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DIPOLAR CYCLOADDITIONS OF NITRONES IN AQUEOUS MEDIA

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Abstract — 1,3-Dipolar cycloadditions of nitrones in aqueous media have been recently exploited as a non-conventional protocol in the synthesis of the fully- or partly-saturated isoxazole ring. Water as the reaction medium can affect positively both cycloaddition rates and yields, while the large array of latent functionalities displayed by the cycloadducts is of interest in their further transformations. A systematic review of literature data is given; improvements with respect to the nitrone cycloaddition carried out in organic solvents will be taken into account.

CONTENTS

I. INTRODUCTION

Although water is the solvent of choice for nature to perform its chemical transformations, the overwhelming majority of organic chemists carries out their reactions in non-aqueous media. This is a consequence of the well-known fact that water can be aggressive towards many classes of organic functionalities and intermediates, thus leading to a strict exclusion of water from reaction mixtures. On the other hand, the use of water as the reaction medium displays a number of desirable features: (*i*) the pH can be easily monitored,[1] (*ii*) reaction rates can be significantly increased,[2-9] (*iii*) product separation can often be achieved by simple filtration of the crude reaction mixture,[10,11] and (*iv*) environmentally-friendly procedures can be successfully elaborated in some cases.[12,13] In the light of these considerations it is not surprising that some general reviews[14-22] and books[23-26] have appeared in the last decade covering the field of water-promoted organic reactions. Among the organic transformations which appear to benefit from aqueous media, 1,3-dipolar cycloadditions occupy a prominent place and their behaviour in water has

been recently reviewed.[27-29] Recent papers on this subject are related to azides,[30-33] nitrile oxides,[34,35] and nitrilimines[36-40] as a fertile source of heterocycles. Curiously enough, nitrone cycloadditions in aqueous media have received little attention in such reviews despite the large array of latent functionalities displayed by the fully- or partly-saturated isoxazole ring in the cycloadducts.[41]

The aim of this paper is to present the first systematic review devoted to the growing field of nitrone cycloadditions carried out in aqueous media. Improvements with respect to the cycloadditions performed in organic solvents will be taken in account as well as novel fascinating topics like micelle-promoted[42] and organocatalytic nitrone cycloadditions.

II. INTERMOLECULAR CYCLOADDITIONS

Nitrones were first prepared by von Beckmann in 1890,[43] and they were soon recognised as species "capable to undergo addition 1,3".[44] Seven decades later, the monumental work on 1,3-dipolar cycloadditions performed by Huisgen allowed the classification of nitrones as belonging to the family of azomethinium betaines.[45-47] The behaviour of nitrones in organic solvents was then studied deeply[48-50] and the issue of cycloaddition regio- and stereoselectivity was rationalised in the light of the FMO theory.[51,52]

It is well-known that 1,3-dipolar cycloadditions are usually concerted processes whose rate is scarcely influenced by the solvent.[47] The speed-up of cycloaddition rates in water is mainly due to the hydrophobic effect,[43,54] which expresses the tendency of non-polar, little water-soluble organic species to aggregate themselves in order to reduce the contact surface between water and the non-polar organic substrates. Such an effect is enforced by the volumetric contraction of the reagents along the reaction coordinate, this means that 1,3-dipolar cycloadditions which show negative activation volumes[55,56] are sensitive to the hydrophobic effect.

For the sake of clarity, the presentation of intermolecular nitrone cycloadditions performed in water or in aqueous media is divided into three parts: kinetic evidences, nitrone-ethylene cycloadditions and nitrone-acetylene cycloadditions.

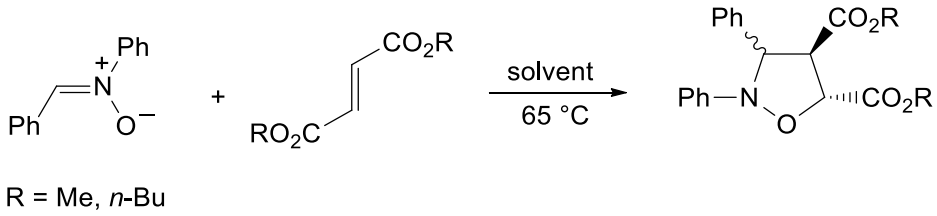
II.1. Kinetic evidences

The cycloadditions between *C*,*N*-diphenylnitrone and di-*n*-butyl fumarate or dimethyl fumarate were investigated in water, aqueous solutions and organic solvents at 65 °C.[57] Second-order rate constants were determined, their values are listed in the Table 1 and deserve some comments. In organic solvents, the rate constants observed in the cycloaddition with dimethyl fumarate were higher than those reported with di-*n*-butyl fumarate. The authors explained this behaviour as a consequence of the larger steric demands of the bulky *n*-butyl group compared to the methyl one. Then, the cycloaddition rates were found to

decrease with increasing polarity of the organic solvent, which was expressed through the normalised Dimroth-Reichardt parameter E_T^N.[58] The following linear relationship between second-order rate constants and E_T^N was found.

$$\text{Log } k_2 = -2.754 - 1.182\ E_T^N$$

The second-order rate constants as a function of R were just reversed in the case of the cycloadditions performed in water or aqueous solutions. This points to the facts that: (*i*) as can be supposed from their concerted nature, the nitrone-olefin cycloadditions are scarcely influenced by the solvent polarity, (*ii*) the dramatic speed-up of cycloaddition rates in water or aqueous solutions[59] depends upon the hydrophobic effect. In fact, the presence of alkali metal salts in water markedly increased the cycloaddition rate of the more lipophilic di-*n*-butyl fumarate; the increase of alkyl chain lenght enhances the hydrophobicity of the fumarate giving more effective hydrophobic interactions. By contrast, the presence of urea in water incresases the solubility of non-polar organic species thus decreasing the hydrophobicity of the reactants and hence the cycloaddition rates.



R = Me, *n*-Bu

Scheme 1

Table 1. Second-order rate constants of the cycloaddition between *C*,*N*-diphenylnitrone and di-*n*-butyl fumarate or dimethyl fumarate at 65 °C

Solvent	E_T^N	k_2 ($10^4 M^{-1}s^{-1}$)	
		di-*n*-butyl fumarate	dimethyl fumarate
n-hexane	31.0	19.4	23.0
toluene	33.9	5.8	11.2
benzene	34.3	5.6	9.4
THF	37.4	5.9	12.6
DMF	43.8	2.5	5.1
1-propanol	50.9	2.2	3.1
EtOH	51.9	1.9	2.9
ethylene glycol	56.3	34.9	17.0
water	63.1	237	379
water + KCl (2M)	—	876	42.8
water + NaCl (2M)	—	924	47.1
water + LiCl (2M)	—	985	74.3
water + urea (2M)	—	142	25.2

Second-order rate constants of the cycloadditions between *C,N*-diphenylnitrone and di-*n*-butyl fumarate in aqueous solutions of ethanol and 1-propanol were also obtained. The increase of the cycloaddition rate at low mole fractions of water is quite slow. At higher mole fractions of water in ethanol, the cycloaddition rates increases more rapidly compared with the solutions in 1-propanol. This can be due to the better ability of 1-propanol to dissolve the organic reactants thus decreasing their hydrophobicity.

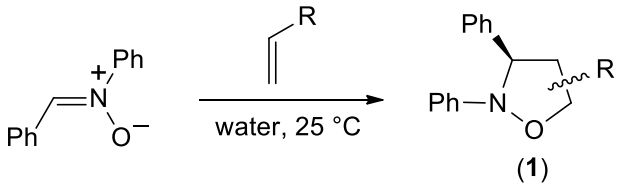
The activation parameters have been calculated in the case of the cycloaddition between *C,N*-diphenyl-nitrone and dimethyl fumarate in various solvents including water.[57] The values listed in the Table 2 show that the activation entropy in water is positive in contrast with organic solvents. This may be due to the presence of organic aggregates which are capable to partly destroy the well-ordered structure of water. The positive sign of the $T\Delta S^{\neq}$ terminus implies higher cycloaddition rates compared to organic solvents.

Table 2. Activation parameters of the cycloaddition between *C,N*-diphenylnitrone and dimethyl fumarate

Solvent	$\Delta H^{\neq}$ (KJ/mole)	$T\Delta S^{\neq}$ (J/K mole)	E_a (KJ/mole)
toluene	54.8	– 47.6	57.6
benzene	56.8	– 46.1	59.6
DMF	56.8	– 47.7	59.6
1-propanol	59.7	– 46.2	62.5
ethylene glycol	82.2	– 19.0	85.1
water	123.9	+ 24.2	126.7

II.2. Nitrone-ethylene cycloadditions

The reaction between *C,N*-diphenylnitrone and methyl acrylate, acrylonitrile or vinyl acetate constitutes one of the first examples of intermolecular nitrone-olefin cycloadditions in water (Scheme 2).[60] As can be inferred from Table 3, the reactions performed in water gave better yields compared to benzene, although isoxazolidine cycloadducts (**1**) were obtained as mixtures of regio- and stereoisomers. In particular, the cycloaddition between *C,N*-diphenylnitrone and methyl acrylate in water at 25 °C gave a complex mixture of regio- and stereoisomeric cycloadducts (see Scheme 3) whose ratio did not change significantly in benzene. It was found that the concentration of the organic reactants suspended in water did not affect cycloaddition rates and yields. This behaviour was rationalised by the authors as the result of hydrogen bonding occurring between water and the carbonyl oxygen of the dipolarophile. Within this picture, the reactivity of the conjugated dipolarophiles should be enhanced due to the greater electrophilic charachter of the β-carbon subjected to nitrone attack.[61] A similar degree of complexity was observed in the reaction of the tymine-based nitrone (**2**) with alkyl acrylates (Scheme 4, Table 4).[62]

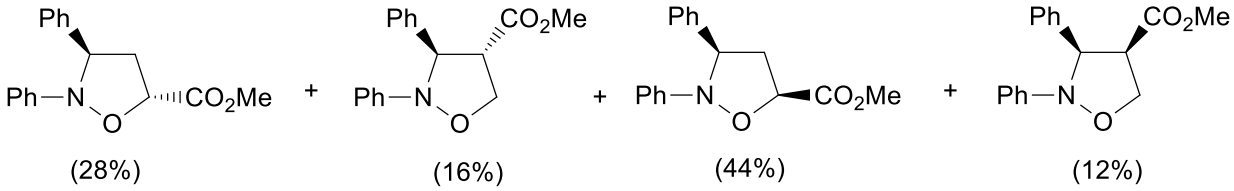


R = CO_2Me, CN, OAc

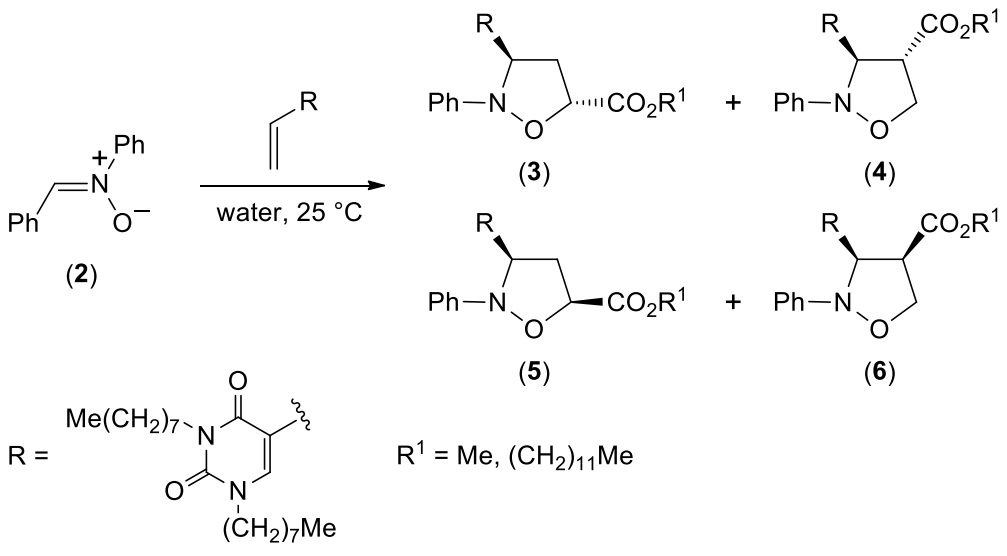
Scheme 2

Table 3. Cycloadditions between *C,N*-diphenylnitrone and ethylenic dipolarophiles at 25 °C

R	Solvent	T (h)	(**1**) (%)
CO_2Me	benzene	3	30
CO_2Me	water	3	95
CN	benzene	2.5	15
CN	water	2.5	95
OAc	benzene	18	0.5
OAc	water	18	45



Scheme 3

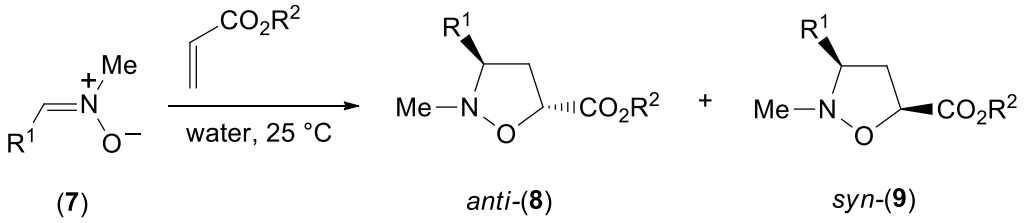


Scheme 4

Table 4. Cycloadditions between nitrone (**2**) and alkyl acrylates at 25 °C

R^1	Solvent	T (h)	Overall yield (%)	Cycloadduct ratio (**3**) : (**4**) : (**5**) : (**6**)
Me	toluene	53	100	50 : 38 : 10 : 2
Me	water	6	100	49 : 41 : 9 : 1
Me	water + LiCl (3M)	5	100	48 : 42 : 9 : 1
$(CH_2)_{11}Me$	toluene	60	94	57 : 43 : 0 : 0
$(CH_2)_{11}Me$	water	5	95	52 : 48 : 0 : 0
$(CH_2)_{11}Me$	water + LiCl (3M)	5	95	50 : 50 : 0 : 0

A moderate diastereopreference to the *anti*-isoxazolidine (**8**) was observed by reacting the decanal-derived nitrone (**7**) with methyl- or dodecyl acrylate, as shown in Scheme 5 and Table 5.[63] Both overall yields and stereoselectivity were scarcely affected from the reaction medium.



(**7**) *anti*-(**8**) *syn*-(**9**)

$R^1 = (CH_2)_8Me$

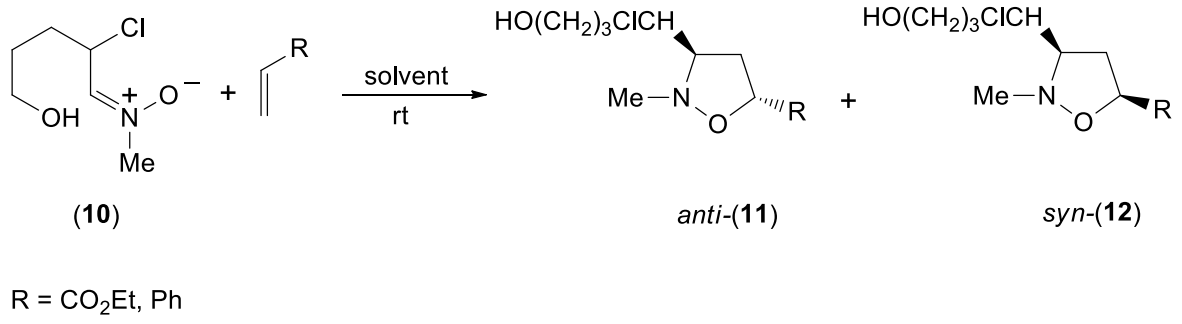
$R^2 = Me, (CH_2)_{11}Me$

Scheme 5

Table 5. Cicloaddition between nitrone (**7**) and alkyl acrylates at 25 ºC

R^2	Solvent	T (h)	Overall yield (%)	*anti*-(**8**) : *syn*-(**9**)
Me	CH_2Cl_2	6	71	77:23
Me	water	1	72	73:27
$(CH_2)_{11}Me$	CH_2Cl_2	6	68	82:18
$(CH_2)_{11}Me$	water	1	69	76:24

A similar behaviour in regio- and stereoselectivity was found in the case of the cycloadditions of chiral (racemic) nitrone (**10**) with ethyl acrylate or styrene (Scheme 6, Table 6).[64-66] The outcome of the reactions carried out in water at rt is much better than that in dichloromethane.



(**10**) *anti*-(**11**) *syn*-(**12**)

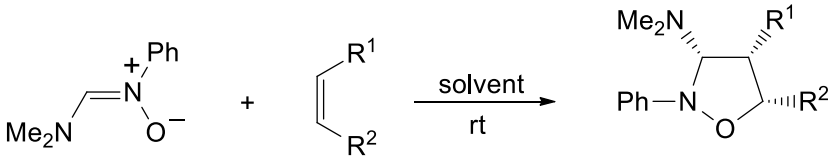
R = CO_2Et, Ph

Scheme 6

Table 6. Cycloaddition between *N*-methyl-*C*-(1-chloro-4-hydroxy)butylnitrone (**10**) and ethyl acrylate or styrene

R^1	R^2	Solvent	T (h)	Overall yield (%)	*anti*-(**11**) : *syn*-(**12**)
CO_2Et	H	CH_2Cl_2	34	69	68:32
CO_2Et	H	water	4	92	72:28
Ph	H	CH_2Cl_2	38	67	67:33
Ph	H	water	5	91	75:25

The nitrone-olefin cycloaddition allows the obtainment of isoxazolidines with significant anti-bacterial properties.[67] An example is given by the reactions between *N*-phenyl-*C*-dimethylaminonitrone (**13**) and several mono- or 1,2-disubstituted ethylenic dipolarophiles (Scheme 7); such cycloadditions gave the *syn*-isoxazolidines (**14**) as single regio- and stereoisomers.[68] It can be inferred from Table 7 that reactions performed in water at rt required shorter times and gave better yields compared to dichloromethane.



(**13**) (**14**)

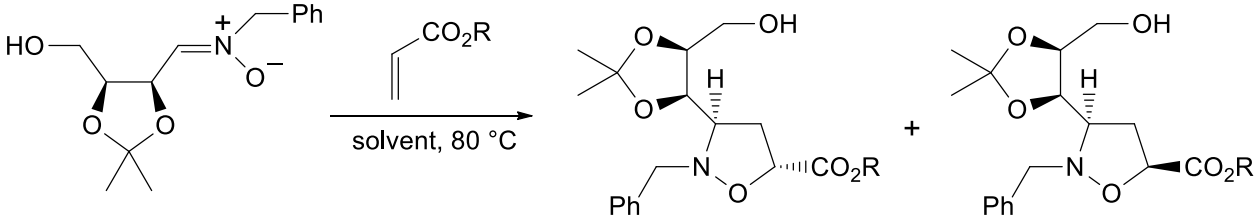
R^1, R^2 = CON(Me)CO,
R^1, R^2 = CON(Et)CO,
R^1, R^2 = CON(4-$MeOC_6H_4$)CO,
R^1 = CO_2Et, R^2 = H,
R^1 = COMe, R^2 = H

Scheme 7

Table 7. Cycloaddition between *N*-phenyl-*C*-dimethylaminonitrone (**13**) and mono- or 1,2-disubstituted ethylenic dipolarophiles

R^1	R^2	Solvent	T (h)	(**14**) (%)
-CON(Me)CO-		CH_2Cl_2	44	57
-CON(Me)CO-		water	4	96
-CON(Et)CO-		CH_2Cl_2	38	54
-CON(Et)CO-		water	4	94
-CON(4-MeO-C_6H_4)CO-		CH_2Cl_2	41	62
-CON(4-MeO-C_6H_4)CO-		water	5	95
CO_2Et	H	CH_2Cl_2	40	60
CO_2Et	H	water	5	93
COMe	H	CH_2Cl_2	42	55
COMe	H	water	5	91

Enantiopure nitrones (**15**) and (**18**) were synthesised from D-ribose and used as key intermediates in the synthesis of aza-C-disaccharides and modified nucleosides.[69] Cycloaddition of (**15**) to alkyl acrylates at 80 °C gave a couple of 5-substituted enantiopure isoxazolidines *anti*-(**16**) and *syn*-(**17**) with low diastereoselectivity (Scheme 8, Table 8).[69] The preferred product *anti*-(**16**) arises from the corresponding *endo* transition state. As far as the cyclic nitrone (**18**) is concerned, a similar behaviour compared to (**15**) was experienced at 25 °C (Scheme 9, Table 9).[69]



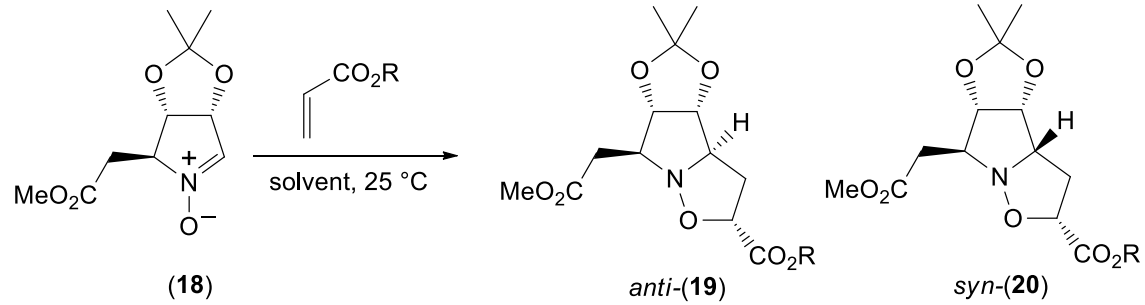
(**15**) *anti*-(**16**) *syn*-(**17**)

R = Me, $(CH_2)_{11}Me$

Scheme 8

Table 8. Cycloaddition of enantiopure nitrone (**15**) to alkyl acrylates at 80 °C

R	Solvent	T (h)	Overall yield (%)	*anti*-(**16**) : *syn*-(**17**)
Me	toluene	144	60	66:34
Me	water	6	65	66:34
$(CH_2)_{11}Me$	toluene	144	65	62:38
$(CH_2)_{11}Me$	water	12	70	62:38

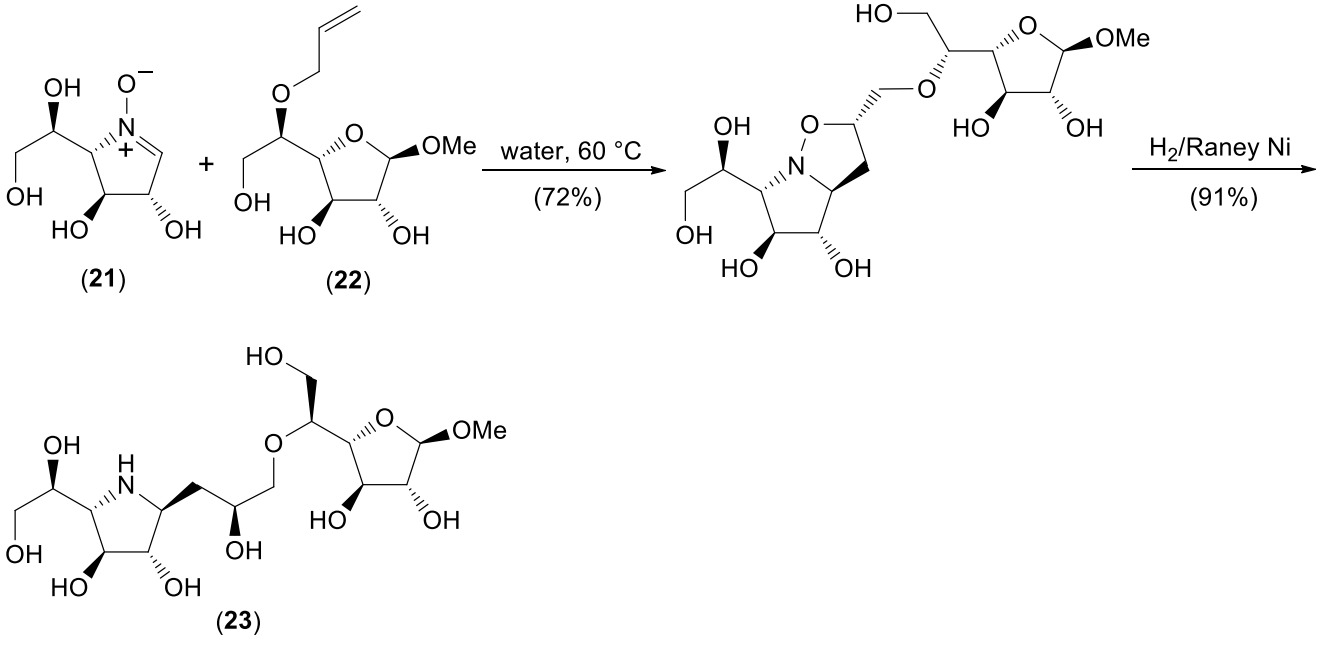


Scheme 9

Table 9. Cycloaddition of enantiopure nitrone (**18**) to alkyl acrylates at 25 °C

R	Solvent	T (h)	Overall yield (%)	*anti*-(**19**) : *syn*-(**20**)
Me	CH_2Cl_2	12	95	67:33
Me	water	5	98	75:25
Me	water + LiCl (3M)	3	98	78:22
$(CH_2)_{11}Me$	toluene	60	80	58:42
$(CH_2)_{11}Me$	water	5	89	62:38
$(CH_2)_{11}Me$	water + LiCl (3M)	5	95	64:36

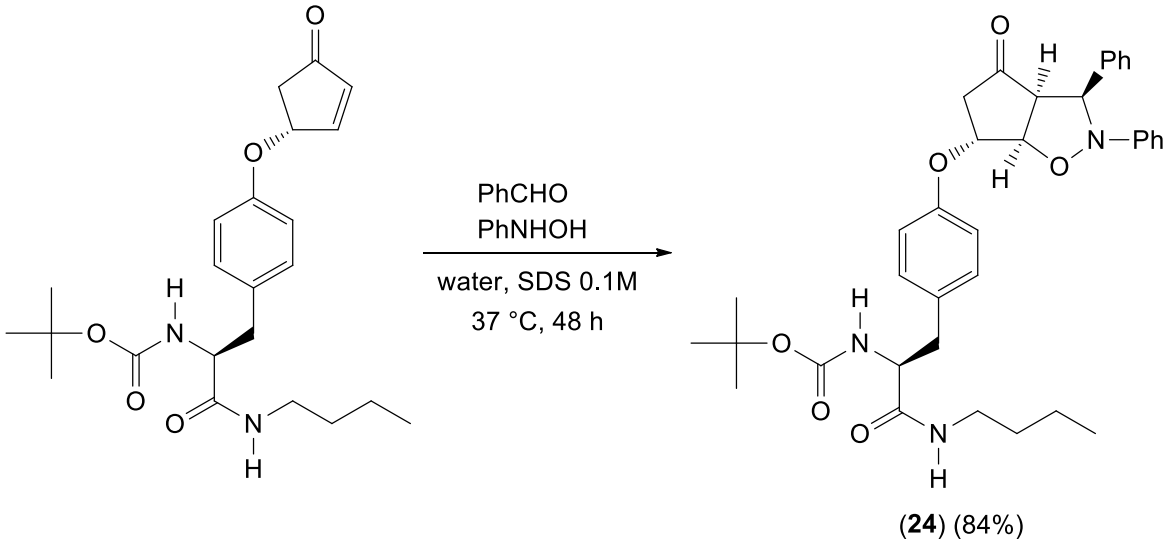
The galactofuranoside disaccharide (**23**) has been obtained as single diastereoisomer in the enantiopure form through a synthetic protocol in which the key step is the cycloaddition between the water-soluble nitrone (**21**) and the *O*-allyl-galactofuranoside (**22**) (Scheme 10).[70]



Scheme 10

To this point, it can be perceived that the acceleration of water-nitrone cycloadditions arises from an interplay of factors. It is known that the rate of nitrone cycloadditions is slightly lowered a little by enhancing the polarity of the solvent,[71,72] so that the high polarity of water[73] can be ruled out as the accelerating cause. A simple but rather partial rationale may be provided on the basis of the FMO theory.[74] Generally speaking, the ethylenic dipolarophiles are weak hydrogen-bond acceptors so that their FMOs are only slightly affected by hydrogen-bond interactions. Conversely, it is known that nitrones are capable to complex Lewis acids,[75-77] thus their FMOs are stabilised in protic solvents. Since nitrone cycloadditions to electron rich ethylenes are usually controlled by the LUMO of the dipole, a better $LUMO_{nitrone}$-$HOMO_{dipolarophile}$ interaction can be envisaged in water. On the other hand, the main reason that explains the observed rate enhancements are mainly due to the hydrophobic effect.[53,54] This statement is substantiated by the beneficial effect of alkali metal salts used as additives, which enhance the ionic strenght of the aqueous medium. A further evidence is provided by the product outcome. Major *anti* isoxazolidines arise from the corresponding *endo* transition states which are tighter than the diastereoisomeric *exo* one[48] so that the former can minimise its barely polar surface with respect to bulk water.

An interesting development of the nitrone-olefine cycloaddition in water is related to the presence of a surfactant in the aqueous medium; this protocol was used to synthesise the novel amino acid (**24**) with orthogonal functionality to the natural amino acid side chains (Scheme 11).[78]

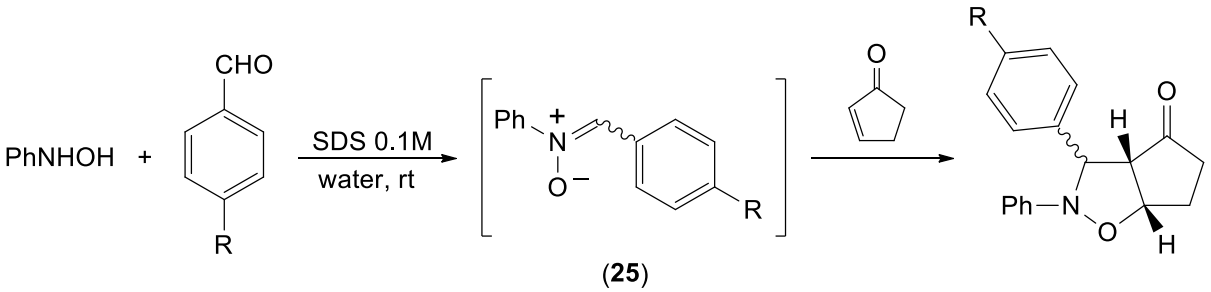


Scheme 11

C,*N*-Diarylnitrones (**25**) were generated *in situ* by the appropriate precursors in the presence of 2-cyclopenten-1-one and sodium dodecylsulfate (SDS) (Scheme 12).[78] The SDS concentration was set as 100 mM. It may be useful to recall that: (*i*) the definition of the critical micellar concentration (CMC) states that "it is the concentration above which molecular aggregates, or micelles, are formed in solution";[79] and (*ii*) the

CMC value for SDS is known to be 8.2 mM.[8] Thus, the generation of nitrones (**25**) and the subsequent cycloaddition occur into a micelle being favoured by the high local concentration of the reagents, since the inner part of the micelle behaves as an hydrophobic nanoreactor.

The plot of Logk_R/k_H as a function of Hammett σ_p is linear with slope $\rho = -0.94$. Such value is consistent with a transition state less polar than the reagents, thus suggesting that the cycloaddition should be faster with electron-donating R.



R = H, OH, OMe, $N(Me)_2$, Me, Cl, CN, NO_2

Scheme 12

In water or aqueous medium, the presence of the surfactant plays a key role in the generation step of nitrones. This is apparent by considering the formation extent of *N*-phenyl-*C*-(2-nitrophenyl)nitrone (**26a**) by condensation between phenylhydroxylamine and 2-nitrobenzaldehyde (Table 10).[80]

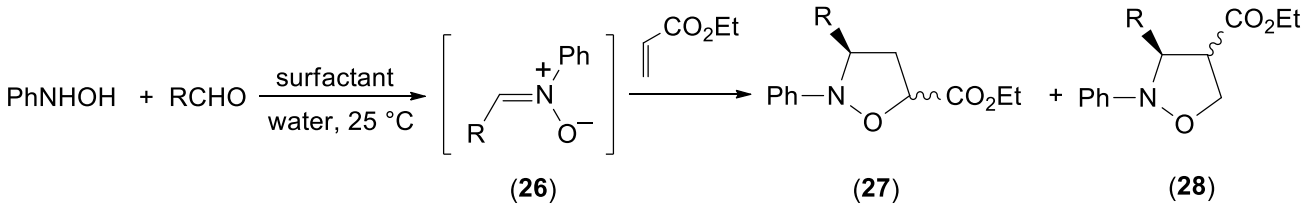
Table 10. Condensation between phenylhydroxylamine and 2-nitrobenzaldehyde at 25 °C

Reaction medium	T(h)	(**26a**) (%)
water + 10% MeOH	> 48	10
water	> 48	—
water + surfactant[a]	1	> 90

[a]SDS or cetyltrimethylammonium bromide (CTAB).

Nitrones (**26**) have been submitted to reaction with ethyl acrylate in the presence of a surfactant giving complex mixtures of regio- and stereoisomeric isoxazolidines (Scheme 13, Table 11).[80] The detailed composition of these mixtures was established through NOE experiments.

The effect of a chiral hydrophobic environment onto the nitrone-olefin cycloaddition was studied by using 3,12-diacryloyl sodium deoxycholate (**29**) as dipolarophilic surfactant (Scheme 14).[60] Treatment of (**29**) with *C*,*N*-diphenylnitrone in water gave a mixture of the corresponding regio- and stereoisomeric steroidal isoxazolidines.



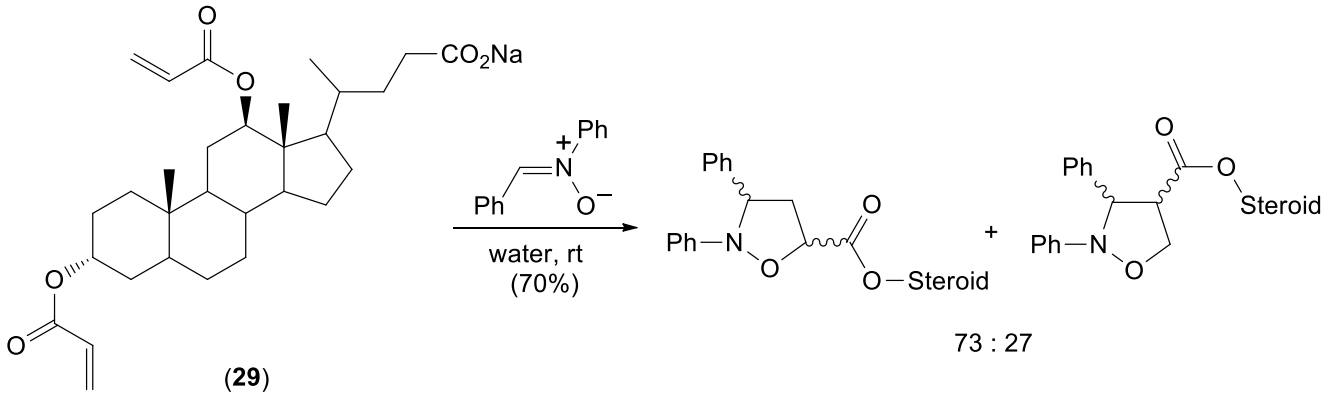
(**26**) (**27**) (**28**)

R = 2-$NO_2C_6H_4$, 3-NO_2-C_6H_4, 4-NO_2-C_6H_4, 4-$MeOC_6H_4$, 2,5-$(MeO)_2C_6H_3$, 4-Cl-C_6H_4, 3-pyridyl, PhCH=CH, $(CH_2)_2Me$

Scheme 13

Table 11. Cycloaddition between nitrones (**26**) and ethyl acrylate in the presence of surfactants

R	Surfactant	T (h)	Overall yield (%)	(**27**) *anti/syn*	(**28**) *anti/syn*
2-NO_2-C_6H_4	SDS	18	79	68/32	—
2-NO_2-C_6H_4	CTAB	18	85	68/32	—
3-NO_2-C_6H_4	SDS	30	81	54/46	—
3-NO_2-C_6H_4	CTAB	26	89	54/46	—
4-NO_2-C_6H_4	SDS	16	76	—	100/0
4-NO_2-C_6H_4	CTAB	16	81	—	100/0
4-MeO-C_6H_4	SDS	76	84	0/100	100/0
4-MeO-C_6H_4	CTAB	72	89	0/100	100/0
2,5-$(MeO)_2$-C_6H_3	SDS	121	27	100/0	—
2,5-$(MeO)_2$-C_6H_3	CTAB	121	38	100/0	—
4-Cl-C_6H_4	SDS	40	90	51/49	100/0
4-Cl-C_6H_4	CTAB	40	91	51/49	100/0
3-pyridyl	SDS	74	89	58/42	—
3-pyridyl	CTAB	70.5	91	58/42	—
PhCH=CH	SDS	50	87	69/31	65/35
PhCH=CH	CTAB	50	90	69/31	65/35
$Me(CH_2)_2$	SDS	48	85	57/43	—
$Me(CH_2)_2$	CTAB	48	85	57/43	—



(**29**)

Scheme 14

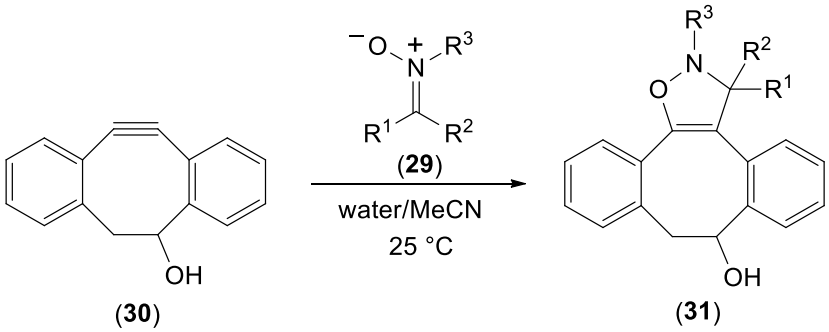
It was reported that in water-based microemulsions the ethylenic dipolarophile can act both as a reagent and as a component of the microemulsion.[81] The cycloaddition between nitrones (**25**) and acrylonitrile has been exploited as a function of the water molar fraction in the microemulsion that constitutes the reaction medium. In the case of the microemulsion composed by water (20%), acrylonitrile (50%), *n*-butanol (20%) and SDS (10%) the formation of an inverse micelle occurs, in which the water droplets are dispersed in acrylonitrile. It was supposed that the nitrone accumulates to the interface between water and acrylonitrile; nitrone reactivity may be spurred as a result of its high local concentration. Compared to the cycloadditions between nitrones (**25**) and acrylonitrile carried out in refluxing toluene, the reactions in microemulsions were featured with mild conditions (25 °C) and better yields (60-80%), although mixtures of diastereoisomeric isoxazolidines (**1**) (R = CN) were always obtained.

Cycloaddition between (**25**) and acrylonitrile has been also pursued in the presence of metal triflates as water-soluble Lewis acid catalysts.[81] The effectiveness of these additives was shown to decrease in the following order: $Cu(OTf)_2 > Sc(OTf)_3 > La(OTf)_3 > Yb(OTf)_3$.

II.3. Nitrone-acetylene cycloadditions

The nitrone-alkyne cycloaddition carried out in organic solvents is a well-known reaction.[82-84] Surprisingly, very few examples of this process have been described in aqueous medium.

Second-order rate constants were measured for the cycloadditions between nitrones (**29**) and the highly-strained dibenzocyclooctynol (**30**) in water/acetonitrile mixtures (Scheme 15, Table 12).[85] This methodology was used in a one-pot three-step protocol for the site-selective modification of peptides and proteins. The cycloaddition rate was dependent by the electronic features of R^2; electron-withdrawing groups speed up the reaction rate due to the better charge localisation of the dipolar reactant. It needs to be added that the presence of water in the reaction medium did not enhance the reaction rate compared to toluene (see footnote **b** in Table 12). Dibenzo-azacyclooctyne (**32**) (Figure 1) was also used as strained dipolarophile, its cycloaddition with *N*-methyl-*C*-(benzyl)amidocarbonyl-nitrone was 17 times faster than that with the less polar dibenzocyclooctynol (**30**) (Figure 1).

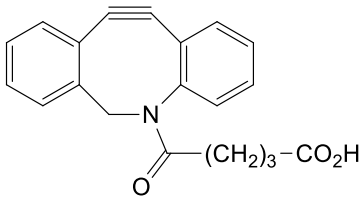


Scheme 15

Table 12. Cycloaddition between nitrones (**29**) and dibenzocyclooctynol (**30**) in water/MeCN[a]

R^1	R^2	R^3	k_2 ($l\ mol^{-1}\ s^{-1}$)	k_{rel}	(**31**) (%)
H	Ph	Me	0.013[b]	1	95
H	$PhCH_2$	Me	0.032	3	80
H	Ph	Ph	> 0.2	> 17	89
Me	CH_2CO_2Et	Me	< 0.01	< 0.1	33
H	CO_2Et	Me	3.9	330	92
H	$CONHCH_2Ph$	Me	2.2	180	93

[a]Water-MeCN 2:1, 25 °C. [b]In toluene: k_2 = 0.022 l mol^{-1} s^{-1}.



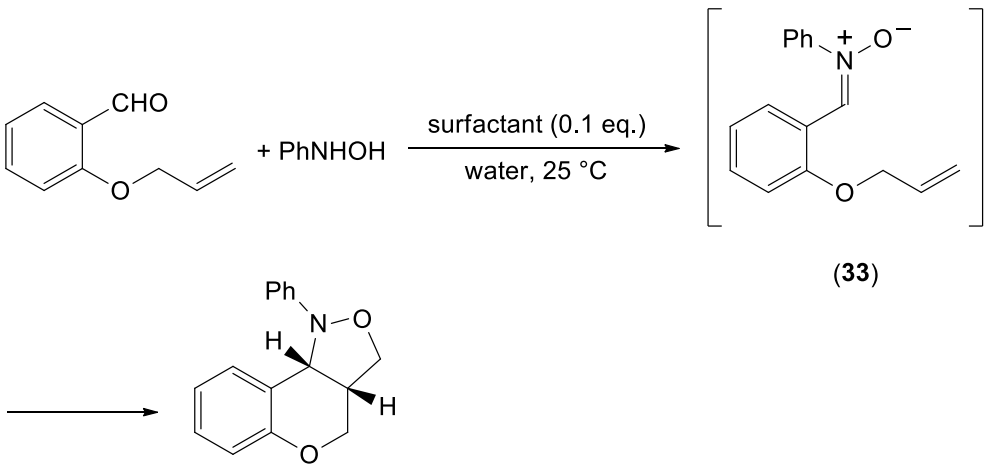
(**32**)

Figure 1

III. INTRAMOLECULAR CYCLOADDITIONS

Compared to the corresponding intermolecular process, intramolecular nitrone cycloadditions usually display: (*i*) better reactivity due to the favourable activation entropies, (*ii*) better stereoselectivity, and (*iii*) the opportunity to obtain fused- or bridged isoxazolidines.[86]

As far as the aqueous medium is concerned, the allyloxynitrone (**33**) was generated *in situ* by treating the corresponding phenylhydroxylamine in the presence of a surfactant (Scheme 16, Table 13).[87]



(**33**)

(**34**)

Scheme 16

Table 13. Intramolecular cycloaddition of nitrone (**33**) in water in the presence of surfactant at 25 °C

Surfactant	T (h)	(**34**) (%)
—	48	0
CTAB	9	92
SDS	18	82
SBDS	20	80
Triton X-100	48	56
Tween 20	48	58
Tween 80	48	55
Triton CF 10	48	60

Reaction times listed in Table 13 are greater than that measured in toluene,[88] but in this latter case the reaction was performed at 110 °C. The intramolecular cycloaddition leading to the chromano[4,3-*c*]-isoxazolidine (**34**) was also attempted in water/cosolvent mixtures but the results were poor due to the ability of the cosolvent to destroy the micelles (Table 14).

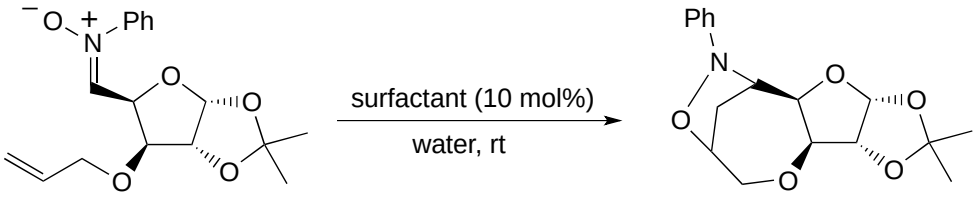
Table 14. Intramolecular cycloaddition of nitrone (**33**) in water in the presence of cosolvent at 25 °C

Cosolvent (%)	T (h)	(**34**) (%)
—	48	0
MeOH (10%)	48	8
MeOH (10%) + CTAB (10%)	48	28
MeCN (15%)	48	10
MeCN (15%) + CTAB (10%)	48	22
THF (10%)	48	5

The stereoselective cycloaddition of the 3-*O*-allylfuranose-derived nitrone (**35**) in water and in the presence of a surfactant gave the bridged tricyclic adduct (**36**) as single enantiopure diastereoisomer (Scheme 17, Table 15).[89] As was pointed out in the case of the allyloxynitrone (**33**), the type of surfactant influenced both the yield and the reaction time (Table 15).

Biosynthetic 1,3-dipolar cycloadditions are very rare.[90] The transannular cycloaddition between a nitrone and an enone in a nine-membered cycle has been proposed as a key step in the biosynthesis of two *Lycopodium* alkaloids, namely lycojaponicumins A and B (see Scheme 18).[91] DFT calculations at the M06-2X level of theory were used to predict whether this cycloaddition could constitute a feasible step in a biosynthetic pathway. These quantum mechanical calculations predicted that the rate of the uncatalyzed

reaction in water is compared with the rate enhancement theoretically achievable when the reaction is catalyzed by a theozyme (theoretical enzyme).[92]

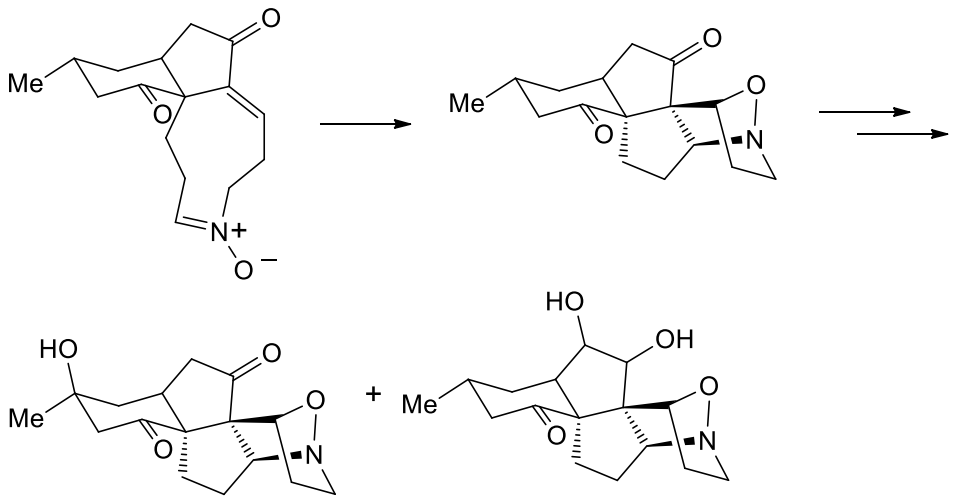


(**35**) (**36**)

Scheme 17

Table 15. Intramolecular cycloaddition of nitrone (**35**) in water in the presence of surfactant at 25 °C

Surfactant	T (h)	(**36**) (%)
—	48	0
CTAB	8	79
SDS	8	75
SBDS	8	75
Triton X-100	30	80
Tween 20	30	80
DBSA	16	61
Triton CF-10	36	79

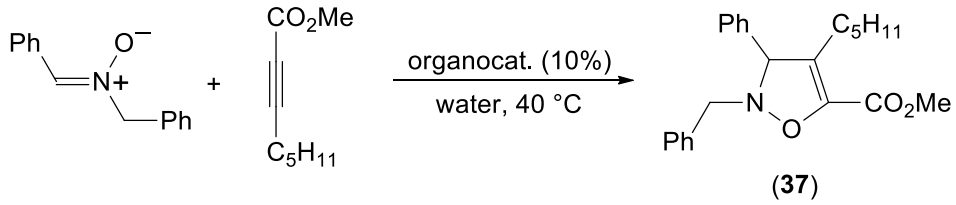


lycojaponicumin A lycojaponicumin B

Scheme 18

IV. ORGANOCATALYSED CYCLOADDITIONS

The reaction between *C*-phenyl-*N*-benzylnitrone and methyl 2-octinoate represents the first example of organocatalysed nitrone cycloaddition in aqueous medium.[93] Several molecules with different steric and electronic features were chosen as the organocatalyst (Scheme 19, Table 16). The isoxazoline cycloadduct (**37**) was obtained with variable yield only in the presence of the organocatalyst, while no reactions occurred in organic solvents. The best results were achieved in the presence of lithium chloride as the additive, in such cases the increase of ionic strenght drives to the enhancement of the hydrophobic effect. The authors recommend to add the reagents to the aqueous medium following the order nitrone-alkynoate (2 equiv.)-catalyst.



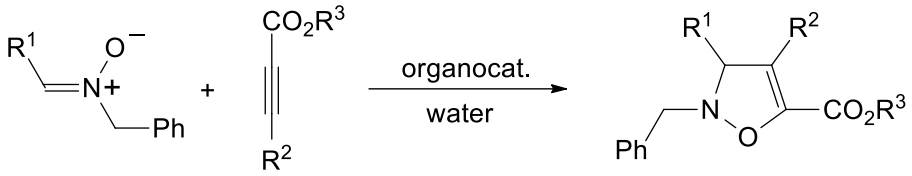
Scheme 19

Table 16. Organocatalysed cycloadditions between *C*-phenyl-*N*-benzylnitrone and methyl 2-octinoate at 40 °C

Solvent	Organocatalyst	T (h)	(**37**) (%)
water	—	48	0
water	Ph_3P	48	10
water – LiCl (3M)	Ph_3P	48	68
water – LiCl (3M)	quinine	48	57
water – LiCl (3M)	DABCO	48	38
water – LiCl (3M)	DMAP	48	36
water – LiCl (3M)	isoquinoline	48	51
toluene	Ph_3P	24	0
CH_2Cl_2	Ph_3P	24	0

The generalisation of the above cycloaddition to other *C*-substituted nitrones and other alkynoates (Scheme 20, Table 17) gave results which are not easy to rationalise since: (*i*) the presence of lithium chloride does not implies necessarily better results, and (*ii*) in some cases quinuclidine act as the organocatalyst of choice while triphenylphosphine plays this role in some other cases.[93]

Anyway, in the presence of triphenylphosphine as the organocatalyst the proposed mechanism relies upon the catalytic cycle outlined in Figure 2. The intervention of the allenolate intermediate (**38**) was substantiated by calculations into the frame of the DFT theory, and the nitrone-allenolate regioselectivity is predictable on the basis of FMO theory.



(**37**)

R^1 = Ph, *n*-Pr, *i*-Pr, Cy, *n*-heptyl

R^2 = Ph, Me, CO_2Et, *n*-pentyl, Cy

R^3 = Me, Et

Scheme 20

Table 17. Organocatalised cycloadditions between *C*-substituted-*N*-benzylnitrones and alkyl 2-alkynoates

R^1	R^2	R^3	Additive	Organocatalyst	T (°C)	(**37**) (%)
Ph	*n*-pentyl	Me	LiCl (3M)	Ph_3P	40	68
Ph	CO_2Et	Et	—	Ph_3P	25	99
Ph	Me	Et	—	Ph_3P	25	35
Ph	Me	Et	LiCl (3M)	quinuclidine	40	49
Ph	Ph	Et	—	Ph_3P	25	61
Ph	cyclohexyl	Et	LiCl (3M)	Ph_3P	40	71
n-Pr	*n*-pentyl	Me	—	Ph_3P	25	81
n-Pr	CO_2Et	Et	—	Ph_3P	25	95
n-Pr	Me	Et	—	Et_3N	25	44
n-Pr	Me	Et	—	quinuclidine	25	26
n-Pr	Ph	Et	—	Ph_3P	25	94
n-Pr	Ph	Et	—	quinuclidine	40	81
n-Pr	*n*-pentyl	Et	—	Ph_3P	25	70
i-Pr	*n*-pentyl	Me	LiCl (3M)	Ph_3P	40	43
i-Pr	*n*-pentyl	Me	LiCl (3M)	quinuclidine	40	75
cyclohexyl	*n*-pentyl	Me	LiCl (3M)	Ph_3P	40	37
cyclohexyl	*n*-pentyl	Me	LiCl (3M)	quinuclidine	40	79
n-heptyl	*n*-pentyl	Me	LiCl (3M)	Ph_3P	40	54
n-heptyl	*n*-pentyl	Me	LiCl (3M)	quinuclidine	40	75

Recently, an interesting organocatalytic strategy has been developed which allows the one-pot synthesis of tetrahydronaphthyl isoxazolidines in aqueous medium at rt by using 2-(*S*)-(diphenyltrimethylsilyl)-methylpyrrolidine (**39**) as the organocatalyst (Jørgensen organocatalyst, Scheme 21, Table 18).[94] Fused tricyclic isoxazolidines (**40**) have been obtained with very high diastereoselectivity; this result is worth of noting because of the five stereocentres of the target molecules, furthermore the enantiomeric excesses were always > 99%.

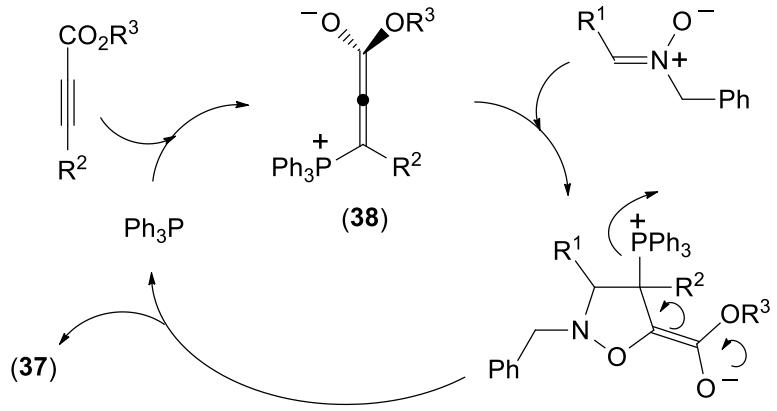
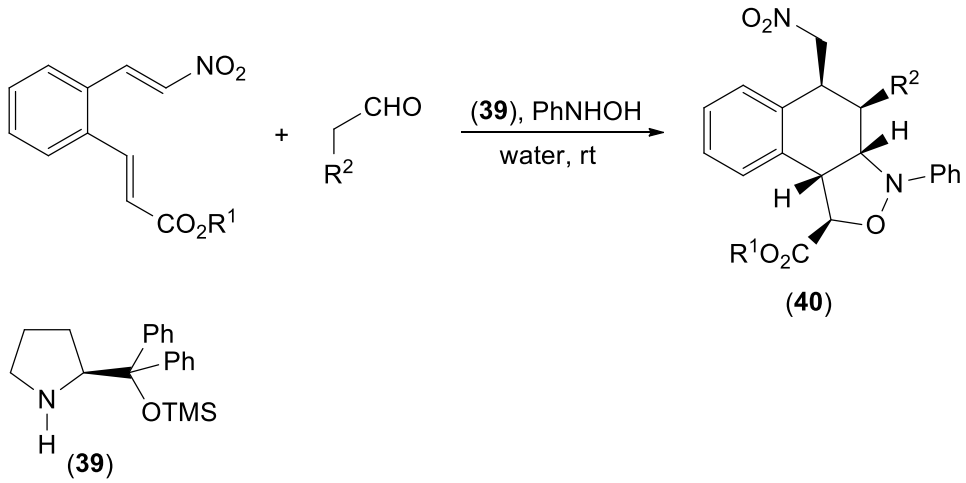


Figure 2



Scheme 21

Table 18. Organocatalysed tandem Michael/condensation/cycloaddition reactions

R^1	R^2	T (h)	(**40**) (%)	D.R.[a]
Et	*n*-Pr	8	73	98:2
Et	Me	6	77	95:5
Et	Et	7	83	98:2
Et	*i*-Pr	22	48	99:1
Et	*n*-hexyl	11	71	99:1
Et	CH_2Ph	8	72	98:2
Et	CH_2CH_2OPh	16	51	97:3
Et	*n*-Pr	10	63	97:3
CH_2Ph	CH_2Ph	10	73	98:2
CH_2Ph	CH_2CH_2OPh	20	52	96:4

[a]Diastereoisomeric ratio.

The catalytic cycle depicted in the Figure 3 give some mechanistic insight about the formation of products (**40**). The initial role of the organocatalyst (**39**) is to convert the carbonyl reagent into the corresponding iminium salt. Subsequent tautomerisation give a transient enamine which is able to give a stereoselective Michael addition to the nitrostyrene moiety. Next, the nitrone intermediate (**41**) is generated and the following stereoselective intramolecular cycloaddition give the target products (**40**). In summary, this organocatalytic reaction cascade implies the sequence: stereoselective Michael addition/nitrone generation/stereoselective intramolecular nitrone cycloaddition.

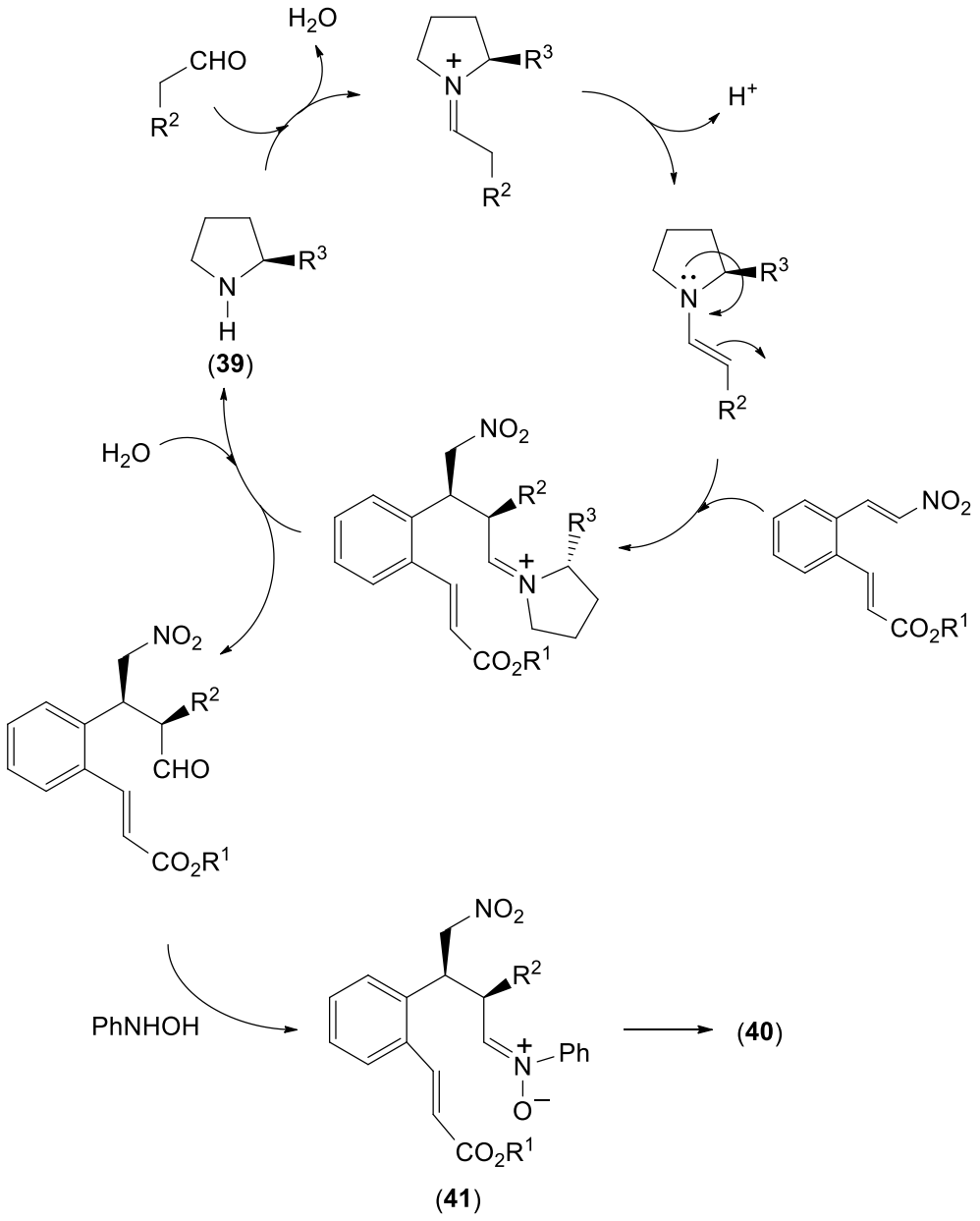
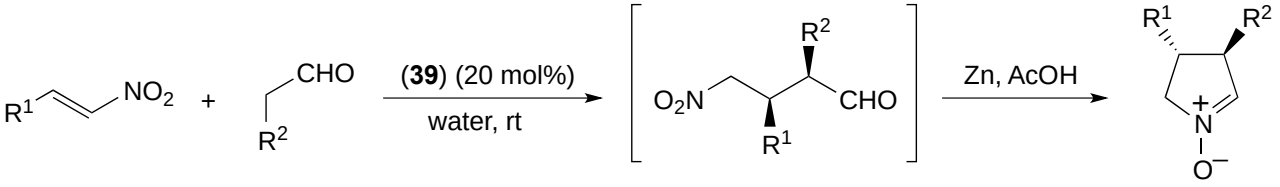


Figure 3

The organocatalytic approach based upon stereoselective Michael addition to nitrostyrenes was also effective in the one-pot synthesis of enantiopure nitrones in water, the best organocatalyst for this reaction being the chiral pyrrolidine (**39**) (Scheme 22, Table 19).[95] The γ-nitroaldehyde intermediates were not isolated since their reduction occurred *in situ* giving enantiopure nitrones (**42**) with e.e. > 99%.



R^1 = Ph, 4-$MeOC_6H_4$, 2-furyl

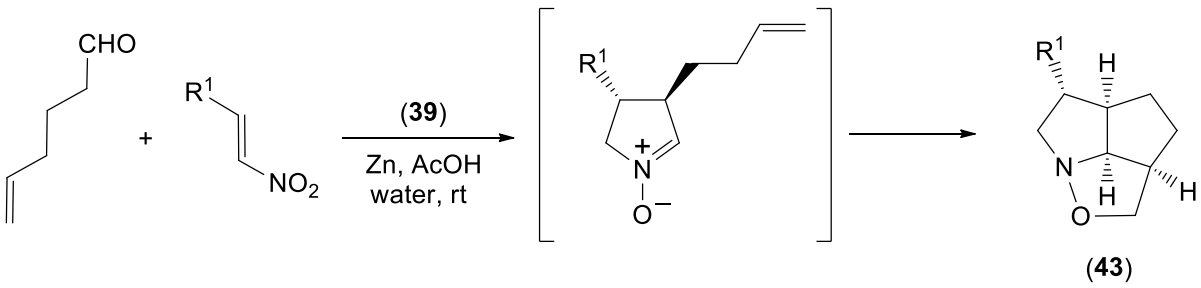
R^2 = Me, *n*-Pr, *i*-Pr

Scheme 22

Table 19. Organocatalysed synthesis of nitrones (**42**)

R^1	R^2	(**42**) (%)
Ph	Me	68
Ph	*n*-Pr	65
Ph	*i*-Pr	70
4-MeO-C_6H_4	*n*-Pr	68
2-furyl	*n*-Pr	62

By using 5-hexenal as the starting aldehyde, the corresponding nitrones were not isolable since their spontaneous stereoselective cycloaddition occurred giving the tricyclic isoxazolidines (**43**) as single diastereoisomer in the enantiopure form (Scheme 23).[95]



R^1 = Ph (68%), 4-$MeOC_6H_4$ (65%), 4-Br-C_6H_4 (70%), 2-furyl (62%)

Scheme 23

CONCLUSIONS

The present review describes the development of 1,3-dipolar cycloadditions of nitrones in water or aqueous media. Examples of intermolecular as well as intramolecular cycloadditions were discussed focusing on the advantages with respect to the cycloadditions performed in organic solvents. The interplay of factors driving to the rate acceleration of the 1,3-dipolar cycloadditions in aqueous media were discussed giving a picture of the beneficial hydrophobic effect at work in the 1,3-dipolar cycloadditions of nitrones. The valuable effects produced by surfactants and the fruitful water-based organocatalytic approach of nitrone cycloadditions were also described.

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