Tetrahedron xxx (2017) 1–12

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

The hydrogen bond directing effect in nitrile oxide cycloadditions to allylic substituted cyclopentenes

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ARTICLE INFO

Article history:
Received 24 January 2017
Received in revised form
27 February 2017
Accepted 13 March 2017
Available online xxx

Keywords:
Hydrogen bond
Nitrile oxide
Cyclopentenols
Cyclopentene amide
Solvent effect

ABSTRACT

A quantitative evaluation of the H-bond directing effect on the stereoselectivity in the cycloaddition of nitrile oxides to 2-cyclopenten-1-ol and allylic cyclopentenyl amides is reported. In apolar solvents the H-bond directing effect promotes a high *syn* stereoselectivity while H-bond acceptor solvents divert the reactions to the *anti* face of the dipolarophile. Taft's β parameter gives a good description of the solvent effect on the H-bond directing effect. The persistence of some *syn* stereoselectivity even in good H-bond acceptor solvents points out the existence of some residual hydrogen bond direction. The *syn* stereoselectivity in the presence of M(II) salts was also investigated and the results discussed in the light of the potential application of these scaffolds in nucleoside synthesis.

1. Introduction

Among the directing effects which assume relevance in the control of stereoselectivity in many organic reactions, the intermolecular Hydrogen Bond (HB) between reactants is perhaps the most known, powerful and extensively explored for synthetic purposes.[1] One of the earliest examples of HB directed reactions is the Henbest peracid epoxidation[2] of cyclic allylic alcohols (2-cyclohexenol, 2-cyclopentenol) which causes a remarkably *syn* stereoselection when the reaction is performed in apolar solvents, while the substrates are stereorandomly oxidized when alcohols are used as solvents. A quantitative assessment of the solvent effect on the stereoselectivity of the peracid epoxidation is however difficult since the solvent can interact either with the alcoholic function or with the peracid hydroxyl group. In the latter case a rate retardation is observed, as shown by kinetic measurements in the epoxidation of cyclohexene.[3] Other reagents have been developed and of special interest are catalytic procedures which utilize transition-metal catalysts, mainly TBHP/Ti(O*i*Pr)$_4$,[4] VO(acac)$_2$,[5] methyl-trioxorhenium (MTO)[6] and Mn(Salen)[7] complexes, achieving best results in term of stereoselection. Besides peracids, dimethyl dioxirane (DMD)[8] is another purely organic non-metal oxidant which is less prone to HB effects[9] and hexafluoroacetone perhydrate (HFAH)[10] which is a non-metal catalyst for higher *syn*-selective oxidations *via* a hydrogen bonded transition structure similar to that of a peracid with a catalytic oxygen transfer process.

HB directing effects have been observed in nitrile oxide cycloadditions and affect stereoselection remarkably.[11–13] We have exploited the HB directing effects for the stereoselective synthesis of bicyclic isoxazolines, which serve as building blocks for the synthesis of modified nucleosides.[15] With the exception of one case where an intramolecular HB prevents the establishment of the intermolecular HB needed for the heteroatom directing effect, stereoselectivity was satisfactorily tuned with the appropriate solvents.

On pursuing our interests in cyclopentene-based nucleoside analogues synthesis,[16] we report here a quantitative evaluation of the solvent effect on the HB directing effects in the cycloaddition of nitrile oxide to 2-cyclopenten-1-ol and allylic *N*-cyclopentenyl amides, which serve as reference data for more complex systems. The persistence of some *syn* stereoselectivity even in good H-bond acceptor solvents and comparisons with the stereoselectivities of the *O*- and *N*-methyl derivatives point out the existence of some residual hydrogen bond direction. The *syn*-stereoselectivity in the presence of M(II) salts was also investigated and a brief discussion is given, in light of potential applications in nucleoside analogue synthesis using 2-cyclopenten-1-ol or allylic *N*-cyclopentenyl amides as scaffolds for these targets.

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http://dx.doi.org/10.1016/j.tet.2017.03.042
0040-4020/

2. Results

2.1. Solvent effect in nitrile oxide cycloaddition reactions

2.1.1. Cycloadditions to 2-cyclopenten-1-ol and 3-methoxy-cyclopentene

Cycloadditions of benzonitrile oxide (BNO) to 2-cyclopenten-1-ol (**1A**) and 3-methoxy-cyclopentene (**1B**) afforded the known four regio and stereoisomeric cycloadducts **2Aa-d** and **2Ba-d**, respectively (Scheme 1).[12] The solvent effect was investigated by performing the reactions in 13 solvents of different polarities and Hydrogen Bond Acceptor (HBA) abilities and the product distribution was determined with quantitative HPLC analyses. Table 1 gives the reaction yields and the regio and stereoisomeric ratios of **2a-d** along with the Taft's β parameter,[14] a descriptor of the HBA ability of the solvents.

As a whole, cycloadditions to cyclopentenol give good yields (60–95%) of the adducts, while the product distribution shows a remarkable solvent dependence.

In non-HBA solvents (β = 0.00–0.10; entries 1–6), the *6syn* cycloadduct **2Aa**, which derives from the HB directed cycloaddition shown in **3**, is the major regioisomer and amounts to 55–68% of the cycloaddition products. In HBA acceptor solvents (entries 7–13) the HB directing effect decreases because of the competing effect of the solvent for the HB and the amount of cycloadduct **2Aa** steadily drops with the increasing β values of the solvent. Meanwhile, the *anti* adducts **2Ad** and **2Ab** steadily increase maintaining between them a rather constant ratio **2d**/**2b**, ranging from 2.5 to 3.0. The major *anti* cycloadduct is the *4anti* stereoisomer **2Ad**, in accordance with Frontier Orbital (FO) and electrostatic expectations.[12a] The *4syn* cycloadduct **2Ac** is nearly negligible in all the cases owing to the steric hindrance between the hydroxyl substituent and the nitrile oxide phenyl substituent.[11,12,17]

A graphical illustration of the effect is given in Fig. 1, where the log of the percentage of the adduct *6syn* **2Aa** in the mixture is plotted against solvent β values. In non-HBA solvents (β equal or proximal to 0.00), the HB directing effect is fairly active and constant and all the points cluster together. HBA solvents cause the drop of the points along a line with slope −1.02. The linear regression is fair (r^2 = 0.95) and shows that the β parameter satisfactorily accounts for the solvent effect on the stereoselectivity. Conversely, the related cycloaddition to 3-methoxy-cyclopentene does not show any noticeable solvent dependence (Table 1, entries 14–17). At the bottom of Fig. 1 the red squares show the constance of the *6syn* adduct **2Ba** in the mixtures. The major adducts are the *anti* regioisomer **2Bd** and **2Bb** in a ratio *ca.* 2:1 similar to that reported in the case of the alcohols.

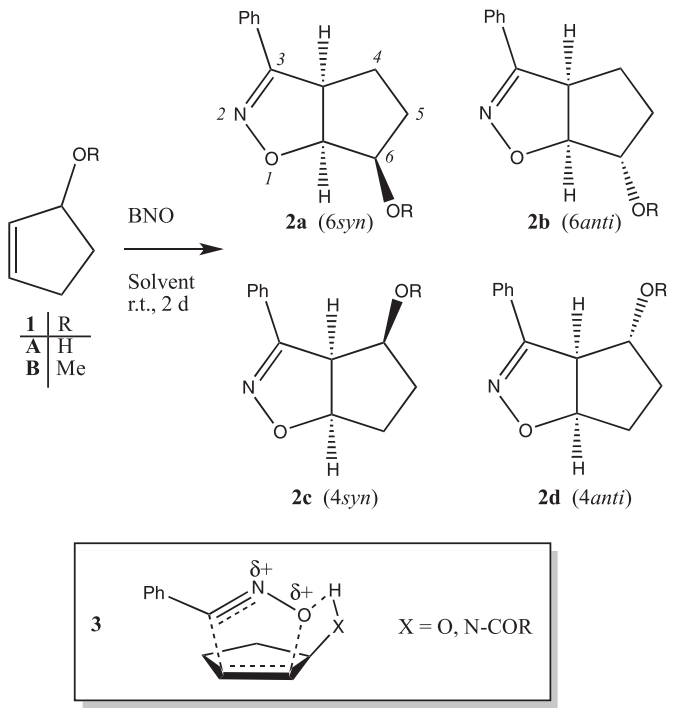
Table 1
Reaction yields and regioisomeric ratios of cycloadducts **2a-d** in the cycloadditions to 2-cyclopenten-1-ol and 3-methoxy-cyclopentene.

Entry	Solvents (β)[a]	Yield %	2a	2b	2c	2d	2d/2b
*2-cyclopenten-1-ol (**1A**)*							
1	Cy (0.00)	82	68	8	–	24	3.0
2	*n*Hex (0.00)	87	60	10	1	29	2.9
3	CCl_4 (0.00)	65	64	9	–	27	3.0
4	CH_2Cl_2 (0.00)	82	58	11	1	30	2.7
5	$CHCl_3$ (0.00)	81	55	12	2	31	2.8
6	Bz (0.10)	88	58	11	3	28	2.5
7	DIOX (0.37)	95	20	22	5	53	2.4
8	AcOEt (0.45)	79	23	21	2	54	2.6
9	Acetone (0.48)	86	21	21	1	57	2.7
10	THF (0.55)	90	20	22	5	53	2.4
11	MeOH (0.62)	66	12	23	1	64	2.8
12	DMF (0.69)	63	10	24	5	61	2.5
13	EtOH (0.77)	60	13	22	1	64	2.9
*3-methoxy-cyclopentene (**1B**)*							
14	CH_2Cl_2 (0.00)	72	6	30	5	58	1.9
15	Bz (0.10)	84	7	30	7	56	1.9
16	AcOEt (0.45)	82	6	31	5	58	1.9
17	MeOH (0.62)	72	7	30	5	58	1.9

[a] β values, see ref. 14.

2.2. Cycloadditions to cyclopentenyl amides

We have investigated the solvent effect in the cycloadditions of BNO to the *N*-cyclopentenyl amides **4A-D** which afford the regioisomeric adducts **5a-d** (Scheme 2). Preparative cycloaddition of BNO



Scheme 1. BNO cycloaddition reaction to 2-cyclopenten-1-ol and 3-methoxy-cyclopentene.

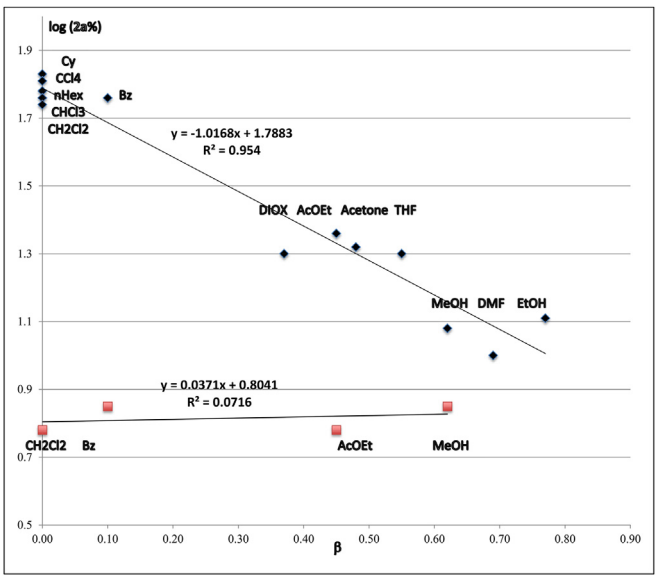


Fig. 1. Plot and linear regression of the log(**2a**%) *vs* solvents β values.

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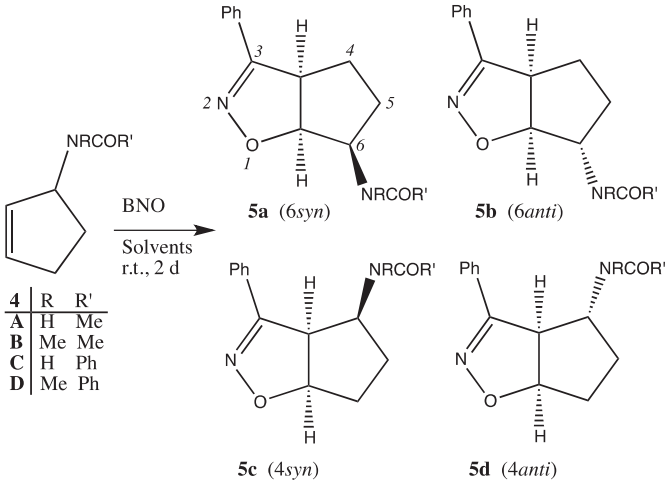

Scheme 2. BNO cycloaddition reaction to cyclopentenyl amides.

to *N*-cyclopentenyl-acetamide (**4A**) in methanol gave the stereoisomeric cycloadducts **5Aa-d**. Chromatographic separation of the reaction mixture furnished the cycloadducts **5Aa** (30%) and **5Ad** (41%), which are known compounds,[13e] and the unknown regioisomers **5Ab** (6%) and **5Ac** (8%), whose structures were assigned upon their analytical and spectroscopic data. Methylation of the adducts with NaH/CH_3I in THF afforded the *N*-methyl derivatives **5Ba-d**. The solvent effect on the cycloaddition to acetamide **4A** was investigated in 13 solvents according to the procedures previously reported. HPLC analyses of the reaction mixtures gave the reaction yields and the isomeric ratios, which are reported in Table 2.

All the reactions afford the cycloadducts in good yields (73–96%). In apolar or non-HBA solvents (entries 1–6) cycloadduct **5Aa** (*6syn*) is resolutely predominant (76–82%) while the isomer *4anti* **5Ad** stands around 18% along with small amounts of the other isomers.

In moderate HBA solvents (entries 7–10) the HB directing effect decreases and almost equimolecular amounts of **5Aa** and **5Ad** are formed. In alcohols and DMF (entries 11–13) the *4anti* isomer **5Ad** outweighs the *6syn* isomer **5Aa** (ratio 1.5:1 to 2.8:1) and small, but noteworthy, amounts (~10%) of the other isomers are formed. The regioisomeric ratio **5Ad**/**5Ab** for the *anti* addition ranges around 6.

When plotting the log of percentage of the adduct *6syn* **5Aa** against the solvent β values (Fig. 2) we obtained a fair linear regression ($r^2 = 0.90$) with a slope of −0.63 slightly smaller with respect to the case of cyclopentenol. The related cycloaddition to the *N*-methyl-*N*-cyclopentenyl-acetamide (**4B**) affords mainly the *anti* adducts **5Bd** and **5Bb** in a ratio ranging from 2:1 to 2.6:1 and does not show any remarkable solvent dependence. The red squares in Fig. 2 show the level of the *6syn* adduct **5Ba**, with respect to the line of the unsubstituted adduct **5Aa**.

The *N*-benzoyl-amides **4C** and **4D** behave similarly. The cycloaddition of BNO to the benzoyl derivative **4C** in methanol yielded a mixture of the four cycloadducts **5Ca-d** (85% overall yield) which have been separated by column chromatography, characterized spectroscopically and converted by methylation into the *N*-methyl derivatives **5Da-d**. The influence of the solvent effects on the cycloadditions to **4C** and **4B** has been tested in a few cases (Table 2) and is almost identical to the cases of the acetamide analogues.

Table 2
Reaction yields and isomeric ratios of cycloadducts **5a-d** in the cycloaddition to cyclopentenyl-amides.

Entry	Solvents (β)[a]	Yield %	5a	5b	5c	5d	5d/5b
*N-cyclopentenyl-acetamide (**4A**)*							
1	Cy (0.00)	91	82	–	3	15	
2	*n*Hex (0.00)	94	79	–	3	18	
3	CCl_4 (0.00)	94	81	–	3	16	
4	CH_2Cl_2 (0.00)	96	76	–	4	20	
5	$CHCl_3$ (0.00)	95	77	–	4	19	
6	Bz (0.10)	95	78	–	3	19	
7	DIOX (0.37)	90	47	5	7	41	6.8
8	THF (0.55)	94	43	7	5	45	6.4
9	AcOEt (0.45)	96	43	6	7	44	7.3
10	Acetone (0.48)	88	40	8	6	46	5.7
11	MeOH (0.62)	94	32	9	10	49	5.4
12	DMF (0.69)	73	20	13	10	57	4.4
13	EtOH (0.77)	91	33	9	9	49	5.4
*N-methyl-N-cyclopentenyl-acetamide (**4B**)*							
14	CH_2Cl_2 (0.00)	99	5	32	–	63	2.0
15	Bz (0.10)	96	4	27	–	69	2.6
16	AcOEt (0.45)	89	4	29	–	67	2.3
17	MeOH (0.62)	82	5	30	–	65	2.2
*N-cyclopentenyl-benzamide (**4C**)*							
18	CH_2Cl_2 (0.00)	95	89	1	10		
19	Bz (0.10)	93	81	2	17		
20	AcOEt (0.45)	86	72	4	24		
21	MeOH (0.62)	73	67	5	28		
*N-methyl-N-cyclopentenyl-benzamide (**4D**)*							
22	CH_2Cl_2 (0.00)	86	3	29	1	67	2.3
23	Bz (0.10)	88	3	32	–	65	2.0
24	AcOEt (0.45)	89	3	31	–	66	2.1
25	EtOH (0.77)	80	3	33	–	64	1.9

[a] β values, see ref. 14.

3. Metal-mediated stereocontrol in cycloaddition reactions

In recent years some metal-mediated approaches have been proposed for nitrile oxide cycloaddition reactions to acyclic allylic alcohols. The use of magnesium allylic alkoxides as dipolarophiles in nitrile oxide cycloadditions was proposed by Kanemasa.[18] The same approach was extended by Ryu to the cycloaddition of nitrile oxides to α,β-unsaturated carbonyl compounds.[19] Other metal alkoxides, such as lithium, zinc, nickel and aluminium, have been tested but they were less effective.[18] Nevertheless, magnesium salts were successfully employed in ion-mediated 1,3-dipolar cycloadditions, showing moderate catalytic efficiency, ligand acceleration effect and providing a promising access to a catalyzed version of the 1,3-dipolar cycloaddition reaction.[20]

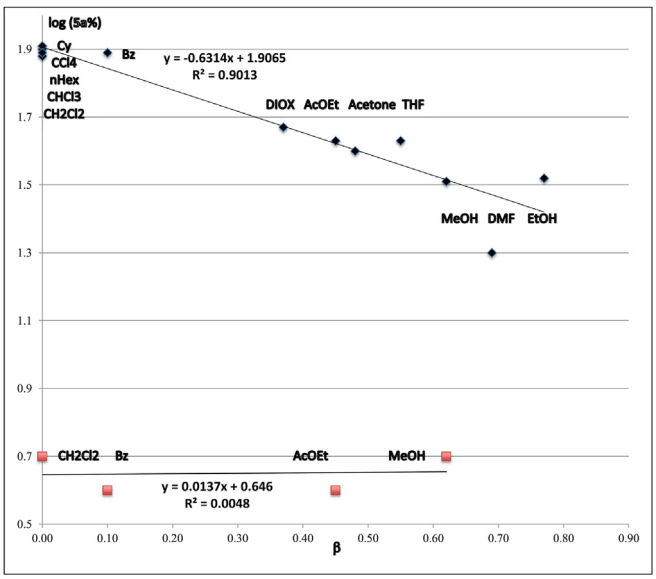

Fig. 2. Plot and linear regression of the log(**5a**%) *vs* solvents β values.

In order to improve the regio- and stereocontrol of the 1,3-dipolar cycloaddition of nitrile oxides to 2-cyclopenten-1-ol and allylic *N*-cyclopentenyl amides, we have also studied the opportunity to perform the previously reported cycloadditions in the presence of representative bivalent M(II) salts.

3.1. Cycloadditions of benzonitrile oxide to 2-cyclopenten-1-ol

We have investigated the effect of the presence of bivalent metal M(II) salts on the cycloaddition outcome by performing the cycloadditions of BNO to 2-cyclopenten-1-ol (**1A**) in DCM solutions (Scheme 1).[12] The solvent choice is based on the necessary comparison with the results obtained in the absence of any metal ion. DCM is a typical non-HBA (Taft's parameter $\beta = 0.00$) and the directing effect of the dipolarophile (see **3** in Scheme 1) is the sole effect at work. Moreover, DCM displays a good ability to dissolve the inorganic salts under the experimental conditions applied.

Table 3 reports the reaction yields as well as regio- and stereoisomeric ratios of cycloadducts **2a-d** when M(II) salts are present in equimolar amounts. The values are the average results of at least two independent experiments.

All the reactions gave nearly quantitative yields of the cycloadducts after one day of reaction time instead of two, as a result of increased reaction rate in accordance with literature observations.[18–21] The regio- and stereoisomeric ratios of the cycloadducts **2a-d** in the experiments of entries 2 and 3 performed with $Mg(II)X_2$ salts (X = Br, Tf) and those of entries 4, 5 and 8 conducted in the presence of $Zn(II)X_2$ salts (X = Br, Tf, ClO_4) strongly resemble the result obtained in the absence of any metal catalyst as reported in the entry 1. DCM being a typical non-HBA solvent, the *syn* selectivity seems to be enforced by the HB directing effect of the OH group of the dipolarophile **1** towards BNO, even in the presence of salts. The *anti* isomers maintain a nearly constant ratios (**2d/2b** ranges from 2.3 to 2.6) in fair accordance with the value of 2.7 in entry 1. The *anti* isomer **2d** remains the major one in keeping with the FO and electrostatic expectations.[12] The 4-*syn* cycloadduct **2c** is nearly negligible in all the cases because of the steric hindrance between the substituents.[11,12,17]

These observations support the suggestion that only the HB directing effect is at work in governing the selectivity or that the coordination to the metal centre is imperfect from low availability of the metal ions or from a geometrical point of view, marginally only influencing the reaction rate. The geometrical features are of strong relevance for an efficient directing activity of the metal ions and these are determined by the dimension of the metal centre and the space occupied by the reagents that are the ligands of the metal.

When $Mg(ClO_4)_2$ was used (entry 6) the cycloaddition reaction proceeds at 25 °C quantitatively with high *syn*-selectivity affording the adduct **2a** nearly as single product (92%). Adducts **2b** and **2d** are 4% of the mixture while the adduct **2c** was absent. In light of this result, we explored the reaction temperature effect and the results are collected in Table 3, entries 11–17. A series of experiments were conducted at 0 °C in DCM as solvent in the presence of Mg(II) and Zn(II) (entries 11–14) without any significant change in regio- and stereoselectivity. With $Mg(ClO_4)_2$ (entry 15) a slight improvement was observed both in terms of reaction yield (97%) and selectivity: adduct **2a** was 96% of the mixture. Lower temperatures (−20 °C or −40 °C) were also tested without significant changes with respect to those obtained at 0 °C.

It is worth noting that the M(II) salts were used in equimolar amounts with respect to the reagents. For this reason, we performed a couple of experiments reducing the amount of the metal salts limiting the case to $Mg(ClO_4)_2$ (entries 9 and 10). While the chemical yields remained good, a neet decrease of the regio- and stereoselectivities was progressively observed upon the reduction of the amount of salt from 0.5 to 0.2 equivs. The adduct **2a** is nearly halved in the reaction mixture and the **2d/2b** ratio is nearly tripled as a sign of the FO interactions prevailing over the metal directing effect. It seems that the catalytic Mg(II), instead of directing the cycloaddition, plays the opposite role, occupying the *syn* face and reversing the selectivity outcome. These results indicate that Mg(II) is the metal of choice for performing the reaction with a significative increase of regio- and stereoselectivity when the metal is used as a reagent and not as a catalyst. The counterion ClO_4 has a decisive role in the selectivity outcome; it is known to be a less-coordinating anion leaving the naked metal cation able to coordinate the cycloaddends for an efficient cycloaddition process. Other perchlorates of Ni(II) and Zn(II) were tested both at 25 °C (entries 7 and 8) and 0 °C (entries 16 and 17); the regio- and stereoselectivities remained at the levels obtained with bromides or triflates as a confirmation of the importance of the metal dimension for the correct approach of the cycloaddends at reaction distance.

Table 3
Reaction yields and regioisomeric ratios of cycloadducts **2a-d** in the cycloadditions to 2-cyclopenten-1-ol (**1A**).

Entry	M(II)X (1.0 equivs.)	Yield %	2a	2b	2c	2d	2d/2b
Reaction conducted at 25 °C							
1	/	82	58	11	1	30	2.7
2	$MgBr_2$	98	51	14	2	33	2.4
3	$MgTf_2$	99	52	13	2	33	2.5
4	$ZnBr_2$	98	56	12	2	30	2.5
5	$ZnTf_2$	84	59	12	2	27	2.3
6	$Mg(ClO_4)_2$	99	92	4	–	4	1.0
7	$Ni(ClO_4)_2$	98	57	12	2	29	2.4
8	$Zn(ClO_4)_2$	98	60	12	1	27	2.3
9[a]	$Mg(ClO_4)_2$	93	65	11	1	23	2.1
10[b]	$Mg(ClO_4)_2$	89	51	13	2	34	2.6
Reaction conducted at 0 °C							
11	$MgBr_2$	98	51	14	2	33	2.4
12	$MgTf_2$	99	51	14	2	33	2.4
13	$ZnBr_2$	99	54	13	1	32	2.5
14	$ZnTf_2$	91	59	12	1	28	2.3
15	$Mg(ClO_4)_2$	97	96	2	–	2	1.0
16	$Ni(ClO_4)_2$	92	58	11	2	29	2.6
17	$Zn(ClO_4)_2$	98	61	12	–	27	2.3

[a] With 0.5 equivs. of catalysts.
[b] With 0.2 equivs. of catalysts.

3.2. Cycloadditions of 4-chlorobenzonitrile oxide to 2-cyclopenten-1-ol

We have investigated the cycloaddition of 4-chlorobenzonitrile oxide (pClBNO) to 2-cyclopenten-1-ol (**1A**) in DCM solutions in the presence of M(II) salts with the aim to have more insight into the potential effect of Et_3N and its hydrochloride salt when the base is used to generate the nitrile oxide species as they can be potential competitors in the HB directing effects or in the construction of the metal complexes (Scheme 3). pClBNO can be prepared as a moderately stable nitrile oxide upon base treatment of the corresponding α-chloroxime in diethyl ether as solvent. Evaporation of the solvent affords the solid nitrile oxide, found to be stable for at least one day without appreciable dimerization.

The reaction afforded the four stereoisomeric cycloadducts **6a-d** in 80% overall yield that were separated through column chromatography and fully characterized *via* their analytical and spectroscopic data. Table 4 reports the relative amounts of the four cycloadducts in the experiments performed; the data are the average of at least two independent experiments.

All the reactions performed in the presence of M(II) salts gave excellent yields, in many cases nearly quantitative after one day of reaction. The analysis of these results reveals that the absence of

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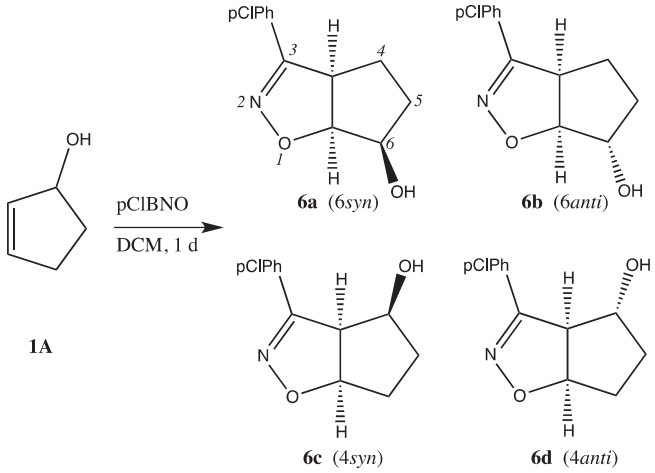
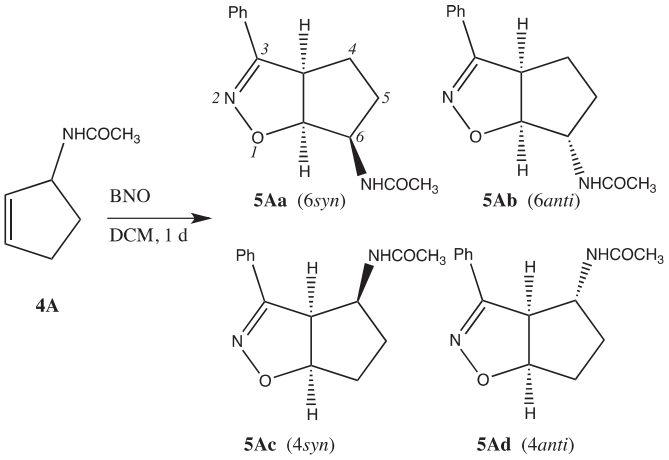


Scheme 3. pClBNO cycloaddition reaction to 2-cyclopenten-1-ol (**1A**).



Scheme 4. BNO cycloaddition reaction to cyclopentenyl amide (**4A**).

the couple $Et_3N/Et_3N{\cdot}HCl$ smoothly increases the *syn* selectivity. Stereoisomer **6a**, the major component, increases its percentage within the reaction mixture with good performances even with Mg(II) bromides or triflates (Table 4, entries 2–5) as well as with the same Zn(II) salts.

The use of $Mg(ClO_4)_2$ (entry 6) afforded the best result for the reaction conducted at 25 °C: 99% yield, 96% of isomer **6a**. The other perchlorates (entries 7 and 8) did not give the same performances and a reduction of the amount of salts (entries 9 and 10) is detrimental for the *syn*-selectivity, as previously reported.

Further improvements were obtained at 0 °C for the reaction conducted in the presence of $Mg(ClO_4)_2$ (entry 15) where the stereoisomer **6a** was obtained nearly as single component (99%) with a nearly quantitative yield. For the other cases the temperature did not influence the stereochemical outcome very much (entries 11–14 and 16–17).

3.3. Cycloadditions to cyclopentenyl amide *4A*

To complete the picture, we have investigated the effect of M(II) salts on the cycloadditions of BNO to the *N*-cyclopentenyl amide **4A** in DCM as solvent. The reactions afforded the regioisomeric adducts **5Aa-d** (Scheme 4) and the data are reported in Table 5.

With respect to the reaction performed in the absence of any metal ion (Table 5, entry 1), the chemical yields are slightly better with the remarkable exception of the cases of $MgBr_2$ (entries 2 and 11). The effect of the metal coordination on the regio- and stereoselectivity is modest. The major adduct **5Aa** never surpasses 86% at 25 °C and 87% at 0 °C with $Mg(ClO_4)_2$ (entries 6 and 15). Adduct **5Ab** is totally absent in all the reaction mixtures, **5Ac** ranges around 1–4% while **5AdB** is always present in 14–27% in the reaction mixtures. Temperature does not give substantial improvements in terms of selectivities.

Cyclopentenyl amides seem to be less apt to obey the strict rules for an efficient direction in the nitrile oxide cycloaddition reactions conducted in the presence of metals. Reasonably, the amide group strongly competes as a ligand in the coordination of metal ions, diverting the metal centre far from the orientation of the cycloaddends. Here the coordination to the metal can be defined as imperfect.

4. Discussion

The fair correlations between the percentage of the directed cycloadducts **2Aa** and **5Aa** in the cycloaddition mixtures and the Taft's β parameter support the idea of a HB direction in these

Table 4
Reaction yields and regioisomeric ratios of cycloadducts **6a-d** in the cycloadditions to 2-cyclopenten-1-ol (**1A**).

Entry	M(II)X (1.0 equivs.)	Yield %	6a	6b	6c	6d	6d/6b
Reaction conducted at 25 °C							
1	–	80	55	12	3	30	2.5
2	$MgBr_2$	98	67	10	1	22	2.2
3	$MgTf_2$	99	52	13	2	33	2.5
4	$ZnBr_2$	97	66	10	2	22	2.2
5	$ZnTf_2$	97	74	8	2	16	2.0
6	$Mg(ClO_4)_2$	99	96	2	–	2	1.0
7	$Ni(ClO_4)_2$	92	61	10	2	27	2.7
8	$Zn(ClO_4)_2$	98	59	11	3	27	2.5
9[a]	$Mg(ClO_4)_2$	97	77	7	1	15	2.1
10[b]	$Mg(ClO_4)_2$	89	59	11	3	27	2.5
Reaction conducted at 0 °C							
11	$MgBr_2$	99	66	10	1	23	2.3
12	$MgTf_2$	99	62	10	2	26	2.6
13	$ZnBr_2$	99	66	9	1	24	2.7
14	$ZnTf_2$	99	76	8	2	14	1.8
15	$Mg(ClO_4)_2$	99	99	–	–	1	–
16	$Ni(ClO_4)_2$	95	61	10	2	27	2.7
17	$Zn(ClO_4)_2$	98	60	10	3	27	2.3

[a] With 0.5 equivs. of catalysts.
[b] With 0.2 equivs. of catalysts.

Table 5
Reaction yields and regioisomeric ratios of cycloadducts **5a-d** in the cycloadditions to *N*-cyclopentenyl acetamide (**4A**).

Entry	M(II)X (1.0 equivs.)	Yield %	5a	5b	5c	5d	5d/5b
Reaction conducted at 25 °C							
1	–	96	76	–	4	20	
2	$MgBr_2$	67	75	–	3	22	–
3	$MgTf_2$	99	79	–	3	19	–
4	$ZnBr_2$	99	81	–	2	17	–
5	$ZnTf_2$	97	85	–	1	14	–
6	$Mg(ClO_4)_2$	95	86	–	1	13	–
7	$Ni(ClO_4)_2$	98	79	–	2	19	–
8	$Zn(ClO_4)_2$	98	69	–	4	27	–
Reaction conducted at 0 °C							
11	$MgBr_2$	68	75	–	3	23	–
12	$MgTf_2$	98	79	–	2	19	–
13	$ZnBr_2$	99	76	–	3	21	–
14	$ZnTf_2$	96	84	–	1	15	–
15	$Mg(ClO_4)_2$	95	87	–	1	12	–
16	$Ni(ClO_4)_2$	97	78	–	2	19	–
17	$Zn(ClO_4)_2$	98	69	–	4	27	–

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reactions and point out that β is the descriptor of choice for the practical tuning of stereoselectivity.

The directing effect of the acetamido group is slightly larger than that of the OH, well in keeping with the slightly higher HB acidity of the amide group, as determined by thermochemical studies[22] and theoretical calculations.[23] Somewhat surprisingly, however, the sensitivity to the solvent effect is slightly larger for the alcohol than in the case of amides, as shown by the different slopes in Figs. 1 and 2.

There are some other intriguing aspects in the results discussed above, which deserve attention. While synthetically useful, the size of the solvent effect is somewhat smaller than what we had expected. The strength of a moderate HB, *e.g.* between an ether or an amide with *n*-butanol, is usually estimated at 3–4 kcal/mol ($-\Delta H_f$)[24] while the change in stereoselectivity ($\Delta\Delta G\neq$) on going from the apolar solvents to DMF is only 1.04 kcal/mol in the case cyclopentenol and even less in the case of amides (0.76 kcal/mol). Moreover Figs. 1 and 2 seem to indicate a persistence of the HB directivity even in good HBA solvents, since the points relative to alcoholic solvents and DMF lie well above the reference points of the methyl derivatives. Although entropic effects on the stereoselectivity ($\Delta\Delta G\neq$) may be involved and the steric bulk of the *O*- and *N*-methylated substituents may overcome that of the solvated directing groups, the most immediate impression is that only a part of the HB directing effect is lost in the solvation of the directing groups. We have already noted a similar case of persistence of *syn*-direction in HBA solvents in the cycloaddition of BNO to 4-benzoylamino-cyclopentenone[15] and we attributed it to the Cieplak effect by analogy to the explanation given for the moderate stereoselection of the Diels-Alder reaction of cyclopentadiene with 4-substituted cyclopentenones.[25]

The conformational preferences of the dipolarophiles are summarized in Scheme 5. In the case of cyclopentenol (**1A**) two axial and two equatorial outside staggered conformers with the OH bond near or far with respect to the double bond can be drawn and lie *ca.* 1 kcal/mol above the inside conformation. This conformational preference has been ascribed to the lack of the repulsion between the oxygen lone pairs and the π bond.[26] Solvent effects do not sizeably alter the conformational equilibrium of **1A** according to the COSMO calculations in cyclohexane, methanol and water.[27]

In the case of the amide **4A** steric effects determine the conformational preferences. The acetamide substituent is more rigid and the equatorial and axial conformers with the NH bond directed outside the ring are about 3 kcal/mol higher in energy, the bulky *N*-acetyl moiety staggering the C–C bonds of the ring.

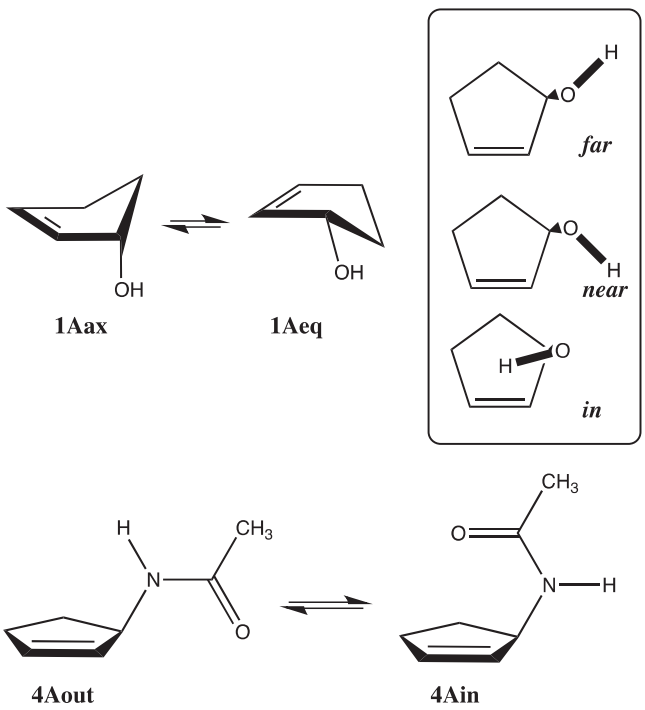
The Transition State **3** (TS) shown in Scheme 1 nicely accounts for the HB directing effect for both the dipolarophiles. This arrangement requires for the cyclopentenol **1A *in*** conformer to be populated, a relatively easy process taking into account the small energy differences involved. Nevertheless, the same small energetic differences among the various conformers are partly the reason for the imperfect HB directivity in non-HBA solvents (β = 0.00–0.10; Table 1, entries 1–6) where the amounts of the *anti* isomers are not negligible. This situation is repeated in the case of the amide **4A**. The lower sensitivity to the solvent effect is due to the conformational preference that leaves the acetyl group outside the ring pointing the N–H bond in the correct direction to orient the incoming nitrile oxide. Moreover, polar and protic solvents can be diverted from interacting with the NH group by the carbonyl group other than the lone pair on the nitrogen atom, determining a consistent level of direction in the cycloaddition reaction.

The persistence of the HB even in good HBA solvents can then be attributed to the residual interaction between the XH and the nitrile oxide oxygen. The directing groups give rise to a sort of bifurcated hydrogen bond with two interactions of different magnitude and presumably influence to each other. Bifurcated hydrogen bonds have been frequently noted in theoretical calculations[28] and the main evidence of their role comes from structural studies, which show that they are very common (Fig. 3).[24] Spectroscopic evidence for their importance has been recently provided.[29]

The results obtained in the studies of the metal-mediated cycloaddition reaction between nitrile oxides and 2-cyclopenten-1-ol (**1A**) and cyclopentenyl amide **4A** as dipolarophiles showed a general increase of the reaction rates due to the simple coordination of dipole/dipolarophile. This coordination does not always influence the reaction selectivity since it remains at the same level reached by simple H-bonding effect, implying an incorrect geometry of the complexes.

As far as the Mg-complexed cycloaddends are concerned as drawn in Fig. 4, the metal ion must have the correct size to be coordinated by the cyclopentenol (**1A**) that is prone to receive the nitrile oxide on the *syn* face as shown in **TS_A**. Mg(II) ion has an ionic radius of 0.65 Å while Ni(II) and Zn(II) possess larger values (0.72 Å and 0.74 Å, respectively).

This implies a distortion of the resulting complex or an



Scheme 5. Conformers of 2-cyclopenten-1-ol (**1A**) and cyclopentenyl amide **4A**.

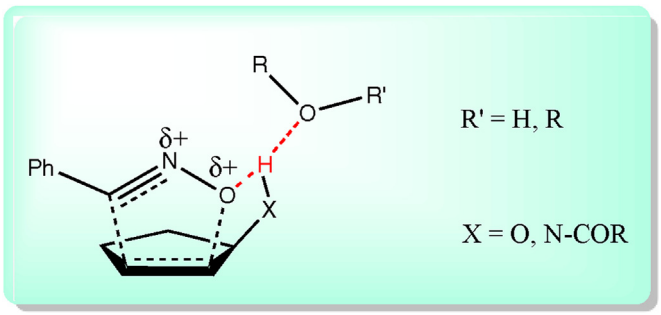


Fig. 3. Bifurcated hydrogen bonding.

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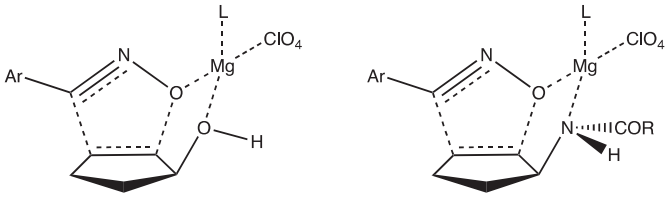


Fig. 4. TSs of Mg-complexed cycloaddends.

impossibility to build a complex and as a consequence the impossibility for the nitrile oxide moiety to add according to the direction imposed by the interacting FOs.[30] Hence, the directing effects are just determined by the H-bonding producing the same selectivities as observed in the absence of any metal ion. This type of preference of metal ions is often found in catalyzed reactions and mainly in 1,3-dipolar cycloadditions.[31] In parallel, perchlorates are often preferred as counterions because of their low coordinating ability, leaving the metal free to act as an aggregation centre for the reacting ligands.[31] The need for a stable and correctly built complex is part of the reason why the required amount of magnesium salt is equimolar with the reagents. Mg(II) is not a catalyst and the construction of the complex, the consequent cycloaddition and release of the metal ion are time consuming with respect to the simple cycloaddition governed by H-bonding effects that still are competitive with the coordinative process.

The case of the cyclopentenyl amide **4A** is similar although with some potential complications: **TS_B** in Fig. 4 shows a single type of coordination that excludes the carbonyl oxygen that can have a role in diverting the metal ion from the possibility to orientate the addition of the nitrile oxide. This cannot be excluded or avoided and for this reason the results were less impressive than the cases of cyclopentenol (**1A**).

If it is easy to depict the temperature effect in stabilizing the complexes without slowing down the reaction rates (0 °C seems a good compromise), it is more complex to define the effect of the couple $Et_3N/Et_3N{\cdot}HCl$ on the selectivity. When nitrile oxides are generated *in situ* from the corresponding α-chloroxime in the presence of a base and its conjugated acid cannot be avoided and this aspect has never been thoroughly investigated with the exception of a single control experiment.[32] This adds complexity to the system under investigation and Et_3N^+-H is surely able to H-bond to both the cycloaddends, competing with the factor playing in favour of a *syn* selectivity in the cycloaddition. The results obtained with the isolable pClBNO demonstrated that the absence of Et_3N and $Et_3N{\cdot}HCl$ simplifies the system and slightly ameliorated both chemical yields and selectivities in the reaction with the cyclopentenol (**1A**).

5. Conclusions

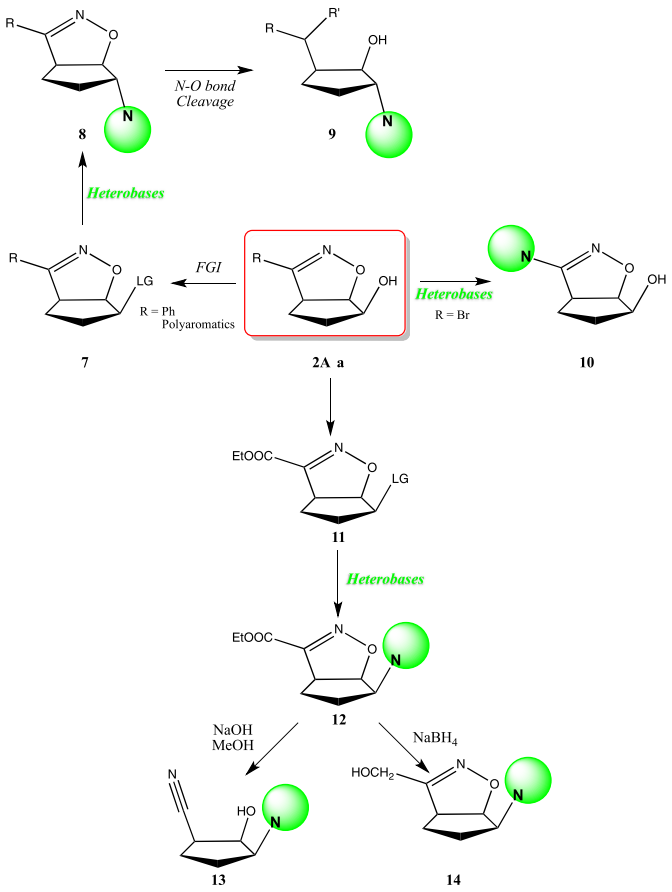
The solvent effect on the HB directing effect of allylic hydroxy and acylamino substituents in the cycloaddition of nitrile oxide to cyclopentenol and *N*-cyclopentenyl amide has been studied. The *syn* stereoselectivity decreases with the increasing HBA ability of solvents and Taft's β parameter is a satisfactory descriptor. The directing effect decreases but does not vanish completely even in good HBA solvents and the residual reactivity is likely due to the instalment of a bifurcated HB between the HB proton with the HBA solvent and the nitrile oxide oxygen. Bifurcated hydrogen bonds are well known in structural chemistry and we suggest their involvement in a case of reactivity.

The use of bivalent metal salts was also investigated as a tool for increasing the directing effect. Magnesium perchlorate was found to be the salt of choice for efficient *syn* selectivity and the reaction conditions can be properly tuned up by decreasing the reaction temperature and removing hydrogen-bond donors or acceptors, such as the bases and their hydrochlorides used to generate the 1,3-dipoles. These results open the way to the introduction of chiral ligands on Mg(II) for an enantioselective route to cycloadducts of the type **2Aa**.

Cycloadduct **2Aa** is the ideal candidate for our synthetic strategies towards nucleoside analogues. Scheme 6 shows the opportunities that previous investigations open in this field. Cycloadducts of type **2Aa**, bearing a simple aromatic group or polyaromatic substituents with fluorescent properties, can be easily converted into derivatives of type **7** containing a good leaving group (LG) for a stereoselective introduction of nucleophilic heterobases to give the bicyclic nucleoside analogues **8**, with an *anti*-relationship between the heterobases and the isoxazoline ring, these latter conformers can be eventually elaborated into the simple carbocyclic derivatives **9** by cleavage of the N–O bond of the isoxazoline ring.[16,32]

On the other hand, cycloadducts **2Aa** obtained from bromonitrile oxide undergo easy substitution of the bromine atom with nucleophilic heterobases to give the *syn*-substituted nucleoside analogues of type **10**.[33]

Finally, cycloadducts **2Aa** obtained from the carbetoxynitrile oxide bearing a good LG, as in **11**, can be submitted to heterobases substitution reaction to afford **12** that can undergo two different pathways: a basic hydrolysis cleaves the isoxaoline ring to give the β-hydroxy nitrile derivatives **13** while the reduction of the



Scheme 6. Synthetic strategies from cycloadduct **2Aa** towards nucleoside syntheses.

Please cite this article in press as: Cardarelli AM, et al., The hydrogen bond directing effect in nitrile oxide cycloadditions to allylic substituted cyclopentenes, Tetrahedron (2017), http://dx.doi.org/10.1016/j.tet.2017.03.042

carboethoxy functionality allows for the introduction of a polar/protic hydroxymethylene group suitable for increasing solubility of these compounds.[34]

Due to the low level of selectivity obtained with the cyclopentenyl amides, the corresponding cycloadducts will not be used to access other nucleoside analogues.

6. Experimental section

All melting points are uncorrected. Elemental analyses were done on a C. Erba 1106 elemental analyzer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AVANCE 300 and Bruker AC 200 spectrometers in $CDCl_3$ solutions unless otherwise stated. Chemical shifts are expressed in ppm from internal tetramethylsilane (δ). IR spectra (nujol mulls) were recorded on an FT-IR Perkin-Elmer Paragon 1000. HPLC quantitative analyses have been performed with a Waters 510 HPLC apparatus equipped with an UV 490 E detector: column RP C-18 Intersil ODS-2 (2.5 μm, id = 4.6 mm, 250 mm length); eluant water/acetonitrile. Column chromatography and TLC: silica gel H60 and GF_{254} (Merck), respectively, eluant cyclohexane/ethyl acetate 9:1 to 5:5. The identification of samples from different experiments was secured by mixed mps and superimposable IR spectra.

6.1. Materials

Benzhydroximoyl chloride, the precursor of BNO,[35] was obtained by treatment of benzaldoxime with sodium hypochlorite.[36] 4-Chlorobenzhydroxymoyl chloride, the precursor of pClBNO,[35] was obtained by treatment of the corresponding 4-chlorobenzaldoxime with sodium hypochlorite.[36]

2-Cyclopenten-1-ol (**1A**) and 3-methoxy-cyclopentene (**1B**) were prepared from freshly distilled cyclopentadiene by addition of gaseous HCl and basic hydrolysis of the obtained 3-chloro-cyclopentene with $NaHCO_3/H_2O$ for **1A** and $NaHCO_3$/MeOH for **1B**, respectively.[37]

N-Cyclopentenyl-amides **4A-D** were prepared according to the procedures reported by Curran.[13e]

Mg(II), Zn(II) and Ni(II) salts were purchased from Sigma-Aldrich; $MgBr_2$ and $ZnBr_2$ were dried at 140 °C for one day under vacuum.

6.2. Cycloaddition of benzonitrile oxide to 2-cyclopenten-1-ol (*1A*)[12]

To a stirred solution of 2-cyclopenten-1-ol (**1A**) (5.0 g, 59 mmol) and benzhydroximoyl chloride (7.7 g, 50 mmol) in benzene (120 mL), 8 mL of triethylamine (57 mmol) in the same solvent (20 mL) were added over a 0.5 h period. After stirring the reaction 2 days at r.t., the mixture was evaporated under reduced pressure leaving a residue which was separated by column chromatography affording the stereoisomeric cycloadducts **2Aa-d**.[12] These cycloadducts served as references for the analyses conducted for the investigation of the solvent effect. Hereby, we report the chemical yields and NMR data for reference.

2Aa. 5.28 g (52%). ^{1}H NMR (δ, $CDCl_3$): 1.51–154 (m, 2H, CH_2), 1.92–1.95 (m, 2H, CH_2), 2.40 (bs, 1H, OH), 4.10–4.15 (m, 1H, CH–OH), 4.22–4.25 (m, 1H, H4-isox.), 5.20 (dd, 1H, J = 9.3, 5.0 Hz, H5-isox.), 7.42–7.44 (m, 3H, arom.), 7.69–7.71 (m, 2H, arom.); ^{13}C NMR (δ, $CDCl_3$): 26.6, 30.9 (CH_2), 50.8 (CH), 76.0 (CH–OH), 85.3 (CH–O), 126.9, 128.0, 128.7, 130.0 (arom.), 159.4 (C=N).

2Ab. 1.02 g (10%). ^{1}H NMR (δ, $CDCl_3$): 1.68 (s, 1H, OH), 1.77–1.81 (m, 2H, CH_2), 1.94–1.96 (m, 1H, CH_2), 2.34–2.38 (m, 1H, CH_2), 4.20–4.24 (m, 1H, H4-isox.), 4.48 (dt, 1H, J = 9.0, 2.0 Hz, CH–OH), 4.99 (d, 1H, J = 9.0 Hz, H5-isox.), 7.41–7.45 (m, 3H, arom.), 7.70–7.74 (m, 2H, arom.); ^{13}C NMR (δ, $CDCl_3$): 28.5, 31.3 (CH_2), 50.9 (CH), 77.6 (CH–OH), 91.9 (CH–O), 126.8, 128.6, 129.7, 129.8 (arom.), 158.7 (C=N).

2Ac. 0.20 g (2%). ^{1}H NMR (δ, $CDCl_3$): 1.45 (s, 1H, OH), 1.80–1.84 (m, 1H, CH_2), 2.20–2.24 (m, 1H, CH_2), 2.01–2.04 (m, 2H, CH_2), 4.10–4.12 (m, 1H, H4-isox.), 4.60 (dd, 1H, J = 9.4, 7.2 Hz, CH–OH), 5.22–5.26 (m, 1H, H5-isox.), 7.40–7.44 (m, 3H, arom.), 7.76–7.80 (m, 2H, arom.); ^{13}C NMR (δ, $CDCl_3$): 30.6, 33.8 (CH_2), 56.7 (CH), 75.4 (CH–OH), 88.0 (CH–O), 126.8, 128.6, 129.7, 130.0 (arom.), 156.0 (C=N).

2Ad. 2.34 g (23%). ^{1}H NMR (δ, $CDCl_3$): 1.56 (s, 1H, OH), 1.79–1.82 (m, 2H, CH_2), 2.26–2.30 (m, 2H, CH_2), 4.00 (dd, 1H, J = 8.8, 1.0 Hz, H4-isox.), 4.44–4.48 (m, 1H, CH–OH), 5.34 (ddd, 1H, J = 8.8, 5.0, 1.0 Hz, H5-isox.), 7.41–7.45 (m, 3H, arom.), 7.76–7.80 (m, 2H, arom.); ^{13}C NMR (δ, $CDCl_3$): 32.4, 33.0 (CH_2), 61.6 (CH), 76.5 (CH–OH), 87.2 (CH–O), 126.7, 128.7, 129.0, 129.8 (arom.), 155.8 (C=N).

6.3. Cycloaddition of benzonitrile oxide to 3-methoxy-cyclopentene (*1B*)[12]

To a stirred solution of 3-methoxy-cyclopentene (**1B**) (5.0 g, 51 mmol) and benzhydroximoyl chloride (6.7 g, 43 mmol) in benzene (120 mL), 7 mL of triethylamine (51 mmol) in the same solvent (20 mL) were added over a 0.5 h period. After stirring the reaction 2 days at r.t., the mixture was evaporated under reduced pressure leaving a residue which was separated by column chromatography affording the stereoisomeric cycloadducts **2Ba-d**.[12] These cycloadducts served as references for the analyses conducted for the investigation of the solvent effect. Hereby, we report the chemical yields and NMR data for reference.

2Ba. 0.56 g (6%) ^{1}H NMR (δ, $CDCl_3$): 1.59–1.62 (m, 1H, CH_2), 1.92–1.94 (m, 3H, CH_2), 3.53 (s, 3H, OCH_3), 3.90 (qi, 1H, J = 5.2 Hz, CH–OH), 4.09 (dt, 1H, J = 8.5, 2.6 Hz, H4-isox.), 5.10 (dd, 1H, J = 8.5, 4.6 Hz, H5-isox.), 7.38.7.42 (m, 3H, arom.), 7.68–7.72 (m, 2H, arom.); ^{13}C NMR (δ, $CDCl_3$): 26.1, 27.2 (CH_2), 50.4 (CH), 57.9 (OCH_3), 83.9 (CH–OH), 85.2 (CH–O), 126.9, 128.4, 128.7, 129.8 (arom.), 158.5 (C=N).

2Bb. 2.62 g (28%). ^{1}H NMR (δ, $CDCl_3$): 1.60–1.63 (m, 1H, CH_2), 1.91–1.94 (m, 2H, CH_2), 2.18–2.22 (m, 1H, CH_2), 3.40 (s, 3H, OCH_3), 3.94 (d, 1H, J = 3.8 Hz, CH–OH), 4.17 (dt, 1H, J = 9.0, 2.0 Hz, H4-isox.), 5.05 (d, 1H, J = 9.0 Hz, H5-isox.), 7.42–7.45 (m, 3H, arom.), 7.70–7.73 (m, 2H, arom.); ^{13}C NMR (δ, $CDCl_3$): 28.4, 28.8 (CH_2), 51.1 (CH), 56.7 (OCH_3), 86.8 (CH–OH), 89.5 (CH–O), 126.9, 128.7, 128.8, 129.8 (arom.), 158.8 (C=N).

2Bc. 0.47 g (5%). ^{1}H NMR (δ, $CDCl_3$): 1.89–1.93 (m, 3H, CH_2), 2.15–2.18 (m, 1H, CH_2), 3.17 (s, 3H, OCH_3), 4.08–4.12 (m, 2H, CH–OH and H4-isox.), 5.18–5.22 (m, 1H, H5-isox.), 7.36–7.40 (m, 3H, arom.), 7.70–7.74 (m, 2H, arom.); ^{13}C NMR (δ, $CDCl_3$): 29.6, 30.6 (CH_2), 55.9 (CH), 57.5 (OCH_3), 84.1 (CH–OH), 87.4 (CH–O), 127.0, 128.1, 129.1, 130.6 (arom.), 156.7 (C=N).

2Bd. 4.67 g (50%). ^{1}H NMR (δ, $CDCl_3$): 1.57–1.60 (m, 1H, CH_2), 1.95–1.99 (m, 1H, CH_2), 2.12–2.16 (m, 2H, CH_2), 3.37 (s, 3H, OCH_3), 3.89 (dt, 1H, J = 4.4, 1.0 Hz, CH–OH), 4.04 (dt, 1H, J = 8.8, 1.0 Hz, H4-isox.), 5.26–5.30 (m, 1H, J = 8.8, 3.0, 1.2 Hz, H5-isox.), 7.42–7.44 (m, 3H, arom.), 7.74–7.78 (m, 2H, arom.); ^{13}C NMR (δ, $CDCl_3$): 27.9, 32.5 (CH_2), 56.4 (CH), 59.3 (OCH_3), 85.3 (CH–OH), 87.1 (CH–O), 126.6, 128.7, 129.2, 129.8 (arom.), 155.7 (C=N).

6.4. Cycloaddition of benzonitrile oxide to N-cylopentenyl-acetamide (*4A*)

To a stirred solution of *N*-cyclopentenyl-acetamide (**4A**) (6.0 g, 48 mmol) and benzhydroximoyl chloride (6.2 g, 40 mmol) in methanol (120 mL), 7 mL of triethylamine (45 mmol) in the same

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solvent (20 mL) were added over a 0.5 h period. After stirring the reaction 2 days at r.t., the mixture was evaporated under reduced pressure leaving a residue which was separated by column chromatography affording the stereoisomeric cycloadducts **5Aa-d**.

5Aa. 2.93 g (30%). Colorless solid, mp 163-4 °C from *i*-Pr_2O. R_f (1:1 cyclohexane/AcOEt) 0.67. IR (cm^{-1}): ν_{NH} 3246, $\nu_{C=O}$ 1637. ^1H NMR (δ, $CDCl_3$): 2.04 (s, 3H, $COCH_3$), 1.0–1.06 (m, 2H, CH_2), 1.97–2.01 (m, 2H, CH_2), 4.13–4.17 (m, 1H, H4-isox.), 4.44–4.46 (m, 1H, CH–NH), 5.03 (dd, 1H, J = 8.4, 5.1 Hz, H5-isox.), 6.11 (d, 1H, J = 8.4 Hz, NH), 7.41–7.43 (m, 3H, arom.), 7.68–7.71 (m, 2H, arom.). ^{13}C NMR (δ, $CDCl_3$): 23.2 ($COCH_3$), 27.7, 28.3 (CH_2), 50.8 (CH), 55.3 (CHNH), 84.2 (CH–O), 126.9, 128.0, 128.7, 130.1 (arom.), 159.2 (C=N), 169.9 (C=O). Elemental analysis: C 68.81%, H 6.61%, N 11.50%; calcd. for $C_{14}H_{16}N_2O_2$ (244.3) C 68.83%, H 6.60%, N 11.47%.

5Ab. 0.59 g (6%). Colorless solid, mp 150-1 °C from benzene. R_f (1:1 cyclohexane/AcOEt) 0.33. IR (cm^{-1}): ν_{NH} 3285, $\nu_{C=O}$ 1645. ^1H NMR (δ, $CDCl_3$): 2.04 (s, 3H, $COCH_3$), 1.78–1.82 (m, 2H, CH_2), 2.16–2.20 (m, 2H, CH_2), 4.18 (dt, 1H, J = 9.1, 2.6 Hz, H4-isox.), 4.39–4.42 (m, 1H, CH–NH), 5.10 (dd, 1H, J = 9.1, 1.8 Hz, H5-isox.), 5.66 (d, 1H, J = 6.0 Hz, NH), 7.40–7.44 (m, 3H, arom.), 7.68–7.72 (m, 2H, arom.). ^{13}C NMR (δ, $CDCl_3$): 23.3 ($COCH_3$), 29.3, 29.4 (CH_2), 51.0 (CH), 58.2 (CHNH), 90.6 (CH–O), 126.9, 128.6, 128.7, 129.9 (arom.), 158.4 (C=N), 169.8 (C=O). Elemental analysis: C 68.79%, H 6.58%, N 11.46%; calcd. for $C_{14}H_{16}N_2O_2$ (244.3) C 68.83%, H 6.60%, N 11.47%.

5Ac. 0.78 g (8%). Colorless solid, mp 155-6 °C from *i*-Pr_2O. R_f (1:1 cyclohexane/AcOEt) 0.45. IR (cm^{-1}): ν_{NH} 3257, $\nu_{C=O}$ 1643. ^1H NMR (δ, $CDCl_3$): 1.41 (s, 3H, $COCH_3$), 1.50–2.30 (m, 4H, CH_2), 4.26 (t, 1H, J = 8.8 Hz, H4-isox.), 4.70–4.72 (m, 1H, CH–NH), 5.10 (d, 1H, J = 9.0 Hz, NH), 5.25 (dd, 1H, J = 8.8, 4.0 Hz, H5-isox.), 7.38–7.42 (m, 3H, arom.), 7.64–7.66 (m, 2H, arom.). ^{13}C NMR (δ, $CDCl_3$): 22.5 ($COCH_3$), 29.5, 31.0 (CH_2), 52.7 (CH), 53.5 (CHNH), 88.0 (CH–O), 126.7, 128.5, 129.6, 129.7 (arom.), 156.9 (C=N), 169.8 (C=O). Elemental analysis: C 68.82%, H 6.59%, N 11.45%; calcd. for $C_{14}H_{16}N_2O_2$ (244.3) C 68.83%, H 6.60%, N 11.47%.

5Ad. 4.01 g (41%). Colorless solid, mp 199–200 °C from benzene. R_f (1:1 cyclohexane/AcOEt) 0.42. IR (cm^{-1}): ν_{NH} 3289, $\nu_{C=O}$ 1637. ^1H NMR (δ, $CDCl_3$): 2.03 (s, 3H, $COCH_3$), 1.78–1.82 (m, 2H, CH_2), 2.17–2.21 (m, 2H, CH_2), 4.23 (d, 1H, J = 9.0 Hz, H4-isox.), 4.39 (t, 1H, J = 5.0, CH–NH), 5.26 (dd, 1H, J = 9.0, 5.0 Hz, H5-isox.), 5.82 (d, 1H, J = 5.0 Hz, NH), 7.40–7.44 (m, 3H, arom.), 7.80–7.82 (m, 2H, arom.). ^{13}C NMR (δ, $CDCl_3$): 23.2 ($COCH_3$), 29.2, 33.7 (CH_2), 55.6 (CH), 59.5 (CHNH), 85.9 (CH–O), 127.2, 128.5, 128.6, 129.8 (arom.), 156.2 (C=N), 170.2 (C=O). Elemental analysis: C 68.79%, H 6.61%, N 11.49%; calcd. for $C_{14}H_{16}N_2O_2$ (244.3) C 68.83%, H 6.60%, N 11.47%.

6.5. Methylation of cycloadducts *5Aa-d*

To a stirred solution of the cycloadducts **5Aa-d** (0.24 g, 1 mmol) in anhydrous THF (10 mL), NaH (0.029 g, 1.2 mmol) was added portionwise in the presence of a slight excess of CH_3I (1 mL, 2 mmol). After stirring the reactions 5 h at r.t., methanol was added first, followed by water and the reaction mixtures extracted with chloroform. The dry organic phases were evaporated and affording in quantitative yields the crude methylated compounds **5Ba-d**, which were recrystallized from suitable solvents and characterized.

5Ba. 0.19 g (75%). Colorless solid, mp 104–105 °C from ligroin. R_f (1:1 cyclohexane/AcOEt) 0.50. IR (cm^{-1}): $\nu_{C=O}$ 1651. ^1H NMR (δ, $CDCl_3$): 1.70–2.00 (m, 4H, CH_2), 2.17 (s, 3H, $COCH_3$), 3.09 (s, 3H, N–CH_3), 4.07–4.10 (m, 1H, H4-isox.), 4.82–4.86 (m, 1H, CH–NH), 5.20 (dd, 1H, J = 8.5, 4.4 Hz, H5-isox.), 7.38–7.42 (m, 3H, arom.), 7.65–7.69 (m, 2H, arom.). ^{13}C NMR (δ, $CDCl_3$): 22.3, 22.7 (CH_2), 27.2 (N–CH_3), 33.4 ($COCH_3$) 50.3 (CH), 58.9 (CH–N), 85.8 (CH–O), 126.7, 128.2, 128.6, 129.8 (arom.), 158.7 (C=N), 171.5 (C=O). Elemental analysis: C 69.73%, H 7.01%, N 10.82%; calcd. for $C_{15}H_{18}N_2O_2$ (258.3) C 69.74%, H 7.02%, N 10.85%.

5Bb. 0.17 g (65%). Colorless solid, mp 116–118 °C from ethanol. R_f (1:1 cyclohexane/AcOEt) 0.30. IR (cm^{-1}): $\nu_{C=O}$ 1643. ^1H NMR (δ, $CDCl_3$): 1.89–1.92 (m, 2H, CH_2), 2.38–2.42 (m, 2H, CH_2), 2.20 (s, 3H, $COCH_3$), 3.00 (s, 3H, N–CH_3), 4.23–4.27 (m, 1H, H4-isox.), 5.00–5.03 (m, 1H, CH–NH), 5.38–5.42 (m, 1H, H5-isox.), 7.40–7.44 (m, 3H, arom.), 7.66–7.70 (m, 2H, arom.); ^{13}C NMR (δ, $CDCl_3$): 22.8, 28.9 (CH_2), 29.6 (N–CH_3), 36.0 ($COCH_3$) 51.9 (CH), 67.3 (CH–N), 89.4 (CH–O), 126.9, 128.3, 129.8, 130.1 (arom.), 159.3 (C=N), 170.9 (C=O). Elemental analysis: C 69.69%, H 6.98%, N 10.82%; calcd. for $C_{15}H_{18}N_2O_2$ (258.3) C 69.74%, H 7.02%, N 10.85%.

5Bc. 0.13 g (52%); Straw colored oil. R_f (1:1 cyclohexane/AcOEt) 0.55. IR (cm^{-1}): $\nu_{C=O}$ 1634. ^1H NMR (δ, $CDCl_3$): 1.67–1.72 (m, 2H, CH_2), 1.89–1.92 (m, 2H, CH_2), 1.64 (s, 3H, $COCH_3$), 2.42 (s, 3H, N–CH_3), 4.36 (t, 1H, J = 1.3 Hz, H4-isox.), 5.02–5.06 (m, 1H, CH–NH), 5.18–5.22 (m, 1H, H5-isox.), 7.36–7.40 (m, 3H, arom.), 7.64–7.68 (m, 2H, arom.). ^{13}C NMR (δ, $CDCl_3$): 22.6, 25.1 (CH_2), 29.3 (N–CH_3), 30.8 ($COCH_3$) 51.0 (CH), 58.1 (CH–N), 87.2 (CH–O), 126.7, 128.4, 129.5, 129.7 (arom.), 157.3 (C=N), 171.8 (C=O). Elemental analysis: C 69.75%, H 6.98%, N 10.86%; calcd. for $C_{15}H_{18}N_2O_2$ (258.3) C 69.74%, H 7.02%, N 10.85%.

5Bd. 0.12 g (48%); Straw colored oil. R_f (1:1 cyclohexane/AcOEt) 0.33. IR (cm^{-1}): $\nu_{C=O}$ 1643. ^1H NMR (δ, $CDCl_3$): 1.98–2.02 (m, 2H, CH_2), 2.32–2.37 (m, 2H, CH_2), 2.11 (s, 3H, $COCH_3$), 2.95 (s, 3H, N–CH_3), 4.12–4.16 (m, 1H, H4-isox.), 4.60–4.64 (m, 1H, CH–NH), 5.33–5.37 (m, 1H, H5-isox.), 7.36–7.40 (m, 3H, arom.), 7.58–7.62 (m, 2H, arom.). ^{13}C NMR (δ, $CDCl_3$): 22.7, 29.2 (CH_2), 32.8 (N–CH_3), 34.3 ($COCH_3$) 56.4 (CH), 63.7 (CH–N), 87.8 (CH–O), 126.7, 128.1, 128.9, 130.2 (arom.), 157.8 (C=N), 170.3 (C=O). Elemental analysis: C 69.74%, H 6.98%, N 10.87%; calcd. for $C_{15}H_{18}N_2O_2$ (258.3) C 69.74%, H 7.02%, N 10.85%.

6.6. Cycloaddition of benzonitrile oxide to N-cyclopentenyl-benzamide (*4C*)

To a stirred solution of *N*-cyclopentenyl-benzamide (**4C**) (4.0 g, 21 mmol) and benzhydroximoyl chloride (5.0 g, 32 mmol) in methanol (120 mL), 5 mL of triethylamine (36 mmol) in the same solvent (20 mL) were added over a 0.5 h period. After stirring the reaction 2 days at r.t., the mixture was evaporated under reduced pressure leaving a residue which was separated by column chromatography affording the stereoisomeric cycloadducts **5Ca-d**.

5Ca. 2.45 g (25%). Colorless solid, mp 195–196 °C from ethyl acetate. R_f (1:1 cyclohexane/AcOEt) 0.40. IR (cm^{-1}): ν_{NH} 3349, $\nu_{C=O}$ 1638. ^1H NMR (δ, DMSO): 1.55–2.35 (m, 4H, CH_2), 4.33 (t, 1H, J = 8.5 Hz, H4-isox.), 4.40–4.44 (m, 1H, CH–NH), 5.09 (dd, 1H, J = 8.5, 5.0 Hz, H5-isox.), 7.48–7.52 (m, 6H, arom.), 7.66–7.71 (m, 2H, arom.), 7.91–7.94 (m, 2H, arom.), 8.47 (d, 1H, J = 7.0 Hz, NH). ^{13}C NMR (δ, DMSO): 26.8, 27.2 (CH_2), 50.3 (CH), 56.3 (CHNH), 84.4 (CH–O), 126.7, 127.5, 128.1, 128.4, 128.9, 129.8, 131.1, 134.2 (arom.), 158.7 (C=N), 166.2 (C=O). Elemental analysis: C 74.50%, H 5.91%, N 9.19%; calcd. for $C_{19}H_{18}N_2O_2$ (306.4) C 74.49%, H 5.92%, N 9.15%.

5Cb. 0.29 g (3%). Colorless solid, mp 188–189 °C from ethyl acetate. R_f (1:1 cyclohexane/AcOEt) 0.51. IR (cm^{-1}): ν_{NH} 3295, $\nu_{C=O}$ 1675. ^1H NMR (δ, DMSO): 1.85–2.35 (m, 4H, CH_2), 4.30–4.34 (m, 2H, H4-isox. and CH–NH), 5.09 (dd, 1H, J = 9.2, 1.0 Hz, H5-isox.), 7.46–7.50 (m, 6H, arom.), 7.70–7.72 (m, 2H, arom.), 7.85–7.88 (m, 2H, arom.), 8.49 (d, 1H, J = 6.5 Hz, NH). ^{13}C NMR (δ, DMSO): 29.7, 32.9 (CH_2), 55.4 (CH), 58.3 (CHNH), 86.7 (CH–O), 126.8, 127.5, 128.1, 128.8, 128.9, 129.8, 131.2, 134.3 (arom.), 156.2 (C=N), 166.5 (C=O). Elemental analysis: C 74.48%, H 5.89%, N 9.12%; calcd. for $C_{19}H_{18}N_2O_2$ (306.4) C 74.49%, H 5.92%, N 9.15%.

5Cc. 1.18 g (12%). Colorless solid, mp 204–205 °C from benzene. R_f (1:1 cyclohexane/AcOEt) 0.70. IR (cm^{-1}): ν_{NH} 3325, $\nu_{C=O}$ 1660. ^1H NMR (δ, DMSO): 1.77–2.09 (m, 4H, CH_2), 4.38 (t, 1H, J = 7.6 Hz, H4-isox.), 4.67–4.70 (m, 1H, CH–NH), 5.18 (dd, 1H, J = 8.5, 2.0 Hz,

Please cite this article in press as: Cardarelli AM, et al., The hydrogen bond directing effect in nitrile oxide cycloadditions to allylic substituted cyclopentenes, Tetrahedron (2017), http://dx.doi.org/10.1016/j.tet.2017.03.042

H5-isox.), 7.16–7.20 (m, 7H, arom.), 7.32–7.36 (m, 1H, arom.), 7.55–7.58 (m, 2H, arom.), 8.11 (d, 1H, J = 8.0 Hz, NH). ^{13}C NMR (δ, DMSO): 27.9, 30.6 (CH_2), 49.4 (CH), 52.2 (CHNH), 87.7 (CH–O), 126.5, 126.9, 127.4, 128.1, 128.9, 129.8, 130.5, 134.2 (arom.), 158.7 (C=N), 166.6 (C=O). Elemental analysis: C 74.51%, H 5.91%, N 9.11%; calcd. for $C_{19}H_{18}N_2O_2$ (306.4) C 74.49%, H 5.92%, N 9.15%.

5Cd. 5.00 g (51%). Colorless solid, mp 193–195 °C from ethanol. R_f (1:1 cyclohexane/AcOEt) 0.60. IR (cm^{-1}): ν_{NH} 3401, $\nu_{C=O}$ 1663. ^{1}H NMR (δ, DMSO): 1.57–2.39 (m, 4H, CH_2), 4.28 (d, 1H, J = 9.0 Hz, H4-isox.), 4.34 (t, 1H, J = 5.8 Hz, CH–NH), 5.27 (dd, 1H, J = 9.0, 5.0 Hz, H5-isox.), 7.48–7.52 (m, 6H, arom.), 7.90–7.93 (m, 4H, arom.), 8.57 (d, 1H, J = 5.8 Hz, NH). ^{13}C NMR (δ, DMSO): 29.7, 32.9 (CH_2), 55.4 (CH), 58.3 (CHNH), 86.7 (CH–O), 126.8, 127.5, 128.1, 128.8, 128.9, 129.8, 131.2, 134.3 (arom.), 156.2 (C=N), 166.5 (C=O). Elemental analysis: C 74.47%, H 5.90%, N 9.20%; calcd. for $C_{19}H_{18}N_2O_2$ (306.4) C 74.49%, H 5.92%, N 9.15%.

6.7. Methylation of cycloadducts **5Ca-d**

To a stirred solution of the cycloadducts **5Ca-d** (0.31 g, 1 mmol) in anhydrous THF (10 mL), NaH (0.029 g, 1.2 mmol) was added portionwise in the presence of a slight excess of CH_3I (1 mL, 2 mmol). After stirring the reactions 5 h at r.t., methanol was added first, followed by water and the reaction mixtures extracted with chloroform. The dry organic phases were evaporated and affording in quantitative yields the crude methylated compounds **5Da-d**, which were recrystallized from suitable solvents and characterized.

5Da. 0.25 g (66%). Colorless solid, mp 137–138 °C from ethanol. R_f (1:1 cyclohexane/AcOEt) 0.36. IR (cm^{-1}): $\nu_{C=O}$ 1633. ^{1}H NMR (δ, $CDCl_3$): 1.99 (m, 4H, CH_2), 3.12 (s, 3H, N–CH_3), 4.17 (bs, 1H, H4-isox.), 4.92 (bs, 1H, CH–NH), 5.44 (bs, 1H, H5-isox.), 7.42.7.46 (m, 6H, arom.), 7.70–7.73 (m, 4H, arom.); ^{13}C NMR (δ, $CDCl_3$): 24.4, 27.3 (CH_2), 29.6 (N–CH_3), 50.5 (CH), 60.0 (CH–N), 85.9 (CH–O), 126.8, 128.3, 128.7, 129.3, 130.0, 136.7 (arom.), 158.7 (C=N), 172.2 (C=O). Elemental analysis: C 74.95%, H 6.30%, N 8.72%; calcd. for $C_{20}H_{20}N_2O_2$ (320.4) C 74.97%, H 6.29%, N 8.74%.

5Db. 0.22 g (57%). Colorless solid, mp 141–144 °C from ethanol. R_f (1:1 cyclohexane/AcOEt) 0.18. IR (cm^{-1}): $\nu_{C=O}$ 1626. ^{1}H NMR (δ, $CDCl_3$): 1.80–2.50 (m, 4H, CH_2), 3.08 (s, 3H, N–CH_3), 4.22 (bs, 1H, H4-isox.), 4.36.4.40 (m, 1H, CH–NH), 5.40 (bs, 1H, H5-isox.), 7.40–7.44 (m, 6H, arom.), 7.47–7.50 (m, 2H, arom.), 7.86–7.89 (m, 2H, arom.). ^{13}C NMR (δ, $CDCl_3$): 28.9, 29.6 (CH_2), 31.8 (N–CH_3), 51.5 (CH), 67.4 (CH–N), 84.9 (CH–O), 126.9, 127.1, 127.2, 128.4, 128.5, 128.7, 129.6, 129.9137.9 (arom.), 156.9 (C=N), 169.5 (C=O). Elemental analysis: C 74.92%, H 6.28%, N 8.73%; calcd. for $C_{20}H_{20}N_2O_2$ (320.4) C 74.97%, H 6.29%, N 8.74%.

5Dc. 0.23 g (58%). Colorless solid, mp 107–108 °C from ethanol. R_f (1:1 cyclohexane/AcOEt) 0.33. IR (cm^{-1}): $\nu_{C=O}$ 1634. ^{1}H NMR (δ, $CDCl_3$): 1.80–2.40 (m, 4H, CH_2), 2.54 (s, 3H, N–CH_3), 4.51 (t, 1H, J = 8.5 Hz, H4-isox.), 5.10–5.14 (m, 1H, CH–NH), 5.31 (dd, 1H, J = 8.5, 3.5 Hz, H5-isox.), 7.27–7.31 (m, 6H, arom.), 7.40–7.43 (m, 2H, arom.), 7.76–7.78 (m, 2H, arom.); ^{13}C NMR (δ, $CDCl_3$): 24.4, 27.0 (CH_2), 29.3 (N–CH_3), 51.3 (CH), 59.0 (CH–N), 87.8 (CH–O), 126.7, 126.8, 128.0, 128.7, 129.4, 129.8 (arom.), 157.6 (C=N), 172.2 (C=O). Elemental analysis: C 75.00%, H 6.29%, N 8.72%; calcd. for $C_{20}H_{20}N_2O_2$ (320.4) C 74.97%, H 6.29%, N 8.74%.

5Dd. 0.24 g (61%). Colorless solid, mp 148–150 °C from ethanol. R_f (1:1 cyclohexane/AcOEt) 0.24. IR (cm^{-1}): $\nu_{C=O}$ 1607. ^{1}H NMR (δ, $CDCl_3$): 1.99–2.50 (m, 4H, CH_2), 3.06 (s, 3H, N–CH_3), 4.21 (bs, 1H, H4-isox.), 4.43 (bs, 1H, CH–NH), 5.38 (bs, 1H, H5-isox.), 7.20–7.70 (m, 10H, arom.); ^{13}C NMR (δ, $CDCl_3$): 29.6, 29.7 (CH_2), 33.0 (N–CH_3), 55.3 (CH), 55.4 (CH–N), 87.5 (CH–O), 126.4, 126.9, 128.3, 128.8, 129.5, 130.1 (arom.), 157.9 (C=N), 171.7 (C=O). Elemental analysis: C 74.96%, H 6.25%, N 8.69%; calcd. for $C_{20}H_{20}N_2O_2$ (320.4) C 74.97%, H 6.29%, N 8.74%.

6.8. Cycloaddition of 4-chlorobenzonitrile oxide to 2-cyclopenten-1-ol (**1A**)

To a stirred solution of 2-cyclopenten-1-ol (**1A**) (5.0 g, 59 mmol) and 4-chlorobenzhydroxymoyl chloride (9.5 g, 50 mmol) in benzene as solvent (120 mL), 8 mL of triethylamine (57 mmol) dissolved in the same solvent (20 mL) were added over a 0.5 h period. After stirring the reaction 2 days at room temperature, the mixture was evaporated under reduced pressure leaving a residue that was submitted to chromatographic separation to isolate the cycloadducts **6a-d**, which were fully characterized.

6a. 5.23 g (44%); Colorless solid, mp 199 °C (dec.) from ethanol. R_f (1:1 cyclohexane/AcOEt) 0.36. IR (cm^{-1}): ν_{OH} 3380, $\nu_{C=N}$ 1589. ^{1}H NMR (δ, $CDCl_3$): 1.49–1.52 (m, 1H, CH_2), 1.90–1.93 (m, 3H, CH_2), 4.06–4.09 (m, 1H, H4-isox.), 4.19–4.22 (m, 1H, CH–OH), 5.03 (dd, 1H, J = 9, 5 Hz, H5-isox.), 7.31–7.70 (AA'BB' syst., 4H, arom.). ^{13}C NMR (δ, $CDCl_3$): 26.2, 27.5 (CH_2), 50.0 (CH), 81.9 (CH–OH), 85.3 (CH–O), 126.9, 127.0, 128.7, 135.7 (arom.), 157.6 (C=N). Elemental analysis: C 60.62%, H 5.04%, N 5.90%; calcd. for $C_{12}H_{12}NO_2Cl$ (237.7) C 60.64%, H 5.09%, N 5.89%.

6b. 1.19 g (10%); Colorless solid, mp 143–144 °C from ethanol. R_f (1:1 cyclohexane/AcOEt) 0.52. IR (cm^{-1}): ν_{OH} 3366, $\nu_{C=N}$ 1589. ^{1}H NMR (δ, $CDCl_3$): 1.77–1.81 (m, 3H, CH_2), 2.21–2.24 (m, 1H, CH_2), 4.16 (dt, 1H, J = 5, 1 Hz, H4-isox.), 4.43 (d, 1H, J = 2 Hz, CH–OH), 4.99 (d, 1H, J = 5 Hz, H5-isox.), 7.31–7.70 (AA'BB' syst., 4H, arom.). ^{13}C NMR (δ, $CDCl_3$): 28.6, 31.5 (CH_2), 50.8 (CH), 77.1 (CH–OH), 92.3 (CH–O), 128.1, 128.6, 129.0, 135.8 (arom.), 157.9 (C=N). Elemental analysis: C 60.60%, H 5.06%, N 5.86%; calcd. for $C_{12}H_{12}NO_2Cl$ (237.7) C 60.64%, H 5.09%, N 5.89%.

6c. 0.24 g (2%); Colorless solid, mp 169–170 °C from ethanol. R_f (1:1 cyclohexane/AcOEt) 0.30. IR (cm^{-1}): ν_{OH} 3395, $\nu_{C=N}$ 1590. ^{1}H NMR (δ, $CDCl_3$): 1.70–2.30 (m, 4H, CH_2), 4.04 (dd, 1H, J = 9, 7 Hz, H4-isox.), 4.55–4.58 (m, 1H, CH–OH), 5.20–5.23 (m, 1H, H5-isox.), 7.31–7.70 (AA'BB' syst., 4H, arom.). ^{13}C NMR (δ, $CDCl_3$): 30.6, 33.8 (CH_2), 56.3 (CH), 75.5 (CH–OH), 88.3 (CH–O), 128.2, 128.6, 128.8, 135.6 (arom.), 155.3 (C=N). Elemental analysis: C 60.66%, H 5.07%, N 5.86%; calcd. for $C_{12}H_{12}NO_2Cl$ (237.7) C 60.64%, H 5.09%, N 5.89%.

6d. 2.85 g (24%); Colorless solid, mp > 200 °C (dec.) from ethanol. R_f (1:1 cyclohexane/AcOEt) 0.44. IR (cm^{-1}): ν_{OH} 3386, $\nu_{C=N}$ 1599. ^{1}H NMR (δ, $CDCl_3$): 1.73–1.76 (m, 2H, CH_2), 2.21–2.24 (m, 2H, CH_2), 3.93 (d, 1H, J = 5 Hz, H4-isox.), 4.36 (d, 1H, J = 2 Hz, CH–OH), 5.28–5.31 (m, 1H, H5-isox.), 7.31–7.70 (AA'BB' syst., 4H, arom.). ^{13}C NMR (δ, $CDCl_3$): 32.4, 32.9 (CH_2), 61.4 (CH), 76.4 (CH–OH), 87.6 (CH–O), 128.0, 128.2, 129.0, 135.8 (arom.), 155.1 (C=N). Elemental analysis: C 60.65%, H 5.10%, N 5.88%; calcd. for $C_{12}H_{12}NO_2Cl$ (237.7) C 60.64%, H 5.09%, N 5.89%.

6.9. Solvent effect and HPLC determinations

The dipolarophiles **1A,B** and **4A-D** (1.2 equivs.) were dissolved in the desired solvent (25 mL) and 1 equiv. of benzhydroximoyl chloride (62.4 mg, 0.4 mmol), the precursor of BNO, was added to the solution, followed by 1.2 equivs. of triethylamine and stirred for 2 days until complete consumption of BNO. The reaction mixtures were evaporated to dryness, taken up with acetonitrile and submitted to HPLC analyses for quantitative determinations. Yields and regioisomeric ratios have been determined upon external standard method or internal normalization.

Cycloaddition of BNO to **1A**: isocratic elution H_2O/CH_3CN 70/30 (1.2 mL/min); UV detection at λ = 262 nm.

Cycloaddition of BNO to **1B**: isocratic elution H_2O/CH_3CN 60/40 (1.3 mL/min); UV detection at λ = 264 nm.

Cycloaddition of BNO to **4A**: elution gradient from H_2O/CH_3CN 80/20 to 60/40 (1.3 mL/min); UV detection at λ = 264 nm.

Cycloaddition of BNO to **4B**: isocratic elution H_2O/CH_3CN 70/30

Please cite this article in press as: Cardarelli AM, et al., The hydrogen bond directing effect in nitrile oxide cycloadditions to allylic substituted cyclopentenes, Tetrahedron (2017), http://dx.doi.org/10.1016/j.tet.2017.03.042

(1.3 mL/min); UV detection at λ = 264 nm.

Cycloaddition of BNO to **4C**: isocratic elution H_2O/CH_3CN 55/45 (1.0 mL/min); UV detection at λ = 264 nm.

Cycloaddition of BNO to **4D**: isocratic elution H_2O/CH_3CN 50/50 (1.3 mL/min); UV detection at λ = 264 nm.

Cycloadditions to 2-cyclopenten-1-ol (**1A**) in the presence of M(II) salts and hplc determinations: general methods.

6.9.1. Method A

In a 5 mL vial the dipolarophile **1A** (1.2 equivs.) and 1.2 equivs. of the M(II) salts were dissolved in anhydrous DCM (1 mL) at the desired temperature. Benzhydroxymoyl chloride (64 mg, 1 equiv.), dissolved in 1 mL of DCM, was added to the solution, followed by 1.2 equivs. of triethylamine and left under stirring for 1 day. The reaction mixtures were then diluted with DCM, washed carefully with water and the organic phase dried over anhydrous Na_2SO_4. Evaporation of DCM leaves a residue that was taken up with acetonitrile and the resulting solution filtered on cationic and anionic exchange resins (SUPELCO LC-SAX SPE 504815 and 504920) to ensure complete elimination of inorganic salts. The solution volume was then adjusted to 25 mL and analyzed through HPLC for quantitative determinations. Yields and stereoisomeric ratios were determined upon internal normalization.

HPLC conditions: Isocratic elution H_2O/MeCN 70/30 (1.2 mL/min); UV detection at λ = 262 nm.

6.9.2. Method B

In a 5 mL vial the dipolarophile **1A** (1.2 equivs.) and 1.2 equivs. of the M(II) salts were dissolved in anhydrous DCM (1 mL) at the desired temperature. 4-Chlorobenzhydroxymoyl chloride (63 mg, 1 equiv.), dissolved in 1 mL of DCM, was added to the solution, followed by 1.2 equivs. of triethylamine and left under stirring for 1 day. The reaction mixtures were then diluted with DCM, washed carefully with water and the organic phase dried over anhydrous Na_2SO_4. Evaporation of DCM leaves a residue that was taken up with acetonitrile and the resulting solution filtered on cationic and anionic exchange resins (SUPELCO LC-SAX SPE 504815 and 504920) to ensure complete elimination of inorganic salts. The solution volume was then adjusted to 25 mL and analyzed through HPLC for quantitative determinations. Yields and stereoisomeric ratios were determined upon internal normalization.

HPLC conditions: Isocratic elution H_2O/MeCN 70/30 (1.3 mL/min); UV detection at λ = 268 nm.

6.9.3. Method C

In a 5 mL vial the dipolarophile **4A** (1.2 equivs.) and 1.2 equivs. of the M(II) salts were dissolved in anhydrous DCM (1 mL) at the desired temperature. Benzhydroxymoyl chloride (64 mg, 1 equiv.), dissolved in 1 mL of DCM, was added to the solution, followed by 1.2 equivs. of triethylamine and left under stirring for 1 day. The reaction mixtures were then diluted with DCM, washed carefully with water and the organic phase dried over anhydrous Na_2SO_4. Evaporation of DCM leaves a residue that was taken up with acetonitrile and the resulting solution filtered on cationic and anionic exchange resins (SUPELCO LC-SAX SPE 504815 and 504920) to ensure complete elimination of inorganic salts. The solution volume was then adjusted to 25 mL and analyzed through HPLC for quantitative determinations. Yields and stereoisomeric ratios were determined upon internal normalization.

HPLC conditions: Elution gradient from H_2O/CH_3CN 80/20 to 60/40 (1.3 mL/min); UV detection at λ = 264 nm.

Acknowledgments

Financial support of University of Pavia and MIUR (PRIN 2011, CUP: F11J12000210001) is gratefully acknowledged. Many tranks are due to CINMPIS for a research grant to AMC.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2017.03.042.

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Please cite this article in press as: Cardarelli AM, et al., The hydrogen bond directing effect in nitrile oxide cycloadditions to allylic substituted cyclopentenes, Tetrahedron (2017), http://dx.doi.org/10.1016/j.tet.2017.03.042