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Allene cyclization

The Cyclization of Allenyl-Substituted Hydroxylamines to 1,2-Oxazines: an Experimental and Computational Study

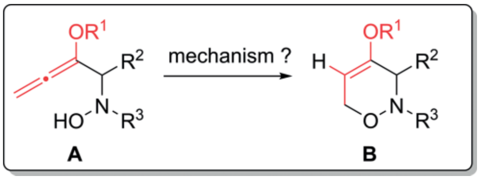
Greta Utecht-Jarzyńska,[a] Marcin Jasiński,*[a] Ernst-Ulrich Würthwein,*[b] and Hans-Ulrich Reissig*[c]

Dedicated to Professor Grzegorz Mlostoń on the occasion of his 70th birthday

Abstract: To gain a deeper understanding of the formation of the synthetically important 3,6-dihydro-2*H*-1,2-oxazines, the 6-*endo-trig* cyclization of allenyl-substituted hydroxylamines was experimentally investigated in detail employing a model compound. The solvent effect was moderate with respect to the rate, but crucial to suppress side-product formation. Surprisingly, acids or bases had no big influence on the cyclization rate. With O-deuterated allenyl hydroxylamine a high primary isotope effect was found, indicating that the proton transfer is crucial in the rate-determining step. DFT calculations evidence that the allenyl-substituted hydroxylamine is converted into an energetically similar zwitterionic intermediate with an allyl cation subunit. It cyclizes to the 1,2-oxazine as the most stable species. Alternative pathways starting from the zwitterion were computationally investigated. Interestingly, it can also undergo a fragmentation to give a pentadiene derivative and a nitroso compound. The hetero Diels–Alder reaction of these components may also deliver the 1,2-oxazine. To evaluate an alternative mechanistic scenario, calculations of the protonated allenyl-substituted hydroxylamine were also performed.

Introduction

The addition of lithiated alkoxyallenes[1] to nitrones[2] provides after aqueous work-up allenyl-substituted hydroxylamines **A** that undergo a spontaneous 6-*endo-trig* cyclization to synthetically very useful 3,6-dihydro-2*H*-1,2-oxazine derivatives **B** thereby constituting an overall [3+3] annulation process (Scheme 1).[3] The use of chiral nitrones afforded the corresponding 1,2-oxazine derivatives generally with very high diastereoselectivity. Despite of numerous synthetic applications of the alkoxyallene-nitrone chemistry for the preparation of natural products and their analogs,[1h,4] the cyclization step leading from **A** to the key 1,2-oxazine intermediates **B** was not fully understood and only speculative mechanistic proposals were discussed.[1g] The rate of the cyclization depends on the substitution pattern of the hydroxylamine moiety; sterically hindered derivatives react considerably slower. The seemingly uncatalyzed ring closure of these hydroxylamine derivatives has to be compared with the related cyclizations of hydroxyl- or amino-substituted alkoxyallenes that require strongly basic conditions for their cyclizations to dihydrofuran[5] or dihydropyrrole derivatives,[6] respectively. As a favored alternative method, mild Lewis acids, such as gold(I) complexes, could also induce these cyclizations to the five-membered heterocycles.[7] On the other hand, with related allenyl-substituted thiols a spontaneous formation of vinyl thiiranes was observed.[8]



Scheme 1. Spontaneous 6-*endo-trig* cyclization of allenyl-substituted hydroxylamines **A** into 3,6-dihydro-2*H*-1,2-oxazines **B**.

In Scheme 2 we depict two probable cyclization pathways discussed in the past.[9] In analogy to the Lewis acid-catalyzed processes mentioned above, a proton catalysis via intermediates **C** and **D** could provide the product **B**. The required proton

[a] Dr. G. Utecht-Jarzyńska, Dr. M. Jasiński
Faculty of Chemistry, University of Łódź,
Tamka 12, 91403 Łódź, Poland
E-mail: marcin.jasinski@chemia.uni.lodz.pl
[b] Prof. E.-U. Würthwein
Organisch-Chemisches Institut and Center for Multiscale Theory and Computation (CMTC), Westfälische Wilhelms-Universität Münster,
Corrensstrasse 40, 48149 Münster, Germany
E-mail: wurthwe@uni-muenster.de
[c] Prof. H.-U. Reissig
Institut für Chemie und Biochemie, Freie Universität Berlin,
Takustrasse 3, 14195 Berlin, Germany
E-mail: hreissig@chemie.fu-berlin.de
http://www.bcp.fu-berlin.de/en/chemie/chemie/forschung/OrgChem/reissig/index.html
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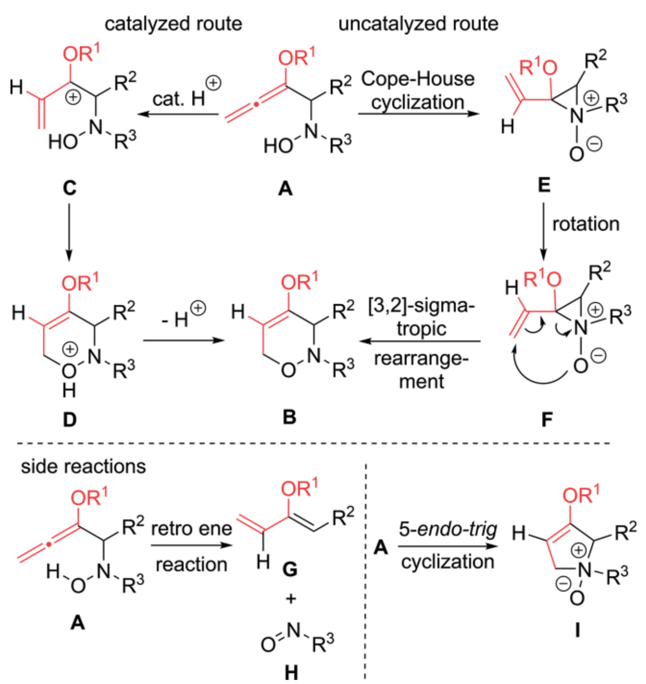
may be delivered by the solvent (and its impurities, the drying agent applied during work-up etc.), or by the hydroxylamine itself, serving as a mild acid (estimated pK_a value ca. 14).[10] An alternative mechanism without involvement of a catalyst follows a suggestion of Dulcère et al.,[11] reported for the related cyclizations of allenyl-substituted hydroxylamines lacking alkoxy groups. Two concerted steps are proposed, first a reverse Cope elimination (also known as Cope-House cyclization) to the vinyl-substituted aziridinium *N*-oxide **E** that, after a rotation of the vinyl group to conformer **F**, undergoes a sigmatropic rearrangement to the 1,2-oxazine derivative **B** (Meisenheimer 3,2-rearrangement). This elegant mechanism has the charm that no catalysts are required; it requires the hydroxylamine functional group and cannot occur with the above mentioned hydroxy- or amino-substituted allenes.



Scheme 2. Two pathways for the 6-*endo-trig* cyclization of **A** → **B**: proton-catalyzed route via intermediate **C** (left hand side) and uncatalyzed route with two concerted steps via **E** and **F** (right hand side); side reactions: retro ene reaction of **A** leading to **G** and **H** and its 5-*endo-trig* cyclization to pyrroline *N*-oxide **I**.

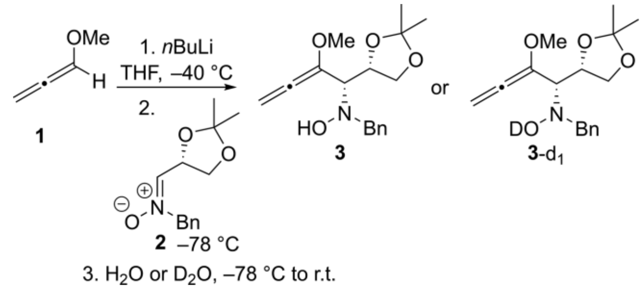
The 6-*endo-trig* cyclization of **A** to **B** was clearly the major reaction pathway in all studied cases, however, in many examples we also found fragmentation products of type **G** with a 3-alkoxy-1,3-butadiene moiety (ca. 90:10 *E*/*Z* mixture, only one isomer shown).[3c] These compounds probably arise from a retro ene reaction and in a few cases products derived from the second fragment, the nitroso compound **H**, could be identified (the corresponding oximes if R^3 bears an α-CH unit). A second side-reaction occurred essentially only when cyclic nitrones were employed as precursor. In their reaction with lithiated alkoxyallenes not only the expected bicyclic 1,2-oxazines **B** were formed, but also the isomeric pyrroline *N*-oxides **I**, formed by a 5-*endo-trig* cyclization.[3b,12]

This study describes the influence of solvents and various additives on the rate of the 6-*endo-trig* cyclization of **A** to **B** employing a suitable model allenyl hydroxylamine and its O-deuterated derivative. We also examined the effect of the reaction conditions on the formation of side products such as **G** and **I**. These experimental studies are supplemented by comprehensive DFT calculations that provide information about the energy profiles of the different mechanistic cyclization scenarios.

Results and Discussion

Experimental Investigations

As a model compound for our experimental studies, we selected the easily available allenyl hydroxylamine **3**.[3a,3c] Applying the standard method, generation of lithiated methoxyallene from **1** and *n*-butyllithium in tetrahydrofuran and subsequent addition to enantiopure D-glyceraldehyde-derived nitrone **2** at low temperature furnished after aqueous work-up the corresponding adduct **3** (Scheme 3). The THF/Et_2O solution of crude allenyl hydroxylamine **3** could be stored for weeks in a container cooled by dry ice, and aliquots of this solution were used for the subsequent kinetic studies. Typical ^{1}H-NMR signals of **3** refer to the allenic protons at ca 5.1–5.6 ppm (AB system in C_6D_6 δ 5.15, 5.24, J_{AB} = 8 Hz). The depicted *syn*-configuration of product **3** is deduced from its cyclization to 1,2-oxazine **4** (see below) whose 3*S*,4′*S*-configuration has unequivocally been proven earlier; subsequent reactions of **4** allowed X-ray analyses of products or comparison with known enantiopure compounds. The O-deuterated derivative **3**-d_1 was analogously prepared when D_2O was used for quenching the reaction. It was important that the washing of the organic extract of this mixture was also performed with deuterated water to avoid the fast H/D exchange at the hydroxylamine oxygen. Under these prerequisites the degree of O-deuteration is > 95 % as shown by the cyclization of **3**-d_1 to **4**-d_1 (see below), where this high level of D-incorporation could be proven by the ^{13}C-NMR signal of C-5 (92.5 ppm, $J_{C\text{-}D}$ = 24.1 Hz).



Scheme 3. Lithiation of methoxyallene **1** and subsequent reaction with D-glyceraldehyde-derived nitrone **2** to allenyl hydroxylamines **3** and **3**-d_1.

Aliquots of the THF solution of **3** were rapidly evaporated at room temperature and the resulting crude allenyl hydroxylamine **3** was then dissolved in the corresponding deuterated solvent (Scheme 4). Its cyclization at 21 °C was immediately followed by ^{1}H-NMR spectroscopy (200 MHz) observing the decreasing signals of **3** at 5.1–5.6 ppm (=CH_2) and the increasing

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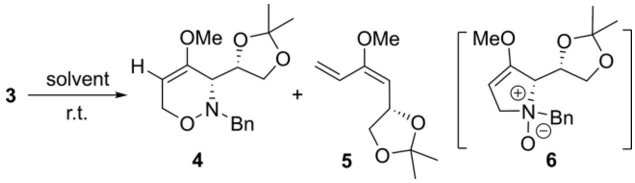
Table 1. Conversion of hydroxylamine derivative **3** into 1,2-oxazine **4** and 1,3-diene **5** according to Scheme 4 (cyclization of **3**-d_1 into **4**-d_1 in bold, entry 7) at 21 °C as determined by ^{1}H-NMR spectroscopy at 200 MHz.

Entry	Solvent	$E_T(30)$[a] (kcal/mol)	Ratio of **4**/**5**	$k_{exp} \times 10^{-5}$ (s^{-1})[b,c]	$t_{1/2(exp)}$ [min][b]	$k_{1(exp)} \times 10^{-5}$ (s^{-1})	$k_{2(exp)} \times 10^{-5}$ (s^{-1})
1	[D_{12}]cyclohexane	31.2	82:18	40	29	33	7
2	[D_8]toluene	33.9	91:9	83	14	75	8
3	[D_6]benzene	34.5	95:5	102	11	97	5
4	[D_{10}]Et_2O	34.6	76:24	14	84	11	3
5	[D_8]THF	37.4	79:21	16	71	13	3
6	$CDCl_3$	39.1	100:0	344	3	344	–
7[d]	**$CDCl_3$**	**39.1**	**100:0**[e]	**51**	**23**	**51**	**–**
8	[D_5]pyridine	40.2	91:9	24	48	22	2
9	CD_2Cl_2	41.1	100:0	348	3	348	–
10	[D_6]acetone	42.2	97:3	81	14	78	3
11	[D_6]DMSO	45.0	96:4	22	52	21	1
12	CD_3CN	46.0	99:1	199	6	197	2

[a] $E_T(30)$ values for non-deuterated solvents (Ref.[13]). [b] The *k* values should be considered as a consumption rate of **3** or **3**-d_1. [c] Coefficient of determination $R^2 > 0.998$. [d] **3**-d_1 was employed as starting material. [e] Under these conditions the by-product **5** was not observed.

signals of 1,2-oxazine **4** at 4.8–5.0 ppm (5-H) and/or 3.1–3.6 ppm (3-H) and of 1,3-diene **5** at 5.05–5.25, 5.6–5.9, and 6.4–6.8 ppm. The ratio of the cyclization product **4** and the fragmentation product **5** considerably depends on the solvent employed (Table 1).



Scheme 4. Cyclization of allenyl hydroxylamine **3** in different solvents to 1,2-oxazine **4** and 1,3-diene derivative **5** (for details also see Table 1 and Table 2).

In the ether solvents [D_8]THF and [D_{10}]diethyl ether (entries 4 and 5) the results of preparative experiments were confirmed, where 5–20 % of the side product **5** were isolated.[3c] Relatively high amounts of this compound were also observed in other solvents of low polarity (entries 1–3) according to the $E_T(30)$ scale of Reichardt.[13] On the other hand, 1,3-diene **5** was formed in a much lower extent when chlorinated solvents (entries 6, 7 and 9) or aprotic polar solvents (entries 10–12), for instance [D_3]acetonitrile, were employed. Only, [D_5]pyridine was exceptional in this respect, since it also promoted the formation of ca. 9 % of **5** (entry 8). In none of the experiments the formation of the pyrroline *N*-oxide **6** could be detected within the limit of NMR accuracy.

The ^{1}H-NMR experiments also allowed a determination of the experimental rate constant k_{exp} and half-life time $t_{1/2}$ in the different solvents (columns 5 and 6 of Table 1). The consumption of allenyl hydroxylamine **3** is consist with a first-order rate law (for details see Supporting Information). Within the limits of NMR accuracy (2 %, only [D_5]pyridine as solvent caused broadened signals resulting in lower accuracy), the ratio of the two resulting products **4** and **5** was constant during the reactions and therefore the overall rate constant k_{exp} could be divided into the two rate constants, k_1 for formation of 1,2-oxazine **4** and k_2 for that of 1,3-diene **5** (columns 7 and 8). It is remarkable that the fragmentation of **3** to **5** is slightly decelerated in more polar solvents and completely suppressed in the two chlorinated solvents $CDCl_3$ and CD_2Cl_2. This moderate influence of the solvent polarity is compatible with a mechanism of the retro ene reaction with low charge separation in the transition state.

The solvent dependence of the cyclization of **3** to the major product **4** does not correlate with the $E_T(30)$ values and therefore its interpretation is not simple. The slowest rates were determined for diethyl ether and tetrahydrofuran and as a consequence the fragmentation to **5** occurs to considerable extent in these solvents. But relatively slow cyclizations were also observed in cyclohexane, pyridine and DMSO (all solvents are perdeuterated). On the other hand, acetonitrile and the two chlorinated solvents $CDCl_3$ and CD_2Cl_2 provided the highest rate constants k_1. For the cyclization in $CDCl_3$ a high primary kinetic isotope effect of ca. 6.7 was determined (entries 6 and 7), demonstrating that the migration of the proton/deuteron is involved in the rate-determining step. We also attempted to perform a similar experiment of **3**-d_1 in [D_5]pyridine but observed fast partial D/H exchange of the hydroxylamine moiety (probably due to traces of water and catalyzed by the basic solvent). Hence the results of this experiment are questionable, however, the consumption of **3**-d_1 was slower by a factor of ca. 6 and only **4**-d_1 was formed as deuterated compound whereas no deuterium was incorporated into 1,3-diene **5** formed in ca. 10 %.

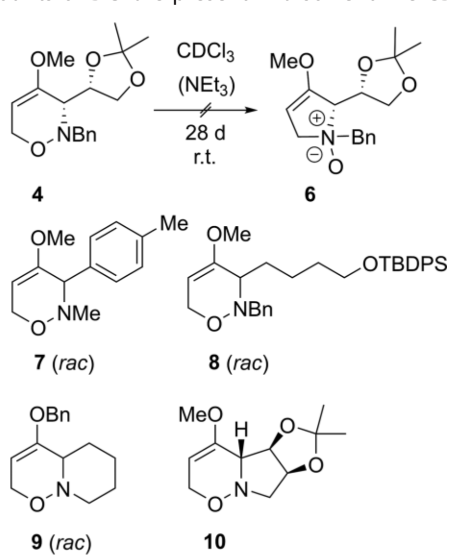
The k_1 values of Table 1 could suggest that the cyclization of allenyl hydroxylamine **3** is faster in solvents were traces of acids might be present (DCl in CD_2Cl_2 and $CDCl_3$ or DCN in [D_3]acetonitrile) and slower in basic solvents such as ethers, pyridine or DMSO. We therefore examined the influence of additives on the selectivity and rate of **3** (Table 2). The experiments were performed in CD_2Cl_2 as solvent since only the 1,2-oxazine derivative **4** is formed and no fragmentation was observed without additive (entry 1). The addition of an excess of acid, even the strong toluenesulfonic acid, (entries 2 and 3) or bases (entries 4–7) has essentially no influence on the rate of the cyclization. With the two acids even a slight retardation of the cyclization was observed; interestingly, the strong *p*-toluenesulfonic acid did not react with the potentially acid sensitive enol ether moieties of **3** and **4** in the relatively short reaction times. The fragmentation product **5** was not identified in these experiments, however, it cannot be excluded that small amounts are decomposed by the acidic additives.

Table 2. Cyclization of hydroxylamine derivative **3** into 1,2-oxazine **4** in CD_2Cl_2 at room temperature in the presence of different additives according to Scheme 4.

Entry	Additive	Equivalents	$k_{exp} \times 10^{-5}$ (s^{-1})	$t_{1/2(exp)}$ [min]
1	none	–	348	3.3
2	*p*TosOH	2.7	240	4.9
3	AcOH	10.3	170	6.9
4	DABCO	8.4	300	3.9
5	DMAP	8.6	320	3.7
6	Et_3N	14.5	340	3.4
7	DBU	15.7	240	4.8

For a proton-catalyzed cyclization a stronger influence of the acidic and basic additives can be expected. Overall, the kinetic results, in particular the high primary kinetic isotope effect, are in agreement with a mechanism of the cyclization **3** → **4** (and generally of **A** → **B**) with transfer of the hydroxylamine hydrogen in the rate-determining step.

Finally, we checked whether the above-mentioned pyrroline *N*-oxides **I** are formed from 1,2-oxazine derivatives **B** by a ring contraction process (reverse Meisenheimer 1,2-rearrangement). For this purpose, we examined the long-term stability of several typically substituted 1,2-oxazine derivatives in $CDCl_3$ under exclusion of light (Scheme 5). Compounds **4** and **7**–**10** were stable for at least four weeks, no changes could be seen in their ^{1}H-NMR spectra. These experiments were repeated in the presence of an excess of triethylamine, but again no changes were observed. We conclude that the 1,2-oxazines are stable even if small amounts of DCl are present in a solvent like $CDCl_3$.

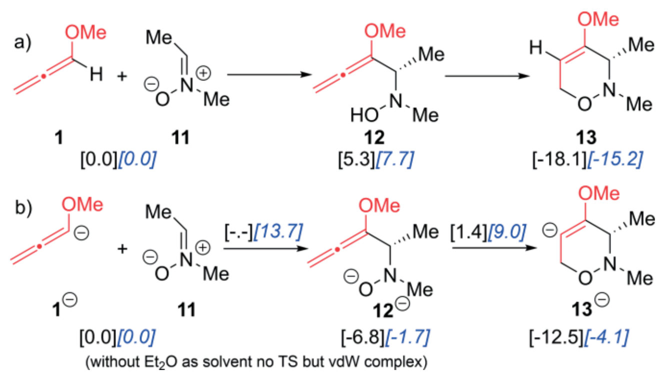


Scheme 5. Examination of stability of 1,2-oxazine derivatives **4** and **7**–**10** in $CDCl_3$ at room temperature.

Computational Study

In order to mechanistically evaluate the many conceivable pathways of the highly reactive allenyl-substituted hydroxylamines, quantum chemical DFT calculations for model compound **12** and its various subsequent products were performed. On the TPSSTPSS/def2tzvp[14,15] + GD3BJ[16] level of theory first optimizations for the gas phase were performed.[17,18] PCM calculations[19] using a solvent sphere of diethyl ether, one of the solvents used in the experiments, were done in order to estimate the influence of this polar environment on the intermediates and products. In the following, we discuss Gibbs free energies [kcal/mol], for the PCM-diethyl ether model the data are given in italics in the text and with blue color in the Schemes *[kcal/mol]* (see also Supporting Information for details). Results of PCM calculations for the more polar solvent acetonitrile did not deviate significantly from the diethyl ether results and are therefore not presented in the Schemes.

We first calculated the stability of the species involved employing nitrone **11** as precursor of model compound **12**. Combination of methoxyallene **1** with **11** to furnish allenyl hydroxylamine **12** is a moderately endothermic process, however, the subsequent cyclization to the 1,2-oxazine **13** clearly demonstrates that the overall process is thermodynamically very favorable (Scheme 6, equation a). The alkoxyallene subunits of **1** and **12** certainly contribute to their relatively high energy level. It should be noted in this context that the Huisgen reaction (1,3-dipolar cycloaddition)[20] of methoxyallene **1** with nitrone **2** proceeds very slowly at room temperature (even in the presence of Lewis acids) and affords mixtures of isoxazolidine derivatives with low regio- and stereoselectivity.[21] To realize the formation of allenyl hydroxylamine **12** requires the deprotonation of **1** and therefore the thermochemistry of the involved anionic species was also calculated (Scheme 6, equation b). Now, the addition step of $\mathbf{1}^-$ to nitrone **11** is exothermic (in agreement with the experiments), and the barrier leading to $\mathbf{12}^-$ is very low. Despite of the better stabilization of the negative charge in $\mathbf{12}^-$ this species is still not particularly stable due to the allenyl moiety. As a consequence, the 6-*endo-trig* cyclization (via a low barrier) to the 1,2-oxazine anion $\mathbf{13}^-$ is again an exothermic step. Experimentally this very last step is not observed since the lithium counterion plays a crucial role, which has been neglected in the calculations summarized in this equation. Due to the worse solvation of the lithium counterion



Scheme 6. Energetics of the formation of allenyl-substituted hydroxylamines **12** and 1,2-oxazine **13**: a) starting from neutral components **1** and **11**; b) starting from allenyl anion $\mathbf{1}^-$ and **11** (in this and all subsequent schemes only relative configurations are defined by the drawn formulas).

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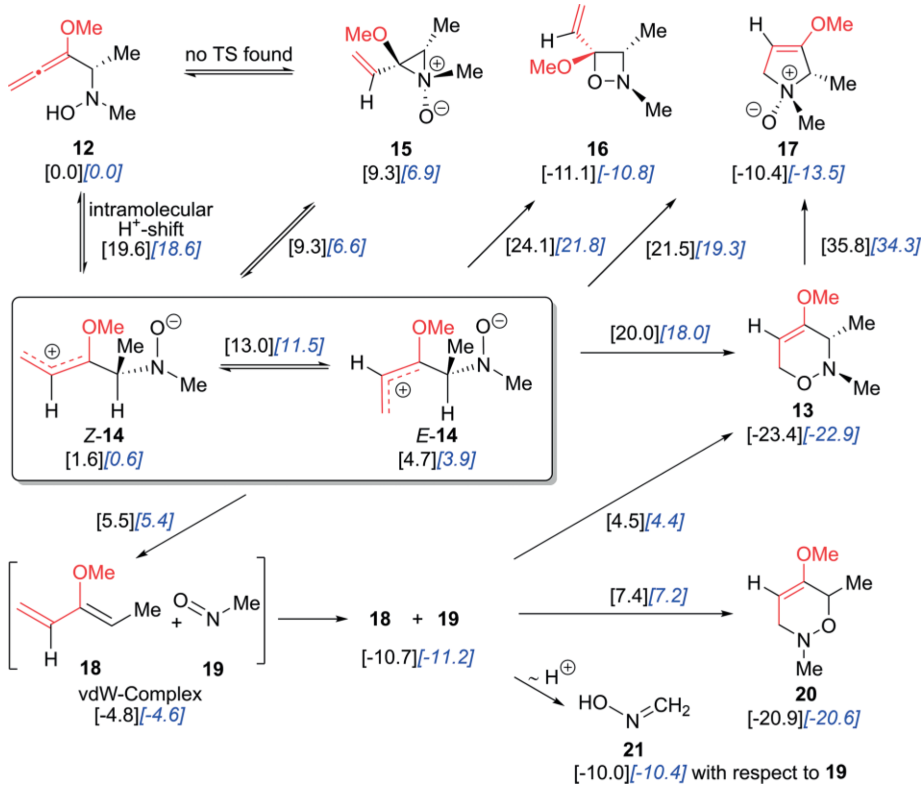

Scheme 7. Formation of 1,2-oxazine **13** via zwitterionic intermediates *Z*-**14** and *E*-**14** and other possible pathways/products.

of the intermediate anion **13**⁻ the cyclization of the ion pair is calculated to be endothermic (17.4 kcal/mol) and the barrier is higher (23.0 kcal/mol).[22]

In compounds like **12** a number of highly reactive functional groups are combined: an allene subunit, an enol ether and a hydroxylamine functionality with Lewis and Brønsted basic and acidic centers as well as with nucleophilic and electrophilic sites. With regard to the Brønsted acidity, the hydroxylamine subunit is of most interest. Its pK_a value (ca. 14)[10] is close to that of water or to that of the dimethylammonium cation, whereas the methoxyallene moiety may well act as a Brønsted base. Thus, as shown in Scheme 7, the zwitterionic tautomers **14** are almost equal in relative energy compared to **12**. Inter- or intramolecular proton transfer may establish an equilibrium of **12** and **14**. The calculated values for the intramolecular H-shifts are given in Scheme 7 and the transition state of this process is depicted in Figure 1. Unfortunately, intermolecular H-shifts cannot be calculated reliably. We assume that the barriers are substantially lower than intramolecular barriers due to the influence of the diethyl ether solvent for proton transfer reactions.

Thus, as central reactive intermediate we assume the zwitterions *Z*-**14** and *E*-**14** which may interconvert via a relatively low barrier or via **12** by proton exchange. From these key intermediates, various possible products were calculationally generated: the three-membered aziridinium *N*-oxide **15**, which is higher in energy by 9.3/*6.9* kcal/mol, is situated on an extremely flat hyperface, with a transition state energy very close to the local minimum for **15**. Thus, this species may play a role in equilibria

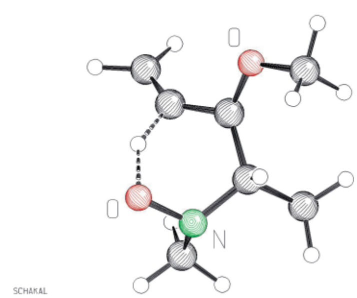

Figure 1. Transition state of the intramolecular proton transfer of allenyl hydroxylamine **12** leading to zwitterion *Z*-**14**.

under the reaction conditions, but there is no chance for experimental identification. The four- and five-membered ring systems **16** and **17** might be formed exothermically via the respective 4-*exo-trig* and 5-*endo-trig* cyclizations, the barriers for their formation (19–24 kcal/mol) are compatible with the reaction conditions. By far lowest in energy (thermodynamic control) [ca. –23 kcal/mol] among all considered possible products is the experimentally observed 1,2-oxazine derivative **13**. It may result from **14** by a 6-*endo-trig* cyclization (barrier ca. 17–18 kcal/mol) (Figure 2), but also by an alternative pathway involving a hetero-Diels–Alder reaction (see below). It is also interesting to note, that a ring contraction **13** → **17** (reverse Meisenheimer 1,2-rearrangement)[23] involves a high barrier (ca. 35 kcal/mol) and is thermodynamically unfavorable. This computational result is in full agreement with the experimental observations (see Scheme 5).

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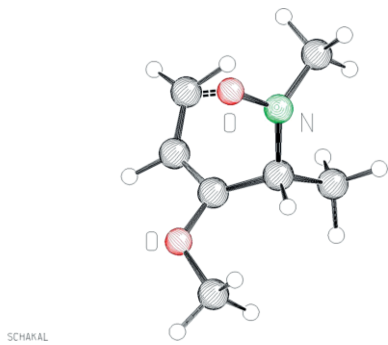


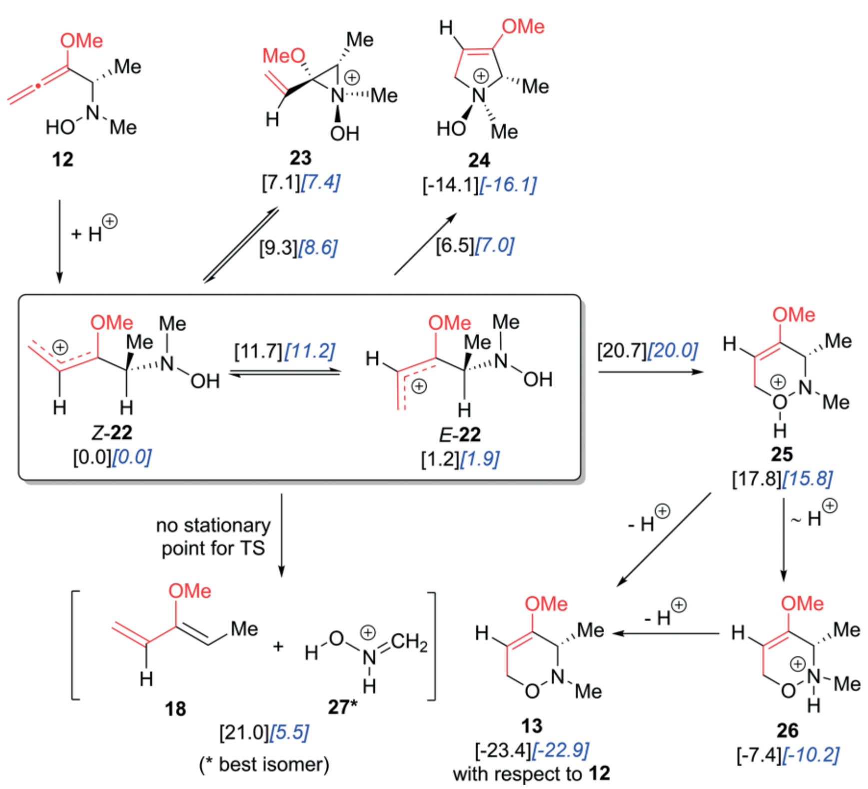
Figure 2. Transition state of the 6-*endo-trig* cyclization of zwitterion *E*-**14** to 1,2-oxazine derivative **13**.

An unexpected feature of the zwitterions **14** is their low stability towards N-C-bond rapture leading to a van der Waals complex of the neutral fragments 3-methoxy-1,3-pentadiene (**18**) and nitrosomethane (**19**) and – quite likely – after tautomerism to its more stable isomer formaldehyde oxime (**21**). Compound **5** (see above) was isolated from the reaction mixture as a representative example of these C-N-rapture products. The very low barrier and the higher stability of **18**/**19** compared to **14** may allow an important contribution of these species in the equilibrium. So far, we interpreted the fragmentation of allenyl-substituted hydroxylamines as a concerted retro ene reaction,[24] however, the calculations indicate that a two-step process with a proton transfer preceding the N-C bond cleavage is very likely.

A recombination of **18**/**19** by hetero-Diels–Alder reaction may also afford 1,2-oxazine **13**,[25] the most stable species of the system, and/or its isomer **20** (experimentally not observed), which is accessible via a slightly higher barrier and also less stable. This pathway to **13** was not considered so far and it does not easily explain the observed retention of configuration at C-3 of the 1,2-oxazine **13**. Calculationally, the van der Waals complex **18**/**19** was localized for the fragmentation products; however, proton transfer reactions or subsequent cycloadditions could not be derived directly from this complex but only from its free components **18** and **19**.

In summary, starting from neutral **12** the formation of four-, five- and six-membered heterocyclic rings is possible with not very different barriers via zwitterions **14**. However, from the thermodynamic point of view, the formation of the 1,2-oxazine derivative is clearly favored. Although the lowest barrier was found for the formation of the (unstable) aziridinium *N*-oxide **15** no direct pathway could computationally be identified leading from this species to 1,2-oxazine **13**.

As second scenario the involvement of protonated species (see structure **C** of Scheme 2) should be considered, which are formed either by self-protonation by the acidic hydroxylamine group or by addition of external acids. We therefore investigated the protonated compounds by DFT calculations in order to get insight into pathways of **12** in the presence of acids. The results are summarized in Scheme 8 with the allylic cation *Z*-**22** as reference of energy. Quite similar as in the zwitterionic case (see **14** in Scheme 7) the formation of a three-membered N-hydroxy aziridinium ion **23** from *Z*-**22** seems to be feasible in an equilibrium situation; again experimental identification is unlikely due to its high relative energy and the low barrier towards the reverse reaction. Formation of the five-membered



Scheme 8. Formation of 1,2-oxazine **13** via allylic cations *Z*-**22** and *E*-**22** as key intermediates and alternative pathways.

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ring system **24** cannot be excluded which is accessible over an only very small barrier (6–7 kcal/mol); its calculated energy (–14.1/–*16.1* kcal/mol), however, allows return to the allyl cations **22**. Cyclization to form the protonated 1,2-oxazine derivative is possible considering the calculated barrier (ca. 20 kcal/mol). Due to the protonated oxygen atom the primary cyclization product **25** is energetically disfavored (16–18 kcal/mol) but a subsequent intra- or (preferably) intermolecular proton shift may give access to the thermodynamically favored N-protonated isomer **26** (–7.4/–*10.2*). A deprotonation of **25** or **26** to the neutral product **13** will provide strong thermodynamic driving force for the overall cyclization process.

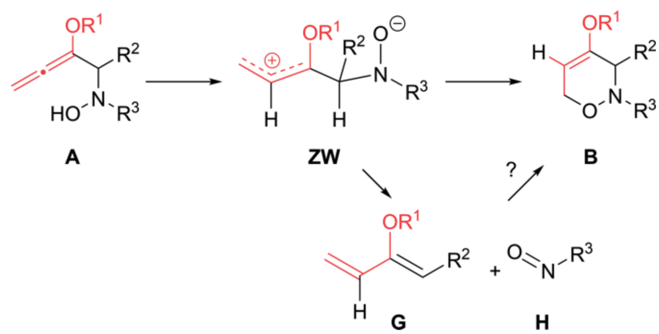
As for zwitterion **14**, we also studied the C-N-bond cleavage reaction of allyl cations **22**. Due to the primary formation of the very unfavorable O-protonated nitrosomethane fragment besides the 3-methoxy-1,3-pentadiene (**18**), no transition state could be localized. After proton shift from Me-N=O-H^+ the much better tautomer **27** is formed.

To summarize the computational results of the protonated species shown in Scheme 8, the cyclization to the observed 1,2-oxazine derivative **13** has to pass an intermediate **25** of relatively high energy though its deprotonation is energetically very favorable. The best direct cyclization pathway leads to the protonated pyrrolidine *N*-oxide **24** which is not compatible with the experimental results. Furthermore, the observed fragmentation products should not be as easily accessible as via the zwitterionic intermediates **14**. With exception of the five-membered ring system **17**, the relative energies (with respect to **14** or **22**) of the neutral compounds and the barriers are similar or slightly lower than the protonated forms. Thus, zwitterions **14** and C-protonated allenes **22** are expected to exert similar reactivity in most cases.

Conclusions

The experiments performed with allenyl-substituted hydroxylamine **3** and its O-deuterated analog **3**-d_1 show that the rate of the formation of 1,2-oxazine derivative **4** and **4**-d_1, respectively, cannot be correlated with the solvent polarity. The fragmentation product **5** is formed only in ethereal solvents in higher extent (up to 24 %). The high primary isotope effect of ca. 6.7 clearly reveals that a proton/deuteron transfer is involved in the rate-determining step. The cyclization rate is also not dependent on the presence of acidic or basic additives, therefore, the neutral allenyl-substituted hydroxylamines seem to be the reactive key species.

The computational results confirm that for protonated species no favorable direct pathway is accessible for the 1,2-oxazine formation. In contrast, the calculations starting with neutral model compound **12** offer an attractive – so far undiscussed – pathway to the six-membered ring system. By intra- or (more likely) intermolecular proton transfer the zwitterionic intermediates **14** are easily formed and show similar stability as their precursor **12**. The zwitterions **14** have various options for further reactions, but the cyclization to 1,2-oxazine **13** via a feasible barrier leads directly to the most stable compound of the system. The formation of a vinyl-substituted aziridinium *N*-oxide **15** has an even lower barrier, but the product is of similar energy as the transition state and no pathway could be identified leading from **15** to 1,2-oxazines **13**. Based on these calculations the two pathways proposed in Scheme 2 are not confirmed and the mechanisms as shown in Scheme 9 with zwitterion **ZW** as key intermediate are more likely. The cyclization to **B** has a moderate barrier, but the fragmentation to **G** and **H** is also very favorable. These products of a two-step retro ene reaction can recombine to give 1,2-oxazine **B** by a hetero-Diels–Alder reaction, a mechanism we did not consider so far. Experiments should be designed to prove or disprove this alternative pathway to 1,2-oxazine **B**.



Scheme 9. Formation of 1,2-oxazines **B** from **A** via zwitterion **ZW**.

Experimental Section

General information: reagents and solvents were purchased (Sigma-Aldrich, Acros, Fluorochem) and used as received without further purification. Tetrahydrofuran was dried with sodium metal in the presence of benzophenone and distilled just before usage. Reactions were carried out under argon in a flame-dried flask with addition of the components by using syringes; subsequent manipulations were conducted in air. Products were purified by flash chromatography on silica gel LC60A (70–200 micron, Fluorochem). Unless stated otherwise, reported yields refer to analytically pure samples. NMR spectra were measured with a Bruker AVIII 600 or with a Varian Gemini 2000 BB 200 MHz instrument. Chemical shifts are reported relative to solvent residual peaks.[26] All ^{13}C-NMR spectra are proton-decoupled; substitution patterns of the carbon atoms were determined by 2D NMR spectroscopy (COSY, HMQC, HMBC) and are indicated as ^{13}C NMR peak multiplicity; coupling constants *J* are given in Hz. IR spectra were measured with a FTIR NEXUS spectrometer (as KBr pellets or thin films). MS spectra were performed with a Varian 500-MS LC Ion Trap or with a Waters SYNAPT G2-S HDMS instrument. Melting points were measured in capillaries with a Mel-Temp II apparatus (Aldrich) and are uncorrected. Elemental analyses were obtained with a Vario EL III instrument.

General procedure for the synthesis of allenyl hydroxylamines and 1,2-oxazines: The lithiated alkoxyallene was generated in situ under inert atmosphere of dry argon by treatment of a solution of the corresponding alkoxyallene (3.50 mmol) in freshly dried THF (10 mL) with *n*-butyllithium (2.5 M in hexanes, 1.2 mL, 3.0 mmol) at –40 °C. After 5 min, the resulting solution was cooled to –78 °C, and a solution of the corresponding nitrone (1.0 mmol) in THF (2.0 mL) was added dropwise. The mixture was stirred for 2–4 h, H_2O (15 mL) was added at –78 °C, and the mixture was warmed to room temperature followed by extraction with diethyl ether (3 ×

10 mL). The combined organic layers were dried (Na_2SO_4) to provide the intermediate hydroxylamines. Their cyclization was monitored by TLC and after completion, the solvents were removed under reduced pressure and the crude 1,2-oxazines were purified by column chromatography.

The syntheses and analytical data for (3*S*,4′*S*)-2-benzyl-3-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)-4-methoxy-3,6-dihydro-2*H*-1,2-oxazine (**4**),[3c] 2-benzyl-3-[4′-(*tert*-butyldiphenylsiloxy)-butyl]-4-methoxy-3,6-dihydro-2*H*-1,2-oxazine (**8**),[27] and (4a*S*,5*R*,6*S*)-5,6-isopropylidenedioxy-4-methoxy-4a,5,6,7-tetrahydro-2*H*-pyrrolo[1,2-*b*][1,2]-oxazine (**10**)[28] were fully described in the literature. The ^{1}H- and ^{13}C-NMR spectra of the obtained 1,2-oxazines **4**, **8** and **10** are in full accordance to those reported.

Synthesis of 3-d$_1$ and 4-d$_1$: Following the general procedure, lithiated methoxyallene (4.00 mmol) was treated with D-glyceraldehyde-derived nitrone (235 mg, 1.00 mmol) in freshly dried THF (12 mL) at –78 °C for 2 h. The resulting mixture was quenched with D_2O (3.0 mL) and the mixture was allowed to reach room temperature. The layers were separated and the organic layer was washed with D_2O (2 × 2 mL). Solid Na_2SO_4 (1.5 g) was added and the cyclization of the hydroxylamine **3**-d$_1$ was monitored by TLC (SiO_2, petroleum ether/EtOAc, 7:1, visualization with *p*-anisaldehyde stain). After 24 h the mixture was filtered, the solvent was removed in vacuo, and crude product was purified by column chromatography (SiO_2, petroleum ether/EtOAc, 6:1) to give 1,2-oxazine **4**-d$_1$ (191 mg, 63 %, degree of deuteration at C-5 >95 %) as a colorless oil.

$[\alpha]_D^{20}$ = +33.1 (*c* = 0.26, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 1.35, 1.40 (2 s, 3 H each, 2 Me), 3.31 (d$_{br}$, *J* ≈ 7.0 Hz, 1 H, 3-H), 3.56 (s, 3 H, OMe), 3.91 (d, *J* = 7.0 Hz, 2 H, 5′-H), 4.14 (s, 2 H, C*H*$_2$Ph), 4.15 (d, *J* = 14.6 Hz, 1 H, 6-H), 4.42 (d$_{br}$, *J* ≈ 14.6 Hz, 1 H, 6-H), 4.55 (q, *J* = 7.0 H, 1 H, 4′-H), 7.23–7.26, 7.29–7.32, 7.41–7.43 (3 m, 1 H, 2 H, 2 H, Ph) ppm; ^{13}C NMR ($CDCl_3$, 151 MHz): δ = 26.1, 26.6 (2 q, 2 Me), 54.1 (q, OMe), 58.3 (t, *C*H$_2$Ph), 63.4 (d, C-3), 64.3 (t, C-6), 66.8 (t, C-5′), 75.0 (d, C-4′), 92.5 (t, J_{C-D} = 24.1 Hz, C-5), 108.6 (s, C-2′), 127.0, 128.2, 128.7, 137.9 (3 d, s, Ph), 151.4 (s, C-4) ppm; IR (film): $\tilde{\nu}$ = 3055–2855 (=C-H, C-H), 1625 (C=C), 1470, 1255, 1145, 1100, 1035, 835 cm^{-1}; ESI-MS (*m/z*): 307.2 (100, [M + H]$^+$). Anal. calcd. for $C_{17}H_{22}DNO_4$ (306.2): C 66.64, H/D 7.90, N 4.57; found C 66.67, H/D 7.72, N 4.59.

4-Methoxy-2-methyl-3-(*p*-tolyl)-3,6-dihydro-2*H*-1,2-oxazine (7): Following the general procedure, *N*-methyl-*C*-(*p*-tolyl)nitrone (149 mg, 1.00 mmol) was treated with lithiated methoxyallene (2 h). After the cyclization of intermediate allenyl hydroxylamine was complete (16 h), the crude mixture was purified by column chromatography (SiO_2, hexanes/EtOAc, 4:1) to give **7** (160 mg, 73 %) as a pale yellow solid.

M.p. 29–31 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 2.34 (s, 3 H, Tol), 2.43 (s, 3 H, NMe), 3.48 (s, 3 H, OMe), 4.05 (s, 3-H), 4.42, 4.58 (2 s$_{br}$, 1 H each, 6-H$_2$), 4.88 (*pseudo*-t, *J* ≈ 3.2 Hz, 1 H, 5-H), 7.14, 7.21 (2 d$_{br}$, *J* ≈ 8.2 Hz, 2 H each, Tol) ppm; ^{13}C NMR ($CDCl_3$, 151 MHz): δ = 21.2, 42.9, 54.7 (3 q, Tol, NMe, OMe), 66.5 (t, C-6), 70.6 (d, C-3), 92.4 (d, C-5), 128.9, 129.5, 133.9, 137.7 (2 d, 2 s, Tol), 154.6 (s, C-4) ppm; IR (KBr): $\tilde{\nu}$ = 3025–2820 (=C-H, C-H), 1670 (C=C), 1360, 1225, 1085, 1045 (C-O) cm^{-1}; ESI-MS (*m/z*): 220.2 (100, [M + H]$^+$). Anal. calcd. for $C_{13}H_{17}NO_2$ (219.1): C 71.21, H 7.81, N 6.39; found C 71.49, H 7.73, N 6.16.

4-Benzyloxy-2,4a-dihydropiperidino[1,2-*b*][1,2]-oxazine (9): Following the general procedure, 2,3,4,5-tetrahydropiperidine *N*-oxide (99.1 mg, 1.00 mmol) was treated with lithiated benzyloxyallene at ca. –100 °C (Et_2O/CO_2 bath) for 4 h. The resulting allenyl hydroxylamine required 2 days for complete cyclization. The crude product was purified by column chromatography (SiO_2, petroleum ether/EtOAc, 5:1) to afford **9** (106 mg, 44 %) as a colorless solid.

M.p. 100–103 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 1.23–1.39 (m, 2 H, 5-H, 7-H), 1.67–1.80 (m, 3 H, 6-H$_2$, 7-H), 2.25 (d$_{br}$, *J* ≈ 13.0 Hz, 1 H, 5-H), 2.54–2.60 (m, 1 H, 8-H), 3.12 (d$_{br}$, *J* ≈ 11.3 Hz, 1 H, 4a-H), 3.34–3.38 (m, 1 H, 8-H), 4.19 (dd, *J* = 2.7, 14.1, 1 H, 2-H), 4.64 (d$_{br}$, *J* ≈ 14.1 Hz, 1 H, 2-H), 4.74 (m$_c$, 1 H, 3-H), 4.76 (s, 2 H, C*H*$_2$Ph), 7.28–7.37 (m, 5 H, Ph) ppm; ^{13}C NMR ($CDCl_3$, 151 MHz): δ = 23.7, 25.3, 27.0 (3 t, C-7, C-6, C-5), 55.9 (t, C-8) 65.6 (d, C-4a), 66.4 (t, C-2), 69.0 (t, *C*H$_2$Ph), 92.4 (d, C-3), 127.1, 127.7, 128.4, 137.1 (3 d, s, Ph), 153.4 (s, C-4) ppm; IR (KBr): $\tilde{\nu}$ = 3060–2815 (=C-H, C-H), 1665 (C=C), 1225, 1205, 1175, 1095 (C-O) cm^{-1}; EI-HRMS: calcd. for $C_{15}H_{19}NO_2$ ([M]$^+$) 245.1416; found 245.1420. Anal. calcd. for $C_{15}H_{19}NO_2$ (245.1): C 73.44, H 7.81, N 5.71; found C 73.64, H 7.80, N 5.69.

Preparation of allenyl hydroxylamine samples for kinetic measurements: Following the general protocols for the preparation of hydroxylamines **3** or **3**-d$_1$, the mixture was quenched with water or D_2O at –78 °C and allowed to reach 0 °C. Cold diethyl ether was added in the case of **3** to achieve separation of the layers. The organic layer was separated and very quickly washed with either H_2O or D_2O and dried with solid Na_2SO_4 (1.5 g) at 4 °C. After ca. 15 min. of drying the first sample (0.6–1.0 mL for **3**, 0.2–0.3 mL for **3**-d$_1$) was transferred via syringe into a flame-dried flask, and the solvent was removed in vacuo (at room temperature) to give a thick oil. The residue was dissolved in 0.8 mL of the corresponding deuterated solvent (optionally with an additive) and the ^{1}H-NMR spectra were measured. The remaining solution of the allenylhydroxylamine was stored in the presence of the drying agent in a Dewar container with dry ice until the next sample for the kinetics was required.

^{1}H NMR of **3**: ([D$_8$]THF, 200 MHz): δ = 1.27, 1.31 (2 s, 3 H each, 2 Me), 3.34 (d$_{br}$, *J* = 5.7 Hz, 1 H), 3.37 (s, 3 H, OMe), 3.75 (dd, *J* = 7.0, 8.3 Hz, 1 H), 3.88, 3.91 (AB system, *J* = 8.6 Hz, C*H*$_2$Ph), 3.96 (dd, *J* = 6.4, 8.3 Hz, 1 H), 4.46 (dt, *J* ≈ 6.7, 8.3 Hz, 1 H), 5.47 (s$_{br}$, 2 H, =CH$_2$), 7.13–7.26, 7.30–7.37 (2m, 3 H, 2 H, Ph) ppm; ^{1}H NMR of **3**-d$_1$: ($CDCl_3$, 200 MHz): δ = 1.37 (s$_{br}$, 6 H, 2 Me), 3.41 (d$_{br}$, *J* = 6.8 Hz, 1 H), 3.45 (s, 3 H, OMe), 3.75–3.81 (m, 1 H), 3.92–4.15 (m, 3 H), 4.48–4.60 (m, 1H), 5.53 (s$_{br}$, 2 H, =CH$_2$), 7.23–7.42 (m, 5 H, Ph) ppm.

Quantum chemical calculations: Quantum chemical calculations at the DFT level TPSSTPSS/def2-TZVP+GD3BJ dispersion correction[14–16] were performed using the Gaussian 09, Revision D.01[17] and the Gaussian 16, Revision B.01[18], packages of programs for the gas phase as well as for diethyl ether and acetonitrile as solvent using the PCM solvent sphere.[19] The transition state localizations were started with reaction path calculations by stepwise, independent elongation of relevant bonds. Then transition state searches or QST2 calculations on the basis of the obtained 3D-hyperfaces followed. We cannot exclude that due to the steric complexity of the reacting systems further transition state conformations and configurations exist. In many cases, for transition states IRC-calculations were subsequently performed in order to characterize them unambiguously, followed be complete geometry optimizations leading to the respective minima.

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Keywords: Allenes · Cyclization · DFT calculation · 1,2-Oxazine · Reaction mechanisms

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