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Addition of HO-acids to *N,N*-Bis(oxy)enamines: Mechanism, Scope and Application to the Synthesis of Pharmaceuticals

Yana A. Naumovich, Ivan S. Golovanov, Alexey Yu. Sukhorukov,* Sema L. Ioffe

Dedicated to Professor Vladimir Tartakovsky on the occasion of his 85th birthday

Abstract: The regioselectivity of the addition of HO-acids to the activated π-bond in *N,N*-bis(oxy)enamines was found to be dramatically dependent on the solvent. Mechanism investigations and quantum-chemical calculations revealed that solvent affects the reaction pathway. In basic solvents (DMF, NMP, DMSO), *N,N*-bis(oxy)enamines are converted into nitrosoalkenes through a Lewis base promoted process followed by the oxy-Michael addition of HO-acid. In non-polar solvents (toluene, CH_2Cl_2), reaction follows an acid-promoted S_N' substitution of *N*-oxy-group *via* highly reactive *N*-vinyl-*N*-alkoxynitrenium species. Based on these studies, general and efficient protocols for oximinoalkylation of various HO-acids (carboxylic acids, phenols, hydroxamic, phosphoric and sulfonic acids) employing readily available *N,N*-bis(oxy)enamines were developed. These methods proved to be applicable for post-modification of natural molecules bearing acidic OH-groups (such as steroidal hormones, bile acids, protected amino acids and peptides) and ligands (BINOL). The resulting α-oxyoximes were demonstrated to be useful precursors of valuable 1,2-amino alcohol or 1,2-hydroxylamino alcohol derivatives, including the antiarrhythmic drug Mexiletine and a potent MMP inhibitor.

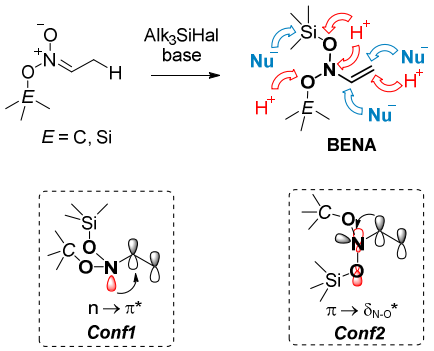
Introduction

Additions of protic acids across the unsaturated C,C-bonds are among the most valuable and atom-economical reactions used for the construction of carbon-heteroatom bonds.[1] Under catalyst-free conditions, non-activated alkenes react efficiently only with strong Brønsted acids, yet the presence of functional groups conjugated with a π-bond results in enhancement of its reactivity.[2] Functional groups may not only affect the regioselectivity of addition, but also change mechanism (for example, switching from electrophilic to nucleophilic[3]) or even directly participate in chemical transformations induced by protonation or specific acid catalysis.[4] In this connection, studies of Ad-type reactions of protic acids to alkenes bearing reactive functionalities (acetals, epoxides, aziridines, etc.) represent fundamental interest and may lead to elaboration of new methods for the synthesis of valuable polyfunctionalized products and building blocks.[4a, b]

Here, we wish to report a comprehensive study (optimization, mechanism, scope and application) on the hitherto unknown addition of HO-acids to a π-system activated with a nitrosoacetal group. These fundamental studies led to the development of efficient and general protocols for oximinoalkylation various HO-acids (carboxylic acids, phenols, phosphoric and sulfonic acids, etc.). α-Oxyoximes prepared in this way were shown to be convenient precursors of various bioactive vicinal amino alcohol and *N*-hydroxylamino alcohol derivatives, which are of high demand by medicinal chemistry.

Results and Discussion

In our studies, *N,N*-bis(oxy)enamines **BENA**, which are readily accessible by silylation of nitronates or nitroalkanes,[5] were used as model substrates (Scheme 1).[6] **BENA** possess multiple reaction sites, which can be involved in reactions with protic acids. In particular, protonation of C,C-double bond, nitrogen atom as well as oxygen atoms can be expected. Subsequent addition of O-nucleophile to the resulting cations would lead to different products. More importantly, the reactivity of **BENA** may depend on the conformation. In the conformation **Conf1**, β-carbon atom of double C,C-bond is nucleophilic (basic) due to n→π* conjugation, while in **Conf2** same carbon atom is electrophilic because of π→$\delta_{N\text{-}O}$* donation.[7]



Scheme 1. Synthesis and multiple reactivity of *N*-silyloxyenamines **1**.

Model experiments

In our model experiment, we reacted *N,N*-bis(oxy)enamine **1a**, possessing two distinct *N*-oxy-groups (OTMS and OAlk), with acetic acid in different solvents (Table 1). In most experiments, full consumption of starting material was observed within 2 h. Remarkably, two products of the acetate addition were identified, namely the open-chain oxime **2a** and the cyclic oxime ether **3a**, which result from the cleavage of *endo*- and

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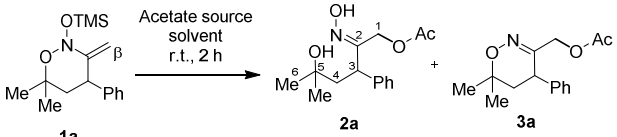
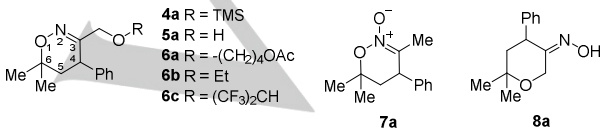
exo-cyclic N–O bonds, respectively. TMS-ether **4a**[6c] (isomeric to initial enamine **1a**[8]), as well as some other by-products resulting from solvent specific reactions, were also identified in reaction mixtures (for their structures see footnote to Table 1).

Table 1. Addition of acetic acid to cyclic *N*-alkoxy,*N*-silyloxyenamine **1a**.



Entry	Solvent	AcO^- source (1 equiv), additive	Conversion, %[a]	Yields of products, %[a]		
				2a	3a	4a
1	CH_2Cl_2	AcOH	100	-	69	24
2	CCl_4	AcOH	83	-	46	27
3	hexane	AcOH	100	-	68	23
4	**toluene**	**AcOH**	**100**	**-**	**74**	**25**
5	THF	AcOH	100	-	61	19[b]
6	EtOAc	AcOH	82	-	45	19
7	acetone	AcOH	75	4	31	13
8	CH_3CN	AcOH	100	16	41	0[c]
9	NMP	AcOH	100	53	23	5
10	DMSO	AcOH	93	69	11	3
11	**DMF**	**AcOH**	**100**	**82**	**-**	**-**
12	$BMIMBF_4$	AcOH	100	-	54	40
13	EtOH	AcOH	100	-	50	32[d]
14	AcOH	AcOH	100	-	63	31
15	HFIP	AcOH	100	-	10	41[e]
16	DMF	AcONa	100	-	-	-[f]
17	CH_2Cl_2	AcOH + Et_3N (1 equiv)	100	75	<5	-
18	CH_2Cl_2	AcOH + Et_3N (0.1 equiv)	100	<5	56	28

[a] Yields and conversion were determined by ^1H NMR with an internal standard. [b] Also 6% of ether **6a** was detected. [c] 33% of alcohol **5a**[8b] was also detected. [d] 11% of ether **6b**[5d] was also detected. [e] 23% of ether **6c** and 25% of nitronate **7a** were also detected. [f] Only formation of pyranone oxime **8a**[9] was observed (yield: 86%). Structures of other products:



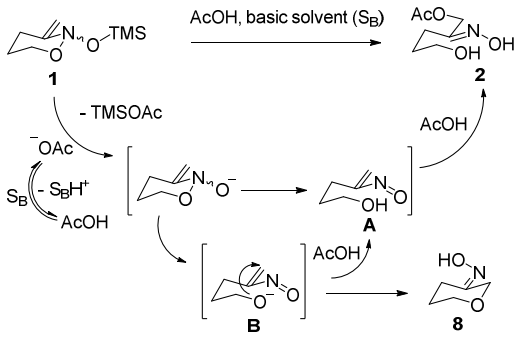
Strikingly, the selectivity proved to be highly dependent on the solvent used. In non-polar and low-polar solvents (Table 1, entries 1-6) the cyclic acetate **3a** was found to be predominant (accompanied by some amount of TMS-ether **4a**). In dipolar aprotic solvents, mixtures of acetates **2a** and **3a** were formed with the later being the major product in acetonitrile and acetone (Table 1, entries 7, 8). Acyclic derivative **2a** dominated over **3a** in NMP and DMSO (Table 1, entries 9, 10). In DMF, exclusive formation of acyclic oxime **2a** was observed (Table 1, entry 11).

The use of ionic liquid $BMIMBF_4$ led a similar result as with non-polar solvents, yet somewhat increase of the amount of by-product **4a** was observed (Table 1, entry 12). No ring-opening product **2a** was detected when reactions were carried out in protic solvents (Table 1, entries 13-15). In ethanol and HFIP (hexafluoroisopropanol), also products of alcohol addition (**6b** and **6c**, see footnote to Table 1) were identified both retaining cyclic structures. Surprisingly, HFIP was the only solvent, in which nitronate **7a** was detected among the products (Table 1, entry 15).

No products of acetate addition were observed in the experiment employing sodium acetate instead of acetic acid (Table 1, entry 16). Here, pyranone oxime derivative **8a** was exclusively formed. The use of AcOH/Et_3N (1 : 1) mixture gave acyclic oxime **2a**, while the use of catalytic amount of Et_3N resulted in the cyclic acetate **3a** (Table 1, entries 17, 18).

Mechanism studies

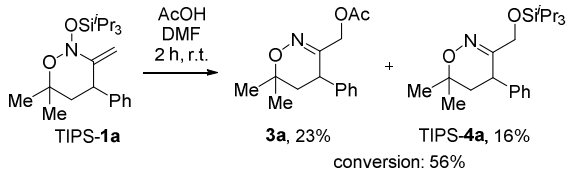
As can be seen from data in Table 1, a complete switch of chemoselectivity of AcOH addition can be achieved, most easily, by changing solvent (for example, from toluene to DMF). To rationalize the observed solvent effects, mechanism studies were performed. Apparently, the formation of open-chain and cyclic products **2a** and **3a** cannot occur through a same route. Open-chain oxime **2a** is likely to arise from a Michael-type addition of acetic acid to a nitrosoalkene intermediate **A**, while the 1,2-oxazine product **3a** cannot form *via* this intermediate (Scheme 2).



Scheme 2. Plausible mechanism of the formation of oximes **2** and **8**.

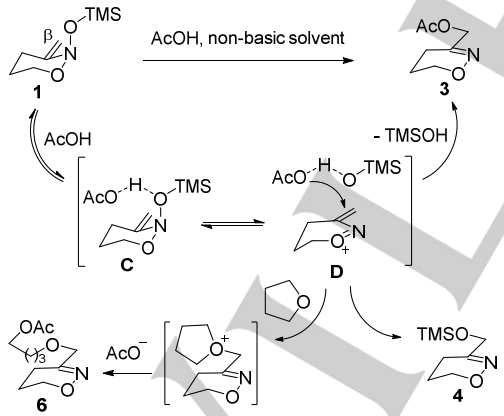
The generation of nitrosoalkene **A** requires the initial nucleophilic attack on the silicon atom that initiates ring-opening/Michael addition cascade through the cleavage of

nitrosoacetal unit (Scheme 2). This is confirmed by the experiment with *N*,*N*-bis(oxy)enamine bearing a sterically hindered TIPS-group (TIPS-**1a**) instead of TMS (Scheme 3). Here, no ring-opening occurred in DMF indicating that nitrosoalkene **A** is not generated (only cyclic products **3a** and TIPS-**4a** were detected).



Scheme 3. Interaction of sterically hindered enamine TIPS-**1a** with AcOH in DMF.

The initial nucleophile attacking silicon atom may be solvent itself or the acetate anion, which is formed in result of dissociation of acetic acid. The latter seems to be more likely, since no conversion of bis(oxy)enamine **1a** was observed upon exposition in DMF solution for 2 h at rt. The participation of the acetate anion as a Lewis base catalyst is also confirmed by the formation of oxime **2a** in reaction with AcOH/Et_3N (1 : 1) mixture in CH_2Cl_2 (Table 1, entry 17). However, with sodium acetate, only cyclic pyranone oxime **8a** is formed, evidently, in result of Michael-type cyclization of the transient anion **B** (Scheme 2).[9] Therefore, a basic solvent (such as DMF[10]) serves both as a co-catalyst generating acetate anions and creates a buffer, which protonates intermediate **B** preventing its cyclization.



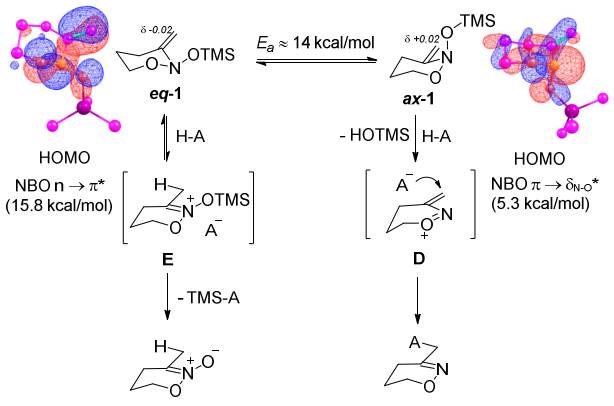
Scheme 4. Plausible mechanism of the formation of 1,2-oxazines **3**, **4** and **6**.

In non-polar solvent, dissociation of acetic acid does not take place, and, therefore, it is logical to assume that bis(oxy)enamine **1a** reversibly forms a hydrogen-bonded complex with acetic acid. The cyclic structure of products **3a** and **4a** suggests that oxygen atom of *exo*-cyclic N–O bond is involved in the interaction with acetic acid forming hydrogen-bounded complex **C** (Scheme 4). The latter can directly enter S_N' substitution of HOTMS to give product **3a**. Alternatively intermediate **C** can dissociate to form *N*-vinyl-*N*-alkoxynitrenium cation **D**, which directly reacts with the acetate-anion to give **3a** through Michael addition on the β-C-atom.

To gain further insights into the mechanism of the formation of cyclic ethers **3** quantum-chemical calculations were performed at DFT-D3 rm062x/cc-pvtz level of theory (in CH_2Cl_2, SMD model, unsubstituted enamine **1** and formic acid were used as models, Figure 1). Calculations support the formation of hydrogen-bonded complexes **C** (conformers **C1** and **C2**). Two early transition states (**TS1** and **TS2**) leading directly from complexes **C1** and **C2** to product **3** were located. Both of these transition states have a pronounced cationic character as confirmed by their half-chair geometries and high calculated charges on β-carbon atoms (CM5 model[11]). Computations also predict an almost barrierless attack of carboxylate on the β-carbon atom (**TS4**) proceeding *via* initial dissociation of complex **C1** to the ion pair **D** (through **TS3** having slightly lower energy than **TS1** and **TS2**). Attack of carboxylate on the nitrogen atom of cation **D** followed by a [3,3]-sigmatropic rearrangement of the resulting N-acyloxy-enamine[12] was predicted to have a considerably higher activation barrier.

Although the calculated activation barriers for **TS1**-**TS3** appear to be somewhat overestimated (conversion **1**→**3** is fast at rt), the experimentally observed formation of solvent (THF) insertion product **6a** (Table 1, entry 5 and Scheme 4) supports the participation of cationic species in this process.[13],[14] It is noteworthy, that we were not able to locate any transition states involving two molecules of acid.

Another important experimental observation is the formation of nitronate **7a** (together with acetate **3a**) in the reaction carried out in HFIP (Table 1, entry 15). Apparently, nitronate **7a** arises from the Markovnikov protonation of C,C-double bond in enamine **1a** with a subsequent elimination of TMS-group from the resulting cation **E** (Scheme 5).



Scheme 5. Competitive A_dE and S_N' processes for bis(oxy)enamine **1** in HFIP.

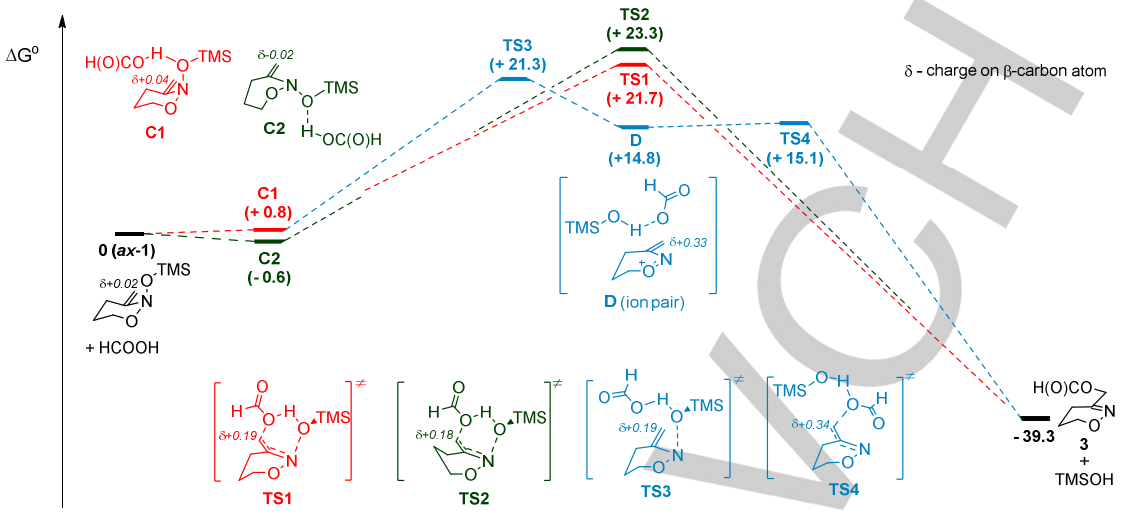


Figure 1. Computed energy profile for the reaction of enamine **1** with formic acid (for a more detailed reaction profile see Supporting information).

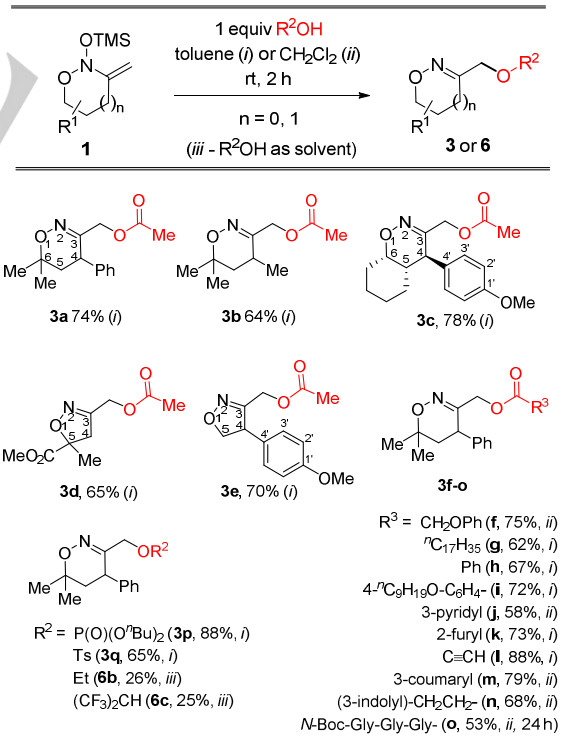
From stereochemical reasons, A_dE-type addition of acid HA should occur to the conformation ***eq*-1**, in which lone electron pair of nitrogen is conjugated with the π-bond that is confirmed by calculations of NBO, charges and analysis of HOMO (Scheme 5). At the same time, interaction of acid with conformation ***ax*-1** should provide products **3** through the S_N' pathway discussed above. Since both conformations are known to co-exist for enamines **1**,[15] it can be suggested that HFIP interacts with both conformations with comparable reaction rates. Thus, in HFIP bis(oxy)enamine **1** acts as a "stereoelectronic chameleon"[16], since β-C atom can act both as a nucleophile and as an electrophile.

As can be seen from these experiments, solvent dramatically influences the direction of acetic acid addition to bis(oxy)enamines **1** through changing the reaction mechanism. In reaction of bis(oxy)enamine **1** with AcOH, basic solvents (DMF, DMSO, NMP) promote the nitrosoalkene pathway. In non-polar solvents (toluene, CH_2Cl_2), the initial nucleophilic attack on the silicon atom is blocked and reaction proceeds through a Brønsted acid-mediated S_N' substitution of OTMS-group. In protic solvents, such as HFIP, Ad_E-type addition to the C,C-double bond becomes possible in addition to the S_N' process. Understanding of these important solvent effects holds the key to the development of efficient procedures for oximinoalkylation of HO-acids with nitrosoalkenes and *N*-vinyl-*N*-alkoxynitrenium cations.

Substrate scope studies of Brønsted acid Promoted S_N' substitution of OTMS in *N*-oxy-enamines 1

Addition of HO-acids to cyclic bis(oxy)enamines **1**, proceeding through a Brønsted acid promoted mechanism, can be considered as useful strategy for the synthesis of bioactive N–O heterocycles bearing various carboxylic acid residues. Therefore, the scope of this transformation was studied in more detail (Table 2).

Table 2. Addition of HO-acids to cyclic bis(oxy)enamines **1**.

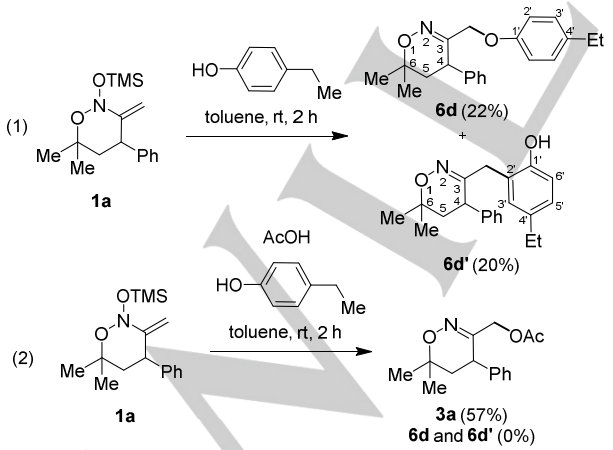


As can be seen from Table 2, the reaction of various six- and five-membered cyclic *N,N*-bis(oxy)enamines **1** with acetic acid in toluene (procedure *i*) proved to be general and afforded corresponding isoxazolines and 5,6-dihydro-4*H*-1,2-oxazines **3a**-**e** adducts in 64-78% yields. The open-chain adducts of type **2** were detected in none of these reactions (TMS-ethers **4** were the major by-products observed). Various carboxylic acids successfully underwent addition to a model bis(oxy)enamine **1a**, including those containing nucleophilic indole and pyridine fragments. In some cases, CH_2Cl_2 was used as solvent instead of toluene (procedure *ii*) to ensure complete solubility of carboxylic acid.

This approach can be used to construct hybrid systems, containing two tethered, bioactive units (for example, two bioactive heterocycles). In particular, adduct **3m** can be viewed as an analogue of Trichodermamides,[17] a recently isolated family of unusual marine metabolites comprised of 5,6-dihydro-4*H*-1,2-oxazine and coumarine heterocycles. Another example is the successful synthesis of 1,2-oxazine-labeled peptide **3o** (on the bioactivity of peptides labeled with N–O heterocycles see ref.[18]).

Importantly, even acidic dibutyl phosphate and TsOH reacted with enamine **1a** to give stable phosphate **3p** and tosylate **3q**, respectively, in good yields. Alcohols (ethanol and hexafluoroisopropanol) proved to be unreactive under these conditions, yet the corresponding adducts **6b** and **6c** could still be prepared in low yields by running the reaction in corresponding alcohols (procedure *iii*).

Reaction of enamine **1a** with 4-ethylphenol (1 equiv.) turned out to be ambiguous. Here, in addition to the expected ether **6d**, its C-linked isomer **6d'** was detected [Scheme 6, eq. (1)]. The latter, probably, arises from the Friedel-Crafts-type alkylation of 4-ethylphenol with *N*-vinyl-*N*-alkoxynitrenium cation **D** or from the [3,3]-sigmatropic rearrangement of the intermediate *N*-aryloxyenamine formed in result of N-attack of 4-ethylphenol on the cation **D** (cf. with Figure 1).



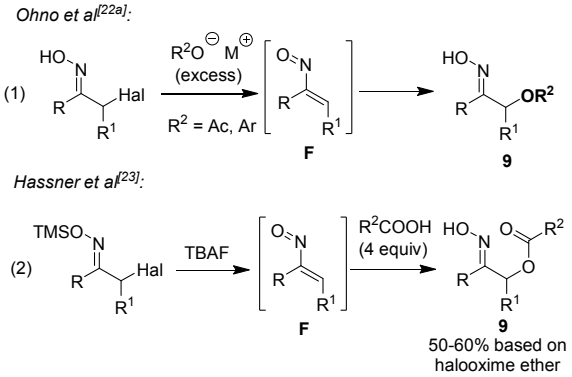
Scheme 6. Interaction of enamine **1a** with 4-ethylphenol.

In a competitive experiment with a mixture of 4-ethylphenol and acetic acid, the addition of the latter was observed only, demonstrating that the reaction rate depends on the acidity of HO-acid [Scheme 6, eq. (2)]. Therefore, site-selectivity in oximinoalkylation of substrates bearing different hydroxyl groups can be expected. The competitive experiment also strongly supports the mechanistic scheme shown in Figure 1 and, particularly, the fact that only one molecule of HO-acid is involved in the transition states leading to product **3**.

Oximinoalkylation of HO-acids through a nitrosoalkene pathway

Mechanistic investigations on enamines **1** were also helpful in developing a general procedure for oximinoalkylation of HO-acids to give acyclic α-oxyoximes **9**, which are important building blocks and intermediates in the synthesis of 1,2-amino alcohol derivatives,[19] 1,2-hydroxyhydroxylamines,[20] and bioactive heterocycles.[19b, 21]

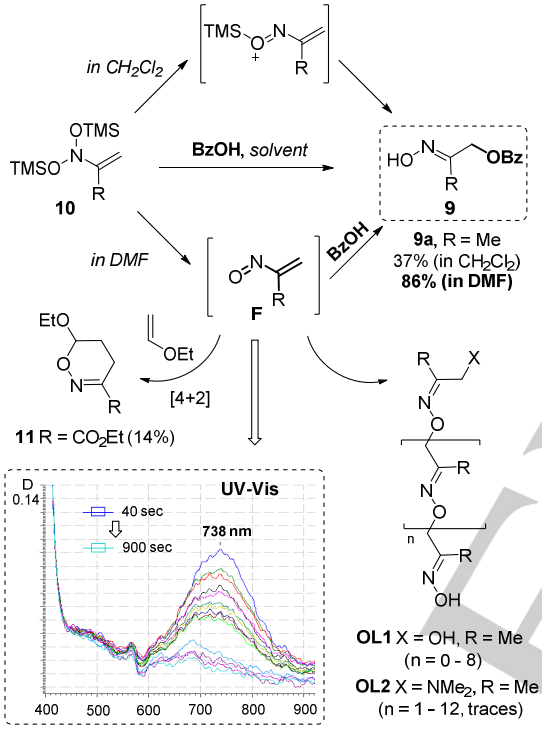
Direct oximinoalkylation of O-nucleophiles is a challenging task. In a few reports dealing with this problem, alkylation of alkali metal carboxylates or phenolates with α-halooximes was used [Scheme 7, eq. (1)].[22] Since substitution in α-halooximes proceeds through an elimination/nucleophilic addition mechanism, an excess of carboxylate or phenolate acting both as a base and a nucleophile is needed.[22b] This procedure is especially non-efficient when complex and expensive O-nucleophiles are used. Alternatively, OTMS ethers of α-halooximes have been suggested by Hassner[23] as sources of nitrosoalkene intermediates **F** upon the action of an equimolar amount of TBAF [Scheme 7, eq. (2)]. Although, O-nucleophiles in form of free acids (not salts) were used, the method required a 4-fold excess of carboxylic acid with respect to the α-halooxime silyl ether.



Scheme 7. Previous approaches to the direct oximinoalkylation of O-nucleophiles.

We reasoned that the use of readily available *N,N*-bis(silyloxy)enamines **10**[5b,c,24] as reagents under certain solvent-promoted conditions could provide α-oxyoximes **9** directly from HO-acids in a much more selective manner. In the

case of enamines **10** both the elimination/addition and S_N' substitution pathways would result in a same product after desilylation (Scheme 8). Accordingly, both pathways were tested in order to identify the most efficient one. In a model experiment, the acyclic bis(oxy)enamine **10a** (R = Me) was reacted with benzoic acid in DMF and CH_2Cl_2, in which different mechanisms were expected to be realized (Scheme 8). In DMF, the desired α-benzoyloxyoxime **9a** was the only product (86% yield), while in CH_2Cl_2 only 37% of **9a** was detected[25] (for more solvents tested see Supporting information).

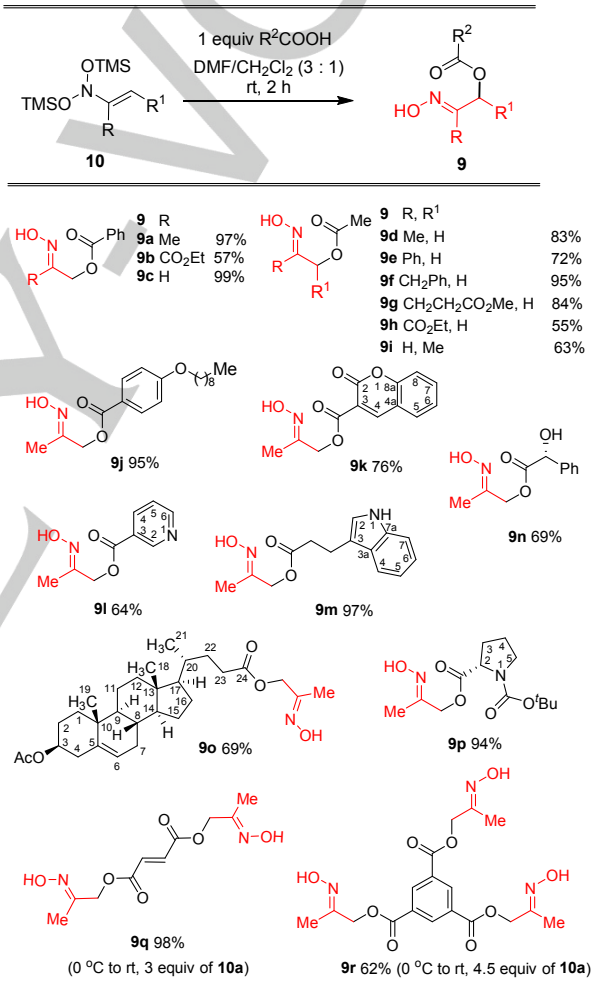


Scheme 8. Addition of benzoic acid to *N,N*-bis(silyloxy)enamines **10**.

Unlike cyclic *N*-alkoxy,*N*-silyloxyenamines **1**, their bis-silylated analogs **10** turned out to be unstable in DMF and completely converted into a mixture of oligomeric products **OL1** and **OL2** within 15 min at ambient temperature. The formation and degradation of unstable nitrosoalkene intermediate **F** could be followed by UV-Vis spectroscopy (λ_{max} = 738 nm, Scheme 8). Furthermore, the generation of nitrosoalkene intermediate was additionally proved by the formation of a [4+2] adduct **11** with ethyl vinyl ether in the reaction of enamine **10b** (R = CO_2Et) with DMF. It, therefore, can be concluded that DMF itself can promote cleavage of nitrosoacetal unit in enamines **10** acting as a Lewis base catalyst. In order to prevent degradation of enamine **10** during the reaction with acid, it was introduced in form of a 1 M solution in CH_2Cl_2 to a solution of acetic acid in DMF. This slight modification of procedure increased the yield of target adduct **9a** up to 97%.

To check the generality of this protocol, the substrate scope studies were performed using optimized conditions. In a first series of experiments, the effect of substituents in *N,N*-bis(siloxy)enamines was examined (Table 3). Various bis(oxy)enamines **10** reacted smoothly with acetic acid in a 1 : 1 molar ratio under mild conditions and within short reaction periods, providing corresponding α-acetyloxy-oximes **9** in good to high yields (Table 3). Among the bis(oxy)enamines studied, the most electron-deficient substrate **10b** (R = CO_2Et, R^1 = H) proved to be the least selective.

Table 3. Oximinoalkylation of carboxylic acids with bis(oxy)enamines **10**.

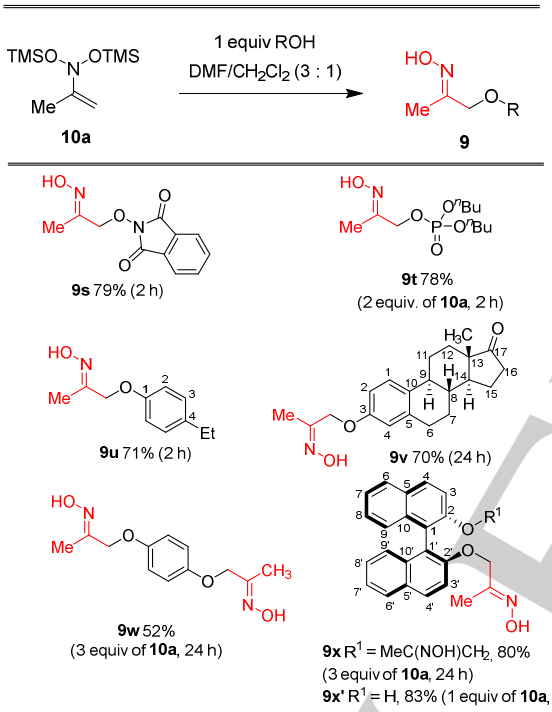


Various carboxylic acids readily reacted with model *N,N*-bis(oxy)enamine **10a**, including natural ones (nicotinic acid, 3-indolepropionic acid, (–)-mandelic acid and amino acids derivatives, Table 3). The reaction proved to be well-tolerated by nucleophilic pyridine, indole and aliphatic alcohol groups, yet for the amino group a suitable protection is needed.[26] Importantly, selective double and triple alkylation of bis- and tris-carboxylic acids could be successfully performed, demonstrating the high efficacy of the designed protocol (1.5 excess of **10a** was used in

both cases to ensure exhaustive alkylation). Triply oximinoalkylated trimesic acid (tris-oxime **9r**) can be viewed as an interesting ligand and building block for supramolecular chemistry.

Not only carboxylic acids, but also other HO-acids smoothly reacted with *N,N*-bis(oxy)enamines **10** (Table 4). *N*-Hydroxysuccinimide as well as dibutylphosphate in reaction with **10a** afforded the corresponding α-oxyoxime adducts **9s** and **9t** in good yields. Aliphatic alcohols (EtOH, $PhCH_2OH$) were unreactive under these conditions, yet phenols produced the corresponding oximinoalkylated adducts in good yields (Table 4).

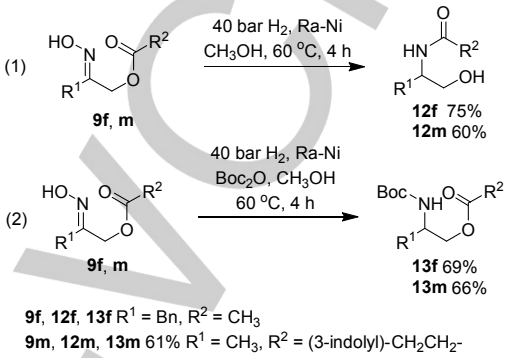
Table 4. Oximinoalkylation of HO-acids with enamines **10**.



This procedure was successfully used for modification of natural phenols such as estrone to give oximinoalkylated steroid **9v** (products of this type are known to exhibit high anti-proliferative activity[27]). (*S*)-BINOL was also selectively transformed into either mono- or bis-oximinoalkylated products (**9x** or **9x'**) depending on the amount of enamine **10a** used (prolonged reaction times were needed to achieve full conversion of phenols). Strong acids, such as TsOH produced complex mixtures of undecipherable products. Overall, these results demonstrate that HO-acids with pKa within the range of 2–10 can be successfully oximinoalkylated with the *N,N*-bis(oxy)enamines **10**/DMF system.

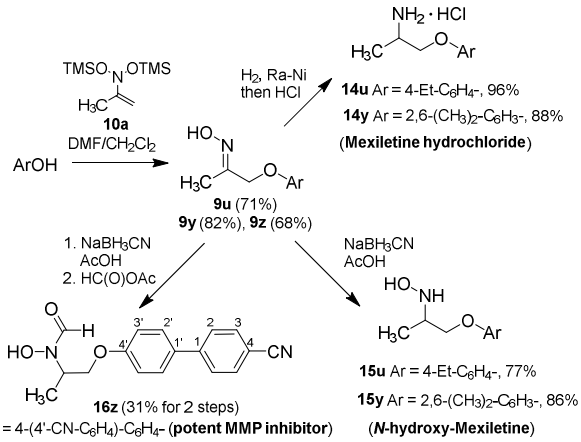
Synthetic utility of α-oxyoximes 9

α-Oxyoximes **9** obtained by our route are useful precursors of 1,2-amino alcohol derivatives, which are of high demand by medicinal chemistry. This was demonstrated by the reduction of two α-acyloxyoximes **9f** and **9m** (Scheme 9). Upon catalytic hydrogenation, these α-acyloxyoximes underwent reduction of the oxime group and subsequent intramolecular migration of the acyl group that led to amides of 1,2-amino alcohols **12f** and **12m** [Scheme 9, eq. (1)]. The intramolecular ester-amide isomerization can be prevented by performing hydrogenation in the presence of Boc_2O that provides protected 1,2-amino alcohol esters **13f** and **13m** [Scheme 9, eq. (2)].



Scheme 9. Reduction of α-acyloxyoximes **9**.

The suggested approach to α-aryloxyoximes was successfully employed in the synthesis of pharmaceutically relevant compounds such as β-aryloxyamines **14** and β-aryloxy-*N*-hydroxylamines **15** (Scheme 10). In particular, oxyminoalkylation of 2,6-dimethylphenol and subsequent exhaustive hydrogenation of the resulting α-aryloxyoxime **9y** provided antiarrhythmic drug Mexiletine **14y**.[28] Reduction of the same oxime **9y** with $NaBH_3CN$ gave *N*-hydroxy-Mexiletine **15y**[28a] in high yield. In a similar manner, a potent and bioavailable matrix metalloproteinase (MMP) inhibitor **16z**[20a] was easily prepared by hydride reduction and formylation of α-aryloxyoxime **9z** derived from 4'-hydroxy-4-biphenylcarbonitrile.



Scheme 10. Synthesis of bioactive amines and hydroxylamines from α-aryloxyoximes **9**.

Conclusions

In summary, we have revealed that *N,N*-bis(oxy)enamines exhibit divergent reactivity towards HO-acids. At least three distinct reaction pathways were identified, namely: (1) Brønsted acid promoted S_N' substitution of *N*-oxy-group for an O-nucleophile *via* unusual *N*-vinyl-*N*-alkoxynitrenium species, (2) Lewis base promoted transformation of *N,N*-bis(oxy)enamines into nitrosoalkenes through the attack of O-nucleophile on silicon and subsequent Michael addition, (3) standard A_dE-type addition of HO-acid to an enamine C,C-double bond. In these transformations, not only the bielectrophilic (silicon and β-carbon centers), but also "chameleonic" nature of *N,N*-bis(oxy)enamines (as both β-C-electrophiles and β-C-nucleophiles) is realized. Most importantly, these pathways can be modulated by solvent allowing for the efficient selectivity switch in these reactions.

These results led to the development of general and efficient protocols for the direct oximinoalkylation of HO-acids with nitrosoalkenes or vinyl-*N*-alkoxynitrenium cations as reactive intermediates. Unlike previous protocols, our approach employs stoichiometric amounts of HO-acid and alkylating agent (*N,N*-bis(oxy)enamine) without the use of any additives (bases, fluoride sources or heavy metals). Various HO-acids, such as carboxylic acids, phenols, hydroxamic acids, phosphoric and sulfonic acids were successfully oximinolalkylated using the designed method under mild conditions.

The suggested approach allows efficient post-modification of functional and bioactive molecules bearing acidic OH-groups that can be used in the design of pharmaceuticals, ligands and materials. Furthermore, α-oxyoximes prepared by this route can serve as useful precursors of various 1,2-amino alcohol or 1,2-hydroxylamino alcohol derivatives, which are widely used in pharmaceuticals.

Experimental section

All reactions were carried out in oven-dried (150°C) glassware. NMR spectra were recorded at room temperature with residual solvents peaks as an internal standard. Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), m (multiplet), br (broad). Atoms numbering is given in Tables 1-4, Schemes 6,10 and in the Supporting information. Peaks in FTIR-spectra data are reported in cm^{-1} with the following relative intensities: s (strong), m (medium), w (weak), br (broad), sh (shoulder). HRMS were measured on electrospray ionization (ESI) instrument with a time-of-flight (TOF) detector. Concentrations c in optical rotation angles are given in g/100 mL. $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. Column chromatography was performed using Kieselgel 40-60μm 60A. Analytical thin-layer chromatography was performed on silica gel plates with QF-254. Visualization was accomplished with UV light and solution of ninhydrine/acetic acid in ethanol or solution of anisaldehyde/H_2SO_4 in ethanol. DMF was distilled from CaH_2 under reduced pressure. CH_2Cl_2, CH_3CN, CCl_4, and Et_3N were distilled from CaH_2. THF distilled first from $LiAlH_4$, stored under sodium benzophenone ketyl and distilled using vacuum trap-to-trap technique prior use. Methanol, hexane, toluene, acetone, pentane, diethyl ether, methyl *tert*-butyl ether, and ethyl acetate were distilled without drying agents. All reagents were commercial grade and were used as received. Initial bis(oxy)enamines **1**,[5a,6a,d,9] TIPS-**1a**[6a] and **10**[5b,c] were prepared in accordance with literature procedures from corresponding nitronates **7** or nitro compounds (for details see Supporting information).

Quantum-chemical calculations were performed with the Gaussian 09 Rev D.01 program. For calculations of thermodynamics and kinetics DFT-D3 rm062x/cc-pvtz level of theory was used. All these calculations were performed in CH_2Cl_2 (SMD model), the approach of Martin and co-workers was followed.[29] Cartesian coordinates are given in angstroms, absolute energies for all substances are given in hartrees. Analysis of vibrational frequencies was performed for all optimized structures. All compounds except transition state structures were characterized by only real vibrational frequencies, transition structures had one imaginary frequency. Wavefunction stability was also checked for all calculations.

General procedure for model experiments 1-15 in Table 1. To a stirred solution of bis(oxy)enamine **1a** (52 mg, 0.179 mmol) in the indicated solvent (2.5 mL) was added acetic acid (11 mg, 0.179 mmol) at rt. The mixture was stirred for 2 h, and concentrated in vacuum (entries 1-8, 13, 17, 18) or subjected to a standard aqueous work-up with Et_2O/H_2O system (entries 9-12, 15, 16). The residue was analyzed by ^1H NMR with internal standard ($ClHC=CCl_2$). NMR spectra of products **4a**,[6c] **5a**,[8b] **6b**,[5d] **7a**[5a] are in agreement with previously published data and with spectra of authentic samples.

Experiment 16 in Table 1. To a stirred solution of NaOAc (10.3 mg, 0.125 mmol) in DMF (0.25 mL) was added 0.25 mL of 0.5 M solution of bis(oxy)enamine **1a** (0.125 mmol) in CH_2Cl_2 at r.t. The mixture was stirred for 2 h at r.t., and then transferred into a mixture of Et_2O (5 mL) and 0.25 M $NaHSO_4$ solution (5 mL). The aqueous layer was back-extracted with Et_2O (5 mL). Combined organic layers were washed with water (5 mL), and brine (5 mL), dried (Na_2SO_4), and evaporated in vacuum. The residue was analyzed by ^1H NMR with internal standard ($ClHC=CCl_2$). NMR spectra of product **8a** are in agreement with literature data.[9]

Experiments 17 and 18 in Table 1. To a stirred solution of acetic acid (7.1 μL, 0.125 mmol) and indicated amount of Et_3N in CH_2Cl_2 (0.25 mL) was added 0.25 mL of 0.5 M solution of bis(oxy)enamine **1a** (0.125 mmol) in CH_2Cl_2 at r.t. The mixture was stirred for 2 h at r.t., and then concentrated in vacuum. The residue was analysed by ^1H NMR with internal standard ($ClHC=CCl_2$).

5-Hydroxy-2-(hydroxyimino)-5-methyl-3-phenylhexyl acetate (2a). To a stirred solution of AcOH (30 mg, 0.5 mmol) in DMF (1.5 mL) was added a 0.5 M solution of *N,N*-bis(oxy)enamine **1a** in CH_2Cl_2 (1 mL, 0.5 mmol). The mixture was stirred at r.t. for 2 h and then evaporated under reduced pressure at c.a. 50°C. The residue was subjected to a column chromatography on silica gel (eluent hexane/AcOEt from 4 : 1 to 1 :1) to give 134 mg (96%) of oxime **2a**. Oil. Dynamic mixture of *E*- and *Z*-isomers, ratio 4.3 : 1. R_f = 0.07 (AcOEt-hexane = 1 : 3). ^1H NMR (300 MHz, Chloroform-*d*, *E*-isomer) δ 10.93 (s, 1H, NOH), 7.33 (dd, *J* = 7.5, 6.9 Hz, 2H, *m*-C_6H_5), 7.27 (t, *J* = 6.9 Hz, 1H, *p*-C_6H_5) 7.20 (d, *J* = 7.5 Hz, 2H, *o*-C_6H_5), 6.00 (s, 1H, OH), 5.07 (d, *J* = 15.1 Hz, 1H, H_2C-1), 4.59 (d, *J* = 15.1 Hz, 1H, H_2C-1), 3.96 (dd, *J* = 11.0, 3.6 Hz, 1H, HC-3), 2.46 (dd, *J* = 15.2, 11.0 Hz, 1H, HC-4), 1.94 (s, 3H, $CH_3C(O)$), 1.82 (dd, *J* = 15.2, 3.8 Hz, 1H, HC-4), 1.32 and 1.27 (2 s, 3H and 3H, 2 H_3C-6). ^{13}C NMR (75 MHz, JMOD, DMSO-d_6, *E*-isomer) δ 170.12 (C=O), 157.46 (C-2), 142.03 (*i*-C_6H_5), 128.85, 127.75 and 127.00 (*o*-, *m*-, *p*-C_6H_5), 70.53 (C-5), 58.46 (C-1), 47.67 (C-4), 45.37 (C-3), 31.64 and 27.69 (2 CH_3), 20.47 (CH_3). ^1H NMR (300 MHz, Chloroform-*d*, *Z*-isomer, characteristic signals) δ 9.19 (br s, 1H, NOH), 4.94 (dd, *J* = 8.7, 5.2 Hz, 1H, HC-3), 4.62 (d, *J* = 13.1 Hz, 1H, H_2C-1), 4.55 (d, *J* = 13.1 Hz, 1H, H_2C-1), 2.32 (dd, *J* = 14.2, 8.7 Hz, 1H, HC-4), 2.16 (dd, *J* = 14.2, 5.2 Hz, 1H, HC-4), 1.95 (s, 3H, $CH_3C(O)$), 1.30 and 1.25 (2 s, 3H and 3H, 2 H_3C-6). ^{13}C NMR (75 MHz,

JMOD, DMSO-d_6, *Z*-isomer) δ 170.34 (C=O), 157.74 (C-2), 140.20 (*i*-C_6H_5), 128.64, 128.22 and 127.00 (*o*-, *m*-, *p*-C_6H_5), 71.03 (C-5), 62.44 (C-1), 43.78 (C-4), 37.60 (C-3), 30.47 and 29.00 (2 CH_3), 20.60 (CH_3). HRMS: calcd. for $[C_{15}H_{21}NO_4Na]^+$ 302.1363; found 302.1366 ($[M+Na]^+$).

General procedures for the synthesis of carboxy-substituted cyclic oxime ethers 3 and 6. *Method i*: To a stirred solution of *N,N*-bis(oxy)enamine **1** (0.5 mmol) in toluene (3 mL, procedure *i*) was added the corresponding HO-acid (0.5 mmol) at r.t. The mixture was stirred for 2 h and then concentrated in vacuum. The residue was subjected to column chromatography on silica gel. *Method ii*: To a stirred solution of carboxylic acid (0.5 mmol) in CH_2Cl_2 (2 mL) was added the 0.5M solution of *N,N*-bis(oxy)enamine **1** (1 mL, 0.5 mmol) at r.t. The mixture was stirred for 2 h (if not stated otherwise) and then concentrated in vacuum. The residue was subjected to column chromatography on silica gel. *Method iii*: To *N,N*-bis(oxy)enamine **1** (0.5 mmol) was added corresponding alcohol (1 mL, ethanol for synthesis of **6b** and HFIP for synthesis of **6c**). The resulting solution was stirred for 2 h at r.t., and then concentrated in vacuum. The residue was subjected to column chromatography on silica gel.

(6,6-Dimethyl-4-phenyl-5,6-dihydro-4*H*-1,2-oxazin-3-yl)methyl acetate (3a). Prepared according to general procedure (*i*) from acetic acid (30 mg, 0.5 mmol) and bis(oxy)enamine **1a** (0.5 mmol). Yield: 97 mg (74%). Oil. R_f = 0.63 (AcOEt-hexane = 1 : 1). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.41-7.26 (m, 3H, *m,p*-C_6H_5), 7.24-7.15 (d, *J* = 6.9 Hz, 2H, *o*-C_6H_5), 4.45 (d, *J* = 13.1 Hz, 1H, CH_2O), 4.40 (d, *J* = 13.1 Hz, 1H, CH_2O), 3.55 (dd, *J* = 11.9, 7.9 Hz, 1H, H_{ax}C-4), 2.11 (dd, *J* = 13.6, 7.9 Hz, 1H, H_{eq}C-5), 1.99 (s, 3H, $CH_3C(O)$), 1.92 (dd, *J* = 13.6, 11.9 Hz, 1H, H_{ax}C-5), 1.39 and 1.33 (2 s, 3H and 3H, 2 CH_3). ^{13}C NMR (75 MHz, DEPT135, $CDCl_3$) δ 170.1 (C=O), 153.92 (C=N), 139.34 (*i*-C_6H_5), 129.08, 128.19 and 127.51 (*o*-, *m*-, *p*-C_6H_5), 74.95 (C-6), 64.07 (CH_2O), 40.31 (C-5), 38.01 (C-4), 28.37, 22.72 and 20.53 (3 CH_3). HRMS: calcd. for $[C_{15}H_{20}NO_3]^+$ 262.1438; found 262.1444 ($[M+H]^+$).

(4,6,6-Trimethyl-5,6-dihydro-4*H*-1,2-oxazin-3-yl)methyl acetate (3b). Prepared according to general procedure (*i*) from acetic acid (30 mg, 0.5 mmol) and bis(oxy)enamine **1b** (0.5 mmol). Yield: 64 mg (64%). White crystals. Mp = 54-57°C (pentane-Et_2O). R_f = 0.51 (AcOEt-hexane = 1 : 1). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 4.89 (d, *J* = 12.5 Hz, 1H, CH_2O), 4.59 (d, *J* = 12.5 Hz, 1H, CH_2O), 2.44 (m, 1H, HC-4), 2.12 (s, 3H, $CH_3C(O)$), 1.87 (dd, *J* = 13.4, 7.4 Hz, 1H, H_{eq}C-5), 1.50 (dd, *J* = 13.4, 12.2 Hz, 1H, H_{ax}C-5), 1.34 and 1.22 (2 s, 3H and 3H, 2 CH_3), 1.18 (d, *J* = 7.2 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.39 (C=O), 155.49 (C-3), 74.70 (C-6), 64.04 (CH_2O), 38.84 (C-5), 28.24, 24.77, 23.29, 20.75 and 16.85 (4 CH_3 and C-4). Anal. calcd. for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60; N, 7.03. Found C, 60.08; H, 8.64; N, 7.11.

***Rel*-((4*S*,4a*R*,8a*R*)-4-(4-methoxyphenyl)-4a,5,6,7,8,8a-hexahydro-4*H*-benzo[e][1,2]oxazin-3-yl)methyl acetate (3c).** Prepared according to general procedure (*i*) from acetic acid (30 mg, 0.5 mmol) and bis(oxy)enamine **1c** (0.5 mmol). Yield: 123 mg (78%). White crystals. Mp = 90-92°C (pentane-Et_2O). R_f = 0.59 (AcOEt-hexane = 1 : 1). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.08 (d, *J* = 8.5 Hz, 2H, HC-3'), 6.88 (d, *J* = 8.5 Hz, 2H, HC-2'), 4.68 (d, *J* = 12.6 Hz, 1H, CH_2O), 4.56 (d, *J* = 12.6 Hz, 1H, CH_2O), 4.05 (br s, 1H, HC-6), 3.81 (s, 3H, OCH_3), 3.17 (s, 1H, HC-4), 2.15-2.05, 1.82-1.55 and 1.53-1.23 (3 m, 1H, 4H and 4H, C-5 and CH_2 of cyclohexane ring), 1.95 (s, 3H, CH_3). ^{13}C NMR (75 MHz, JMOD, $CDCl_3$) δ 170.32 (C=O), 158.75 (C-3), 151.18 (C-1'), 132.94 (C-4'), 129.19 (C-3'), 114.24 (C-2'), 68.95 (C-6), 64.53 (CH_2O), 55.29 (OCH_3), 43.68 and 38.89 (C-4 and C-5), 29.21, 27.54, 25.00 and 19.89 (CH_2 of cyclohexane ring), 20.54 (CH_3). Anal. calcd. for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.30; N, 4.41. Found C, 68.01; H, 7.29; N, 4.43.

Methyl 3-(acetoxymethyl)-5-methyl-4,5-dihydroisoxazole-5-carboxylate (3d). Prepared according to general procedure (*i*) from acetic acid (15 mg, 0.25 mmol) and bis(oxy)enamine **1d** (0.25 mmol). Yield: 35 mg (65%). Oil. R_f = 0.5 (AcOEt-hexane = 1 : 1). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 4.83 (s, 2H, CH_2O), 3.79 (s, 3H, OCH_3), 3.53 (d, *J* = 17.6 Hz, 1H, H_2C-4), 2.88 (d, *J* = 17.6 Hz, 1H, H_2C-4), 2.11 (s, 3H, $CH_3C(O)$), 1.63 (s, 3H, CH_3). ^{13}C NMR (75 MHz, JMOD, $CDCl_3$) δ 172.18 and 170.30 (2 C=O), 154.38 (C-3), 86.23 (C-5), 58.56 (CH_2O), 53.05 (OCH_3), 45.07 (C-4), 23.52 and 20.60 (2 CH_3). HRMS: calcd. for $[C_9H_{14}NO_5]^+$ 216.0866; found 216.0876 ($[M+H]^+$).

(4-(4-Methoxyphenyl)-4,5-dihydroisoxazol-3-yl)methyl acetate (3e). Prepared according to general procedure (*i*) from acetic acid (18 mg, 0.3 mmol) and bis(oxy)enamine **1e** (0.3 mmol). Yield: 52 mg (70%). Oil. R_f = 0.54 (AcOEt-hexane = 1 : 1). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.11 (d, *J* = 8.3 Hz, 2H, HC-3'), 6.88 (d, *J* = 8.3 Hz, 2H, HC-2'), 4.81 (d, *J* = 13.4 Hz, 1H, CH_2O), 4.73-4.65 and 4.43-4.29 (2 m, 1H and 2H, HC-4 and H_2C-5), 4.62 (d, *J* = 13.4 Hz, 1H, CH_2O), 3.80 (s, 3H, OCH_3), 1.95 (s, 3H, CH_3). ^{13}C NMR (75 MHz, JMOD, $CDCl_3$) δ 170.17 (C=O), 159.38 and 156.85 (C-3 and C-1'), 129.80 (C-4'), 128.68 (C-3'), 114.63 (C-2'), 77.46 and 57.50 (CH_2O and C-5), 55.36 and 53.85 (OCH_3 and C-4), 20.45 (CH_3). HRMS: calcd. for $[C_{13}H_{15}NO_4Na]^+$ 272.0893; found 272.0895 ($[M+Na]^+$).

3-((Benzyloxy)methyl)-6,6-dimethyl-4-phenyl-5,6-dihydro-4*H*-1,2-oxazine (3f). Prepared according to general procedure (*ii*) from phenoxyacetic acid (76 mg, 0.5 mmol) and bis(oxy)enamine **1a** (0.5 mmol). Yield: 132 mg (75%). Oil, which crystallized upon standing. Mp = 77-79°C. R_f = 0.45 (AcOEt-hexane = 1 : 3). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.42-7.27 (m, 5H, 2 *m*-C_6H_5 and *p*-C_6H_5), 7.17 (d, *J* = 7.7 Hz, 2H, *o*-C_6H_5), 7.05 (t, *J* = 7.3 Hz, 1H, *p*-C_6H_5), 6.91 (d, *J* = 8.4 Hz, 2H, *o*-C_6H_5), 4.62 (d, *J* = 12.6 Hz, 1H, CH_2O), 4.61 (s, 2H, CH_2OPh), 4.56 (d, *J* = 12.6 Hz, 1H, CH_2O), 3.49 (dd, *J* = 12.4, 7.9 Hz, 1H, H_{ax}C-4), 2.10 (dd, *J* = 13.2, 7.9 Hz, 1H, H_{eq}C-5), 1.94 (dd, *J* = 13.2, 12.4 Hz, 1H, H_{ax}C-5), 1.41 and 1.30 (2 s, 3H and 3H, 2 CH_3). ^{13}C NMR (75 MHz, DEPT135, $CDCl_3$) δ 168.29 (C=O), 157.79 (C_{Ar}-O), 153.44 (C-3), 139.16 (*i*-C_6H_5), 129.61, 129.18, 128.23, 127.61, 121.77 and 114.61 (2 *o*-, *m*-, *p*-C_6H_5), 75.18 (C-6), 64.98 and 64.70 (2 CH_2O), 40.17 (C-5), 37.94 (C-4), 28.36 and 22.72 (2 CH_3). FTIR (KBr): 3058 (w), 2977 (m, sh), 2928 (m, sh), 1764 (s, C=O), 1600 (m), 1590 (m), 1495 (s), 1457 (m), 1433 (m), 1391 (m, sh), 1363 (m), 1312 (m), 1270 (m), 1236 (m), 1190 (s), 1122 (m), 1095 (s), 1029 (m), 926 (m, sh), 858 (m), 784 (m), 756 (s), 705 (m), 687 (m), 590 (m), 540 (w), 510 (m) cm^{-1}. Anal. calcd. for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found C, 71.20; H, 6.60; N, 3.90.

(6,6-Dimethyl-4-phenyl-5,6-dihydro-4*H*-1,2-oxazin-3-yl)methyl stearate (3g). Prepared according to general procedure (*i*) from stearic acid (142 mg, 0.5 mmol) and bis(oxy)enamine **1a** (0.5 mmol). Yield: 150 mg (62%). White solid. Mp = 50-52°C (CH_3OH). R_f = 0.7 (AcOEt-hexane = 1 : 3). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.41-7.24 (m, 3H, *m*-,*p*-C_6H_5), 7.19 (d, *J* = 6.7 Hz, 2H, *o*-C_6H_5), 4.47 (d, *J* = 12.6 Hz, 1H, CH_2O), 4.42 (d, *J* = 12.6 Hz, 1H, CH_2O), 3.56 (dd, *J* = 12.3, 7.8 Hz, 1H, H_{ax}C-4), 2.25 (t, *J* = 7.5 Hz, 2H, -CH_2C(O)), 2.11 (dd, *J* = 13.4, 7.8 Hz, 1H, H_{eq}C-5), 1.94 (dd, *J* = 13.4, 12.3 Hz, 1H, H_{ax}C-5), 1.62-1.52 and 1.31-1.25 (2 m, 2H and 28H, -CH_2-CH_2-), 1.39 and 1.33 (2 s, 3H and 3H, 2 CH_3), 0.90 (t, *J* = 6.4 Hz, 3H, CH_3-CH_2). ^{13}C NMR (75 MHz, DEPT135, $CDCl_3$) δ 172.89 (C=O), 154.11 (C-3), 139.40 (*i*-C_6H_5), 129.07, 128.19 and 127.48 (*o*-, *m*-, *p*-C_6H_5), 74.90 (C-6), 63.92 (CH_2O), 40.39 (C-5), 38.03 (C-4), 33.93, 31.91, 29.66, 29.45, 29.34, 29.25, 29.09 and 24.83 (16 CH_2), 28.37 and 22.68 (2 CH_3), 14.08 (CH_3). Anal. calcd. for $C_{31}H_{51}NO_3$: C, 76.65; H, 10.58; N, 2.88. Found C, 76.59; H, 10.41; N, 2.80.

(6,6-Dimethyl-4-phenyl-5,6-dihydro-4*H*-1,2-oxazin-3-yl)methyl benzoate (3h). Prepared according to general procedure (*i*) from benzoic

acid (61 mg, 0.5 mmol) and bis(oxy)enamine **1a** (0.5 mmol). Yield: 108 mg (67%). White solid. Mp = 66-68°C (Et_2O-pentane). R_f = 0.72 (AcOEt-hexane = 1 : 1). ^1H NMR (300 MHz, Chloroform-*d*) δ 7.98 (d, *J* = 7.2 Hz, 2H, *o*-$C_6H_5C(O)$), 7.59 (t, *J* = 7.4 Hz, 1H, *p*-$C_6H_5C(O)$), 7.45 (dd, *J* = 7.4, 7.2 Hz, 2H, *m*-$C_6H_5C(O)$), 7.38-7.26 (m, 3H, *m,p*-C_6H_5), 7.22 (d, *J* = 7.0 Hz, 2H, *o*-C_6H_5), 4.74 (d, *J* = 12.6 Hz, 1H, CH_2O), 4.69 (d, *J* = 12.6 Hz, 1H, CH_2O), 3.66 (dd, *J* = 11.8, 7.9 Hz, 1H, $H_{ax}C$-4), 2.15 (dd, *J* = 13.6, 7.9 Hz, 1H, $H_{eq}C$-5), 2.02 (dd, *J* = 13.6, 11.8 Hz, 1H, $H_{ax}C$-5), 1.42 and 1.37 (2 s, 3H and 3 H, 2 CH_3). ^{13}C NMR (75 MHz, DEPT135, $CDCl_3$) δ 165.70 (C=O), 154.20 (C-3), 139.32 (*i*-C_6H_5), 133.08, 129.63, 129.15, 128.36, 128.23 and 127.53 (*o,m,p*-C_6H_5, *o,m,p,i*-$C_6H_5C(O)$), 75.04 (C-6), 64.59 (CH_2O), 40.37 (C-5), 38.10 (C-4), 28.39 and 22.72 (2 CH_3). Anal. calcd. for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33. Found C, 74.23; H, 6.65; N, 4.34.

(6,6-Dimethyl-4-phenyl-5,6-dihydro-4*H*-1,2-oxazin-3-yl)methyl 4-(nonyloxy)benzoate (3i). Prepared according to general procedure (*i*) from 4-(nonyloxy)benzoic acid (132 mg, 0.5 mmol) and bis(oxy)enamine **1a** (0.5 mmol). Yield: 168 mg (72%). White solid. Mp = 56-57°C (pentane). R_f = 0.82 (AcOEt-hexane = 1 : 1). ^1H NMR (300 MHz, Chloroform-*d*) δ 7.92 (d, *J* = 8.6 Hz, 2H, 2 HC-3'), 7.37-7.26 (m, 3H, *m,p*-C_6H_5), 7.21 (d, *J* = 7.5 Hz, 2H, *o*-C_6H_5), 6.92 (d, *J* = 8.6 Hz, 2H, 2 HC-2'), 4.71 (d, *J* = 12.4 Hz, 1H, $CH_2OC(O)$), 4.65 (d, *J* = 12.4 Hz, 1H, $CH_2OC(O)$), 4.03 (t, *J* = 6.5 Hz, 2H, -CH_2CH_2O), 3.65 (dd, *J* = 11.8, 7.9 Hz, 1H, $H_{ax}C$-4), 2.14 (dd, *J* = 13.4, 7.9 Hz, 1H, $H_{eq}C$-5), 1.99 (dd, *J* = 13.4, 12.4 Hz, 1H, $H_{ax}C$-5), 1.87-1.76, 1.55-1.43 and 1.37-1.26 (3 m, 2H, 2H and 10H, CH_2), 1.41 and 1.37 (2 s, 3H and 3H, 2 CH_3), 0.91 (t, *J* = 6.4 Hz, 3H, CH_3-CH_2-). ^{13}C NMR (75 MHz, DEPT135, $CDCl_3$) δ 165.48 (C=O), 163.13 (C-1'), 154.47 (C-3), 139.41 (*i*-C_6H_5), 131.66 (C-3'), 129.11, 128.24 and 127.48 (*o,m,p*-C_6H_5), 121.82 (C-4'), 114.10 (C-2'), 74.97 (C-6), 68.25 and 64.30 (2 CH_2O), 40.42 (C-5), 38.10 (C-4), 31.89, 29.55, 29.35, 29.11 and 25.99 (7 CH_2), 28.40 and 22.70 (2 CH_3), 14.11 (CH_3). Anal. calcd. for $C_{29}H_{39}NO_4$: C, 74.81; H, 8.44; N, 3.01. Found C, 74.65; H, 8.60; N, 2.94.

(6,6-Dimethyl-4-phenyl-5,6-dihydro-4*H*-1,2-oxazin-3-yl)methyl nicotinate (3j). Prepared according to general procedure (*ii*) from nicotinic acid (61.5 mg, 0.5 mmol) and bis(oxy)enamine **1a** (0.5 mmol). Yield: 94 mg (58%). Oil. R_f = 0.24 (AcOEt-hexane = 1 : 1). ^1H NMR (300 MHz, Chloroform-*d*) δ 9.13 (d, *J* = 2.3 Hz, 1H, HC-2'), 8.76 (d, *J* = 4.8 Hz, 1H, HC-6'), 8.19 (dt, *J* = 7.9, 2.1 Hz, 1H, HC-4'), 7.47-7.08 (m, 6H, *o,m,p*-C_6H_5 and HC-5'), 4.73 (s, 2H, CH_2O), 3.61 (dd, *J* = 12.1, 7.8 Hz, 1H, $H_{ax}C$-4), 2.12 (dd, *J* = 13.6, 7.8 Hz, 1H, $H_{eq}C$-5), 1.96 (dd, *J* = 13.6, 12.1 Hz, 1H, $H_{ax}C$-5), 1.38 and 1.33 (2 s, 3H and 3H, 2 CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.34 (C=O), 153.53 (C-3), 153.46 and 150.75 (C-2' and C-6'), 139.13 (*i*-C_6H_5), 137.14 (C-4'), 129.17, 128.17 and 127.59 (*o,m,p*-C_6H_5), 125.63 (C-3'), 123.31 (C-5'), 75.15 (C-6), 64.85 (CH_2O), 40.26 (C-5), 38.15 (C-4), 28.33 and 22.72 (2 CH_3). HRMS: calcd. for $[C_{19}H_{20}N_2O_3Na]^+$ 347.1366; found 347.1361 ([M+H]$^+$).

(6,6-Dimethyl-4-phenyl-5,6-dihydro-4*H*-1,2-oxazin-3-yl)methyl furan-2-carboxylate (3k). Prepared according to general procedure (*i*) from 2-furanoic acid (56 mg, 0.5 mmol) and bis(oxy)enamine **1a** (0.5 mmol). Yield: 114 mg (73%). White solid. Mp = 84-87°C (pentane-Et_2O). R_f = 0.4 (AcOEt-hexane = 1 : 3). ^1H NMR (300 MHz, Chloroform-*d*) δ 7.60 (d, *J* = 1.5 Hz, 1H, HC-5'), 7.39-7.25 (m, 3H, *m,p*-C_6H_5), 7.22 (d, *J* = 7.6 Hz, 2H, *o*-C_6H_5), 7.15 (d, *J* = 3.5 Hz, 1H, HC-3'), 6.52 (dd, *J* = 3.5, 1.5 Hz, 1H, HC-4'), 4.69 (d, *J* = 12.6 Hz, 1H, CH_2O), 4.64 (d, *J* = 12.6 Hz, 1H, CH_2O), 3.63 (dd, *J* = 12.0, 7.9 Hz, 1H, $H_{ax}C$-4), 2.13 (dd, *J* = 13.6, 7.9 Hz, 1H, $H_{eq}C$-5), 1.97 (dd, *J* = 13.6, 12.0 Hz, 1H, $H_{ax}C$-5), 1.40 and 1.35 (2 s, 3H and 3H, 2 CH_3). ^{13}C NMR (75 MHz, JMOD, $CDCl_3$) δ 157.84 and 153.89 (C=O and C-3), 146.54 (C-5'), 144.15 (C-2'), 139.23 (*i*-C_6H_5), 129.16, 128.29 and 127.58 (*o,m,p*-C_6H_5), 118.31 and 111.87 (C-3' and C-4'), 75.14 (C-6), 64.34 (CH_2O), 40.32 (C-5), 38.05 (C-4), 28.41 and 22.76 (2 CH_3). Anal. calcd. for $C_{18}H_{19}NO_4$: C, 69.00; H, 6.11; N, 4.47. Found C, 69.07; H, 6.19; N, 4.48.

(6,6-Dimethyl-4-phenyl-5,6-dihydro-4H-1,2-oxazin-3-yl)methyl propiolate (3l). Prepared according to general procedure (*i*) from propiolic acid (35 mg, 0.5 mmol) and bis(oxy)enamine **1a** (0.5 mmol). Yield: 119 mg (88%). Oil. R_f = 0.61 (AcOEt-hexane = 1 : 1). ^1H NMR (300 MHz, Chloroform-*d*) δ 7.42-7.26 (m, 3H, *m,p*-C_6H_5), 7.21 (d, *J* = 7.6 Hz, 2H, *o*-C_6H_5), 4.55 (s, 2H, CH_2O), 3.58 (dd, *J* = 12.1, 7.8 Hz, 1H, $H_{ax}C$-4), 2.92 (d, *J* = 1.5 Hz, 1H, ≡CH), 2.13 (dd, *J* = 13.6, 7.8 Hz, 1H, $H_{eq}C$-5), 1.95 (dd, *J* = 13.6, 12.1 Hz, 1H, $H_{ax}C$-5), 1.40 and 1.34 (2 s, 3H and 3H, 2 CH_3). ^{13}C NMR (75 MHz, JMOD, $CDCl_3$) δ 152.95 and 151.77 (C-3 and C=O), 138.88 (*i*-C_6H_5), 129.22, 128.20 and 127.68 (*o,m,p*-C_6H_5), 75.57 (≡C-H), 75.29 (C-6), 74.07 (≡C), 65.52 (CH_2O), 39.87 (C-5), 37.69 (C-4), 28.32 and 22.72 (2 CH_3). HRMS: calcd. for $[C_{16}H_{17}NO_3Na]^+$ 294.1101; found 294.1106 ([M+Na]$^+$).

(6,6-Dimethyl-4-phenyl-5,6-dihydro-4*H*-1,2-oxazin-3-yl)methyl 2-oxo-2*H*-chromene-3-carboxylate (3m). Prepared according to general procedure (*ii*) from coumarin-3-carboxylic acid (95 mg, 0.5 mmol) and bis(oxy)enamine **1a** (0.5 mmol). Yield: 162 mg (79%). White solid. Mp = 136-137°C (pentane-Et_2O). R_f = 0.43 (AcOEt-hexane = 1 : 1). ^1H NMR (300 MHz, Chloroform-*d*) δ 8.47 (s, 1H, HC-4'), 7.80-7.52 and 7.42-7.15 (2 m, 2H and 7H, HC-5', HC-6', HC-7' HC-8' and *o,m,p*-C_6H_5), 4.69 (s, 2H, CH_2O), 3.82 (dd, *J* = 11.2, 9.1 Hz, 1H, $H_{ax}C$-4), 2.14 (dd, *J* = 12.7, 9.1 Hz, 1H, $H_{eq}C$-5), 1.97 (t, *J* = 12.7, 11.2 Hz, 1H, $H_{ax}C$-5), 1.40 and 1.36 (2 s, 3H and 3H, 2 CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.57, 155.30, 156.48 and 154.11 (C=O, C-2', C-3 and C-8a), 139.46 (*i*-C_6H_5), 149.33, 134.56, 129.67, 129.16, 128.43, 127.52, 124.93, 116.81 (C-4', C-5', C-6', C-7', C-8' and *o,m,p*-C_6H_5), 117.85 and 117.65 (C-4a' and C-3'), 75.36 (C-6), 65.25 (CH_2O), 40.29 (C-5), 37.84 (C-4), 28.42 and 22.72 (2 CH_3). Anal. calcd. for $C_{23}H_{21}NO_5$: C, 70.58; H, 5.41; N, 3.58. Found C, 70.37; H, 5.48; N, 3.59.

(6,6-Dimethyl-4-phenyl-5,6-dihydro-4*H*-1,2-oxazin-3-yl)methyl 3-(1*H*-indol-3-yl)propanoate (3n). Prepared according to general procedure (*ii*) from 3-indolepropionic acid (Oxigon®) (94 mg, 0.5 mmol) and bis(oxy)enamine **1a** (0.5 mmol). Yield: 133 mg (68%). Oil. R_f = 0.24 (AcOEt-hexane = 1 : 3). ^1H NMR (300 MHz, Chloroform-*d*) δ 8.04 (br s, 1H, HN-1'), 7.61 (d, *J* = 7.7 Hz, 1H, HC-7'), 7.39 (d, *J* = 8.0 Hz, 1H, HC-4'), 7.36-7.14 (m, 5H, *m,p*-C_6H_5, HC-5' and HC-6'), 7.12 (d, *J* = Hz, 2H, *o*-C_6H_5), 6.98 (s, 1H, HC-2'), 4.47 (s, 2H, CH_2O) 3.47 (dd, *J* = 12.3, 7.8 Hz, 1H, $H_{ax}C$-4), 3.06 and 2.70 (2 t, *J* = 7.6 Hz and *J* = 7.6 Hz, 2H and 2H, CH_2-CH_2), 2.07 (dd, *J* = 13.5, 7.9 Hz, 1H, $H_{eq}C$-5), 1.92 (dd, *J* = 13.5, 12.3 Hz, 1H, $H_{ax}C$-5), 1.39 and 1.29 (2 s, 3H and 3H, 2 CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.63 (C=O), 154.37 (C-3), 139.32 and 136.43 (C-7a' and *i*-C_6H_5), 129.13, 128.26 and 127.55 (*o,m,p*-C_6H_5), 127.17 (C-3a'), 122.00, 121.68, 119.27 and 118.60 (C-2', C-4', C-5' and C-6'), 114.47 (C-3'), 111.37 (C-7'), 75.16 (C-6), 64.10 (CH_2O), 40.32 (C-5), 37.97 (C-4), 34.58 and 20.60 (CH_2-CH_2), 28.43 and 22.74 (2 CH_3). Anal. calcd. for $C_{24}H_{26}N_2O_3$: C, 73.82; H, 6.71; N, 7.17. Found C, 73.83; H, 6.86; N, 6.99.

6,6-Dimethyl-4-phenyl-5,6-dihydro-4*H*-1,2-oxazin-3-yl)methyl (*tert*-butoxycarbonyl)glycylglycylglycinate (3o). To a stirred solution of bis(oxy)enamine **1a** (75 mg, 0.26 mmol) in CH_2Cl_2 (0.9 mL) was added *N*-^{t}butoxycarbonyl-glycyl-glycyl-glycine (75 mg, 0.26 mmol) at r.t. The mixture was stirred for 96 h at r.t., and then concentrated in vacuum. The residue was subjected to column chromatography on silica gel (eluent hexane-AcOEt = 5 : 1→1 : 1 → 0 : 1 → AcOEt-MeOH = 10 : 1 → 5 : 1) to give 67 mg (53%) of product **3o**. Also, a fraction containing 23 mg (40%) of **5a** was obtained. Oil. R_f = 0.05 (AcOEt-hexane = 1 : 1). ^1H NMR (300 MHz, Chloroform-*d*) δ 7.43-7.08 (m, 7H, *o,m,p*-C_6H_5, 2 NH), 5.59 (t, *J* = 5.8 Hz, 1H, NHBoc), 4.52 (d, *J* = 12.8 Hz, 1H, CH_2O), 4.46 (d, *J* = 12.8 Hz, 1H, CH_2O), 3.99 (m, 2H, CH_2N), 3.94 (d, *J* = 5.6 Hz, 2H, CH_2N), 3.81

(d, J = 5.7 Hz, 2H, CH_2N), 3.54 (dd, J = 11.8, 7.8 Hz, 1H, $H_{ax}C$-4), 2.19-2.04 (dd, J = 12.9, 7.8 Hz, 1H, $H_{ax}C$-5), 1.91 (dd, J = 12.9, 11.8 Hz, 1H, $H_{ax}C$-5), 1.43 (s, 9H, ^{t}Bu), 1.37 and 1.29 (2 s, 3H and 3H, 2 CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.48, 169.46 and 169.09 (3 C=O), 153.63 (C=N and ^{t}BuO*C*=O), 139.11 (*i*-C_6H_5), 129.25, 128.28 and 127.68 (*o,m,p*-C_6H_5), 80.47 (O*C*$(CH_3)_3$), 75.35 (C-6), 64.76 (CH_2O), 44.42, 42.83, 41.08 and 40.13 (3 CH_2N and C-5), 37.85 (C-4), 28.36 and 22.78 (2 CH_3 and OC(*C*$H_3)_3$). HRMS: calcd. for $[C_{24}H_{34}N_4O_7Na]^+$ 513.2325; found 513.2332 ($[M+Na]^+$).

***N*-^{t}Butoxycarbonyl-glycyl-glycyl-glycine.** To a stirred solution of triglycine (494 mg, 2.61 mmol) in a mixture of DMF (10 mL) and concentrated aqueous solution of $NaHCO_3$ (12.8 mL) was added Boc_2O (706 mg, 3.24 mmol) at 0°C. After stirring for 15 min, the mixture was allowed to warm to r.t. and kept for 30 h. Then, pH was adjusted to 5 with aqueous hydrochloric acid (c.a. 20 mass%), the solution was concentrated in vacuum, and the residue was dried in vacuum. The resulting solid was treated with ethanol (20 mL), inorganic precipitate was removed by filtration and the solution was concentrated in vacuum to give 765 mg (98%) of *N*-^{t}butoxycarbonyl-glycyl-glycyl-glycine (Boc-Gly-Gly-Gly-OH) as white solid.

Dibutyl ((6,6-dimethyl-4-phenyl-5,6-dihydro-4*H*-1,2-oxazin-3-yl)methyl) phosphate (3p). Prepared according to general procedure (*i*) from di(n-butyl)phosphate (105 mg, 0.5 mmol) and bis(oxy)enamine **1a**. Yield: 180 mg (88%). Oil. R_f = 0.37 (AcOEt-hexane = 1 : 1). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.38-7.13 (m, 5H, *o,m,p*-C_6H_5), 4.41 (dd, J = 11.3, 6.0 Hz, 1H, CH_2O), 4.30 (dd, J = 11.3, 7.9 Hz, 1H, CH_2O), 4.10-3.75 (m, 4H, 2 ^{n}Pr*C*H_2O), 3.67 (dd, J = 11.9, 7.9 Hz, 1H, $H_{ax}C$-4), 2.10 (dd, J = 13.6, 7.9 Hz, 1H, $H_{eq}C$-4), 1.89 (dd, J = 13.6, 11.9 Hz, 1H, $H_{ax}C$-4), 1.74-1.45 (m, 4H, $CH_3C*H*_2C*H*_2CH_2O$), 1.43-1.25 (m, 4H, $CH_3C*H*_2C*H*_2CH_2O$), 1.37 and 1.32 (2 s, 3H and 3H, 2 CH_3), 0.91 (t, J = 7.2 Hz, 3H, C*H*$_3$CH$_2$), 0.88 (t, J = 7.3 Hz, 3H, C*H*$_3$CH$_2$). ^{13}C NMR (75 MHz, JMOD, $CDCl_3$) δ 154.45 (d, J = 8.7 Hz, C-3), 139.52 (*i*-C_6H_5), 129.10, 128.41 and 127.45 (*o,m,p*-C_6H_5), 75.29 (C-6), 67.63 (d, J = 6.0 Hz, CH_2O), 67.51 (d, J = 6.0 Hz, CH_2O) and 67.11 (d, J = 5.6 Hz, CH_2O), 40.21 (C-5), 37.05 (C-4), 32.26 and 32.17 (2 d, J = 4.2 Hz and J = 4.2 Hz, 2 $CH_3CH_2*C*H_2CH_2O$), 28.38 and 22.70 (2 CH_3), 18.62 (d, J = 3.0 Hz, 2 $CH_3*C*H_2CH_2CH_2O$), 13.57 (2 CH_3). ^{31}P NMR (121 MHz, $CDCl_3$) δ -0.57. HRMS: calcd. for $[C_{21}H_{35}NO_5P]^+$ 412.2233; found 412.2247 ($[M+H]^+$).

(6,6-Dimethyl-4-phenyl-5,6-dihydro-4*H*-1,2-oxazin-3-yl)methyl 4-methylbenzenesulfonate (3q). Prepared according to general procedure (*i*) from TsOH•H_2O (95 mg, 0.5 mmol) and bis(oxy)enamine **1a** (0.5 mmol) in presence of MS 4Å (0.25 g). Product was isolated by crystallization from MeO^{t}Bu. Yield: 121 mg (65%). White solid. Mp = 130-132°C (MeO^{t}Bu). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.65 (d, J = 8.1 Hz, 2H, 2 HC-2'), 7.36-7.23 (m, 5H, *o,m,p*-C_6H_5), 7.15 (d, J = 8.1 Hz, 2H, 2 HC-3'), 4.39 (d, J = 11.0 Hz, 1H, CH_2O), 4.33 (d, J = 11.0 Hz, 1H, CH_2O), 3.61 (dd, J = 11.9, 7.9 Hz, 1H, $H_{ax}C$-4), 2.44 (s, 3H, CH_3), 2.11 (dd, J = 13.7, 7.9 Hz, 1H, $H_{eq}C$-5), 1.89 (dd, J = 13.7, 11.9 Hz, 1H, $H_{ax}C$-5), 1.37 and 1.28 (2 s, 3H and 3H, 2 CH_3). ^{13}C NMR (75 MHz, DEPT135, DMSO-d_6) δ 152.80 (C-3), 144.91 and 138.79 (C-4' and *i*-C_6H_5), 129.84, 129.18, 128.29, 127.96 and 127.51 (C-1', C-2', C-3' and *o,m,p*-C_6H_5), 75.72 (C-6), 69.85 (CH_2O), 39.74 (C-5), 37.10 (C-4), 28.28, 22.72 and 21.62 (3 CH_3). HRMS: calcd. for $[C_{20}H_{24}NO_4S]^+$ 374.1421; found 374.1421 ($[M+H]^+$).

4-((6,6-Dimethyl-4-phenyl-5,6-dihydro-4*H*-1,2-oxazin-3-yl)methoxy)butyl acetate (6a). To a stirred solution of *N,N*-bis(oxy)enamine **1a** (146 mg, 0.5 mmol) in THF (3 mL) was added acetic acid (28.6 µL, 0.5 mmol) at r.t. The mixture was stirred for 2 h and then concentrated in vacuum. The residue was subjected to column chromatography on silica gel (eluent hexane-EtOAc = 10 : 1 → 5 : 1 → 3 : 1). Two fractions were collected: first one contained TMS-ether **4a** (14 mg, 19%), second one (90 mg) contained a mixture of acetates **3a** (61%) and **6a** (6%). Additional careful column chromatography of fraction 2 provided pure **3a** and a fraction enriched with **6a** (ratio **3a**/**6a** = 4.0 : 1.0), which was used for characterization of by-product **6a**. R_f = 0.58 (AcOEt-hexane = 1 : 1). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.39-7.26 (m, 3H, *m,p*-C_6H_5), 7.24-7.15 (d, J = 6.9 Hz, 2H, *o*-C_6H_5), 4.05 (t, J = 6.4 Hz, 2H, C*H*$_2$OAc), 3.81 (s, 2H, C(N)CH_2O), 3.58 (dd, J = 12.5, 8.1 Hz, 1H, $H_{ax}C$-4), 3.18 and 3.39 (2 m, 2H, CH_2O), 2.10 (dd, J = 13.0, 8.1 Hz, 1H, $H_{eq}C$-5), 2.06 (s, 3H, CH_3C(O)), 1.92 (dd, J = 13.0, 12.5 Hz, 1H, $H_{ax}C$-5), 1.69-1.51 (m, 4H, –CH_2–CH_2–), 1.32 and 1.38 (2 s, 3H and 3H, 2 CH_3). ^{13}C NMR (75 MHz, DEPT135, $CDCl_3$) δ 171.13 (C=O), 156.25 (C=N), 140.17 (*i*-C_6H_5), 128.88, 128.40 and 127.17 (*o*-, *m*-, *p*-C_6H_5), 74.58 (C-6), 70.49, 69.88 and 64.25 (3 CH_2O), 40.15 (C-5), 37.32 (C-4), 26.03 and 25.43 (–CH_2–CH_2–), 28.49, 22.80 and 21.0 (3 CH_3). HRMS: calcd. for $[C_{19}H_{28}NO_4]^+$ 334.2013; found 334.2006 ($[M+H]^+$).

3-(((1,1,1,3,3,3-Hexafluoropropan-2-yl)oxy)methyl)-6,6-dimethyl-4-phenyl-5,6-dihydro-4*H*-1,2-oxazine (6c). Prepared according to procedure *iii* from enamine **1a** (146 mg, 0.5 mmol) and HFIP (1 mL). Yield: 25% (46 mg). Also, 60 mg (55%) of nitronate **7a** was isolated. Oil. R_f = 0.73 (AcOEt-hexane = 1 : 1). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.47-7.26 (m, 3H, *m,p*-C_6H_5), 7.26-7.11 (d, J = 6.9 Hz, 2H, *o*-C_6H_5), 4.22 (d, J = 11.5 Hz, 1H, CH_2O), 4.16 (d, J = 11.5 Hz, 1H, CH_2O), 4.12 (m, 1H, $CH(CF_3)_2$), 3.63 (dd, J = 11.9, 7.8 Hz, 1H), 2.14 (dd, J = 13.7, 7.7 Hz, 1H), 1.94 (t, J = 12.7 Hz, 1H), 1.41 (s, 3H), 1.33 (s, 3H). ^{13}C NMR (75 MHz, JMOD, $CDCl_3$) δ 153.89 (C=N), 139.23 (*i*-C_6H_5), 129.28, 128.38 and 127.68 (*o*-, *m*-, *p*-C_6H_5), 121.5 (m, $J_{C\text{-}F}$ = 285 Hz, 2 CF_3), 75.59 (C-6), 74.56 (*C*H$(CF_3)_2$), 73.49 (C-6), 39.53 (C-5), 37.08 (C-4), 28.48 and 22.81 (2 CH_3). ^{19}F NMR (282 MHz, $CDCl_3$) δ -74.4. HRMS: calcd. for $[C_{16}H_{18}F_6NO_2]^+$ 370.1236; found 370.1234 ($[M+H]^+$).

3-((4-Ethylphenoxy)methyl)-6,6-dimethyl-4-phenyl-5,6-dihydro-4*H*-1,2-oxazine (6d). Prepared according to general procedure (*i*) from 4-ethylphenol (91.5 mg, 0.75 mmol) and bis(oxy)enamine **1a** (0.75 mmol). Products were isolated by column chromatography. Two fractions were isolated. First contained 54 mg of product **6d** (22%), second fraction contained 59 mg of product **6d'** containing ca. 20% (by mass) of unreacted 4-ethylphenol. White solid. Mp = 49-52°C (MeO^{t}Bu-pentane). R_f = 0.78 (AcOEt-hexane = 1 : 1). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.39-7.21 (m, 5H, *o,m,p*-C_6H_5), 7.07 (d, J = 8.6 Hz, 2H, HC-3'), 6.80 (d, J = 8.6 Hz, 2H, HC-2'), 4.53 (d, J = 11.7 Hz, 1H, CH_2O), 4.35 (d, J = 11.7 Hz, 1H, CH_2O), 3.57 (dd, J = 11.8, 8.0 Hz, 1H, $H_{ax}C$-4), 2.58 (q, J = 7.6 Hz, 2H, C*H*$_2$CH$_3$), 2.09 (dd, J = 13.6, 8.0 Hz, 1H, $H_{eq}C$-5), 1.95 (dd, 1H, J = 13.6, 11.8 Hz, $H_{ax}C$-5), 1.38 and 1.20 (2 s, 3H and 3H, 2 CH_3), 1.19 (t, J = 7.6 Hz, 3H, CH_2CH_3). ^{13}C NMR (75 MHz, DEPT135, $CDCl_3$) δ 156.01 and 155.84 (C-3 and =C-O), 139.88 and 137.01 (C-4' and *i*-C_6H_5), 128.98, 128.64, 128.38 and 127.29 (C-3' and *o,m,p*-C_6H_5), 115.02 (C-2'), 74.94 (C-6), 68.19 (CH_2O), 40.15 (C-5), 37.31 (C-4), 28.45 (*C*H$_2$CH$_3$), 27.97 and 22.55 (2 CH_3), 15.83 (CH_2CH_3). Anal. calcd. for $C_{21}H_{25}NO_2$: C, 77.98; H, 7.79; N, 4.33. Found C, 77.83; H, 7.80; N, 4.21.

2-((6,6-Dimethyl-4-phenyl-5,6-dihydro-4*H*-1,2-oxazin-3-yl)methyl)-4-ethylphenol (6d'). Oil, containing ca. 20% of 4-ethylphenol. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.45-7.35 (m, 3H, *m,p*-C_6H_5), 7.21 (d, J = 2.1 Hz, 2H, HC-3'), 7.20 (d, J = 7.9 Hz, 2H, *o*-C_6H_5), 6.98 (dd, J = 8.2, 2.1 Hz, 1H, HC-5'), 6.87 (d, J = 8.2 Hz, 1H, HC-6'), 6.34 (s, 1H, OH), 3.46 (dd, J = 11.5, 8.1 Hz, 1H, $H_{ax}C$-4), 3.43 (d, J = 14.4 Hz, 1H, C*H*$_2$C=N), 3.25 (d, J = 14.4 Hz, 1H, C*H*$_2$C=N), 2.49 (q, J = 7.6 Hz, 1H, C*H*$_2$CH$_3$), 2.08 (dd, J = 13.8, 8.1 Hz, 1H, $H_{eq}C$-5), 1.98 (dd, J = 13.8, 11.5 Hz, 1H, $H_{ax}C$-5), 1.37 and 1.20 (2 s, 3H and 3H, 2 CH_3), 1.18 (t, J = 7.6 Hz, 3H, CH_2CH_3). ^{13}C NMR (75 MHz, DEPT135, HMBC, $CDCl_3$) δ 160.50 and 154.08 (C-3 and C-1'), 139.46 and 135.72 (C-4' and *i*-C_6H_5), 129.81, 129.19 and 128.73 (*o,m,p*-C_6H_5), 127.99 and 127.62 (C-5' and C-6'), 122.30 (C-2'), 117.44 (C-6'), 75.14 (C-6), 40.80 (C*H*$_2$C=N), 39.47 (C-4), 35.84 (C-5),

27.87 (CH_2CH_3), 28.26 and 22.65 (2 CH_3), 15.79 (CH_2CH_3). HRMS: calcd. for $[C_{21}H_{26}NO_2]^+$ 324.1958; found 324.1954 ($[M+H]^+$).

General procedure for oximinoalkylation of HO-acids (synthesis of α-oxyoximes 2 and 9). To a stirred solution of OH-acid (1 mmol) in DMF (3 mL) was added a 1 M solution of *N,N*-bis(oxy)enamine **10** in CH_2Cl_2 (amount indicated in Tables 3 and 4) at r.t. The mixture was stirred for time indicated in Tables 3 and 4, and then evaporated under reduced pressure at ca. 50°C (for large scale experiments, reaction mixtures were treated with an excess of methanol for 1 h prior evaporation to cleave TMS-oxime ethers). The residue was subjected to a column chromatography on silica gel.

2-(Hydroxyimino)propyl benzoate (9a). Prepared according to general procedure from 122 mg (1 mmol) of benzoic acid and 1 mmol of bis(oxy)enamine **10a**. Yield: 187 mg (97%). White crystals. Mp = 47-50°C (Et_2O-pentane). R_f = 0.49 (AcOEt-hexane = 1 : 1). Dynamic mixture of *E*/*Z*-isomers, ratio 20 : 1. ^{1}H NMR (300 MHz, Chloroform-*d*, *E*-isomer) δ 9.26 (s, 1H, OH), 8.09 (d, *J* = 7.3 Hz, 2H, *o*-C_6H_5), 7.60 (t, *J* = 7.4 Hz, 1H, *p*-C_6H_5), 7.47 (dd, *J* = 7.4 Hz, 7.3 Hz, 2H, *m*-C_6H_5), 4.91 (s, 2H, CH_2), 2.03 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, *E*-isomer) δ 166.17 (C=O), 153.78 (C=N), 133.28, 129.78 and 128.44 (*o*-, *m*-, *p*-C_6H_5), 129.57 (*i*-C_6H_5), 65.68 (CH_2), 11.78 (CH_3). ^{1}H NMR (300 MHz, Chloroform-*d*, *Z*-isomer, characteristic signals) δ 9.19 (br s, 1H, OH), 5.25 (s, 2H), 2.05 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, *Z*-isomer, characteristic signals) δ 60.31 (CH_2), 16.58 (CH_3). Anal. calcd. for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.74; N, 7.25. Found C, 61.85; H, 5.67; N, 7.33.

3-Ethoxy-2-(hydroxyimino)-3-oxopropyl benzoate (9b). Prepared according to general procedure from 91.5 mg (0.75 mmol) of benzoic acid and 0.75 mmol of bis(oxy)enamine **10b**. Yield: 107 mg (57%). After column chromatography, three fractions were collected containing pure minor *E*-isomer (oil), a mixture of *E*/*Z*-isomers (ratio 1 : 1.1, oil) and almost individual *Z*-isomer. Upon storage at r.t., the isomeric ratio changes. Overall ratio *E*/*Z* = 1 : 2.9 (after column chromatography). *Z*-isomer: oil, which solidified upon standing; Mp = 77-81°C; R_f = 0.28 (AcOEt-hexane = 1 : 3). *E*-isomer: oil; R_f = 0.37 (AcOEt-hexane = 1 : 3). ^{1}H NMR (300 MHz, Chloroform-*d*, *Z*-isomer) δ 10.00 (br, 1H, OH), 8.05 (d, *J* = 7.6 Hz, 2H, *o*-C_6H_5), 7.60 (t, *J* = 7.3 Hz, 1H, *p*-C_6H_5), 7.44 (dd, *J* = 7.6, 7.3 Hz, 2H, *m*-C_6H_5), 5.30 (s, 2H, CH_2OBz), 4.36 (q, *J* = 7.1 Hz, 2H, CH_3CH_2O), 1.32 (t, *J* = 7.1 Hz, 3H, CH_3CH_2O). ^{13}C NMR (75 MHz, $CDCl_3$, *Z*-isomer) δ 166.11 and 162.20 (2 C=O), 147.24 (C=N), 133.30, 129.86 and 128.44 (*o*-, *m*-, *p*-C_6H_5), 129.46 (*i*-C_6H_5), 62.30 (CH_2OBz), 54.53 (CH_3CH_2O), 14.04 (CH_3). ^{1}H NMR (300 MHz, Chloroform-*d*, *E*-isomer) δ 12.60 (br s, 1H, OH), 8.05 (d, *J* = 7.6 Hz, 2H, *o*-C_6H_5), 7.60 (t, *J* = 7.3 Hz, 1H, *p*-C_6H_5), 7.48 (dd, *J* = 7.6, 7.3 Hz, 2H, *m*-C_6H_5), 5.18 (s, 2H, CH_2OBz), 4.38 (q, *J* = 7.1 Hz, 2H, CH_3CH_2O), 1.32 (t, *J* = 7.1 Hz, 3H, CH_3CH_2O). ^{13}C NMR (75 MHz, $CDCl_3$, *E*-isomer) δ 165.85 and 162.39 (2 C=O), 143.78 (C=N), 133.37, 129.76 and 128.49 (*o*-, *m*-, *p*-C_6H_5), 129.41 (*i*-C_6H_5), 62.46 (CH_2OBz), 54.52 (CH_3CH_2O), 13.90 (CH_3). HRMS: calcd. for $[C_{12}H_{14}NO_5]^+$ 252.0866; found 252.0862 ($[M+H]^+$).

2-(Hydroxyimino)ethyl benzoate (9c). Prepared according to general procedure from 244 mg (2 mmol) of benzoic acid and 2 mmol of bis(oxy)enamine **10c**. Yield: 353 mg (99%). White crystals. Mp = 62-66°C (Et_2O-pentane). R_f = 0.57 (AcOEt-hexane = 1 : 1). Dynamic mixture of *E*/*Z*-isomers, ratio 5.3 : 1. ^{1}H NMR (300 MHz, Chloroform-*d*, *E*-isomer) δ 8.14 (s, 1H, OH), 8.10 (d, *J* = 7.3 Hz, 2H, *o*-C_6H_5), 7.67 (t, *J* = 5.6 Hz, 1H, N=CH), 7.60 (t, *J* = 7.4 Hz, 1H, *p*-C_6H_5), 7.47 (dd, *J* = 7.4 Hz, 6.9 Hz, 2H, *m*-C_6H_5), 4.95 (d, *J* = 5.6 Hz, 2H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$, JMOD, *E*-isomer) δ 166.25 (C=O), 146.34 (C=N), 133.40, 129.85 and 128.50 (*o*-, *m*-, *p*-C_6H_5), 129.46 (*i*-C_6H_5), 61.47 (CH_2). ^{1}H NMR (300 MHz, Chloroform-d, *Z*-isomer) δ 8.44 (s, 1H, OH), 8.10 (d, *J* = 6.5 Hz, 2H, *o*-C_6H_5), 7.59 (t, *J* = 7.4 Hz, 1H, *p*-C_6H_5), 7.48 (dd, *J* = 7.4 Hz, 6.5 Hz, 2H, *m*-C_6H_5), 7.01 (t, *J* = 3.8 Hz, 1H, N=CH), 5.21 (d, *J* = 3.8 Hz, 2H, CH_2). 13C NMR (75 MHz, $CDCl_3$, JMOD, *Z*-isomer) δ 166.31 (C=O), 148.33 (C=N), 133.44, 129.81 and 128.54 (*o*-, *m*-, *p*-C_6H_5), 129.46 (*i*-C_6H_5), 58.92 (CH_2). Anal. calcd. for $C_9H_9NO_3$: C, 60.33; H, 5.06; N, 7.82. Found C, 60.41; H, 5.03; N, 7.80.

2-(Hydroxyimino)propyl acetate (9d). Prepared according to general procedure from 60 mg (1 mmol) of acetic acid and 1 mmol of bis(oxy)enamine **10a** (product is volatile, evaporation should be conducted carefully). Yield: 109 mg (83%). Colorless oil. Dynamic mixture of *E*/*Z*-isomers, ratio 12 : 1. R_f = 0.53 (AcOEt-hexane = 1 : 1). ^{1}H NMR (300 MHz, DMSO-d_6, *E*-isomer) δ 8.87 (br, 1H, OH), 4.64 (s, 2H, CH_2), 2.13 and 1.95 (2 s, 3H and 3H, 2 CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, DEPT135, *E*-isomer) δ 170.74 (C=O), 153.38 (C=N), 65.12 (CH_2), 20.60 ($CH_3C(O)$), 11.65 ($CH_3C(N)$). ^{1}H NMR (300 MHz, Chloroform-*d*, *Z*-isomer, characteristic signals) δ 4.99 (s, 2H, CH_2), 2.15 and 1.92 (2 s, 3H and 3H, 2 CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, DEPT135, *Z*-isomer, characteristic signals) δ 154.9 (C=N), 59.83 (CH_2), 16.34 ($CH_3C(N)$). Anal. calcd. for $C_5H_9NO_3$: C, 45.80; H, 6.92; N, 10.68. Found C, 45.30; H, 7.17; N, 10.56.

2-(Hydroxyimino)-2-phenylethyl acetate (9e). Prepared according to general procedure from 60 mg (1 mmol) of acetic acid and 1 mmol of bis(oxy)enamine **10e**. Yield: 139 mg (72%). After column chromatography, two fractions were collected, one contained pure *E*-isomer, second one contained a mixture of *E*/*Z*-isomers (ratio 1 : 1.2). White solid. Mp = 40-42°C (Et_2O-pentane, *E*-isomer). Oil (dynamic mixture of *E*/*Z*-isomers). R_f = 0.36 (*E*-isomer) and 0.26 (two isomers, AcOEt-hexane = 1 : 1). ^{1}H NMR (300 MHz, DMSO-d_6, *E*-isomer) δ 9.39 (br, 1H, OH), 7.60 (dd, *J* = 7.3 Hz, 1.64 Hz, 2H, *o*-C_6H_5), 7.40-7.50 (m, 3H, *m*- and *p*-C_6H_5), 5.00 (s, 2H, CH_2), 2.05 (s, 3H, CH_3). ^{13}C NMR (75 MHz, DEPT135, $CDCl_3$, *E*-isomer, characteristic signals) δ 153.38 (C=N), 129.67, 128.35 and 128.30 (*o*-, *m*-, *p*-C_6H_5), 64.63 (CH_2). ^{1}H NMR (300 MHz, Chloroform-*d*, *Z*-isomer) δ 8.82 (s, 1H, OH), 7.58 (m, 2H, *o*-C_6H_5), 7.36-7.50 (m, 3H, *m*- and *p*-C_6H_5), 5.33 (s, 2H, CH_2), 2.02 (s, 3H, CH_3). ^{13}C NMR (75 MHz, DEPT135, $CDCl_3$, *Z*-isomer, characteristic signals) δ 154.97 (C=N), 129.55, 128.48 and 126.84 (*o*-, *m*-, *p*-C_6H_5) 56.00 (CH_2). Unassigned signals of both isomers: ^{13}C NMR (75 MHz, DEPT135, $CDCl_3$) δ 170.52 and 170.44 (C=O), 133.40 and 133.23 (*i*-C_6H_5), 20.67 and 20.63 (CH_3). Anal. calcd. for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.74; N, 7.25. Found C, 62.15; H, 5.71; N, 7.20.

2-(Hydroxyimino)-3-phenylpropyl acetate (9f). Prepared according to general procedure from 54 mg (0.9 mmol) of acetic acid and 0.9 mmol of bis(oxy)enamine **10f**. After keeping for 2 h at r.t., the mixture was treated with MeOH (10 mL) for 24 h to desilylate oxime groups and then concentrated in vacuum. After column chromatography two fractions were collected, major fraction contained pure *E*-isomer, while minor one contained a mixture of *E*/*Z*-isomers (ratio 3.1 : 1.0). Yield: 177 mg (95%). White low-melting crystals. Mp = 24-26°C (Et_2O-pentane, *E*-isomer). Oil (dynamic mixture of isomers). R_f = 0.52 (AcOEt-hexane = 1 : 1). ^{1}H NMR (300 MHz, Chloroform-*d*, *E*-isomer) δ 9.15 (s, 1H, OH), 7.37-7.22 (m, 5H, *o*-, *m*-, *p*-C_6H_5), 4.63 (s, 2H, CH_2O), 3.83 (s, 2H, CH_2), 2.04 (s, 3H, CH_3). ^{13}C NMR (75 MHz, DEPT135, $CDCl_3$) δ 170.45 (C=O), 154.71 (C=N), 135.49 (*i*-C_6H_5), 129.09, 128.68 and 126.75 (*o*-, *m*-, *p*-C_6H_5), 63.55 (CH_2O), 31.91 (CH_2), 20.59 (CH_3). ^{1}H NMR (300 MHz, Chloroform-*d*, *Z*-isomer) δ 9.47 (s, 1H, OH), 7.37-7.22 (m, 5H, *o*-, *m*-, *p*-C_6H_5), 4.98 (s, 2H, CH_2O), 3.66 (s, 2H, CH_2), 2.02 (s, 3H, CH_3). Anal. calcd. for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76. Found C, 63.89; H, 6.47; N, 6.92.

Methyl 5-acetoxy-4-(hydroxyimino)pentanoate (9g). Prepared according to general procedure from 60 mg (1 mmol) of acetic acid and 1 mmol of bis(oxy)enamine **10g**. Yield: 170 mg (84%). White low-melting crystals. Mp = 25-27°C (Et_2O-pentane). Dynamic mixture of *E*/*Z*-isomers, ratio 13 : 1. R_f = 0.3 (AcOEt-hexane = 1 : 3). ^{1}H NMR (300 MHz,

Chloroform-*d*, *E*-isomer) δ 9.37 (s, 1H, OH), 4.65 (s, 2H, CH_2), 3.67 (s, 3H, OCH_3), 2.54-2.70 (m, 4H, CH_2-CH_2), 2.03 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, DEPT135, *E*-isomer) δ 173.07 and 170.56 (2 C=O), 154.90 (C=N), 64.38 (CH_2O), 51.84 (CH_3O), 29.55 and 21.72 (CH_2-CH_2), 20.64 (CH_3). ^{1}H NMR (300 MHz, Chloroform-*d*, *Z*-isomer) δ 9.22 (s, 1H, OH), 4.95 (s, 2H, CH_2), 3.67 (s, 3H, OCH_3), 2.54-2.70 (m, 4H, CH_2-CH_2), 2.11 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, DEPT135, *Z*-isomer, characteristic signals) δ 59.29 (CH_2O), 30.03 and 25.77 (CH_2-CH_2). Anal. calcd. for $C_8H_{13}NO_5$: C, 47.29; H, 6.45; N, 6.89. Found C, 47.35; H, 6.46; N, 6.91.

Ethyl 3-acetoxy-2-(hydroxyimino)propanoate (9h). Prepared according to general procedure from 60 mg (1 mmol) of acetic acid and 1 mmol of bis(oxy)enamine **10b**. Yield: 104 mg (55%). Also, 3-hydroxy-2-(hydroxyimino)propanoate[30] (46 mg, 31%) was isolated by column chromatography as a by-product. Oil, which solidified upon standing. Mp = 36-40°C. R_f = 0.15 (AcOEt-hexane = 1 : 3). Dynamic mixture of *E*/*Z*-isomers, ratio 1 : 5.3. ^{1}H NMR (300 MHz, Chloroform-*d*, *Z*-isomer) δ 10.30 (s, 1H, OH), 5.03 (s, 2H, CH_2OAc), 4.33 (q, *J* = 7.1 Hz, 2H, CH_2CH$_3$), 2.08 (s, 3H, CH_3), 1.34 (t, *J* = 7.1 Hz, 3H, CH_2CH_3). ^{13}C NMR (75 MHz, JMOD, $CDCl_3$, *Z*-isomer) δ 170.61 and 162.22 (2 C=O), 147.25 (C=N), 62.22 (*C*H_2OAc), 53.97 (*C*H_2CH$_3$), 20.55 and 14.04 (2 CH_3). ^{1}H NMR (300 MHz, Chloroform-*d*, *E*-isomer) δ 12.11 (s, 1H, OH), 4.89 (s, 2H, CH_2OAc), 4.36 (q, *J* = 7.1 Hz, 2H, CH_2CH$_3$), 2.08 (s, 3H, CH_3), 1.35 (t, *J* = 7.1 Hz, 3H, CH_2CH_3). ^{13}C NMR (75 MHz, JMOD, $CDCl_3$, *E*-isomer, characteristic signals) δ 61.76 (*C*H_2OAc). HRMS: calcd. for $[C_7H_{12}NO_5]^+$ 190.0710; found 190.0710 ([M+H]$^+$).

1-(Hydroxyimino)propan-2-yl acetate (9i). Prepared according to general procedure from 60 mg (1 mmol) of acetic acid and 1 mmol of bis(oxy)enamine **10i**. Yield: 83 mg (63%, product is volatile, evaporation should be conducted carefully). Also, 2-hydroxypropanal oxime[30] (17 mg, 19%, *E*/*Z* = 8.3 : 1.0) was isolated by column chromatography as a by-product. Oil. R_f = 0.71 (AcOEt-hexane = 1 : 1). Dynamic mixture of *E*/*Z*-isomers, ratio 1.2 : 1.0. ^{1}H NMR (300 MHz, Chloroform-*d*, *E*-isomer) δ 8.62-8.44 (br s, 1H, NOH), 7.38 (d, *J* = 5.4 Hz, 1H, =CH), 5.87 (m, 1H, CHOAc), 2.05 (s, 3H, C(O)CH_3), 1.37 (d, *J* = 6.7 Hz, 3H, CH_3). ^{1}H NMR (300 MHz, Chloroform-*d*, *Z*-isomer) δ 8.70-8.88 (br s, 1H, NOH), 6.69 (d, *J* = 5.3 Hz, 1H, =CH), 5.42 (m, 1H, CHOAc), 2.04 (s, 3H, C(O)CH_3), 1.37 (d, *J* = 6.7 Hz, 3H, CH_3). NMR spectra are in accordance with literature data.[31] MS (EI): m/z = 132 [M+H]$^+$ (1%), 114 [M–OH]$^+$ (2%), 87 [M–AcOH]$^+$ (5%).

2-(Hydroxyimino)propyl 4-(nonyloxy)benzoate (9j). Prepared according to general procedure from 264 mg (1 mmol) of 4-(nonyloxy)benzoic acid and 1 mmol of bis(oxy)enamine **10a**. Yield: 317 mg (95%). Single *E*-isomer. White solid. Mp = 61-63°C (pentane). R_f = 0.68 (AcOEt-hexane = 1 : 1). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.01 (d, *J* = 8.8 Hz, 2H, CH_{Ar}), 7.79 (s, 1H, OH), 6.93 (d, *J* = 8.8 Hz, 2H, CH_{Ar}), 4.85 (s, 2H, CH_2O), 4.03 (t, *J* = 6.5 Hz, 2H, OCH_2-^{n}C$_7$H$_{15}$), 2.01 (s, 3H, CH_3), 1.88-1.75, 1.55-1.42 and 1.40-1.22 (3 m, 2H, 2H and 10H), 0.90 (t, *J* = 6.5 Hz, 3H, CH_3-CH_2). ^{13}C NMR (75 MHz, DEPT135, $CDCl_3$) δ 165.93 and 163.26 (C=O and C_{Ar}-O), 153.97 (C=N), 131.81 and 114.16 (2 *C*H_{Ar}), 121.66 (C_{Ar}), 68.26 and 65.38 (2 CH_2O), 31.88, 29.54, 29.34, 29.31, 29.09, 25.97, 22.66 (7 CH_2), 14.09 and 11.70 (2 CH_3). FTIR (KBr): 3141 (m, br, OH), 2923 (s, sh), 2850 (m, sh), 1717 (s, C=O), 1693 (m), 1605 (s), 1578 (m), 1510 (m), 1472 (m), 1421 (m, sh), 1390 (m), 1289 (s), 1253 (s, sh), 1165 (s), 1116 (m, sh), 1032 (m), 1020 (m), 987 (m), 889 (m), 846 (w), 802 (w), 769 (w), 695 (w), 636 (m), 544 (w) cm^{-1}. Anal. calcd. for $C_{19}H_{29}NO_4$: C, 68.03; H, 8.71; N, 4.18. Found C, 68.68; H, 9.06; N, 4.03.

2-(Hydroxyimino)propyl 2-oxo-2H-chromene-3-carboxylate (9k). Prepared according to general procedure from 190 mg (1 mmol) of coumarin-3-carboxylic acid and 1 mmol of bis(oxy)enamine **10a**. Yield: 199 mg (76%). Single *E*-isomer. White solid. Mp = 176-178°C (Et_2O). R_f = 0.14 (AcOEt-hexane = 1 : 3). ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.05 (s, 1H, OH), 8.80 (s, 1H, HC-4), 7.94 (d, *J* = 7.8 Hz, 1H, HC-8), 7.75 (t, *J* = 7.8 Hz, 1H, HC-7), 7.48 – 7.36-7.47 (m, 2H, HC-5 and HC-6), 4.80 (s, 2H, CH_2O), 1.89 (s, 3H, CH_3). ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.64 and 156.31 (C=O and C-2), 155.06 and 151.28 (C=N and C-8a), 149.65, 135.11, 130.85, 125.30 and 116.61 (C-4, C-5, C-6, C-7 and C-8), 118.22 and 117.56 (C-4a and C-3), 66.83 (CH_2O), 12.00 (CH_3). Anal. calcd. for $C_{13}H_{11}NO_5$: C, 59.77; H, 4.24; N, 5.36. Found C, 59.28; H, 4.40; N, 5.71.

2-(Hydroxyimino)propyl nicotinate (9l). Prepared according to general procedure from 123 mg (1 mmol) of nicotinic acid and 1 mmol of bis(oxy)enamine **10a**. Title compound precipitated from reaction mixture. Yield: 125 mg (64%). Single *E*-isomer. White solid. Mp = 215-218°C (CH_2Cl_2-DMF). ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.18 (s, 1H, OH), 9.23 (s, 1H, HC-2), 8.88 and 8.81 (2 d, *J* = 6.9 Hz and *J* = 6.0 Hz, 1H and 1H, HC-4 and HC-6), 8.06 (dd, *J* = 6.0 and 6.9 Hz, 1H, HC-5), 5.46 (s, 2H, CH_2), 1.87 (s, 3H, CH_3). ^{13}C NMR (50 MHz, DEPT135) δ 169.42 (C=O), 155.46 (C=NOH), 148.52 and 148.39 and 148.35 (C-2, C-4 and C-6), 140.06 (C-3), 130.55 (C-5), 66.06 (CH_2), 14.65 (CH_3). HRMS: calcd. for $[C_9H_{11}N_2O_3]^+$ 195.0764; found 195.0762 ([M+H]$^+$).

2-(Hydroxyimino)propyl 3-(1*H*-indol-3-yl)propanoate (9m). Prepared according to general procedure from 189 mg (1 mmol) of 3-indolepropionic acid (Oxigon®) and 1 mmol of bis(oxy)enamine **10a**. Yield: 251 mg (97%). Single *E*-isomer. White solid. Mp = 102-103°C (Et_2O-pentane). R_f = 0.39 (AcOEt-hexane = 1 : 1). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.99 and 7.68 (2 br s, 1H and 1H, OH and NH), 7.63 and 7.38 (2 d, *J* = 7.6 Hz and *J* = 7.8 Hz, 1H and 1H, HC-4 and HC-7), 7.23 and 7.15 (2 dd, *J* = 7.6, 7.1 Hz and *J* = 7.8, 7.1 Hz, 1H and 1H, HC-5 and HC-6), 7.04 (d, *J* = 1.6 Hz, 1H, HC-2), 4.64 (s, 2H, CH_2O), 3.16 (2 t, *J* = 7.6 Hz and *J* = 7.6 Hz, 2H and 2H, CH_2-CH_2), 1.86 (s, 3H, CH_3). ^{13}C NMR (75 MHz, DEPT135, $CDCl_3$) δ 172.95 (C=O), 153.74 (C=N), 136.32 (C-7a), 127.15 (C-3a), 122.09, 121.51, 119.37, 118.66 and 111.15 (C-2, C-4, C-5, C-6 and C-7), 114.71 (C-3), 65.12 (CH_2O), 34.76 and 20.63 (CH_2-CH_2), 11.52 (CH_3). Anal. calcd. for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found C, 64.77; H, 6.24; N, 10.61.

2-(Hydroxyimino)propyl 2-hydroxy-2-phenylacetate (9n). Prepared according to general procedure from 152 mg (1 mmol) of (-)-(*R*)-mandelic acid and 1 mmol of bis(oxy)enamine **10a**. Yield: 153 mg (69%). Dynamic mixture of *E*/*Z*-isomers, ratio 9 : 1. White solid. Mp = 69-72°C (Et_2O-MeOH). R_f = 0.37 (AcOEt-hexane = 1 : 1). $[\alpha]_D$ = -62.4 (MeOH, c = 1.0, 23°C). ^{1}H NMR (300 MHz, Chloroform-*d*, *E*-isomer) δ 9.02 (br s, 1H, NOH), 7.46-7.31 (m, 5H, *o*-, *m*-, *p*-C_6H_5), 5.25 (s, 1H, CHO), 4.68 (s, 2H, CH_2O), 4.16 (br s, 1H, OH), 1.75 (s, 3H, CH_3). ^{13}C NMR (75 MHz, JMOD135, $CDCl_3$, *E*-isomer) δ 173.32 (C=O), 153.07 (C=N), 137.98 (*i*-C_6H_5), 128.68, 128.66 and 126.62 (*o*-, *m*-, *p*-C_6H_5), 73.14 (CHO), 66.27 (CH_2O), 11.44 (CH_3). ^{1}H NMR (300 MHz, Chloroform-*d*, *Z*-isomer, characteristic signals) δ 5.27 (s, 1H, CH), 5.12 (d, *J* = 16.4 Hz, 1H, CH_2O), 4.99 (d, *J* = 16.4 Hz, 1H, CH_2O), 1.59 (s, 3H, CH_3). ^{13}C NMR (75 MHz, JMOD135, $CDCl_3$, *Z*-isomer, characteristic signals) δ 61.09 (CH_2O), 15.96 (CH_3). Anal. calcd. for $C_{11}H_{13}NO_4$: C, 59.19; H, 5.87; N, 6.27. Found C,59.20; H, 5.86; N, 6.25.

2-(Hydroxyimino)propyl (3β)-3-(acetyloxy)chol-5-en-24-oate (9o). Prepared according to general procedure from 315 mg (0.75 mmol) of (3β)-3-(acetyloxy)chol-5-en-24-oic acid and 0.7 mmol of bis(oxy)enamine **10a**. Yield: 234 mg (69%). Dynamic mixture of *E*- and *Z*-isomers, ratio 14 : 1. White solid. Mp = 137-140°C (Et_2O-MeOH). R_f = 0.6 (AcOEt-hexane = 1 : 1). $[\alpha]_D$ = - 36.0 (MeOH, c = 1.0, 24°C). ^{1}H NMR (300 MHz, Chloroform-*d*, *E*-isomer) δ 7.49 (s, 1H, NOH), 5.39 (d, *J* = 5.2 Hz, 1H, HC-6), 4.63 (s and m, 3H, CH_2O and HC-3), 2.49-2.23, 2.00-1.75, 1.70-

1.26 and 1.26-1.05 (4 m, 25H, H_2C-1, H_2C-2, H_2C-4, H_2C-7, HC-8, HC-9, H_2C-11, H_2C-12, HC-14, H_2C-15, H_2C-16, HC-17, HC-20, H_2C-22 and H_2C-23), 2.05 (s, 3H, CH_3C(O)), 1.94 (s, 3H, CH_3C(N)), 1.04 and 0.70 (2 s, 3H and 3H, H_3C-18 and H_3C-19), 0.95 (d, J = 6.2 Hz, 3H, H_3C-21). ^{13}C NMR (75 MHz, JMOD, $CDCl_3$, *E*-isomer) δ 173.82 and 170.65 (2 C=O), 153.69 (C=N), 139.72 (C-5), 122.63 (C-6), 74.06 (C-3), 65.12 (CH_2O), 56.72 and 55.84 (C-14 and C-17), 50.07 (C-9), 42.45 (C-13), 39.77, 38.18, 37.06, 36.65, 31.11, 31.01, 28.15, 27.83, 24.30 and 21.09 (C-1, C-2, C-4, C-7, C-11, C-12, C-15, C-16, C-22 and C-23), 35.40 (C-20), 31.94 (C-8), 31.92 (C-10), 21.48 (CH_3C(O)), 19.36, 18.36, 11.94 and 11.66 (CH_3C(N), C-18, C-19 and C-20). ^{1}H NMR (300 MHz, Chloroform-*d*, *Z*-isomer, characteristic signals) δ 4.99 (CH_2O). HRMS: calcd. for $[C_{29}H_{45}NO_5Na]^+$ 510.3195; found 510.3186 ([M+Na]$^+$).

1-(*tert*-Butyl) 2-(2-(hydroxyimino)propyl) (*S*)-pyrrolidine-1,2-dicarboxylate (9p). Prepared according to general procedure from 215 mg (1 mmol) of *N*-Boc-L-proline and 1 mmol of bis(oxy)enamine **10a**. Yield: 270 mg (94%). Dynamic mixture of *E*/*Z*-isomers, ratio 1.3 : 1. Oil, which solidified upon standing. Mp = 102-103°C. R_f = 0.51 (AcOEt-hexane = 1 : 1). $[\alpha]_D$ = - 48.6 (MeOH, c = 1.0, 24°C). ^{1}H NMR (300 MHz, Chloroform-*d*, *E*-isomer) δ 9.24 (s, 1H, OH), 4.63 (s, 2H, CH_2O), 4.25 (dd, J = 8.6, 3.9 Hz, 1H, HC-2), 3.62-3.30 (m, 2H, H_2C-5), 2.34-2.09 and 2.05-1.79 (2 m, 1H and 3H), 1.89 (s, 3H, CH_3), 1.39 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$, JMOD, *E*-isomer) δ 172.73 (C=O), 153.84 and 152.78 (N-C=O and C=N), 80.18 (($CH_3)_3C$-O), 65.78 (CH_2O), 59.06 (C-2), 46.32 (C-5), 30.84 and 23.58 (C-3 and C-4), 28.28 (($CH_3)_3C$-O), 11.61 (CH_3). ^{1}H NMR (300 MHz, Chloroform-*d*, *Z*-isomer) δ 9.18 (s, 1H, OH), 4.70 (d, J = 12.7 Hz, 1H, CH_2O), 4.70 (d, J = 12.7 Hz, 1H, CH_2O), 4.36 (dd, J = 8.5, 3.2 Hz, 1H, HC-2), 3.62-3.30 (m, 2H, H_2C-5), 2.34-2.09 and 2.05-1.79 (2 m, 1H and 3H), 1.89 (s, 3H, CH_3), 1.44 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$, JMOD, *Z*-isomer) δ 172.58 (C=O), 154.45 and 153.32 (N-C=O and C=N), 79.97 (($CH_3)_3C$-O), 65.75 (CH_2O), 58.78 (C-2), 46.54 (C-5), 29.90 and 24.27 (C-3 and C-4), 28.39 (($CH_3)_3C$-O), 11.46 (CH_3). HRMS: calcd. for $[C_{13}H_{23}N_2O_5]^+$ 287.1603; found 287.1601 ([M+H]$^+$).

Bis(2-(hydroxyimino)propyl) fumarate (9q). To a stirred solution of fumaric acid (116 mg, 1 mmol) in DMF (3 mL) was added a 1 M solution of bis(oxy)enamine **10a** (3 mL, 3 mmol) at 0°C under argon atmosphere. After 15 min, the mixture was allowed to warm to room temperature. After 2 h of stirring, the reaction mixture was concentrated in vacuum at 50°C and the residue was subjected to a column chromatography on silica gel (eluent hexane-AcOEt from 5 : 1 to 0 : 1). Yield: 252 mg (98%). White solid. Mp = 117-122°C (Et_2O-MeOH). Single *E*,*E*-isomer. R_f = 0.78 (AcOEt-MeOH = 5 : 1). ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.02 (s, 2H, 2 OH), 6.85 (s, 2H, 2 =CH), 4.72 (s, 4H, 2 CH_2O), 1.82 (s, 6H, 2 CH_3). ^{13}C NMR (75 MHz, JMOD, DMSO-d_6) δ 163.88 (2 C=O), 150.46 (2 C=N), 133.15 (2 =CH), 66.21 (2 CH_2O), 11.45 (2 CH_3). Anal. calcd. for $C_{10}H_{14}N_2O_6$: C, 46.51; H, 5.46; N, 10.85. Found C, 45.90; H, 5.82; N, 11.29.

Tris(2-(hydroxyimino)propyl) benzene-1,3,5-tricarboxylate (9r). To a stirred solution of trimesic acid (210 mg, 1 mmol) in DMF (2 mL) was added a 1 M solution of bis(oxy)enamine **10a** (4.5 mL, 4.5 mmol) at 0°C under argon atmosphere. After 15 min, the mixture was allowed to warm to room temperature. After 2 h of stirring, the reaction mixture was concentrated in vacuum at 50°C and the residue was subjected to a column chromatography on silica gel (eluent hexane-AcOEt from 5 : 1 to 0 : 1). Yield: 264 mg (62%). Dynamic mixture of *E*,*E*,*E*- and *E*,*E*,*Z*-isomers, ratio 4 : 1. White solid. Mp = 139-141°C (Et_2O-MeOH). R_f = 0.36 (AcOEt-hexane = 1 : 1). ^{1}H NMR (300 MHz, DMSO-d_6, *E*,*E*,*E*-isomer) δ 11.06 (s, 3H, 3 OH), 8.70 (s, 3H, 3 CH_{Ar}), 4.92 (s, 6H, 3 CH_2O), 1.88 (s, 9H, 3 CH_3). ^{13}C NMR (75 MHz, JMOD, DMSO-d_6, *E*,*E*,*E*-isomer) δ 163.64 (3 C=O), 150.44 (3 C=N), 133.72 (3 =CH), 130.90 (3 C_{Ar}), 66.49 (3 CH_2O), 11.47 (3 CH_3). ^{1}H NMR (300 MHz, DMSO-d_6, *E*,*E*,*Z*-isomer) δ 10.89 and 10.44 (2 br, 3H, 3 OH), 8.72 and 8.71 (2 s, 1H and 2H, 3 CH_{Ar}), 5.16 (s, 2H, CH_2O of *Z*-fragment), 4.92 (s, 4H, 2 CH_2O of *E*-fragments), 1.88 (s, 6H, 2 CH_3 of *E*-fragments), 1.76 (s, 3H, CH_3 of *Z*-fragment). ^{13}C NMR (75 MHz, JMOD, DMSO-d_6, *E*,*E*,*Z*-isomer) δ 63.10 (CH_2O), 16.22 (CH_3) (characteristic signals of *Z*-oximinoalkyl fragment). FTIR (KBr): 3348 (s, br, OH), 3140 (m, br), 3080 (m), 2925 (m, br), 1740 (s, C=O), 1490 (w), 1450 (m, sh), 1371 (m), 1335 (w), 1268 (s), 1235 (s, sh), 1154 (m, sh), 1113 (w), 1063 (w), 1037 (w), 960 (m), 928 (m), 871 (w), 733 (s), 638 (m), 544 (w) cm^{-1}. Anal. calcd. for $C_{18}H_{21}N_3O_9$: C, 51.07; H, 5.00; N, 9.93. Found C, 50.72; H, 5.29; N, 9.73.

2-(2-(Hydroxyimino)propoxy)isoindoline-1,3-dione (9s). Prepared according to general procedure from 166 mg (1 mmol, 98% purity) of *N*-hydroxyphthalimide and 1 mmol of bis(oxy)enamine **10a**. Yield: 184 mg (79%). Dynamic mixture of *E*- and *Z*-isomers, ratio 5.7 : 1. White solid. Mp = 168-171°C. R_f = 0.43 (AcOEt-hexane = 1 : 1). ^{1}H NMR (300 MHz, DMSO-d_6, *E*-isomer) δ 11.12 (s, 1H, OH), 7.89 (s, 4H, CH_{Ar}), 4.64 (s, 2H, CH_2O), 1.98 (s, 3H, CH_3). ^{13}C NMR (75 MHz, JMOD, DMSO-d_6, *E*-isomer) δ 162.92 (C=O), 150.68 (C=N), 134.87 and 123.27 (CH_{Ar}), 128.27 (C_{Ar}), 78.64 (CH_2O), 12.22 (CH_3). ^{1}H NMR (300 MHz, DMSO-d_6, *Z*-isomer) δ 10.81 (s, 1H, OH), 7.83 (s, 4H, CH_{Ar}), 4.64 (s, 2H, CH_2O), 1.98 (s, 3H, CH_3). ^{13}C NMR (75 MHz, JMOD, DMSO-d_6, *Z*-isomer, characteristic signals) δ 134.44 and 123.88 (CH_{Ar}), 66.18 (CH_2O), 18.42 (CH_3). FTIR (KBr): 3359 (s, br, OH), 3103 (w), 3041 (w), 3026 (w), 1781 (m), 1724 (s, C=O), 1709 (s, C=O), 1467 (m, sh), 1395 (m), 1367 (m), 1269 (w), 1190 (m, sh), 1141 (m), 1063 (w, sh), 1021 (w), 975 (m), 948 (m), 931 (m), 881 (m), 833 (w), 789 (w), 720 (w), 706 (m, sh), 609 (w), 519 (m) cm^{-1}. Anal. calcd. for $C_{11}H_{10}N_2O_4$: C, 56.41; H, 4.30; N, 11.96. Found C, 56.45; H, 4.28; N, 11.75.

Dibutyl (2-(hydroxyimino)propyl) phosphate (9t). Prepared according to general procedure from 210 mg (1 mmol) of di(*n*-butyl)phosphate and 2 mmol of bis(oxy)enamine **10a**. Yield: 218 mg (78%). Dynamic mixture of *E*- and *Z*-isomers, ratio 6.7 : 1. Oil. R_f = 0.43 (AcOEt-hexane = 1 : 1). ^{1}H NMR (300 MHz, Chloroform-*d*, *E*-isomer) δ 8.55 (br, 1H, OH), 4.54 (d, J = 7.5 Hz, 2H, CH_2O), 4.06 (q, J = 6.6 Hz, 4H, ^{n}PrCH_2O), 1.96 (s, 3H, CH_3), 1.79-1.55 (m, 4H, $CH_3CH_2CH_2CH_2O$), 1.50-1.33 (m, 4H, $CH_3CH_2CH_2CH_2O$), 0.93 (t, J = 7.4 Hz, 6H, 2 CH_3CH_2). ^{13}C NMR (75 MHz, JMOD, $CDCl_3$) δ 153.35 (d, J = 8.1 Hz, C=N), 68.46 and 67.92 (2 d, J = 5.3 Hz and J = 6.0 Hz, 3 CH_2O), 32.26 (d, J = 6.9 Hz, 2 $CH_3CH_2CH_2CH_2O$), 18.66 (2 $CH_3CH_2CH_2CH_2O$), 13.57 and 11.23 (3 CH_3). ^{1}H NMR (300 MHz, Chloroform-*d*, *Z*-isomer, characteristic signals) δ 4.91 (d, J = 8.2 Hz, 2H, CH_2O), 1.89 (s, 3H, CH_3), 0.94 (t, J = 7.4 Hz, 6H, 2 CH_3CH_2). ^{13}C NMR (75 MHz, JMOD, $CDCl_3$, *Z*-isomer, characteristic signals) δ 67.99 (d, J = 6.0 Hz, 2 $CH_3CH_2CH_2CH_2O$), 62.67 (d, J = 4.8 Hz, CH_2O), 32.29 (d, J = 6.9 Hz, 2 $CH_3CH_2CH_2CH_2O$), 16.25 (CH_3C(N)). ^{31}P NMR (121 MHz, $CDCl_3$) δ -0.85. HRMS: calcd. for $[C_{11}H_{25}NO_5P]^+$ 282.1465; found 282.1469 ([M+H]$^+$).

1-(4-Ethylphenoxy)propan-2-one oxime (9u). Prepared according to general procedure from 122 mg (1 mmol) of *p*-ethylphenol and 1 mmol of bis(oxy)enamine **10a**. Yield: 137 mg (71%). Dynamic mixture of *E*- and *Z*-isomers, ratio 4.4 : 1. Oil. R_f = 0.43 (AcOEt-hexane = 1 : 1). ^{1}H NMR (300 MHz, Chloroform-*d*, *E*-isomer) δ 8.18 (s, 1H, OH), 7.13 (d, J = 8.4 Hz, 2H, HC-3), 6.89 (d, J = 8.5 Hz, 2H, HC-2), 4.56 (s, 2H, CH_2O), 2.61 (q, J = 7.5 Hz, 2H, CH_2CH_3), 2.03 (s, 3H, CH_3), 1.23 (t, J = 7.5 Hz, 3H, CH_2CH_3). ^{13}C NMR (75 MHz, JMOD, $CDCl_3$, *E*-isomer) δ 156.41 and 155.45 (C=N and C-1), 137.20 (C-4), 128.84 (C-3), 114.82 (C-2), 69.47 (CH_2O), 28.05 (CH_2CH_3), 15.85 (CH_2CH_3), 11.49 (CH_3). ^{1}H NMR (300 MHz, Chloroform-*d*, *Z*-isomer, characteristic signals) δ 7.09 (d, J = 8.4 Hz, 2H, HC-3), 6.78 (d, J = 8.5 Hz, 2H, HC-2), 4.56 (s, 2H, CH_2O), 1.94 (s, 3H, CH_3). ^{13}C NMR (75 MHz, JMOD, $CDCl_3$, *Z*-isomer, characteristic signals) δ 155.98 and 155.45 (C=N and C-1), 128.80 (C-3), 114.87 (C-2), 74.78 (CH_2O),

28.05 (CH_2CH_3), 12.13 (CH_3). HRMS: calcd. for $[C_{11}H_{16}NO_2]^+$ 194.1181; found 194.1184 ($[M+H]^+$).

3-{[2-(Hydroxyimino)propyl]oxy}estra-1(10),2,4-trien-17-one (9v). To a stirred solution of estrone (270 mg, 1 mmol) in DMF (3 mL) was added a 1 M solution of bis(oxy)enamine **10a** (1 mL, 1 mmol) at r.t. After 24 h of stirring, the reaction mixture was concentrated in vacuum at 50°C and the residue was subjected to a column chromatography on silica gel (eluent hexane-AcOEt from 5 : 1 to 0 : 1). Yield: 238 mg (70%). Dynamic mixture of *E*- and *Z*-isomers, ratio 5.8 : 1. White amorphous solid. Mp = 42-52°C (^{i}PrOH-pentane). R_f = 0.36 (AcOEt-hexane = 1 : 3). $[\alpha]_D$ = +125.4 (CH_3OH, c = 1.0, 23°C). ^{1}H NMR (300 MHz, Chloroform-*d*, *E*-isomer) δ 8.97 (br s, 1H, OH), 7.21 (d, *J* = 8.3 Hz, 1H, HC-1), 6.77 (d, *J* = 8.3 Hz, 1H, HC-2), 6.62 (s, 1H, HC-4), 4.56 (s, 2H, CH_2O), 2.90 (m, 2H, H_2C-6), 2.53 (dd, *J* = 8.8, 19.0 Hz, 1H, HC-16), 2.39 (m, 1H, HC-11), 2.31-2.17 (m, 2H, HC-9 and HC-16), 2.15-1.90 and 1.71-1.38 (2 m, 9H, H_2C-7, HC-8, HC-11, H_2C-12, HC-14 and H_2C-15), 2.03 (s, 3H, CH_3C(N)), 0.93 (s, 3H, CH_3). ^{13}C NMR (75 MHz, JMOD, $CDCl_3$, *E*-isomer) δ 221.30 (C=O), 156.35 and 155.20 (C=N and C-3), 137.89 and 132.73 (C-5 and C-10), 126.41 (C-1), 114.96 and 112.37 (C-2 and C-4), 69.32 (CH_2O), 50.43 (C-14), 48.07 (C-13), 43.99 (C-9), 38.33 (C-8), 35.92 (C-16), 31.58 and 29.64 (C-6 and C-12), 26.54 and 25.91 (C-7 and C-11), 21.62 (C-15), 13.88 and 11.48 (2 CH_3). ^{1}H NMR (300 MHz, Chloroform-*d*, *Z*-isomer, characteristic signals) δ 7.15 (d, *J* = 8.4 Hz, 1H, HC-1), 6.62 (s, 1H, HC-4), 4.92 (s, 2H, CH_2O), 1.96 (s, 3H, CH_3C(N)). ^{13}C NMR (75 MHz, JMOD, $CDCl_3$, *Z*-isomer, characteristic signals) δ 221.35, 154.00 (C=N), 126.45 (C-1), 115.42 and 112.99 (C-2 and C-4), 63.14 (CH_2O), 38.41 (C-8), 31.58 and 29.51 (C-6 and C-12). HRMS: calcd. for $[C_{21}H_{27}NO_3K]^+$ 380.1628; found 380.1615 ($[M+K]^+$).

1,1'-[1,4-Phenylenebis(oxy)]diacetone dioxime (9w). To a stirred solution of hydroquinone (110 mg, 1 mmol) in DMF (3 mL) was added a 1 M solution of bis(oxy)enamine **10a** (3 mL, 3 mmol) at r.t. After 24 h of stirring, the reaction mixture was concentrated in vacuum at 50°C and the residue was subjected to a column chromatography on silica gel (eluent hexane-AcOEt from 5 : 1 to 0 : 1). Yield: 130 mg (52%). Dynamic mixture of *E,E*- and *E,Z*-isomers, ratio 2.1 : 1. White solid. Mp = 85-88°C (washed with H_2O). R_f = 0.51 (AcOEt-hexane = 1 : 1). ^{1}H NMR (300 MHz, DMSO-d_6, *E,E*-isomer) δ 10.90 (s, 2H, OH), 6.91 (s, 4H, 4 CH_{Ar}), 4.49 (s, 4H, 2 CH_2O), 1.83 (s, 6H, 2 CH_3). ^{13}C NMR (75 MHz, JMOD, DMSO-d_6, *E,E*-isomer) δ 152.26 and 152.12 (2 C=N and 2 C_{Ar}), 115.79 (4 CH_{Ar}), 69.97 (2 CH_2O), 11.40 (2 CH_3). ^{1}H NMR (300 MHz, DMSO-d_6, *E,Z*-isomer, characteristic signals) δ 10.90 (s, 1H, OH, *E*-fragment), 10.80 (s, 1H, OH, *Z*-fragment), 4.53 (s, 2H, CH_2O, Z-fragment), 4.49 (s, 2H, CH_2O, *E*-fragment), 1.89 and 1.75 (2 s, 3H and 3H, 3 CH_3). ^{13}C NMR (75 MHz, JMOD, DMSO-d_6, *E,Z*-isomer) δ 154.65 (C=N, *Z*-fragment), 152.82 and 152.57 (C=N and 2 C_{Ar}), 115.86 (4 CH_{Ar}), 74.70 (CH_2O, *Z*-fragment) and 69.44 (CH_2O, *E*-fragment), 12.07 (CH_3, *Z*-fragment), 11.31 (CH_3, *E*-fragment). Anal. calcd. for $C_{12}H_{16}N_2O_4$: C, 57.13; H, 6.39; N, 11.10. Found C, 56.78; H, 6.65; N, 11.74.

(*S*)-1,1'-[1,1'-binaphthalene-2,2'-diylbis(oxy)]diacetone dioxime (9x). To a stirred solution of (*S*)-(−)-1,1'-bi(2-naphthol) (71.5 mg, 0.25 mmol) in DMF (0.75 mL) was added a 1 M solution of bis(oxy)enamine **10a** (0.75 mL, 0.75 mmol) at r.t. After 24 h of stirring, the reaction mixture was concentrated in vacuum at 50°C and the residue was subjected to a column chromatography on silica gel (eluent hexane-AcOEt from 5 : 1 to 1 : 1). Yield: 86 mg (80%). White solid. Dynamic mixture of *E,E*- and *E,Z*-isomers, ratio 2.3 : 1. Mp = 44-48°C. R_f = 0.16 (AcOEt-hexane = 1 : 3). $[\alpha]_D$ = -40.6 (CH_3OH, c = 1.0, 22°C). ^{1}H NMR (300 MHz, Chloroform-*d*, *E*-isomer) δ 9.06 (br s, 2H, OH), 7.93 (d, 2H, *J* = 9.0 Hz, HC-4), 7.86 (d, 2H, *J* = 8.0 Hz, HC-6), 7.43 (d, 2H, *J* = 9.0 Hz, HC-3), 7.35 (dd, *J* = 8.0, 6.0 Hz, 2H, HC-7), 7.26 (d, *J* = 7.8 Hz, 2H, HC-9), 7.20 (dd, *J* = 7.8, 6.0 Hz, 2H, HC-8), 4.51 (d, 2H, *J* = 11.9 Hz, CH_2O), 4.45 (d, 2H, *J* = 11.9 Hz, CH_2O), 1.38 (s, 6H, 2 CH_3). ^{13}C NMR (75 MHz, JMOD, DMSO-d_6, *E,E*-isomer) δ 155.54 and 153.69 (C=N and C-2), 134.09 (C-10), 129.65 (C-5), 129.59 (C-4), 127.98, 126.48, 125.47 and 124.00 (C-6, C-7, C-8 and C-9), 120.72 (C-1), 115.81 (C-3), 70.96 (CH_2O), 10.75 (CH_3). ^{1}H NMR (300 MHz, DMSO-d_6, *E,Z*-isomer) δ 9.06 (br s, 2H, OH), 7.93 (d, 2H, *J* = 9.0 Hz, HC-4), 7.86 (d, 2H, *J* = 8.0 Hz, HC-6), 7.43 (d, 2H, *J* = 9.0 Hz, HC-3), 7.35 (dd, *J* = 8.0, 6.0 Hz, 2H, HC-7), 7.26 (d, *J* = 7.8 Hz, 2H, HC-9), 7.20 (dd, *J* = 7.8, 6.0 Hz, 2H, HC-8), 4.52 (d, *J* = 11.9 Hz, 2H, CH_2O), 4.45 (d, *J* = 11.9 Hz, 2H, CH_2O), 1.84 (s, 3H, CH_3, *Z*-fragment), 1.38 (s, 3H, CH_3, *E*-fragment). ^{13}C NMR (75 MHz, JMOD, DMSO-d_6, *E,Z*-isomer) δ 155.81 and 155.74 (2 C=N), 153.61 (C-2), 134.09 (C-10), 129.65 (C-5), 129.59 (C-4), 127.98, 126.48, 125.43 and 124.00 (C-6, C-7, C-8 and C-9), 120.56 (C-1), 115.66 (C-3), 74.55 (CH_2O, *Z*-fragment), 70.62 (CH_2O, *E*-fragment), 15.63 (CH_3, *Z*-fragment), 11.55 (CH_3, *E*-fragment). HRMS: calcd. for $[C_{26}H_{24}N_2O_4Na]^+$ 451.1628; found 451.1619 ($[M+Na]^+$).

(*S*)-1-((2'-hydroxy-[1,1'-binaphthalen]-2-yl)oxy)propan-2-one oxime (9x'). To a stirred solution of (*S*)-(-)-1,1'-bi(2-naphthol) (30 mg, 0.1 mmol) in DMF (0.3 mL) was added a 1 M solution of bis(oxy)enamine **10a** (0.1 mL, 0.1 mmol) at 0°C. After 1 h the mixture was allowed to warm to r.t. After 24 h, methanol (2 mL) was added and the mixture was stirred for additional 1 h. The resulting solution was concentrated in vacuum at 50°C and the residue was subjected to a column chromatography on silica gel (eluent hexane-AcOEt from 5 : 1 to 1 : 1). Yield: 30 mg (83%). Oil, which solidified upon standing. Dynamic mixture of *E*- and *Z*-isomers, ratio 5 : 1. Mp = 45-47°C. R_f = 0.54 (AcOEt-hexane = 1 : 3). $[\alpha]_D$ = -45.5 (CH_3OH, c = 1.0, 21°C). ^{1}H NMR (300 MHz, *E*-isomer, Chloroform-*d*) δ 8.7-8.3 (br s, 1H, NOH), 8.05-7.84 (m, 4H, HC-4, HC-4', HC-6 and HC-6'), 7.45-7.17 (m and d, *J* = 8.4 Hz, 7H and 1H, HC-3, HC-3', HC-7, HC-7', HC-8 and HC-8', HC-9 and HC-9'), 6.3-5.8 (br s, 1H, OH), 4.63 (d, *J* = 13.6 Hz, 1H, CH_2O), 4.50 (d, *J* = 13.5 Hz, 1H, CH_2O), 1.55 (s, 3H, CH_3). ^{13}C NMR (75 MHz, *E*-isomer, $CDCl_3$) δ 154.88, 154.17 and 151.47 (C=N, C-2 and C-2'), 134.10 and 133.92 (C-10 and C-10'), 130.78 and 129.81 (C-4 and C-4'), 129.87 and 129.25 (C-5 and C-5'), 128.16, 128.13, 127,27, 126.46, 125.33, 125.00, 124.54 and 123.34 (C-6, C-6', C-7, C-7', C-8, C-8', C-9 and C-9'), 118.30 (C-1 and C-1'), 115.06 (C-3 and C-3'), 69.68 (CH_2O), 11.01 (CH_3). ^{1}H NMR (300 MHz, *Z*-isomer, Chloroform-*d*, characteristic signals) δ 4.87 (s, 2H, CH_2), 1.33 (s, 3H, CH_3). ^{13}C NMR (75 MHz, *Z*-isomer, $CDCl_3$, characteristic signals) δ 154.88, 154.31 and 151.47 (C=N, C-2 and C-2'), 134.10 and 133.92 (C-10 and C-10'), 131.43, 131.21, 129.89, 128.47, 128.31, 127.57, 127.52, 126.49, 124.80 and 124.08 (C-5, C-5', C-6, C-6', C-7, C-7', C-8, C-8', C-9 and C-9'), 117.87 and 117.46 (C-1 and C-1'), 114.15 (C-3 and C-3'), 64.27 (CH_2O), 15.54 (CH_3). HRMS: calcd. for $[C_{23}H_{19}NO_3Na]^+$ 380.1257; found 380.1252 ($[M+Na]^+$).

1-(2,6-Dimethylphenoxy)propan-2-one oxime (9y). To a stirred solution of 2,6-dimethylphenol (610 mg, 5 mmol) in DMF (15 mL) was added a 1 M solution of bis(oxy)enamine **10a** (5 mL, 5 mmol) at 0°C. After 1 h the mixture was allowed to warm to r.t. After stirring for 24 h at r.t., the reaction mixture was concentrated in vacuum at 50°C and the residue was subjected to a column chromatography on silica gel (eluent hexane-AcOEt from 5 : 1 to 1 : 1). Yield: 791 mg (82%). Single *E*-isomer. White solid. Mp = 79-81°C (lit.[32] 70-71°C). R_f = 0.46 (AcOEt-hexane = 1 : 1). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 9.02 (s, 1H, OH), 7.05 (d, *J* = 7.3 Hz, 2H, HC-3), 6.97 (m, 1H, HC-4), 4.35 (s, 2H, CH_2O), 2.33 (s, 6H, 2 CH_3), 2.17 (s, 3H, CH_3). NMR spectra are in accordance with literature data.[32] Anal. calcd. for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found C, 68.41; H, 7.88; N, 7.26.

4'-(2-(Hydroxyimino)propoxy)-[1,1'-biphenyl]-4-carbonitrile (9z). To a stirred solution of 4'-hydroxy-[1,1'-biphenyl]-4-carbonitrile (195 mg, 1 mmol) in DMF (3 mL) was added a 1 M solution of bis(oxy)enamine **10a** (1 mL, 1 mmol) at 0°C. After 1 h the mixture was allowed to warm to r.t.

After stirring for 24 h at r.t., the reaction mixture was concentrated in vacuum at 50°C and the residue was treated with AcOEt/pentane mixture. The resulting precipitate was filtered to give 106 mg of oxime **9z**. Evaporation of mother liquor and subsequent crystallization from AcOEt/pentane gave additional 74 mg of **9z**. Yield: 68%. Single *E*-isomer. White solid. Mp = 164-167°C (AcOEt/pentane). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.98 (s, 1H, OH), 7.89 and 7.85 (2 d, J = 8.5 Hz and J = 8.5 Hz, 2H and 2H, HC-2 and HC-3), 7.72 (d, J = 8.5 Hz, 2H, HC-2'), 7.12 (d, J = 8.5 Hz, 2H, HC-3'), 4.65 (s, 2H, CH_2O), 1.87 (s, 3H, CH_3). ^{13}C NMR (75 MHz, DMSO-d_6) δ 158.74 and 151.69 (C=N and C-4'), 144.08 (C-1), 130.79 (C-1'), 132.64, 128.19 and 126.81 (C-2, C-2' and C-3), 118.85 (C≡N), 115.40 (C-3'), 109.15 (C-4), 69.50 (CH_2O), 11.34 (CH_3). Anal. calcd. for $C_{16}H_{14}N_2O_2$: C, 72.17; H, 5.30; N, 10.52. Found C, 71.52; H, 5.13; N, 10.54.

Generation of nitrosoalkene intermediate F and oligomers OL1 and OL2. To bis(oxy)enamine **10a** (58 mg, 0.25 mmol) was added DMF (0.4 mL). Almost immediately, light blue color appeared (UV-Vis, 738 nm, N=O), which stayed for about 15 minutes. NMR control revealed the absence on initial enamine **10a**. After keeping for 24 h at r.t., the mixture was concentrated in vacuum. Analysis of the residue by NMR and HRMS revealed it oligomeric structure **OL1** (n = 0-8). Also, oligomers **OL2** were detected by HRMS analysis in trace amount (n = 1-12).

2-Nitrosoprop-1-ene (nitrosoalkene F). UV-Vis: 738 nm (N=O).

Oligomers OL1 (n = 0-8). Oil. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.94-8.19 (br, terminal NOH groups), 4.65-4.49 (br s, 2H, CH_2O fragments), 2.11-1.79 (br s, 3H, CH_3 groups). ^{13}C NMR (75 MHz, JMOD, $CDCl_3$) δ 155.86, 155.79 and 155.48 (C=N), 74.79 (br) and 64.12 (CH_2O fragments), 12.26, 11.51 and 11.08 (CH_3 groups). HRMS: calcd. for $[C_6H_{13}N_2O_3]^+$ 161.0926; found 161.0960 ($[M+H]^+$) (n = 0); calcd. for $[C_9H_{18}N_3O_4]^+$ 232.1297; found 232.1306 ($[M+H]^+$) (n = 1); calcd. for $[C_{12}H_{23}N_4O_5]^+$ 303.1668; found 303.1664 ($[M+H]^+$) (n = 2); calcd. for $[C_{15}H_{28}N_5O_6]^+$ 374.2040; found 374.2024 ($[M+H]^+$) (n = 3); calcd. for $[C_{18}H_{33}N_6O_7]^+$ 445.2410; found 445.2397 ($[M+H]^+$) (n = 4); calcd. for $[C_{21}H_{38}N_7O_8]^+$ 516.2782; found 516.2770 ($[M+H]^+$) (n = 5). calcd. for $[C_{24}H_{43}N_8O_9]^+$ 587.3153; found 587.3150 ($[M+H]^+$) (n = 6); calcd. for $[C_{27}H_{48}N_9O_{10}]^+$ 657.3440; found 657.3445 ($[M+H]^+$) (n = 7); calcd. for $[C_{30}H_{53}N_{10}O_{11}]^+$ 729.3889; found 729.3895 ($[M+H]^+$) (n = 8).

Oligomers OL2 (n = 1-12). Detected by HRMS together with oligomers **OL2**. HRMS: calcd. for $[C_{11}H_{23}N_4O_3]^+$ 259.1770; found 259.1763 ($[M+H]^+$) (n = 1); calcd. for $[C_{17}H_{33}N_6O_5]^+$ 401.2512; found 401.2493 ($[M+H]^+$) (n = 3); calcd. for $[C_{20}H_{38}N_7O_6]^+$ 472.2883; found 472.2875 ($[M+H]^+$) (n = 4); calcd. for $[C_{23}H_{43}N_8O_7]^+$ 543.3255; found 543.3240 ($[M+H]^+$) (n = 5); calcd. for $[C_{26}H_{48}N_9O_8]^+$ 614.3626; found 614.3622 ($[M+H]^+$) (n = 6); calcd. for $[C_{29}H_{53}N_{10}O_9]^+$ 685.3997; found 685.3985 ($[M+H]^+$) (n = 7); calcd. for $[C_{32}H_{58}N_{11}O_{10}]^+$ 756.4368; found 756.4359 ($[M+H]^+$) (n = 8); calcd. for $[C_{35}H_{63}N_{12}O_{11}]^+$ 827.4739; found 827.4732 ($[M+H]^+$) (n = 9); calcd. for $[C_{38}H_{68}N_{13}O_{12}]^+$ 898.5110; found 898.5107 ($[M+H]^+$) (n = 10); calcd. for $[C_{41}H_{73}N_{14}O_{13}]^+$ 969.5482; found 969.5485 ($[M+H]^+$) (n = 11); calcd. for $[C_{44}H_{78}N_{15}O_{14}]^+$ 1040.5853; found 1040.5847 ($[M+H]^+$) (n = 12).

Interception of nitrosoalkene intermediate with ethyl vinyl ether. To a stirred solution of ethyl vinyl ether (0.72 mL, 7.5 mmol) in DMF (2.25 mL) was added a 1M solution of bis(oxy)enamine **10b** (1.5 mL, 1.5 mmol) at 0°C under argon atmosphere. After 1 h, the mixture was allowed to warm to r.t. and kept overnight. The resulting solution was concentrated in vacuum and subjected to column chromatography on silica gel (eluent hexane-AcOEt = 10 : 1→ 0 : 1). Three fractions were collected: the first one contained cycloadduct **11** (43 mg, 14%), the second one contained 3-hydroxy-2-(hydroxyimino)propanoate[30] (110 mg, 50%), the third fraction (61 mg) contained a mixture of oligomeric products.

Ethyl 6-ethoxy-5,6-dihydro-4*H*-1,2-oxazine-3-carboxylate (11). Oil. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 5.18 (t, J = 2.6 Hz, 1H, HC-6), 4.33 (q, J = 7.1 Hz, 2H, CH_3CH_2O), 3.87 (m, 1H, CH_3CH_2O), 3.63 (m, 1H, CH_3CH_2O), 2.59-2.34 (m, 2H, H_2C-4), 2.06 (m, 1H, HC-5), 1.83 (m, 1H, HC-5), 1.36 (t, J = 7.1 Hz, 3H, CH_3CH_2O), 1.19 (t, J = 7.1 Hz, 3H, CH_3CH_2O). NMR spectra are in accordance with literature data.[24]

***Rac*-*N*-(1-Hydroxy-3-phenylpropan-2-yl)acetamide (12f)**. Raney nickel (c.a. 0.05 g, washed with methanol) was placed in a test tube equipped with a magnetic stirrer bar and charged with a solution of oxime **9f** (192 mg, 0.93 mmol) in methanol (1 mL). The test tube was placed in a steel autoclave which was then flushed and filled with H_2 to a pressure of 40 bar. The mixture was stirred at 60°C for 4 h. After cooling to r.t., the autoclave was slowly depressurized. The catalyst was filtered off and the solvent was evaporated under reduced pressure. The residue was dissolved in toluene (3 mL), the solution was refluxed for 1 h and then concentrated in vacuum. The residue was subjected to column chromatography on silica gel to give 136 mg (75%) of product **12f**. White solid (triturated with pentane). Mp = 86-89°C (lit.[33a] 90-95°C). R_f = 0.52 (AcOEt-hexane = 1 : 1). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.49-7.01 (m, 5H, *o,m,p*-C_6H_5), 5.92 (br s, 1H, NH), 4.18 (m, 1H, CH), 3.68 (dd, J = 11.1, 3.6 Hz, 1H, CH_2O), 3.58 (dd, J = 11.1, 5.1 Hz, 1H, CH_2O), 3.0-2.5 (br, 1H, OH), 2.88 (d, J = 7.3 Hz, 2H, CH_2Ph), 1.98 (s, 3H, CH_3). ^{13}C NMR (75 MHz, JMOD, $CDCl_3$) δ 170.90 (C=O), 137.78 (*i*-C_6H_5), 129.25, 128.65 and 126.68 (*o,m,p*-C_6H_5), 63.86 (CH_2O), 52.91 (CH), 37.07 (CH_2), 23.36 (CH_3). NMR spectra are in agreement with literature data.[33b,c]

***Rac*-*N*-(1-Hydroxypropan-2-yl)-3-(1*H*-indol-3-yl)propanamide (12m).** Raney nickel (c.a. 0.05 g, washed with methanol) was placed in a test tube equipped with a magnetic stirrer bar and charged with a solution of oxime **9m** (124 mg, 0.48 mmol) in methanol (0.9 mL). The test tube was placed in a steel autoclave which was then flushed and filled with H_2 to a pressure of 40 bar. The mixture was stirred at 60°C for 4 h. After cooling to r.t., the autoclave was slowly depressurized. The catalyst was filtered off and the solvent was evaporated under reduced pressure. The residue was dissolved in toluene (3 mL), the solution was refluxed for 1 h and then concentrated in vacuum. The residue was subjected to column chromatography on silica gel to give 71 mg (60%) of product **12m**. Also 11 mg (11%) of 3-indolepropionic acid methyl ester was isolated. White solid. Mp = 92-94°C ($CHCl_3$). R_f = 0.2 (AcOEt-hexane = 1 : 3). ^{1}H NMR (200 MHz, DMSO-d_6) δ 10.76 (br s, 1H, NH), 7.63 (br d, J = 8.1 Hz, 1H, NH-C(O)), 7.54 and 7.34 (2 d, J = 7.7 Hz and J = 8.0 Hz, 1H and 1H, HC-4 and HC-7), 7.10 (s, 1H, HC-2), 7.07 (2 dd, J = 7.7 and 7.1 Hz, J = 7.7 and 7.0 Hz, 1H and 1H, HC-5 and HC-6), 4.66 (t, J = 5.6 Hz, 1H, OH), 3.79 (m, 1H, HC), 3.36 and 3.19 (2 m, 1H and 1H, CH_2O), 2.92 and 2.43 (2 t, J = 7.7 Hz and J = 7.6 Hz, 2H and 2H, CH_2-CH_2), 1.01 (d, J = 6.6 Hz, 3H, CH_3). ^{13}C NMR (50 MHz, DEPT135, DMSO-d_6) δ 171.41 (C=O), 136.21 and 127.06 (C-3a and C-7a), 122.04, 120.84, 118.35, 118.07 and 111.26 (C-2, C-4, C-5, C-6 and C-7), 113.94 (C-3), 64.53 (CH_2O), 46.36 (CH), 36.39 and 21.05 (CH_2-CH_2), 17.20 (CH_3). HRMS: calcd. for $[C_{14}H_{19}N_2O_2]^+$ 247.1441; found 247.1441 ($[M+H]^+$).

***Rac*-2-((*tert*-Butoxycarbonyl)amino)-3-phenylpropyl acetate (13f).** A solution of oxime **9f** (100 mg, 0.48 mmol) and Boc_2O (211 mg, 0.96 mmol) in methanol (1 mL) was placed in a test tube equipped with a magnetic stirrer bar and Raney nickel (c.a. 0.05 g, washed with methanol) was added. The test tube was placed in a steel autoclave which was then flushed and filled with H_2 to a pressure of 40 bar. The mixture was stirred at 60°C for 4 h. After cooling to r.t., the autoclave was slowly depressurized. The catalyst was filtered off and the solvent was evaporated under reduced pressure. The residue was subjected to column chromatography on silica gel to give 97 mg (69%) of product **13f**. Oil. R_f = 0.63 (AcOEt-hexane = 1 : 1). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.37-7.16 (m, 5H, *o,m,p*-C_6H_5), 4.71 (br s, 1H, NH), 4.13 (m, 1H, HC),

4.07-4.00 (m, 2H, CH_2O), 2.95-2.71 (m, 2H, CH_2), 2.09 (s, 3H, CH_3), 1.43 (s, 9H, ^{t}Bu). ^{13}C NMR (75 MHz, JMOD, $CDCl_3$) δ 170.82 (C=O), 155.22 (N-C=O), 137.26 (*i*-C_6H_5), 129.28, 128.58 and 126.65 (*o,m,p*-C_6H_5), 79.58 ($(CH_3)_3C$-O), 65.15 (CH_2O), 50.72 (CH), 38.00 (CH_2), 28.36 ($(CH_3)_3$C-O), 20.80 (CH_3). HRMS: calcd. for $[C_{16}H_{24}NO_4]^+$ 294.1700; found 294.1703 ($[M+H]^+$).

***Rac*-2-((*tert*-Butoxycarbonyl)amino)propyl 3-(1*H*-indol-3-yl)propanoate (13l).** A solution of oxime **9m** (115 mg, 0.44 mmol) and Boc_2O (192 mg, 0.88 mmol) in methanol (1 mL) was placed in a test tube equipped with a magnetic stirrer bar and Raney nickel (c.a. 0.05 g, washed with methanol) was added. The test tube was placed in a steel autoclave which was then flushed and filled with H_2 to a pressure of 40 bar. The mixture was stirred at 60°C for 4 h. After cooling to r.t., the autoclave was slowly depressurized. The catalyst was filtered off and the solvent was evaporated under reduced pressure. The residue was subjected to column chromatography on silica gel to give 100 mg (66%) of product **13m**. Oil, which crystallized upon standing. Mp = 84-86°C. R_f = 0.63 (AcOEt-hexane = 1 : 1). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.06 (br s, 1H, NH), 7.63 and 7.38 (2 d, *J* = 7.7 Hz and *J* = 7.9 Hz, 1H and 1H, HC-4 and HC-7), 7.22 (2 dd, *J* = 7.7, 7.3 Hz and *J* = 7.9, 7.4 Hz, 1H and 1H, HC-5 and HC-6), 7.04 (s, 1H, HC-2), 4.49 (br s, 1H, NH), 4.05 (m, 2H, CH_2O), 3.94 (br m, 1H, CH), 3.14 and 2.78 (2 t, *J* = 7.6 Hz and *J* = 7.6 Hz, 2H and 2H, CH_2-CH_2), 1.47 (s, 9H, ^{t}Bu), 1.09 (d, *J* = 6.7 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.35 (C=O), 155.23 (HNC=O), 136.37 (C-7a), 127.21 (C-3a), 122.17, 121.54, 119.44 and 118.75 (C-2, C-4, C-5 and C-6), 114.91 (C-3), 111.24 (C-7), 80.12 ($(CH_3)_3C$-O), 67.27 (CH_2O), 45.53 (*C*HNHBoc), 34.93 and 20.78 (CH_2-CH_2), 28.48 ($(CH_3)_3$C-O), 17.67 (CH_3). HRMS: calcd. for $[C_{19}H_{27}N_2O_4]^+$ 347.1965; found 347.1968 ($[M+H]^+$).

***Rac*-1-(4-Ethylphenoxy)propan-2-amine hydrochloride (14u).** A solution of oxime **9u** (110 mg, 0.57 mmol) in methanol (1.5 mL) was placed in a vial equipped with a magnetic stirrer bar and Raney nickel (c.a. 0.05 g, washed with methanol) was added. The vial was placed in a steel autoclave which was then flushed and filled with H_2 to a pressure of 40 bar. The mixture was stirred at 60°C for 4 h. After cooling to r.t., the autoclave was slowly depressurized. The catalyst was filtered off and the solvent was evaporated under reduced pressure. The residue was dissolved in diethyl ether (2 mL) and 63 µL of 38% aqueous HCl (0.77 mmol) was added. The resulting precipitate was filtered, washed with diethyl ether and dried in vacuum to give 117 mg (96%) of salt **14y**. White solid. Mp = 158-160°C ($CHCl_3$). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.57 (br s, 3H, NH_3), 7.06 (d, *J* = 7.9 Hz, 2H, HC-3), 6.90 (d, *J* = 7.9 Hz, 2H, HC-2), 4.05 (br m, 2H, CH_2O), 3.61 (br m, 1H, CH), 2.57 (q, *J* = 7.6 Hz, 2H, C*H*$_2$CH$_3$), 1.41 (br s, 3H, CH_3), 1.19 (t, *J* = 7.5 Hz, 3H, CH_2C*H*$_3$). ^{13}C NMR (75 MHz, JMOD, $CDCl_3$) δ 155.89 (C-1), 137.31 (C-4), 128.74 (C-3), 114.84 (C-2), 68.48 (CH_2O), 47.74 (CH), 28.02 (CH_2), 15.90 and 15.30 (2 CH_3). Anal. calcd. for $C_{11}H_{18}ClNO$: C, 61.25; H, 8.41; N, 6.49. Found C, 60.61; H, 8.68; N, 6.45.

***Rac*-1-(2,6-Dimethylphenoxy)propan-2-amine hydrochloride (Mexiletine hydrochloride, 14y)**.[28a] A solution of oxime **9y** (200 mg, 1.04 mmol) in methanol (2 mL) was placed in a vial equipped with a magnetic stirrer bar and Raney nickel (c.a. 0.05 g, washed with methanol) was added. The vial was placed in a steel autoclave which was then flushed and filled with H_2 to a pressure of 40 bar. The mixture was stirred at 60°C for 4 h. After cooling to r.t., the autoclave was slowly depressurized. The catalyst was filtered off and the solvent was evaporated under reduced pressure. The residue was dissolved in diethyl ether (3 mL) and 91 µL of 38% aqueous HCl (1.03 mmol) was added. The resulting precipitate was filtered, washed with diethyl ether and dried in vacuum to give 197 mg (88%) of salt **14y**. White solid. Mp = 205-207°C (lit.[28b] 215-216°C, lit.[28c] 202°C). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.54 (br s, 3H, NH_3), 7.04 (d, *J* = 7.3 Hz, 2H, HC-3), 6.95 (t, *J* = 7.3 Hz, 1H, HC-4), 3.85 (d, *J* = 5.2 Hz, 2H, CH_2O), 3.57 (m, 1H, CH), 2.26 (s, 6H, 2 CH_3), 1.38 (d, *J* = 6.6 Hz, 3H, CH_3). NMR spectra are in accordance with literature data.[28b]

***Rac-N*-(1-(4-Ethylphenoxy)propan-2-yl)hydroxylamine (15u).** To a stirred solution of oxime **9u** (73 mg, 0.38 mmol) in glacial AcOH (3.7 mL) was added $NaBH_3CN$ (155 mg, 2.46 mmol) under argon atmosphere at ambient temperature. After 30 min, second portion of $NaBH_3CN$ (52 mg, 0.82 mmol) was added. After stirring for additional 30 minutes, the resulting solution was poured into a mixture of ethyl acetate (50 mL) and saturated solution of K_2CO_3 (50 mL). The aqueous layer was back-extracted with ethyl acetate (50 mL). Combined organic layers were washed with saturated solution of K_2CO_3 (50 mL), water (50 mL), and brine (50 mL), dried (Na_2SO_4), and evaporated in vacuum. The residue was subjected to column chromatography on silica gel to give 57 mg (77%) of **15u**. Oil. R_f = 0.44 (AcOEt-hexane = 1 : 1). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.13 (d, *J* = 8.4 Hz, 2H, HC-3), 6.87 (d, *J* = 8.5 Hz, 2H, HC-2), 6.75-5.75 (br s, 2H, NHOH), 4.01-3.93 (m, 2H, CH_2O), 3.41 (m, 1H, CH), 2.62 (q, *J* = 7.6 Hz, 2H, C*H*$_2$CH$_3$), 1.24 (t, *J* = 7.0 Hz, 3H, CH_2C*H*$_3$), 1.23 (d, *J* = 7.0 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, JMOD, $CDCl_3$) δ 156.81 (C-1), 136.76 (C-4), 128.74 (C-3), 114.54 (C-2), 68.46 (CH_2O), 56.41 (CH), 28.02 (CH_2), 15.88 and 14.52 (2 CH_3). HRMS: calcd. for $[C_{11}H_{18}NO_2]^+$ 196.1332; found 196.1337 ($[M+H]^+$).

***Rac-N*-(1-(2,6-Dimethylphenoxy)propan-2-yl)hydroxylamine (*N*-hydroxy-Mexiletine, 15y).**[28d] To a stirred solution of oxime **9y** (200 mg, 1.03 mmol) in glacial AcOH (4.6 mL) was added $NaBH_3CN$ (195 mg, 3.09 mmol) under argon atmosphere at ambient temperature. After 1.5 h, second portion of $NaBH_3CN$ (126 mg, 2.0 mmol) was added. After stirring for additional 30 minutes, the resulting solution was poured into a mixture of ethyl acetate (50 mL) and saturated solution of K_2CO_3 (50 mL). The aqueous layer was back-extracted with ethyl acetate (50 mL). Combined organic layers were washed with saturated solution of K_2CO_3 (50 mL), water (50 mL), and brine (50 mL), dried (Na_2SO_4), and evaporated in vacuum. The residue was subjected to column chromatography on silica gel to give 173 mg (86%) of **15y**. Oil, which crystallized upon standing. Mp = 69-71°C (lit.[28d] 72-73°C). R_f = 0.33 (AcOEt-hexane = 1 : 1). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.04 (d, *J* = 7.4 Hz, 2H, HC-3), 6.95 (t, *J* = 7.4 Hz, 2H, HC-4), 7.0-5.5 (br s, 2H, NHOH), 3.81 (m, 2H, CH_2O), 3.45 (m, 1H, CH), 2.32 (s, 6H, 2 CH_3), 1.27 (d, *J* = 6.6 Hz, 3H, CH_3). NMR spectra are in accordance with literature data.[28d]

***Rac*-4'-(2-(Hydroxyamino)propoxy)-[1,1'-biphenyl]-4-carbonitrile (15z).** To a stirred solution of oxime **9z** (100 mg, 0.38 mmol) in glacial AcOH (1.7 mL) was added $NaBH_3CN$ (71 mg, 1.13 mmol) under argon atmosphere at ambient temperature. After 1.5 h, second portion of $NaBH_3CN$ (47 mg, 0.74 mmol) was added. After stirring for additional 30 minutes, the resulting solution was poured into a mixture of ethyl acetate (50 mL) and saturated solution of K_2CO_3 (50 mL). The aqueous layer was back-extracted with ethyl acetate (50 mL). Combined organic layers were washed with saturated solution of K_2CO_3 (50 mL), water (50 mL), and brine (50 mL), dried (Na_2SO_4), and evaporated in vacuum. The residue was subjected to column chromatography on silica gel to give 60 mg (59%) of **15z**. Oil, which crystallized upon standing. Mp = 100-104°C. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.71 and 7.64 (2 d, *J* = 8.1 Hz and *J* = 8.1 Hz, 2H and 2H, HC-2 and HC-3), 7.54 (d, *J* = 8.3 Hz, 2H, HC-3'), 7.03 (d, *J* = 8.3 Hz, 2H, HC-2'), 6.13 (br s, 2H, NHOH), 4.05 (d, *J* = 5.5 Hz, 2H, CH_2O), 3.45 (m, 1H, CH), 1.26 (d, *J* = 6.7 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, JMOD, $CDCl_3$) δ 159.41 (C-4'), 145.18 (C-1), 131.83 (C-1'), 132.61, 128.41 and 127.15 (C-2, C-2', C-3), 119.08 (C≡N), 115.24 (C-3'), 110.24 (C-4), 68.47 (CH_2O), 56.36 (CH), 14.55 (CH_3). HRMS: calcd. for $[C_{16}H_{17}N_2O_2]^+$ 269.1285; found 269.1287 ($[M+H]^+$).

***N*-(1-((4'-Cyano-[1,1'-biphenyl]-4-yl)oxy)propan-2-yl)-*N*-hydroxyformamide (16z).**[20a,b] To a stirred solution of hydroxylamine **15z** (30 mg, 0.11 mmol) in CH_2Cl_2 (1 mL) was added acetic formic anhydride[34] (18 μL, 0.22 mmol) at r.t. under argon atmosphere. The solution was kept overnight, evaporated and the residue was subjected to column chromatography on silica gel to give 17 mg (52%) of hydroxamic acid **16z**. White solid. Mp 57-59°C (CH_3O^tBu-pentane). R_f = 0.1 (AcOEt-hexane = 1 : 1). ^1H NMR (300 MHz, DMSO-d_6, mixture of two rotamers 1.6 : 1.0) δ 9.90 (s, 1H, OH, minor rotamer) and 9.45 (br s; 1H, OH, major rotamer), 8.35 (s, 1H, C(O)H, minor rotamer), 8.03 (s, 1H, C(O)H, major rotamer), 7.89 and 7.85 (d, *J* = 8.5 Hz and *J* = 8.5 Hz, 2H and 2H, HC-2 and HC-3, both rotamers), 7.72 (d, *J* = 8.4 Hz, 1H, HC-2', both rotamers), 7.07 (d, *J* = 8.4 Hz, 1H, HC-3', both rotamers), 4.68 (m, 1H, CH, minor rotamer), 4.25-3.94 (m, 3H, CH of major rotamer and CH_2 of both rotamers), 1.25 (d, *J* = 6.2 Hz, 3H, CH_3, major rotamer), 1.19 (d, *J* = 6.0 Hz, 3H, CH_3, minor rotamer). HRMS: calcd. for $[C_{17}H_{17}N_2O_3]^+$ 297.1236; found 297.1234 ($[M+H]^+$). NMR spectra are in accordance with literature data.[20b]

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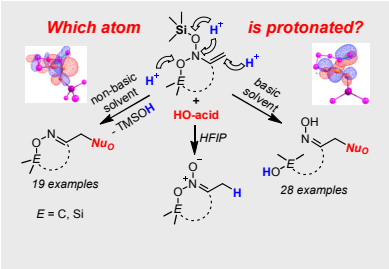
Reactive intermediates

FULL PAPER

The reactivity of *N,N*-bis(oxy)enamines towards HO-acids was found to be divergent and dramatically dependent on the solvent, which affects the reaction pathway.



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Addition of HO-acids to *N,N*-Bis(oxy)enamines: Mechanism, Scope and Application to the Synthesis of Pharmaceuticals