An Experimental and Computational Approach to Understanding the Reactions of Acyl Nitroso Compounds in [4+2]-Cycloadditions

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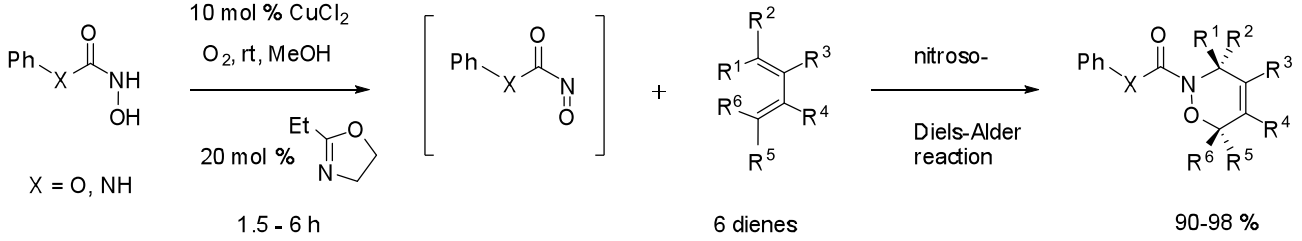
Abstract

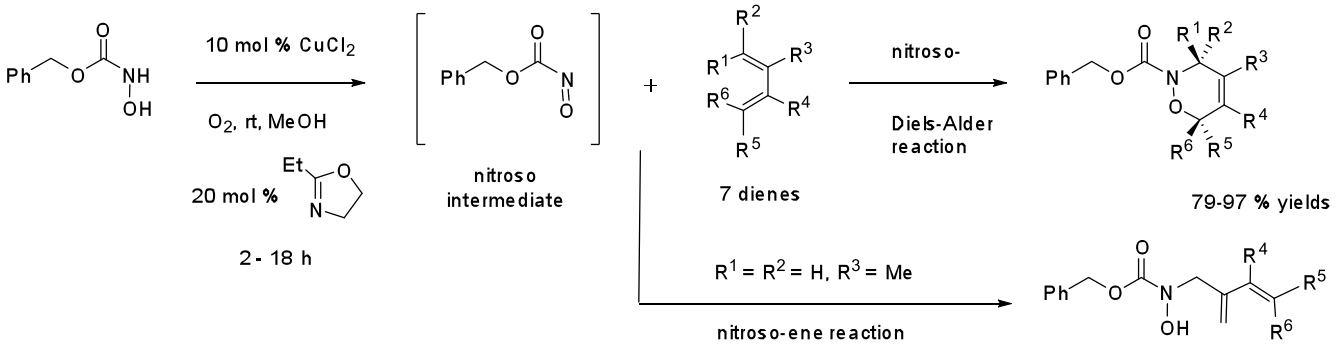


Catalytic aerobic oxidation of phenyl hydroxycarbamate **1** and 1-hydroxy-3-phenylurea **2** using $CuCl_2$ and 2-ethyl-2-oxazoline in methanol gave acyl nitroso species *in situ*, which were trapped in nitroso-Diels-Alder (NDA) reactions with various dienes to afford the corresponding cycloadducts in high yields (90-98%). Competing ene products were also present for dienes containing both alkene π-bonds and allylic σ-bonds, and the ene yields are higher with **1** than with **2**. The use of the chiral hydroxamic acid, (*R*)-1-hydroxy-3-(1-phenylethylurea) **3** (same conditions) gave NDA cycloadducts in high yields (97-99%) with no ene product from 2,3-dimethyl-1,3-butadiene. NDA cycloadducts were not obtained from other hydroxamic acid analogues [RCONHOH (R = $PhCH_2$ **4**; $Ph(CH_2)_2$ **5**; $Ph(CH_2)_3$ **6**; $Ph(CH_2)_4$ **7**; Ph **8**; 2-pyridyl **9**; 3-pyridyl **10**], with various dienes using the copper-oxidation, but were obtained using sodium periodate, resulting in variable NDA yields (13-51%) from hydroxamic acids **1-10** with cyclohexa-1,3-diene and 2,3-dimethyl-1,3-butadiene (several cycloadducts characterized by X-ray crystallography). The NDA and nitroso-ene reaction pathways of nitroso intermediates with dienes were mapped by DFT computations (B3LYP/6-31G*) which showed that the acyl nitroso species are super-

reactive and activation energies in the NDA processes are lower than the isomerization barriers between some *cis*- and *trans*-butadienes.

Introduction

Nitroso compounds have been widely used and studied in organic chemistry for over a century, with Baeyer's synthesis of nitroso benzene reported in 1874.[1] Since then, not only have the methods of synthesis improved substantially (Baeyer reacted diphenylmercury with nitroso bromide), but the range of nitroso species accessible and their range of reactions has increased substantially.[2] Indeed, the hetero-Diels-Alder reaction has been widely used not only to derive oxazine systems,[2] but also for a wide-range of synthetic applications,[3] including asymmetric synthesis[4] and recently in flow chemistry.[5] Although nitroso arenes are probably most well known as nitroso dienophiles, many of which are also commercially available or readily prepared, one of the most useful, and indeed, reactive classes of nitroso dienophiles are the acyl nitroso (or nitroso carbonyl) species.[3] However, unlike their nitroso arene counterparts, these compounds have not been isolated or characterized, being generated *in situ*, generally by the oxidation of hydroxamic acids. The resulting acyl nitroso species are then trapped by suitable dienes to yield the corresponding [4+2]-cycloaddition products. As part of a program to develop wider applications of acyl nitroso compounds in synthetic applications, we and others,[6] have been involved in developing cleaner *in situ* methods for the oxidation of hydroxamic acids, that improve upon the use of periodates, DMSO-based oxidants and lead(IV)-based reagents etc.[7] Even though peroxides are less toxic, the yields depend upon the substrate, oxidant and catalyst.[7] We recently reported the use of a Cu(II)-catalyzed, air-based, *in situ* hydroxamic acid oxidation reaction, as shown in Scheme 1,[8] which was particularly clean and efficient, and related reactions have been widely used in synthesis.[3,4,9-11] During these studies, it is clear that both the regiochemistry of nitroso-Diels-Alder (NDA) reactions, and often the chemoselectivity of the acyl nitroso species is not always predictable, and is difficult to control.[8-11] As a consequence, we undertook to study systematically this reaction both experimentally and theoretically, in order to develop an understanding of the principles which govern the reactivity of acyl nitroso compounds of different types with variously substituted dienes, and herein, we discuss our findings.



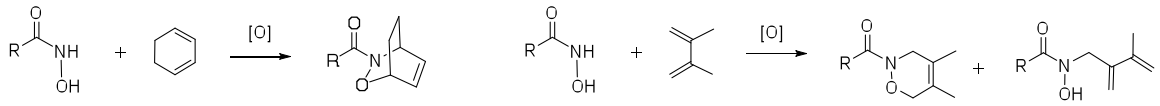
Scheme 1. Reactions of *N*-(benzyloxycarbonyl)hydroxylamine with various dienes using the copper-oxazoline catalyst and air system.

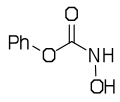
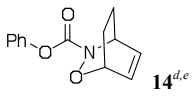
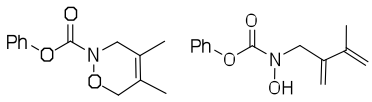
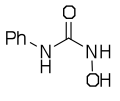
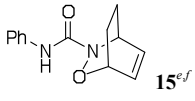
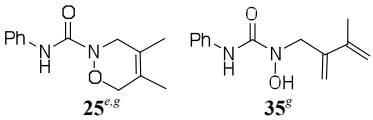
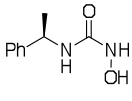
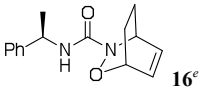
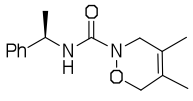
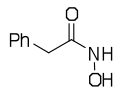
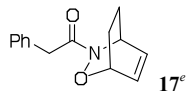
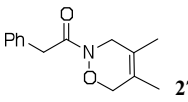
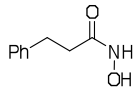
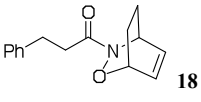
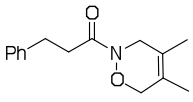
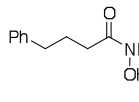
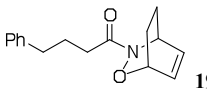
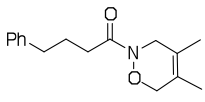
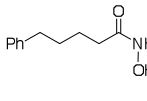
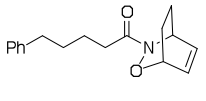
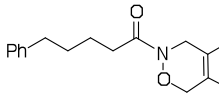
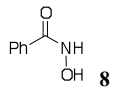
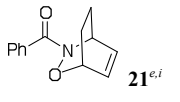
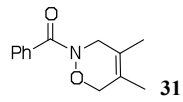
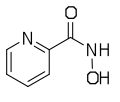
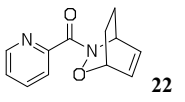
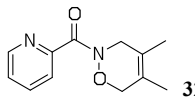
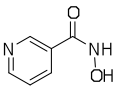
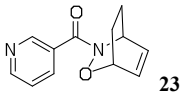
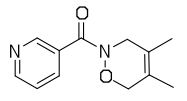
Results and discussion

Syntheses and Characterizations of Compounds 1-53

The hydroxamic acids **1-12** listed in Table 1 and were prepared from reactions of hydroxylamine hydrochloride with appropriate chlorides, isocyanates, carboxylic acids or esters. A new compound **13** was obtained in 13% yield from (*R*)-(1-isocyanatoethyl)benzene with hydroxylamine hydrochloride in the synthesis of (*R*)-1-hydroxy-3-(1-phenylethylurea) **3**.

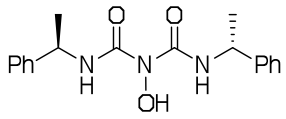
Table 1. Reactions of cyclohexa-1,3-diene and 2,3-dimethyl-1,3-butadiene with nitroso compounds prepared *in situ* from oxidations of hydroxamic acids, **1-10**.



Hydroxamic Acid	*Entry*	Cycloadduct from cyclohexa-1,3-diene	GP1[a] Yield	GP2[b] Yield	GP3[c] Yield	*Entry*	Product(s) from 2,3-dimethyl-1,3-butadiene	GP1[a] Yield	GP2[b] Yield	GP3[c] Yield
 **1**	*1*	 **14**[d,e]	51	98	-	*11*	 **24** **34** **24**:**34** Ratio 1:0 from GP1; 6:1 from GP2	47	95	-
 **2**[e]	*2*	 **15**[e,f]	49	98	-	*12*	 **25**[e,g] **35**[g] **25**:**35** Ratio 1:0 from GP1; 9:1 from GP2	45	90	-
 **3**[e]	*3*	 **16**[e]	42	97	-	*13*	 **26**	13	99	-
 **4**	*4*	 **17**[e]	48	0	61	*14*	 **27**	42[h]	0	0
 **5**	*5*	 **18**	49	0	65	*15*	 **28**	37[h]	0	0
 **6**	*6*	 **19**	32	0	73	*16*	 **29**	40[h]	0	0
 **7**	*7*	 **20**	38	0	78	*17*	 **30**	41[h]	0	0
 **8**	*8*	 **21**[e,i]	53	0	49	*18*	 **31**	46	0	0
 **9**[e]	*9*	 **22**	42	0	0	*19*	 **32**[e]	21	0	0
 **10**	*10*	 **23**	31	0	0	*20*	 **33**	18	0	0

[a]GP1: MeOH (30 mL), diene (2 equivalent), $NaIO_4$(0.83 mmol), hydroxamic acid (0.83 mmol), stirred at rt, 2-4 h. At completion, the solvent evaporated and the product was purified by silica gel chromatography. Isolated yields quoted after purification [b]GP2: MeOH(5 mL), diene (2 equivalent), $CuCl_2$ (0.06 mmol), 2-ethyl-2-oxazoline (0.12 mmol),hydroxamic acid (0.63 mmol), stirred at rt in air 2-6 h. At completion, the solvent evaporated and the product was purified by silica gel chromatography. Isolated yields quoted after purification. [c]GP3: Toluene (5 mL), diene (2 equivalent), $CuCl_2$ (0.14 mmol), 2-ethyl-2-oxazoline (0.28 mmol),, hydroxamic acid (1.40 mmol), heated under reflux and stirred in air, 4-20 h. At completion, the solvent evaporated and the product was purified by silica gel chromatography. Isolated yields quoted after purification. [d]Reference 12. [e]X-ray structure obtained in this study. [f]Reference 9. [g]Reference 13. [h]Ene and methanolysis products also observed. [i]References 14 and 15. Note: All chiral cycloadducts are racemic.

11 **12**



13

Initially, *in situ* oxidations of the hydroxamic acids **1**-**12** with sodium periodate in the presence of cyclohexa-1,3-diene or 2,3-dimethyl-1,3-butadiene were employed to establish whether cycloadducts can be formed (Table 1, Entries 1-20, method GP1). The reactions were complete in 4 hours with low to moderate yields of 13-53% of the desired cycloadducts **14**-**33** from hydroxamic acids **1**-**10**. However, two hydroxamic acids, *N*-hydroxy-2-(pyridin-2-yl)acetamide **11** and 2-amino-*N*-hydroxybenzamide **12**, gave only black tars after oxidation.

The aerobic oxidation procedure (method GP2), successfully used on *N*-(benzyloxycarbonyl)-hydroxylamine (Scheme 1), with 10 mol% $CuCl_2$ and 20 mol% 2-ethyl-2-oxazoline at room temperature in methanol was then applied to hydroxamic acids **1**-**10** (Table 1). Only three hydroxamic acids **1**-**3** gave the expected cycloadducts **14**-**16** from cyclohexa-1,3-diene (Table 1, Entries 1-3, GP2) and cycloadducts **24**-**26** from 2,3-dimethyl-1,3-butadiene (Table 1, Entries 11-13, GP2). Nevertheless, the cycloadduct yields from this method of 90-99% were remarkably high compared to 13-51% yields with the periodate method for the three hydroxamic acids **1**-**3**.

Nitroso ene products were also present from the copper-catalyzed oxidations of acids **1** and **2** with dimethyl-1,3-butadiene (Table 1, Entries 11 and 12, GP2). The NDA:ene ratios were 6:1 (**24**:**34**) and 9:1 (**25**:**35**) from **1** and **2**, respectively, indicating that the nitroso intermediate from **2** was more selective than the nitroso species from **1**. Despite several attempts, the ene products **34** and **35** could not be isolated as pure compounds. These ene products were not observed with the periodate method (GP1) here and elsewhere,[12] suggesting that the copper method promoted the nitroso-ene process. Curiously, the chiral hydroxamic acid **3** did not give an ene product using the copper procedure (Table 1, Entry

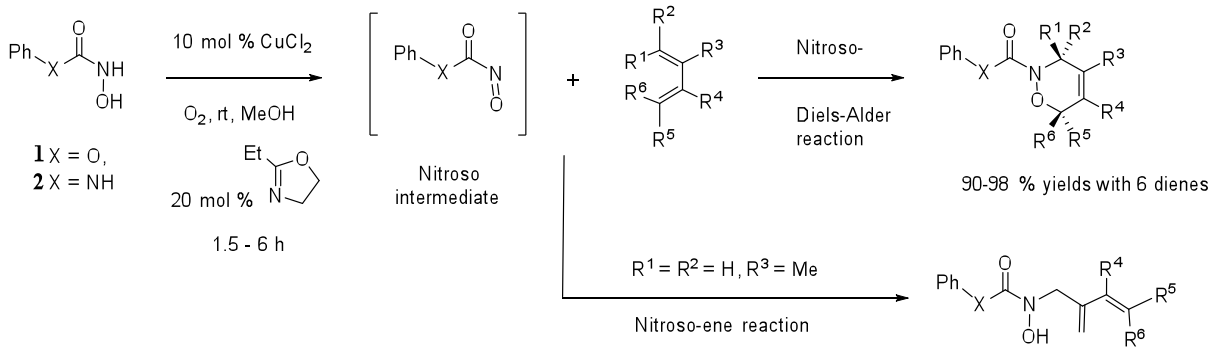
13), which might be interpreted by the accessibility of several conformations, all of which are reactive with no major conformation having an ability to control facial reactivity effectively.

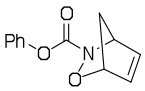
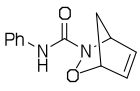
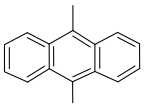
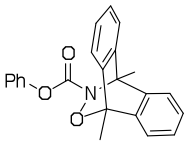
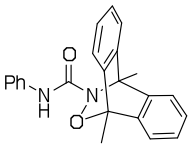
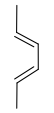
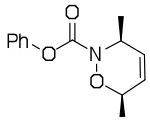
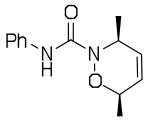
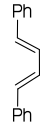
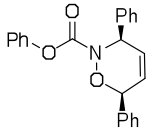
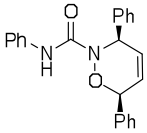
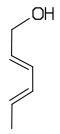
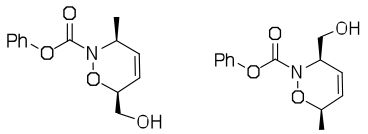
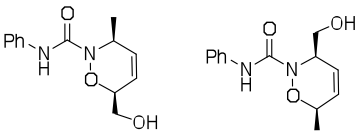
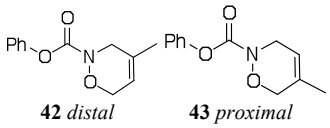
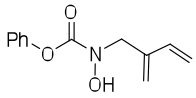
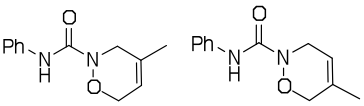
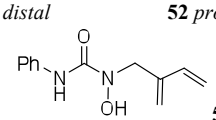
A third aerobic oxidation method (GP3) was applied to hydroxamic acids **4**-**10** using refluxing toluene instead of methanol at room temperature to facilitate the generation of the nitroso intermediates. The expected cycloadducts were formed in 49-78% yields from cyclohexa-1,3-diene with hydroxamic acids **4**-**8** (Table 1, Entries 4-8, GP3) but no cycloadducts were obtained from 2,3-dimethyl-1,3-butadiene with the same acids (Table 1, Entries 14-18, GP3). This suggested that cyclohexa-1,3-diene was a much more efficient reagent than 2,3-dimethyl-1,3-butadiene in the nitroso-Diels-Alder process under these reaction conditions.[16]

No cycloadducts were obtained from the hydroxamic acids containing pyridyl groups, **9** and **10**, (Table 1, Entries 9, 10, 19, 20) or from hydroxamic acids **11** and **12** (Chart 1) when the copper-catalyzed oxidation methods (GP2 and GP3) were used. It appeared that chelation takes place between the pyridyl or amine group and the copper complex preventing the oxidation process, as indicated by the rapid formation of an insoluble light blue precipitate which did not dissolve even after several days and no further reaction occurred.

The hydroxamic acids, phenyl hydroxycarbamate **1** and 1-hydroxy-3-phenylurea **2**, gave high yields of the cycloadducts with cyclohexa-1,3-diene and 2,3-dimethyl-1,3-butadiene using the room temperature copper catalyst method (GP2), hence, this method was examined further on **1** and **2** with six dienes, cyclopentadiene, dimethylanthracene (DMA), 1,4-dimethyl-1,3-butadiene, 1,4-diphenyl-1,3-butadiene, 1-hydroxymethyl-4-methyl-1,3-butadiene and 2-methyl-1,3-butadiene (Table 2). The yields of the cycloadducts from these dienes were also high (90-99 %), except for the reactions with DMA and 1,4-diphenyl-1,3-butadiene. These latter reactions required longer times of 24-48 hours, yet were still not complete, giving lower yields of the cycloadducts (30-82%). The known cycloadduct **46** from **2** and DMA undergoes cyclo-reversion on standing,[17] and thus a 10% yield was estimated here (Table 2, Entry 8).

Table 2. Reactions of various dienes with nitroso compounds prepared *in situ* from copper-catalyzed oxidations of hydroxamic acids, **1** and **2**.



Diene	*Entry*[a]	Product(s) from **1**	Yield[b]	*Entry*[a]	Product(s) from **2**	Yield[b]
	*1*	 **36**[c]	99	*7*	 **45**[d]	96
	*2*	 **37**	80[e]	*8*	 **46**[h]	(10)[f, g]
	*3*	 **38**	93	*9*	 **47**	97
	*4*	 **39**	82[e]	*10*	 **48**	30[f]
	*5*	 **40** *proximal* **41** *distal* **40**:**41** Ratio 1 : 1	93	*11*	 **49** *proximal* **50** *distal* **49**:**50** Ratio 1.5 : 1.0	90
	*6*	 **42** *distal* **43** *proximal*  **44** **42**:**43**:**44** Ratio 1.9 : 1.1 : 1.0	90	*12*	 **51** *distal* **52** *proximal*  **53** **51**:**52**:**53** Ratio 7.4 : 1.6 : 1.0	95

[a] For reactions of **1** and **2** with two other dienes see Entries 1, 2, 11 and 12 in Table 1. [b] From GP2 – see Table 1 for details. Isolated yields quoted after purification. [c] X-ray structure determined in this study. [d] Reference 12. [e] After 24 h. [f] After 48 h. [g] Yield not accurately obtained due to cyclo-reversion process of the cycloadduct. [h] Reference 17. Note: All chiral cycloadducts are racemic.

The unsymmetric diene, 1-hydroxymethyl-4-methyl-1,3-butadiene, upon reaction with the oxidation product of acid **1**, gave two cycloadducts **40** and **41** in equal amounts indicating no preference for one adduct over the other (Table 2, Entry 5). However, a preference of one cycloadduct **49** over adduct **50** was observed when the oxidation product of acid **2** was employed, with a proximal:distal ratio of 3:2 showing some selectivity (Table 2, Entry 11). The identities of **40**, **41**, **49** and **50** were determined with the aid of 2D ^{1}H NOESY spectra. The product selectivities increased when 2-methyl-1,3-butadiene is used with ratios of 1.7:1 for distal:proximal adducts **42**:**43** from **1** (Table 2, Entry 6), and 4.5:1 for distal:proximal adducts **51**:**52** obtained from **2** (Table 2, Entry 12). In addition, there was an increase in selectivity of the adducts over the ene products (**44** and **53**) observed in the reactions with a 3:1 NDA:ene ratio for **1** and 9:1 NDA:ene ratio for **2**. Despite attempts, the cycloadduct **50** and the ene-products **44** and **53** could not be isolated as pure substances. The identities of **42**, **43**, **51** and **52** were determined on the basis of similar cycloadducts reported elsewhere.[8]

The cycloadducts reported herein were all characterized by ^{1}H NMR, ^{13}C NMR, IR spectroscopies and mass spectrometry (Figures S14-S45 for NMR spectra). While most adducts showed only one conformer in solution from NMR studies at ambient temperature, the bicyclic oxazaoctene **22** existed as a pair of rotamers (Figure 1). NMR observations of a pair of rotamers have been reported previously for **21** at lower temperatures.[9,15]

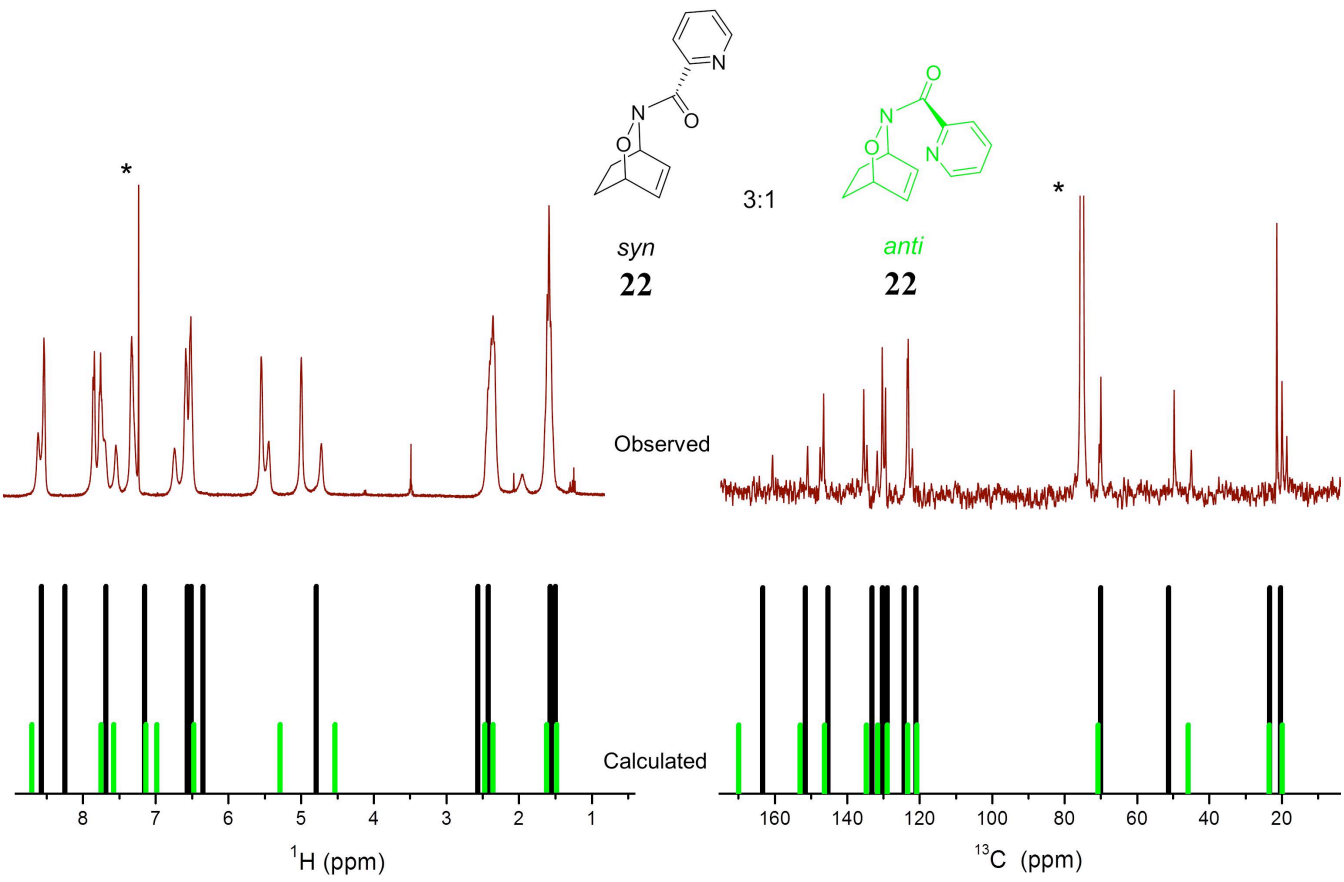


Figure 1. Comparison of observed and computed (GIAO) ^{1}H and ^{13}C NMR spectra for the two rotamers of **22**. Peaks with asterisks correspond to chloroform as solvent.

Crystal Structures

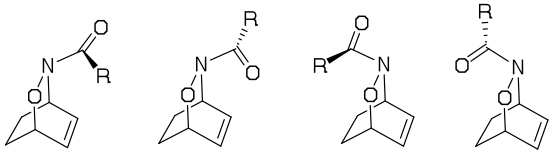
X-ray crystal determinations were carried out on three hydroxamic acids (**2**, **3** and **9**), five adducts from the cyclohexadiene nitroso-Diels-Alder (NDA) reactions (**14-17** and **21**), two from 2,3-dimethyl-1,3-butadiene NDA reactions (**25** and **32**) and one from the cyclopentadiene NDA reaction (**36**) (Figures S46-48 and Table S1). The cyclohexadiene NDA adducts may contain four distinct bicyclic oxaazaoctene geometries **A-D** (Figure 2). Compound **14** has conformer **B**, where the carbonyl C=O bond is orientated *syn* to the N-O bond, and the C=O group located adjacent to the C=C double bond in the bicycle whereas adducts **15-17** and **21** were of conformer **A** type, with the carbonyl C=O bond orientated *anti* to the N-O bond (Figure 3).

The bicyclic oxaazaoctene geometries structurally characterized previously included two examples of conformer **B** with a -COOR group (R = cyclohexyl containing -Me and -CMe_2-naphthyl substituents)[18] and a -COPh group[19] at the bicyclic nitrogen atom. Four reported geometries were of conformer **A** with -$COOCH_2Ph$ groups,[8,20] a -CO-camphoryl[21] and a -COCH(OH)Ph[22] group at the bicyclic nitrogen. For bicyclic oxaazaoctenes structurally characterized to date, the -COOR and -COPh groups at the bicyclic nitrogen atom adopted the *anti*-conformer **A** or the *syn*-conformer **B** whereas others, with -COR groups at the bicyclic nitrogen atom, adopted the *anti* conformer **A**. All of these bicyclic oxaazaoctenes, **14**-**17** and **21**, contained the C=O group located adjacent to the C=C double bond in the bicycle. Conformers **C** and **D** have not been reported for these systems and were assumed to be less favorable.

The dimethylbutadiene NDA adducts, **25** and **32**, contain the carbonyl C=O bond oriented *anti* to the N-O bond with -CONHPh and -COPy groups at the oxazine nitrogen atom. Many *anti*-conformer geometries have been determined with a -COR group at the oxazine nitrogen atom.[23] There have been reported oxazine structures where the carbonyl C=O bonds were oriented *syn* to the N-O bond with -COOR (R = ^{t}Bu, $PhCH_2$) groups at the cyclic nitrogen atom.[24] There seems to be little preference for either the *syn*- or *anti*-geometry in oxazines with -COR groups at the nitrogen atom except for -CONHR, for which the *anti* geometry is expected, with a distance of 2.183 Å found for the favorable N-H..O interaction in **25**.

The cyclopentadiene NDA adduct **36** contained a COOPh group at the nitrogen atom of the bicyclic oxaazaheptene skeleton where the C=O bond was *syn* to the N-O bond. The only published bicyclic oxaazaheptene with a -COR group at the nitrogen atom is the *anti* conformer for R = -$CHMeNHOCOCH_2Ph$.[25]

Table 3. Conformers **A**-**D** and calculated relative and rotation barrier energies (kcal mol^{-1}) for **14**, **15**, **21** and **22**.



	R	**A** *anti*	**B** *syn*	**C** *anti*	**D** *syn*	**A / B** rotation barrier
14	OPh	0.0	0.8	0.9	2.5	13.8
15	NHPh	0.0	8.8	2.2	10.4	17.4
21	Ph	0.0	3.6	1.1	5.3	14.1
22	2-Py	0.1	0.0	2.0	1.7	14.7

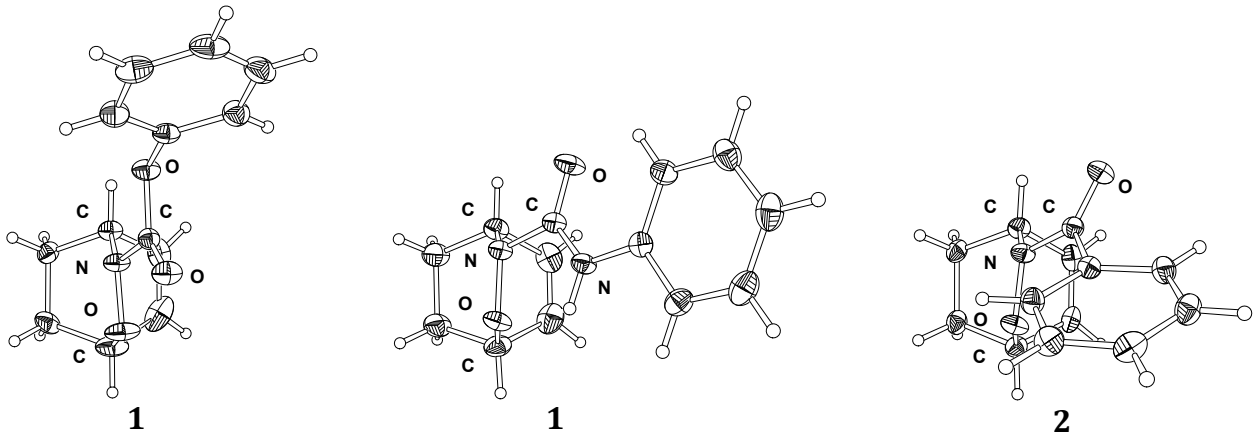


Figure 2. Views of the substituents at N3 with respect to the bicyclic framework in molecular structures of **14**, **15** and **21**.

Computations on NDA Cycloadducts

Geometry optimizations were carried out via DFT calculations in the gas-phase at the B3LYP/6-31G* level on **14**, **15** and **21** to compare with their solid-state geometries as determined by X-ray diffraction, and also to estimate the relative energies of the *syn* and *anti* conformers **A**-**D**. Comparison between the bond lengths of X-ray and computed geometries revealed a very good agreement with differences not exceeding 0.011 Å, except for the N-C bonds between N-O and C=O, which are computed to be longer by 0.017-0.034 Å than observed experimentally (Table S2). The latter differences may have been due to an overestimation of the lone pair contribution from the nitrogen donor atom and the electron-poor carbonyl carbon atom with the B3LYP functional. Similar N-C bond length overestimations (0.014-0.027 Å) were found for optimized geometries of **14**, **15** and **21** using the larger 6-311++G** *versus* 6-31G* basis set.

Relative energies for the conformers **A**-**D** of **14**, **15** and **21** showed a preference for the *anti* conformer **A** (Table 3). While the preference was in accord with observed experimental geometries for **15** and **21**, the experimental geometry in **14** is the *syn* conformer **B**. Conformer **B** was only 0.8 kcal mol^{-1} higher in energy than conformer **A** for **14**. As two rotamers of **22** were observed by NMR spectra at room temperature (Figure 1), conformers **A**-**D** for **22** were also examined computationally with the *syn* conformer **B** calculated to be lower in energy than the *anti*-conformer **A** by only 0.1 kcal mol^{-1} in energy.

The rotational energy barriers between *anti* and *syn* conformers **A** and **B** of **14**, **15**, **21** and **22** were estimated computationally (Figure 1). The calculated value of 14.1 kcal mol^{-1} was in good agreement with the reported[14] experimental value of 13.8 kcal mol^{-1} for **21**. The lower energy barrier of 13.8 kcal mol^{-1} for **14** suggested that **14** was fluxional in solution between the two conformers at room temperature as observed for **21**. While the rotational energy barrier of 17.4 kcal mol^{-1} for **15** suggested that two conformers were present in the NMR spectra, the strong preference for the *anti* conformer **A** over the *syn* form **B** was reflected by an energy difference of 8.8 kcal mol^{-1}. This indicated that only the *anti* conformer for **15** was observed experimentally in solution and likely to be due to the favorable intramolecular hydrogen interaction between the hydrogen atom at N1 and the oxygen atom O2 in the bicycle with an experimentally determined distance of 2.136 Å with the hydrogen atom in a calculated position (Figure 2).

The NMR spectra of **22** showed both conformers at room temperature (Figure 1) as the *anti* and *syn* conformers were very similar in energies and the rotational energy barrier between these conformers in **22** were slightly higher than in **14** and **21** (Figure 2). The *syn* conformer was the major component based on comparison of observed NMR chemical shifts with computed GIAO-NMR chemical shifts where the computed peak intensities assumed a 3:1 *syn*:*anti* conformer ratio. The agreement between observed and computed ^{1}H NMR shifts was not expected to be very good as ^{1}H NMR chemical shifts are strongly influenced by the nature of the solvent. Nevertheless, the agreement between observed and computed ^{13}C NMR shifts for **22** was very good when the different observed peak intensities expected from different types of carbon groups were taken into account which were not modeled computationally.

Reaction Pathway Computations

There have only been three computational studies on intermolecular nitroso-Diels-Alder (NDA) reactions of nitroso species with dienes.[26,27] The excellent 2001 study by Leach and Houk looked at the transition states for reactions of several nitroso species (RNO where R = H, alkyl, Ph, *s-trans* CHO and *s-cis* CHO) with butadiene and substituted butadienes with MeO, Me and CN as substituents.[26] They showed that the *endo*-NDA pathway was the favored one over the *exo*-NDA and nitroso-ene pathways for all reactions.

From the 2001 investigation, the transition state enthalpies from the acyl nitroso HCONO species and butadiene to the nitroso-Diels-Alder adduct (III) are only 3.6 and 4.9 kcal mol^{-1} above the starting butadiene and the nitroso species *s-trans* HCONO and *s-cis* HCONO, respectively. These values were confirmed here if the starting geometries were assumed to be the *trans*-butadiene and *s-trans*-HCONO (I in Figure 3, Tables S3 and S4). However, the *cis*-butadiene geometry was clearly the precursor along with *s-trans*-HCONO (II in Figure 3) to the *endo* NDA transition state (TS-II,III) so the transition-state enthalpy was calculated as a negative(!) value at -0.1 kcal mol^{-1} instead of the reported value of 3.6 kcal mol^{-1}. Obviously, there must be a local minimum (LM) between *cis*-butadiene and *s-trans* HCONO that is lower in energy than the NDA transition state and such a local minimum II(LM) (Figures 3 and 4) was found with an energy of 1.8 kcal mol^{-1} lower than the energy of the NDA transition state (TS-II,III). The intriguing aspect of the acyl nitroso-butadiene pathway is that the transition-state energy of the geometry located (TS-I,II in Figure 3) in the *s-trans* and *s-cis* butadiene conversion was <u>higher</u> than the transition-state energy of the NDA adduct formation irrespective of whether local minima (LM) are

located (Figure 3). This view indicated that acyl nitroso species are super-reactive species, as noted elsewhere.[28]

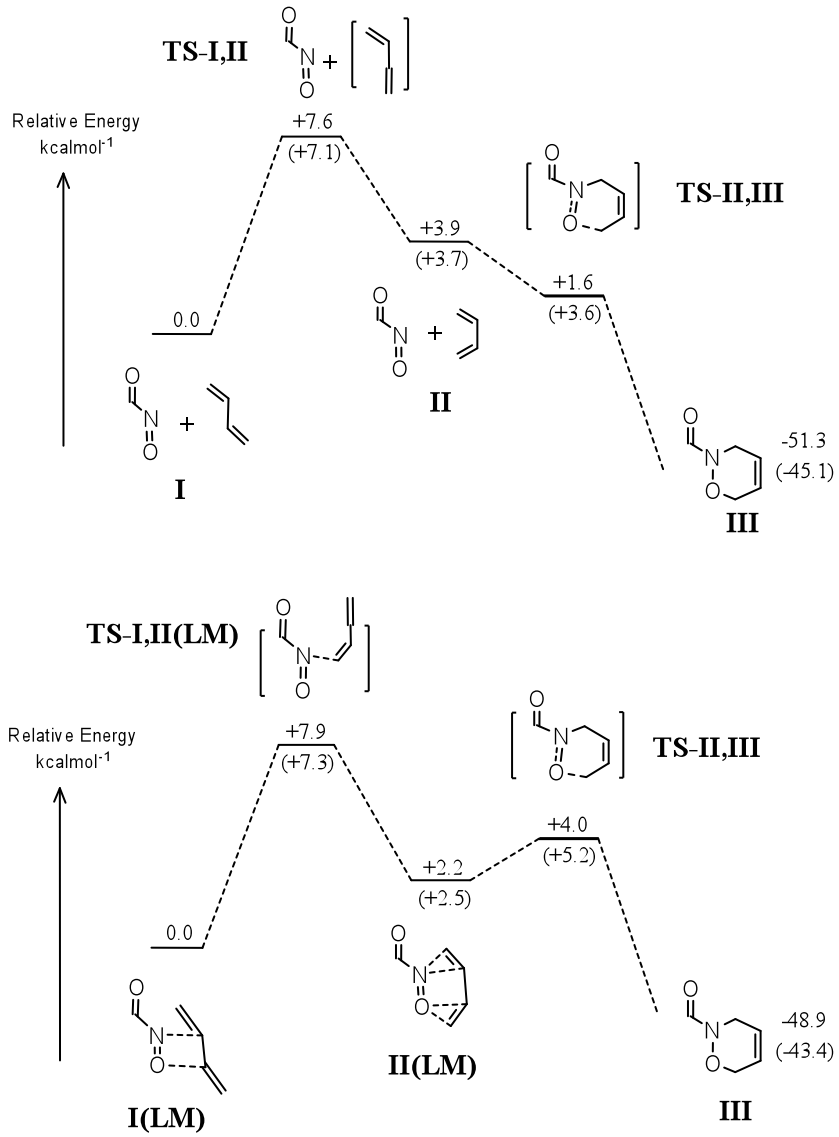
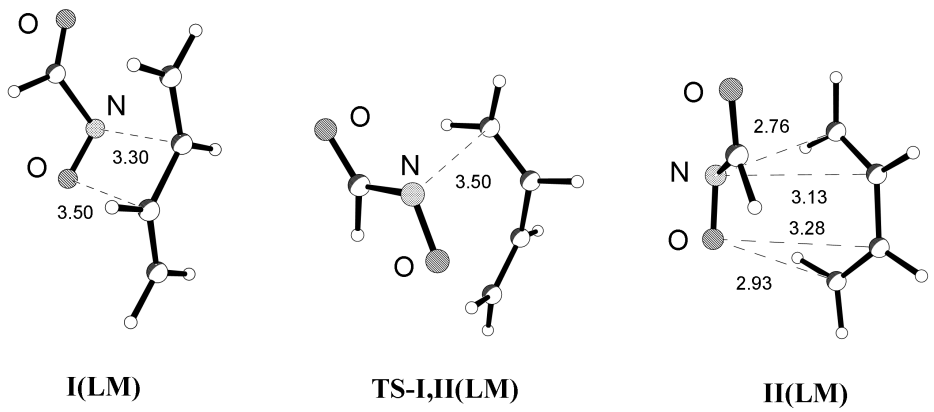


Figure 3. Reaction pathways (top) without local minima of starting molecules and (bottom) with local minima of the starting molecules. Energies in parentheses are based on computed enthalpy values and are in agreement with those reported in reference 26.



I(LM) **TS-I,II(LM)** **II(LM)**

Figure 4. Geometries of butadiene-acylnitroso association complex local minima.

The pathways of the reactions carried out experimentally in this study were explored computationally using MeOCONO and MeNHCONO as models for PhOCONO and PhNHCONO species generated from oxidations of the hydroxamic acids **1** and **2**, respectively. While the *s-trans*-form was much more stable than the *s-cis*-form by 3.3 kcal mol^{-1} in HCONO, the energy differences between *s-trans* and *s-cis* forms were much smaller in MeOCONO and MeNHCONO being only 0.8 and 0.1 kcal mol^{-1}, respectively, with the most stable forms being *s-cis* and *s-trans* for MeOCONO and MeNHCONO, respectively (Table S5). Both conformations were considered in all NDA reaction pathways investigated here. The *s-trans*-forms were the preferred reagents in all computed NDA reaction pathways containing the lowest transition energies overall.

The relative energies of the local minima (LM), transition states (TS) and products are shown in Figure 5 and Tables S6 and S7 with cyclohexa-1,3-diene, 2,3-dimethylbutadiene, 1,4-diphenylbutadiene and 9,10-dimethylanthracene (DMA) as the dienes in reaction pathways with MeOCONO and MeNHCONO. The cyclohexa-1,3-diene - acyl nitroso pathway was clearly very favorable with: i) NDA transition state energies of only 2.4-2.8 kcal mol^{-1} higher than the energies of the local minima of the reactants; and ii) the energies of adducts being lower by over -30 kcal mol^{-1} than the energies of the local minima of the starting reactants. The DMA - acyl nitroso pathway was less favorable with higher energy barrier of 5.9 kcal mol^{-1} for MeOCONO which explained the need for a longer reaction time to obtain a high yield of the cycloadduct **37**. The energy of the MeNHCONO cycloadduct at -15.4 kcal mol^{-1}, relative to the starting nitroso species and DMA, shows that it was susceptible to cyclo-reversion thus the corresponding known[17]adduct **46** could not be obtained in high yield experimentally.

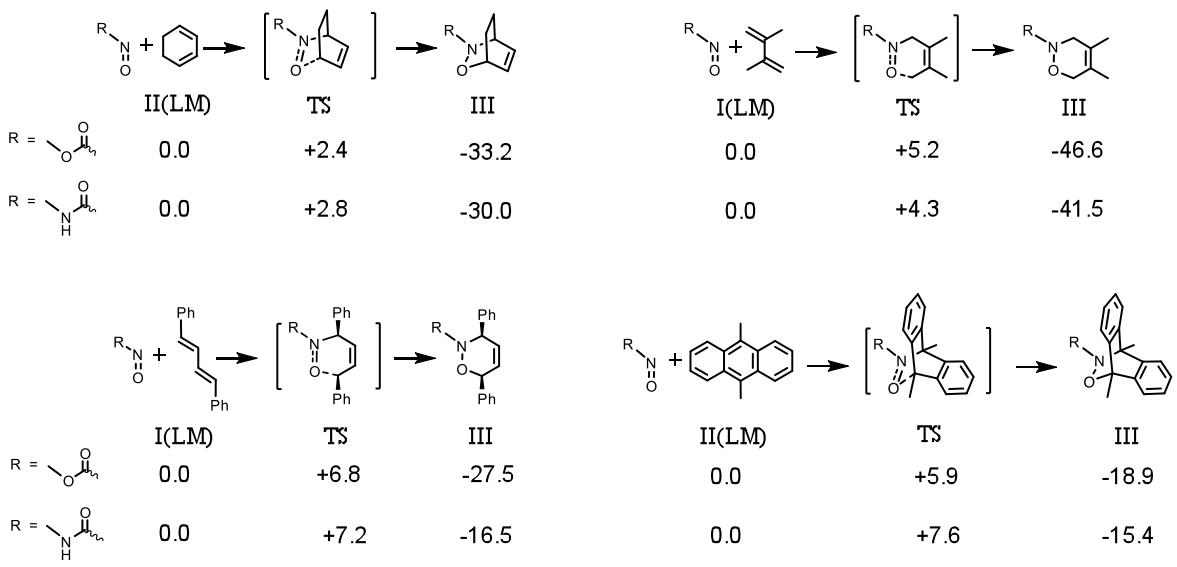
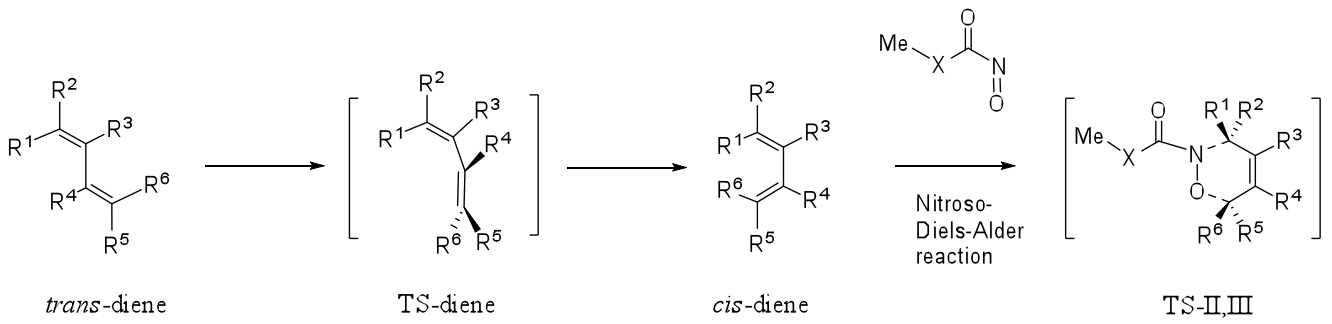


Figure 5. Relative energies (kcal mol^{-1}) for computed nitroso-Diels-Alder model pathways.

For the acyclic dienes, the energy barriers for isomerization from the *s-trans* to *s-cis* diene geometries are higher than the energies of the NDA transition states in all cases except for 2,3-dimethylbutadiene and MeNHCONO as shown in Figure 6. The experimental *s-trans*- to *s-cis* diene rotational interconversion barriers for 2,3-dimethylbutadiene and 2-methyl-1,3-butadiene were estimated at 3.4 and 3.9 kcal mol^{-1}, respectively, which were lower than our computed 'gas-phase' values of 4.8 and 6.7 kcal mol^{-1}.[29] As discussed for the simple model HNO + butadiene reaction, there were competing energy barriers between the *s-trans and s-cis* diene rotational interconversion and the NDA adduct formation. The longer reaction time required for a high yield of the cycloadduct **39** from 1,4-diphenylbutadiene was due to the comparatively high energy *s-trans* to *s-cis* diene conformation barrier of 10.0 kcal mol^{-1}, and the *s-trans* diene was more stable than the *s-cis* diene by 6.2 kcal mol^{-1}. The NDA adduct from 1,4-diphenylbutadiene and MeNHCONO was only -16.5 kcal mol^{-1} lower in energy compared to the combined energy of the starting reactants thus cyclo-reversion would be expected in **48**.



	trans-diene	TS-diene	*cis*-diene	TS-II,III (X = O) - nitroso	TS-II,III (X = N) - nitroso
R^3,R^4 = Me; R^1,R^2,R^5,R^6 = H	0.0	4.8	2.5	5.2	4.3
R^2,R^5 = Me; R^1,R^3,R^4,R^6 = H	0.0	7.7	4.2	4.4	4.2
R^2,R^5 = Ph; R^1,R^3,R^4,R^6 = H	0.0	10.0	6.2	6.8	7.2
R^3 = Me; R^1,R^2,R^4,R^5,R^6 = H	0.0	6.7	3.1	5.1	4.5

Figure 6. Relative energies (kcal mol^{-1}) for computed acyclic diene and nitroso-Diels-Alder model pathways.

The observed NDA products from *in situ* oxidations of **1** and **2** in the presence of 2-methyl-1,3-butadiene gave distal and proximal isomers with a preference for the distal form, particularly from urea **2** (Table S7). The computed reaction pathways showed a preference for the proximal form with MeOCONO but distal form with MeNHCONO and transition state energy differences of only 0.7 and 0.4 kcal mol^{-1}, respectively. Such small differences were reflected in both proximal and distal forms being observed experimentally. The reported[19] reaction of MeOCONO with 2-[(*tert*-butyldimethylsilyl)oxy]methyl-1,3-butadiene gave the proximal form as the major isomer, hence, the isomer ratio would depend on whether MeOCONO or PhOCONO was used.

The presence of ene products, **34**, **35**, **44** and **53**, from 2,3-dimethylbutadiene and 2-methylbutadiene with **1** and **2** suggested that ene reaction pathways from these dienes with MeOCONO and MeNHCONO are competing with NDA pathways. By computing the pathways with *s-cis* or *s-trans* dienes as starting reactants, we located transition states with energies at least 5 kcal mol^{-1} higher than the corresponding *endo* NDA transition state energies (Figure 7 and Table S8). Attempts to establish complete ene reaction pathways with diradical species were unsuccessful. The ene products observed were assumed to form from reaction pathways involving the copper complex as: i) the predicted transition state energies for the ene pathways were too high to compete with the NDA pathways; and ii) the copper-free periodate method (GP1) did not give ene products from **1** and **2**.

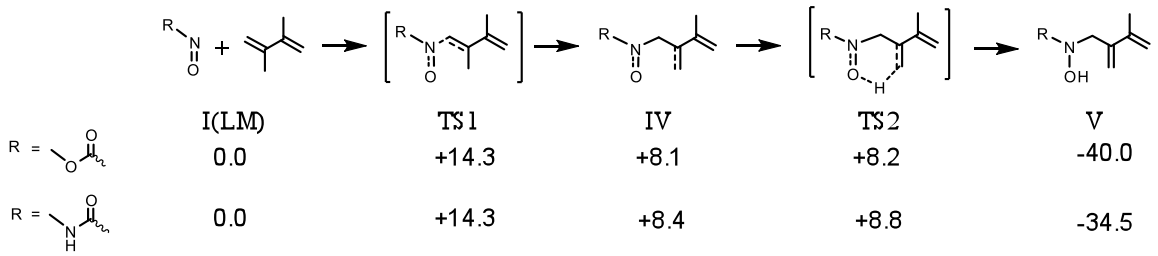


Figure 7. Nitroso-ene pathways with relative energies in kcal mol^{-1}.

Unlike intramolecular NDA pathways where predictions of relative transition energies are straightforward,[30] intermolecular NDA pathways are difficult to model given that there are many possible starting points, different conformers and local minima of the two reactant molecules. This difficulty is compounded by super-reactive acyl nitroso species, such as MeOCONO and MeNHCONO, where the *endo*-NDA transition state can be only 2.0 kcal mol^{-1} higher than the starting diene and nitroso species. Nevertheless, the computations here showed that the preferred reaction pathway was *via* the *endo*-NDA transition-state, over both the *exo*-NDA and ene transition-states (Table S9), as also reported elsewhere.[26] The data also showed that the *endo*-NDA transition-states can be lower in energy than the transition states involved in the *s-trans* to *s-cis* diene isomerization processes for acyclic dienes.

The low yields of cycloadducts **46** and **48** from urea **2** and 9,10-dimethylanthracene and 1,4-diphenylbutadiene (Table 2, entries 8 and 10) can be understood by the fact that the calculated energies of the cycloadducts were close in energies to the combined energies of their corresponding diene and nitroso species, and thus were susceptible to cycloreversion processes. As the ene reaction pathways show considerably higher energy barriers than the NDA pathways for 2,3-dimethylbutadiene and 2-methylbutadiene with nitroso species, we suggest here that the copper complex present in solution is involved in the ene pathways and thus, the copper-mediated ene pathways compete with the NDA pathways. This assumption is supported by a reported[10] copper-mediated procedure specific for reactions of acylnitroso species with alkenes to give ene products in high yields at ambient temperatures.

Summary and conclusions

From the work shown here, we conclude that: 1) the copper-oxazoline complex is an excellent catalyst for the aerobic oxidation of acyl hydroxamic acid to generate the corresponding acyl nitroso species; 2) this system can only be used with a hydroxamic acid containing a hetero-atom between the aryl and carbonyl group; 3) the nitroso species generated *in situ* can be trapped by most dienes resulting in the

corresponding cycloadducts; 4) the yield of the products varied from high to moderate, depending upon the reaction time because there is competitive decomposition of the nitroso species, reducing the yield of the NDA adduct. The longer the trapping time (slower NDA reaction), the lower the yield, generally; 5) the chemoselectivity of this system depends upon the reactivity of the hydroxamic acid - the higher the reactivity, the lower the chemoselectivity. Overall, the catalytic aerobic oxidation is a particularly efficient, mild, clean, simple and environmentally benign method for generating acyl nitroso species *in situ* and trapping them via a NDA reaction. When these types of reactions are examined by DFT calculations, the preference for *endo* transition-states, over *exo* and *ene* transition states, was confirmed. Interestingly, for the super reactive acyl nitroso species, diene rotational conformational interconversion between *s-cis* and *s-trans* forms, can be slower than the nitroso-DA reaction, since the transition-state energies are lower for the DA reaction *via* the *endo* transition-state. This could explain variable yields in some cases, because the acyl nitroso compounds were inherently unstable and decomposition could compete on this basis. In addition, the inherent reversibility in these reactions also likely played a major role in reaction yields. Calculated energies confirm the greater reversibility of certain diene - nitroso species combinations, again, providing time for nitroso species decomposition. The reversibility has also likely to impact upon observed both regio- and stereo-control in these reactions. This issue has not been addressed to a major extent in the literature, but the prediction of considerable reversibility in these reactions means that a detailed examination of kinetic *versus* thermodynamic effects on the reaction outcome would shed further light upon the selectivity in the nitroso-DA reactions.

Experimental Section

General

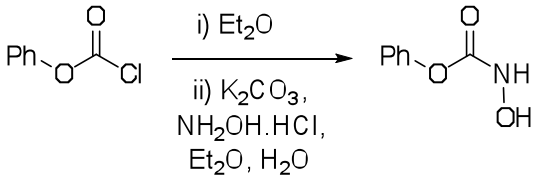
All reactions were performed in the presence of air, unless otherwise stated. All reagents were purchased from commercial sources and were used as received without further purification unless otherwise stated. Solvents (AR grade) were used as received. ^{1}H NMR spectra were recorded at 400, 500, 600 or 700 MHz and $^{13}C\{^{1}H\}$ spectra were recorded at 101, 125, 150, or 176 MHz, in $CDCl_3$ or DMSO-d_6 as solvents. ^{1}H NMR chemical shifts are reported with reference to TMS using residual proton on non deuterated solvent ($CDCl_3$: 7.26 ppm; DMSO-d_6: 2.50 ppm; 3.33 ppm for water present in DMSO-d_6) whereas ^{13}C NMR spectra are reported with reference to TMS using the carbon signals of the deuterated solvent ($CDCl_3$: 77.23 ppm; DMSO-d_6: 39.52 ppm). All chromatography was carried out using 40-63 μm silica gel. The removal of solvent was performed on a rotary evaporator under vacuum. Melting points were determined using a melting point apparatus and are uncorrected. Low resolution

mass spectrometry was carried out on a TQD equipped with a UPLC and an electrospray ion source, and high resolution mass spectrometry was carried out on a TOF-MS equipped with an electrospray ion source.

Hydroxamic acid syntheses

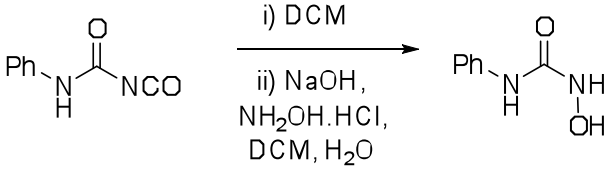
Compounds **1-12** have been reported elsewhere[31-42] using different procedures to those described here.

Phenyl hydroxycarbamate[31] **1**



A solution of phenyl chloroformate (5.32 g, 34.0 mmol) in ether was added dropwise in 30 min to a stirred solution of hydroxylamide hydrochloride (2.36 g, 34.0 mmol) and potassium carbonate (5.17 g, 37.4 mmol) in 30 mL of ether and 5 mL of water at 5 °C. After the addition, the reaction was stirred at room temperature for 4 h. The organic layer was separated and dried over $MgSO_4$. The solvent was evaporated *in vacuo* to yield a white solid product **1** (3.10 g, 59%) this compound was used in the next experiment without purification; m.p. 98 – 101 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.33 (s, 1H), 9.08 (s, 1H), 7.42 – 7.36 (m, 2H), 7.25 – 7.19 (m, 1H), 7.13 – 7.07 (m, 2H), ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 155.5, 150.7, 129.4, 125.1, 121.5; FTIR (thin film) *inter alia* 3299, 1687 (C=O), 1511, 1492, 1284, 1201, 1105, 795, 687; LRMS (ESI+) m/z 176.1 (M^+ +Na); HRMS (ESI+) m/z Calcd for $C_7H_7NO_3Na$ 176.0324 found 176.0333.

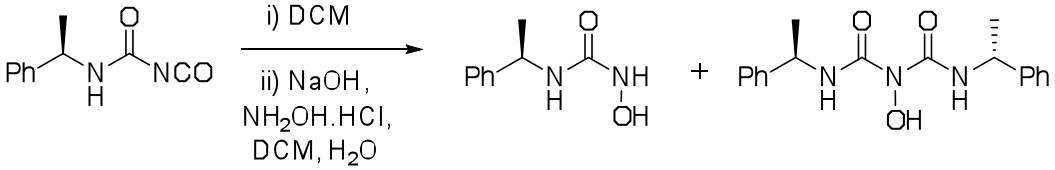
1-Hydroxy-3-phenylurea[32,33] **2**



A solution of phenylisocyanate (4.00 g, 33.6 mmol) in 10 mL of DCM was added dropwise over 30 min to a solution of sodium hydroxide (1.34 g, 33.6 mmol) and hydroxylamine hydrochloride (2.33 g, 33.6 mmol) in 5 mL of water and 60 mL of DCM at 0 °C. After the addition, the reaction was warmed to the room temperature and stirred for 3 h to yield a white solid. The reaction was washed by 20 mL of water

and 20 mL of DCM. The precipitate was collected by filtration and recrystalized from ethyl acetate to give the product **2** as a white solid (2.53 g, 50 %); m.p. 148 – 150 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.96 (s, 1H), 8.81 (s, 1H), 8.75 (s, 1H), 7.59 (d, J = 8.5 Hz, 2H), 7.23 (t, J = 7.9 Hz, 2H), 6.95 (t, J = 7.3 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 159.0, 139.8, 128.9, 122.6, 119.6; FTIR (thin film) *inter alia* 3221, 2951, 2894, 1630, 1595, 1537, 1501, 1449, 1074, 755, 688 cm^{-1}; LRMS (ESI+) m/z 175.1 (M^+ +Na); HRMS (ESI+) m/z Calcd for $C_7H_8N_2O_2Na$ 175.0483 found 175.0483.

(*R*)-1-Hydroxy-3-(1-phenylethyl)urea[32,34] **3** and *N*-Hydroxy-*N'*-[(*R*)-1-Phenylethyl]-*N*-[(*R*)-1-Phenylethylcarbamoyl]urea **13**



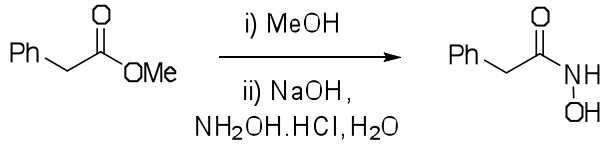
A solution of (*R*)-(1-isocyanatoethyl)benzene (1.00 g, 6.79 mmol) in 10 mL of DCM was added dropwise over 30 min to a solution of sodium hydroxide (0.27 g, 6.79 mmol) and hydroxylamine hydrochloride (0.47 g, 6.79 mmol) in 1 mL of water and 20 mL of DCM at 0 °C. After the addition, the reaction was warmed to the room temperature and stirred for 3 h. The reaction was washed by 20 mL of water and 20 mL of DCM. The organic phase was separated and dried over $MgSO_4$. The removal of solvent gave a colorless oil which then was separated by column chromatography (ethyl acetate as eluent) to yield 0.60 g (49%) of product **3**; m.p. 106-108 °C ; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.67 (d, J = 0.8 Hz, 1H), 8.40 (s, 1H), 7.42 – 7.34 (m, 4H), 7.30 – 7.24 (m, 1H), 7.00 (d, J = 8.7 Hz, 1H), 4.94-4.86 (m, 1H), 1.45 (d, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 161.0, 145.8, 128.6, 126.9, 126.5, 48.6, 23.1; FTIR (thin film) *inter alia* 3311, 2931, 1649 (C=O), 1514, 766, 698 cm^{-1}; LRMS (ESI+) m/z 203.5 (M^+ +Na); HRMS (ESI+) m/z Calcd for $C_9H_{12}N_2O_2Na$ 203.0796 found 203.0796 and an orange oil side product **13** (0.31 g, 13%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.30 (s, 1H), 7.32 – 7.08 (m, 12H), 4.87 (s, 2H), 1.45 (s, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 153.1, 142.0, 127.7, 126.4, 124.9, 49.2, 21.7; FTIR (thin film) *inter alia* 3270, 3029, 2971, 1691 (C=O), 1658 (C=O), 1491, 1209, 696 cm^{-1}; LRMS (ESI+) m/z 350.7 (M^+ +Na); HRMS (ESI+) m/z Calcd for $C_{18}H_{21}N_3O_3Na$ 350. 1481 found 350.1472.

General procedure of hydroxamic acid synthesis from esters (**GPHA**)[35]

Four equivalents of sodium hydroxide were dissolved in water followed by two equivalents of hydroxylamine hydrochloride. Then, this solution was added dropwise to the appropriate ester in

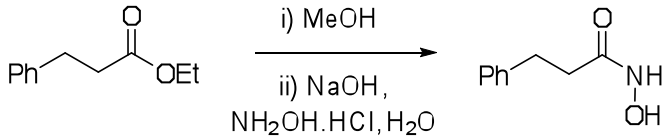
methanol. The reaction was stirred at room temperature for 4 h and monitored by TLC. When the reaction was finished, the solution was acidified with 5% HCl to pH 5.5. The solvent was removed in vacuo to yield a mixture of product and sodium chloride, which was then redissolved in methanol. The sodium chloride was removed by filtration. The methanol was removed in vacuo to give the corresponding product, which then recrystallized from hot water to give the pure product.

N-Hydroxy-2-phenylacetamide[36] **4**



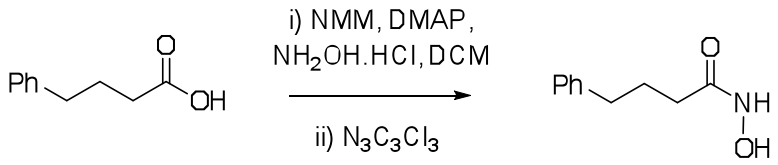
The reaction was performed according to **GPHA**, using methylphenylacetate (10.2 g, 67.9 mmol) in 200 mL of methanol, sodium hydroxide (10.9 g, 272 mmol), hydroxylamine hydrochloride (9.4 g, 135 mmol) in 200 mL of water. The product **4** was isolated as an off-white solid (5.6 g, 54%); m.p. 139–142 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.67 (s, 1H), 8.84 (s, 1H), 7.32 – 7.19 (m, 5H), 3.28 (s, 2H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 167.0, 136.1, 128.9, 128.1, 126.4, 39.4; FTIR (thin film) *inter alia* 3186, 3002, 2902, 1631 (C=O), 1548, 1495, 1455, 1054, 978, 715; LRMS (ESI-) m/z 150.2 (M^+ - H); HRMS (ESI+) m/z Calcd for $C_8H_8NO_2$ 150.0555 found 150.0555.

N-Hydroxy-3-phenylpropanamide[36] **5**



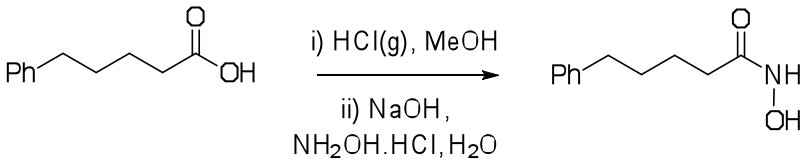
The reaction was performed according to **GPHA**, using ethylhydrocinnamate (9.4 g, 52.7 mmol) in 200 mL of methanol, sodium hydroxide (8.4 g, 210 mmol), hydroxylamine hydrochloride (7.3 g, 105 mmol) in 200 mL of water. The product **5** was isolated as a white solid (4.9 g, 56%); m.p. 75 – 77 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.20 (s, 2H), 7.25 – 7.20 (m, 2H), 7.18 – 7.10 (m, 3H), 2.87 (t, J = 8 Hz, 2H), 2.38 (t, J = 8 Hz, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 171.1, 140.2, 128.6, 128.3, 126.4, 34.6, 31.3; FTIR (thin film) *inter alia* 3296, 3062, 2782, 1662 (C=O), 1626, 1557, 1496, 1455, 1062, 995, 695; LRMS (ESI+) m/z 188.2 (M^+ +Na); HRMS (ESI+) m/z Calcd for $C_9H_{11}NO_2Na$ 188.0687 found 188.0689.

N-Hydroxy-4-phenylbutanamide[36,37] **6**



4-Phenylbutyric acid (7.4 g, 45.1 mmol), NMM (5.0 g, 50.5 mmol), DMAP (0.06 g, 0.05 mmol) and hydroxylamine hydrochloride (3.5 g, 50.5 mmol) were dissolved in 150 mL of DCM. The mixture was stirred and cooled to 0 °C. Then cyanuric chloride (2.5 g, 15.0 mmol) was added to the solution and the mixture was warmed to room temperature. The reaction was stirred for 24 h. After completion, the solution was filtered through Celite, then washed with 45 mL of 1 M HCl (3X). The organic layer was separated and dried over $MgSO_4$. The solvent was evaporated in vacuo to yield a white solid product, which was then purified by silica gel column chromatography (EtOAc as eluent) to give product **6** (2.00 g, 25%); m.p. 71 – 74 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.36 (s, 1H), 8.71 (s, 1H), 7.28 – 7.23 (m, 2H), 7.18 – 7.14 (m, 3H), 2.54 (t, J = 8.0 Hz, 2H), 1.95 (t, J = 8.0 Hz, 2H), 1.82 – 1.71 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 168.8, 141.6, 128.3, 128.3, 125.7, 34.6, 31.8, 27.0; FTIR (thin film) *inter alia* 3170, 3024, 2908, 1622 (C=O), 1542, 1495, 1459, 1065, 1016, 742, 694; LRMS (ESI+) m/z 202.2 (M^+ +Na); HRMS (ESI+) m/z Calcd for $C_{10}H_{13}NO_2Na$ 202.0844 found 202.0849.

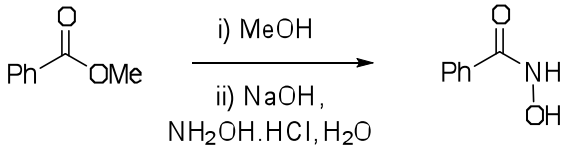
N-Hydroxy-5-phenylpentanamide[38] **7**



Hydrogen chloride gas, generated from dropping 36% HCl into 98% H_2SO_4, was bubbled into a solution of 5-phenylvaleric acid (5.0 g, 28.1 mmol) in 150 mL of methanol at room temperature for 15 min. Then sodium hydroxide (4.5 g, 112 mmol), and hydroxylamine hydrochloride (3.9 g, 56.2 mmol) in 100 mL of water were added dropwise to the solution. The reaction was stirred for 24 h and then acidified to pH 5.5 using 10% HCl. The solvents were removed under vacuum. The residue was redissolved in methanol and the sodium chloride was removed by filtration. The solvent then removed to yield a yellow oil, which was recrystalized from ether to yield a white solid product **7** (3.60 g, 67%); m.p. 68 – 71 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.32 (s, 1H), 8.67 (s, 1H), 7.27 (t, J = 7.5 Hz, 2H), 7.20 – 7.14 (m, 3H) 2.56 (t, J = 6.7 Hz, 2H), 1.97 (t, J = 6.8 Hz, 2H), 1.63 – 1.39 (m, 4H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 169.0, 142.0, 128.2, 128.2, 125.6, 34.8, 32.1, 30.5, 24.8; FTIR (thin

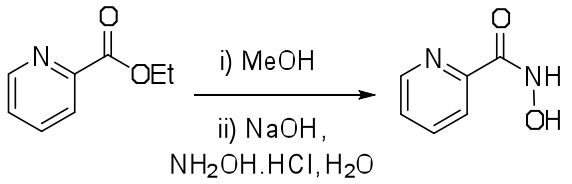
film) *inter alia* 3186, 3038, 2910, 1618 (C=O), 1434, 1085, 992, 962, 749, 698; LRMS (ESI+) m/z 216.2 (M^+ +Na); HRMS (ESI+) m/z Calcd for $C_{11}H_{15}NO_2Na$ 216.1000 found 216.1007.

N-Hydroxybenzamide[36] **8**



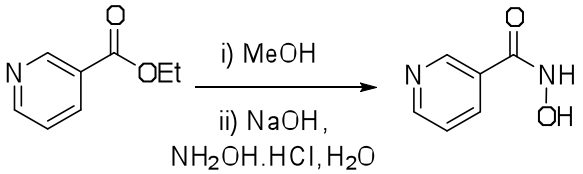
The reaction was performed according to **GPHA**, using methylbenzoate (5.30 g, 38.9 mmol) in 100 mL of methanol, sodium hydroxide (6.23 g, 156 mmol), and hydroxylamine hydrochloride (5.41 g, 77.9 mmol) in 100 mL of water. The product **8** was isolated as a white solid (3.4 g, 64%); m.p. 121 – 123 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.22 (s, 1H), 9.05 (s, 1H), 7.82 – 7.68 (m, 2H), 7.54 – 7.48 (m, 1H), 7.48 – 7.36 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 164.7, 133.3, 131.6, 128.8, 127.3; FTIR (thin film) *inter alia* 3292, 3062, 2746, 1644, 1602, 1557, 1490, 1316, 1163, 1022, 897, 787, 689; LRMS (ESI+) m/z 138.2 (M^+ +H); HRMS (ESI+) m/z Calcd for $C_7H_8NO_2$ 138.0555 found 138.055.

2-Pyridinehydroxamic acid[39] **9**



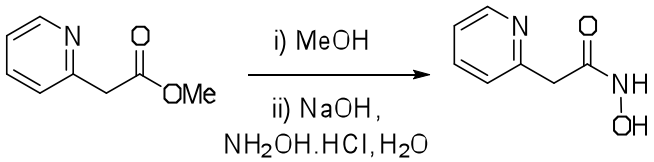
The reaction was performed according to **GPHA**, using ethyl-2-picolinate (5.00 g, 33 mmol) in 100 mL of methanol, sodium hydroxide (5.29 g, 132 mmol), and hydroxylamine hydrochloride (4.60 g, 66 mmol) in 100 mL of water. The product **9** was isolated as a white solid (3.00 g, 66%); m.p. 119 – 120 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.46 (s, 1H), 9.24 (s, 1H), 8.63 (dt, J = 4.8, 1.3 Hz, 1H), 8.04 – 7.97 (m, 2H), 7.64 – 7.57 (m, 1H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 162.2, 151.0, 149.4, 138.5, 127.2, 122.7.; FTIR (thin film) *inter alia* 3264 (broad), 2778 (broad), 1662 (C=O), 1592, 1570, 1516, 1475, 1177, 1030, 816; LRMS (ESI-) m/z 161.4 (M^+ Na); HRMS (ESI+) m/z Calcd for $C_6H_6N_2O_2Na$ 161.0327 found 161.0323.

3-Pyridinehydroxamic acid[40] **10**



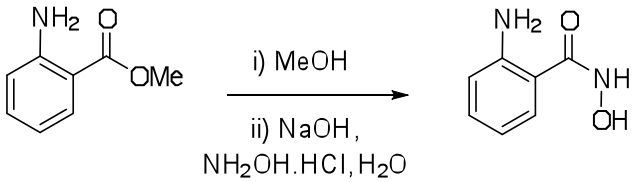
The reaction was performed according to **GPHA**, using ethyl nicotinate (5.00 g, 33 mmol) in 100 mL of methanol, sodium hydroxide (5.29 g, 132 mmol), and hydroxylamine hydrochloride (4.60 g, 66 mmol) in 100 mL of water. The product **10** was isolated as a white solid (2.70 g, 59%): m.p. 160 – 161 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.37 (s, 1H), 9.59 – 8.99 (m, 1H), 8.89 (dt, *J* = 20.8, 10.4 Hz, 1H), 8.74 – 8.61 (m, 1H), 8.18 – 8.00 (m, 1H), 7.49 (ddd, *J* = 7.9, 4.8, 0.8 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 162.9, 152.3, 148.3, 135.1, 128.9, 124.0; FTIR (thin film) *inter alia* 1634 (C=O), 1594, 1495, 1472, 1422, 1305, 1024, 700; LRMS (ESI-) m/z 137.1 (M^+ -H); HRMS (ESI-) m/z Calcd for $C_6H_5N_2O_2$ 137.0351 found 137.0332.

N-Hydroxy-2-(pyridin-2-yl)acetamide[41] **11**



The reaction was performed according to **GPHA**, using ethyl 2-pyridylacetate (2.00 g, 12.1 mmol) in 50mL of methanol, sodium hydroxide (1.94 g, 48.4 mmol), and hydroxylamine hydrochloride (1.68 g, 24.2 mmol) in 50 mL of water. The product **11** was isolated as a white solid (0.93g, 50%), which was used in the next experiment without purification: m.p. 159 – 161 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.93 (s, 1H), 8.97 (s, 1H), 8.57 (d, *J* = 4.3 Hz, 1H), 7.96 (dd, *J* = 7.6, 6.4 Hz, 1H), 7.52 (d, *J* = 7.8 Hz, 1H), 7.47 – 7.41 (m, 1H), 3.64 (s, 2H); ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ 165.3, 154.5, 146.7, 139.1, 124.9, 122.8, 40.5; FTIR (thin film) *inter alia* 1677 (C=O), 1645, 1600, 1546, 1442, 1044, 1012, 797, 764, 616; LRMS (ESI+) m/z 175.4 (M^+ Na); HRMS (ESI+) m/z Calcd for $C_7H_8N_2O_2Na$ 175.0483 found 175.0473.

2-Amino-*N*-hydroxybenzamide[42] **12**



The reaction was performed according to **GPHA**, using methyl 2-aminobenzoate (10.00 g, 66.2 mmol) in 200 mL of methanol, sodium hydroxide (10.60 g, 265 mmol), and hydroxylamine hydrochloride (9.20 g, 132 mmol) in 200 mL of water. The product **12** was isolated as a pale yellow solid (6.10 g, 60%): m.p. 143-145 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.91 (s, 1H), 8.89 (s, 1H), 7.30 (dd, *J* = 13.1, 6.5 Hz, 1H), 7.12 (ddd, *J* = 8.5, 7.2, 1.5 Hz, 1H), 6.69 (dd, *J* = 8.2, 1.0 Hz, 1H), 6.51 – 6.44 (m, 1H), 6.22 (s, 2H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 166.8, 149.2, 131.5, 127.5, 116.2, 114.7, 113.2; FTIR (thin film) *inter alia* 3163, 2950, 2856, 1618, 1560, 1493, 1449, 1348, 1249, 1021, 741, 671; LRMS (ESI+) m/z 175.1 (M^+ +Na); HRMS (ESI+) m/z Calcd for $C_7H_8N_2O_2Na$ 175.0483 found 175.0473.

Nitroso-Diels-Alder reactions

General Procedure 1, GP1*: General procedure for the formation of acyl cycloadducts using sodium periodate oxidation of hydroxamic acids*

Hydroxamic acid dissolved in methanol (10 mL) was added dropwise to a solution of diene, and sodium periodate in methanol (20 mL) at room temperature. The reaction mixture was stirred for 4 h and was monitored by TLC. Then the solvent was removed under vacuum. The crude product was purified by silica gel chromatography (6:1 v/v, hexane/EtOAc).

General Procedure 2, GP2*: General procedure for the formation acyl cycloadducts using copper-oxazoline catalyzed oxidation of hydroxamic acids in methanol*

To a methanol (5 ml) solution of 2 equivalents of diene, 10 mol% $CuCl_2$ and 20 mol% 2-ethyl-2-oxazoline was added the hydroxamic acid**.** The resulting solution was stirred and monitored by TLC. The completion of the reaction was confirmed by the disappearance of the starting material. The solvent was removed by evaporation and the crude product was purified by silica gel chromatography (hexane:ethyl acetate, 6:1 v/v, as eluent).

General Procedure 3, GP3*: General procedure for the formation of acyl cycloadducts using copper-oxazoline catalyzed oxidation of hydroxamic acids in refluxing toluene*

To a toluene (5 ml) solution of 2 equivalents of diene, 10 mol% $CuCl_2$ and 20 mol% 2-ethyl-2-oxazoline was added the hydroxamic acid**.** The resulting solution was heated under reflux with stirring, and the reaction was monitored by TLC. The completion of the reaction was confirmed by the

disappearance of the starting material. The solvent was removed by evaporation and the crude product was purified by silica gel chromatography (hexane:ethyl acetate, 6:1 v/v, as eluent).

Reactions of hydroxamic acids with 1,3-cyclohexadiene

Entry 1, Table 1: *Phenyl-2-oxa-3-azabicyclo[2.2.2]oct-5-ene-3-carboxylate **14***

A) The reaction was performed according to **GP1**, using phenyl hydroxycarbamate **1** (128 mg, 0.83 mmol), 1,3-cyclohexadiene (134 mg, 1.68 mmol), and sodium periodate (179 mg, 0.83 mmol). The reaction mixture was stirred for 2 h. The product **14** was obtained as a white solid (99 mg, 51 %); m.p. 127–129 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.28 (m, 2H), 7.21 – 7.15 (m, 1H), 7.14 – 7.06 (m, 2H), 6.73 – 6.64 (m, 1H), 6.63 – 6.57 (m, 1H), 4.99 – 4.90 (m, 1H), 4.88 – 4.80 (m, 1H), 2.31 – 2.17 (m, 2H), 1.59 – 1.52 (m, 1H), 1.48 – 1.40 (m, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 155.9, 150.9, 132.0, 131.8, 129.3, 125.6, 121.5, 71.4, 50.3, 23.4, 20.7; FTIR (thin film) *inter alia* 1716 (C=O), 1389, 1196, 1067, 994, 750, 691 cm^{-1}; LRMS (ESI+) m/z 254.2 (M^+ + Na); HRMS (ESI+) m/z Calcd for $C_{13}H_{13}NO_3Na$ 254.0793 found 254.0800.

B) The reaction was performed according to **GP2** using phenyl hydroxycarbamate **1** (103 mg, 0.67 mmol), 1,3-cyclohexadiene (66 mg, 0.80 mmol), $CuCl_2$ (9 mg, 0.07 mmol) and 2-ethyl-2-oxazoline (13 mg, 0.13 mmol), the reaction was complete in 2 h giving **14** (152 mg, 98 %) as a white solid.

Entry 2, Table 1: *N-Phenyl-2-oxa-3-azabicyclo[2.2.2]oct-5-ene-3-carboxamide **15***

A) The reaction was performed according to **GP1**, using 1-hydroxy-3-phenylurea **2** (131 mg, 0.86 mmol), 1,3-cyclohexadiene (138 mg, 1.72 mmol), and sodium periodate (184 mg, 0.86 mmol). The reaction mixture was stirred for 2 h. The product **15** was obtained as a white solid (97 mg, 49%); m.p. 102 – 104 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (s, 1H), 7.44 (dd, J = 8.6, 1.0 Hz, 2H), 7.28 (dd, J = 10.9, 5.4 Hz, 2H), 7.10 – 7.01 (m, 1H), 6.62 – 6.56 (m, 1H), 6.55 – 6.47 (m, 1H), 5.06 – 4.98 (m, 1H), 4.83 – 4.75 (m, 1H), 2.25 – 2.13 (m, 2H), 1.61 – 1.53 (m, 1H), 1.43 – 1.36 (m, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 159.3, 137.7, 132.7, 130.4, 128.9, 123.5, 119.3, 71.2, 50.0, 23.9, 20.0; FTIR (thin film) *inter alia* 1667 (C=O), 1594, 1531, 1445, 1228, 907, 767, 701 cm^{-1}; LRMS (ESI+) m/z 253.2 (M^+ + Na); HRMS (ESI+) m/z Calcd for $C_{13}H_{14}N_2O_2Na$ 253.0953 found 253.0958.

B) The reaction was performed according to **GP2**, using 1-hydroxy-3-phenylurea **2** (105 mg, 0.69 mmol), 1,3-cyclohexadiene (68 mg, 0.83 mmol), $CuCl_2$ (9 mg, 0.07 mmol) and 2-ethyl-2-oxazoline (14 mg, 0.14 mmol), the reaction complete in 4 h giving **15** (156 mg, 98%) as a white solid.

Entry 3, Table 1: *N-[(R)-1-Phenylethyl]-2-oxa-3-azabicyclo[2.2.2]oct-5-ene-3-carboxamide **16***

A) The reaction was performed according to **GP1**, using (*R*)-1-hydroxy-3-(1-phenylethyl)urea **3** (125 mg, 0.70 mmol), 1,3-cyclohexadiene (112 mg, 1.39 mmol), and sodium periodate (149 mg, 0.70 mmol). The reaction mixture was stirred for 2 h. The product **16** was obtained as a white solid (76 mg, 42%); m.p. 92-94 °C; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.33 – 7.22 (m, 3H), 7.22 – 7.17 (m, 2H), 6.54 – 6.40 (m, 2H), 5.99 (dd, *J* = 22.7, 7.1 Hz, 1H), 4.96 – 4.84 (m, 2H), 4.64 (d, *J* = 2.1 Hz, 1H), 2.16 – 2.03 (m, 2H), 1.52 – 1.45 (m, 1H), 1.41 (dd, *J* = 12.6, 6.9 Hz, 3H), 1.34 – 1.28 (m, 1H); ^{13}C{^{1}H} NMR (176 MHz, $CDCl_3$) δ 161.5, 161.4, 143.7, 143.5, 132.2, 132.1, 130.2, 130.2, 128.5, 128.4, 127.1, 127.0, 126.0, 125.9, 70.5, 50.3, 50.1, 49.1, 49.1, 23.9, 23.9, 22.4, 22.3, 20.1, 20.0. FTIR (thin film) *inter alia* 1651, 1515, 1494, 1230, 906, 766, 699, 667 cm^{-1}; LRMS (ESI+) m/z 281.2 (M^+ + Na); HRMS (ESI+) m/z Calcd for $C_{15}H_{18}N_2O_2Na$ 281.1266 found 281.1268.

B) The reaction was performed according to **GP2**, using (*R*)-1-hydroxy-3-(1-phenylethyl)urea **3** (99 mg, 0.55 mmol), 1,3-cyclohexadiene (53 mg, 0.66 mmol), $CuCl_2$ (7 mg, 0.05 mmol) and 2-ethyl-2-oxazoline (11 mg, 0.11 mmol), the reaction was complete in 4 h giving **16** (141 mg, 97%) as a white solid.

Entry 4, Table 1: *2-Oxa-3-azabicyclo[2.2.2]oct-5-en-3-yl)-2-phenyl-ethanone **17***

A) The reaction was performed according to **GP1**, using *N*-hydroxy-2-phenylacetamide **4** (290 mg, 1.92 mmol), 1,3-cyclohexadiene (307 mg, 3.84 mmol), and sodium periodate (410 mg, 1.92 mmol). The reaction mixture was stirred for 4 h. The product **17** was obtained as an off-white solid (275 mg, 48 %); m.p. 74 -76 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.19 (m, 5H), 6.66 – 6.56 (m, 1H), 6.50 – 6.42 (m, 1H), 5.33 – 5.22 (m, 1H), 4.80 – 4.70 (m, 1H), 3.70 – 3.57 (m, 2H), 2.17 – 1.99 (m, 2H), 1.50 – 1.39 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 170.5, 134.8, 132.9, 131.3, 129.5, 128.2, 126.5, 71.9, 46.6, 40.1, 23.4, 21.0; FTIR (thin film) *inter alia* 1640 (C=O), 1412, 1086, 955, 900, 828, 734, 698 cm^{-1}; LRMS (ESI+) m/z 252.3 (M^+ + Na); HRMS (ESI+) m/z Calcd for $C_{14}H_{15}NO_2$ Na 252.1000 found 252.1010.

B) The reaction was performed according to **GP3**, using *N*-hydroxy-2-phenylacetamide **4** (208 mg, 1.38 mmol), 1,3-cyclohexadiene (220 mg, 2.75 mmol), $CuCl_2$ (19 mg, 0.14 mmol) and 2-ethyl-2-oxazoline (27 mg, 0.28 mmol), the reaction was heated at reflux and was complete in 10 h to yield the product as an off-white solid **16** (192 mg, 61 %).

Entry 5, Table 1: *2-Oxa-3-azabicyclo[2.2.2]oct-5-en-3-yl)-3-phenylpropan-1-one **18***

A) The reaction was performed according to **GP1**, using *N*-hydroxy-3-phenylpropanamide **5** (171 mg, 1.03 mmol), 1,3-cyclohexadiene (166 mg, 2.06 mmol), and sodium periodate (221 mg, 1.03 mmol). The reaction mixture was stirred for 4 h. The product **18** was obtained as colorless oil (123 mg, 49 %); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.26 (m, 2H), 7.24 – 7.18 (m, 3H), 6.69 – 6.59 (m, 1H), 6.53 – 6.48 (m, 1H), 5.30 (s, 1H), 4.74 (s, 1H), 2.91 (t, *J* = 8.0 Hz, 2H), 2.70 – 2.62 (m, 1H), 2.59 – 2.51 (m, 1H), 2.19 – 2.12 (m, 1H), 2.12 – 2.05 (m, 1H), 1.52 – 1.45 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 171.1, 140.4, 132.0, 130.3, 127.4, 127.3, 124.9, 70.8, 45.4, 33.9, 29.3, 22.5, 20.1; FTIR (thin film) *inter alia* 1644 (C=O), 1453, 1166, 954, 902, 748, 699 cm^{-1}; LRMS (ESI+) m/z 266.3 (M^+ + Na); HRMS (ESI+) m/z Calcd for $C_{15}H_{17}NO_2$ Na 266.1157 found 266.1169.

B) The reaction was performed according to **GP3**, using *N*-hydroxy-3-phenylpropanamide **5** (189 mg, 1.14 mmol), 1,3-cyclohexadiene (183 mg, 2.29 mmol), $CuCl_2$ (15 mg, 0.11 mmol) and 2-ethyl-2-oxazoline (23 mg, 0.23 mmol), the reaction was heated at reflux and was complete in 5 h. The product was obtained as colorless oil (181 mg, 65 %).

Entry 6, Table 1: *2-Oxa-3-azabicyclo[2.2.2]oct-5-en-3-yl)-4-phenylbutan-1-one **19***

A) The reaction was performed according to **GP1**, using *N*-hydroxy-4-phenylbutanamide **6** (153 mg, 0.85 mmol), 1,3-cyclohexadiene (137 mg, 1.70 mmol), and sodium periodate (183 mg, 0.85 mmol). The reaction mixture was stirred for 4 h. The product **19** was obtained as colorless oil (70 mg, 32 %); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 – 7.16 (m, 2H), 7.14 – 7.06 (m, 3H), 6.55 (t, *J* = 6.6 Hz, 1H), 6.42 (t, *J* = 6.6 Hz, 1H), 5.20 (s, 1H), 4.66 (s, 1H), 2.60 – 2.51 (m, 2H), 2.31 – 2.17 (m, 2H), 2.13 – 1.94 (m, 2H), 1.88 – 1.77 (m, 2H), 1.47 – 1.35 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 171.9, 141.0, 132.1, 130.2, 127.5, 127.3, 124.8, 70.8, 45.4, 34.4, 31.7, 24.8, 22.6, 20.1; FTIR (thin film) *inter alia* 1644 (C=O), 1453, 955, 902, 833, 746, 699 cm^{-1}; LRMS (ESI+) m/z 280.3 (M^+ + Na); HRMS (ESI+) m/z Calcd for $C_{16}H_{19}NO_2$ Na 280.1313 found 280.1314.

B) The reaction was performed according to **GP3**, using *N*-hydroxy-4-phenylbutanamide (200 mg, 1.12 mmol), 1,3-cyclohexadiene (179 mg, 2.23 mmol), $CuCl_2$ (15 mg, 0.11 mmol) and 2-ethyl-2-oxazoline (22 mg, 0.22 mmol), the reaction was heated at reflux and was complete in 3 h. The product was obtained as colorless oil (210 mg, 73 %)

Entry 7, Table 1: *2-Oxa-3-azabicyclo[2.2.2]oct-5-en-3-yl)-5-phenylpentan-1-one **20***

A) The reaction was performed according to **GP1**, using *N*-hydroxy-5-phenylpentanamide **7** (225 mg, 1.16 mmol), 1,3-cyclohexadiene (187 mg, 2.32 mmol), and sodium periodate (249 mg, 1.16 mmol). The reaction mixture was stirred for 4 h. The product **20** was obtained as colorless oil (120 mg, 38 %); ^{1}H

NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.26 (m, 2H), 7.21 – 7.17 (m, 3H), 6.63 (t, *J* = 6.7 Hz, 1H), 6.52 – 6.47 (m, 1H), 5.29 (s, 1H), 4.75 (s, 1H), 2.63 (t, *J* = 7.2 Hz, 2H), 2.39 – 2.27 (m, 2H), 2.23 – 2.16 (m, 1H), 2.12 – 2.07 (m, 1H), 1.68 – 1.60 (m, 4H), 1.53 – 1.47 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 173.2, 142.5, 133.1, 131.2, 128.4, 128.2, 125.6, 71.7, 46.4, 35.7, 33.0, 31.1, 23.9, 23.6, 21.1; FTIR (thin film) *inter alia* 1648 (C=O), 1452, 1166, 956, 901, 834, 746, 698 cm^{-1}; LRMS (ESI+) m/z 294.3 (M^+ + Na); HRMS (ESI+) m/z Calcd for $C_{17}H_{21}NO_2$ Na 294.1470 found 294.1468.

B) The reaction was performed according to **GP3**, using *N*-hydroxy-5-phenylpentanamide **7** (176 mg, 0.91 mmol), 1,3-cyclohexadiene (146 mg, 1.82 mmol), $CuCl_2$ (12 mg, 0.09 mmol) and 2-ethyl-2-oxazoline (18 mg, 0.18 mmol), the reaction was heated at reflux and was complete in 3 h. The product was obtained as colorless oil (193 mg, 78 %)

Entry 8, Table 1: *2-Oxa-3-azabicyclo[2.2.2]oct-5-en-3-yl(phenyl)methanone **21***

A) The reaction was performed according to **GP1**, using *N*-hydroxybenzamide **8** (594 mg, 4.33 mmol), 1,3-cyclohexadiene (694 mg, 8.66 mmol), and sodium periodate (927 mg, 4.33 mmol). The reaction mixture was stirred for 4 h. The product **21** was obtained as an off-white solid (317 mg, 53%); m.p. 111 – 114 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.64 (s, 2H), 7.46 – 7.33 (m, 3H), 6.66 (br, 1H), 6.54 (s, 1H), 5.38 (br, 1H), 4.79 (s, 1H), 2.36 – 2.18 (m, 2H), 1.58 – 1.45 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 168.9, 134.4, 132.8, 131.8, 130.7, 128.5, 128.0, 71.9, 47.4, 23.5, 21.2; FTIR (thin film) *inter alia* 1638 (C=O), 929, 881, 788, 726, 703 cm^{-1}; LRMS (ESI+) m/z 216.2 (M^+ + H); HRMS (ESI+) m/z Calcd for $C_{13}H_{14}NO_2$ 216.1025 found 216.1037.

B) The reaction was performed according to **GP3**, using *N*-hydroxybenzamide **8** (312 mg, 2.33 mmol), 1,3-cyclohexadiene (373 mg, 4.65 mmol), $CuCl_2$ (31 mg, 0.23 mmol) and 2-ethyl-2-oxazoline (46 mg, 0.47 mmol), the reaction was heated at reflux and was complete in 20 h giving the product (245 mg, 49%) as an off-white solid.

Entry 9, Table 1: *2-Oxa-3-azabicyclo[2.2.2]oct-5-en-3-yl(pyridin-2-yl)methanone **22***

The reaction was performed according to **GP1**, using 2-pyridinehydroxamic acid **9** (0.27 g, 2.0 mmol),1,3-cyclohexadiene (0.31 mg, 3.9 mmol), and sodium periodate (0.42 g, 2.0 mmol). The reaction mixture was stirred for 4 h to give a white solid product **22** (177 mg, 42%); m.p. 110 – 112 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.77 – 8.50 (m, 1H), 8.00 – 7.57 (m, 2H), 7.49 – 7.29 (m, 1H), 6.89 – 6.41 (m, 2H), 5.66 – 5.37 (m, 1H), 5.06 – 4.67 (s, 1H), 2.50 – 2.18 (m, 2H), 1.67 – 1.40 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 162.1, 152.4, 148.1, 137.1, 132.0, 131.1, 125.2, 124.8, 71.8, 51.6, 23.4,

22.0; FTIR (thin film) *inter alia* 2933, 1632 (C=O), 1566, 954, 748, 710, 668 cm^{-1}; LRMS (ESI+) m/z 239.5 (M^+ +Na); HRMS (ESI+) m/z Calcd for $C_{12}H_{12}N_2O_2Na$ 239.0796 found 239.0814.

Entry 10, Table 1: *2-Oxa-3-azabicyclo[2.2.2]oct-5-en-3-yl(pyridin-3-yl)methanone* ***23***

The reaction was performed according to **GP1**, using 3-pyridinehydroxamic acid **10** (143 mg, 1.03 mmol), 1,3-cyclohexadiene (166 mg, 2.06 mmol), and sodium periodate (221 mg, 1.03 mmol). The reaction mixture was stirred for 4 h. The product **23** was obtained as an off-white solid (69 mg, 31 %); m.p. 105 – 107 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (s, 1H), 8.64 (d, *J* = 3.4 Hz, 1H), 7.99 (s, 1H), 7.30 (dd, *J* = 14.7, 7.8 Hz, 1H), 6.73 (s, 1H), 6.54 (s, 1H), 5.43 (s, 1H), 4.78 (s, 1H), 2.37 – 2.17 (m, 2H), 1.56 (p, *J* = 11.2 Hz, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.1, 151.4, 150.1, 136.5, 133.3, 131.7, 129.9, 122.7, 72.3, 47.1, 23.5, 20.9; FTIR (thin film) *inter alia* 1639 (C=O), 1586, 1387, 924, 882, 824, 735, 699 cm^{-1}; LRMS (ESI+) m/z 217.1 (M^+ +H); HRMS (ESI+) m/z Calcd for $C_{12}H_{13}N_2O_2$ 217.0977 found 217.0993.

Reactions of hydroxamic acids with 2,3-dimethyl-1,3-butadiene

Entry 11, Table 1: *Phenyl-4,5-dimethyl-3,6-dihydro-2H-1,2-oxazine-2-carboxylate* ***24***

A) The reaction was performed according to **GP1**, using phenyl hydroxycarbamate **1** (133 mg, 0.87 mmol), 2,3-dimethyl-1,3-butadiene (143 mg, 1.74 mmol), and sodium periodate (186 mg, 0.87 mmol). The product **24** was obtained as colorless oil (95.4 mg, 47%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.34 (m, 2H), 7.24 – 7.19 (m, 1H), 7.19 – 7.13 (m, 2H), 4.34 (s, 2H), 4.09 (s, 2H), 1.73 – 1.69 (m, 3H), 1.66 – 1.59 (m, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 153.6, 150.9, 129.3, 125.6, 123.2, 121.8, 121.6, 72.0, 48.4, 15.2, 13.9; FTIR (thin film) *inter alia* 1720 (C=O), 1388, 1356, 1202, 1162, 1068, 755, 726, 688 cm^{-1}; LRMS (ESI+) m/z 256.2 (M^+ + Na); HRMS (ESI+) m/z Calcd for $C_{13}H_{15}NO_3Na$ 256.0950 found 256.0955.

B) The reaction was performed according to **GP2**, using phenyl hydroxycarbamate **1** (173 mg, 1.13 mmol), 2,3-dimethyl-1,3-butadiene (111 mg, 1.36 mmol), $CuCl_2$ (15 mg, 0.11 mmol) and 2-ethyl-2-oxazoline (22 mg, 0.22 mmol), the reaction was stirred for 3 h giving **24** and **34** (250 mg, 95%) as a colorless oil. The ratio of **24**:**34** is 6:1. The ene product **34** could not be separated in a pure enough state to characterize it fully.

Entry 12, Table 1: *4,5-Dimethyl-N-phenyl-3,6-dihydro-2H-1,2-oxazine-2-carboxamide* ***25***

A) The reaction was performed according to **GP1**, using 1-hydroxy-3-phenylurea **2** (138 mg, 0.91 mmol), 2,3-dimethyl-1,3-butadiene (149 mg, 1.81 mmol), and sodium periodate (194 mg, 0.91 mmol). The product **25** was obtained as a white solid (95 mg, 45%); m.p. 99-102 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (s, 1H), 7.46 (dd, *J* = 19.3, 8.2 Hz, 2H), 7.31 (t, *J* = 7.9 Hz, 2H), 7.06 (t, *J* = 7.4 Hz, 1H), 4.29 (t, *J* = 9.9 Hz, 2H), 3.97 (t, *J* = 10.1 Hz, 2H), 1.78 – 1.68 (m, 3H), 1.63 – 1.61 (m, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 155.5, 138.0, 129.0, 123.4, 122.6, 119.3, 119.3, 72.5, 47.7, 15.5, 13.7; FTIR (thin film) *inter alia* 1652 (C=O), 1594, 1527, 1446, 1435, 1221, 758, 731, 692 cm^{-1}; LRMS (ESI+) m/z 255.3 (M^+ + Na); HRMS (ESI+) m/z Calcd for $C_{13}H_{16}N_2O_2Na$ 255.1109 found 255.1121.

B) The reaction was performed according to **GP2**, using 1-hydroxy-3-phenylurea **2** (186 mg, 1.22 mmol), 2,3-dimethyl-1,3-butadiene (125 mg, 1.47 mmol), $CuCl_2$ (16 mg, 0.12 mmol) and 2-ethyl-2-oxazoline (24 mg, 0.24 mmol), the reaction was stirred for 6 h giving **25** and **35** (255 mg, 90 %) as a white solid. The ratio of **25**:**35** = 9:1. The ene product **35** could not be separated in a pure enough state to characterize it fully.

Entry 13, Table 1: *(R)-4,5-Dimethyl-N-(1-phenylethyl)-3,6-dihydro-2H-1,2-oxazine-2-carboxamide **26***

A) The reaction was performed according to **GP1**, using (*R*)-1-hydroxy-3-(1-phenylethyl)urea (98 mg, 0.54 mmol), 2,3-dimethyl-1,3-butadiene (89 mg, 1.09 mmol), and sodium periodate (116 mg, 0.54 mmol). The product **26** was obtained as a colourless oil (18 mg, 13 %); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.30 (m, 4H), 7.29 – 7.22 (m, 1H), 5.99 (d, *J* = 8.0 Hz, 1H), 5.07 – 4.98 (m, 1H), 4.25 – 4.15 (m, 2H), 3.87 (dt, *J* = 19.8, 9.9 Hz, 2H), 1.71 – 1.64 (m, 3H), 1.61 – 1.56 (m, 3H), 1.52 (d, *J* = 6.9 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 157.8, 143.9, 128.6, 128.6, 127.2, 126.1, 122.7, 122.6, 72.0, 49.2, 48.2, 22.5, 15.5, 13.7; FTIR (thin film) *inter alia* 3308 (NH), 1652 (C=O), 1510, 1209, 1026, 762, 699 cm^{-1}; LRMS (ESI+) m/z 261.1 (M^+ + H); HRMS (ESI+) m/z Calcd for $C_{15}H_{21}N_2O_2$ 261.1603 found 261.1619.

B) The reaction was performed according to **GP2**, using (*R*)-1-hydroxy-3-(1-phenylethyl)urea **3** (64 mg, 0.36 mmol), 2,3-dimethyl-1,3-butadiene (58 mg, 0.71 mmol), $CuCl_2$ (5 mg, 0.04 mmol) and 2-ethyl-2-oxazoline (7 mg, 0.07 mmol)**,** the resulting solution was stirred at room temperature in air. The reaction was complete in 6 h. The product **26** was obtained as a colorless oil (92 mg, 99%).

Entry 14, Table 1:*1-(4,5-Dimethyl-3,6-dihydro-2H-1,2-oxazin-2-yl)-2-phenylethanone **27***

The reaction was performed according to **GP1**, using *N*-hydroxy-2-phenylacetamide (164 mg, 1.09 mmol), 2,3-dimethyl-1,3-butadiene (179 mg, 2.18 mmol), and sodium periodate (233 mg, 1.09 mmol). The product **27** was obtained as colorless oil (105 mg, 42 %); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.26

(m, 4H), 7.26 – 7.21 (m, 1H), 4.03 (s, 4H), 3.79 (s, 2H), 1.66 (s, 3H), 1.59 – 1.51 (m, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 169.9, 135.1, 129.3, 128.5, 126.7, 122.5, 121.8, 73.0, 45.2, 39.7, 15.3, 13.7; FTIR (thin film) *inter alia* 1652 (C=O), 1434, 1223, 711, 694 cm^{-1}; LRMS (ESI+) m/z 254.3 (M^+ + Na); HRMS (ESI+) m/z Calcd for $C_{14}H_{17}NO_2$ Na 254.1157 found 254.1136.

Entry 15, Table 1:*1-(4,5-Dimethyl-3,6-dihydro-2H-1,2-oxazin-2-yl)-3-phenylpropan-1-one* ***28***

The reaction was performed according to **GP1**, using *N*-hydroxy-3-phenylpropanamide **5** (131 mg, 0.80 mmol), 2,3-dimethyl-1,3-butadiene (131 mg, 1.59 mmol), and sodium periodate (170 mg, 0.80 mmol). The product **28** was obtained as colorless oil (72 mg, 37%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.26 (m, 2H), 7.25 – 7.17 (m, 3H), 4.08 (s, 2H), 4.04 (s, 2H), 3.00 – 2.95 (m, 2H), 2.82 – 2.71 (m, 2H), 1.67 (s, 3H), 1.58 – 1.54 (m, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 170.3, 140.44, 127.5, 127.5, 125.1, 121.5, 121.0, 72.0, 44.0, 32.9, 29.8, 14.3, 12.8; FTIR (thin film) *inter alia* 1651 (C=O), 1440, 1212, 750, 699 cm^{-1}; LRMS (ESI+) m/z 268.3 (M^+ + Na); HRMS (ESI+) m/z Calcd for $C_{15}H_{19}NO_2$ Na 268.1313 found 268.1296.

Entry 16, Table 1: *1-(4,5-Dimethyl-3,6-dihydro-2H-1,2-oxazin-2-yl)-4-phenylbutan-1-one* ***29***

The reaction was performed according to **GP1**, using *N*-hydroxy-4-phenylbutanamide (137 mg, 0.77 mmol), 2,3-dimethyl-1,3-butadiene (126 mg, 1.54 mmol), and sodium periodate (164 mg, 0.77 mmol). The product **29** was obtained as colorless oil (80 mg, 40 %); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.26 (m, 2H), 7.23 – 7.16 (m, 3H), 4.16 (s, 2H), 4.02 (s, 2H), 2.72 – 2.66 (m, 2H), 2.47 (t, J = 7.5 Hz, 2H), 2.03 – 1.95 (m, 2H), 1.68 (d, J = 0.8 Hz, 3H), 1.59 (d, J = 0.9 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 171.9, 141.8, 128.5, 128.3, 125.8, 122.5, 122.1, 72.9, 45.0, 35.4, 31.4, 26.1, 15.3, 13.8; FTIR (thin film) *inter alia* 1654 (C=O), 1439, 1216, 749, 699 cm^{-1}; LRMS (ESI+) m/z 282.3 (M^+ + Na); HRMS (ESI+) m/z Calcd for $C_{16}H_{21}NO_2$ 282.1470 Na found 282.1472.

Entry 17, Table 1: *1-(4,5-Dimethyl-3,6-dihydro-2H-1,2-oxazin-2-yl)-5-phenylpentan-1-one* ***30***

The reaction was performed according to **GP1**, using *N*-hydroxy-5-phenylpentanamide (149 mg, 0.77 mmol), 2,3-dimethyl-1,3-butadiene (126 mg, 1.54 mmol), and sodium periodate (164 mg, 0.77 mmol). The product **30** was obtained as colorless oil (86 mg, 41 %); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.24 (m, 2H), 7.24 – 7.13 (m, 3H), 4.17 (s, 2H), 4.02 (s, 2H), 2.65 (t, J = 7.1 Hz, 2H), 2.46 (d, J = 6.4 Hz, 2H), 1.73 – 1.64 (m, 7H), 1.59 (d, J = 0.9 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 172.1, 142.4, 128.4,128.3, 125.7, 122.5,122.10, 72.9, 45.0, 35.7, 32.0, 31.2, 24.4, 15.3, 13.8; FTIR (thin film) *inter alia* 1655 (C=O), 1435, 1212, 748, 699 cm^{-1}; LRMS (ESI+) m/z 296.3 (M^+ + Na); HRMS (ESI+) m/z Calcd for $C_{17}H_{23}NO_2$ Na 296.1626 found 296.1629 .

Entry 18, Table 1: *(4,5-Dimethyl-3,6-dihydro-2H-1,2-oxazin-2-yl)(phenyl)methanone* ***31***

The reaction was performed according to **GP1**, using *N*-hydroxybenzamide **8** (152 mg, 1.14 mmol), 2,3-dimethyl-1,3-butadiene (186 mg, 2.28 mmol), and sodium periodate (243 mg, 1.14 mmol). The product **31** was obtained as a white solid (113 mg, 46 %); m.p. 62-64 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 – 7.65 (m, 2H), 7.49 – 7.44 (m, 1H), 7.43 – 7.38 (m, 2H), 4.18 (s, 2H), 4.14 (s, 2H), 1.71 (s, 3H), 1.59 (dd, *J* = 1.8, 0.9 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 169.5, 133.8, 130.8, 128.5, 127.9, 122.7, 121.9, 72.8, 46.6,15.4, 13.7; FTIR (thin film) *inter alia* 1640 (C=O), 1398, 1222, 1029, 796, 719, 696 cm^{-1}; LRMS (ESI+) m/z 240.2 (M^+ + Na); HRMS (ESI+) m/z Calcd for $C_{13}H_{15}NO_2$ Na 240.1000 found 240.0097.

Entry 19, Table 1: *(4,5-Dimethyl-3,6-dihydro-2H-1,2-oxazin-2-yl)(pyridin-2-yl)methanone* ***32***

The reaction was performed according to **GP1**, using 2-pyridinehydroxamic acid **9** (109 mg, 0.79 mmol), 2,3-dimethyl-1,3-butadiene (130 mg, 1.58 mmol), and sodium periodate (169 g, 0.79 mmol). The reaction mixture was stirred for 4 h. The product **32** was obtained as an off-white solid (36 mg, 21%); m.p. 85-87 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (d, *J* = 4.5 Hz, 1H), 7.78 (td, *J* = 7.8, 1.4 Hz, 1H), 7.61 (s, 1H), 7.38 – 7.33 (m, 1H), 4.24 (s, 4H), 1.70 (s, 3H), 1.60 (d, *J* = 0.8 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 153.0, 148.8, 136.5, 124.8, 123.1, 121.3, 73.2, 45.5, 15.3, 13.8; FTIR (thin film) *inter alia* 1638, 1447, 1415, 1228, 1191, 1024, 993, 806, 748, 690 cm^{-1}; LRMS (ESI+) m/z 219.3 (M^+ + H^+); HRMS (ESI+) m/z Calcd for $C_{12}H_{15}N_2O_2$ 219.1134 found 219.1150.

Entry 20, Table 1: *(4,5-Dimethyl-3,6-dihydro-2H-1,2-oxazin-2-yl)(pyridin-3-yl)methanone* ***33***

The reaction was performed according to **GP1**, using 3-pyridinehydroxamic acid **10** (152 mg, 1.10 mmol), 2,3-dimethyl-1,3-butadiene (181 mg, 2.20 mmol), and sodium periodate (235 g, 1.10 mmol). The reaction mixture was stirred for 2 h. The product **33** was obtained as an off-white solid (43 mg, 18%); m.p. 89-91 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.96 (d, *J* = 1.5 Hz, 1H), 8.68 (dd, *J* = 4.9, 1.7 Hz, 1H), 8.03 (dt, *J* = 7.9, 1.9 Hz, 1H), 7.36 (ddd, *J* = 7.9, 4.9, 0.9 Hz, 1H), 4.20 (s, 2H), 4.13 (s, 2H), 1.73 (d, *J* = 0.8 Hz, 3H), 1.59 (dd, *J* = 1.8, 0.9 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.9, 151.5, 149.6, 136.4, 129.5, 123.0, 122.5, 121.7, 73.0, 46.1, 15.4, 13.7; FTIR (thin film) *inter alia* 1640, 1415, 1230, 1021, 826, 729, 697 cm^{-1}; LRMS (ESI+) m/z 241.1 (M^+ + Na); HRMS (ESI+) m/z Calcd for $C_{12}H_{14}N_2O_2Na$ 241.0953 found 241.0964.

Reactions of 1 with other dienes

Entry 1, Table 2: *Phenyl 2-oxa-3-azabicyclo[2.2.1]hept-5-ene-3-carboxylate* ***36***

The reaction was performed according to **GP2**, using crude phenyl hydroxycarbamate **1** (162 mg, 1.06 mmol), freshly cracked cyclopentadiene (84 mg, 1.27 mmol), $CuCl_2$ (14 mg, 0.11 mmol) and 2-ethyl-2-oxazoline (21 mg, 0.21 mmol), the reaction was stirred for 2 h giving **36** (228 mg, 99%) as a white solid; m.p. 113–114 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.33 (m, 2H), 7.24 – 7.19 (m, 1H), 7.14 – 7.08 (m, 2H), 6.61 (dt, *J* = 5.5, 1.9 Hz, 1H), 6.52 – 6.47 (m, 1H), 5.35 (d, *J* = 1.4 Hz, 1H), 5.21 (s, 1H), 2.12 (dt, *J* = 8.8, 1.9 Hz, 1H), 1.86 (d, *J* = 8.8 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 156.4, 149.7, 133.6, 132.4, 128.4, 124.8, 120.4, 83.3, 64.4, 47.4; FTIR (thin film) *inter alia* 1749 (C=O), 1587, 1489, 1332, 1271, 1192, 1181, 770, 746, 691 cm^{-1}; LRMS (ESI+) m/z 240.2 (M^+ + Na); HRMS (ESI+) m/z Calcd for $C_{12}H_{11}NO_3Na$ 240.0637 found 240.0650.

Entry 2, Table 2: *(9S,10S)-Phenyl-9,10-dimethyl-9,10-dihydro-9,10-(epoxy-imino)-anthracene-11-carboxylate **37***

The reaction was performed according to **GP2**, using crude phenyl hydroxycarbamate **1** (39 mg, 0.25 mmol), 9,10-dimethylanthracene (47 mg, 0.23 mmol), $CuCl_2$ (3 mg, 0.03 mmol) and 2-ethyl-2-oxazoline (5 mg, 0.05 mmol), the reaction was stirred for 24 h giving **37** (70 mg, 80%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 – 7.52 (m, 2H), 7.49 – 7.45 (m, 2H), 7.38 – 7.32 (m, 4H), 7.29 – 7.25 (m, 2H), 7.17 – 7.14 (m, 1H), 6.78 – 6.69 (m, 2H), 2.67 (d, *J* = 13.8 Hz, 3H), 2.34 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 158.1, 150.8, 141.6, 140.4, 129.2, 127.4, 125.6, 121.6, 121.6, 120.8, 79.7, 64.5, 16.4, 15.0; FTIR (thin film) *inter alia* 1725 (C=O), 1274, 1229, 1194, 1016, 741, 688 cm^{-1}; LRMS (ESI+) m/z 380.2 (M^+ + Na); HRMS (ESI+) m/z $C_{23}H_{19}NO_3Na$ 380.1263 found 380.1257.

Entry 3, Table 2: *Phenyl-3,6-dimethyl-3,6-dihydro-2H-1,2-oxazine-2-carboxylate **38***

The reaction was performed according to **GP2**, using crude phenyl hydroxycarbamate **1** (131 mg, 0.86 mmol), 2,4-hexadiene (84 mg, 1.03 mmol), $CuCl_2$ (12 mg, 0.09 mmol) and 2-ethyl-2-oxazoline (17 mg, 0.17 mmol), the reaction was stirred for 3 h giving **38** (185 mg, 93%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.35 (m, 2H), 7.22 (dd, *J* = 10.6, 4.3 Hz, 1H), 7.18 – 7.14 (m, 2H), 5.84 (ddd, *J* = 10.2, 4.3, 2.1 Hz, 1H), 5.79 – 5.71 (m, 1H), 4.85 – 4.73 (m, 1H), 4.64 – 4.57 (m, 1H), 1.42 (d, *J* = 6.7 Hz, 3H), 1.33 (d, *J* = 6.7 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 152.8, 150.8, 129.2, 128.6, 127.5, 125.4, 121.5, 74.3, 50.2, 18.7, 18.1; FTIR (thin film) *inter alia* 1715 (C=O), 1366, 1189, 1037, 748, 725, 689 cm^{-1}; LRMS (ESI+) m/z 256.3 (M^+ + Na); HRMS (ESI+) m/z Calcd for $C_{13}H_{15}NO_3Na$ 256.0950 found 256.0926.

Entry 4, Table 2: *Phenyl-3,6-diphenyl-3,6-dihydro-2H-1,2-oxazine-2-carboxylate **39***

The reaction was performed according to **GP2**, using crude phenyl hydroxycarbamate **1** (92 mg, 0.60 mmol), 1,4-diphenyl-1,3-butadiene (111 mg, 0.54 mmol), $CuCl_2$ (8 mg, 0.06 mmol) and 2-ethyl-2-oxazoline (12 mg, 0.12 mmol), the reaction was stirred for 24 h giving **39** as a white solid (172 mg, 82%); m.p. 144 – 147 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 – 7.57 (m, 2H), 7.50 – 7.46 (m, 2H), 7.44 – 7.34 (m, 8H), 7.24 – 7.20 (m, 1H), 7.15 (d, *J* = 7.6 Hz, 2H), 6.25 – 6.15 (m, 2H), 5.81 – 5.73 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 188.5, 153.1, 150.9, 138.4, 136.8, 129.3, 129.2, 128.8, 128.7, 128.2, 128.1, 127.9, 125.9, 125.7, 121.7, 80.3, 77.2; FTIR (thin film) *inter alia* 1716 (C=O), 1360, 1272, 1194, 868, 747, 726, 689 cm^{-1}; LRMS (ESI+) m/z 380.2 (M^+ + Na); HRMS (ESI+) m/z Calcd for $C_{23}H_{19}NO_3Na$ 380.1263 found 380.1227.

Entry 5, Table 2: *Phenyl-6-(hydroxymethyl)-3-methyl-3,6-dihydro-2H-1,2-oxa-zine-2-carboxylate **40** and phenyl 3-(hydroxymethyl)-6-methyl-3,6-dihydro-2H-1,2-oxazine -2-carboxylate **41***

The reaction was performed according to **GP2**, using crude phenyl hydroxycarbamate **1** (140 mg, 0.91 mmol), 2,4-hexadiene-1-ol (90 mg, 0.91mmol), $CuCl_2$ (12 mg, 0.09 mmol) and 2-ethyl-2-oxazoline (18 mg, 0.18 mmol), the reaction was stirred for 3 h giving **40** and **41** (210 mg, 93 %) as a yellow oil. The ratio of **40**:**41** is 1:1;

40: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.34 (m, 2H), 7.28 – 7.21 (m, 1H), 7.21 – 7.11 (m, 2H), 6.06 – 6.02 (m, 1H) , 5.87 – 5.83 (m, 1H) , 4.63 – 4.56 (m, 1H), 4.55 – 4.45 (m, 2H), 4.11 (dd, *J* = 7.2, 2.3 Hz, 1H), 1.94 (s, 1H), 1.53 (d, *J* = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 153.1, 150.8, 131.26, 129.4, 125.7, 123.0, 121.6, 75.89, 65.6, 63.52, 50.5, 21.0

41: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.34 (m, 2H), 7.28 – 7.21 (m, 1H), 7.21 – 7.11 (m, 2H) , 6.02 – 5.97 (m, 1H), 5.79 (dt, *J* = 10.3, 1.5 Hz, 1H) , 4.86 – 4.80 (m, 1H) , 4.71 – 4.63 (m, 1H) , 3.86 (dd, *J* = 12.5, 3.0 Hz, 1H), 3.75 (dd, *J* = 12.4, 6.3 Hz, 1H), 2.45 (br, 1H), 1.45 (d, *J* = 6.7 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 153.1, 150.8, 130.1, 129.4, 125.7, 123.8, 121.6, 79.3, 63.6, 50.8, 18.3; FTIR (thin film) *inter alia* 1715 (C=O), 1369, 1312, 1188, 1164, 1065, 749, 689 cm^{-1}; LRMS (ESI+) m/z 272.3 (M^+ + Na); HRMS (ESI+) m/z Calcd for $C_{13}H_{15}NO_4Na$ 272.0899 found 272.0907.

Entry 6, Table 2: *Phenyl-4-methyl-3,6-dihydro-2H-1,2-oxazine-2-carboxylate **42** and phenyl-5-methyl-3,6-dihydro-2H-1,2-oxazine-2-carboxylate **43***

The reaction was performed according to **GP2**, using crude phenyl hydroxycarbamate **1** (142 mg, 0.93 mmol), isoprene (70 mg, 1.11 mmol), $CuCl_2$ (12 mg, 0.09 mmol) and 2-ethyl-2-oxazoline (18 mg, 0.18 mmol), the reaction was stirred for 3.5 h giving **42, 43** and **44** (183 mg, 90 %) as a colorless oil. The ratio of **42** and **43**:**44** is 3:1 and the ratio of **42**:**43** is 1.79:1;

42: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.35 (m, 2H), 7.25 – 7.20 (m, 1H), 7.19 – 7.14 (m, 2H), 5.64 – 5.60 (m, 1H), 4.54 – 4.47 (m, 2H), 4.18 – 4.09 (m, 2H), 1.81 – 1.75 (m, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 150.8, 129.4, 125.7, 121.6, 121.6, 118.0, 116.2, 68.9, 48.5, 19.9.
43: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.34 (m, 2H), 7.25 – 7.19 (m, 1H), 7.19 – 7.13 (m, 2H), 5.60 – 5.57 (m, 1H), 4.42 – 4.37 (m, 2H), 4.26 – 4.20 (m, 2H), 1.74 – 1.70 (m, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 153.6, 131.6, 130.1, 125.7, 121.6, 118.0, 115.3, 72.0, 44.8, 18.3; FTIR (thin film) *inter alia* 1717 (C=O), 1383, 1200, 1163, 1070, 752, 688 cm^{-1}; LRMS (ESI+) m/z 242.2 (M^+ + Na); HRMS (ESI+) m/z Calcd for $C_{12}H_{13}NO_3Na$ 242.0793 found 242.0771.

Reactions of 2 with other dienes

Entry 7, Table 2: *N-Phenyl-2-oxa-3-azabicyclo[2.2.1]hept-5-ene-3-carboxamide **45***

The reaction was performed according to **GP2**, using 1-hydroxy-3-phenylurea **2** (182 mg, 1.20 mmol), freshly cracked cyclopentadiene (95 mg, 1.44 mmol), $CuCl_2$ (16 mg, 0.12 mmol) and 2-ethyl-2-oxazoline (24 mg, 0.24 mmol), the reaction was stirred for 4 h giving **45** (249 mg, 96 %) as a white solid; m.p. 108-112 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (t, *J* = 16.2 Hz, 1H), 7.42 (dt, *J* = 8.7, 1.7 Hz, 2H), 7.31 – 7.26 (m, 2H), 7.08 – 7.03 (m, 1H), 6.52 (dt, *J* = 5.5, 1.9 Hz, 1H), 6.39 (ddd, *J* = 5.6, 2.3, 1.6 Hz, 1H), 2.08 (dt, *J* = 8.8, 1.9 Hz, 1H), 1.83 (d, *J* = 8.8 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 159.7, 137.4, 135.6, 132.0, 129.0, 123.8, 119.3, 84.4, 65.2, 48.7. FTIR (thin film) *inter alia* 1660 (C=O), 1596, 1522, 1448, 1338, 753, 690 cm^{-1}; LRMS (ESI+) m/z 270.2 (M^+ + Na); HRMS (ESI+) m/z Calcd for $C_{12}H_{12}N_2O_2Na$ 239.0796 found 239.0782.

Entry 8, Table 2: (*9S,10S)-Phenyl-9,10-dimethyl-9,10-dihydro-9,10-(epoxy-imino)-anthracene-11-carboxamide **46***

The reaction was performed according to **GP2**, using 1-hydroxy-3-phenylurea **2** (37 mg, 0.24 mmol), 9,10-dimethylanthracene (45 mg, 0.22 mmol), $CuCl_2$ (3 mg, 0.02 mmol) and 2-ethyl-2-oxazoline (5 mg, 0.05 mmol), the reaction was stirred for 48 h giving **46** (9 mg, 10%) which decomposes to 9,10-dimethylanthracene and the nitroso species in solution at room temperature.

Entry 9, Table 2: *3,6-Dimethyl-N-phenyl-3,6-dihydro-2H-1,2-oxazine-2-carboxamide **47***

The reaction was performed according to **GP2**, using 1-hydroxy-3-phenylurea **2** (120 mg, 0.79 mmol), 2,4-hexadiene (78 mg, 0.95 mmol), $CuCl_2$ (11 mg, 0.08 mmol) and 2-ethyl-2-oxazoline (16 mg, 0.16 mmol). The reaction was stirred for 4 h giving **47** (177 mg, 97%) as colorless oil; ^{1}H NMR (400 MHz,

$CDCl_3$) δ 7.60 (s, 1H), 7.49 (d, *J* = 8.6, 2H), 7.34 – 7.27 (m, 3H), 7.09 – 7.02 (m, 2H), 5.91 – 5.85 (m, 1H), 5.75 – 5.67 (m, 1H), 4.74 – 4.59 (m, 2H), 1.34 (d, *J* = 6.7 Hz, 3H), 1.30 (d, *J* = 6.7 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 154.4, 138.1, 128.9, 128.6, 128.1, 123.2, 119.3, 75.2, 49.0, 19.0, 16.9; FTIR (thin film) *inter alia* 1669 (C=O), 1649, 1594, 1522, 1444, 1231, 751, 727, 692 cm^{-1}; LRMS (ESI+) m/z 233.2 (M^+ + H); HRMS (ESI+) m/z Calcd for $C_{13}H_{17}N_2O_2$ 233.1290 found 233.1315.

Entry 10, Table 2: *N-3,6-Triphenyl-3,6-dihydro-2H-1,2-oxazine-2-carboxamide **48***

The reaction was performed according to **GP2**, using 1-hydroxy-3-phenylurea **2** (79 mg, 0.52 mmol), 1,4-diphenyl-1,3-butadiene (96 mg, 0.47 mmol), $CuCl_2$ (7 mg, 0.05 mmol) and 2-ethyl-2-oxazoline (10 mg, 0.10 mmol), the reaction was stirred for 48 h **48** (50 mg, 30 %) as colorless oil which slowly decomposed to 1,4-diphenyl-1,3-butadiene and presumably nitroso species during purification; ^1H NMR (400 MHz, $CDCl_3$) δ 7.64 – 7.58 (m, 3H), 7.55 – 7.49 (m, 4H), 7.34 – 7.31 (m, 4H), 7.14 – 7.02 (m, 4H), 6.72 (s, 1H), 6.29 – 6.18 (m, 1H), 6.15 – 6.08 (m, 1H), 5.92 – 5.83 (m, 1H), 5.74 – 5.67 (m, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 153.8, 138.5, 137.9, 136.9, 129.5, 129.0, 128.9, 128.5, 128.3, 128.1, 128.0, 127.5, 126.9, 123.4, 119.4, 81.3, 55.7; FTIR (thin film) *inter alia* 1710 (C=O), 1599, 1526, 1500, 1446, 1314,1225, 1068, 752, 723, 691 cm^{-1}; LRMS (ESI+) m/z 379.3 (M^+ + Na); HRMS (ESI+) m/z Calcd for $C_{23}H_{20}N_2O_2Na$ 379.1422 found 379.1428.

Entry 11, Table 2: *6-(Hydroxymethyl)-3-methyl-N-phenyl-3,6-dihydro-2H-1,2-oxazine-2-carboxamide **49** and 3-(hydroxymethyl)-6-methyl-N-phenyl-3,6-dihydro-2H-1,2-oxazine-2-carboxamide **50***

The reaction was performed according to **GP2**, using 1-hydroxy-3-phenylurea **2** (70 mg, 0.46 mmol), 2,4-hexadien-1-ol (45 mg, 0.46 mmol), $CuCl_2$ (7 mg, 0.05 mmol) and 2-ethyl-2-oxazoline (9 mg, 0.09 mmol). The reaction was stirred for 3 h giving **49** and **50** (103 mg, 90%) as colorless oil. The ratio of **49**:**50** is 1.5:1;

49: ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.52 – 7.43 (m, 2H), 7.36 – 7.29 (m, 2H), 7.13 – 7.03 (m, 1H), 6.02 (ddd, *J* = 10.2, 4.6, 2.3 Hz, 1H), 5.66 (dt, *J* = 10.2, 1.5 Hz, 1H), 4.70 (ddd, *J* = 11.0, 5.5, 3.4 Hz, 2H), , 3.89 – 3.82 (m, 2H), 2.42 (br, 1H), , 1.26 (d, *J* = 6.6 Hz, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 154.6, 137.6, 130.4 (ene), 129.0, 123.7, 123.2(ene), 119.7, 74.5, 63.8, 54.6, 18.9;

50: ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 (s, 1H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.28 (t, *J* = 7.7 Hz, 2H), 7.05 (t, *J* = 7.4 Hz, 1H), 5.85 (d, *J* = 10.6 Hz, 1H), 5.80 (d, *J* = 10.3 Hz, 1H), 4.78 (s, 1H), 4.67 (dd, *J* = 12.6, 6.2 Hz, 1H), 3.84 (s, 1H), 3.76 (s, 1H), 3.18 (s, 1H), 1.31 (d, *J* = 6.7 Hz, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 155.1, 138.0, 131.3 (ene), 128.9, 123.4, 122.9 (ene), 119.6, 80.0, 63.7, 49.3, 17.0; FTIR (thin

film) *inter alia* 1707 (C=O), 1600, 1534, 1501, 1446, 1314, 1224, 1067, 753, 724, 691 cm^{-1}; LRMS (ESI+) m/z 271.2 (M^+ + Na); HRMS (ESI+) m/z Calcd for $C_{13}H_{16}N_2O_3Na$ 271.1083 found 271.1069.

Entry 12, Table 2: *4-Methyl-N-phenyl-3,6-dihydro-2H-1,2-oxazine-2-carboxamide **51** and 5-methyl-N-phenyl-3,6-dihydro-2H-1,2-oxazine-2-carboxamide **52***

The reaction was performed according to **GP2**, using 1-hydroxy-3-phenylurea **2** (140 mg, 0.92 mmol), isoprene (75 mg, 1.10 mmol), $CuCl_2$ (12 mg, 0.092 mmol) and 2-ethyl-2-oxazoline (18 mg, 0.18 mmol), the reaction was stirred for 6 h giving **51, 52** and **53** (191 mg, 95%) as a white solid. After purification by silica gel chromatography, the cycloadducts were separated from the ene-product. However, the separation of the two cycloadducts was not possible due to their similar R_f values. The ene product **53** could not be separated in a pure enough state to characterize it fully. The ratio of **51**:**52** is 4.45:1 and the ratio of **51** and **52**:**53** is 9:1; m.p. 69 – 72 °C;

51: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (s, 1H), 7.48 (dt, *J* = 8.8, 1.7 Hz, 2H), 7.31 (tq, *J* = 5.8, 1.9 Hz, 2H), 7.11 – 7.02 (m, 1H), 5.55 (ddt, *J* = 4.5, 3.0, 1.6 Hz, 1H), 4.47 (dp, *J* = 4.3, 2.1 Hz, 2H), 4.02 (d, *J* = 0.8 Hz, 2H), 1.82 – 1.77 (m, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 155.5, 138.0, 131.0, 129.0, 123.4, 119.3, 117.5, 69.4, 47.8, 19.9.

52: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (s, 1H), 7.48 (dt, *J* = 8.8, 1.7 Hz, 2H), 7.31 (tq, *J* = 5.8, 1.9 Hz, 2H), 7.10 – 7.03 (m, 1H), 5.61 (dd, *J* = 3.3, 1.7 Hz, 1H), 4.36 (d, *J* = 0.7 Hz, 2H), 4.10 (dd, *J* = 3.4, 2.1 Hz, 2H), 1.71 (d, *J* = 1.5 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 155.6, 137.9, 131.1, 129.0, 123.4, 119.3, 117.0, 72.5, 44.0, 18.2; FTIR (thin film) *inter alia* 1644 (C=O), 1593, 1514, 1447, 1215, 751, 725, 689 cm^{-1}; LRMS (ESI+) m/z 241.3 (M^+ + Na); HRMS (ESI+) m/z Calcd for $C_{12}H_{14}N_2O_2Na$ 241.0953 found 241.0940.

X-Ray Crystallography

X-ray diffraction experiments were carried out on a Bruker 3-circle diffractometer with a SMART 6000 CCD area detector, using graphite-monochromated Mo-K_α radiation ($\bar{\lambda}$ =0.71073 Å) and a Cryostream (Oxford Cryosystems) open-flow N_2 cryostat. The structures (see Figs. S46, S47 and S48) were solved by direct methods and refined by full-matrix least squares, using OLEX2[43] and SHELXL[44] (multiple-CPU version 2013/2) software. Compound **9** was studied as a monohydrate; the crystal was a 2-component [0.596(2):0.404(2)] non-merohedral twin; the data were deconvoluted using the TWINABS program.[45] In molecule **17**, the bicyclic system is disordered (in a 55:45 ratio) between two orientations differing by a ca 20° rotation around the C(2)…C(5) axis. Molecule **14** lies astride a crystallographic

mirror plane which passes through C(1), C(2), C(5), O(1), O(2), C(8) and C(11), thus the bicyclic system is disordered equally between two orientations related via this plane. The asymmetric units of **2**, **3** and **16** each comprise two independent molecules, with similar conformations in **2** and substantially different ones in **3** and **16**. The absolute configurations of **3** and **16** could not be determined by X-ray methods (due to the small anomalous scattering) and were assigned according to the chirality of the parent compounds. Selected crystal data are listed in Table S1, full structural information has been deposited at Cambridge Structural Database, CCDC 984694 to 984704.

Computations

All computations were carried out with the Gaussian 09 package.[46] The geometries in this study were optimized at the B3LYP/6-31G* level[47] with no symmetry constraints and also at the B3LYP/6-311++G** level for **14**, **15** and **21**. Diradicals were examined at the unrestricted B3LYP/6-31G* level using the GUESS=(MIX,ALWAYS) command. Unless otherwise indicated, the energies quoted are electronic energies without zero point and thermal energy modifications. The optimized geometries were found to be true minima based on no imaginary frequencies obtained from frequency calculations. The transition-state (TS) geometries were located using the OPT=QST3 keyword method. Frequency calculations on TS geometries revealed each TS geometry to contain one imaginary frequency. All intrinstic reaction pathways shown in Figures 4, 6, 7 and 8 were determined from transition state geometries using the IRC command. Animations (http://community.dur.ac.uk/m.a.fox/Chaiyaveij.ppt) of reaction pathways were generated from the GaussView 4.1 software[48] and modified with the EasyGIF program.[49] Calculated ^{11}B and ^{13}C NMR chemical shifts obtained at the GIAO[50]-B3LYP/6-31G*//B3LYP/6-31G* level on the optimized geometries were referenced to TMS for ^{1}H: δ (^{1}H) = 1.02[32.5 - σ(^{1}H)] and for ^{13}C: δ (^{13}C) = 1.08[184.5 - σ(^{13}C)].

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Supporting Information

Copies of ^{1}H NMR and ^{13}C NMR spectra, X-ray crystallographic data and computational calculations are reported. This material is available free of charge via the Internet at http://pubs.acs.org/.

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