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Gamma-Cyclodextrinas a Catalyst for the Synthesis of 2-Methyl-3,5-diarylisoxazolidines in Water

Giuseppe Floresta,[§,‡] Carmen Talotta,[†] Carmine Gaeta,[†] Margherita De Rosa,[†] Ugo Chiacchio,[§] Placido Neri,*[,†] and Antonio Rescifina*[,§]

[§]Dipartimento di Scienze del Farmaco, Università di Catania, Viale Andrea Doria 6, 95125 - Catania, Italy.

[‡]Dipartimento di Scienze Chimiche, Università di Catania, Viale Andrea Doria 6, 95125 - Catania, Italy.

[†]Dipartimento di Chimica e Biologia "A. Zambelli", Università di Salerno, Via Giovanni Paolo II 132, 84084 - Fisciano (SA), Italy.

E-mail: arescifina@unict.it

E-mail: neri@unisa.it

Supporting Information

ABSTRACT: A green and efficient 1,3-dipolar cycloaddition of nitrones with different styrenes and cinnamates using a catalytic amount of gamma-cyclodextrin (γ-CD) in water has been developed to give substituted isoxazolidines. γ-CD was found to be highly efficacious in carrying out this reaction under eco-friendly environment affording moderate to excellent yields and in some case excellent diastereomeric excess (up to >95%) at 100 °C in 8–12 h. The catalyst can be easily recuperated and recycled for several times without loss of activity. Water, an eco-friendly reaction medium, has been utilized for the first time, to the best of our knowledge, in this reaction. The credit of the presented protocol includes high yields and catalyst reusability, and preclude the use of organic solvents. The use of *in silico* calculations allowed to rationalize the obtained results and to improve the stereoselectivity.

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INTRODUCTION

Isoxazolidines are common scaffold widely used as synthetic intermediates of high significance in organic and medicinal chemistry. They have demonstrated a range of biological activities including antibiotic,[1] gene expression regulation[2] and cancer cell cytotoxicity.[3-10] [3+2] dipolar cycloaddition reactions are most frequently used to synthesize isoxazolidines. The 1,3-dipolar cycloaddition (1,3-DC) is a chemical reaction between a 1,3-dipole and a dipolarophile to form a five-membered heterocyclic ring, normally conducted in an organic solvent.[11-14] From the economic and environmental perspectives, the development of new eco-friendly cycloaddition methods in organic synthesis is particularly attractive.

From the standpoint of green chemistry, water is known to be a potential substitute for organic solvents because it is readily available, environmentally compatible and has been frequently used as solvent in organic synthesis.[15-22] In fact, presently the concept of green chemistry and organic reactions in aqueous phase has attracted the attention of different research groups.[19,21-28]However, the fundamental problem in performing the organic reactions in water is that many organic substrates are hydrophobic and then insoluble in it. But this can be overcome, in different cases, by the use of cyclodextrins as a supramolecular catalyst.[29]

Cyclodextrins are cyclic oligosaccharides of D-(+)-glucopyranosyl units linked by α-1,4-glycosidic bonds whit a hydrophilic outer surface and a hydrophobic central cavity, of different size, and are able to form complexes with the hydrophobic guest in water.[30] They have substrate selective binding ability and catalyze a wide range of chemical reactions through non-covalent bonding forming reversible host-guest complexes just like enzymes. There are several examples in organic chemistry of reactions catalyzed by cyclodextrins. They have been used to catalyze oxidations,[31] reductions,[32,33] ring openings,[34] protections,[35] deprotections,[36,37] and even cycloadditions.[38,39] In all these examples, the cyclodextrins have always been used in a catalytic amount and always recovered and reused. To the best of our knowledge, the use of cyclodextrins in a 1,3-dipolar cycloaddition between a nitrone as a dipole, and different styrenes or cinnamates as a dipolarophile to give isoxazolidines in the aqueous medium is not yet reported.

In this work, we have developed an efficient and green method for the synthesis of 3,5-diarylisoxazolidines in water. In particular, we have studied the reaction between different *para*-substituted nitrones as the dipole, and different styrenes or cinnamates as the dipolarophile. Moreover, an *in silico* study conducted to rationalize the obtained results also allowed to choose dipolarophiles with improved stereoselectivity.In the light of the obtained results, this method could be usefully extendedto similar cycloaddition processes.

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RESULTS AND DISCUSSION

Chemistry

In our initial study towards the development of this methodology, a model reaction between nitrone**1a** and styrene **2A**(Scheme 1), using water as solvent, was investigated in detail by varying the catalyst, in order to develop optimized conditions (Table 1).

Scheme 1. Model Reaction Used to Optimize the Reaction Conditions.

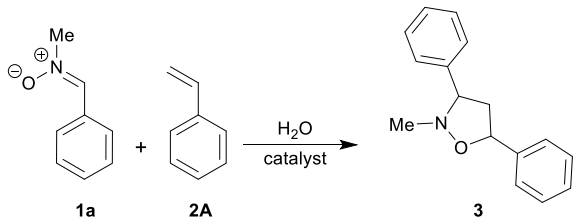

Table 1. Optimization of the Reaction Condition between Nitrone 1a and Styrene 2A

Entry	Catalyst	Eq.	Temp. (°C)	Time (h)	Yield (%)
1	—	—	100	24	—
2	α-CD	1	100	12	—
3	α-CD	2	100	12	—
4	α-CD	2	150	12	—
5	β-CD	1	100	12	—
6	β-CD	2	100	12	traces
7	β-CD	1	150	12	—
8	γ-CD	1	100	12	80
9	γ-CD	1.5	100	12	71
10	γ-CD	2	100	12	traces
11	γ-CD	3	100	12	traces
12	γ-CD	0.5	100	12	80
13	γ-CD	0.1	100	12	82

The screening was initiated by using the main cyclodextrins (α-CD, β-CD, and γ-CD) to determine their catalytic efficiency. The catalytic activity of CD was established on the basis that isoxazolidine formation was not observed in the absence of cyclodextrin in water at 100 °C for 24 h or longer (Table 1, entry 1). The alpha and beta CDs did not show any catalytic activity in the cycloadduct formation. In fact, the reaction does not take place using one or two equivalents of α-CD (Table 1, entries 2–4), probably because the small cavity is not able to form inclusion complexes with the substrates. Of course, β-CD is able to include in its cavity both the nitrone and the dipolarophile, singularly,[40] but using 1 eq. nothing happens and using 2 eq. gives only traces of cycloadducts.

Only γ-CD was able to catalyze the formation of isoxazolidines in excellent yield, giving 70–80% yield at 100 °C for 12 h (Table 1, entry 8). In particular, the reaction with 1 eq. of γ-CD resulted, in

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terms of regioselectivity, stereoselectivity, and yield, identical to that carried out in toluene. Lowering the amount of γ-CD to 0.5 and 0.1 equivalents (Table 1, entries 12 and 13) gave identical results to the former reactions. The results changed using a greater amount of cyclodextrin; in fact, increasing the quantity of catalyst over 1 eq. the yield was reduced and with two or more equivalents only traces of cycloadducts were observed.This behavior could be due to the formation of individual dipole and dipolarophile complexes within the γ-CD cavity preventing the two reactants to come in direct contact, and provides an indirect proof that the γ-CD behaves as an effective chemical reactor.

Then, under the optimized reaction conditions, we carried out 1,3-DC between nitrones**1a**,**b** and styrenes**2A**–**C**in toluene (in the absence of CD) and in water (in the presence of CD) to compare the old with the new strategy andto investigate the effects of *para*-substitution on both substrates (Scheme 2). In all the instances, the reaction proceeds with complete regioselectivity, as expected, but without improvement of yieldsand*cis/trans*stereoselectivity, that resulted in a 3:1 ratio (Table 2).Moreover, the lack of stereoselectivity is in accordance with literature data for similar*para*-substituted reactants.[41,42]

Since CDs are optically pure compounds, one might expect to observe an enantioselectivity in these reactions. Unfortunately, in our case, we obtained only racemic products.

Scheme 2. Reactions of Nitrones**1a**,**b**withStyrenes**2A**–**C**, at the Optimized Conditions.

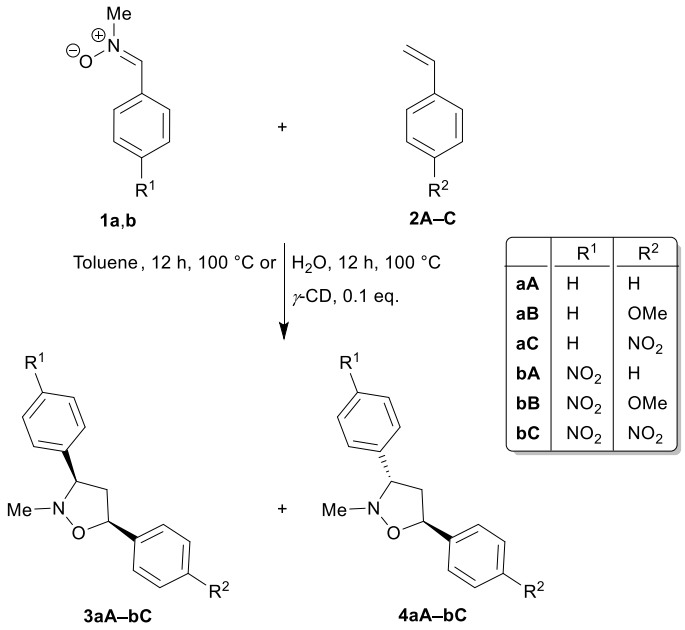

Table 2. Reactions of Nitrones**1a**,**b** and Styrenes**2A**–**C** in both Optimized Conditions in Water and in Toluene

	Reactions in toluene without CD		Reactions in water with CD	
Isoxazolidine	*Cis*/*Trans*Ratio[a]	Total yield (%)	*Cis*/*Trans*Ratio[a]	Total yield (%)
3,**4aA**	3.0/1	79	3.3/1	82

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3,**4aB**	3.1/1	75	3.3/1	75
3,**4aC**	2.8/1	77	2.8/1	76
3,**4bA**	3.3/1	80	3.3/1	82
3,**4bB**	3.1/1	79	3.1/1	77
3,**4bC**	2.7/1	77	2.7/1	75

[a]The relative amount of the cycloadducts was determined by ^{1}H NMR analysis of the crude product mixture.

Studies on the recognition ability of γ-CD toward the reactants

The above described catalytic ability of γ-CD can be explained by the formation of host-guest complexes in which the reactants are hosted inside its lipophilic cavity by means of non-covalent interactions. In this way, the substrates are firstly solubilized in the aqueous medium, where they would be otherwise insoluble. Secondly, the large dimension of the γ-CD cavity would allow the formation of 2:1 ternary complexes, which could be either homo- or hetero-complexes. In particular, the formation of hetero-complexes, in which one nitrone molecule is included together with a styrene one, would be very useful for the catalytic event. To substantiate these arguments, we performed MS and NMR spectroscopic studies on the recognition ability of γ-CD toward the reactants.

HR FT-ICR MALDI-MS studies

Direct evidence of the formation of homo and hetero inclusion complexes between γ-CD and the reactants (nitrone**1a** and styrene **2A**, hereafter named, for convenience, nitrone and styrene) were obtained by HR-MALDI FT-ICR mass spectra.[43] In particular, the HR MALDI-FT-ICR mass spectrum of the H_2O solution of γ-CD (3 mM) and styrene **2A** (6 mM) showed the presence of a molecular ion peak, at *m*/*z* 1543.5131 (Figure 1a, calcd. for $C_{64}H_{96}KO_{40}^+$: 1543.5115), in accordance with the molecular formula of the [(**2A**$_2$⊂γ-CD)+K]$^+$ homo-complex. In details, when styrene was added to the D_2O solution of γ-CD, immediately the formation of an insoluble 2:1 complex was observed between two molecules of styrene and γ-CD, in accordance with the results reported by Tonelli and coworkers.[44] Analogous results were observed for the nitrone**1a**/γ-CD system. In fact, the HR FT-ICR MALDI mass spectrum of an H_2O solution of nitrone**1a** (6 mM) and γ-CD (3 mM) evidenced the formation of the **1a**$_2$⊂γ-CD homo-complex through the presence of a molecular ion peak, at *m*/*z* 1566.5597 (Figure 1b, calcd. for $C_{64}H_{98}N_2O_{42}^+$: 1566.5594).

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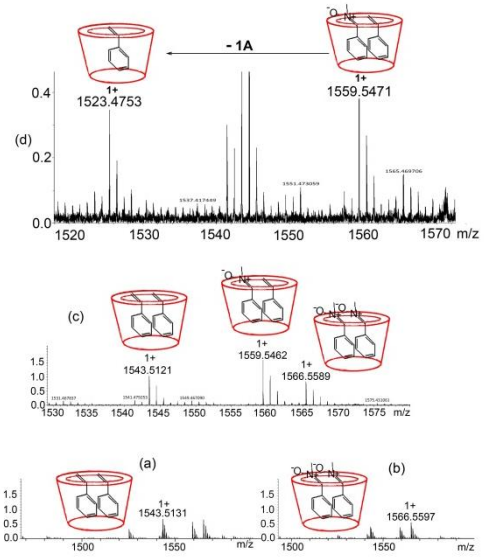

Figure 1. MALDI-FT-ICR spectra of a H_2O solution of: (a) γ-CD (3 mM) and styrene **2A** (6 mM), (b) γ-CD (3 mM) and nitrone**1A** (6 mM), (c) γ-CD (3 mM), styrene **2A** (3 mM) and nitrone**1A** (3 mM). (d) MS/MS spectrum of (**1A**)·(**2A**)⊂γ-CD heterocomplex, CID of the precursor ion 1559.5471.

The formation of the catalytically active nitrone/styrene **1a·2A**⊂γ-CD hetero-complex was confirmed by the HR FT-ICR MALDI spectrum (Figure 1c) of a 1:1:1 mixture of nitrone**1a**/styrene **2A**/γ-CD (3 mM each) in H_2O, which shows three diagnostic peaks (Figure 1c): two were related to the homo-complexes **2A**$_2$⊂γ-CD and **1a**$_2$⊂γ-CD, while the third one at 1559.5462 *m*/*z* (Figure 1c, calcd. For $C_{64}H_{97}NNaO_{41}^+$: 1559.5467) was in accordance with the molecular formula of the hetero-complex [(**1a·2A**⊂γ-CD)+Na]$^+$. Interestingly, fragmentation of the hetero-complex ion peak at 1559.5471 *m*/*z* by collision-induced decomposition (CID) resulted in the accumulation of a daughter ion peak at *m*/*z* 1523.4753 assigned to the 1:1 complex [(**2A**⊂γ-CD)+Na]$^+$ (Figure 1d). Based on this result, we can conclude that nitrone**1a** has a lower kinetic barrier to leave the γ-CD cavity than styrene **2A**.

The formation of inclusion complexes between γ-CD and the stereoisomeric products *cis*-**3aA** and *trans*-**4aA** was also investigated.In detail, the MALDI mass spectrum of a H_2O solution of a 1:1 mixture of *cis*-**3aA** and γ-CD (3 mM each) showed the presence of a molecular ion peak at *m*/*z* 1559.4474 (Figure 2, calcd. for $C_{64}H_{97}NaO_{41}^+$: 1559.4481), in accordance with the molecular formula of the [(*cis*-**3aA**⊂γ-CD)+Na]$^+$ complex. A similar study on a 1:1 mixture of *trans*-**4aA** and γ-CD (3 mM each in D_2O) evidenced no hint of the presence of the inclusion complex in the MALDI mass spectrum. Nevertheless, similar diastereoselectivities are observed in the presence or the absence of CD (Table 2).

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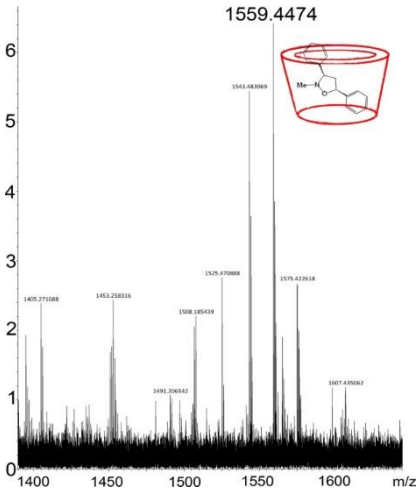

Figure 2. MALDI-FT-ICR spectra of an H_2O solution of γ-CD (3 mM) and *cis*-**3** (3mM).

^{1}H NMR studies

The formation of the inclusion complexes between the reactants and γ-CD was also studied by ^{1}H NMR experiments. When styrene **2A** was added to a D_2O solution of γ-CD (Figure 3a) the ^{1}H NMR spectrum (298 K, 600 MHz, D_2O) evidenced a broadening and a downfield shift of the H_1-H_6 signals of γ-CD (Figure 3b) due to the formation of **2A**$_2$⊂γ-CD homo-complex, which is under a fast exchange regime with respect to the NMR time scale. When **1a** was added to a D_2O solution of γ-CD (Figure 3a) a downfield shift of the H_2-H_6 signals (Figure 3c) of γ-CD was observed (298 K, 600 MHz, D_2O) (Figure 3c).

Finally, the formation of the **1a·2A**⊂γ-CD hetero-complex was also investigated by ^{1}H NMR spectroscopy. A close inspection of the ^{1}H NMR spectrum (Figure 3d) of the 1:1:1 mixture of **1a**, **2A**, and γ-CD in D_2O (3 mM each) evidenced the presence of signals attributable to the **1a·2A**⊂γ-CD hetero-complex, in a slow exchange regime with respect to the NMR time scale (600 MHz). In details, the 5-7 ppm region of the ^{1}H NMR spectrum (Figure 3d) evidenced the presence of three signals at 5.22 (d, J= 10.6 Hz), 5.75 (d, J= 17.4 Hz), and 6.71(dd, J= 10.6 Hz and J= 17. 4 Hz) ppm attributable to the vinyl unit of styrene hosted into the cavity of γ-CD. In addition, further signals relative to the aromatic protons of nitrone and styrene guests were observed in the 7–8 ppm region of the spectrum.

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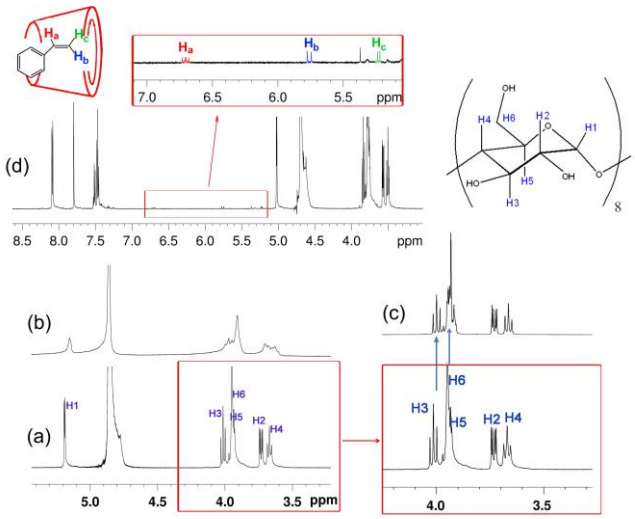

Figure 3.[1]H NMR spectra (600 MHz, D_2O, 298 K): (a) of γ-CD (3 mM), (b) of the mixture γ-CD (3 mM) and styrene **2A** (6 mM) (expansion); (c) of the mixture γ-CD (3 mM), and nitrone**1A** (6 mM) (expansion); (d) of the mixture of γ-CD (3 mM) and styrene **2A** (3 mM) and nitrone**1A** (3 mM).

Molecular Modeling

The cycloaddition process was also rationalized by an *in silico* study utilizing the PM3 semi-empirical Hamiltonian[45] as implemented in MOPAC 2016 package.[46] To perform this task, we conduct a preliminary study taken into consideration the four possible transition states (TSs) arising from the addition of the (*Z*)-and (*E*)-nitrone**1a** to the double bond of styrene moiety **2A** in either an *endo* or *exo*-fashion (Scheme 3). All calculations were conducted using toluene as an implicit solvent by the COSMO solvation model[47] and the energies are collected in Table 3.

The TSs coming from the nitrone in *E*-configuration are about 3 kcal/mol more stable than that derived from the *Z*-one.

So, the predominant formation of the *cis* adduct can be explained by assuming that the *Z*-form of the nitrone**1a** is in equilibrium with a small amount of the *E*-isomer (at ambient temperature the amount of *E*-isomer is undetectable by ^{1}H NMR but when freshly prepared, at –10 °C by oxidation of the corresponding hydroxylamine, a 55:45 *Z*/*E* ratio was observed)[48]and that the major adduct is that derived from the minor, but more reactive rotamer of the nitrone.[49] This is possible because of the *Z*/*E*interconversion, under the conditions of the dipolar cycloaddition, take place by a radical mechanism.[50]

Moreover, the *E-endo* transition state reveals a secondary orbital interaction which favors this approach over its *exo* counterpart, thereby accounting for the preferential formation of the *cis* isomers. The alternative possibility of the *Z-exo* attack, also leading to *cis* isomers, does not appear to be stabilized by any secondary orbital interaction.

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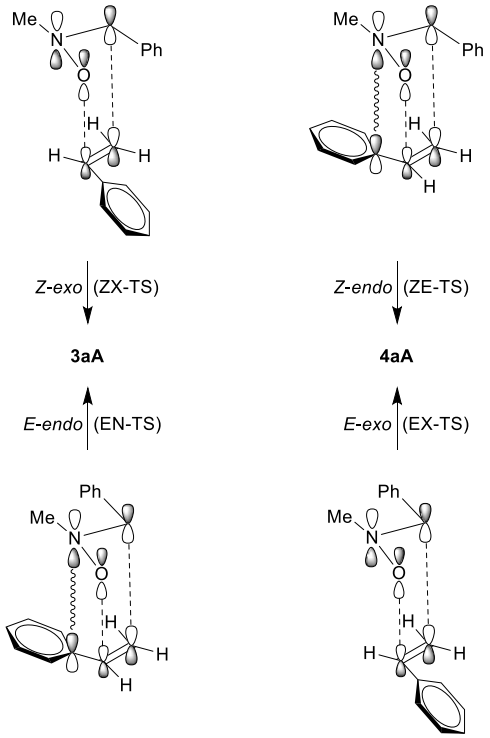
Scheme 3. The Four Possible Combinations to Generate *Cis*and *Trans*Isoxazolidines**3**,**4aA**. The Dashed Lines Indicate the Forming Bonds whereas the Wavy Lines Indicate the Secondary Orbital Interactions



This process was then modelled, for both catalyzed and uncatalyzed reactions, using only the *E*-conformer of nitrone. The calculated enthalpies of formation of all TSs together with the product percentages, calculated in accordance with the Boltzmann distribution equation at 100 °C, are reported in Table 3. These data point out a calculated *cis*/*trans* ratio that is in fairagreement with the experimental one.

Table 3. PM3 Calculation Results on Transition State Structures for Isoxazolidines**3**,**4aA**

Transition state	ΔH_f (kcal/mol)	$\Delta\Delta H_f$ (kcal/mol)	Percent calcd.[c]
3aA-ZX-TS[a]	109.32	0.77	26.2
4aA-ZN-TS[a]	108.55	0.00	73.8
3aA-EX-TS[a]	106.19	0.22	42.6
4aA-EN-TS[a]	105.97	0.00	57.4
3aA-EX-TS-γ-CD[b]	–1614.04	1.19	16.7
4aA-EN-TS-γ-CD[b]	–1615.23	0.00	83.3

[a]Calculations were performed in toluene, as an implicit solvent.[b]Calculations were performed in water, as an implicit solvent.[c]Calculated in accordance with the Boltzmann distribution equation at 100 °C.

The calculation results showed that for the *cis* compounds, in the *E-endo* TS with γ-CD(EN-TS-γ-CD), the phenyl moiety of styrene is inserted into the CD cavity pointing to the down rim whereas the phenyl of the nitrone is out of the CD cavity, at the same height of the secondary alcoholic

functionalities present in the upper rim (Figure 4). So, it is reasonable to suppose that the introduction of an appropriate substituent, in the *meta*/*para* position for the styrene, and/or in *ortho*/*meta* one for nitrone, able to engage H-bonding interactions with the hydroxylic functionalities of CD could improve the stereochemical selectivity.

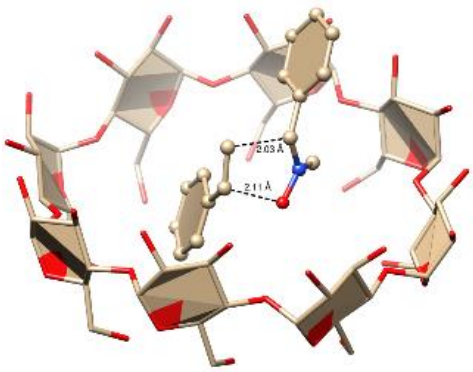
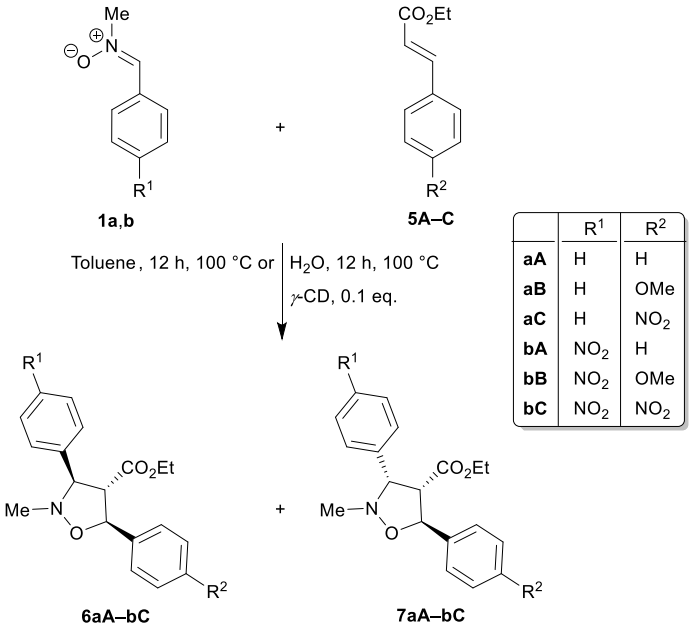


Figure 4.*E-endo* TS of compound **3aA**. All hydrogens have been removed for clarity except the intermolecular one. The dashed lines indicate the forming bonds.

However, the introduction of a nitro or methoxy group in the para position of the styrene does not produce the expected result (Table 2); probably, in these cases, the presence of the polar substituent inverts the orientation inside the CD.[51] Alternatively, a polar substituent at position 4 of the isoxazolidine nucleus could establish the appropriate interactions with the hydroxyls at the upper rim. With this in mind, we designed a series of experiments introducing a carboxylic group at the β-carbon of the styrene (i.e. obtaining cinnamates**5**) to synthesizeisoxazolidines**6** and **7** (Scheme4).

Scheme 4. Reactions of Nitrones**1a**,**b** with Cynnamates**5A**–**C**, at the Optimized Conditions.



	R^1	R^2
aA	H	H
aB	H	OMe
aC	H	NO_2
bA	NO_2	H
bB	NO_2	OMe
bC	NO_2	NO_2

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Interestingly, the preliminary*in silico* calculations conducted on the TS structures leading to compounds **6aA** and **7aA**supported our assumption (Table 4, Figure 6).

Table 4. PM3 Calculation Results on Transition State Structures for Isoxazolidines**6**,**7aA**

Transition state	ΔH_f (kcal/mol)	$\Delta\Delta H_f$ (kcal/mol)	Percent calcd.[c]
6aA-EX-TS[a]	15.37	0.64	29.7
7aA-EN-TS[a]	14.73	0.00	70.3
6aA-EX-TS-γ-CD[b]	–1704.70	2.59	3.0
7aA-EN-TS-γ-CD[b]	–1707.29	0.00	97.0

[a]Calculations were performed in toluene, as an implicit solvent. [b]Calculations were performed in water, as an implicit solvent. [c]Calculated in accordance with the Boltzmann distribution equation at 100 °C.

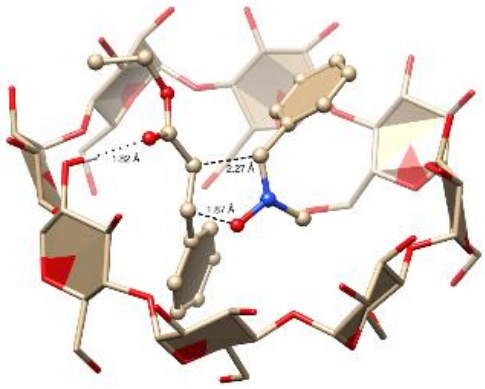

Figure 6.*E-endo* TS of compound **6aA**. All hydrogens have been removed for clarity except the intermolecular one. The dashed lines indicate the forming bonds whereas the dotty line indicates the hydrogen bond.

Improving the stereoselectivity

Animated by the above *in silico*results, we evaluated the catalytic activity of γ-CD in the 1,3-DC reaction of nitrones**1a**,**b** with substituted cinnamates**5A**–**C** as dipolarophiles(Table 5). We were delighted to observe that the experimental results paralleled the computed ones. In fact, the new isoxazolidines**6** and **7** were obtained with an enhanced *cis*/*trans* ratio, in the range of 6:1 to 25:1, contrarily to that obtained conducting the reaction in toluene as solvent.Unfortunately, once again, noenantioselectivity was observed.

Table 5. Reactions of Nitrones**1a**,**b** and Cinnamates**5A**–**C** in both Optimized Conditions in Water and in Toluene

	Reactions in toluene without CD		Reactions in water with CD	
Isoxazolidines	*Cis*/*Trans*Ratio[a]	Total yield (%)	*Cis*/*Trans*Ratio[a]	Total yield (%)
6,**7aA**	2.3/1	82	25/1	85
6,**7aB**	2.6/1	81	25/1	78
6,**7aC**	2.6/1	80	20/1	79
6,**7bA**	4.5/1	78	17/1	80
6,**7bB**	4.0/1	76	20/1	78
6,**7bC**	4.0/1	77	6/1	79

[a]Therelative amount of the cycloadducts was determined by ^{1}H NMR analysis of the crude product mixture.

Accepted Version: doi: 10.1021/acs.joc.7b00227

Reusability

The catalyst reusability was studied on the 1,3-DC reaction of nitrones**1a**,**b** with styrene **2A**, according to the optimized procedure, using the following methodology:at the end of the reaction the crude mixture was cooled to 10 °C and extracted with ethyl acetate (3 × 5 mL);the reaction products and the eventually remaining reagentsand by-products were recovered by the organic phase, whereasto the same aqueous phase, containing only the γ-CD, were added again nitrone and dipolarophile and the mixture was reacted in the same conditions. The results of five experiments, reassumed in Figure 7, clearly demonstrate high catalytic activity during the first three cycles.

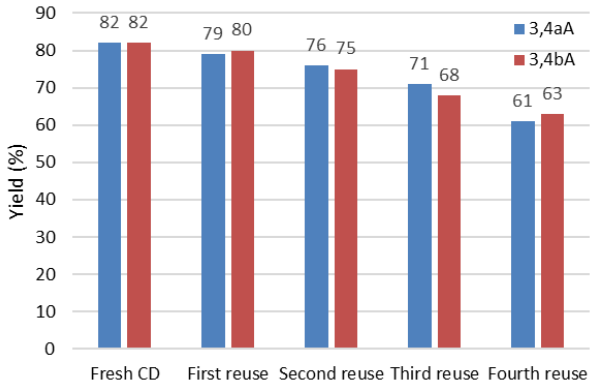

Figure 7. Catalyst reusability study. Reaction conditions:nitrone (0.5 mmol), dipolarophile (0.5 mmol), γ-CD (0.05 mmol), water (1 mL), 100 °C, 12 h.

CONCLUSIONS

In conclusion, we have reported the first example of isoxazolidine synthesis catalysed by gamma-cyclodextrin in water rather than in organic solvents as so far reported. The presented eco-friendly protocol includes high yields with good-to-excellent diastereomeric excess (up to >95%) and catalyst reusability. The catalytic ability of γ-CD can be explained by the formation of water-soluble host-guest complexes in which the reactants are hosted inside its lipophilic cavity by means of non-covalent interactions. The formation of the catalytically active nitrone-styrene⊂γ-CD hetero-complex was confirmed by spectroscopical methods. Theoretical calculations provided a rationalization of the observed stereoselectivity outcome and allowed its improvement up to >95% by a judicious choice of an appropriate substituent able to engage H-bonding interactions with the CD host.

The eco-friendly approach used in this work can be easily extended to other synthetically useful cycloaddition reactions and could benefit from the use of other appropriately designed macrocyclic hosts widely used in supramolecular chemistry.Moreover, considering the large amount of data recently appeared in the literature on the preparation of nanostructured materials decorated with cyclodextrins, our methodology could be applied in heterogeneous conditions, or even in the solid-

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state, using cyclodextrins grafted onto nanostructured materials.[52,53]

EXPERIMENTAL SECTION

General Information. All the required chemicals were purchased from Merck and Aldrich Chemical Company. Pre-coated aluminium sheets (silica gel 60 F254, Merck) were used for thin-layer chromatography (TLC) and spots were visualized under UV light or after treatment with ninhydrin and heating. Silica gel column chromatography was performed using silica gel 60–120 mesh size (RANKEM Limited). IR spectra were recorded on a Nicolet 550 FT-IR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian UNITY Inova or a BrukerAvance spectrometer using $CDCl_3$ as a solvent and tetramethylsilane (TMS) as an internal standard, at 200, 500 or 600 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR.
^{13}C spectra were ^{1}H decoupled and multiplicities were determined by the APT pulse sequence. Chemical shift (δ) values are given in ppm. ESI-HRMS were determined with a Thermo Fischer Scientific LTQ Orbitrap XL.

MALDI-TOF Mass Spectrometry. HR MALDI mass spectra were recorded on an FT-ICR mass spectrometer equipped with a 7T magnet. The samples were ionized in positive ion mode using the MALDI ion source, and 15 laser shots were used for each scan. The mass spectra were calibrated externally, and a linear calibration was applied. To improve the mass accuracy, the spectra were recalibrated internally by matrix ionization (Sinapinic acid). Samples were prepared by mixing 70 µL of analyte in water (2 mg/mL) with 230 µL of a saturated (30 mg/mL) solution of sinapinic acid. In MS/MS analyses the precursor ions were selected by the quadrupole mass analyzer and product ions after CID (collision-induced dissociation) were detected by the ToFmass analyzer. Argon was used as the collision gas (and the CID experiments were performed in the T-wave collision cell by applying a CE from 5 to 20 eV.

Sample Preparation. The matrix microcrystal layer was first densely packed on the stainless steel probe by fast solvent evaporation matrix water solution. The sample solution was prepared with water and then deposited onto the layer and fast evaporated by vacuum to form the second layer. The molar ratio of SA and its complex was 1000:1. The sample plate was finally loaded into the ion source for analysis.

General procedure for the synthesis of nitrones 1a,**b.**Nitrones**1a**,**b** were synthesized from commercially available aldehydes (benzaldehyde or *p*-nitrobenzaldehyde) and *N*-methylhydroxylamine hydrochloride in dichloromethane and using as a base sodium acetate,

according to literature.[42] The crude product was purified by silica gel column chromatography using dichloromethane/methanol (9:1) as eluent.

Optimized general procedure for the synthesis of isoxazolidines 3, 4, 6, and 7.A sealed tube equipped with a stirrer bar was charged with γ-CD (0.05 mmol, 0.10 equiv), respective nitrone (0.5 mmol, 1.0 equiv) and dipolarophile (0.5 mmol, 1.0 equiv). Then water (1 mL) was added and the mixture was stirred for 12 h at 100 °C. After completion of the reaction, the mixture was cooled to room temperature and extracted with EtOAc (3 × 5 mL) and the catalyst was filtered off and washed with EtOAc (2 × 5 mL), the filtrate was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography using *n*-hexane/ethyl acetate (9.5:0.5) as an eluent.The *cis*/*trans* configuration was assigned on the basis of the 1DNOEDS spectra(see experimental) and, for the 4-unsubstituted series, the *cis* is easily distinguishable by the *trans* one on the basis of the chemical shifts of the H-4a and H-4b protons; for the first, they are very far (0.7–1.1 ppm), whereas for the latter they are very close (0.01–0.3 ppm) according to literature.[42]For the *cis* stereoisomers, the irradiation of H-5 proton resonances directly gave a positive NOE with the H-3 proton allowing to assign the configuration with certainty. In all the cases the *cis*isoxazolidines elute prior to the *trans* ones.

(3RS,5SR)-2-methyl-3,5-diphenyl-isoxazolidine **(3aA).**[54] Light yellow oil; ^{1}H NMR (500 MHz, Chloroform-*d*): 2.42 (1H, ddd, *J*=12.4, 9.7, 7.7 Hz, H-4a), 2.70 (3H, s, N-Me), 3.09 (1H, ddd, *J*=12.4, 7.7, 6.8 Hz, H-4b), 3.78 (1H, t, *J*=8.4 Hz, H-3), 5.26 (1H, t, *J*=7.7 Hz, H-5), 7.19–7.33 (4H, m, Ar-H), 7.30–7.39 (4H, m, Ar-H), 7.43–7.50 (2H, m, Ar-H); ^{13}C NMR (50 MHz, Chloroform-*d*): 43.8, 48.7, 73.9, 78.2, 126.0, 127.3, 127.6, 127.7, 128.4, 128.6, 139.1, 143.0; HRMS: *m/z* $[M+H]^+$ calculated for $C_{16}H_{18}NO^+$ 240.1383, found 240.1380.

(3RS,5RS)-2-methyl-3,5-diphenyl-isoxazolidine **(4aA).**[54] Light yellow oil; ^{1}H NMR (500 MHz, Chloroform-*d*): 2.62 (1H, ddd, *J*=12.5, 8.4, 6.8 Hz, H-4a), 2.71 (3H, s, N-Me), 2.70–2.78 (1H, m, H-4b), 3.72 (1H, s, H-3), 5.25 (1H, dd, *J*=8.3, 6.8 Hz, H-5), 7.26–7.33 (2H, m, Ar-H), 7.36 (4H, qd, *J*=6.7, 6.2, 3.9 Hz, Ar-H), 7.40–7.46 (4H, m, Ar-H); ^{13}C NMR (50 MHz, Chloroform-*d*): 43.3, 47.8, 73.4, 78.8, 126.6, 127.7, 127.8, 127.9, 128.5, 128.6, 139.3, 140.8; HRMS: *m/z* $[M+H]^+$ calculated for $C_{16}H_{18}NO^+$ 240.1383, found 240.1378.

(3RS,5SR)-5-(4-methoxyphenyl)-2-methyl-3-phenyl-isoxazolidine **(3aB).**[42] Light yellow oil; ^{1}H NMR (500 MHz, Chloroform-*d*): 2.42 (1H, ddd, *J*=12.5, 9.6, 7.6 Hz, H-4a), 2.70 (3H, s, N-Me), 3.06 (1H, dt, *J*=12.5, 7.2 Hz, H-4b), 3.81 (4H, s, H-3,OMe), 5.23 (1H, t, *J*=7.6 Hz, H-5), 6.86–6.92

(2H, m, Ar-H), 7.24–7.36 (4H, m, Ar-H), 7.36–7.42 (3H, m, Ar-H); ^{13}C NMR (50 MHz, Chloroform-*d*): 43.3, 43.9, 55.2, 73.0, 79.5, 113.8, 127.5, 127.7, 128.6, 129.1, 138.2, 139.2, 153.6; HRMS: *m/z* $[M+H]^+$ calculated for $C_{17}H_{20}NO_2^+$ 270.1489, found 270.1481.

(3RS,5RS)-5-(4-methoxyphenyl)-2-methyl-3-phenyl-isoxazolidine **(4aB).**[42]Light yellow oil; ^{1}H NMR (500 MHz, Chloroform-*d*): 2.56–2.63 (1H, m, H-4a), 2.63–2.72 (4H, m, *N*-Me, H-4b), 3.71 (1H, s, H-3), 3.81 (3H, s, OMe), 5.17–5.24 (1H, m, H-5), 6.86–6.94 (2H, m, Ar-H), 7.24–7.46 (7H, m, Ar-H); ^{13}C NMR (50 MHz, Chloroform-*d*): 42.6, 43.3, 55.3, 75.6, 78.6, 113.9, 127.5, 128.1, 128.6, 128.7, 138.3,139.4, 152.2; HRMS: *m/z* $[M+H]^+$ calculated for $C_{17}H_{20}NO_2^+$ 270.1489, found 270.1484.

(3RS,5SR)-2-methyl-5-(4-nitrophenyl)-3-phenyl-isoxazolidine **(3aC).** Light yellow oil; ^{1}H NMR (500 MHz, Chloroform-*d*): 2.34 (1H, ddd, *J*=12.5, 9.6, 6.9 Hz, H-4a), 2.70 (3H, s, *N*-Me), 3.22 (1H, ddd, *J*=12.5, 8.2, 7.2 Hz, H-4b), 3.71–3.78 (1H, m, H-3), 5.32 (1H, dd, *J*=8.2, 6.9 Hz, H-5), 7.24–7.35 (5H, m, Ar-H), 7.64 (2H, d, *J*=8.5 Hz, Ar-H), 8.18–8.25 (2H, m, Ar-H); ^{13}C NMR (50 MHz, Chloroform-*d*): 43.3, 48.6, 73.9, 76.8, 123.8, 126.4, 127.5, 128.0, 128.7, 138.1, 147.0, 151.7; HRMS: *m/z* $[M+H]^+$ calculated for $C_{16}H_{17}N_2O_3^+$ 285.1234, found 285.1228.

(3RS,5RS)-2-methyl-5-(4-nitrophenyl)-3-phenyl-isoxazolidine **(4aC).** Light yellow oil; ^{1}H NMR (500 MHz, Chloroform-*d*): 2.56 (1H, dq, *J*=13.0, 7.7 Hz, H-4a), 2.74 (3H, s, *N*-Me), 2.79–2.89 (1H, m, H-4b), 3.73 (1H, s, H-3), 5.32–5.39 (1H, m, H-5), 7.29–7.38 (2H, m, Ar-H), 7.41 (3H, dd, *J*=19.2, 7.1 Hz, Ar-H), 7.59 (2H, d, *J*=8.6 Hz, Ar-H), 8.20–8.27 (2H, m, Ar-H); ^{13}C NMR (50 MHz, Chloroform-*d*): 42.9, 48.4, 74.1, 76.5, 124.5, 126.4, 127.6, 127.7, 128.3, 138.1, 147.3, 151.1; HRMS: *m/z* $[M+H]^+$ calculated for $C_{16}H_{17}N_2O_3^+$ 285.1234, found 285.1225.

(3RS,5SR)-2-methyl-3-(4-nitrophenyl)-5-phenyl-isoxazolidine **(3bA).** Light yellow oil; ^{1}H NMR (500 MHz, Chloroform-*d*): 2.34 (1H, dt, *J*=12.6, 8.0 Hz, H-4a), 2.76 (3H, s, *N*-Me), 3.21 (1H, dt, *J*=12.6, 7.6 Hz, H-4b), 3.98 (1H, t, *J*=8.0 Hz, H-3), 5.32 (1H, t, *J*=7.6 Hz, H-5), 7.28 (1H, d, *J*=7.2 Hz, Ar-H), 7.34 (2H, d, *J*=7.8 Hz, Ar-H), 7.40 (2H, d, *J*=7.4 Hz, Ar-H), 7.56 (2H, d, *J*=8.7 Hz, Ar-H), 8.18 (2H, d, *J*=8.7 Hz, Ar-H); ^{13}C NMR (50 MHz, Chloroform-*d*): 44.0, 48.4, 72.5, 78.3, 123.8, 125.9, 127.6, 128.1, 128.5, 141.7, 147.3, 147.8; HRMS: *m/z* $[M+H]^+$ calculated for $C_{16}H_{17}N_2O_3^+$ 285.1234, found 285.1230.

(3RS,5RS)-2-methyl-3-(4-nitrophenyl)-5-phenyl-isoxazolidine **(4bA).** Light yellow oil; ^{1}H NMR (500 MHz, Chloroform-*d*): 2.62–2.73 (2H, m, H-4a,b), 2.73 (3H, s, *N*-Me), 3.86 (1H, t, *J*=8.3 Hz,

H-3), 5.24 (1H, t, *J*=7.6 Hz, H-5), 7.30–7.45 (5H, m, Ar-H), 7.62 (2H, d, *J*=8.7 Hz, Ar-H), 8.20–8.26 (2H, m, Ar-H); ^{13}C NMR (50 MHz, Chloroform-*d*): 43.6, 47.8, 72.4, 79.0, 123.9, 126.5, 128.1, 128.4, 128.6, 140.0, 147.4, 147.5; HRMS: *m/z* $[M+H]^+$ calculated for $C_{16}H_{17}N_2O_3^+$ 285.1234, found 285.1232.

(3RS,5SR)-5-(4-methoxyphenyl)-2-methyl-3-(4-nitrophenyl)-isoxazolidine **(3bB).** Light yellow oil; ^{1}H NMR (500 MHz, Chloroform-*d*): 2.33 (1H, ddd, *J*=12.6, 8.5, 7.6 Hz, H-4a), 2.76 (3H, s, *N*-Me), 3.16 (1H, dt, *J*=12.6, 7.6 Hz, H-4b), 3.80 (3H, s, OMe), 4.00 (1H, t, *J*=8.0 Hz, H-3), 5.29 (1H, t, *J*=7.6 Hz, H-5), 6.85–6.91 (2H, m, Ar-H), 7.31 (2H, d, *J*=8.5 Hz, Ar-H), 7.55–7.61 (2H, m, Ar-H), 8.16–8.22 (2H, m, Ar-H); ^{13}C NMR (50 MHz, Chloroform-*d*): 44.2, 48.3, 55.3, 72.5, 78.2, 114.0, 123.9, 127.5, 128.1, 133.3, 147.4, 148.1, 159.2; HRMS: *m/z* $[M+H]^+$ calculated for $C_{17}H_{19}N_2O_4^+$ 315.1339, found 315.1333.

(3RS,5RS)-5-(4-methoxyphenyl)-2-methyl-3-(4-nitrophenyl)-isoxazolidine **(4bB).** Light yellow oil; ^{1}H NMR (500 MHz, Chloroform-*d*): 2.55–2.72 (2H, m, H-4a,b), 2.71 (3H, s, *N*-Me), 3.82 (3H, s, OMe), 3.85 (1H, t, *J*=8.3 Hz, H-3), 5.19 (1H, t, *J*=7.6 Hz, H-5), 6.91 (2H, d, *J*=8.6 Hz, Ar-H), 7.35 (2H, d, *J*=8.6 Hz, Ar-H), 7.62 (2H, d, *J*=8.6 Hz, Ar-H), 8.23 (2H, d, *J*=8.6 Hz, Ar-H); ^{13}C NMR (50 MHz, Chloroform-*d*): 43.9, 47.3, 51.6, 71.6, 77.4, 112.0, 122.1, 126.9, 130.0, 133.2, 146.1, 149.0, 161.2; HRMS: *m/z* $[M+H]^+$ calculated for $C_{17}H_{19}N_2O_4^+$ 315.1339, found 315.1329.

*(3RS,5SR)-2-methyl-3,5-bis(4-nitrophenyl)-isoxazolidine***(3bC).** Light yellow sticky oil; ^{1}H NMR (500 MHz, Chloroform-*d*): 2.23–2.33 (1H, m, H-4a), 2.74 (3H, s, *N*-Me), 3.27–3.37 (1H, m, H-4b), 3.88–3.96 (1H, m, H-3), 5.38 (1H, dd, *J*=8.2, 6.7 Hz, H-5), 7.47–7.52 (2H, m, Ar-H), 7.57–7.64 (2H, m, Ar-H), 8.15–8.25 (4H, m, Ar-H); ^{13}C NMR (50 MHz, Chloroform-*d*): 43.5, 48.5, 72.7, 76.9, 123.8, 123.9, 126.4, 128.2, 146.4, 147.1, 147.5, 150.6; HRMS: *m/z* $[M+H]^+$ calculated for $C_{16}H_{16}N_3O_5^+$ 330.1084, found 330.1077.

*(3RS,5RS)-2-methyl-3,5-bis(4-nitrophenyl)-isoxazolidine***(4bC).** Light yellow sticky oil; ^{1}H NMR (500 MHz, Chloroform-*d*): 2.63 (1H, ddd, *J*=12.6, 8.5, 6.8 Hz, H-4a), 2.70–2.80 (1H, m, H-4b), 2.75 (3H, s, *N*-Me) 3.84–3.88 (1H, m, H-3), 5.29–5.36 (1H, m, H-5), 7.56–7.64 (4H, m, Ar-H), 8.22–8.27 (4H, m, Ar-H); ^{13}C NMR (50 MHz, Chloroform-*d*): 43.6, 47.7, 72.0, 75.4, 123.8, 124.1, 126.9, 128.4, 146.6, 147.5, 147.7, 147.8; HRMS: *m/z* $[M+H]^+$ calculated for $C_{16}H_{16}N_3O_5^+$ 330.1084, found 330.1081.

Ethyl (3RS,4SR,5SR)-2-methyl-3,5-diphenyl-isoxazolidine-4-carboxylate **(6aA).** Light yellow sticky

foam; ^{1}H NMR (500 MHz, Chloroform-*d*): 1.20 (3H, t, *J*=7.1 Hz), 2.73 (3H, s, *N*-Me), 3.50 (1H, dd, *J*=8.6, 6.3 Hz, H-4), 4.05 (1H, d, *J*=8.6 Hz, H-3), 4.17 (2H, q, *J*=7.1 Hz), 5.42 (1H, d, *J*=6.3 Hz, H-5), 7.27–7.38 (6H, m, Ar-H), 7.38 (2H, d, *J*=7.5 Hz, Ar-H), 7.52 (2H, d, *J*=7.3 Hz, Ar-H); ^{13}C NMR (50 MHz, Chloroform-*d*): 14.1, 43.4, 61.2, 65.8, 76.8, 80.7, 125.9, 127.6, 127.8, 128.1, 128.5, 128.7, 137.7, 171.4; HRMS: *m/z* $[M+H]^+$ calculated for $C_{19}H_{22}NO_3^+$ 312.1594, found 312.1588.

Ethyl (3RS,4SR,5SR)-5-(4-methoxyphenyl)-2-methyl-3-phenyl-isoxazolidine-4-carboxylate **(6aB).** Light yellow sticky foam; ^{1}H NMR (500 MHz, Chloroform-*d*): 1.19 (3H, t, *J*=7.1 Hz), 2.72 (3H, s, *N*-Me), 3.47 (1H, dd, *J*=8.6, 6.6 Hz, H-4), 3.81 (3H, s, OMe), 4.07 (1H, d, *J*=8.6 Hz, H-3), 4.15 (2H, q, *J*=7.1 Hz), 5.37 (1H, d, *J*=6.6 Hz, H-5), 6.87–6.93 (2H, m, Ar-H), 7.24 – 7.46 (8H, m, Ar-H); ^{13}C NMR (50 MHz, Chloroform-*d*): 14.1, 43.5, 55.3, 61.2, 65.7, 80.7, 113.9, 127.4, 127.7, 128.1, 128.7, 133.7, 137.9, 159.1, 171.4; HRMS: *m/z* $[M+H]^+$ calculated for $C_{20}H_{24}NO_4^+$ 342.1700, found 342.1687.

Ethyl (3RS,4SR,5SR)-2-methyl-5-(4-nitrophenyl)-3-phenyl-isoxazolidine-4-carboxylate **(6aC).** Light yellow sticky foam; ^{1}H NMR (500 MHz, Chloroform-*d*): 1.25 (3H, t, *J*=7.1 Hz), 2.71 (3H, s, *N*-Me), 3.42 (1H, dd, *J*=8.8, 5.6 Hz, H-4), 4.00 (1H, d, *J*=8.8 Hz, H-3), 4.21 (2H, q, *J*=7.1 Hz), 5.48 (1H, d, *J*=5.6 Hz, H-5), 7.24–7.33 (5H, m, Ar-H), 7.72 (2H, d, *J*=8.4 Hz, Ar-H), 8.21–8.27 (2H, m, Ar-H); ^{13}C NMR (50 MHz, Chloroform-*d*): 14.1, 43.0, 61.6, 65.7, 76.7, 79.4, 123.9, 126.5, 127.8, 128.4, 128.8, 131.0, 136.8, 150.4, 170.9; HRMS: *m/z* $[M+H]^+$ calculated for $C_{19}H_{21}N_2O_5^+$ 357.1445, found 357.1436.

Ethyl (3RS,4SR,5SR)-2-methyl-3-(4-nitrophenyl)-5-phenyl-isoxazolidine-4-carboxylate **(6bA).** Light yellow sticky foam; ^{1}H NMR (500 MHz, Chloroform-*d*): 1.25 (3H, t, *J*=7.1 Hz), 2.77 (3H, s, *N*-Me), 3.42 (1H, dd, *J*=8.0, 6.3 Hz, H-4), 4.22 (3H, CH_2, H-3), 5.48 (1H, d, *J*=6.3 Hz, H-5), 7.28–7.41 (3H, m, Ar-H), 7.47 (2H, ddd, *J*=8.2, 1.3, 0.6 Hz, Ar-H), 7.55–7.61 (2H, m, Ar-H), 8.16–8.22 (2H, m, Ar-H); ^{13}C NMR (50 MHz, Chloroform-*d*): 14.1, 43.6, 61.6, 65.9, 75.4, 80.8, 123.9, 125.8, 127.9, 128.5, 128.6, 141.0, 146.1, 147.6, 170.8; HRMS: *m/z* $[M+H]^+$ calculated for $C_{19}H_{21}N_2O_5^+$ 357.1445, found 357.1442.

Ethyl (3RS,4SR,5SR)-5-(4-methoxyphenyl)-2-methyl-3-(4-nitrophenyl)-isoxazolidine-4-carboxylate **(6bB).** Light yellow sticky foam; ^{1}H NMR (500 MHz, Chloroform-*d*): 1.24 (3H, t, *J*=7.1 Hz), 2.78 (3H, s, *N*-Me), 3.39 (1H, dd, *J*=7.9, 6.6 Hz, H-4), 3.81 (3H, s, OMe), 4.20 (2H, d, *J*=7.1 Hz), 4.26 (1H, d, *J*=7.9 Hz, H-3), 5.44 (1H, d, *J*=6.6 Hz, H-5), 6.87–6.93 (2H, m, Ar-H), 7.34–7.40 (2H, m, Ar-H), 7.57–7.63 (2H, m, Ar-H), 8.17–8.23 (2H, m, Ar-H)); ^{13}C NMR (126 MHz, Chloroform-*d*):

14.15, 43.8, 55.3, 61.6, 65.9, 75.3, 80.8, 114.0, 123.9, 127.4, 128.4, 132.5, 146.5, 147.7, 159.4, 170.9; HRMS: *m/z* $[M+H]^+$ calculated for $C_{20}H_{23}N_2O_6^+$ 387.1551, found 387.1547.

Ethyl (3RS,4SR,5SR)-2-methyl-3,5-bis(4-nitrophenyl)-isoxazolidine-4-carboxylate **(6bC).** Light yellow sticky foam; ^{1}H NMR (500 MHz, Chloroform-*d*): 1.29 (3H, t, *J*=7.1 Hz), 2.75 (3H, s, *N*-Me), 3.37 (1H, dd, *J*=8.5, 5.6 Hz, H-4), 4.17 (1H, d, *J*=8.5 Hz, H-3), 4.26 (2H, q, *J*=7.1 Hz), 5.54 (1H, d, *J*=5.6 Hz, H-5), 7.52 (2H, d, *J*=8.8 Hz, Ar-H), 7.70 (2H, dd, *J*=8.9, 0.7 Hz, Ar-H), 8.18 (2H, d, *J*=8.9 Hz, Ar-H), 8.25 (2H, d, *J*=8.9 Hz, Ar-H); ^{13}C NMR (50 MHz, Chloroform-*d*): 14.1, 43.1, 62.0, 65.7, 75.3, 79.4, 123.9, 124.0, 126.4, 128.6, 144.8, 147.3, 147.8, 149.5, 170.2; HRMS: *m/z* $[M+H]^+$ calculated for $C_{19}H_{20}N_3O_7^+$ 402.1296, found 402.1292.

Computational details. All calculations were performed with the semi-empirical PM3 Hamiltonian implemented in MOPAC2016 (16.299 W) software and all geometries were fully optimized, in toluene or in water, using the implicit COSMO solvation model. Equilibrium structures were confirmed to have zero imaginary vibrational modes whereas transition states were confirmed to have only one imaginary vibrational mode with the corresponding eigenvector involving the formation of the newly created C—C and C—O bonds.

ASSOCIATED CONTENT

Suporting Information

The Supporting Information is available free of charge on theACS Publications website at DOI: 10.1021/acs.joc.

Copies of ^{1}H,^{13}C NMR, and selected 1DNOESY spectra for all new products and Cartesian coordinates, energies, and frequencies for fully optimized compounds and transition states; MALDI-MS spectrum of α-CD and nitrone**1a**, MALDI-MS spectrum of α-CD and styrene **2A**, MALDI-MS spectrum of α-CD, styrene **2A** and nitrone**1a**;Thermogravimetric analyses (TGA),^{1}H NMR spectra of 1 eq. of γ-CD and 2 eq. of nitrone**1a**, Job's plot of γ-CD and nitrone**1a**, ^{1}H NMR spectrum of 1 eq. of γ-CD and 2 eq. of styrene **2A**, ^{1}H NMR spectrum of 1 eq. of γ-CD, 1eq. of nitrone**1a**, and 1eq. of styrene **2A**(PDF)

AUTHOR INFORMATION

Corresponding Authors

*E-mail: arescifina@unict.it.

*E-mail: neri@unisa.it

ORCID

Antonio Rescifina: 0000-0001-5039-2151

Notes

The authors declare no competing financial interest.

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