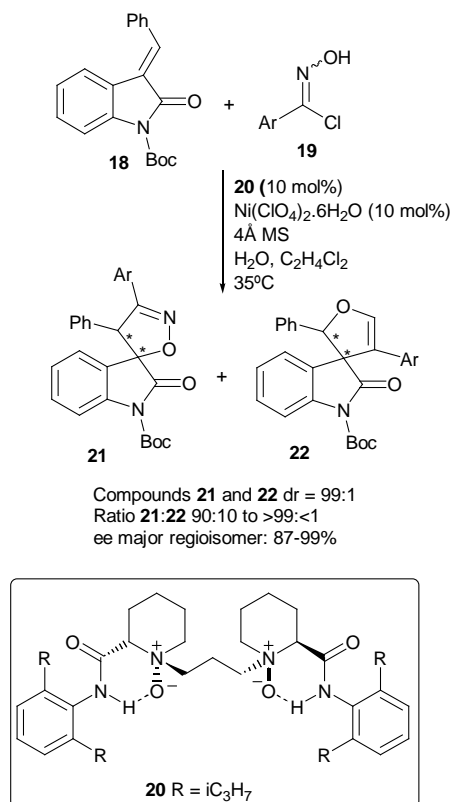
Asymmetric 1,3-DC of NOs and different dipolarophiles have been carried out in the presence of different nickel (II) complexes as Lewis acid catalysts.⁵⁸ For instance, 2-crotonoyl- and 2-acryloylpyrazolidinones **11** and **12** (Scheme 8) react with NOs **13** generated *in situ* from the corresponding hydroximoyl chlorides **14** in the presence of nickel complexes of chiral binaphthyldiimine (BINIM, **15**). Using (R)-BINIM-4(3,5-

xylyl)-2QN **15c** as chiral ligand, highly functionalised chiral cycloadducts **16** and **17** were obtained (67-99% yields) with good regioselectivities (**16:17**>98:2 in all cases studied) and high enantioselectivities (ee = 77-93%).⁵⁹



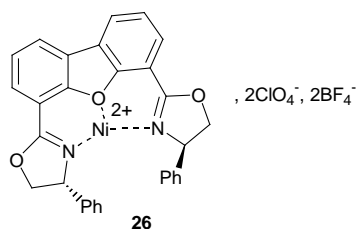
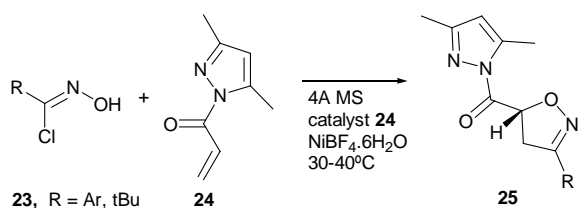
Scheme 8. Asymmetric 1,3-DC of NOs and different dipolarophiles catalyzed by nickel (II) complexes.

A highly stereoselective CA between 3-arylidene-oxindoles **18** and aromatic NOs generated from benzyhydroxymoil chlorides **19** and using a chiral N,N'-dioxide **20**-nickel(II) complex as the catalyst has been described. Excellent enantioselectivities (85-99% ee) and good regioselectivities were achieved in the presence of 4Å molecular sieves, albeit with moderated yields (40-60%) (Scheme 9).⁶⁰



Scheme 9. 1,3-DC of 3-arylidene-oxindoles **18** and aromatic NOs using a chiral N,N'-dioxide **19**-nickel(II) complex as catalyst.

The 4Å MS-mediated generation of NOs has been applied to the catalytic enantioselective CA with monosubstituted alkenes as dipolarophiles. In this way, the 1,3-DC of NOs generated from hydroxymoil chlorides **23** and 1-acryloyl-3,5-dimethylpyrazole **24** afforded isoxazoline cycloadducts **25** in excellent yields (65-94%), regio- and enantioselectivities (ee 90-97%), using the Ni (II)-R,R-DBFOX/Ph complex **26** (Scheme 10).⁶¹



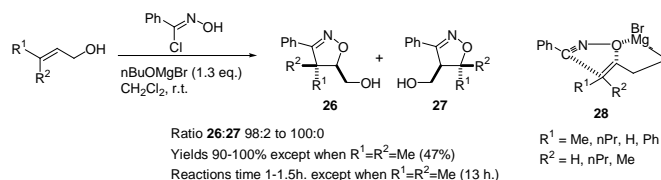
Scheme 10. 1,3-DC of NOs **23** and 1-acryloyl-3,5-

dimethylpyrazole **24** using the Ni (II)-R,R-DBFOX/Ph complex

26 as Lewis acid catalyst.

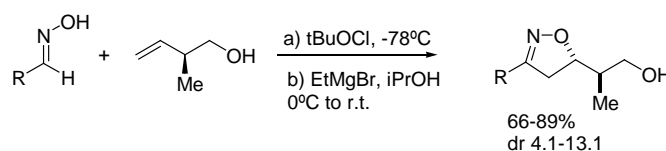
3.1.2. Mg(II) and Cu(II) catalyzed 1,3-DC of NOs.

Magnesium (II)⁶² ion catalysts have been used in NOs cycloadditions. The chelation-controlled cycloadditions of nitrile oxides to the magnesium alkoxides of allylic and homoallylic alcohols have been brilliantly described and discussed by Kanemasa.⁶³ For instance, the cycloadditions of NOs to the magnesium alkoxides of allylic alcohols occurred with high regioselectivities, excellent yields and effective rate acceleration (see for instance Scheme 11). A chelated transition state **28** account for the high regiocontrol as well as the rate enhancement.⁶⁴ The mechanism and energetics of these magnesium-mediated cycloadditions with allylic alcohols have been investigated quantum mechanically.⁶⁵



Scheme 11. Regioselective cycloadditions of NOs to substituted allylic alcohols.

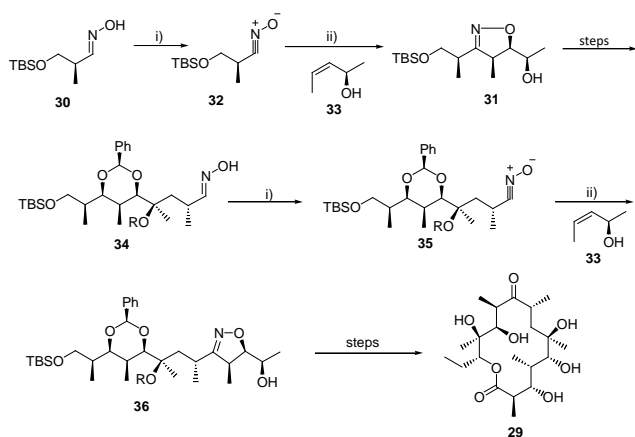
This methodology has been extended to homoallylic alcohols (see for instance Scheme 12).⁶⁶ The selectivity and diastereoselectivity (chiral homoallylic alcohols) in these cycloaddition reactions were explained using conformational analysis of transition structures.⁶⁷



Scheme 12. Diastereoselective dipolar cycloaddition of NOs to homoallylic alcohols.

As a synthetic application,⁶⁸ the stereoselective total synthesis of erythronolide A (the parent of several classic antibiotics, including erythromycin) **29**, using two Mg(II)-mediated CA of NOs has been described. The total synthesis of **29** was completed in 21 linear steps from the readily available oxime **30** which was transformed into isoxazoline **31** in 86% yield and diastereomeric ratio > 95:5 *via* a catalyzed 1,3-DC of NO **32** and allylic alcohol **33**. After transformation of **31** into oxime **34**, a second Mg(II)-mediated 1,3-DC of NO

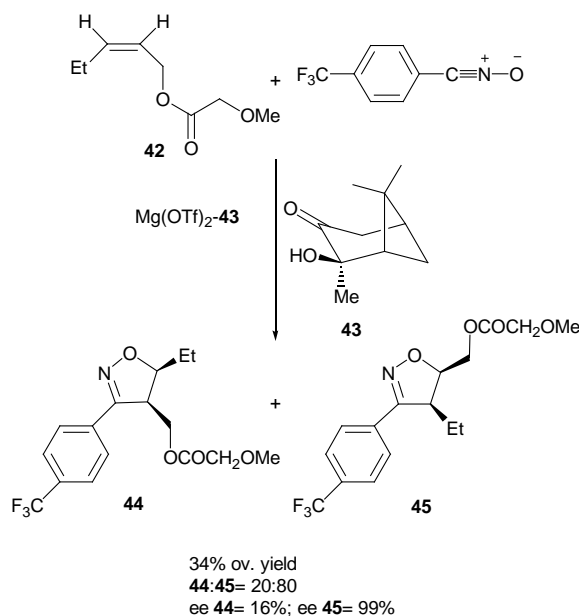
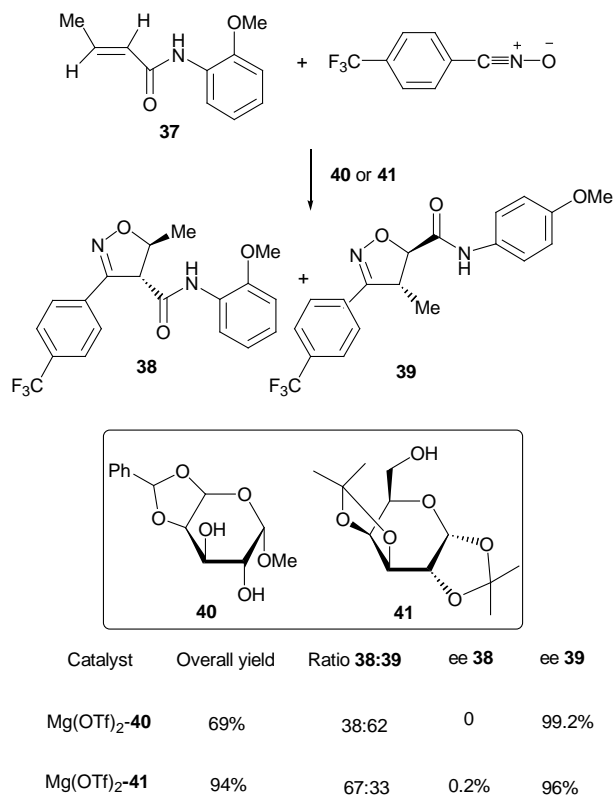
35 with the same allylic alcohol **33** gave compound **36** (86%) as a single diastereomer. From **36**, the target compound **29** was obtained in eight final reaction steps (Scheme 13).



Reaction conditions: i) t-BuOCl, CH₂Cl₂, -78°C, 86%, d.e.: >95:5; ii). i-PrOH, EtMgBr, 0°C to r.t. 86%, d.e. >99:1.

Scheme 13. Synthetic approach to erythronolide A.

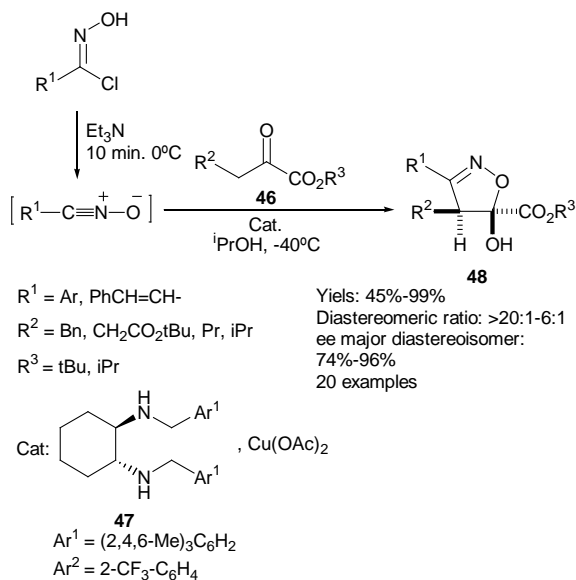
The asymmetric syntheses of a variety of isoxazolines from achiral NOs and alkenes using complexes of Mg (II) salts with chiral ligands have been reported.⁶⁹ Several more recent examples are described as follows: excellent enantioselectivities were achieved in the 1,3-DC of 4-trifluoromethylbenzoxazole with unsaturated amides⁷⁰ such as **37** and esters⁷¹ such as **42** using complexes of Mg(OTf)₂ with the sugar derivatives **40** and **41** and with (+)-2-hydroxy-3-pinane **43** respectively.



Scheme 14. 1,3-DC of NOs catalyzed by Mg(OTf)₂.

Transiently generated enolates of α -keto esters **46** reacted with NOs under Cu(II)-diamine complex

catalyst **47** to give 5-hydroxy-2-isoxazolines **48** (Scheme 15). The catalyst system was found to be compatible with *in situ* NO generation.⁷²

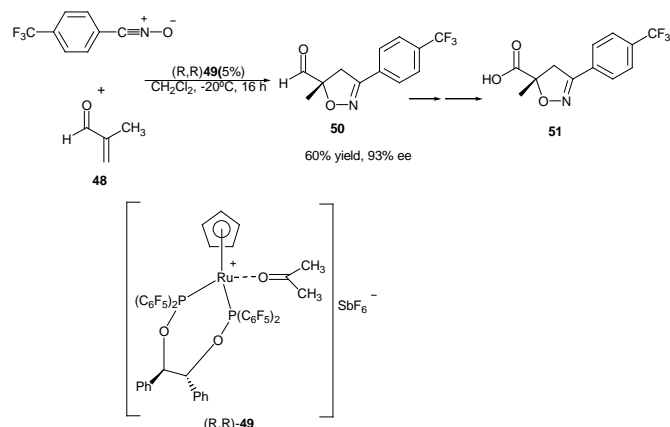


Scheme 15. 1,3-DC of NOs catalyzed by Cu(II) diamine complex **47**.

3.1.3. Ru(II)catalyzed 1,3-DC of NOs.

In general, the cyclopentadienyl-RuL* catalysts show good stability in solution at ambient temperature and efficient catalyst recovery.⁷³ That is the case of the Ru(II) catalyzed 1,3-DC of NOs is the 1,3-DC reactions of NOs with methacrolein **48** in the presence of [Ru(acetone)(R,R)-BIPHOP-F]Cp][SbF₆] **49**. NOs bearing electron-withdrawing substituents at the 4-position on the aromatic ring gave higher ee values than those having electron-donating substituents. That is the case, for instance, of *p*-trifluoromethylbenzoxirone (Scheme 16).⁷⁴ The stereochemistry of the major

enantiomer was deduced as *S* *via* chemical correlation with the known carboxylic acid **51**. The assigned stereochemistry is consistent with an approach of the NO to the C α -Si face of the enal in the *anti-s-trans* conformation in the catalyst site.



Scheme 16. Reaction of NO **26** with methacrolein in presence of catalyst (R,R)-**49**.

3.1.4. Rare earths catalyzed 1,3-DC of NOs.

It is known that the 1,3-DC reactions may be catalyzed by rare earth complexes including reactions of azides⁷⁵ and mesoionic compounds⁷⁶ with different dipolarophiles. In the case of NO cycloadditions the application of chiral ligands such as the carbohydrates **40**, **41** (Scheme 14) and **52**, sparteine **53**, quinine derivatives such as **54** and R-BINOL **55** complexes (Figure 3) with Yb(OTf)₃ and CsF to control of regio- stereo- and enantioselectivity of the dipolar cycloaddition reactions of NOs to amides (Reference

70) and esters (Reference 71) has been extensively explored.

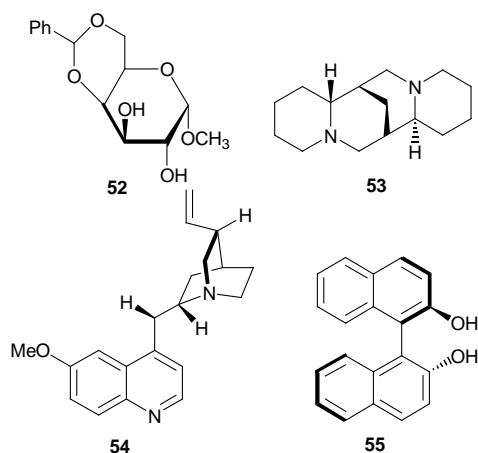
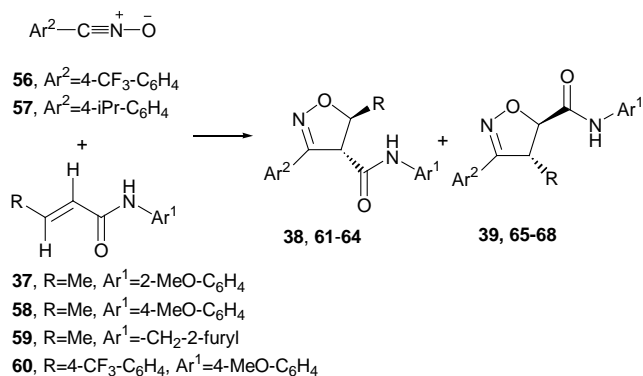


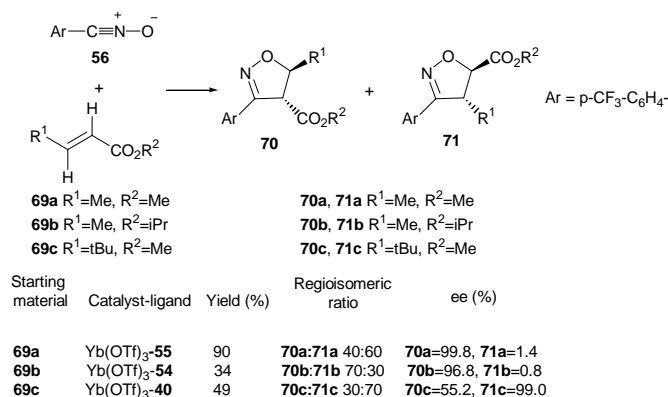
Figure 3. Structure of the catalysts **52-55**.

Some significant examples are quoted in Schemes 16 and 17. Other examples on the use of rare earths as catalyst in 1,3-DC reactions of NOs have also been described.⁷⁷



Scheme 16. Catalyzed 1,3-DC of NOs **56** and **57** and amides **37** and **58-60**. For compounds **37**, **38** and **39** and for catalyst

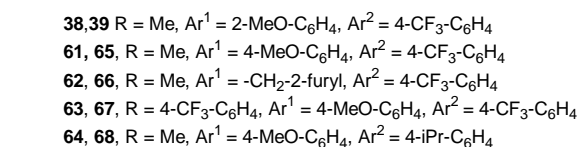
41 see Scheme 14.



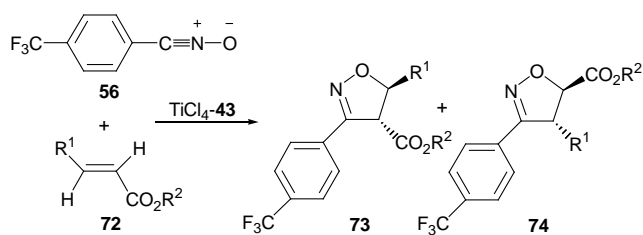
Scheme 17. Catalyzed 1,3-DC of NO **56** and esters **69a-c**. For catalyst **40**, see Scheme 14.

3.1.5. Ti(IV) catalyzed 1,3-DC of NOs.

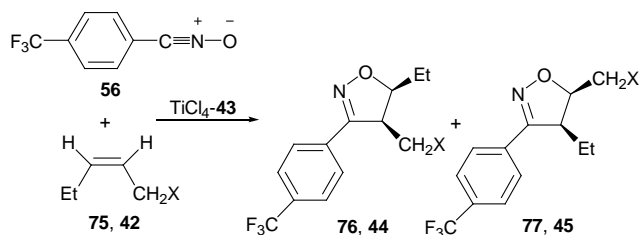
Few cases concerning Ti-catalyzed CA of NOs were reported. Among them, chiral TiCl₄-mediated 1,3-DC reactions of aryl NOs and α,β -unsaturated esters (Reference 71) and amides (Reference 70) have been described. Some significant examples are depicted in Schemes 18 (esters) and 19 (amides).



Starting materials	Catalyst-ligand	Yield (%)	Regioisomeric ratio	ee (%)
37+56	Yb(OTf) ₃ - 52	74	38:39 60:40	38 =0.4, 39 =95
37+56	Yb(OTf) ₃ - 41	84	38:39 80:36	38 =0, 39 =95
37+56	Yb(OTf) ₃ - 53	51	38:39 60:40	38 =1.2, 39 =95
37+56	CsF- 52	74	38:39 28:72	38 =28, 39 =92
37+56	CsF- 41	94	38:39 32:68	38 =2.2, 39 =99
58+56	Yb(OTf) ₃ - 53	40	64:68 79:21	64 =20, 68 =98
59+57	Yb(OTf) ₃ - 54	53	62:66 36:64	62 =3, 66 =94
60+57	Yb(OTf) ₃ - 55	48	63:67 18:82	63 =59, 67 =93



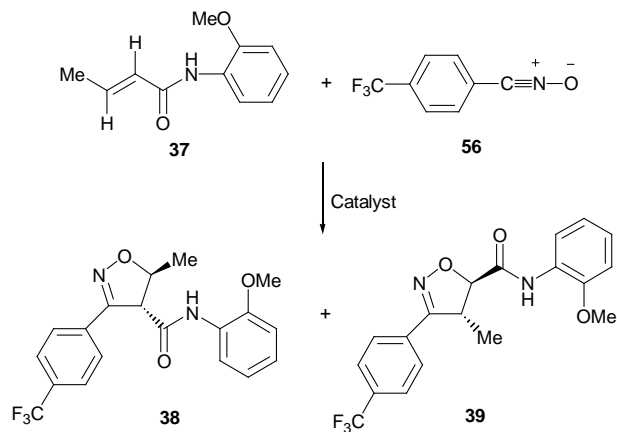
72a, **73a**, **74a**: $\text{R}^1 = \text{Cyclohexyl}$, $\text{R}^2 = \text{Me}$; Yield 37%;
 Ratio **73a**:**74a** = 25:75; ee **73a**=99%, ee **74a**=30.6%
72b, **73b**, **74b**: $\text{R}^1 = \text{Me}$; $\text{R}^2 = \text{Bn}$; Yield 40%;
 Ratio **73b**:**74b** = 65:35; ee **73b**= 93.2%, ee **74b** = 100%



75, **76**, **77**: $\text{X} = \text{CO}_2\text{Me}$ Yield 32%;
 Ratio **76**:**77** = 82:18; ee **76**= 64.6%, ee **77** = 97.2%
42, **44**, **45**: $\text{X} = \text{OCOCH}_2\text{OMe}$; Yield 37%;
 Ratio **44**:**45** = 81:19; ee **44** = 25.8%, ee **45** = 99%

Scheme 18. Ti(IV) catalyzed 1,3-DC of NO **56** and esters **42**, **72** and **75**. For compounds **42**, **44** and **45** and for catalyst **43**

see Scheme 14.



Catalyst	Yield	Ratio 38 : 39	ee 38	ee 39
TiCl_4 - 52	43%	24:76	41%	92%
TiCl_4 - 53	31%	77:27	0	93%

Scheme 19. Ti(IV) catalyzed 1,3-DC of NO **56** and amide **37**.

The structures of **52** and **53** are depicted in Figure 3. For compounds **37**, **38** and **39** see Scheme 14.

4. Cu(I) and Ru(II) Catalyzed 1,3-DC of NOs and Alkynes. Click Chemistry using NOs.

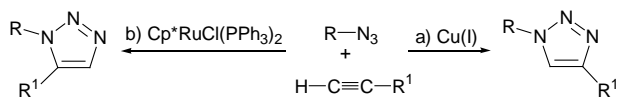
4.1. Click Chemistry. An Overview.

The term "Click Chemistry" was introduced by K. B. Sharpless to describe "stereospecific high yielding reactions, wide in scope, create only by-products that can be removed without chromatography, simple to perform, and conducted in easily removable or benign solvents".⁷⁸

Considering the 1,3-DC reactions, the azide-alkyne cycloaddition giving 1,2,3-triazoles fulfills many of the prerequisites of a typical click chemistry reaction.

However, these thermal 1,3-DCs usually require elevated temperatures and often produce mixtures of the two possible regioisomers when using asymmetric alkynes. Thus, this classic 1,3-DC fails as a true click reaction. Nevertheless, the copper-catalyzed variant [copper(I)-catalyzed alkyne-azide cycloaddition CuAAC]⁷⁹ following a different mechanism regarding the uncatalyzed reaction can be conducted under aqueous conditions⁸⁰ even at room temperature and in a totally regioselective fashion towards the 1,4-disubstituted regioisomer (Scheme 20, a). By contrast, the ruthenium-catalyzed reaction⁸¹ gives the opposite regioselectivity with the formation of 1,5-disubstituted triazoles (Scheme 20, b). Thus, these catalyzed

reactions comply fully with the definition of click chemistry and have put a focus on CuAAC as a prototype click reaction.



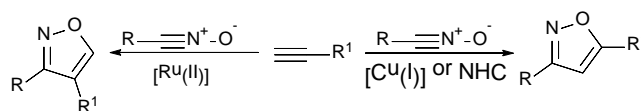
Scheme 20. Regioselectivity in catalyzed azide-alkyne

cycloadditions.

The synthetic applications of “click”-chemistry and, in particular, azide-alkyne CAs have been well documented in recent years in fields such as general synthetic organic chemistry,⁸² synthesis of complex heterocyclic systems,⁸³ medicinal chemistry⁸⁴ (including molecular imaging),⁸⁵ bioconjugation,⁸⁶ radiochemistry,⁸⁷ material science and supramolecular chemistry⁸⁸ (including dendrimer chemistry⁸⁹ and polymeric materials),⁹⁰ development of chemical⁹¹ and electrochemical⁹² sensors, organometallic complexes,⁹³ glycochemistry,⁹⁴ aminoacids,⁹⁵ nucleoside, nucleotide and oligonucleotide chemistry⁹⁶ and peptidomimetics synthesis.⁹⁷ The catalyzed azide-alkyne CA has been successfully achieved under microwave (MW) or ultrasound activation.⁹⁸ The solid-phase synthesis using click chemistry⁹⁹ and the use of copper nanoparticles as catalysts in click reactions¹⁰⁰ have also been developed.

4.2. The Nitrile Oxide “Click” Reactions.

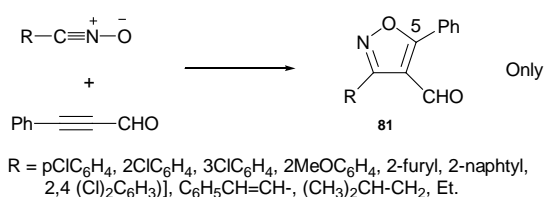
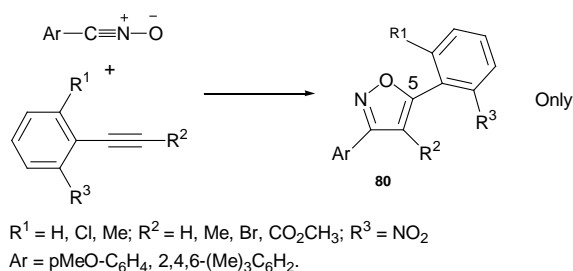
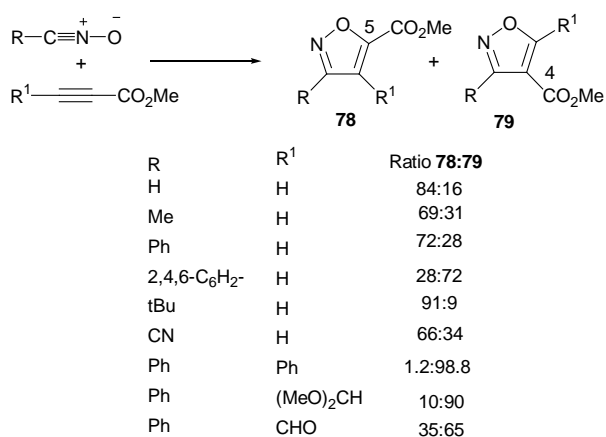
Most CAs between NOs and alkynes are catalyst-free, but regiocomplementary control has been demonstrated in the presence of a copper, a ruthenium catalyst¹⁰¹ or an *N*-heterocyclic carbene (NHC).¹⁰² Both the copper- and the carbene-mediated reactions promote formation of 3,5-disubstituted isoxazoles, whereas ruthenium catalysis favours 3,4-disubstituted ones (Scheme 21). In addition, notorious acceleration was observed for these catalyzed reactions. For instance, thermal cycloaddition of 4-methoxybenzoxynitrile oxide to phenylacetylene resulted, after 8 h at 60°C, in a 4:1 mixture of regioisomers (in favor of the 3,5-isomer) in 62% combined yield, whereas a single 3,5-regioisomer in 92% yield was obtained after 1 h at ambient temperature when copper(I) catalyst was added.¹⁰³



Scheme 21. Catalyst-controlled regioselective cycloaddition reactions between NOs and terminal alkynes.

It should be pointed out that the regioselectivity of the uncatalyzed CA reactions of NOs with unsymmetrical alkynes, in particular with electron-deficient acetylenes, constitutes a puzzle which has led to intense mechanistic and theoretical scrutiny. Some selected examples are quoted in Scheme 22. Although

the 5-substituted isoxazoles **78**, **80** and **81** are usually the major products, significant amounts of the 4-substituted isomer **79** are often obtained depending on the structures of the NO, alkyne¹⁰⁴ and even on the reaction solvent.¹⁰⁵



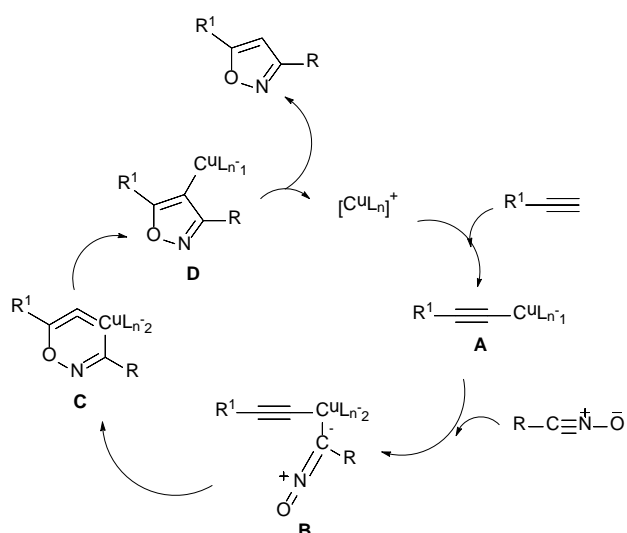
Scheme 22. Some Regioselectivities in the 1,3-DC of NOs and Unsymmetrical Alkynes.

4.2.1. Proposed mechanism of the Cu(I)-catalyzed 1,3-DC of NOs with alkynes.

In the presence of copper(I) acetylides NOs react with alkynes providing 3,5-disubstituted isoxazoles.¹⁰⁶

Computational studies revealed a stepwise mechanism such as follows: the catalytic sequence begins (Scheme 23) with the coordination of the alkyne to the Cu(I) species [CuL_n]⁺ displacing one of the L ligands (intermediate **A**). In the case of acetonitrile ligands this step was calculated to be endothermic, by ca. 0.6 Kcal·Mol⁻¹. However, with water as a ligand, the displacement process becomes exothermic in 11.7 Kcal·Mol⁻¹. 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 oxygen 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⁻¹, some 7 Kcal·Mol⁻¹ lower than for the thermal process. That corresponds to a rate acceleration of 5 orders of magnitude.

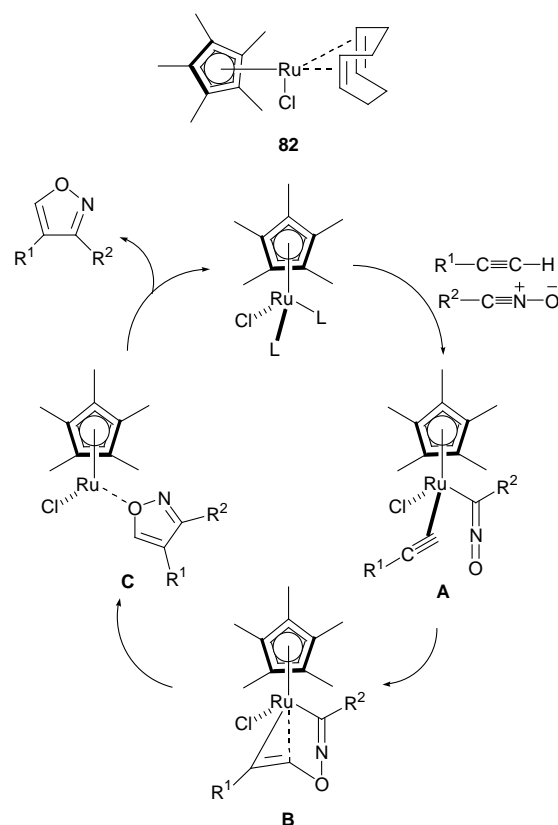


Scheme 23. Proposed Reaction Mechanism for the Cu(I)-Catalyzed 1,3-DC of NOs and Alkynes.

4.2.2. Proposed mechanism of the Ru(II)-catalyzed 1,3-DC of NOs with alkynes.

In the first step of the proposed mechanism¹⁰⁷ for the ruthenium(II)-catalyzed reaction using [Cp**Ru*Cl(cod)] **82** as catalyst (Scheme 24), the displacement of a cyclooctadiene ligand from the ruthenium catalyst¹⁰⁸ 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 nitrile oxide. That represents an unexpected mode of activation of NOs because normally their carbon center is electrophilic and readily reacts with nucleophiles.¹⁰⁹

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.

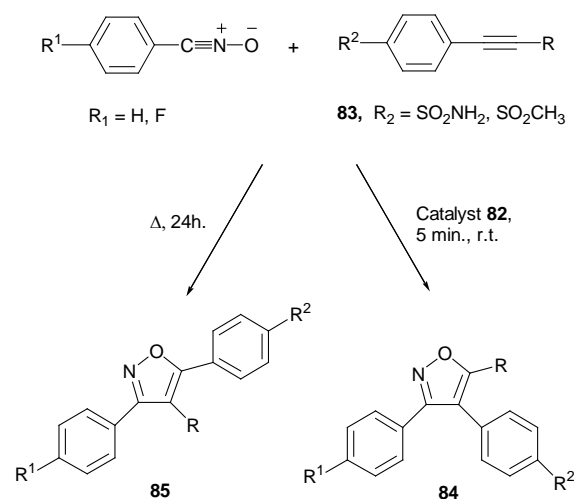


Scheme 24. Proposed Reaction Mechanism for the Ru(II)-Catalyzed 1,3-DC of NOs and Alkynes.

4.3. A brief comparison between catalyzed and thermal 1,3-DC of NOs with alkynes.

At this point it seems convenient to illustrate the difference between catalyzed and non-catalyzed processes in terms of reactivity and regioselectivity. In general, the uncatalyzed, thermal CA reactions of NOs with alkynes are neither chemo- nor regioselective.

This is not surprising considering the high reactivity of NOs faced with the relatively low reactivity of alkynes as dipolarophiles. On the other hand, although copper(I) acetylides have been shown to react regioselectively with NOs to generate 3,5-disubstituted isoxazoles the regiocomplementary 3,4-disubstituted isomers may be easily obtained using Ru(II) derived catalyst. In addition, thermal reactions of NOs with internal alkynes are limited to highly activated alkynes such as acetylene dicarboxylate and other electron-deficient alkynes. In contrast, Ru(II) catalyst allow to carry out this type of reactions. For instance, in a recent report,¹¹⁰ the cycloaddition of aryl NOs and aryl alkynes **83** in the presence of catalyst **82** afforded 3,4-diaryl-substituted isoxazoles **84**. Compounds **84** are valdecoxib-based cyclooxygenase-2 inhibitors.¹¹¹ Interestingly, the reactions achieved under thermal conditions gave the 3,5-diaryl substituted derivatives **85** (Scheme 25).



Scheme 25. Catalyzed and Thermal 1,3DC of NOs and Disubstituted Alkynes.

5. Conclusions.

The utility of nitrile oxides as 1,3 dipoles in cycloaddition reactions (both inter- and intramolecular variants) has been intensively studied during the last four decades 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.

In most cases, the uncatalyzed, thermal cycloaddition reactions of nitrile oxides with asymmetric 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 metal catalysts, including Lewis acids, 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. In general, these procedures constitute interesting tools for the synthesis of cycloadducts in improved yields and regioselectivity compared with the uncatalyzed reactions.

On the other hand, regiocomplementary control has been demonstrated in cycloaddition reactions between nitrile oxides and alkynes in the presence of Cu(I), Ru(II) and NHC-catalysts: the Cu(I)- and NHC-catalyzed variants following a different mechanism regarding the uncatalyzed reaction can be conducted in a totally regioselective fashion towards the 3,5-disubstituted regioisomer. By contrast, the Ru(II)-catalyzed reaction, gives the opposite regioselectivity with the formation of 3,4-disubstituted isoxazoles. Thus, these catalyzed reactions comply fully with the definition of click chemistry and have put a focus on nitrile oxide-alkyne cycloaddition as a prototype click reaction.

This article has reviewed the recent advances of metal-catalyzed nitrile oxide – alkene and alkyne cycloaddition reactions and in our opinion, it cannot be doubted that applications of these reactions will

certainly contribute to future creative advances in fields such as chemical biology and materials science.

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7. Notes: The authors declare no competing financial interest.

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